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(54) Title: COMPOSITIONS AND METHODS FOR INHIBITION OF RAS

(57) Abstract: Provided herein are compounds, or salts, esters, tautomers, prodrugs, zwitterionic forms, or stereoisomers thereof, as well as pharmaceutical compositions comprising the same. Also provided herein are methods of using the same in modulating (e.g., inhibiting) KRAS (e.g., KRAS having a Q61H, G12D, G12V, G12C, G12S, G12A, G12R, or G13D mutation or wild-type KRAS, including wild-type amplified KRAS) and treating diseases or disorders such as cancers in subjects in need thereof.

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COMPOSITIONS AND METHODS FOR INHIBITION OF RAS

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0001] This invention was made with government support under (1) Contract No.: 75N91019D00024 awarded by the National Institutes of Health and (2) Contract No. DE-AC52-07NA27344 awarded by the United States Department of Energy. The government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to United States Provisional Application No. 63/605,348, filed December 1, 2023, United States Provisional Application No. 63/550,896, filed February 7, 2024, and United States Provisional Application No. 63/658,325, filed June 10, 2024, the entirety of each of which is incorporated herein by reference

BACKGROUND

[0003] RAS protein functions as a molecular switch, cycling between inactive ("GDP-bound") and active ("GTP-bound") states. RAS signaling occurs through engagement with effector proteins that adapt the signaling cascades regulating tumor cell survival and proliferation. Aberrant activation of RAS by oncogenic mutations results in increased GTP-bound KRAS and constitutive downstream signaling.

[0004] *RAS* is the most frequently mutated oncogene. Activating mutations in *KRAS* occur in over 90% of pancreatic tumors. Mutated KRAS is also observed at high frequency in other common tumors, including colorectal cancer (~44%) and non–small cell lung cancer (NSCLC; ~20-30%). Cancer-associated mutations in KRAS cluster in three hotspots (G12, G13, and Q61), with a majority (77%) of mutations causing single amino acid substitutions at G12. The KRAS missense mutation G12D is the most predominant variant in human malignancies (35%), followed by G12V (29%). Besides G12, the hotspots G13 and Q61 show mutation rates of 10% and 6% respectively.

[0005] The development of small molecule KRAS inhibitors has proven to be a challenge. Recent clinical development of covalent KRAS G12C inhibitors indicates potential of targeting the KRAS oncogenic protein directly. Results from clinical trials with the two covalent inhibitors, AMG510 (sotorasib) and MRTX849 (adagrasib), have been promising. These inhibitors demonstrated clinical activity primarily in NSCLC, where the KRAS G12C mutation frequency is highest. Unfortunately, they appeared less effective

in KRAS G12C colorectal cancers. Both compounds only target the inactive (GDP-bound) form of KRAS G12C, and a lack of activity against active (GTP-bound) KRAS G12C may contribute to development of drug resistance. Moreover, these covalent inhibitors are limited to the specific G12C mutant that accounts for approximately 13% of all KRAS-driven cancers, leaving a large population of non-G12C KRAS cancers still undruggable. Therefore, KRAS therapeutics that target additional KRAS alterations or combinations thereof are an unmet clinical need. Pan-KRAS inhibitors hold promise for impact across the majority of KRAS mutant alleles, including the most prevalent G12D and G12V, or KRAS wildtype-amplified cancers.

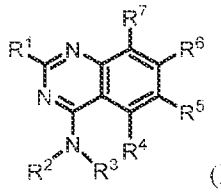
[0006] KRAS is essential for mouse development, whereas NRAS and HRAS are dispensable. This requirement for KRAS creates toxicity concerns when targeting the wild-type KRAS protein. However, when KRAS is replaced with HRAS, mice are viable, which reduces toxicity concerns and suggests that in contrast to the pan-RAS inhibitors that could pose toxicity issues, KRAS isoform-specific inhibitors should be tolerated. If so, additional advantages of pan-KRAS inhibitors could come from targeting cancers with acquired resistance to KRAS G12C inhibitors. Recent reports provide insights into mechanisms of resistance to the KRAS G12C inhibitors in the clinic, suggesting restoration of RAS/MAPK as a driver of the resistance. Acquisition of a diverse set of mutations in response to KRAS G12C inhibitors in addition to activation of the KRAS wildtype allele through upstream RTK signaling has been shown. It is possible that direct pan-KRAS agents may suppress these events. Accordingly, there remains a need for allele-specific and pan-KRAS inhibitors that could be used to treat KRAS-driven cancers regardless of mutation status.

SUMMARY

[0007] The present disclosure provides compounds, as well as compositions and kits comprising the same, and methods of using the same in the treatment of diseases and disorders such as cancers. The present disclosure provides compounds that may be capable of inhibiting one or more mutant forms of KRAS, such as KRAS having a G12D, G12V, G12C, G12S, G12A, G12R, Q61H, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS. Such compounds may be considered pan-KRAS inhibitors. In some embodiments, the compounds provided herein may be capable of targeting both active GTP-bound protein and inactive GDP-bound protein, which inhibitors may provide therapeutic advantages over compounds capable of targeting only the inactive GDP-bound protein. In some embodiments, compounds provided herein have inhibitory activity against a KRAS protein comprising a glycine to aspartic acid, valine, cysteine, serine, alanine, or arginine mutation at codon 12 (i.e., a G12D, G12V, G12C, G12S, G12A, or G12R mutation); or a glycine to aspartic acid mutation at codon 13 (e.g., a G13D mutation); or a

glutamine to histidine mutation at codon 61 (e.g., a Q61H mutation) in both its active and inactive conformations. In some embodiments, compounds provided herein have inhibitory activity against wild-type KRAS, including wild-type amplified KRAS. In some embodiments, compounds provided herein are useful in the treatment of cancers, such as cancers characterized by KRAS proteins having a mutation at codon 12, such as a G12D, G12V, G12C, G12S, G12A, or G12R mutation; or a mutation at codon 13, such as a G13D mutation; or a mutation at codon 61, such as a Q61H mutation, or cancers that may benefit from inhibition of wild-type KRAS, including wild-type amplified KRAS.

[0008] In an aspect, the present disclosure provides compositions comprising compounds represented by Formula X:



(X),

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as provided herein. In some embodiments, the compound is a compound according to any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC' provided herein, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof. In some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, can modulate (e.g., inhibit) the activity of a KRAS protein, such as a KRAS protein having a mutation at codon 12, such as a G12D, G12V, G12C, G12S, G12A, or G12R mutation; a KRAS protein having a mutation at codon 13, such as G13D; a KRAS protein having a mutation at codon 61, such as Q61H; or a wild-type KRAS (e.g., a wild-type amplified KRAS). In some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of interacting with a KRAS protein comprising a glycine to aspartic acid, valine, cysteine, serine, alanine, or arginine mutation at codon 12 (i.e., a G12D, G12V, G12C, G12S, G12A, or G12R mutation) or a glycine to aspartic acid mutation at codon 13 (e.g., a G13D mutation) or a glutamine to histidine mutation at codon 61 (e.g., a Q61H mutation) in both its active and inactive conformations. In some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, has

inhibitory activity against wild-type KRAS, including wild-type amplified KRAS. In some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding a KRAS protein in an active ("GTP-bound") conformation. In some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding a KRAS protein in an inactive ("GDP-bound") conformation. In some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding a KRAS protein in both its active ("GTP-bound") and inactive ("GDP-bound") conformations.

[0009] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound provided herein (e.g., a compound represented by any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC', or any other formula set forth herein), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, together with a pharmaceutically acceptable carrier.

[0010] In a further aspect, the present disclosure provides a method of inhibition of KRAS activity in a human or animal subject for the treatment of a disease such as cancer, including pancreatic cancer (e.g., pancreatic ductal adenocarcinoma (PDAC)), colorectal cancer, endometrial endometrioid adenocarcinoma, rectal adenocarcinoma, gastric cancer, esophageal adenocarcinoma, gastroesophageal junction cancer, invasive ductal carcinoma, lung cancer, and neurofibromatosis type 1 (NF1) using, e.g., a compound provided herein (e.g., a compound represented by any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC', or any other formula set forth herein), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical composition comprising the same.

[0011] In another aspect, the present disclosure provides a use of a compound provided herein (e.g., a compound represented by any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1',

IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC', or any other formula set forth herein), or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, in the manufacture of a medicament for the treatment of a disease, disorder, or condition (e.g., a cancer) ameliorated, treated, inhibited, or reduced by inhibition of KRAS, including KRAS having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), KRAS having a mutation at codon 13 (e.g., a G13D mutation), KRAS having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS, including wild-type amplified KRAS. In some embodiments, the disease, disorder, or condition is pancreatic cancer (e.g., pancreatic ductal adenocarcinoma (PDAC)), colorectal cancer, or lung cancer.

[0012] In a further aspect, the present disclosure provides a compound as provided herein (e.g., a compound represented by any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC', or any other formula set forth herein), or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, for use as a medicament. In some embodiments, the medicament is used in the treatment of a disease, disorder, or condition (e.g., a cancer). In some embodiments, the disease, disorder, or condition is pancreatic cancer (e.g., pancreatic ductal adenocarcinoma (PDAC)), colorectal cancer, or lung cancer.

DETAILED DESCRIPTION

[0013] The present disclosure provides compounds (e.g., compounds of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), which compounds may possess useful KRAS inhibitory activity, and may be used in the treatment or prophylaxis of a disease, disorder, or condition in which KRAS plays an active role. In particular, certain compounds provided herein may possess useful inhibitory activity of a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon 13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein, which KRAS protein is in an active (GTP-bound) or inactive (GDP-bound) conformation. Certain compounds provided

herein may be capable of inhibiting both active and inactive forms of KRAS. The present disclosure also provides pharmaceutical compositions comprising one or more compounds provided herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. The present disclosure also provides methods for inhibiting KRAS, including a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon 13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein, which KRAS is in an active or inactive conformation. In an aspect, the present disclosure provides a method for treating a disorder mediated by KRAS including a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon 13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein in a subject in need of such treatment, which method comprises administering to the subject a therapeutically effective amount of a compound or composition provided herein. Also provided herein is the use of certain compounds provided herein in the manufacture of a medicament for the treatment of a disease, disorder, or condition ameliorated, treated, inhibited, or reduced by inhibition of KRAS, including a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon 13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein. In some embodiments, the disease, disorder, or condition is a cancer (e.g., as described herein).

[0014] When ranges of values are disclosed, and the notation "from n_1 ... to n_2" or "between n_1 ... and n_2" is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μM (micromolar)," which is intended to include 1 μM, 3 μM, and everything in between to any number of significant figures (e.g., 1.255 μM, 2.1 μM, 2.9999 μM, etc.).

[0015] "About," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[0016] "Acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety where the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(O)CH_3$ group. An "alkylcarbonyl" or "alkanoyl" group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[0017] "Alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term "alkenylene" refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(-CH=CH-), (-C::C-)]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term "alkenyl" may include "alkenylene" groups.

[0018] "Alkynyl" refers to either a straight chain or branched-chain hydrocarbon having at least 2 carbon atoms and at least one triple bond and having the number of carbon atoms indicated (*i.e.*, C_{2-6} means to two to six carbons). Alkynyl can include any number of carbons, such as C_2, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{2-7}, C_{2-8}, C_{2-9}, C_{2-10}, C_3, C_{3-4}, C_{3-5}, C_{3-6}, C_4, C_{4-5}, C_{4-6}, C_5, C_{5-6}, and C_6. Examples of alkynyl groups include, but are not limited to, acetylenyl, propynyl, 1-butynyl, 2-butynyl, butadiynyl, 1-pentynyl, 2-pentynyl, isopentynyl, 1,3-pentadiynyl, 1,4-pentadiynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1,3-hexadiynyl, 1,4-hexadiynyl, 1,5-hexadiynyl, 2,4-hexadiynyl, and 1,3,5-hexatriynyl.

[0019] "Alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as described herein. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[0020] "Alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms (*e.g.*, C_{1-20} alkyl). In certain embodiments, said alkyl will comprise from 1 to 10 carbon atoms (*e.g.*, C_{1-10} alkyl). In further embodiments, said alkyl will comprise from 1 to 8 carbon atoms (*e.g.*, C_{1-8} alkyl). In further embodiments, said alkyl will comprise from 1 to 6 carbon atoms (*e.g.*, C_{1-6} alkyl). In further embodiments, said alkyl will comprise from 1 to 3 carbon atoms (*e.g.*, C_{1-3} alkyl). Alkyl groups are unsubstituted or substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, nonyl, and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($-CH_2-$). Unless otherwise specified, the term "alkyl" may include "alkylene" groups.

[0021] "Alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino, and the like.

[0022] "Alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as described herein and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[0023] "Amido" and "carbamoyl," as used herein, alone or in combination, refer to an amino group as described herein attached to the parent molecular moiety through a carbonyl group, or vice versa. The "amido" group as used herein incudes "C-amido" and "N-amido" groups. The term "C-amido" as used herein, alone or in combination, refers to a -C(O)N(RR') group with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated. In some embodiments, the "amido" group includes -C(O)NH_2, C_{1-4}alkylamido, and di(C_{1-4}alkyl)amido. The term "C_{1-4}alkylamido", as used herein, refers to -C(O)NH(C_{1-4}alkyl), wherein C_{1-4}alkyl is as defined herein. The term "N-amido" as used herein, alone or in combination, refers to a RC(O)N(R')- group, with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated. The term "acylamino" as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an "acylamino" group is acetylamino (CH_3C(O)NH-).

[0024] "Amino," as used herein, alone or in combination, refers to -NRR', wherein R and R' are independently selected from hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be unsubstituted or substituted. Additionally, R and R' may combine to form a heterocycloalkyl, which is unsubstituted or substituted. An "amino" group may be a primary amine (*e.g.*, -NH_2), secondary or di-substituted amine (*e.g.*, -NHR where R is not hydrogen), or tertiary or tri-substituted amine (*e.g.*, -NRR' where neither R nor R' is hydrogen).

[0025] "Aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein such polycyclic ring systems are fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl. An aryl moiety may include, for example, between 5 to 20 carbon atoms, such as between 5 to 12 carbon atoms, such as 5 or 6 carbon atoms.

[0026] "Arylalkenyl" or "aralkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[0027] "Arylalkoxy" or "aralkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[0028] "Arylalkyl" or "aralkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[0029] "Aryloxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[0030] "Carbamate," as used herein, alone or in combination, refers to an ester of carbamic acid (-NHCOO-) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which is unsubstituted or substituted as defined herein.

[0031] "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NRR' group, with R and R' as defined herein.

[0032] "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NR'- group, with R and R' as defined herein.

[0033] "Carbonyl," as used herein, when alone includes formyl [-C(O)H] and in combination is a -C(O)- group.

[0034] "Carboxyl" or "carboxy," as used herein, refers to -C(O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a RC(O)O- group, where R is as defined herein. A "C-carboxy" group refers to a -C(O)OR groups where R is as defined herein.

[0035] "Cyano," as used herein, alone or in combination, refers to -CN.

[0036] "Cycloalkyl," or, alternatively, "carbocycle," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic, or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is unsubstituted or substituted as defined herein. A carbocycle may comprise a bridged ring system and/or a spiro ring system (e.g., a system including two rings sharing a single carbon atom). The term "cycloalkenyl" refers to a cycloalkyl group having one or two double bonds. In certain embodiments, said cycloalkyl (or cycloalkenyl) will comprise from 5 to 7 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, tetrahydronapthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl, and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydronaphthalene and octahydronaphthalene, as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

[0037] "Ester," as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[0038] "Ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[0039] "Halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[0040] "Haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0041] "Haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as described herein wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro, or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene (-CFH-), difluoromethylene (-CF_2-), chloromethylene (-CHCl-) and the like.

[0042] "Heteroatom," as used herein, refers to one or more of oxygen, sulfur, nitrogen, phosphorus, boron, or selenium (including, any oxidized form of nitrogen, sulfur, boron, or phosphorus; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR+ (as in N-substituted pyrrolidinyl)).

[0043] "Heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched hydrocarbon chain, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms, e.g., selected from N, O, and S, and wherein the N and S atoms may optionally be oxidized and the N heteroatom may optionally be quaternized. The heteroatom(s) may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3.

[0044] "Heteroaryl," as used herein, alone or in combination, refers to a 3- to 15-membered aromatic monocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which ring or ring system contains at least one heteroatom, e.g., selected from N, O, and S. In certain embodiments, said heteroaryl will comprise from 1 to 4 heteroatoms as ring members. In

further embodiments, said heteroaryl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said heteroaryl will comprise from 5 to 7 atoms. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[0045] "Heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated (but nonaromatic) monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, e.g., wherein each said heteroatom may be independently selected from nitrogen, oxygen, and sulfur. In some embodiments, a heterocycle comprises a heteroaryl ring fused to a saturated, partially unsaturated, or fully unsaturated (but nonaromatic) ring that optionally contains a heteroatom. In some embodiments, a heterocycle comprises an aryl ring fused to a saturated, partially unsaturated, or fully unsaturated (but nonaromatic) ring that contains a heteroatom. In some embodiments, a heterocycle comprises a carbocycle ring fused to a saturated, partially unsaturated, or fully unsaturated ring that contains a heteroatom. In some embodiments, a heterocycle comprises a first ring that is saturated, partially unsaturated, or fully unsaturated ring that contains a heteroatom and a second ring that is saturated, partially unsaturated, or fully unsaturated ring that optionally contains a heteroatom. In some embodiments, the first ring and the second ring share a single heteroatom. In certain embodiments, said heterocycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heterocycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said heterocycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said heterocycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said heterocycloalkyl will comprise from 5 to 6 ring members in each ring. A heterocycle may comprise a bridged ring system and/or a spiro ring system (e.g., a system including two rings sharing a single atom, such as a single carbon atom). "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused

and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycle groups include aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine, 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine, 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine, 1-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine, 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine, 3-oxa-9-azabicyclo[3.3.1]nonane, hexahydro-3,6-epiminofuro[3,2-b]furan, and the like. The heterocycle groups are unsubstituted or substituted unless specifically prohibited.

[0046] "Hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., -N-N-.

[0047] "Hydroxy," as used herein, alone or in combination, refers to -OH.

[0048] "Hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

[0049] "Iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N-O-.

[0050] "Lower amino," as used herein, alone or in combination, refers to -NRR', wherein R and R' are independently selected from hydrogen and lower alkyl (e.g., C_{1-4} alkyl), either of which is unsubstituted or substituted.

[0051] "Mercaptyl" as used herein, alone or in combination, refers to an RS- group, where R is as defined herein.

[0052] "Nitro," as used herein, alone or in combination, refers to $-NO_2$.

[0053] "Oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

[0054] "Oxo," as used herein, alone or in combination, refers to =O.

[0055] "Perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

[0056] "Perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[0057] "Ring," or equivalently, "cycle," as used herein, in reference to a chemical structure or portion thereof, means a group in which every atom is a member of a common cyclic structure. A ring can be saturated or unsaturated, including aromatic, unless otherwise provided, and may have between 3 and 9

members. If the ring is a heterocycle, it may contain between 1 and 4 heteroatoms or heteroatom-comprising groups selected from B, N, O, S, C(O), and $S(O)_m$, wherein m is 0, 1, or 2. Unless specifically prohibited, a ring is unsubstituted or substituted. Two or more rings may be fused together (e.g., they may share a bond and two common atoms). Two or more rings may be linked together in a spiro arrangement such that only a single atom is shared between two rings. Two or more rings may also or alternatively be configured in a bridged arrangement such that three or more atoms are shared between two or more rings.

[0058] "Sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer to the $-SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

[0059] "Sulfanyl," as used herein, alone or in combination, refers to –S–.

[0060] "Sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

[0061] "Sulfonyl," as used herein, alone or in combination, refers to $-S(O)_2-$.

[0062] "N-sulfonamido" refers to a $RS(=O)_2NR'$- group with R and R' as defined herein.

[0063] "S-sulfonamido" refers to a $-S(=O)_2NRR'$, group, with R and R' as defined herein.

[0064] "Tautomer", as used herein, alone or in combination, refers to one of two or more isomers that rapidly interconvert. Generally, this interconversion is sufficiently fast so that an individual tautomer is not isolated in the absence of another tautomer. The ratio of the amount of tautomers can be dependent on solvent composition, ionic strength, and pH, as well as other solution parameters. The ratio of the amount of tautomers can be different in a particular solution and in the microenvironment of a biomolecular binding site in said solution. Examples of tautomers that are well known in the art include keto / enol, enamine / imine, and lactam / lactim tautomers. Examples of tautomers that are well known in the art also include 2-hydroxypyridine / 2(1*H*)-pyridone and 2-aminopyridine / 2(1*H*)-iminopyridone tautomers.

[0065] "Thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

[0066] "Thiol," as used herein, alone or in combination, refers to an –SH group.

[0067] "Thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

[0068] "N-thiocarbamyl" refers to an ROC(S)NR'– group, with R and R' as defined herein.

[0069] "O-thiocarbamyl" refers to a –OC(S)NRR' group, with R and R' as defined herein.

[0070] "Thiocyanato" refers to a –CNS group.

[0071] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the

parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[0072] As described herein, groups may be substituted or unsubstituted (e.g., "optionally substituted"). Unless otherwise specified, any group may be substituted with one or more substituents, such as one or more substituents provided herein. Examples of substituents that may substitute a group include, but are not limited to, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: alkyl (e.g., C_{1-20} alkyl, such as C_{1-10} alkyl, such as C_{1-6} alkyl, such as C_{1-3} alkyl), alkenyl (e.g., C_{2-20} alkenyl, such as C_{2-10} alkenyl, such as C_{2-6} alkenyl), alkynyl (e.g., C_{2-20} alkynyl, such as C_{2-10} alkynyl, such as C_{2-6} alkynyl), alkanoyl (e.g., C_{1-20} alkanoyl, such as C_{1-10} alkanoyl, such as C_{1-6} alkanoyl), heteroalkyl (e.g., a heteroalkyl moiety including 1-20 carbon atoms and 1-6 heteroatoms, such as a heteroalkyl moiety including 1-6 carbon atoms and 1-3 heteroatoms), haloalkyl (e.g., a halo-substituted C_{1-20} alkyl, such as a halo-substituted C_{1-10} alkyl, a halo-substituted C_{1-6} alkyl), haloalkenyl (e.g., a halo-substituted C_{2-20} alkenyl, such as a halo-substituted C_{2-6} alkenyl), haloalkynyl (e.g., a halo-substituted C_{2-20} alkynyl, such as a halo-substituted C_{2-6} alkynyl), perhaloalkyl (e.g., C_{1-20} perhaloalkyl, such as C_{1-6} perhaloalkyl, such as C_{1-3} perhaloalkyl), perhaloalkoxy (e.g., C_{1-20} perhaloalkoxy, such as C_{1-6} perhaloalkoxy), phenyl, aryl (e.g., C_{5-20} aryl, such as C_{5-10} aryl, such as C_{5-6} aryl), aryloxy (e.g., C_{5-20} aryloxy, such as C_{5-10} aryloxy, such as C_{5-6} aryloxy), alkoxy (e.g., C_{1-20} alkoxy, such as C_{1-10} alkoxy, such as C_{1-6} alkoxy), haloalkoxy (e.g., C_{1-20} haloalkoxy, such as C_{1-10} haloalkoxy, such as C_{1-6} haloalkoxy), oxo, acyloxy (e.g., an acyloxy group including 1-20 carbon atoms, such as 1-10 carbon atoms, such as 1-6 carbon atoms), carbonyl (e.g., C(O) or C=O), carboxyl (e.g., C(O)O), alkylcarbonyl (e.g., C_{1-20} alkylcarbonyl, such as C_{1-10} alkylcarbonyl, such as C_{1-6} alkylcarbonyl, such as C_{1-3} alkylcarbonyl), carboxyester (e.g., C(O)OR where R is, e.g., alkyl (e.g., C_{1-20} alkyl, such as C_{1-10} alkyl, such as C_{1-6} alkyl, such as C_{1-3} alkyl), alkenyl (e.g., C_{2-20} alkenyl, such as C_{2-10} alkenyl, such as C_{2-6} alkenyl), or alkynyl (e.g., C_{2-20} alkynyl, such as C_{2-10} alkynyl, such as C_{2-6} alkynyl), any of which may be substituted by any group provided herein), carboxamido, cyano (e.g., CN), hydrogen, halogen (e.g., iodine, bromine, chlorine, or fluorine), hydroxy, amino (e.g., NR'R" where R' and R" are independently, e.g., hydrogen, alkyl (e.g., C_{1-20} alkyl, such as C_{1-10} alkyl, such as C_{1-6} alkyl, such as C_{1-3} alkyl), alkenyl (e.g., C_{2-20} alkenyl, such as C_{2-10} alkenyl, such as C_{2-6} alkenyl), or alkynyl (e.g., C_{2-20} alkynyl, such as C_{2-10} alkynyl, such as C_{2-6} alkynyl), any of which may be substituted by any group provided herein), alkylamino (e.g., NR'R" where R' is alkyl (e.g., C_{1-20} alkyl, such as C_{1-10} alkyl, such as C_{1-6} alkyl, such as C_{1-3} alkyl) and R" is, e.g., hydrogen, alkyl (e.g., C_{1-20} alkyl, such as C_{1-10} alkyl, such as C_{1-6} alkyl, such as C_{1-3} alkyl), alkenyl (e.g., C_{2-}

$_{20}$ alkenyl, such as C_{2-10} alkenyl, such as C_{2-6} alkenyl), or alkynyl (e.g., C_{2-20} alkynyl, such as C_{2-10} alkynyl, such as C_{2-6} alkynyl), any of which may be substituted by any group provided herein), arylamino (e.g., NR'R" where R' is aryl (e.g., C_{5-20} aryl, such as C_{5-10} aryl, such as C_{5-6} aryl) and R" is, e.g., hydrogen, alkyl (e.g., C_{1-20} alkyl, such as C_{1-10} alkyl, such as C_{1-6} alkyl, such as C_{1-3} alkyl), alkenyl (e.g., C_{2-20} alkenyl, such as C_{2-10} alkenyl, such as C_{2-6} alkenyl), or alkynyl (e.g., C_{2-20} alkynyl, such as C_{2-10} alkynyl, such as C_{2-6} alkynyl), any of which may be substituted by any group provided herein), amido (e.g., C(O)NR'R" where R' and R" are independently, e.g., hydrogen, alkyl (e.g., C_{1-20} alkyl, such as C_{1-10} alkyl, such as C_{1-6} alkyl, such as C_{1-3} alkyl), alkenyl (e.g., C_{2-20} alkenyl, such as C_{2-10} alkenyl, such as C_{2-6} alkenyl), or alkynyl (e.g., C_{2-20} alkynyl, such as C_{2-10} alkynyl, such as C_{2-6} alkynyl), any of which may be substituted by any group provided herein), nitro (e.g., NO_2), thiol (e.g., SH), alkylthio (e.g., C_{1-20} alkyl substituted with a thiol group, such as C_{1-10} alkyl substituted with a thiol group, such as C_{1-6} alkyl substituted with a thiol group, such as C_{1-3} alkyl substituted with a thiol group), haloalkylthio (e.g., C_{1-20} haloalkylthio, such as C_{1-10} haloalkylthio, such as C_{1-6} haloalkylthio, such as C_{1-3} haloalkylthio), perhaloalkylthio (e.g., C_{1-20} perhaloalkylthio, such as C_{1-10} perhaloalkylthio, such as C_{1-6} perhaloalkylthio, such as C_{1-3} perhaloalkylthio), arylthiol (e.g., C_{5-20} arylthiol, such as C_{5-10} arylthiol, such as C_{5-6} arylthiol), sulfonate (e.g., $S(O)_2OR$ where R is, e.g., alkyl (e.g., C_{1-20} alkyl, such as C_{1-10} alkyl, such as C_{1-6} alkyl, such as C_{1-3} alkyl), alkenyl (e.g., C_{2-20} alkenyl, such as C_{2-10} alkenyl, such as C_{2-6} alkenyl), or alkynyl (e.g., C_{2-20} alkynyl, such as C_{2-10} alkynyl, such as C_{2-6} alkynyl), any of which may be substituted by any group provided herein), sulfonic acid (e.g., $S(O)_2OH$), trisubstituted silyl (e.g., SiR'R"R* where R', R", and R* are independently selected from, e.g., alkyl (e.g., C_{1-20} alkyl, such as C_{1-10} alkyl, such as C_{1-6} alkyl, such as C_{1-3} alkyl), alkenyl (e.g., C_{2-20} alkenyl, such as C_{2-10} alkenyl, such as C_{2-6} alkenyl), or alkynyl (e.g., C_{2-20} alkynyl, such as C_{2-10} alkynyl, such as C_{2-6} alkynyl), any of which may be substituted by any group provided herein; in some cases, a trisubstituted silyl can be trimethylsilyl), N_3, SCH_3, $C(O)CH_3$, CO_2CH_3, CO_2H, pyridinyl, thiophene, furanyl, carbamate, and urea. Additional groups may also be contemplated. Where structurally feasible, two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms (e.g., N, O, S, etc.), for example forming methylenedioxy or ethylenedioxy. An unsubstituted or substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional

substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "unsubstituted or substituted with."

[0073] The terms R, R', R", R*, etc., appearing by themselves and without a number designation, unless otherwise defined, refer to a moiety selected from hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which is unsubstituted or substituted (*e.g.*, as described herein). Such R and R' groups should be understood to be unsubstituted or substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R" where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (*e.g.*, aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. For example, an unsymmetrical group such as -C(O)N(R)- may be attached to the parent moiety at either the carbon or the nitrogen.

[0074] "Bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[0075] Asymmetric centers may exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, atropisomeric, and epimeric forms, as well as d-isomers and l-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds disclosed herein may exist as geometric isomers. The present disclosure includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this disclosure. Additionally, the compounds provided herein may comprise conformational

isomers, which compounds comprise groups that can orient in different conformations in relation to another moiety. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[0076] "Combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single dose unit (e.g., capsule) having a fixed ratio of active ingredients or in multiple, separate dose units (e.g., capsules) for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0077] "KRAS inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to KRAS activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the assays described generally herein, such as a surface plasmon resonance KRAS-G12D, G12V, G12C, G12S, G12A, G12R, G13D, or Q61H mutation or wild-type KRAS protein binding assay; and/or a KRAS G12D, G12V, G12C, G12S, G12A, G12R, G13D, or Q61H mutation or wild-type KRAS protein-effector protein interaction disruption assay. "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme (*e.g.*, KRAS) to half-maximal level. Certain compounds disclosed herein have been discovered to exhibit inhibition against KRAS. In certain embodiments, compounds exhibit an IC_{50} with respect to KRAS (*e.g.*, a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon 13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein) of no more than about 50 μM; in further embodiments, compounds exhibit an IC_{50} with respect to KRAS (*e.g.*, a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon 13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein) of no more than about 10 μM; in yet further embodiments, compounds exhibit an IC_{50} with respect to KRAS (*e.g.*, a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon 13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein) of not more than about 1 μM; in yet further embodiments, compounds exhibit an IC_{50} with respect to KRAS (*e.g.*, a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon

13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein) of not more than about 200 nanomolar (nM), as measured in the KRAS assay described herein. In some embodiments, compounds exhibit an IC_{50} with respect to KRAS (*e.g.*, a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon 13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein) of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less. In certain embodiments, compounds exhibit an IC_{50} with respect to KRAS (*e.g.*, a KRAS protein having a mutation at codon 12 (e.g., a G12D, G12V, G12C, G12S, G12A, or G12R mutation), a KRAS protein having a mutation at codon 13 (e.g., a G13D mutation), a KRAS protein having a mutation at codon 61 (e.g., a Q61H mutation), or a wild-type KRAS protein) of less than about 1 μM, such as less than about 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less. In some embodiments, compounds exhibit an IC_{50} with respect to KRAS having a G12D mutation of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less. In some embodiments, compounds exhibit an IC_{50} with respect to KRAS having a G12V mutation of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less. In some embodiments, compounds exhibit an IC_{50} with respect to KRAS having a G12R mutation of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less. In some embodiments, compounds exhibit an IC_{50} with respect to KRAS having a G12A mutation of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4

nM, 3 nM, 2 nM, 1 nM, or less. In some embodiments, compounds exhibit an IC_{50} with respect to KRAS having a G12S mutation of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less. In some embodiments, compounds exhibit an IC_{50} with respect to KRAS having a G12C mutation of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less. In some embodiments, compounds exhibit an IC_{50} with respect to KRAS having a G13D mutation of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less. In some embodiments, compounds exhibit an IC_{50} with respect to KRAS having a Q61H mutation of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less. In some embodiments, compounds exhibit an IC_{50} with respect to wild-type KRAS of less than about 50 μM, such as less than about 40 μM, 30 μM, 20 μM, 10 μM, 9 μM, 8 μM, 7 μM, 6 μM, 5 μM, 4 μM, 3 μM, 2 μM, 1 μM, 900 nM, 800 nM, 700 nM, 600 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, or less.

[0078] In some embodiments, a KRAS inhibitor has inhibitory activity against KRAS having a G12D mutation that exceeds its inhibitory activity against KRAS having another mutation, such as a Q61H, G12C, G12R, G12S, G12A, G12V, or G13D mutation. For example, in some embodiments, a KRAS inhibitor provided herein has at least two-fold, five-fold, ten-fold, twenty-fold, thirty-fold, forty-fold, fifty-fold, one hundred-fold, or higher inhibitory activity against KRAS having a G12D mutation relative to KRAS having another mutation such as a Q61H, G12C, G12R, G12S, G12A, G12V, or G13D mutation.

[0079] In some embodiments, a KRAS inhibitor has inhibitory activity against KRAS having a G12V mutation that exceeds its inhibitory activity against KRAS having another mutation, such as a Q61H, G12C, G12R, G12S, G12A, G12D, or G13D mutation. For example, in some embodiments, a KRAS inhibitor provided herein has at least two-fold, five-fold, ten-fold, twenty-fold, thirty-fold, forty-fold, fifty-fold, one

hundred-fold, or higher inhibitory activity against KRAS having a G12V mutation relative to KRAS having another mutation such as a Q61H, G12C, G12R, G12S, G12A, G12D, or G13D mutation.

[0080] In some embodiments, a KRAS inhibitor has inhibitory activity against KRAS having a G12R mutation that exceeds its inhibitory activity against KRAS having another mutation, such as a Q61H, G12C, G12D, G12S, G12A, G12V, or G13D mutation. For example, in some embodiments, a KRAS inhibitor provided herein has at least two-fold, five-fold, ten-fold, twenty-fold, thirty-fold, forty-fold, fifty-fold, one hundred-fold, or higher inhibitory activity against KRAS having a G12R mutation relative to KRAS having another mutation such as a Q61H, G12C, G12D, G12S, G12A, G12V, or G13D mutation.

[0081] In some embodiments, a KRAS inhibitor has inhibitory activity against KRAS having a G12C mutation that exceeds its inhibitory activity against KRAS having another mutation, such as a Q61H, G12R, G12D, G12S, G12A, G12V, or G13D mutation. For example, in some embodiments, a KRAS inhibitor provided herein has at least two-fold, five-fold, ten-fold, twenty-fold, thirty-fold, forty-fold, fifty-fold, one hundred-fold, or higher inhibitory activity against KRAS having a G12C mutation relative to KRAS having another mutation such as a Q61H, G12R, G12D, G12S, G12A, G12V, or G13D mutation.

[0082] In some embodiments, a KRAS inhibitor has inhibitory activity against KRAS having a G12S mutation that exceeds its inhibitory activity against KRAS having another mutation, such as a Q61H, G12C, G12D, G12R, G12A, G12V, or G13D mutation. For example, in some embodiments, a KRAS inhibitor provided herein has at least two-fold, five-fold, ten-fold, twenty-fold, thirty-fold, forty-fold, fifty-fold, one hundred-fold, or higher inhibitory activity against KRAS having a G12S mutation relative to KRAS having another mutation such as a Q61H, G12C, G12D, G12R, G12A, G12V, or G13D mutation.

[0083] In some embodiments, a KRAS inhibitor has inhibitory activity against KRAS having a G12A mutation that exceeds its inhibitory activity against KRAS having another mutation, such as a Q61H, G12C, G12D, G12S, G12R, G12V, or G13D mutation. For example, in some embodiments, a KRAS inhibitor provided herein has at least two-fold, five-fold, ten-fold, twenty-fold, thirty-fold, forty-fold, fifty-fold, one hundred-fold, or higher inhibitory activity against KRAS having a G12A mutation relative to KRAS having another mutation such as a Q61H, G12C, G12D, G12S, G12R, G12V, or G13D mutation.

[0084] In some embodiments, a KRAS inhibitor has inhibitory activity against KRAS having a G13D mutation that exceeds its inhibitory activity against KRAS having another mutation, such as a Q61H, G12C, G12D, G12S, G12R, G12V, or G12A mutation. For example, in some embodiments, a KRAS inhibitor provided herein has at least two-fold, five-fold, ten-fold, twenty-fold, thirty-fold, forty-fold, fifty-fold, one hundred-fold, or higher inhibitory activity against KRAS having a G13D mutation relative to KRAS having another mutation such as a Q61H, G12C, G12D, G12S, G12R, G12V, or G12A mutation.

[0085] In some embodiments, a KRAS inhibitor has inhibitory activity against KRAS having a Q61H mutation that exceeds its inhibitory activity against KRAS having another mutation, such as a G13D, G12C, G12D, G12S, G12R, G12V, or G12A mutation. For example, in some embodiments, a KRAS inhibitor provided herein has at least two-fold, five-fold, ten-fold, twenty-fold, thirty-fold, forty-fold, fifty-fold, one hundred-fold, or higher inhibitory activity against KRAS having a Q61H mutation relative to KRAS having another mutation such as a G13D, G12C, G12D, G12S, G12R, G12V, or G12A mutation.

[0086] In some embodiments, a KRAS inhibitor has inhibitory activity against a wild-type KRAS that exceeds its inhibitory activity against KRAS having a Q61H, G13D, G12C, G12D, G12S, G12R, G12V, or G12A mutation. For example, in some embodiments, a KRAS inhibitor provided herein has at least two-fold, five-fold, ten-fold, twenty-fold, thirty-fold, forty-fold, fifty-fold, one hundred-fold, or higher inhibitory activity against a wild-type KRAS relative to KRAS having a Q61H, G13D, G12C, G12D, G12S, G12R, G12V, or G12A mutation.

[0087] In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a Q61H, G13D, G12D, G12S, G12R, G12V, or G12A mutation or a wild-type KRAS than against KRAS having a G12C mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12D, G12V, or G12R mutation than against KRAS having a G12C mutation.

[0088] In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12D mutation than against KRAS having a G12C mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12D mutation than against KRAS having a G12R mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12D mutation than against a KRAS having a G12S mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12D mutation than against KRAS having a G12A mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12D mutation than against KRAS having a G12V mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12D mutation than against KRAS having a G13D mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12D mutation than against KRAS having a Q61H mutation.

[0089] In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12V mutation than against KRAS having a G12C mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12V mutation than

against KRAS having a G12R mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12V mutation than against a KRAS having a G12S mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12V mutation than against KRAS having a G12A mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12V mutation than against KRAS having a G12D mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12V mutation than against KRAS having a G13D mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12V mutation than against KRAS having a Q61H mutation.

[0090] In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12R mutation than against KRAS having a G12C mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12R mutation than against KRAS having a G12D mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12R mutation than against a KRAS having a G12S mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12R mutation than against KRAS having a G12A mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12R mutation than against KRAS having a G12V mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12R mutation than against KRAS having a G13D mutation. In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against KRAS having a G12R mutation than against KRAS having a Q61H mutation.

[0091] In some embodiments, a KRAS inhibitor provided herein has greater inhibitory activity against active ("GTP-bound") KRAS having a Q61H, G12D, G12V, G12R, G12A, G12S, G12C, or G13D mutation, or wild-type KRAS, than against an inactive ("GDP-bound") KRAS having a Q61H, G12D, G12V, G12R, G12A, G12S, G12C, or G13D mutation or wild-type KRAS. In some embodiments, a KRAS inhibitor provided herein has lower inhibitory activity against active ("GTP-bound") KRAS having a Q61H, G12D, G12V, G12R, G12A, G12S, G12C, or G13D mutation, or wild-type KRAS, than against an inactive ("GDP-bound") KRAS having a Q61H, G12D, G12V, G12R, G12A, G12S, G12C, or G13D mutation or wild-type KRAS. In some embodiments, a KRAS inhibitor provided herein has inhibitory activity against both active ("GTP-bound") and inactive ("GDP-bound") KRAS having a Q61H, G12D, G12V, G12R, G12A, G12S, G12C, or G13D mutation or wild-type KRAS. In some embodiments, a KRAS inhibitor provided herein has similar inhibitory activity against active ("GTP-bound") and inactive ("GDP-bound")

KRAS having a Q61H, G12D, G12V, G12R, G12A, G12S, G12C, or G13D mutation or wild-type KRAS. In some embodiments, a KRAS inhibitor provided herein has inhibitory activity against a K-RAS4a splice variant. In some embodiments, a KRAS inhibitor provided herein has inhibitory activity against a K-RAS4b splice variant. In some embodiments, a KRAS inhibitor provided herein has inhibitory activity against both K-RAS4a and K-RAS4b splice variants.

[0092] "Therapeutically effective amount" refers to an amount of a compound or of a pharmaceutical composition useful for treating or ameliorating an identified disease, disorder, or condition, or for exhibiting a detectable therapeutic or inhibitory effect. The exact amounts will depend on the purpose of the treatment and will be ascertainable by one skilled in the art using known techniques (see, *e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0093] The term "therapeutically acceptable" refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0094] "Treat," "treating," and "treatment" refer to any indicia of success in the treatment or amelioration of an injury, pathology, disease, disorder, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology, disease, disorder, or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; and/or improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters, including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. Treatment may also be preemptive in nature; i.e., it may include prevention of a disease, disorder, or condition, prevention of onset of one or more symptoms of a disease, disorder, or condition, and/or prevention of escalation of a disease, disorder, or condition. Prevention of a disease, disorder, or condition may involve complete protection from disease, and/or prevention of disease progression (e.g., to a later stage of the disease, disorder, or condition). For example, prevention of a disease may not mean complete foreclosure of any effect related to the diseases at any level, but instead may mean prevention of the symptoms of a disease, disorder, or condition to a clinically significant or detectable level.

[0095] "Patient" or "subject" refers to a living organism suffering from or prone to a disease, disorder, or condition that can be treated by administration of a compound or pharmaceutical composition as provided

herein. Non-limiting examples include humans, rats, mice, rabbits, hamsters, guinea pigs, cats, dogs, non-human primates (*e.g.*, monkeys), goats, pigs, sheep, cows, deer, horses, and other non-mammalian animals. Examples of mammals that can be treated by administration of a compound or pharmaceutical composition provided herein include, for example, rodents (*e.g.*, rats, mice, squirrels, guinea pigs, hamsters, etc.), lagomorphs (*e.g.*, rabbits, hares, etc.), primates (*e.g.*, monkeys, apes, etc.), bovines (*e.g.*, cattle), odd-toed ungulates (*e.g.*, horses), even-toed ungulates (*e.g.*, bovines such as cattle, ovine such as sheep, caprine such as goats, porcine such as pigs, etc.), and marsupials (*e.g.*, kangaroo, wallaby, wallaroo, sugar glider, etc.). In some embodiments, the patient or subject is human. In some embodiments, the patient or subject is a companion animal such as a cat or dog. In some embodiments, the patient or subject is a farm animal such as a goat, sheep, cow, pig, or horse. In some embodiments, the patient or subject is an exotic animal such as a primate (*e.g.*, monkey), marsupial (*e.g.*, kangaroo, wallaby, wallaroo, sugar glider, etc.), or a non-domesticated or hybrid cat or dog.

[0096] "Composition," as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product, which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent, or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0097] "Pharmaceutically acceptable excipient" refers to a substance that aids the administration of an active agent to and absorption by a subject. Pharmaceutical excipients useful in the present disclosure include, but are not limited to, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, and colors. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present disclosure.

[0098] The term "prodrug" refers to a compound that is made more active in vivo. Certain compounds disclosed herein may also exist as prodrugs. Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug.

[0099] The compounds disclosed herein can exist as therapeutically acceptable salts (also referred to herein as "pharmaceutically acceptable salts"). The present disclosure includes compounds provided herein in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable.

[0100] The terms "therapeutically acceptable salt" and "pharmaceutically acceptable salt" as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds disclosed herein can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present disclosure contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

[0101] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine,

pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0102] A salt of a compound can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

[0103] "KRAS positive cancer" refers to a cancer characterized by a KRAS mutation, such as a KRAS Q61H, G12C, G12D, G12R, G12A, G12S, G12V, or G13D mutation, and/or by amplified wild-type KRAS activity. In some embodiments, "KRAS positive cancer" refers to a cancer that may benefit from inhibition of KRAS, such as wild-type KRAS or KRAS having a Q61H, G12C, G12D, G12R, G12A, G12S, G12V, or G13D mutation.

[0104] "KRAS G12C-positive cancer" refers to a cancer characterized by a KRAS G12C mutation.

[0105] "KRAS G12D-positive cancer" refers to a cancer characterized by a KRAS G12D mutation.

[0106] "KRAS G12R-positive cancer" refers to a cancer characterized by a KRAS G12R mutation.

[0107] "KRAS G12V-positive cancer" refers to a cancer characterized by a KRAS G12V mutation.

[0108] "KRAS G12A-positive cancer" refers to a cancer characterized by a KRAS G12A mutation.

[0109] "KRAS G12S-positive cancer" refers to a cancer characterized by a KRAS G12S mutation.

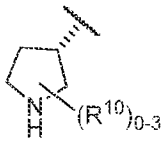
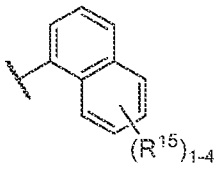
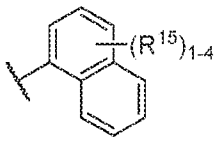
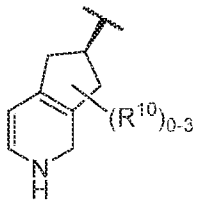
[0110] "KRAS G13D-positive cancer" refers to a cancer characterized by a KRAS G13D mutation.

[0111] "KRAS Q61H-positive cancer" refers to a cancer characterized by a KRAS Q61H mutation.

[0112] "Jointly therapeutically effective amount" as used herein means the amount at which the therapeutic agents, when given separately (in a chronologically staggered manner, especially a sequence-specific manner) to a warm-blooded animal, especially to a human to be treated, show an (additive, but preferably synergistic) interaction (joint therapeutic effect). Whether this is the case can be determined *inter alia* by following the blood levels, showing that both compounds are present in the blood of the human to be treated at least during certain time intervals.

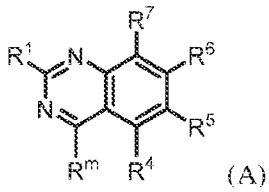
[0113] "Synergistic effect" as used herein refers to an effect of at least two therapeutic agents: a KRAS inhibitor, as defined herein, and an additional agent, which additional agent may be an agent configured to treat a disease, disorder, or condition or a symptom thereof. The effect can be, for example, slowing the symptomatic progression of a proliferative disease, such as cancer, particularly lung cancer, or symptoms thereof. Analogously, a "synergistically effective amount" refers to the amount needed to obtain a synergistic effect.

[0114] "A," "an," or "a(n)", when used in reference to a group of substituents or "substituent group" herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is unsubstituted or substituted with at least one alkyl and/or at least one aryl, wherein each alkyl and/or aryl is optionally different. In another example, where a compound is substituted with "a" substituent group, the compound is substituted with at least one substituent group, wherein each substituent group is optionally different.

[0115] In some embodiments, a "floating" substituent drawn on a ring indicates that a substituent may exist at any position of the ring. For example, for a ring such as  , a substituent may exist at any position and may replace a hydrogen atoms of a CH moiety, a hydrogen atom of an NH moiety, and/or one or both hydrogen atoms of a CH_2 moiety. In some embodiment, a "floating" substituent drawn on one ring of a bicyclic moiety, indicates that a substituent may exist on any ring of the bicyclic moiety (e.g.,  is equivalent to ). A substituent may exist at any position of any ring of the bicyclic moiety, and may replace one or more hydrogen atoms attached to an atom in one or more of the rings of the bicyclic moiety. For example, for a bicyclic moiety such as  , a substituent may exist in either ring, and may replace a hydrogen atom of a CH moiety, a hydrogen atom of an NH moiety, and/or one or both hydrogen atoms of a CH_2 moiety.

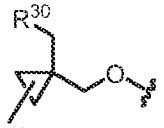
Compounds

[0116] In an aspect, the present disclosure provides a compound represented by Formula A:



(A)

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:



R^1 is selected from H, $-OR^8$, , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^m is selected from H and $-NR^2R^3$;

R^2 is selected from C_{1-6}alkyl;

R^3 is selected from a 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, $-N(R^{12})_2$, and -CN;

each R^{20} is independently selected from =O, -CN, and halogen;

R^{30} is selected from $-N(R^{12})_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

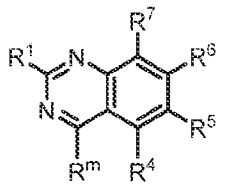
each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-4} alkenyl, and -OR^{12}, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

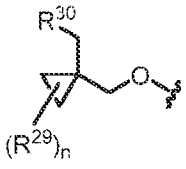
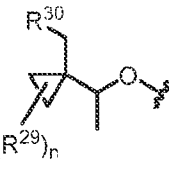
[0117] In some embodiments, the present disclosure provides a compound of Formula A, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0118] In one aspect, the present disclosure provides a compound represented by Formula A':



(A')

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from H, -OR^8,  ,  , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^m is selected from H and -NR^2R^3;

R^2 is selected from C_{1-6}alkyl which is optionally deuterated;

R^3 is selected from a C_{1-6}alkyl, 3- to 6-membered cycloalkyl optionally fused to a 5- or 6-membered heterocycle or heteroaryl, 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10}; or

R^2 and R^3, together with the atom they attach to, form a 4- to 10-membered heterocycle optionally substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, -N(R^{12})$_2$, and -CN;

each R^{20} is independently selected from =O, -CN, -OR^{12}, and halogen;

R^{30} is selected from -N(R^{12})$_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from halogen,-OR^{12}, C_{1-6}alkyl, and C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13};

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

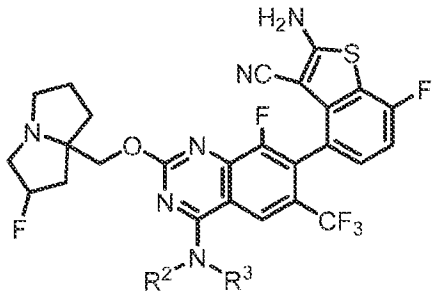
each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-4} alkenyl, , -OR^{12}, a 4- to 10-membered heterocycle, and aryl, wherein any 4- to 10-membered heterocycle or aryl is optionally substituted with one or more R^{28}, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0119] In some embodiments, the present disclosure provides a compound of Formula A, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

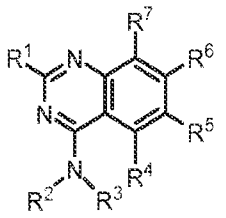
[0120] In some embodiments, the present disclosure provides a compound of Formula A', wherein the compound is of Formula A'-a:



(A'-a)

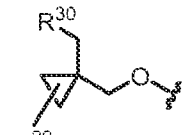
or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein R^2 and R^3 are as defined for Formula A' above and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula A'-a, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0121] In some embodiments, the present disclosure provides a compound of Formula B:



(B)

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^2 is selected from C_{1-6}alkyl;

R^3 is selected from a 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl, wherein the heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, -N(R^{12})$_2$, and -CN;

each R^{20} is independently selected from =O, -CN, and halogen;

R^{30} is selected from -N(R^{12})$_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

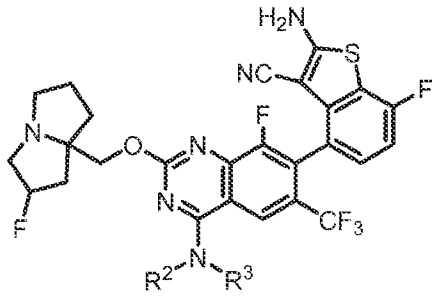
each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, C_{2-4} alkenyl, and -OR^{12}, wherein any C_{1-6}alkyl or C_{2-4} alkenyl is unsubstituted or is substituted with one or more R^{13}.

[0122] In some embodiments, the present disclosure provides a compound of Formula B, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0123] In some embodiments, the present disclosure provides a compound of Formula B, wherein the compound is of Formula B-a:



(B-a)

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein R^2 and R^3 are as defined for Formula B above and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula B-a, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0124] In some embodiments for a compound according to Formula A or A', R^m is H.

[0125] In some embodiments for a compound according to Formula A or A', R^m is $-NR^2R^3$.

[0126] In some embodiments for a compound according to Formula A, A', A'-a, B, or B-a, R^3 is a 4-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, which heterocycle is unsubstituted or substituted with one or more R^{10}. In some embodiments, R^3 is a 4-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, which heterocycle is unsubstituted or substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not include an -NH- moiety. In some embodiments, R^3 is a 4-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, which heterocycle is unsubstituted. In some embodiments, R^3 is a 4-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, which heterocycle is substituted with one or more R^{10}.

[0127] In some embodiments for a compound according to Formula A, A', A'-a, B, or B-a, R^3 is a 4-7 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, which heterocycle is unsubstituted or substituted with one or more R^{10}. In some embodiments, R^3 is a 4-7 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, which heterocycle is unsubstituted. In some embodiments, R^3 is a 4-7 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, which heterocycle is substituted with one or more R^{10}. In some embodiments, R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, which heterocycle is unsubstituted or substituted with one or more R^{10}. In some embodiments, R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, which heterocycle is unsubstituted. In some embodiments, R^3 is a 4-7 membered heterocycle that includes 1 heteroatom

selected from O, S, and N, which heterocycle is substituted with one or more R^{10}. In some embodiments, R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, which heterocycle is substituted with 1-4 R^{10}. In some embodiments, R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, which heterocycle is substituted with 1-4 R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not include an -NH- moiety. In some embodiments, R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, which heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}. In some embodiments, R^3 is a pyrrolidine that is substituted with 0-4 R^{10}. In some embodiments, R^3 is a pyrrolidine that is substituted with 1-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}. In some embodiments, R^3 is a 4-6 membered heterocycle that is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, and each R^{10} is independently selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

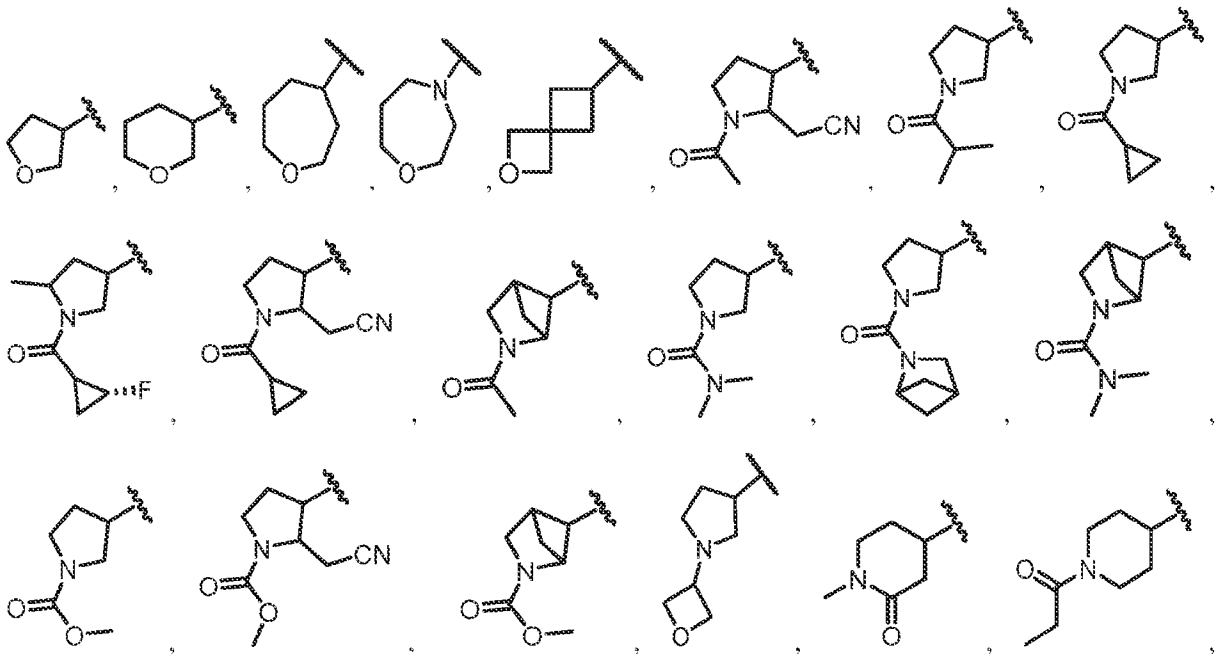
[0128] In some embodiments for a compound according to Formula A, A', A'-a, B, or B-a, R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is unsubstituted or substituted with one or more R^{10}. In some embodiments, R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is unsubstituted or substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not include an -NH- moiety. In some embodiments, R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}. In some embodiments, R^3 is an 8-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}. In some embodiments, R^3 is a 9-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}. In some embodiments, R^3 is a 10-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

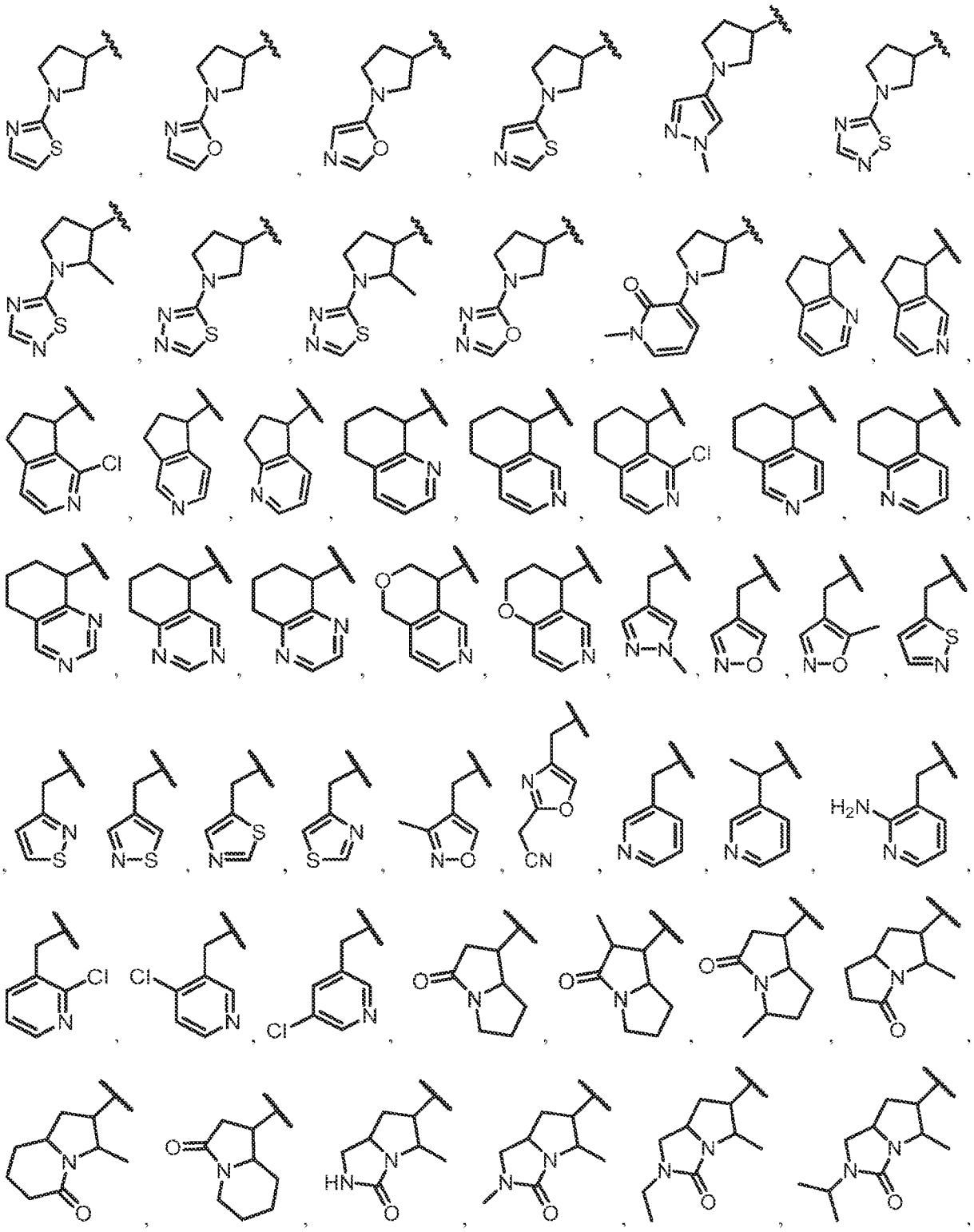
[0129] In some embodiments for a compound according to Formula A, A', A'-a, B, or B-a, R^3 is selected from a 4-10 membered heterocycle that is substituted with one or more R^{10}. In some embodiments, at least one R^{10} is selected from =O, C_{1-6}alkyl, a 3-6 membered carbocycle, and halogen. In some embodiments, at

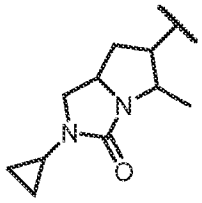
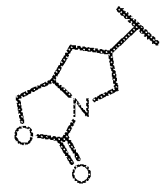
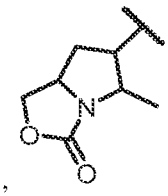
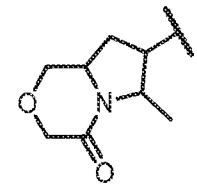
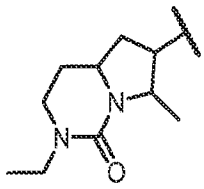
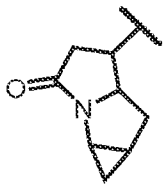
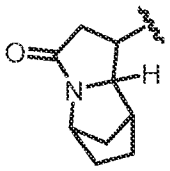
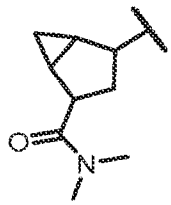
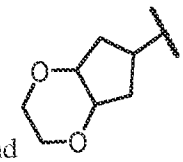
least one R^{10} is =O. In some embodiments, at least one R^{10} is a 3-6 membered carbocycle. In some embodiments, R^{10} is selected from halogen and C_{1-6}alkyl, wherein the C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}. In some embodiments, at least one R^{10} is C_{1-6}alkyl. In some embodiments, at least one R^{10} is a halogen. In some embodiments, at least one R^{10} is selected from -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, and a 3-6 membered heterocycle, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, at least one R^{10} is -C(O)(C_{1-6}alkyl). In some embodiments, at least one R^{10} is -C(O)O(C_{1-6}alkyl). In some embodiments, at least one R^{10} is -C(O)N(R^{14})$_2$. In some embodiments, at least one R^{10} is -C(O)(3-6 membered carbocycle). In some embodiments, at least one R^{10} is -C(O)(3-8 membered heterocycle). In some embodiments, at least one R^{10} is a 5-6 membered heteroaryl. In some embodiments, at least one R^{10} is a 3-6 membered heterocycle.

[0130] In some embodiments for a compound according to Formula A, A', A'-a, B, or B-a, R^3 is -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}. In some embodiments, R^3 is -CH_2(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}. In some embodiments, the heteroaryl is pyrazole, oxazole, isoxazole, thiazole, isothiazole, or pyridine.

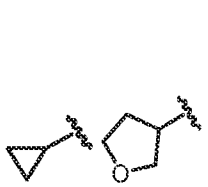
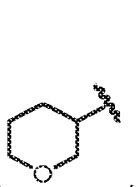
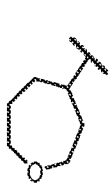
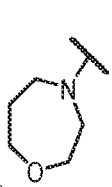
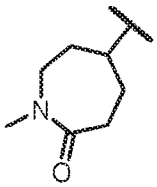
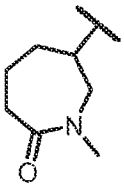
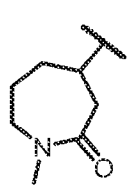
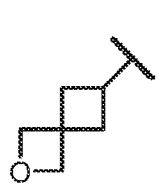
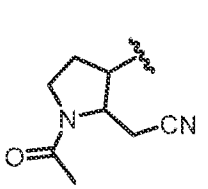
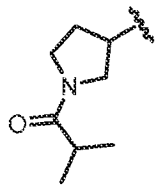
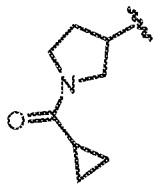
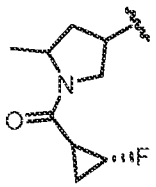
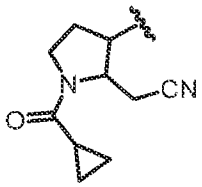
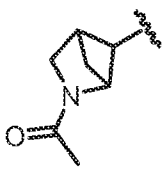
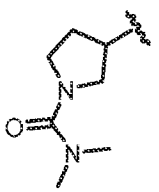
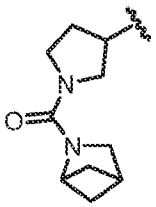
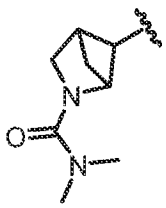
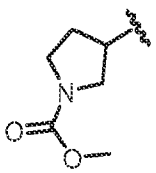
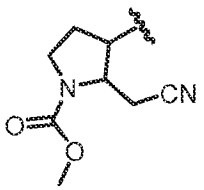
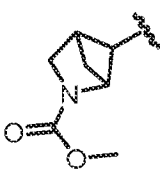
[0131] In some embodiments for a compound according to Formula A, B, or B-a, R^3 is selected from:

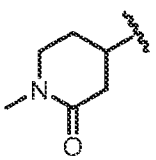
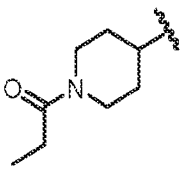
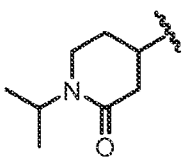
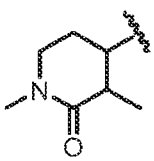
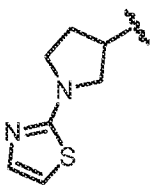
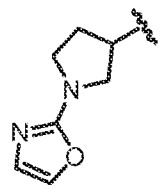
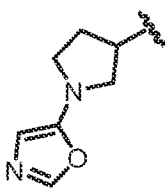
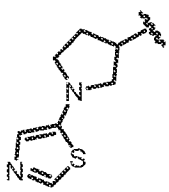
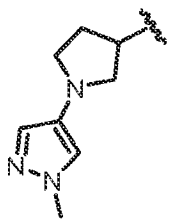
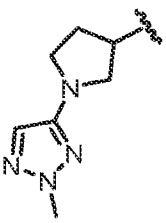
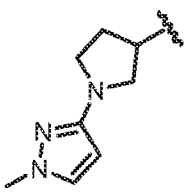
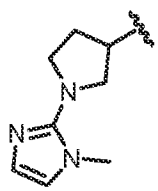


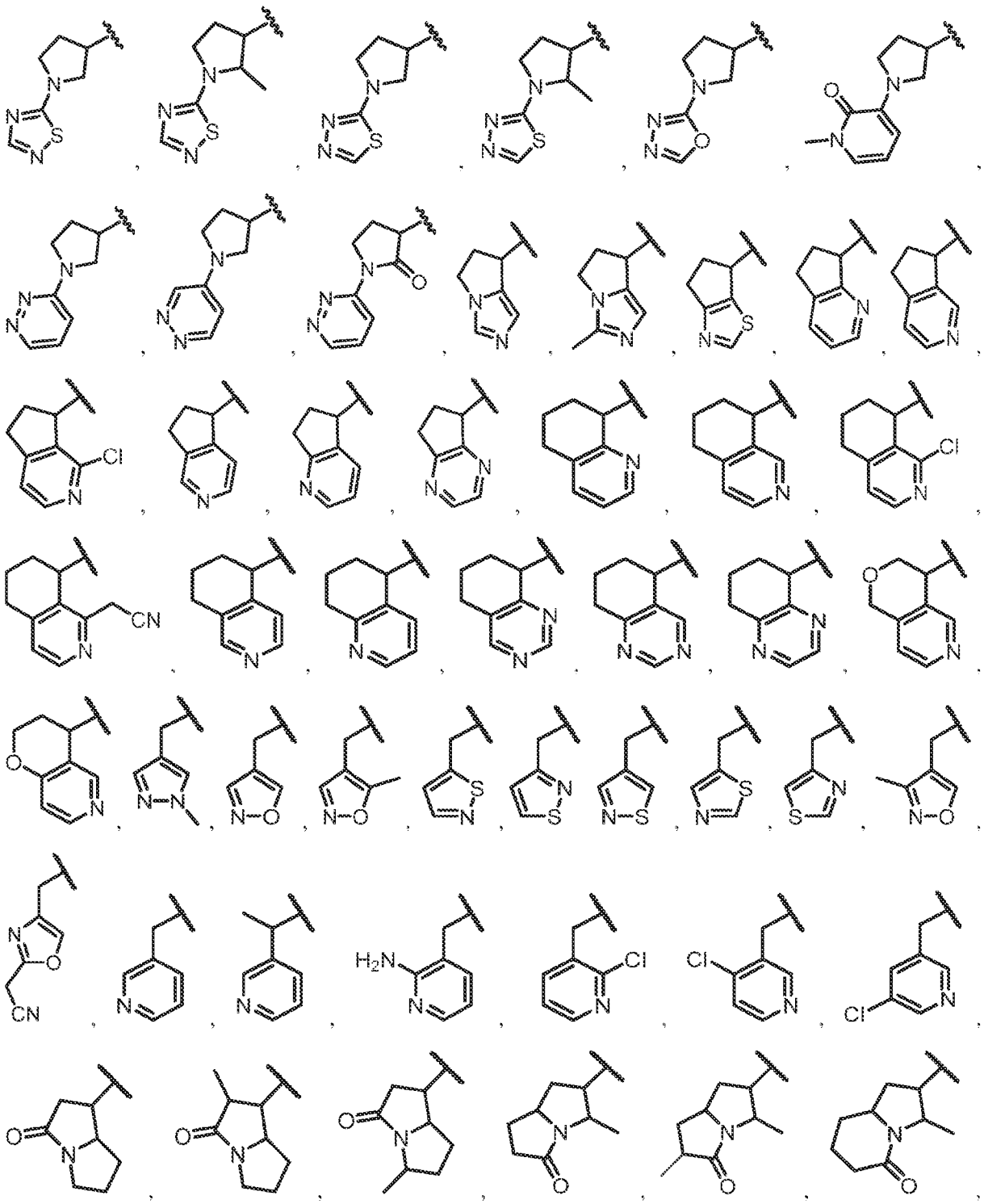


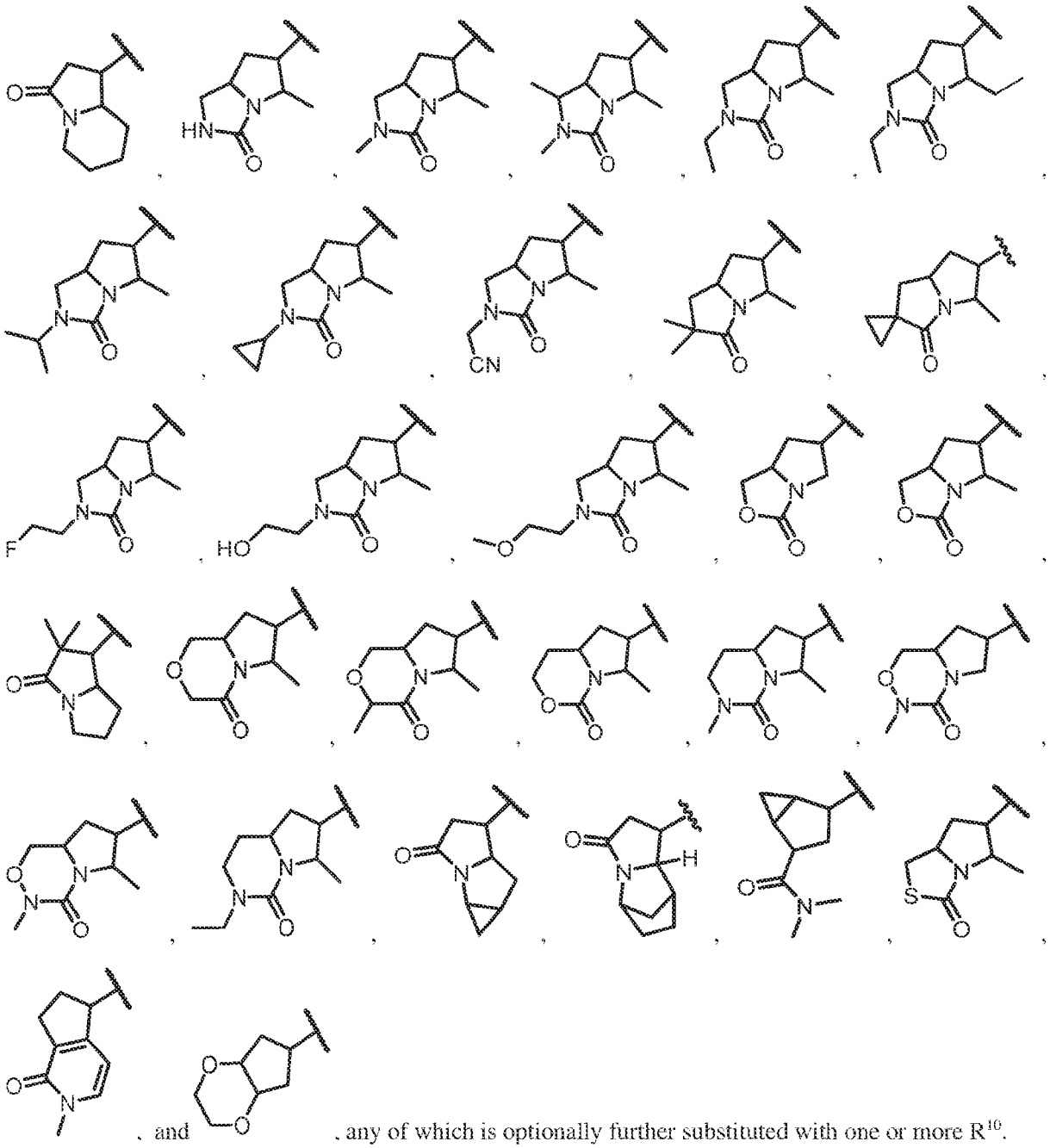








, and  , any of which is optionally further substituted with one or more R^{10}.

[0132] In some embodiments for a compound according to Formula A' or A'-a, R^3 is selected from: $-CH_3$,

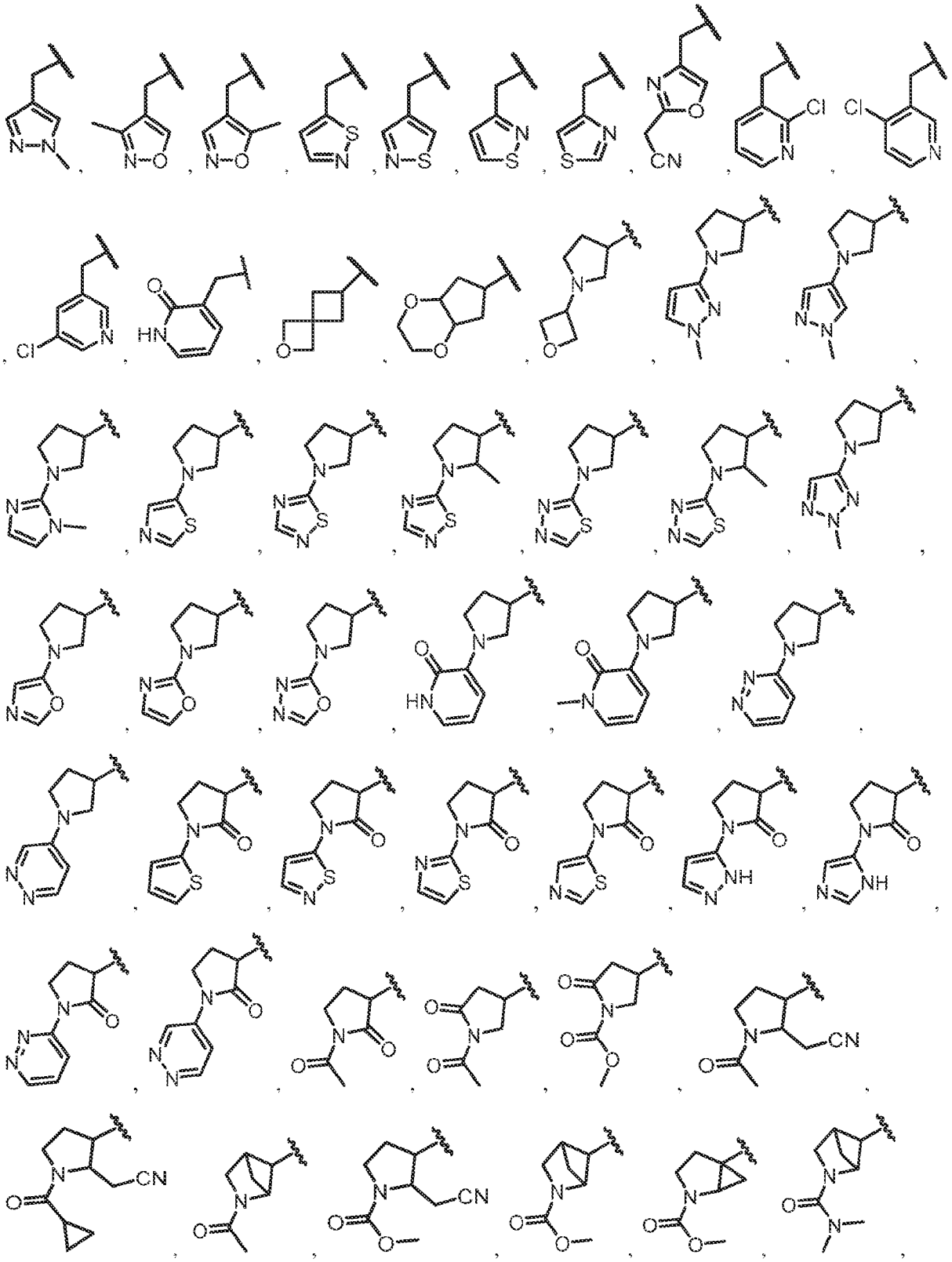













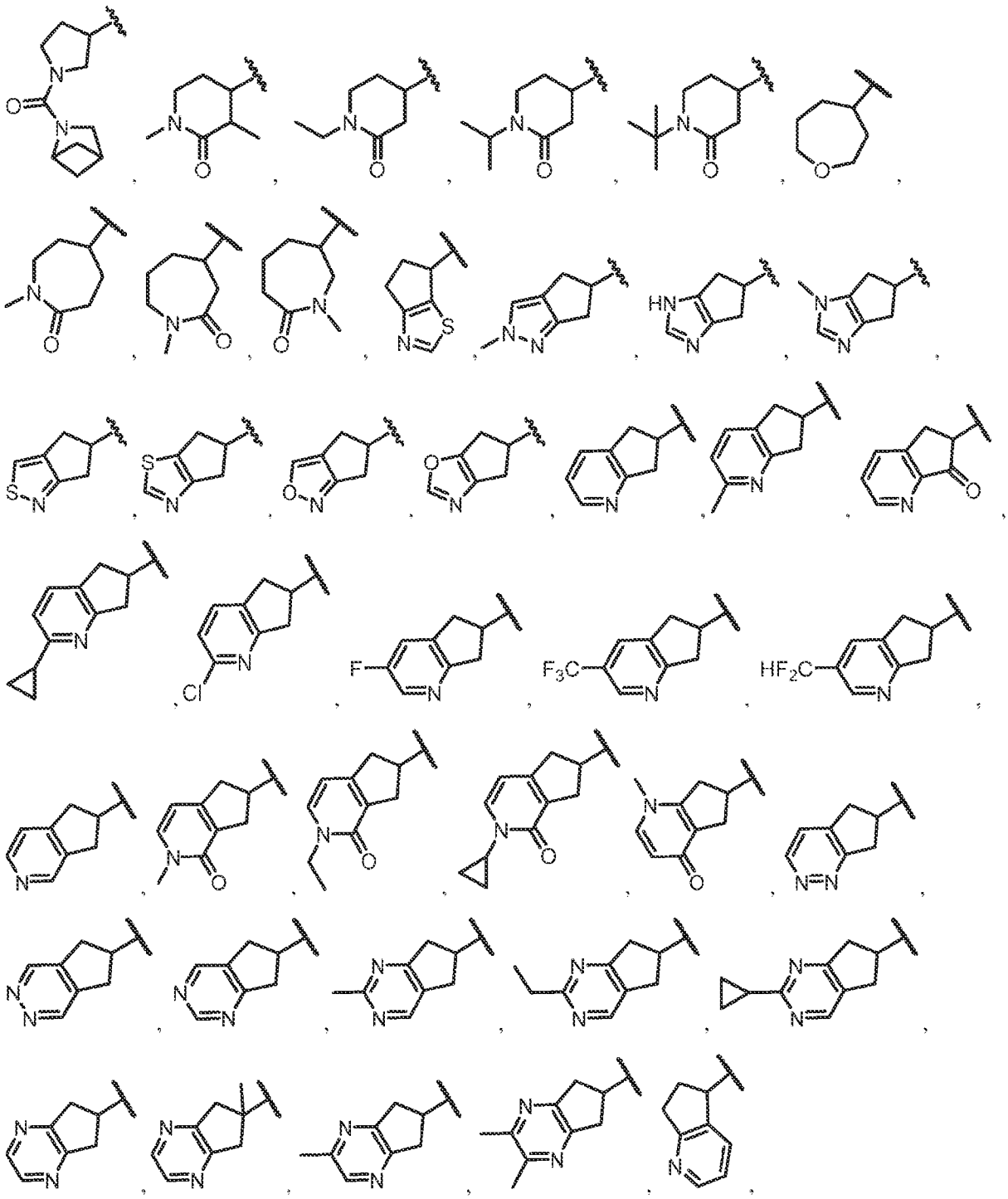


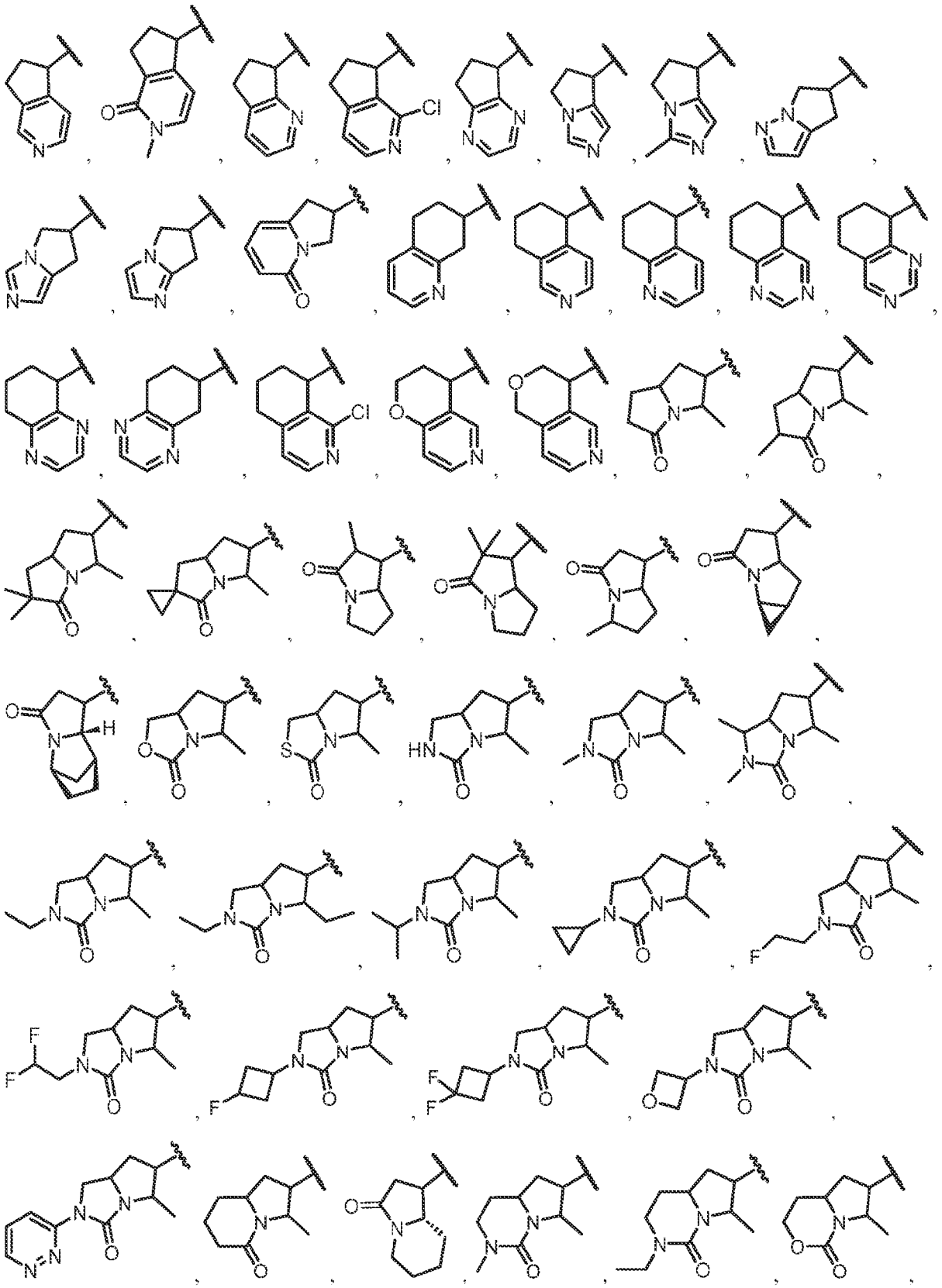


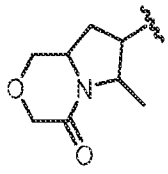
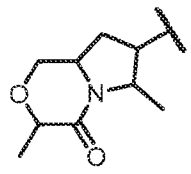
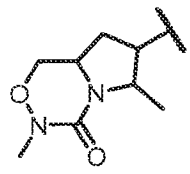
, and , any of which is optionally further substituted with one or more R^{10}.

[0133] In some embodiments according to Formula A, R^3 is selected from:

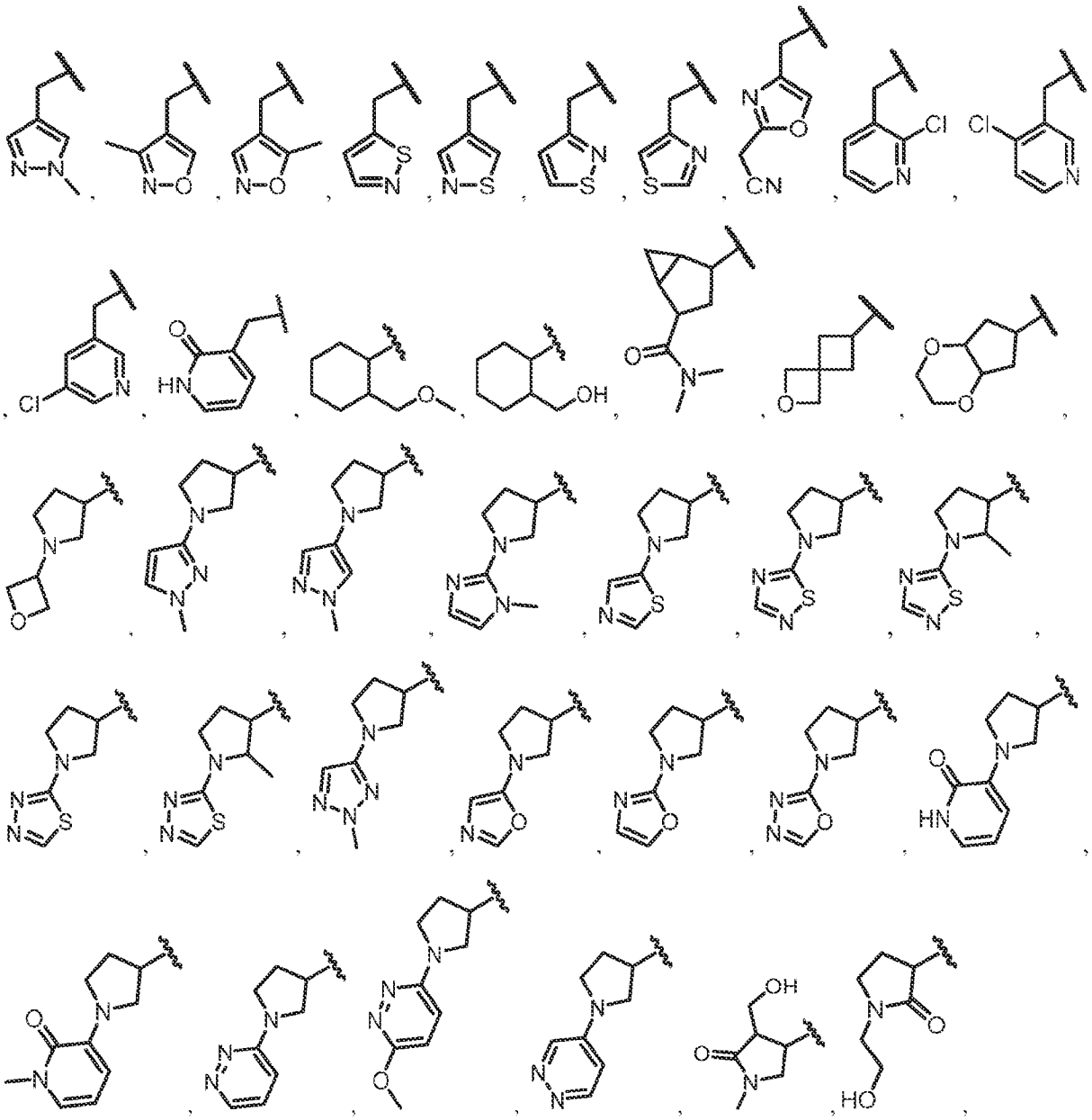


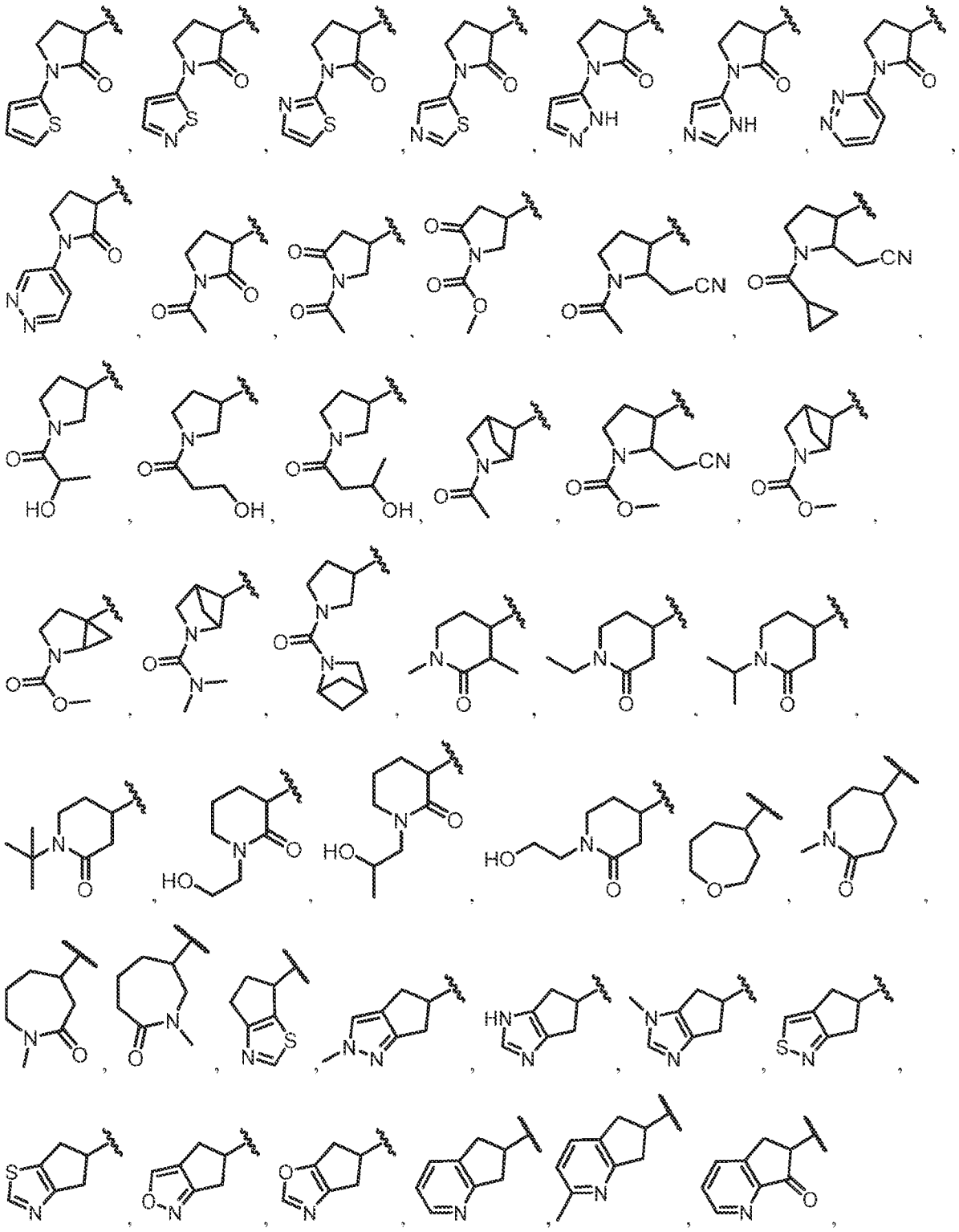


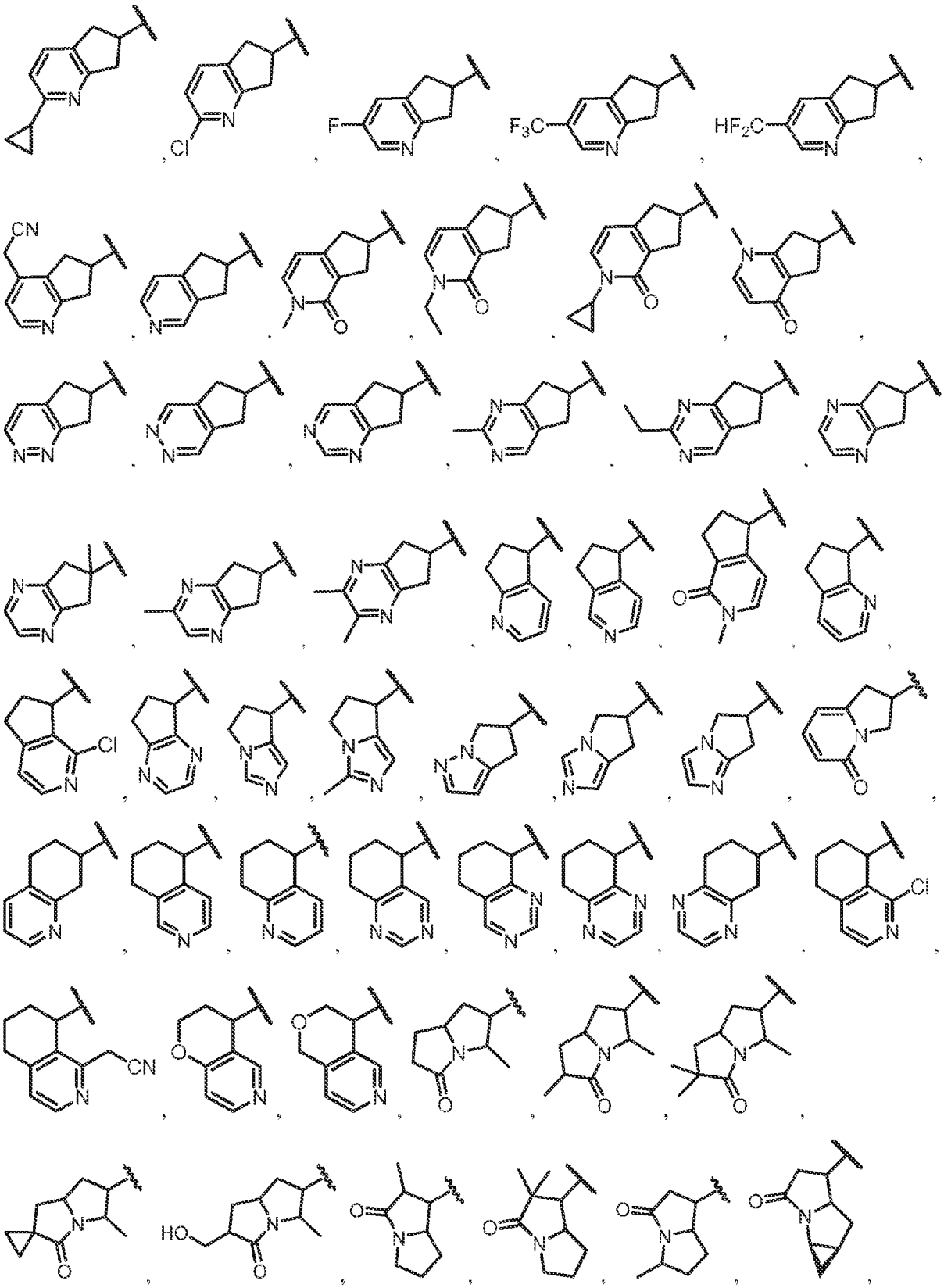


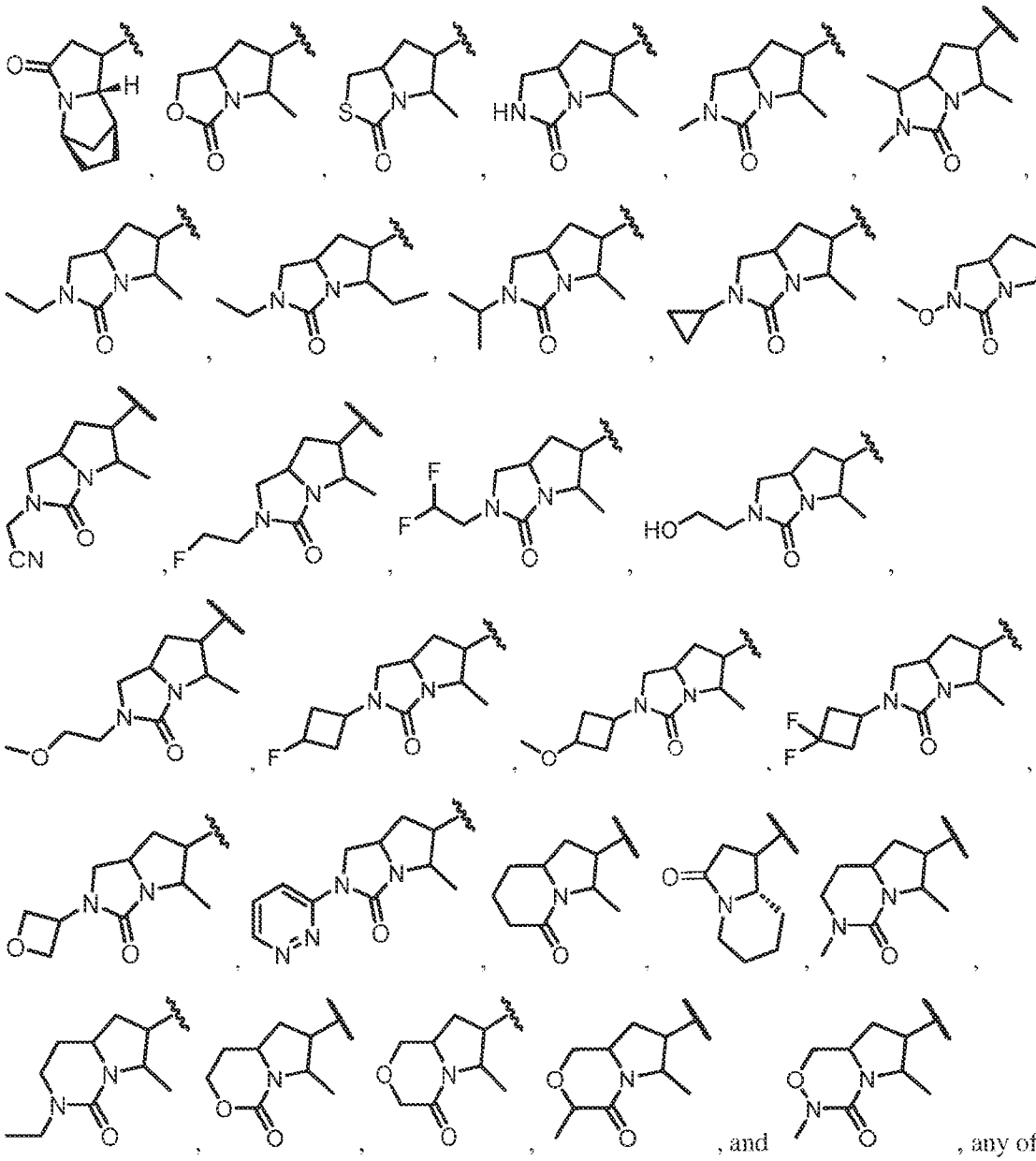


, and  , any of which is optionally further substituted with one or more R^{10}.

[0134] In some embodiments according to Formula A', R^3 is selected from:



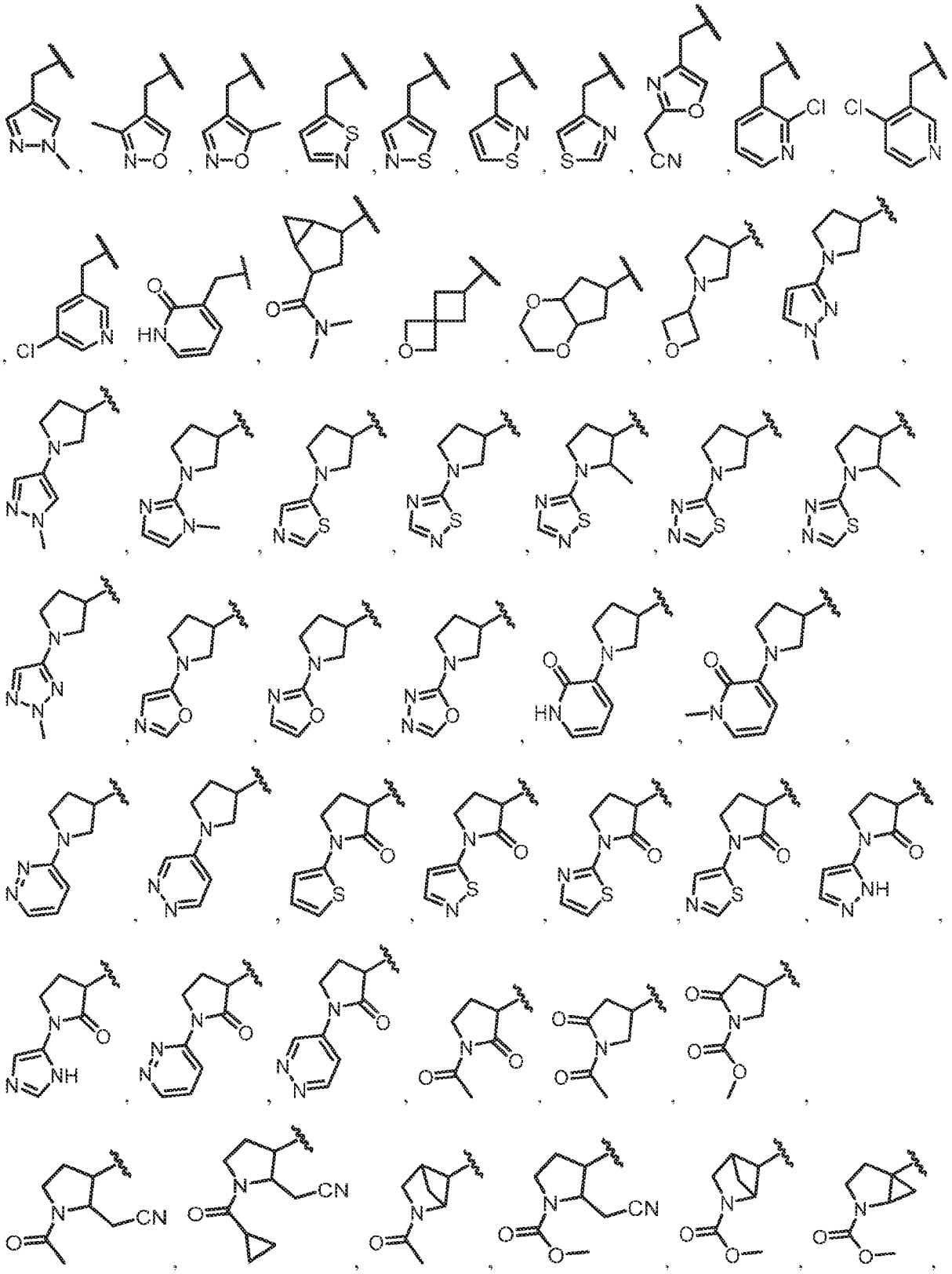


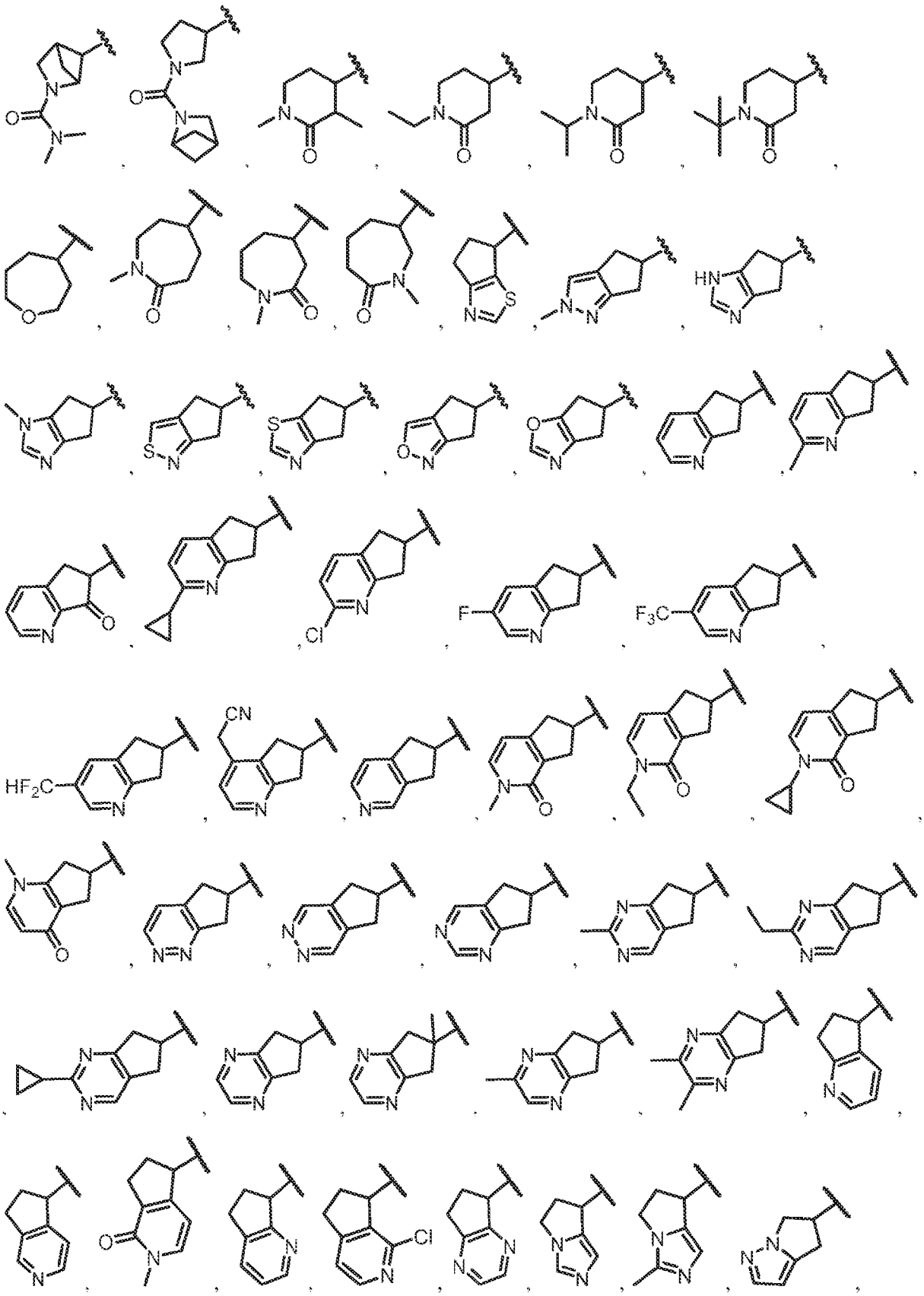


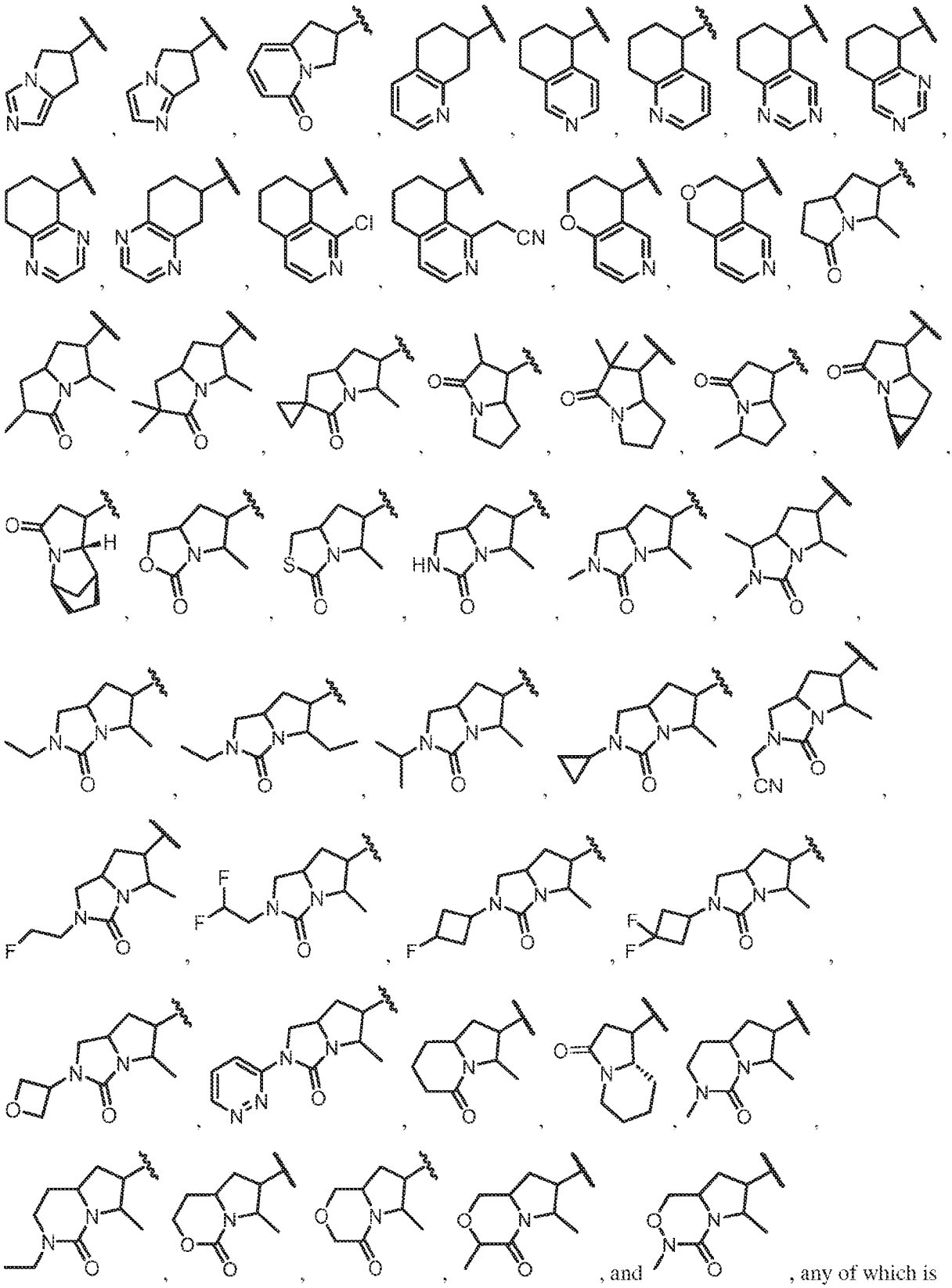


optionally further substituted with one or more R^{10}.

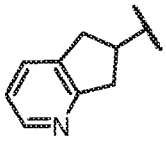
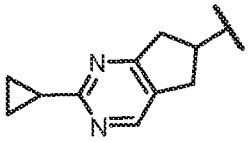
[0135] In some embodiments according to Formula B, R^3 is selected from:

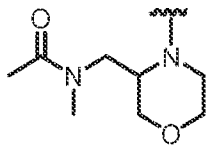
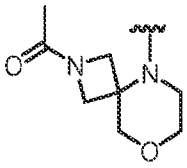






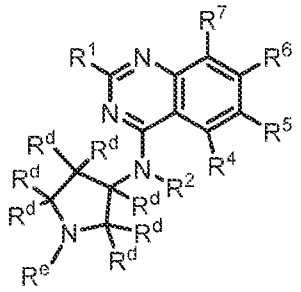
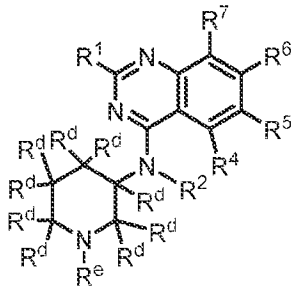
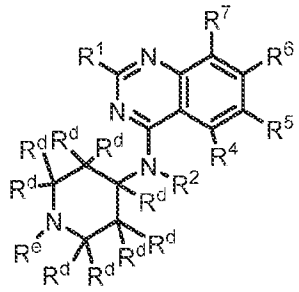
optionally further substituted with one or more R^{10}.

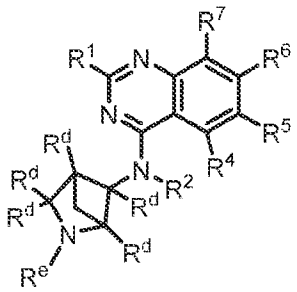
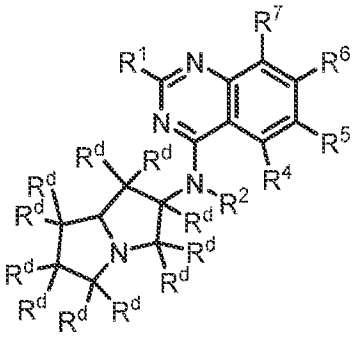
[0136] In some embodiments for a compound according to Formula A, A', or B, R^3 is selected from  or  , either of which is optionally further substituted with one or more R^{10}.

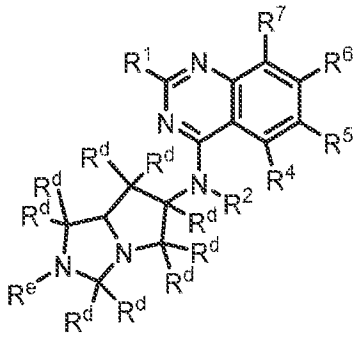
[0137] In some embodiments according to Formula A' or A'-a, R^m is selected from:  ,  or .

[0138] In some embodiments for a compound according to any one of Formulas A, A', A'-a, B, and B-a, (i) when R^3 includes a heterocycle or heteroaryl containing a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle or heteroaryl does not comprise an –NH- moiety.

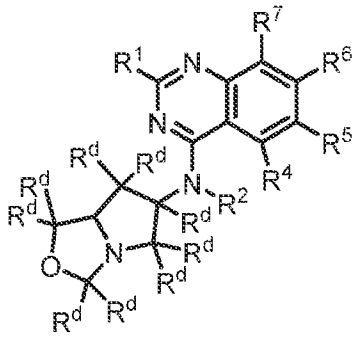
[0139] In some embodiments for a compound according to Formula A, A', A'-a, B, or B-a, the compound is a compound according to Formula BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM:

 (BA),  (BB),  (BC),

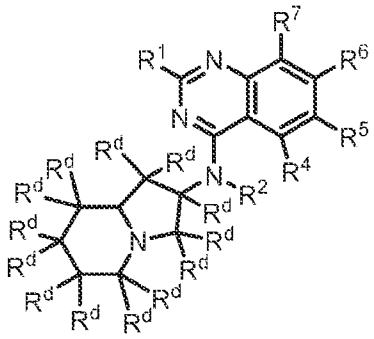
 (BD),  (BE).



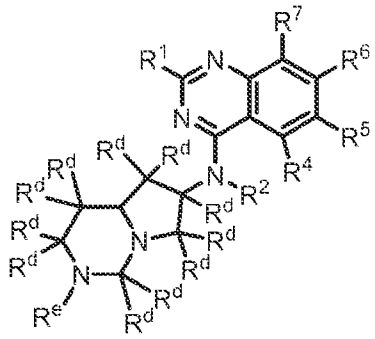
(BF),



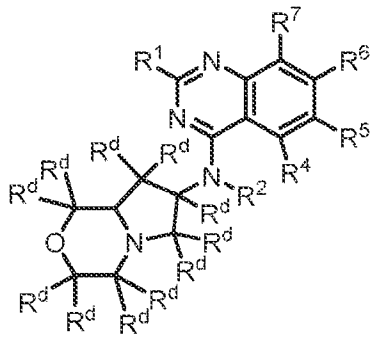
(BG),



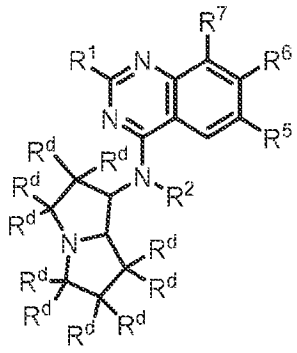
(BH),



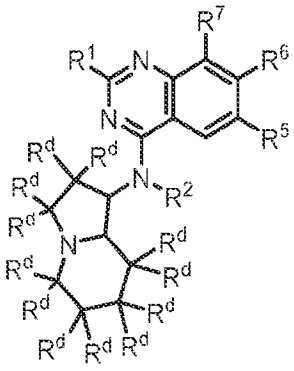
(BI),



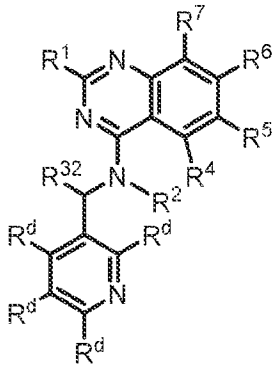
(BJ),



(BK),



(BL),



and (BM),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

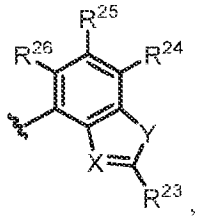
R^{32}, if present, is selected from H and C_{1-5}alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}; and

R^e, if present, is selected from H, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

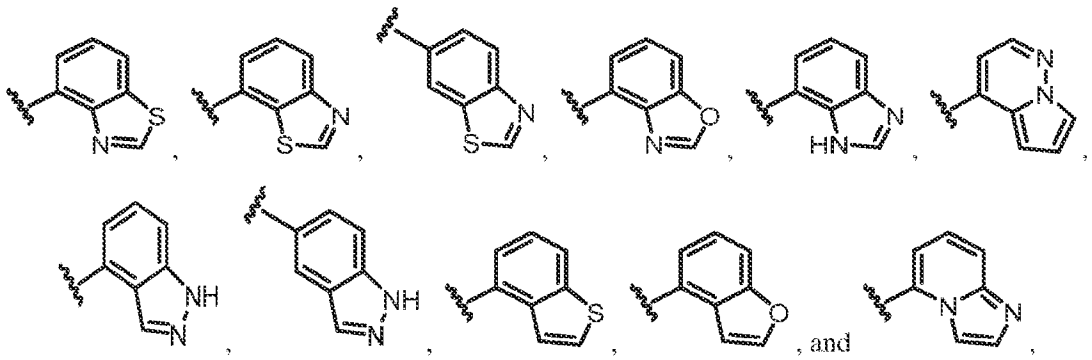
[0140] In some embodiments, the compound is a compound according to Formula BA, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BB, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BC, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BD, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BE, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BF, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BG, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BH, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BI, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BJ, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BK, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BL, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BM, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0141] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM, R^6 is selected from:



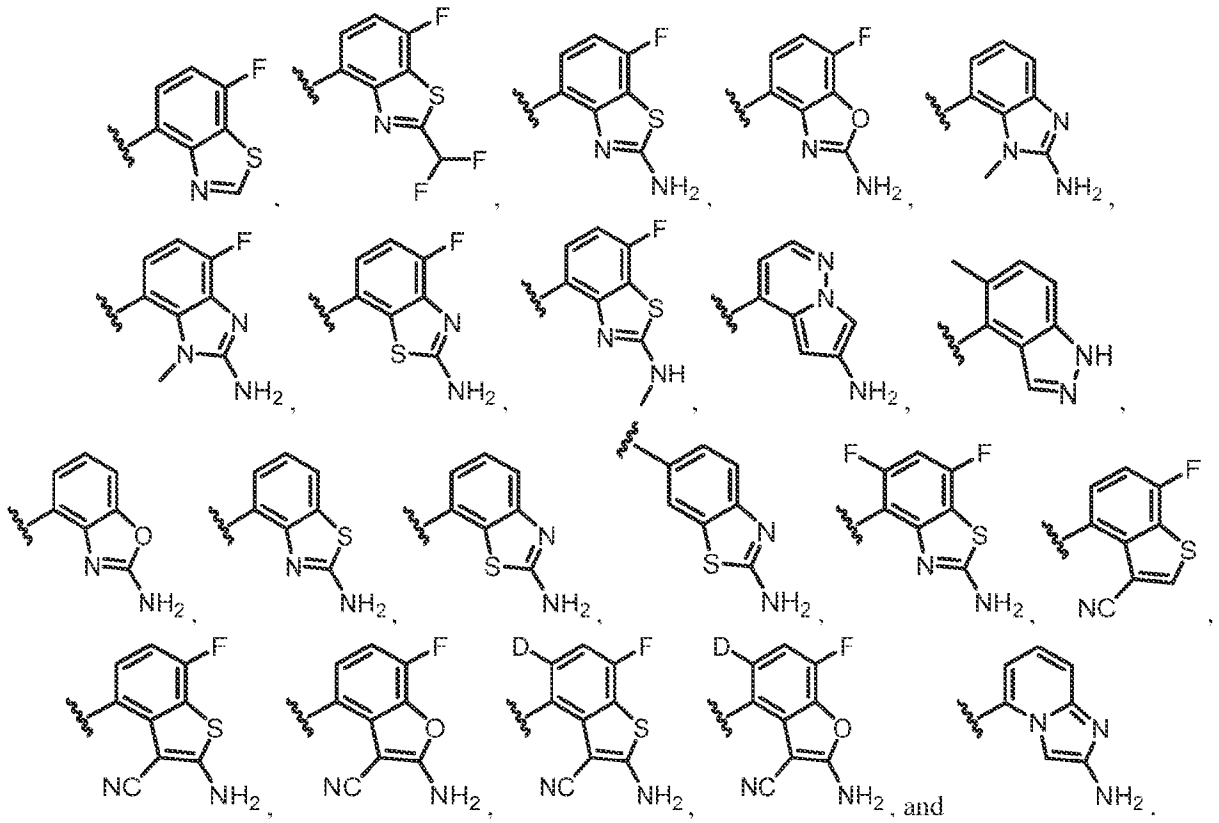
wherein X is selected from N and C-CN; Y is selected from O, S, and Se; R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments, X is C-CN and Y is S. In some embodiments, X is C-CN and Y is O. In some embodiments, X is C-CN and Y is Se. In some embodiments, X is N and Y is S. In some embodiments, X is N and Y is O. In some embodiments, X is N and Y is Se. In some embodiments, X is C-CN, Y is S, and R^{23} is $-N(R^{12})_2$. In some embodiments, X is C-CN, Y is S, and R^{23} is $-NH_2$. In some embodiments, R^{24} is halogen (e.g., fluoro). In some embodiments, R^{26} is deuterium.

[0142] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM, R^6 is selected from:

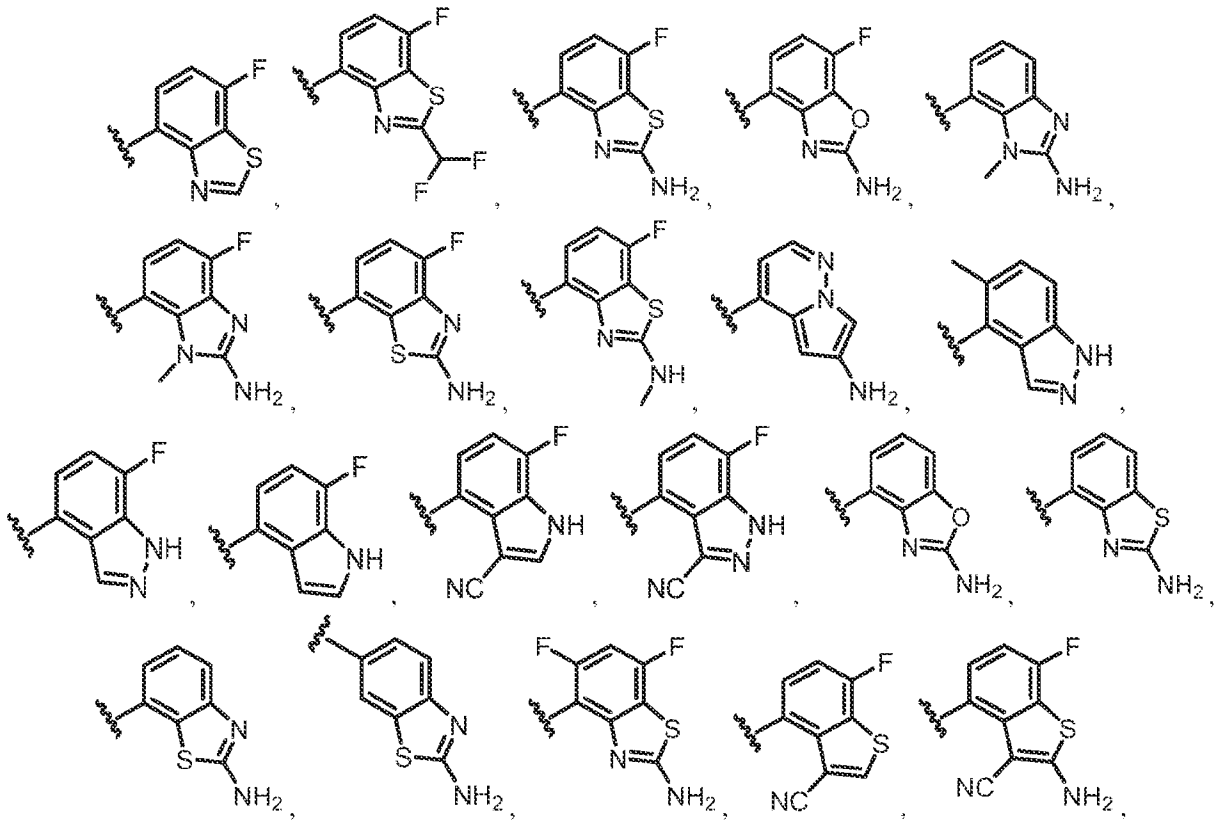


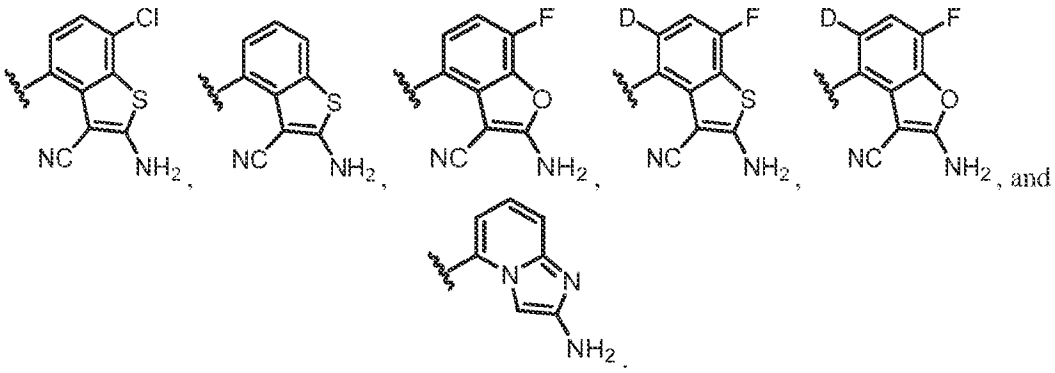
any of which is substituted with one or more R^{15}.

[0143] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM, R^6 is selected from:

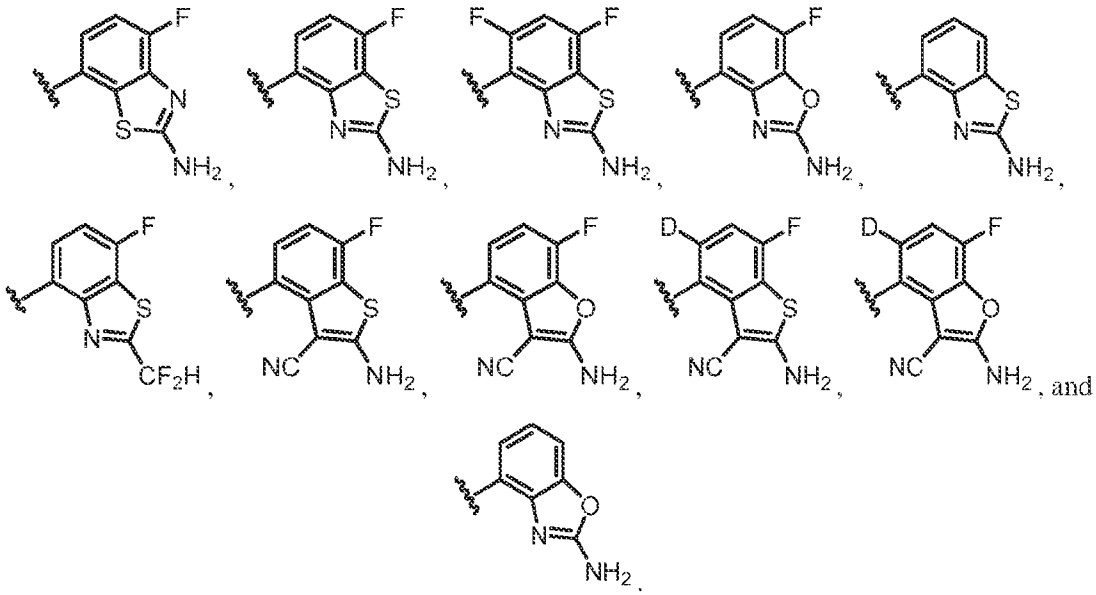


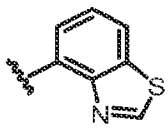
[0144] In some embodiments, for a compound according to Formula A' , R^6 is selected from:

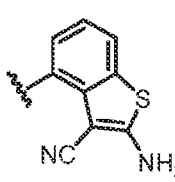
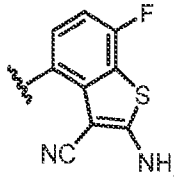
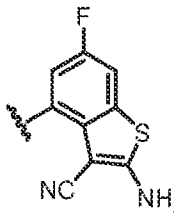
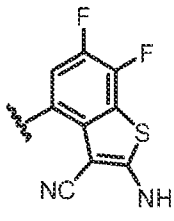
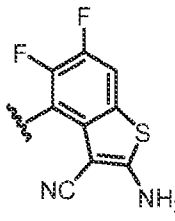
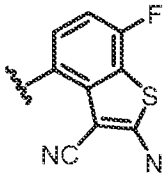




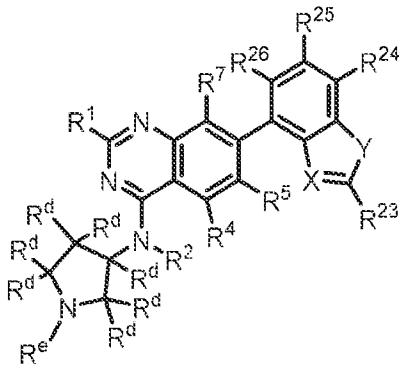
[0145] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM, R^6 is selected from:



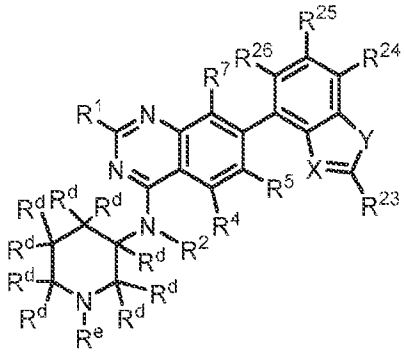
[0146] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM, R^6 is selected from:  , which is substituted

with one or more R^{15}. In some embodiments, R^6 is selected from:  ,  ,  ,  , and  . In some embodiments, R^6 is  .

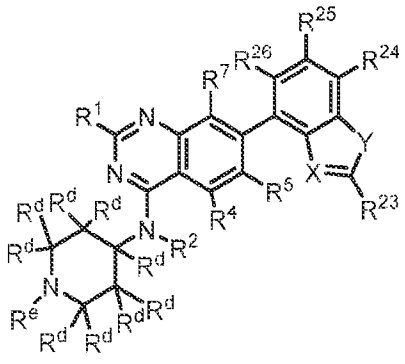
[0147] In some embodiments, the compound is a compound according to Formula BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1:



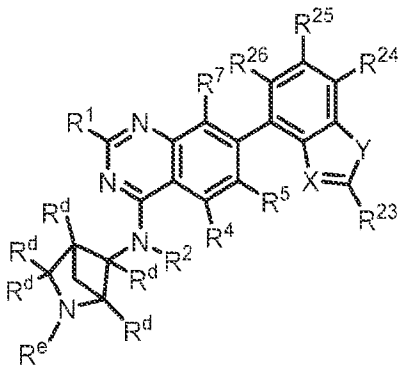
(BA1),



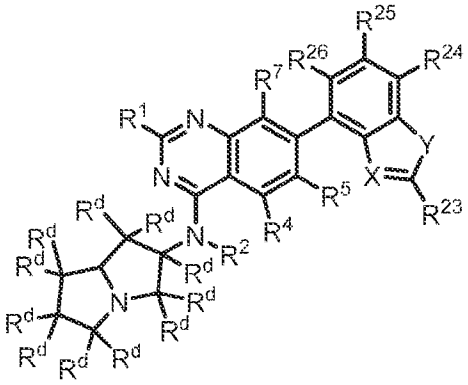
(BB1),



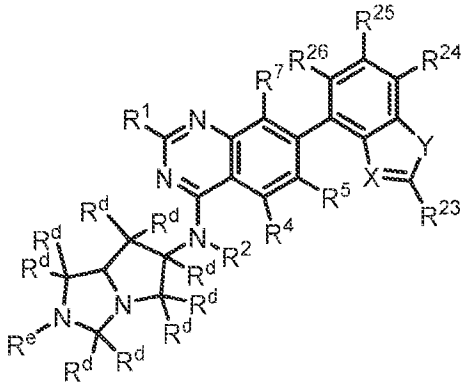
(BC1),



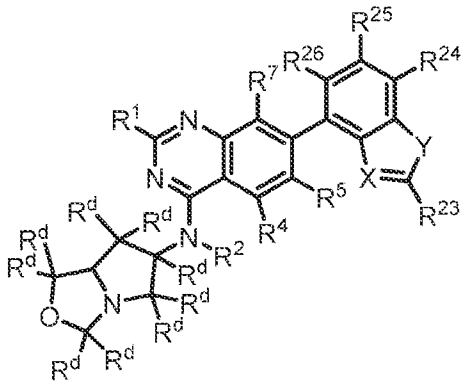
(BD1),



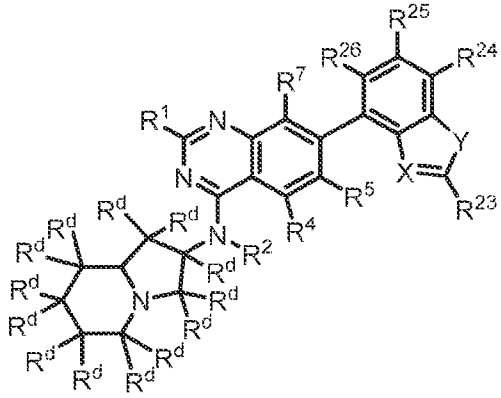
(BE1),



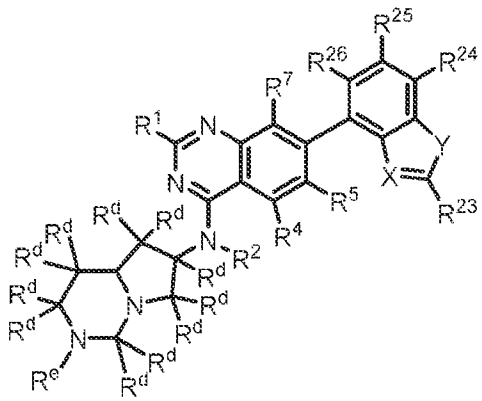
(BF1),



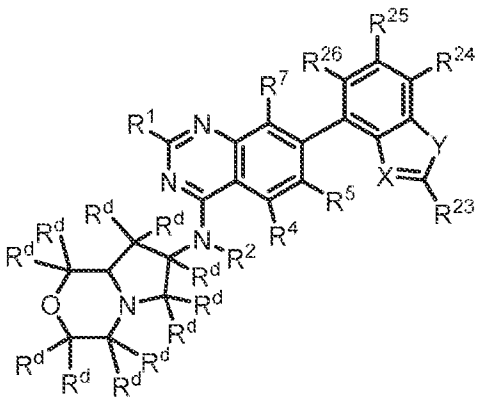
(BG1),



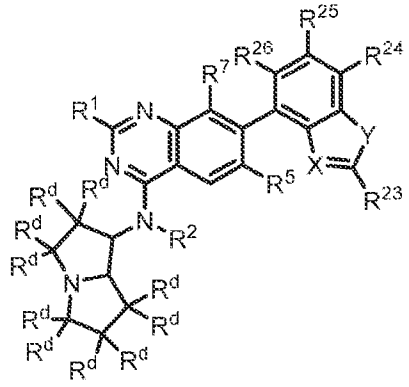
(BH1),



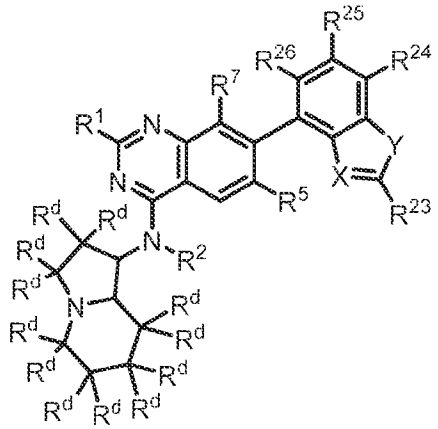
(BI1),



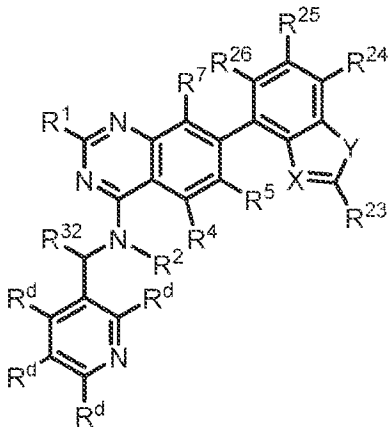
(BJ1),



(BK1),



(BL1), and



(BM1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^{32}, if present, is selected from H and C_{1-5}alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

R^e, if present, is selected from -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is C-CN;

Y is S;

R^{23} is selected from -N(R^{12})$_2$; and

R^{24}, R^{25}, and R^{26} are independently selected from H and halogen.

[0148] In some embodiments, the compound is a compound according to Formula BA1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BB1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BC1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BD, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BE11, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BF1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BG1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BH1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BI1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BJ1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BK1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BL1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula BM1, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0149] In some embodiments for a compound according to any one of Formulas BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

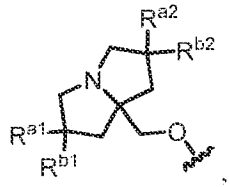
[0150] In some embodiments for a compound according to any one of Formulas BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, R^e is -C(O)(3-6 membered carbocycle). In some embodiments, R^e is selected from -C(O)(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), and -C(O)O(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

[0151] In some embodiments for a compound according to any one of Formulas BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, each R^d is H.

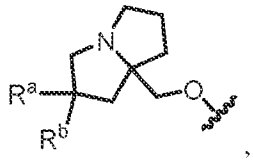
[0152] In some embodiments for a compound according to any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, R^2 is H. In some embodiments, R^2 is selected from C_{1-2}alkyl. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl.

[0153] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, R^1 is selected from $-OR^8$. In some embodiments, R^8 is a heterocycle or an alkylheterocycle, wherein any heterocycle contains 4-8 ring atoms and is substituted with one or more R^a or R^b. In some embodiments, R^8 is a heterocycle that is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, R^8 is an alkylheterocycle that is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, R^8 is $-CH_2$(heterocycle), where the heterocycle is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is a 4-6 membered monocyclic heterocycle having 1-2 heteroatoms independently selected from N, O, and S. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is an 8-membered bicyclic heterocycle having 1-2 heteroatoms independently selected from N, O, and S. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a halogen (e.g., F). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a C_{1-6}alkyl (e.g., methyl). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a $-OR^{12}$ (e.g., $-OCH_3$). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a 3-6 membered carbocycle (e.g., a cyclopropane). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is deuterium.

[0154] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, R^1 is selected from:

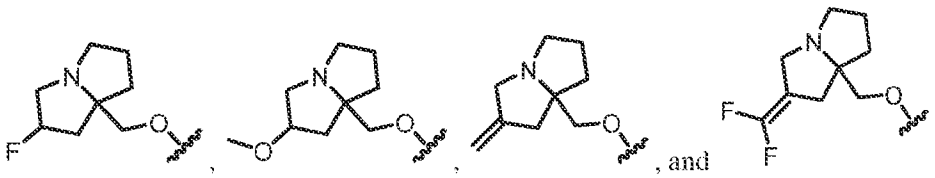


wherein R^{a1}, R^{a2}, R^{b1}, and R^{b2} are each independently selected from deuterium, halogen, $-OR^{12}$, and H, wherein R^{a1} and R^{b1} can optionally join together to form a exocyclic double bond that is unsubstituted or is substituted by halogen. In some embodiments, R^{a1} and R^{b1} are each independently selected from halogen, C_{1-6}alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} is a halogen. In some embodiments, R^{a1} is F. In some embodiments, R^{a1} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} is methyl. In some embodiments, R^{a1} is $-OC_{1-6}$alkyl. In some embodiments, R^{a1} is H. In some embodiments, R^{b1} is H. In some embodiments, R^{b1} is a halogen. In some embodiments, R^{b1} is F. In some embodiments, R^{b1} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{b1} is methyl. In some embodiments, each of R^{a1} and R^{b1} is F. In some embodiments, each of R^{a1} and R^{b1} is methyl. In some embodiments, each of R^{a1} and R^{b1} is H. In some embodiments, R^1 is selected from:



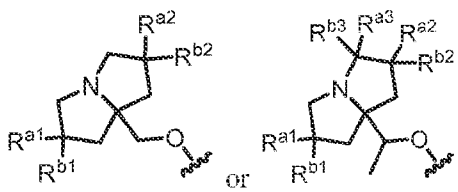
,

wherein R^a and R^b are each independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen. In some embodiments, R^a is a halogen. In some embodiments, R^a is F. In some embodiments, R^a is C_{2-4}alkenyl that is unsubstituted or is substituted with halogen. In some embodiments, R^a is $-OC_{1-6}$alkyl. In some embodiments, R^b is H. In some embodiments, R^b is a halogen. In some embodiments, R^b is F. In some embodiments, R^b is C_{2-4}alkenyl that is unsubstituted or is substituted with halogen. In some embodiments, R^b is methyl. In some embodiments, R^1 is selected from:



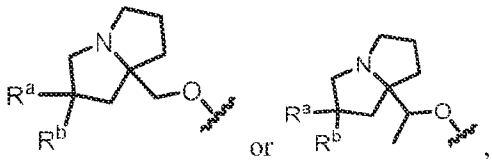
, and .

[0155] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, R^1 is selected from:



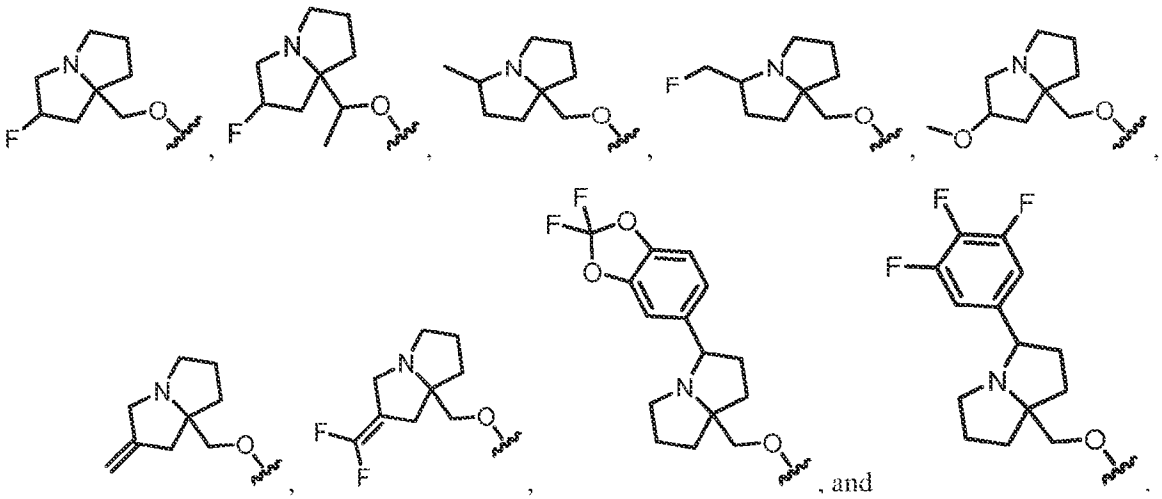
or

wherein R^{a1}, R^{a2}, R^{b1}, R^{b2}, R^{a3}, and R^{b3} are each independently selected from deuterium, halogen, $-OR^{12}$, a 4- to 10-membered heterocycle, and a 4- to 10-membered aryl, wherein any 4- to 10-membered heterocycle or 4- to 10-membered aryl is optionally substituted with one or more R^{28}, and H, wherein R^{a1} and R^{b1} can optionally join together to form a exocyclic double bond that is unsubstituted or is substituted by halogen. In some embodiments, R^{a1} and R^{b1} are each independently selected from halogen, C_{1-6}alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} is a halogen. In some embodiments, R^{a1} is F. In some embodiments, R^{a1} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} is methyl. In some embodiments, R^{a1} is $-OC_{1-6}$alkyl. In some embodiments, R^{a1} is H. In some embodiments, R^{b1} is H. In some embodiments, R^{b1} is a halogen. In some embodiments, R^{b1} is F. In some embodiments, R^{b1} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{b1} is methyl. In some embodiments, each of R^{a1} and R^{b1} is F. In some embodiments, each of R^{a1} and R^{b1} is methyl. In some embodiments, each of R^{a1} and R^{b1} is H. In some embodiments, R^1 is selected from:

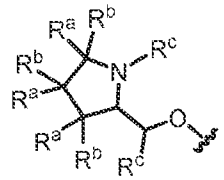


wherein R^a and R^b are each independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen. In some embodiments, R^a is a halogen. In some embodiments, R^a is F. In some embodiments, R^a is C_{2-4}alkenyl that is unsubstituted or is substituted with halogen. In some embodiments, R^a is $-OC_{1-6}$alkyl. In some embodiments, R^b is H. In some embodiments, R^b is a halogen. In some embodiments, R^b is F. In some embodiments, R^b is C_{2-4}alkenyl that is unsubstituted or is substituted with halogen. In some embodiments, R^b is methyl.

[0156] In some embodiments, R^1 is selected from:

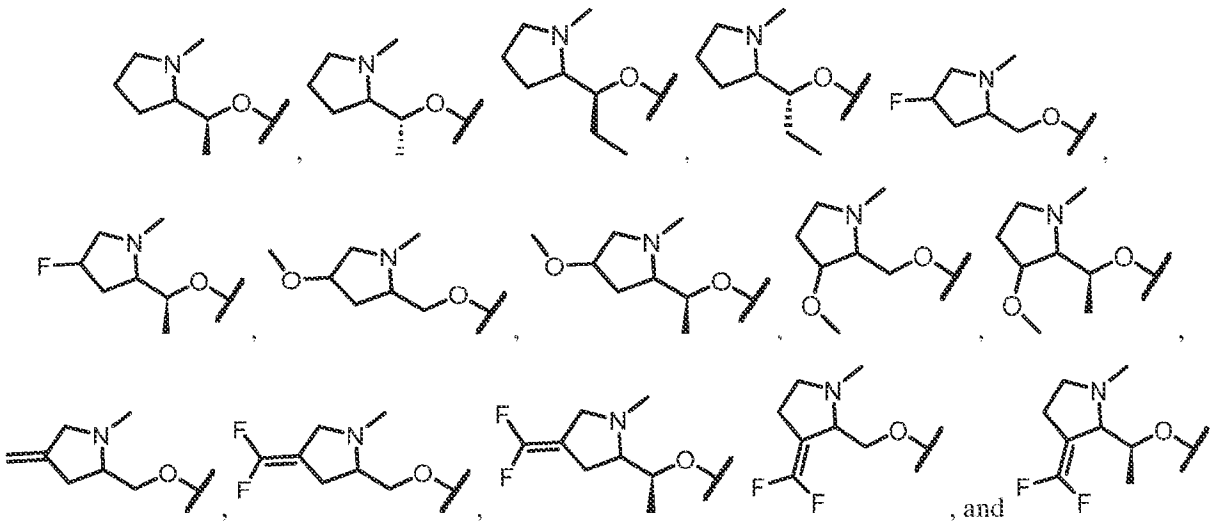


[0157] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, R^1 is selected from:

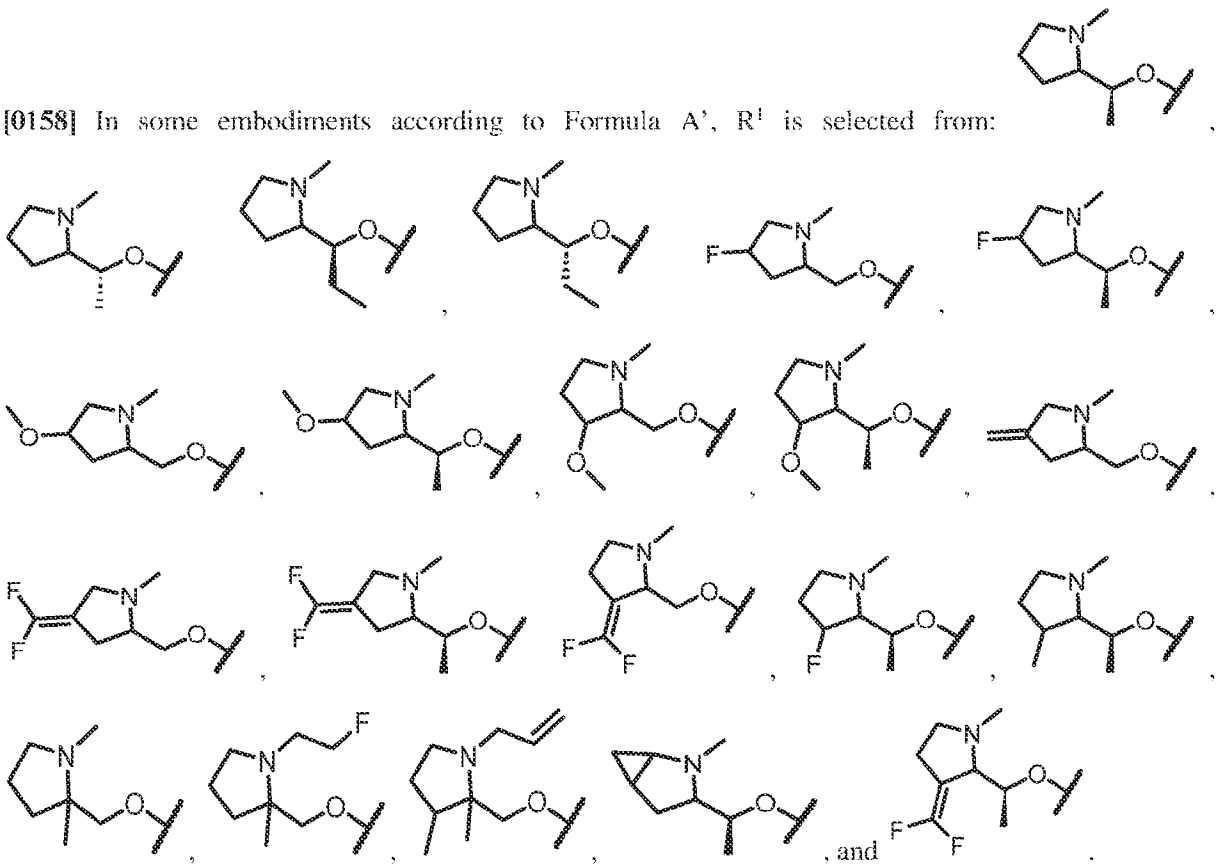


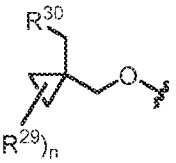
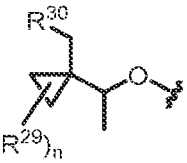
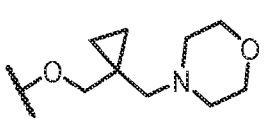
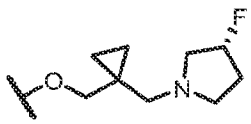
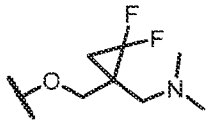
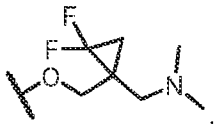
wherein each R^a and R^b is independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H; and each R^c is independently selected from H and C_{1-6} alkyl, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen. In some embodiments, each R^c is independently selected from C_{1-6} alkyl that is unsubstituted. In some embodiments, each R^c is independently selected from C_{1-6} alkyl that is substituted with halogen. In some embodiments, each R^c is independently selected from C_{1-2} alkyl that is unsubstituted. In some embodiments, the R^c that is not linked to a nitrogen atom is H. In some embodiments, each R^a and R^b is H. In some embodiments, one R^a or R^b is selected from halogen, $-OR^{12}$, and C_{2-4} alkenyl, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen, and the other R^a and R^b groups are H. In some embodiments, one R^a or R^b is halogen (e.g., F). In some embodiments, one R^a or R^b is $-OR^{12}$ (e.g., $-OCH_3$). In some embodiments, one R^a or R^b is C_{1-6} alkyl (e.g., methyl). In some embodiments, one R^a is selected from C_{2-4} alkenyl that is unsubstituted or is substituted by halogen and the other R^a and R^b groups are H, provided that the R^b connected to the same atom as the R^a that is substituted or unsubstituted C_{2-4} alkenyl is absent. In some embodiments, one R^a is selected from C_{2-4} alkenyl that is unsubstituted and the other R^a and R^b groups are H, provided that the R^b connected to the same atom as the R^a that is C_{2-4} alkenyl is absent.

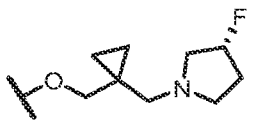
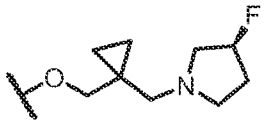
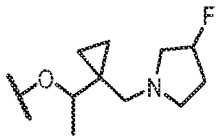
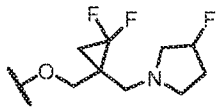
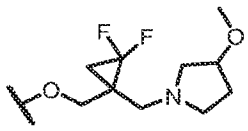
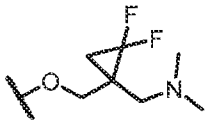
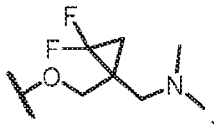
In some embodiments, one R^a is selected from C_{2-4} alkenyl that is substituted by halogen and the other R^a and R^b groups are H, provided that the R^b connected to the same atom as the R^a that is substituted C_{2-4} alkenyl is absent. In some embodiments, R^1 is selected from:



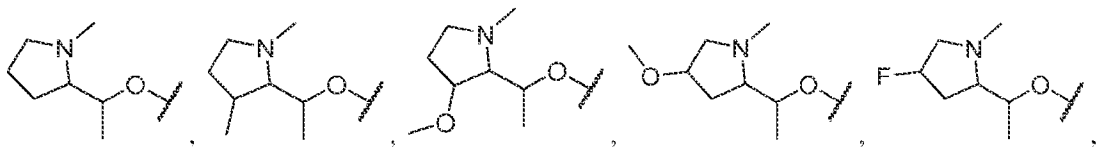
[0158] In some embodiments according to Formula A', R^1 is selected from:

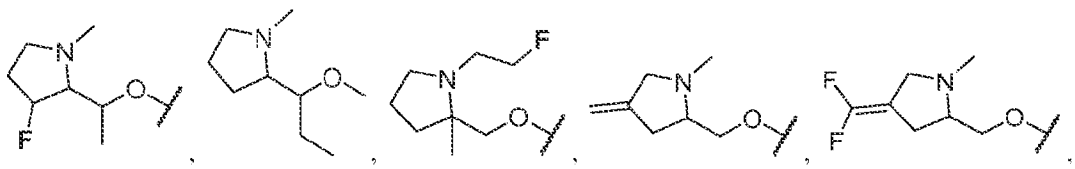


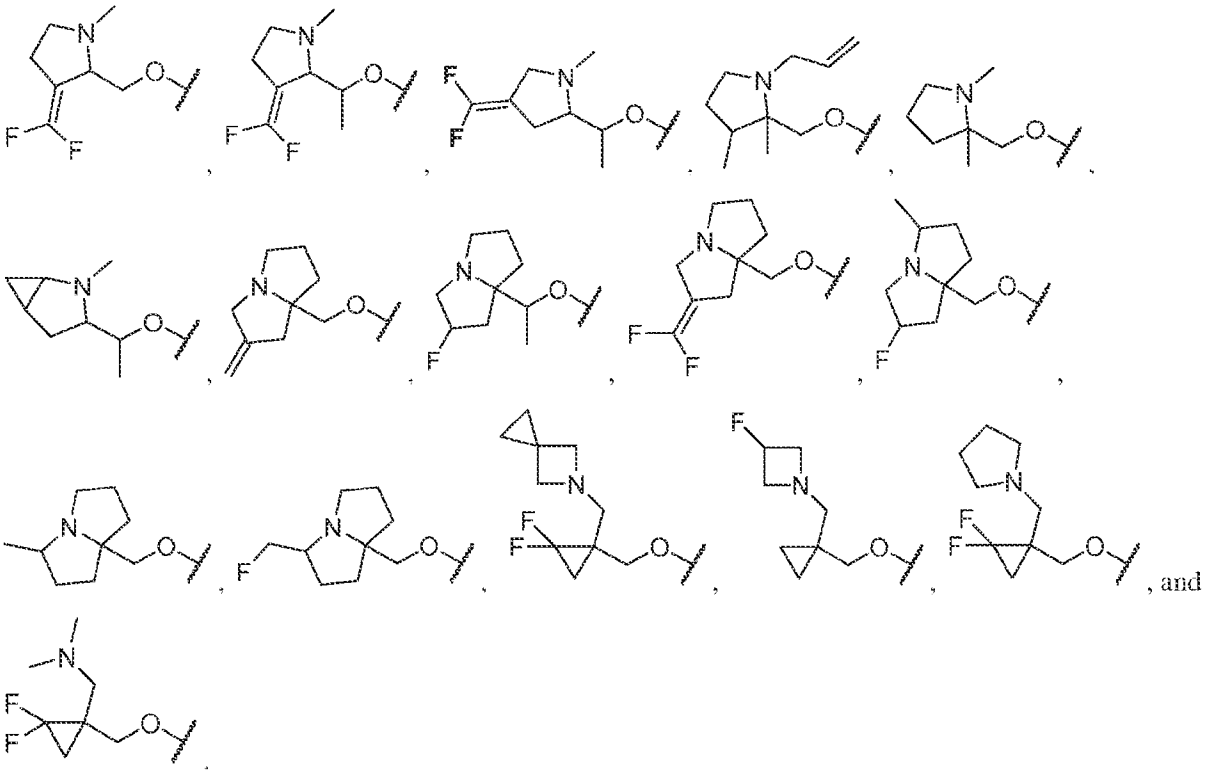
[0159] In some embodiments, for a compound according to any one of Formulas A, A', B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, R^1 is  or  . In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, each R^{29} is independently halogen. In some embodiments, each R^{29} is independently C_{1-6}alkyl. In some embodiments, R^{30} is $-N(R^{12})_2$. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}. In some embodiments, R^1 is selected from  ,  ,  , and  .

[0160] In some embodiments according to Formula A', R^1 is selected from ,  ,  ,  ,  ,  ,  , and  .

[0161] In some embodiments according to Formula A, R^1 is selected from:

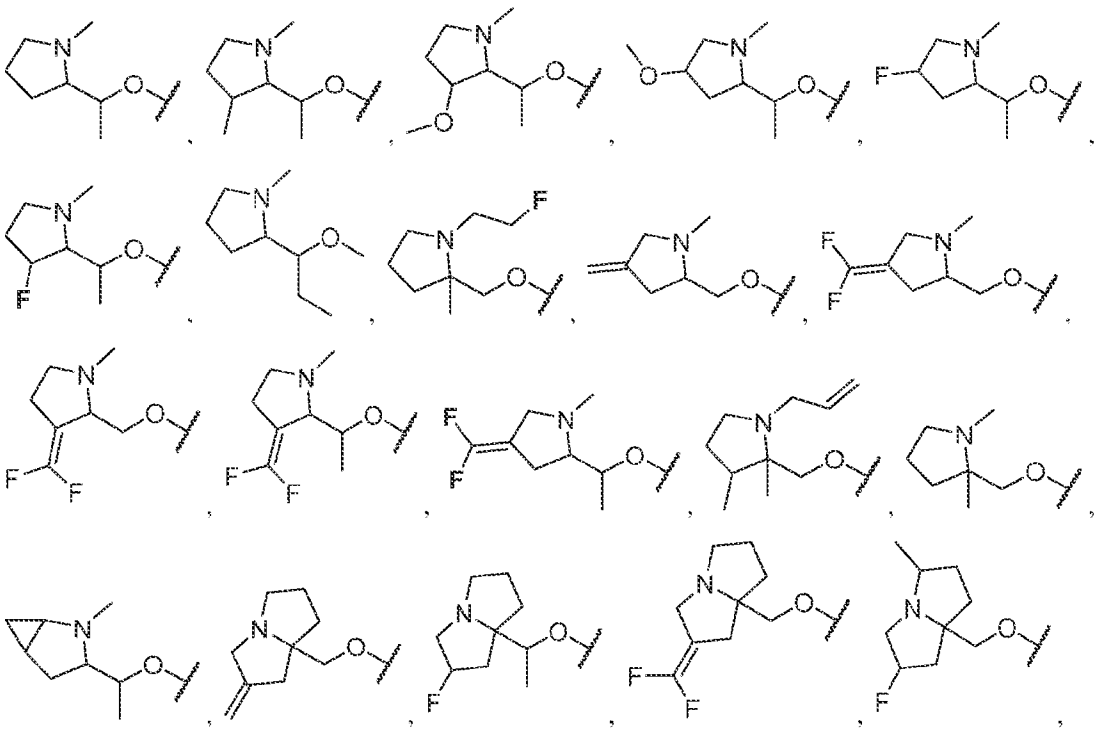


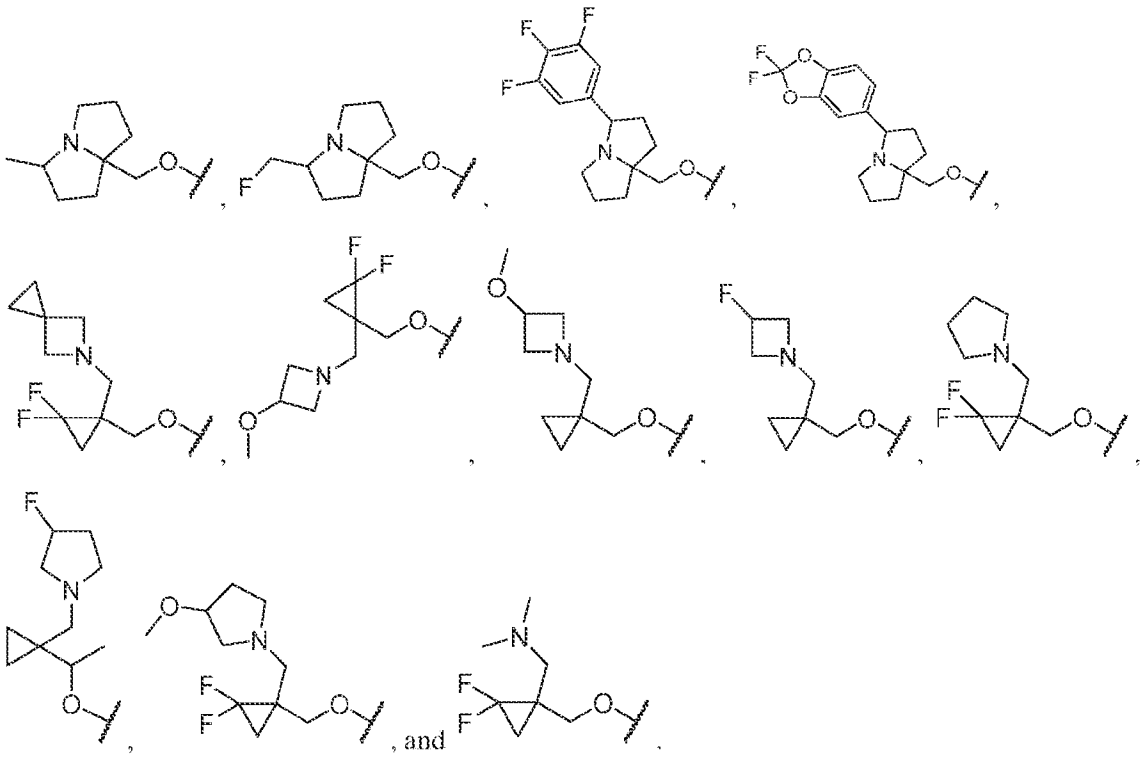




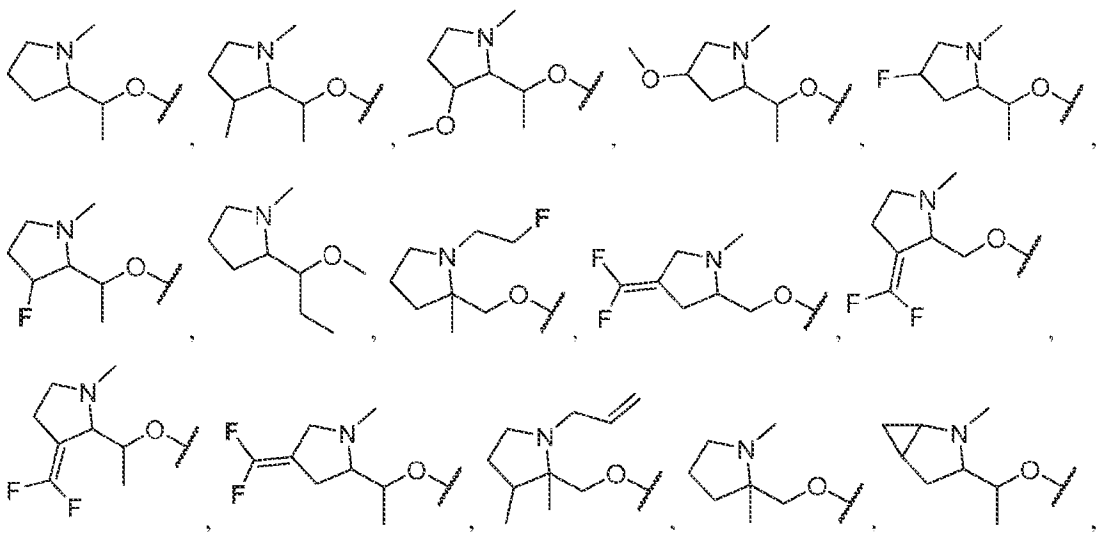
, and

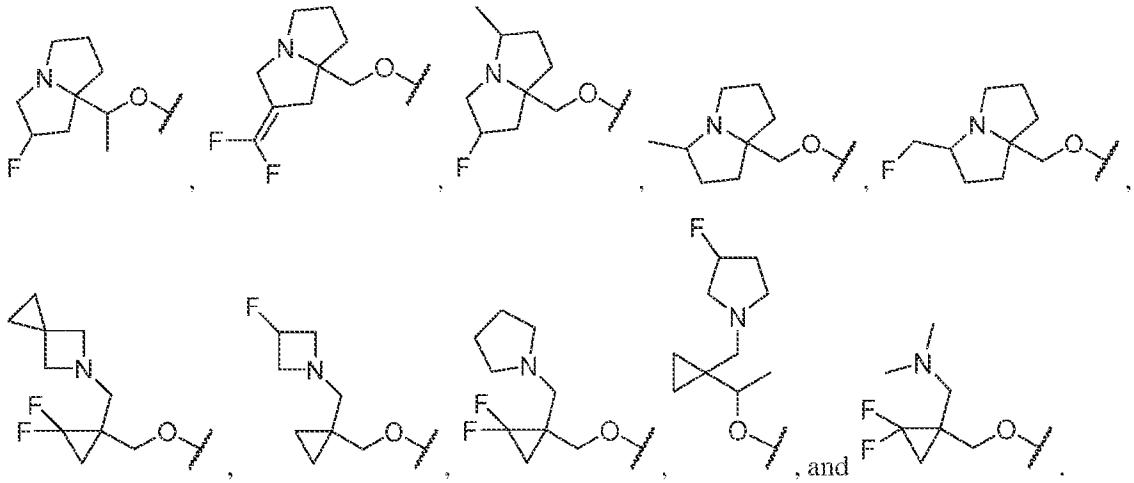
[0162] In some embodiments according to Formula A', R^1 is selected from:





[0163] In some embodiments according to Formula B, R^1 is selected from:

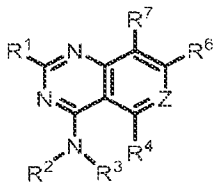




[0164] In some embodiments, for a compound according to any one of Formulas A, A', A'-a, B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, R^5 is selected from C_{1-6}alkyl that is unsubstituted. In some embodiments, R^5 is selected from C_{1-6}alkyl that is substituted with one or more R^{13}. In some embodiments, R^5 is selected from C_{1-6}alkyl that is substituted with one or more F. In some embodiments, R^5 is $-CF_3$.

[0165] In some embodiments, for a compound according to any one of Formulas A, A', A'-a, B, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1, R^7 is Cl. In some embodiments, R^7 is F.

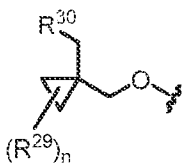
[0166] In another aspect, the present disclosure provides a compound represented by Formula II:



(II)

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

Z is N or C-R^5;

R^1 is selected from H, $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated;

R^3 is selected from 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, a 4-10 membered heterocycle, or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, -OC_{1-6}alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a phenyl or a bicyclic heteroaryl, wherein the phenyl or bicyclic heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen or H;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, -OR^{12}, =O, =S, -CN, -N=S(=O)Me_2, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),-C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), -C(S)(C_{1-6}alkyl), -C(S)O(C_{1-6}alkyl), -C(S)N(C_{1-6}alkyl)$_2$, -C(=N-OR^{12})(C_{1-6} alkyl), -C(O)N(R^{12})OR^{12}, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -N(R^{14})$_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, -OR^{12}, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), $-C(O)OR^{12}$, $-C(O)N(R^{12})_2$, $-S(O)_2R^{12}$, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl, $-OR^{12}$, C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, , $-C_{1-6}$ heteroalkyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0167] In some embodiments, the present disclosure provides a compound of Formula II, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0168] In some embodiments, R^3 is selected from 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, a 5-10 membered heterocycle, or $-(C_{1-6}$ alkylenyl)(5-6 membered heteroaryl), wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10}.

[0169] In some embodiments, the present disclosure provides a compound represented by Formula II, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from $-OR^8$;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated;

R^3 is selected from 3- to 12-membered cycloalkyl that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, -OC_{1-6}alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a phenyl or a bicyclic heteroaryl, wherein the phenyl or bicyclic heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen or H;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, -OR^{12}, =O, =S, -CN, -N=S(=O)Me_2, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),-C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), -C(S)(C_{1-6}alkyl), -C(S)O(C_{1-6}alkyl), -C(S)N(C_{1-6}alkyl)$_2$, -C(=N-OR^{12})(C_{1-6} alkyl), -C(O)N(R^{12})OR^{12}, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -N(R^{14})$_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, -OR^{12}, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, -N(R^{12})$_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), -C(O)OR^{12}, -C(O)$N(R^{12})_2$, -$S(O)_2R^{12}$, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl, -OR^{12}, C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, , -C_{1-6} heteroalkyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0170] In some embodiments, the present disclosure provides a compound represented by Formula II, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from -OR^8;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated;

R^3 is selected from 3- to 12-membered cycloalkyl that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl, wherein the phenyl or bicyclic heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

Each R^{10} is independently selected from deuterium, $-OR^{12}$, =O, =S, -CN, -N=S(=O)Me_2, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),-C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), -C(S)(C_{1-6}alkyl), -C(S)O(C_{1-6}alkyl), -C(S)N(C_{1-6}alkyl)$_2$, -C(=N-OR^{12})(C_{1-6} alkyl), -C(O)N(R^{12})OR^{12}, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -N(R^{14})$_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, -OR^{12}, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, -N(R^{12})$_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), -C(O)OR^{12}, -C(O)N(R^{12})$_2$, -S(O)$_2$$R^{12}$, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl, -OR^{12}, C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is N(R^{12})$_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, , -C_{1-6} heteroalkyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0171] In some embodiments, the present disclosure provides a compound represented by Formula II, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from -OR^8;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated;

R^3 is selected from 3- to 12-membered cycloalkyl fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, a 4-10 membered heterocycle, or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, -OC_{1-6}alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a phenyl or a bicyclic heteroaryl, wherein the phenyl or bicyclic heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen or H;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, -OR^{12}, =O, =S, -CN, -N=S(=O)Me_2, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),-C(O)O(C_{1-}

$_{6}$alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), -C(S)(C_{1-6}alkyl), -C(S)O(C_{1-6}alkyl), -C(S)N(C_{1-6}alkyl)$_2$, -C(=N-OR^{12})(C_{1-6} alkyl), -C(O)N(R^{12})OR^{12}, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -N(R^{14})$_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, -OR^{12}, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, -N(R^{12})$_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), -C(O)OR^{12}, -C(O)N(R^{12})$_2$, -S(O)$_2$R^{12}, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl, -OR^{12}, C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is N(R^{12})$_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl,
,-C_{1-6} heteroalkyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0172] In some embodiments, the present disclosure provides a compound represented by Formula II, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from $-OR^8$;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated;

R^3 is selected from 3- to 12-membered cycloalkyl fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, a 4-10 membered heterocycle, or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl, wherein the phenyl or bicyclic heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, $-OR^{12}$, =O, =S, -CN, -N=S(=O)Me_2, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),-C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), -C(S)(C_{1-6}alkyl), -C(S)O(C_{1-6}alkyl), -C(S)N(C_{1-6}alkyl)$_2$, -C(=N-OR^{12})(C_{1-6} alkyl), -C(O)N(R^{12})OR^{12}, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, $-OR^{12}$, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), $-C(O)OR^{12}$, $-C(O)N(R^{12})_2$, $-S(O)_2R^{12}$, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl, $-OR^{12}$, C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

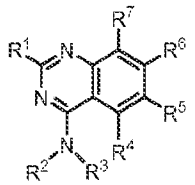
R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

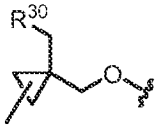
R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, , $-C_{1-6}$ heteroalkyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0173] In another aspect, the present disclosure provides a compound represented by Formula II':



(II')

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:



R^1 is selected from H, $-OR^8$, , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}$alkylene)CN, $-C(O)(C_{1-6}$alkylene)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}$alkylene)(3-6 membered heterocycle), $-S(O)_2(C_{1-6}$alkyl), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), a 3-6 membered carbocycle, phenyl, and halogen;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0174] In some embodiments, the present disclosure provides a compound of Formula II', or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0175] In some embodiments, for a compound of Formula II', R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, or (ii) the heterocycle does not comprise an –NH- moiety.

[0176] In some embodiments, the present disclosure provides a compound represented by Formula II', or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from $-OR^8$;

R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is an alkylheterocycle, wherein the heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of the alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}alkyl)$, a 3-6 membered carbocycle, phenyl, and halogen; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0177] In some embodiments, the present disclosure provides a compound represented by Formula II', or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from -OR^8;

R^2 is selected from C_{1-2}alkyl that is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-2}alkyl that is substituted with one or more R^{15};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is an alkylheterocycle, wherein the heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of the alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -N(R^{14})$_2$, and halogen;

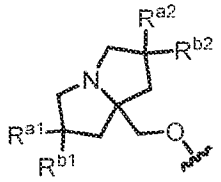
each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, -N(R^{12})$_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), a 3-6 membered carbocycle, phenyl, and halogen; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0178] In some embodiments, the present disclosure provides a compound represented by Formula II', or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from  , wherein R^{a1}, R^{a2}, R^{b1}, and R^{b2} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, -OR^{12}, and H, wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13};

R^2 is selected from C_{1-2}alkyl that is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-2}alkyl that is substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

each R^{10} is independently selected from deuterium, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein

any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

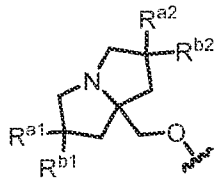
each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, -$N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), a 3-6 membered carbocycle, phenyl, and halogen.

[0179] In some embodiments, the present disclosure provides a compound represented by Formula II', or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

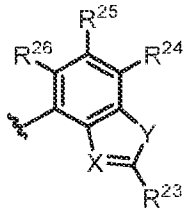
R^1 is selected from  , wherein R^{a1}, R^{a2}, R^{b1}, and R^{b2} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, -OR^{12}, and H, wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13};

R^2 is selected from C_{1-2}alkyl that is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-2}alkyl that is substituted with one or more R^{15};

R^6 is selected from:  , wherein X is selected from N and C-CN; Y is selected from O, S, and Se; R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^7 is selected from halogen;

each R^{10} is independently selected from deuterium, =O, $-C(O)(C_{1-6}$alkylene)CN, $-C(O)(C_{1-6}$alkylene)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}$alkylene)(3-6 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

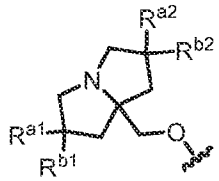
each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated; and

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), a 3-6 membered carbocycle, phenyl, and halogen.

[0180] In some embodiments, the present disclosure provides a compound represented by Formula II', or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

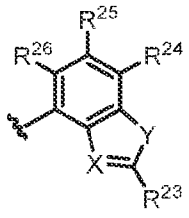
R^1 is selected from  , wherein R^{a1}, R^{a2}, R^{b1}, and R^{b2} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H, wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13};

R^2 is selected from C_{1-2}alkyl that is unsubstituted or is substituted with one or more R^{13};

R^3 is a 4-6 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-2}alkyl that is substituted with one or more R^{13};

R^6 is selected from:  , wherein X is selected from N and C-CN; Y is selected from O, S, and Se; R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^7 is selected from halogen;

each R^{10} is independently selected from deuterium, =O, $-C(O)(C_{1-6}$alkylene)CN, $-C(O)(C_{1-6}$alkylene)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}$alkylene)(3-6 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two

R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

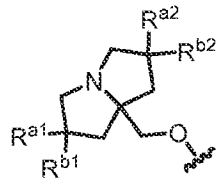
each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated; and

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), a 3-6 membered carbocycle, phenyl, and halogen.

[0181] In some embodiments, the present disclosure provides a compound represented by Formula II', or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

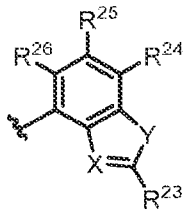
R^1 is selected from  , wherein R^{a1}, R^{a2}, R^{b1}, and R^{b2} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, -OR^{12}, and H, wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13};

R^2 is selected from C_{1-2}alkyl that is unsubstituted or is substituted with one or more R^{13};

R^3 is a 7-10 membered heterocycle comprising a fused ring system that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-2}alkyl that is substituted with one or more R^{13};

R^6 is selected from:  , wherein X is selected from N and C-CN; Y is selected from O, S, and Se; R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any

C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^7 is selected from halogen;

each R^{10} is independently selected from deuterium, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

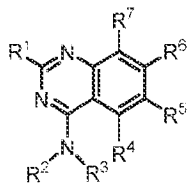
each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -N(R^{14})$_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated; and

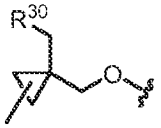
each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), a 3-6 membered carbocycle, phenyl, and halogen.

[0182] In another aspect, the present disclosure provides a compound represented by Formula II'':



(II'')

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:



R^1 is selected from H, $-OR^8$, , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, $-OC_{1-6}$alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen or H;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, $-OR^{12}$, =O, =S, $-C(O)(C_{1-6}$alkylene$)CN$, $-C(O)(C_{1-6}$alkylene$)OH$, $-C(O)(C_{1-6}$alkyl$)$, $-C(O)O(C_{1-6}$alkyl$)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}$alkylene$)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}$alkyl$)$, $-C(S)(C_{1-6}$alkyl$)$, $-C(S)O(C_{1-6}$alkyl$)$, $-C(S)N(C_{1-6}$alkyl$)_2$, $-C(=N\text{-}OR^{12})(C_{1-6}$ alkyl$)$, $-C(O)N(R^{12})OR^{12}$, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, $-OC_{1-6}$ alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), $-C(O)OR^{12}$, $-C(O)N(R^{12})_2$, a 3-6 membered carbocycle, phenyl, and halogen;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

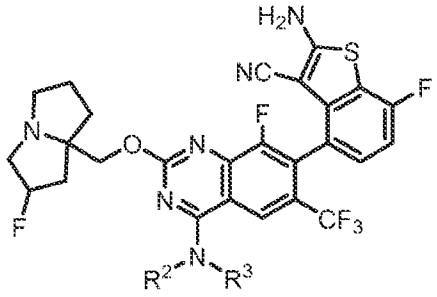
each R^{29} is independently selected from halogen and C_{1-6}alkyl;

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0183] In some embodiments, the present disclosure provides a compound of Formula II', wherein the compound is of Formula II-a:

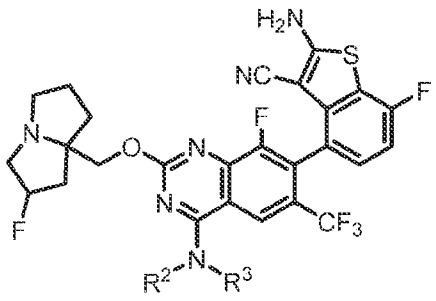


(II-a)

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein R^2 and R^3 are as defined for Formula II' above and described in classes and subclasses herein, both singly and in combination. In some embodiments, R^2 and R^3 are as defined for Formula II' above and described in classes and subclasses herein, both singly and in combination. In some

embodiments, the present disclosure provides a compound of Formula II-a, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0184] In some embodiments, the present disclosure provides a compound of Formula II'', wherein the compound is of Formula II''-a:



(II''-a)

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein R^2 and R^3 are as defined for Formula II'' above and described in classes and subclasses herein, both singly and in combination. In some embodiments, R^2 and R^3 are as defined for Formula II'' above and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula II''-a, or a salt (e.g., pharmaceutically acceptable salt) thereof.

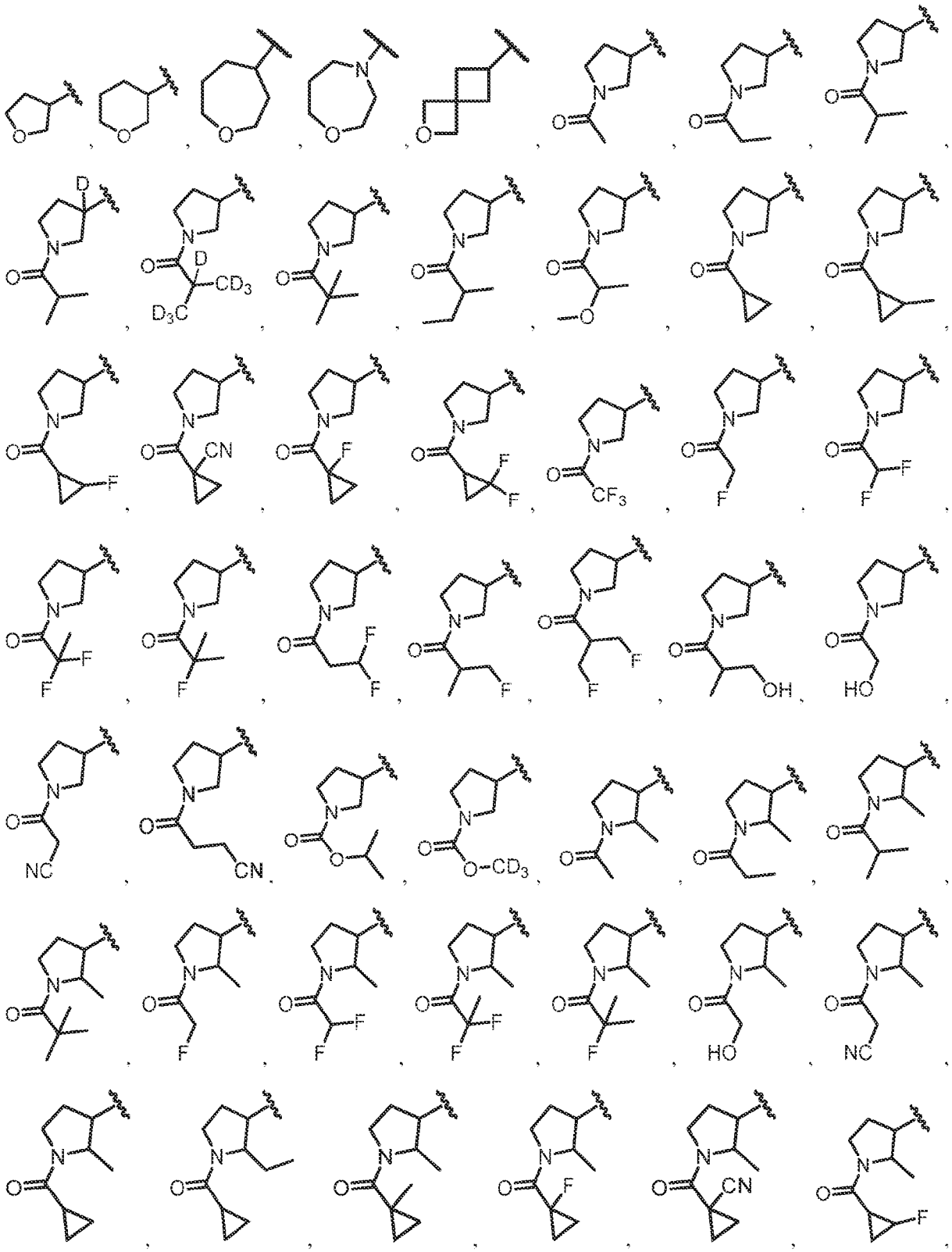
[0185] In some embodiments, for a compound according to Formula II, Z is N. In some embodiments, for a compound according to Formula II, Z is C-R^5.

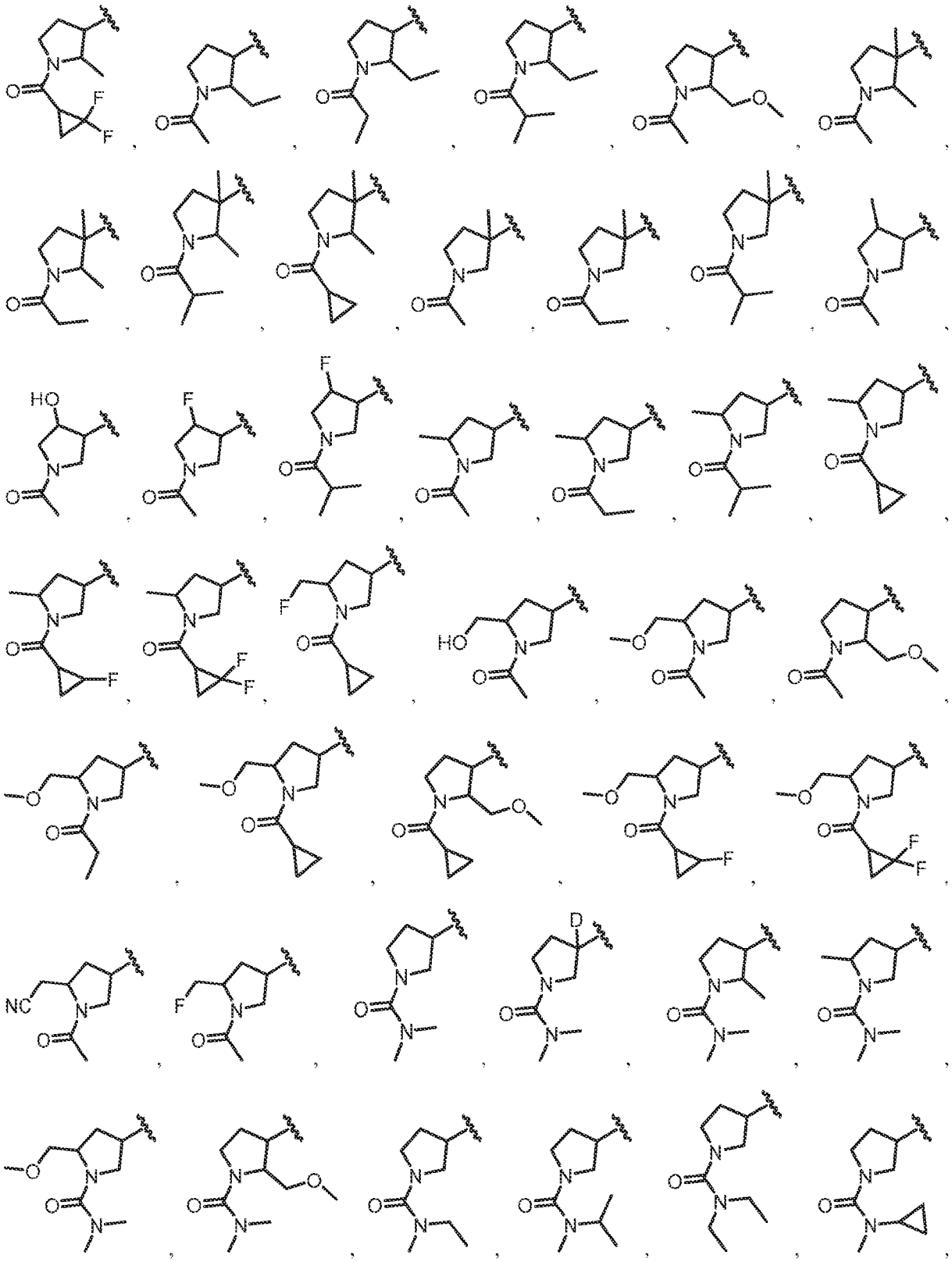
[0186] In some embodiments, for a compound according to Formula II, II', II'', II''-a, II-a, or III, R^3 is a 4-6 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 is a 4-6 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}. In some embodiments, R^3 is a 4-6 membered heterocycle that includes one heteroatom selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}. In some embodiments, R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}. In some embodiments, R^3 is a 4-6 membered heterocycle that includes a nitrogen atom, wherein the heterocycle is substituted with 1-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}. In some embodiments, R^3 is a 4-6 membered heterocycle that includes an oxygen atom, wherein the heterocycle is

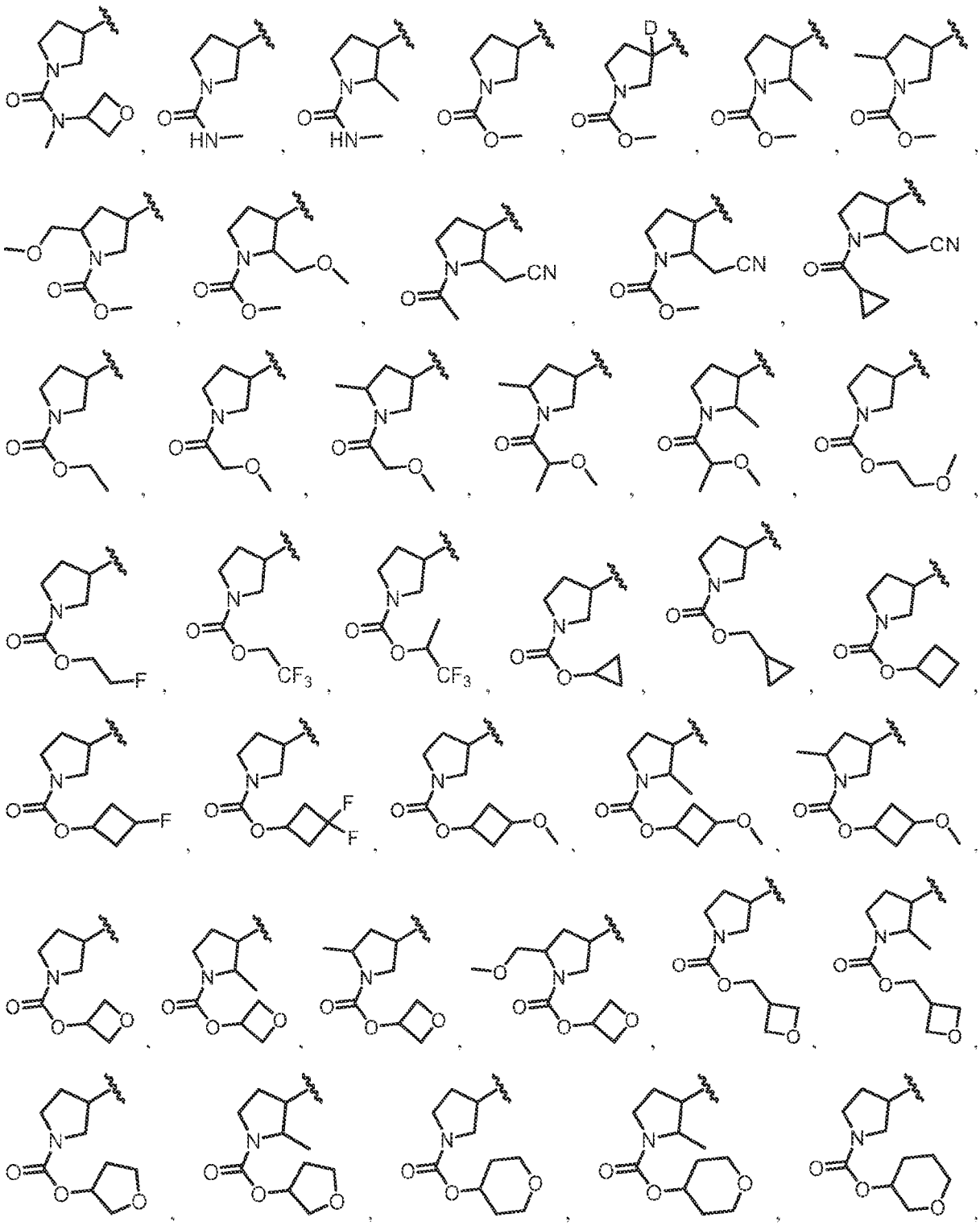
substituted with 1-4 R^{10}. In some embodiments, R^3 is a pyrrolidine that is substituted with 0-4 R^{10}, provided that the nitrogen atom of the heterocycle is substituted with R^{10}. In some embodiments, R^3 is a pyrrolidine that is substituted with 1-4 R^{10}, provided that the nitrogen atom of the heterocycle is substituted with R^{10}. In some embodiments, R^3 is an oxetane that is substituted with 0-4 R^{10}. In some embodiments, R^3 is an oxetane that is substituted with 1-4 R^{10}. In some embodiments, R^3 is a tetrahydrofuran that is substituted with 0-4 R^{10}. In some embodiments, R^3 is a tetrahydrofuran that is substituted with 1-4 R^{10}. In some embodiments, R^3 is a 4-6 membered heterocycle that is substituted with one or more R^{10}, wherein at least one R^{10} is an unsubstituted C_{1-6}alkyl, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}. In some embodiments, R^3 is selected from a 4-6 membered heterocycle that is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with an R^{10} that is selected from -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle. In some embodiments, R^3 is selected from a 4-6 membered heterocycle that is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with an R^{10} that is selected from -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and a 3-6 membered heterocycle, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle. In some embodiments, R^3 is selected from a 4-6 membered heterocycle that is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with an R^{10} that is a 5-6 membered heteroaryl that is unsubstituted or substituted with one or more R^{12} or R^{20}.

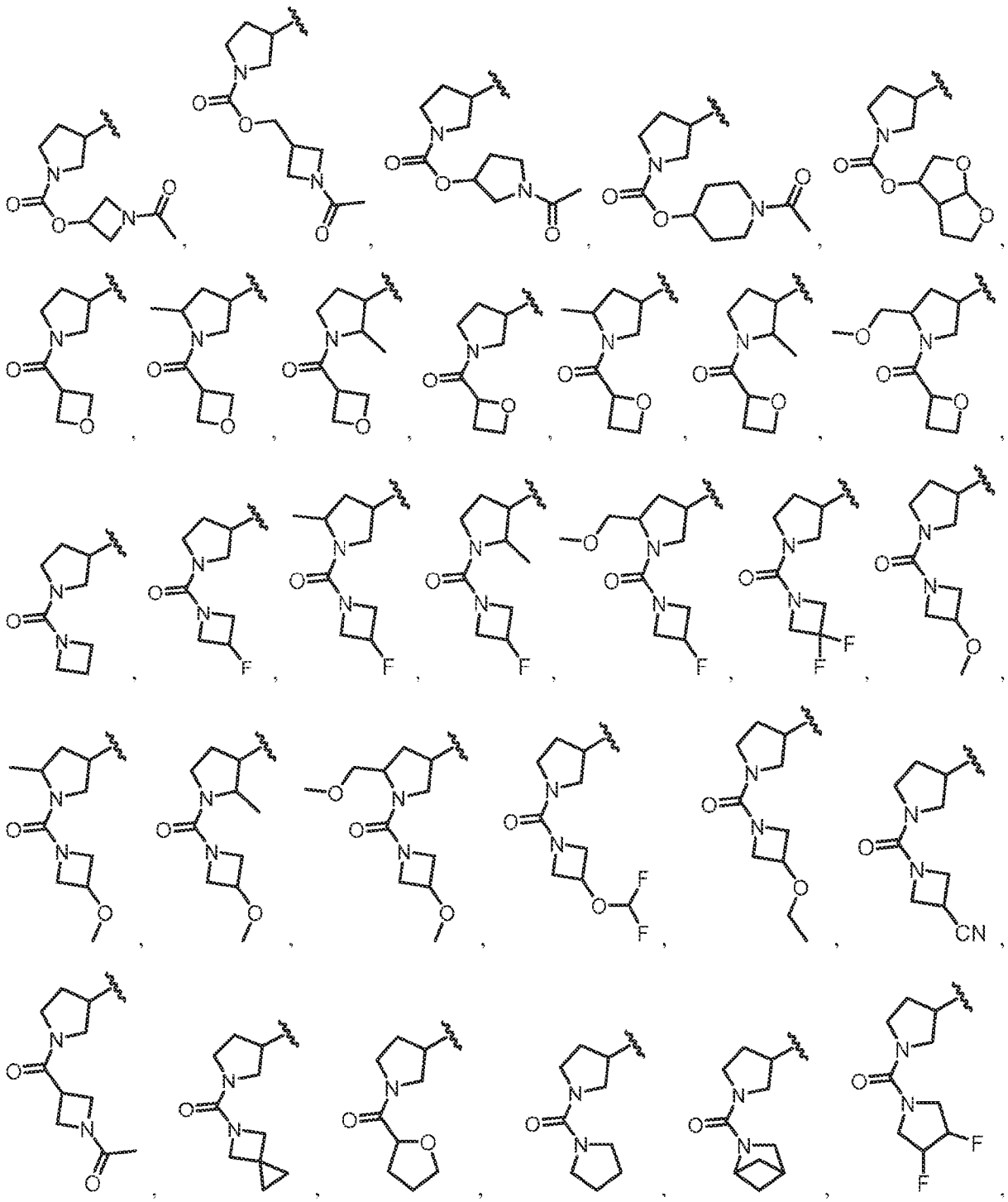
[0187] In some embodiments, for a compound according to Formula II, II', II'', II''-a, II-a, or III, two R^{10}s join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle. In some embodiments, two R^{10}s connected to adjacent atoms join together to form, together with the atoms to which they are attached, a 3-6 membered carbocycle or heterocycle. In some embodiments, two R^{10}s connected to adjacent atoms join together to form, together with the atoms to which they are attached, a 5-6 membered heterocycle, such as a pyrrolidine or oxazolidine. In some embodiments, the 3-6 membered carbocycle or heterocycle formed by the joining of two R^{10}s is substituted with one or more R^{10}. In some embodiments, the 5-6 membered heterocycle formed by the joining of two R^{10}s is substituted with one or more R^{10}. In some embodiments, the 5-6 membered heterocycle (e.g., pyrrolidine or oxazolidine) formed by the joining of two R^{10}s is substituted with =O. In some embodiments, each R^{10} is independently selected from $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)$(3-6 membered carbocycle), $-C(O)N(R^{14})_2$, $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle. In some embodiments, each R^{10} is independently selected from $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)$(3-6 membered carbocycle), $-C(O)N(R^{14})_2$, $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}. In some embodiments, each R^{10} is independently selected from $-OR^{12}$, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}. In some embodiments, each R^{10} is independently selected from $-C(O)(C_{1-6}alkyl)$, $-C(O)$(3-6 membered carbocycle), $-C(O)O(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, each R^{10} is independently selected from deuterium, $-C(O)N(R^{14})_2$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)$(3-6 membered carbocycle), $-C(O)$(3-8 membered heterocycle), a 3-6 membered heterocycle, a 5-6 membered heteroaryl, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

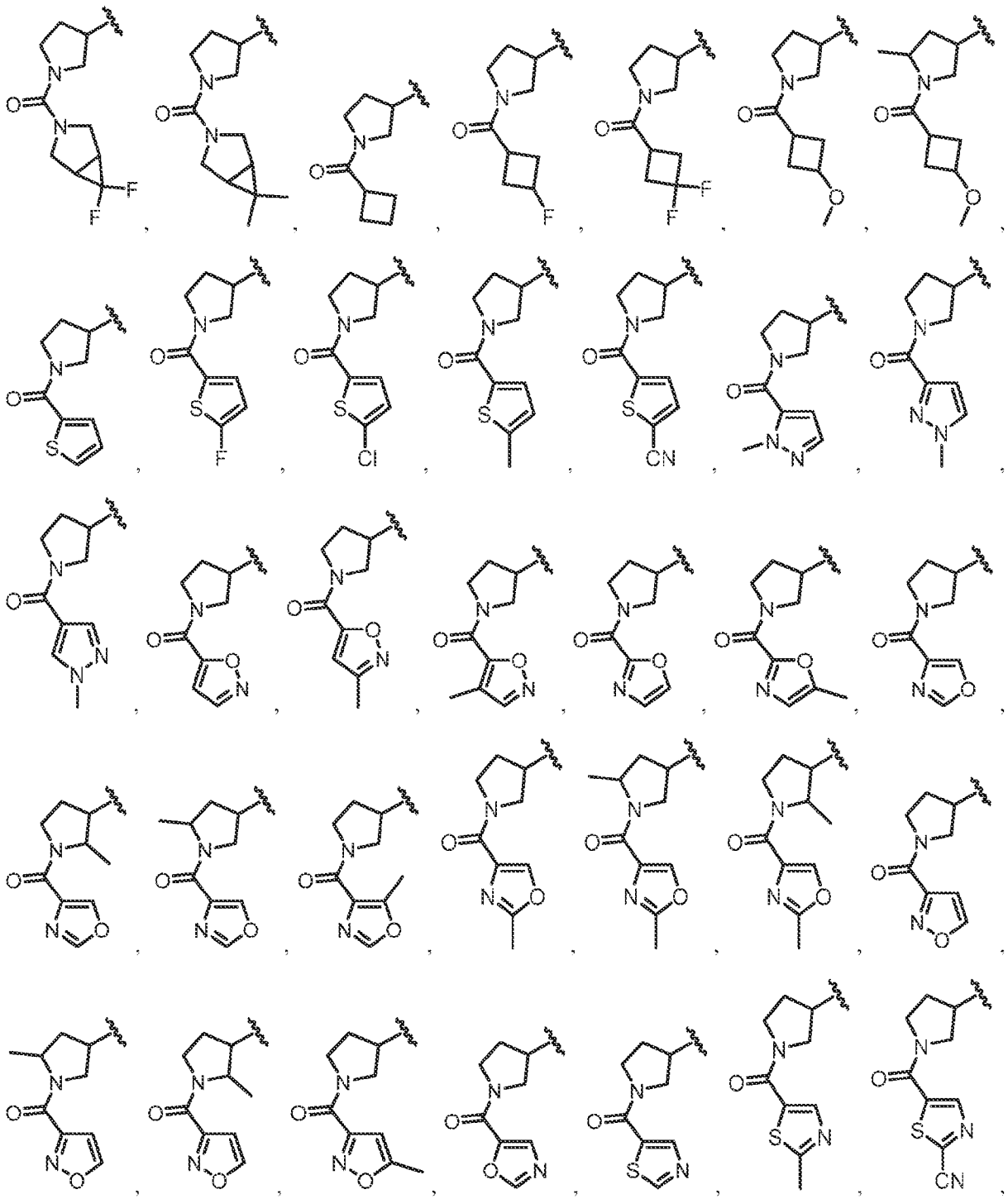
[0188] In some embodiments, for a compound according to Formula II', II-a, or III, R^3 is selected from:

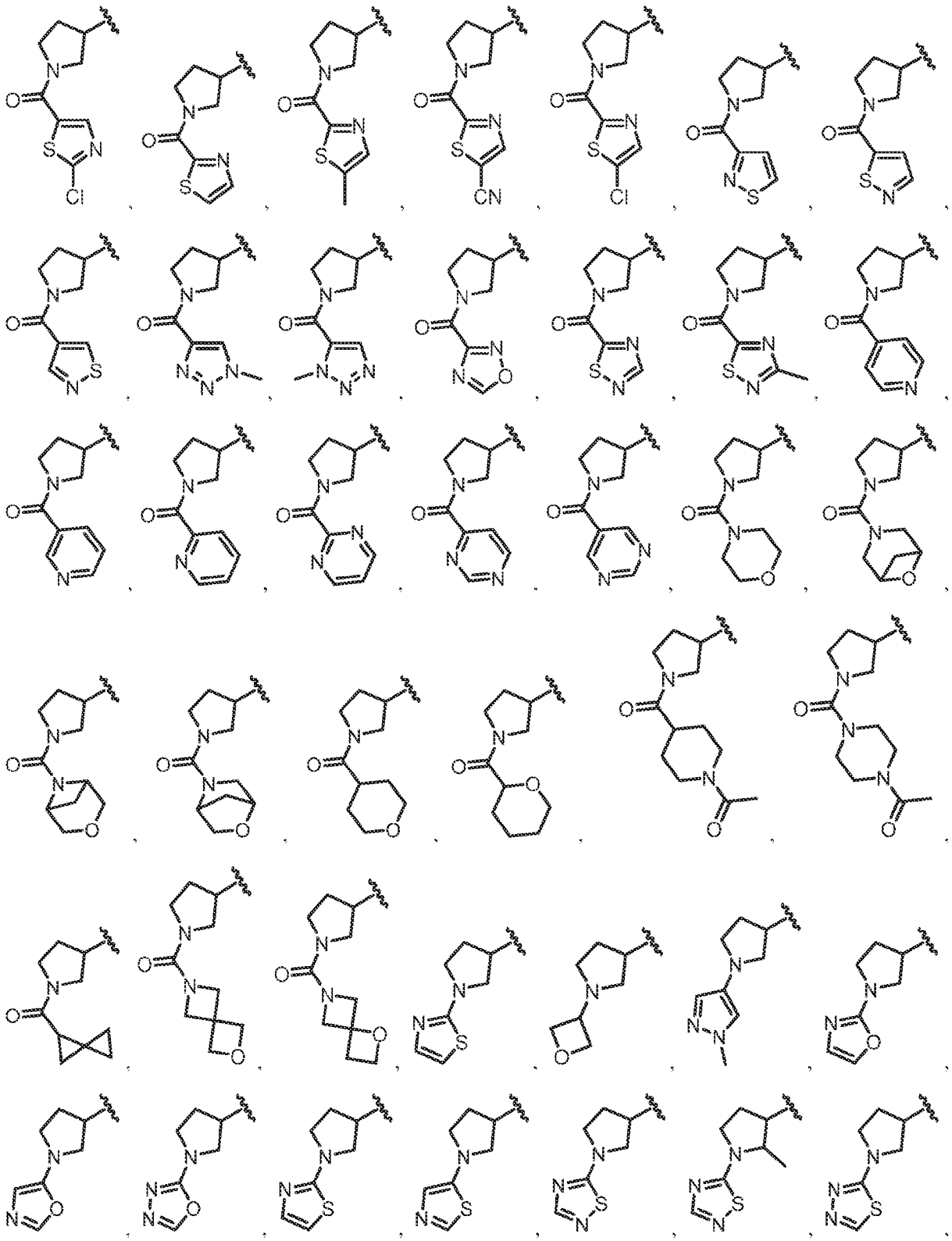


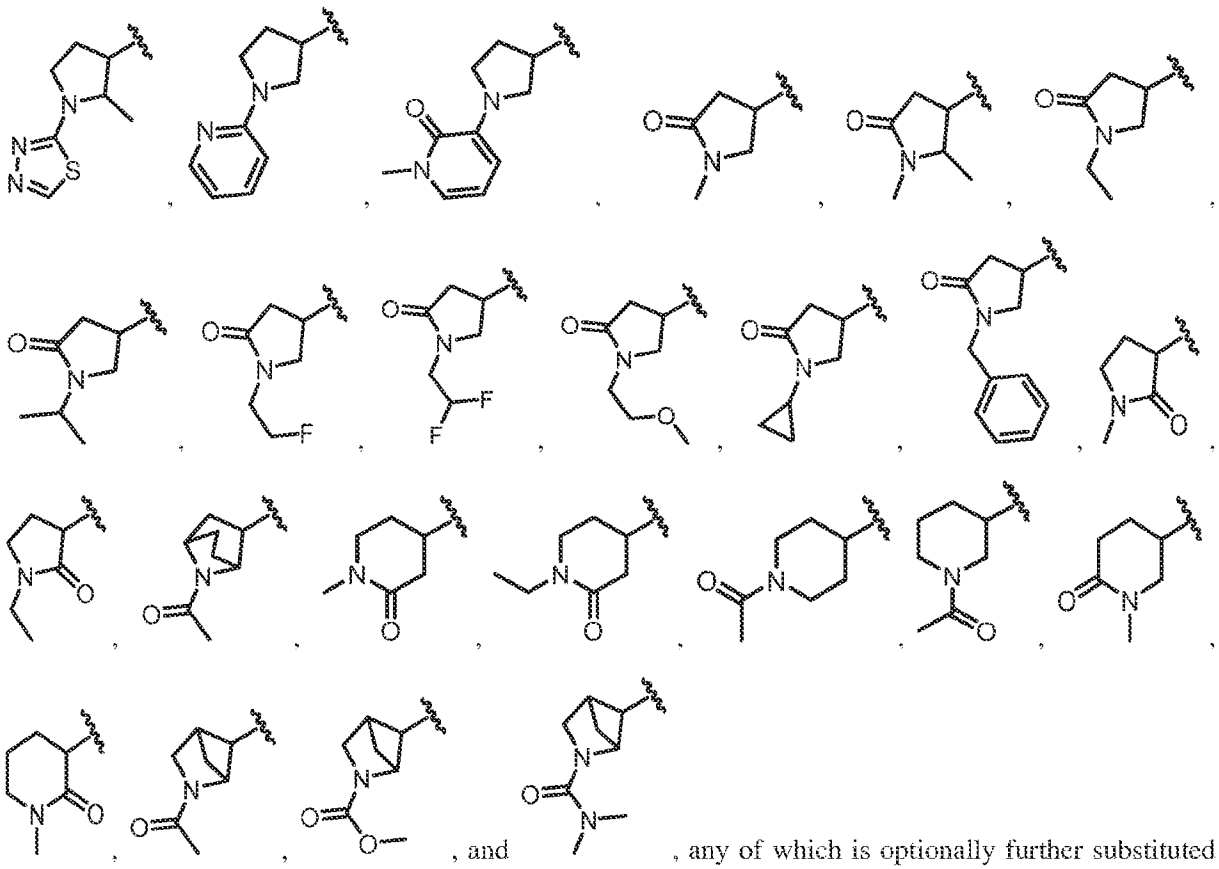






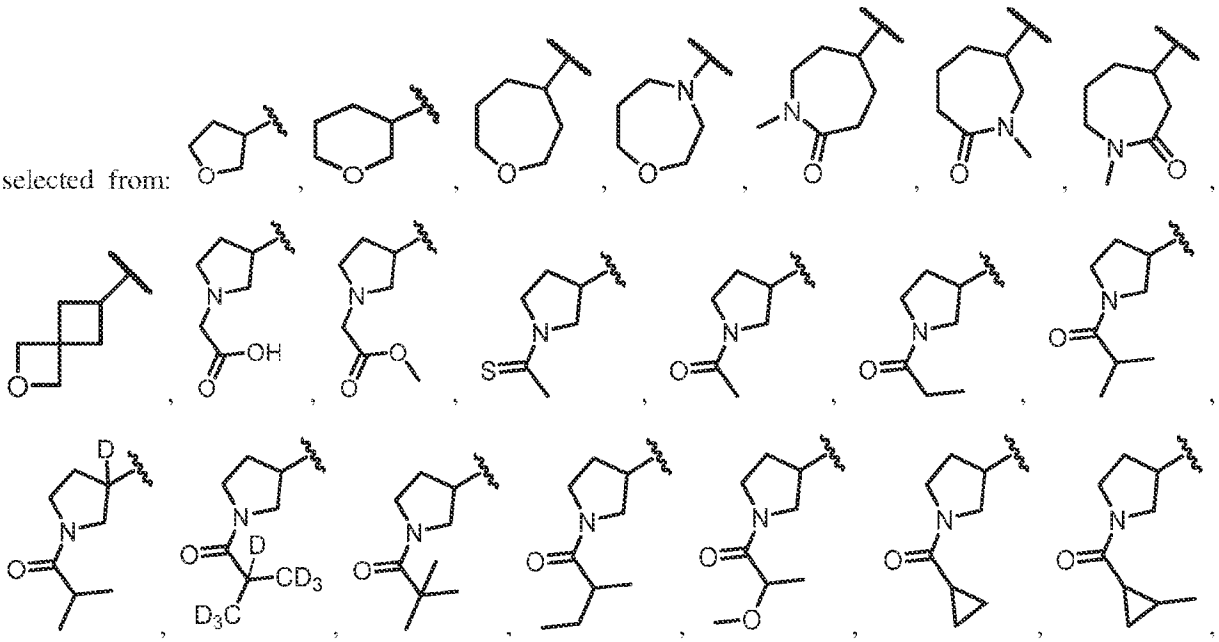


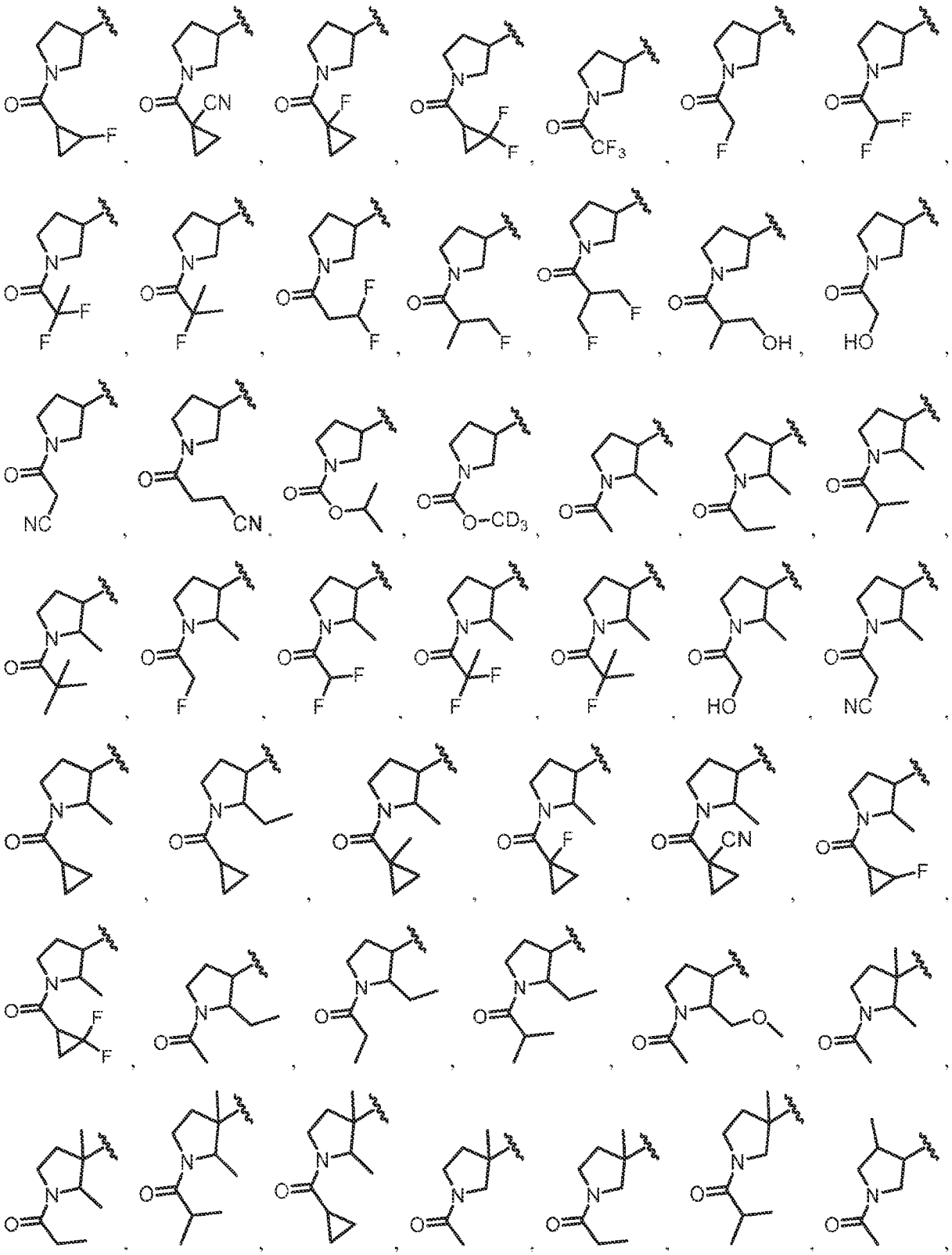


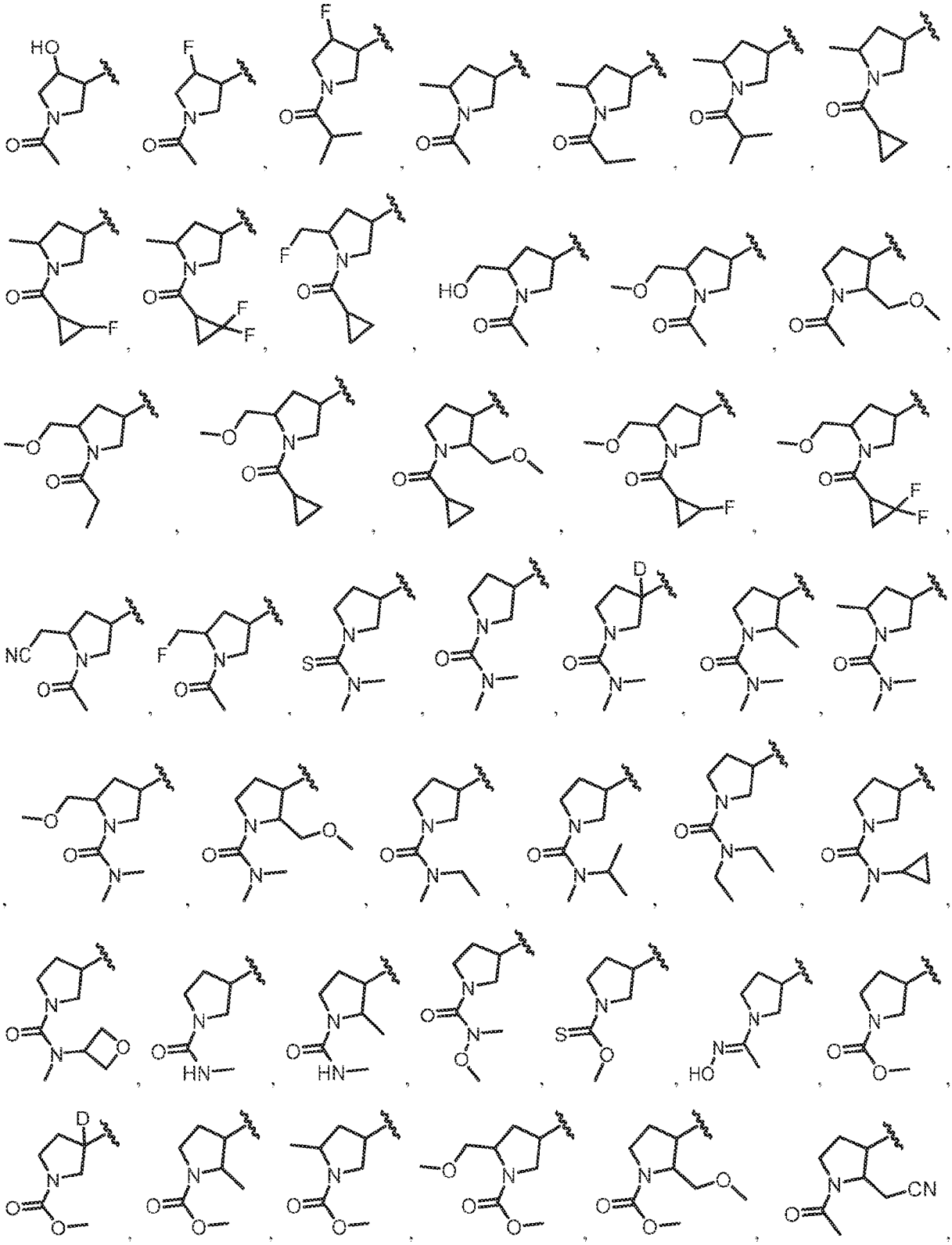


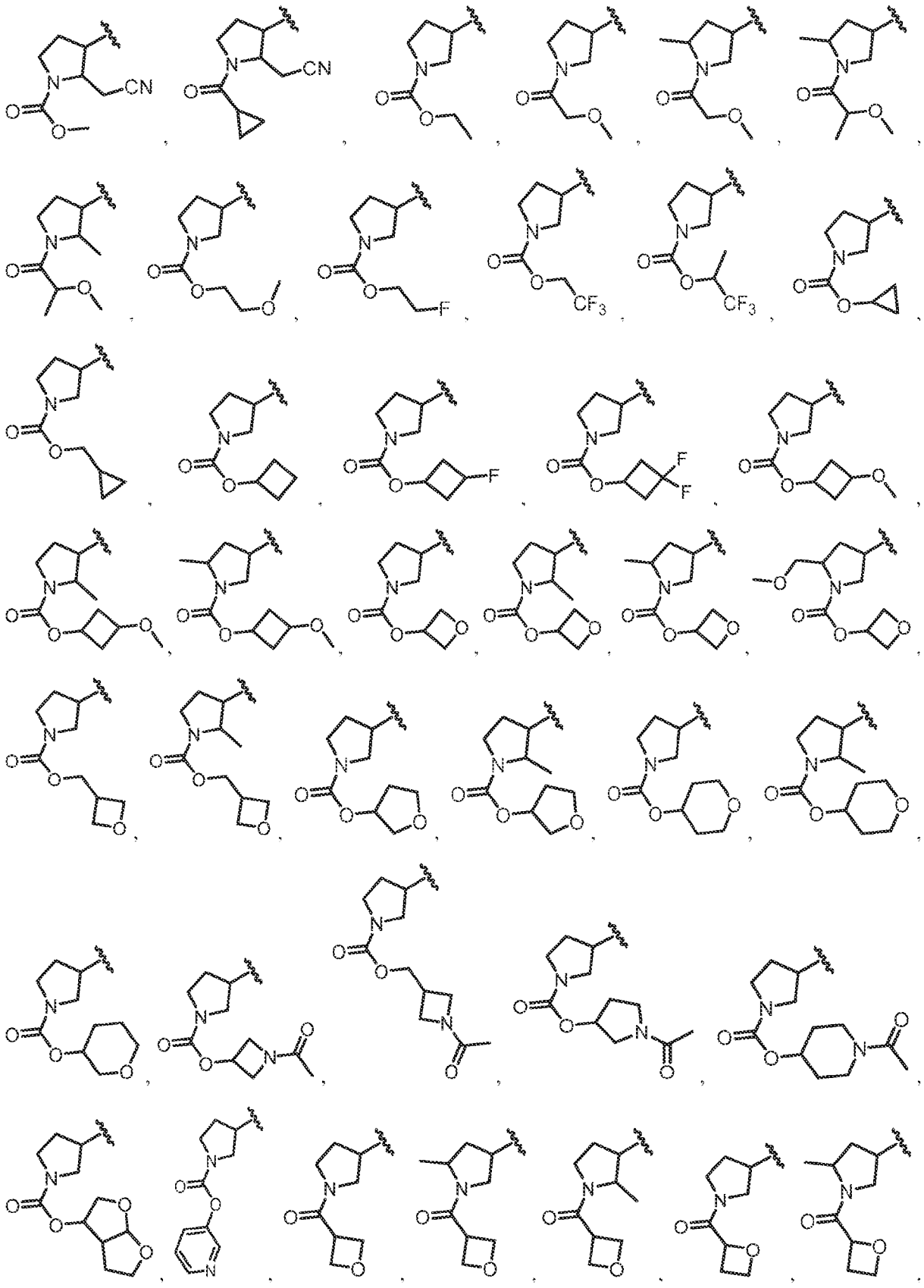
, any of which is optionally further substituted with one or more R^{10}.

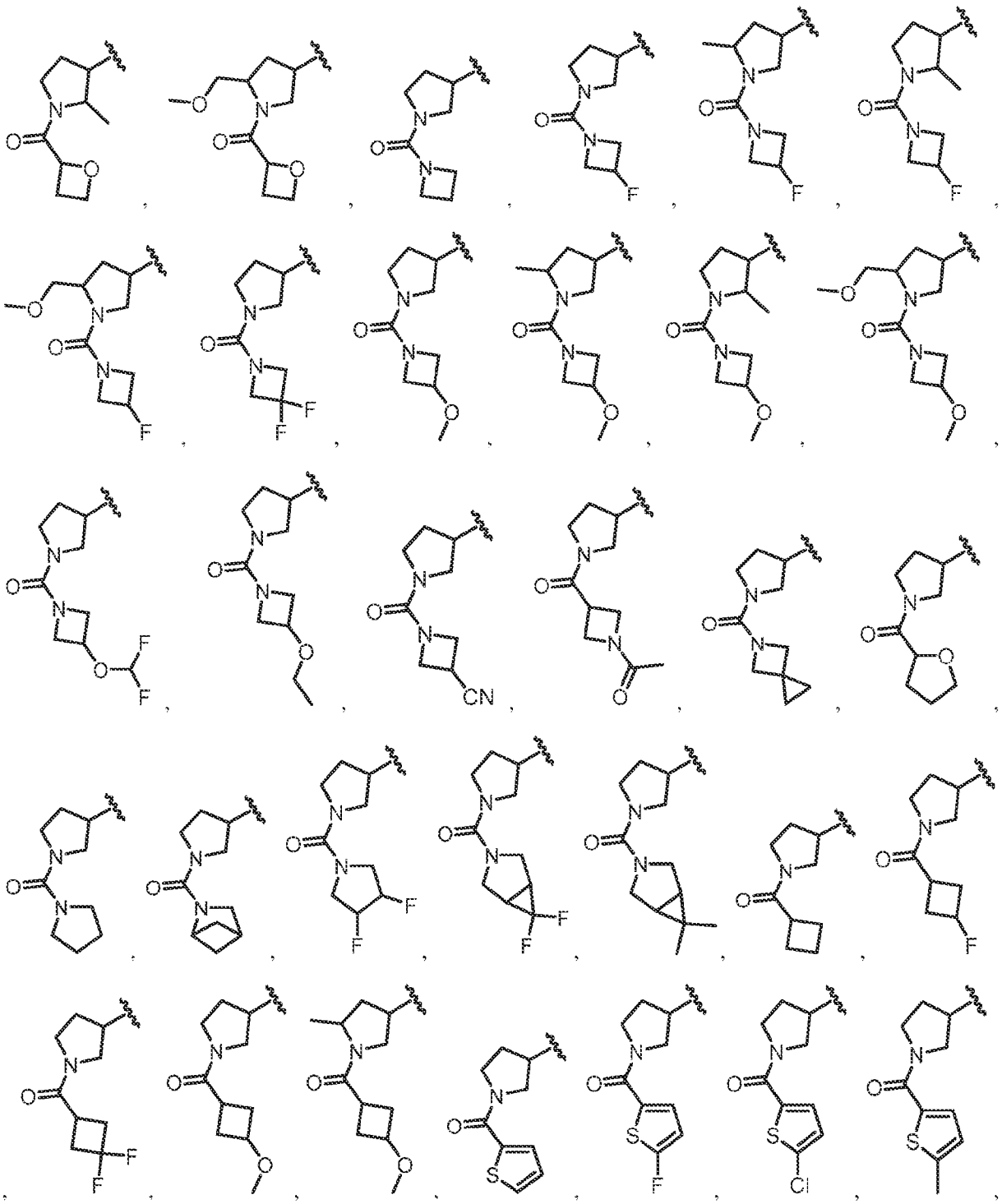
[0189] In some embodiments, for a compound according to Formula II', II'', II''-a, II-a, or III, R^3 is selected from:

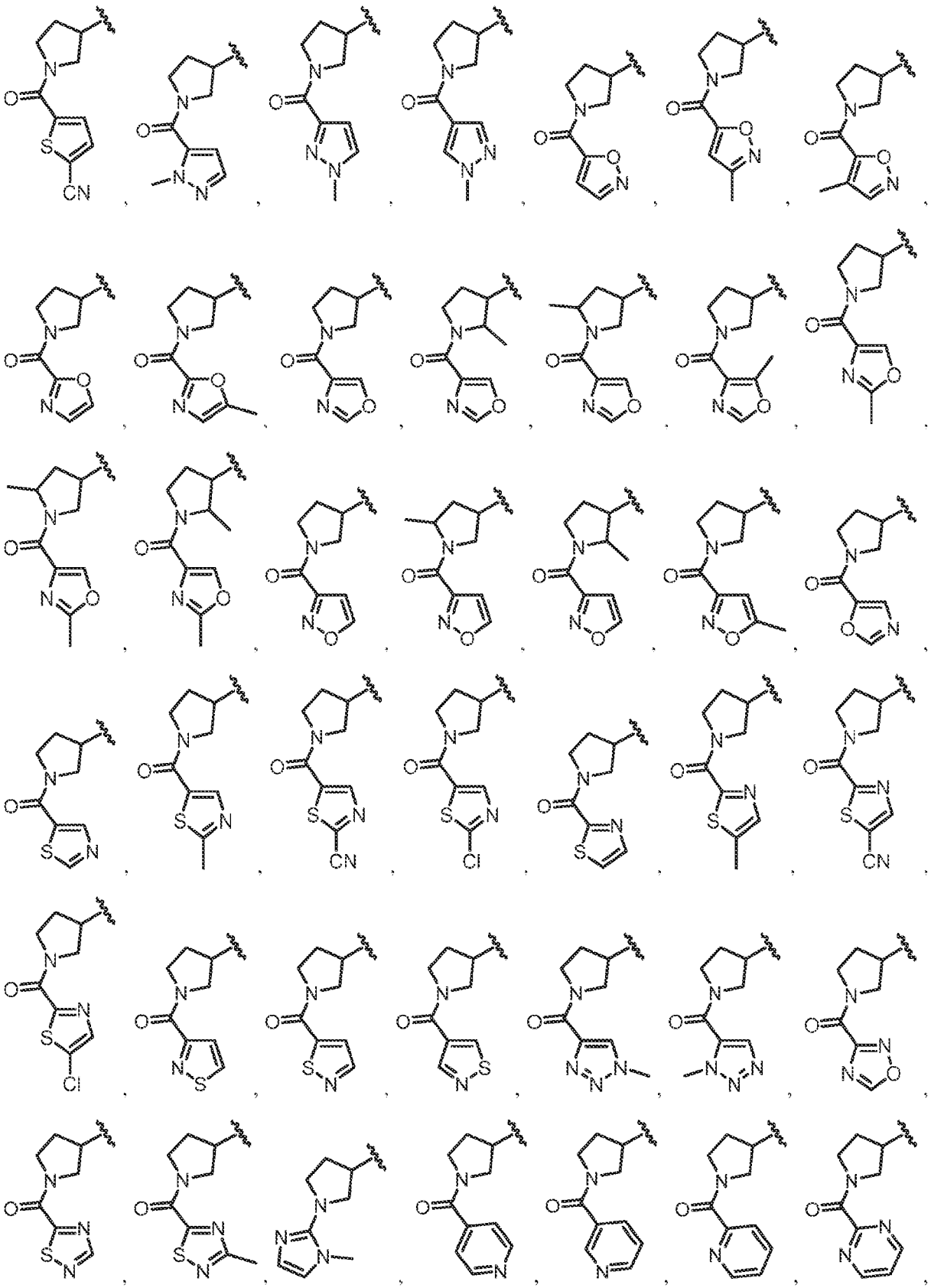


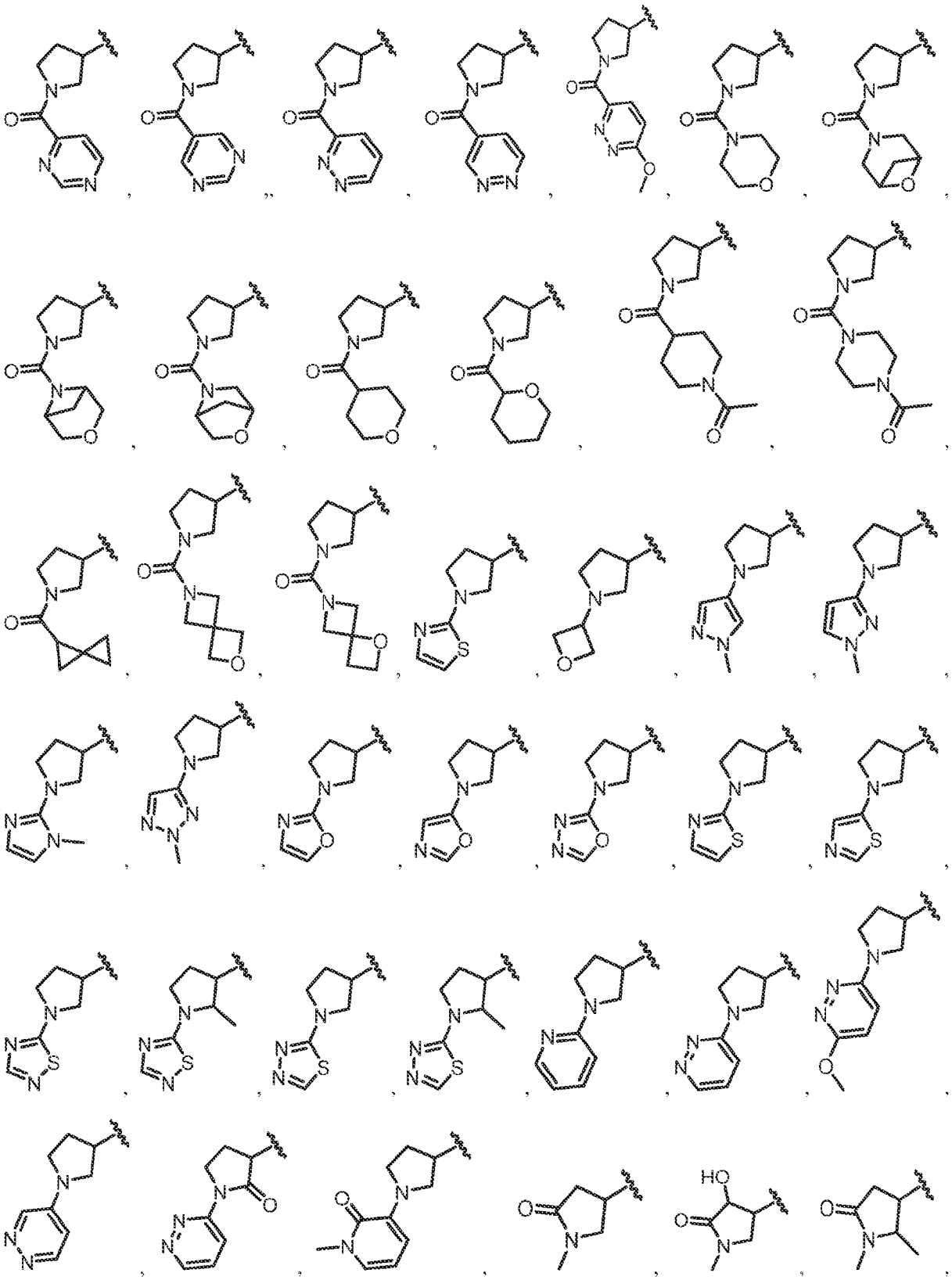


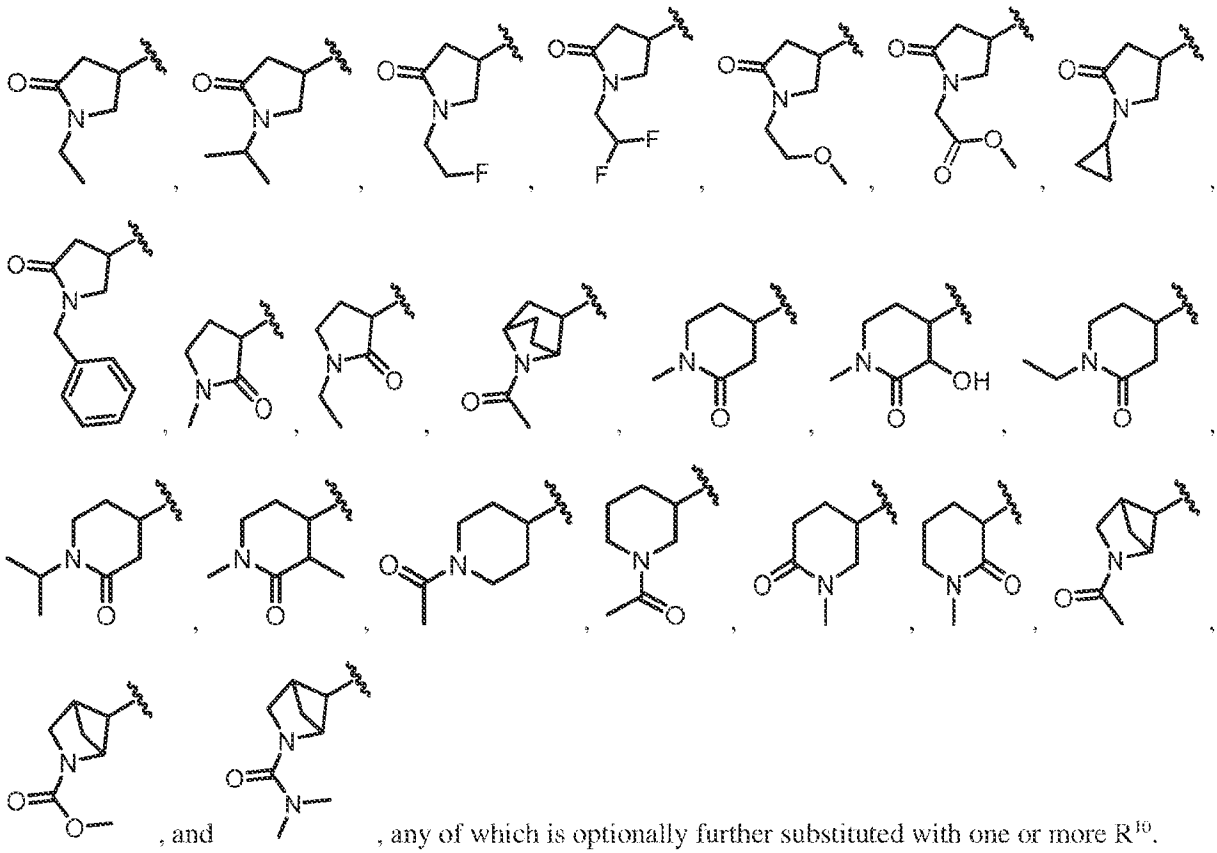






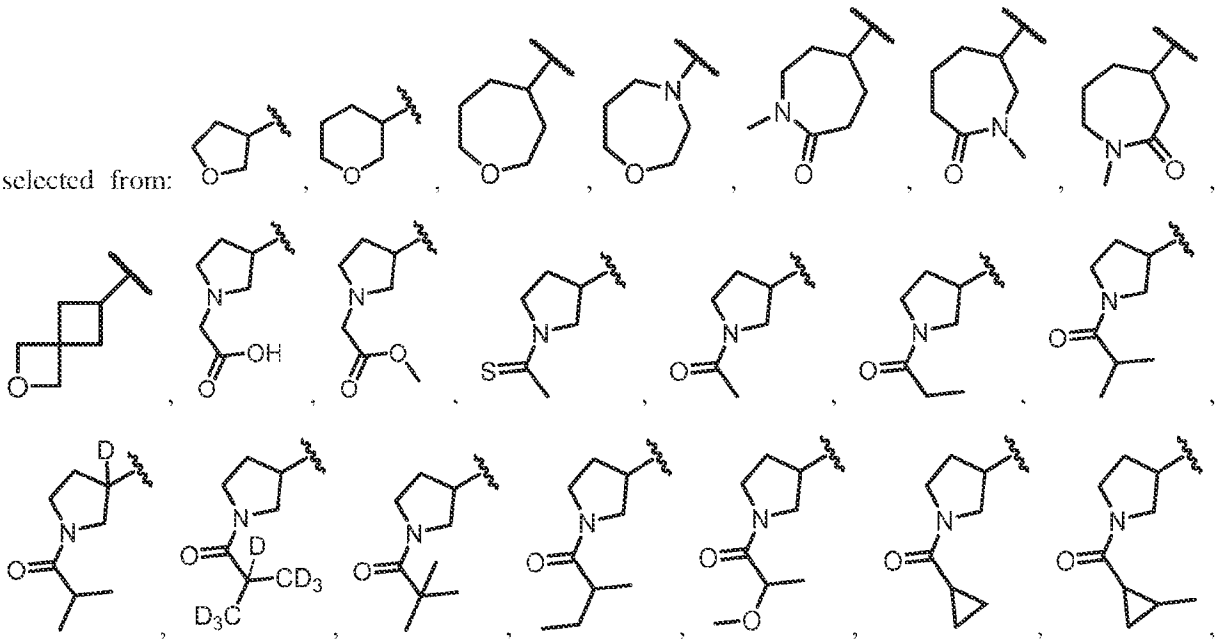


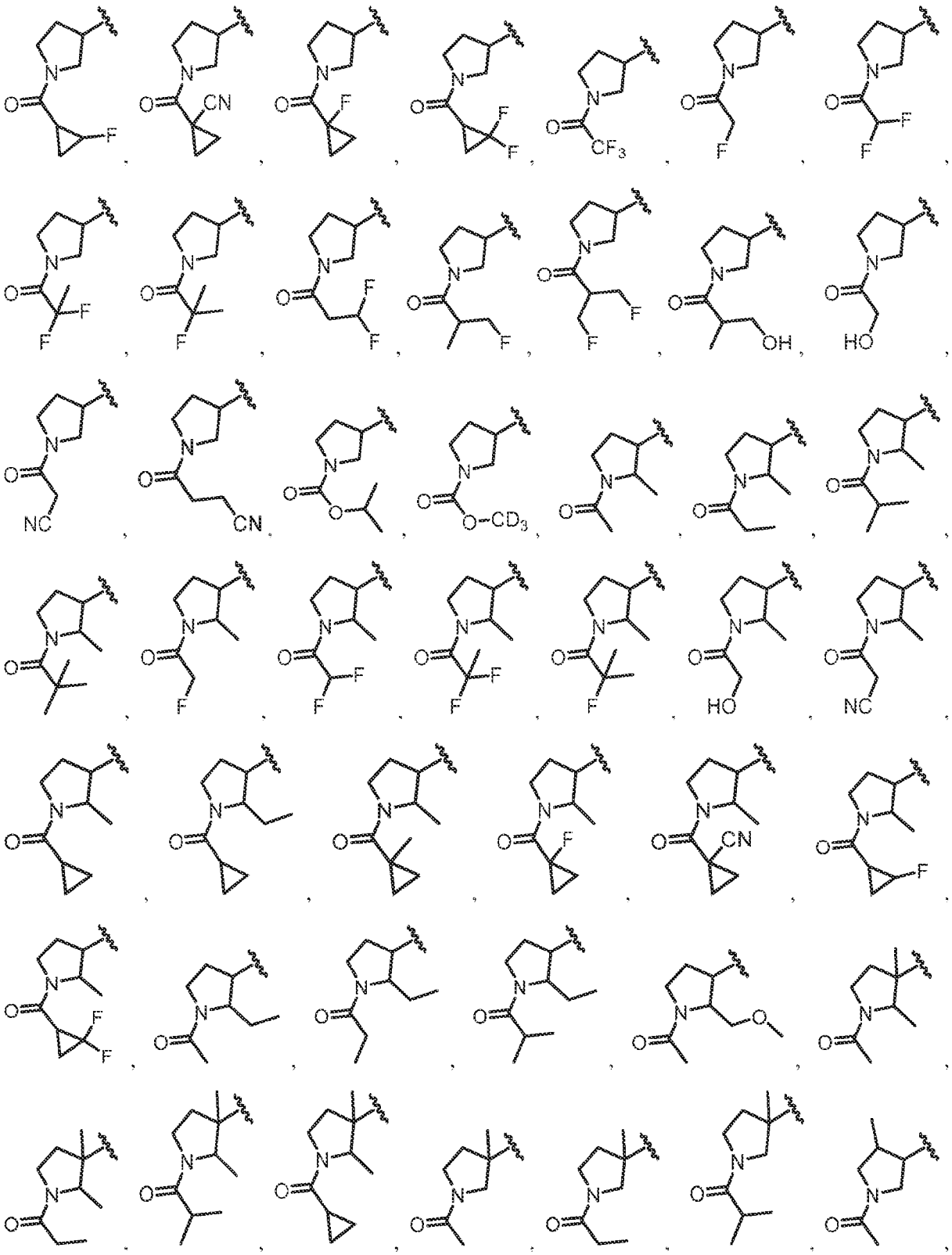


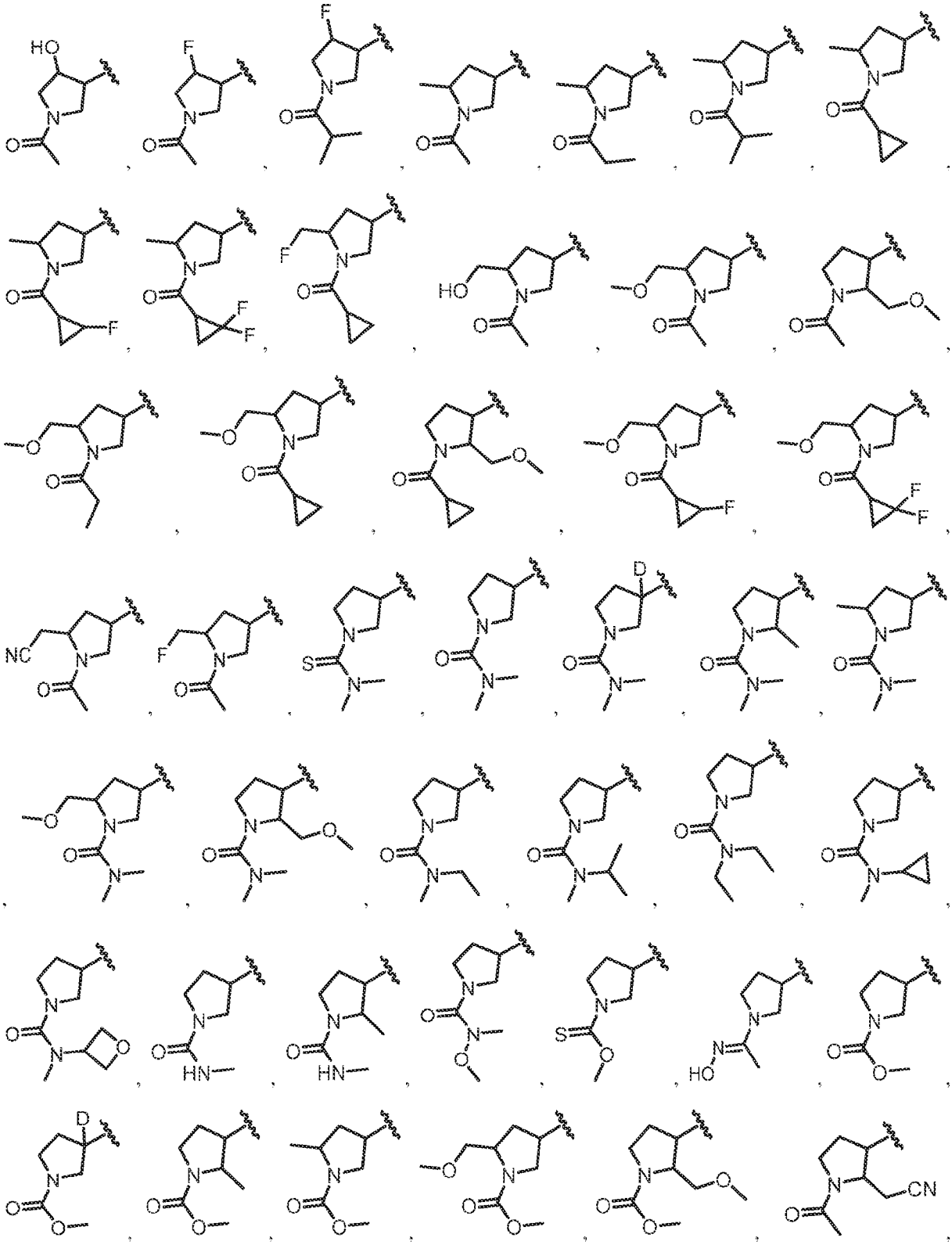


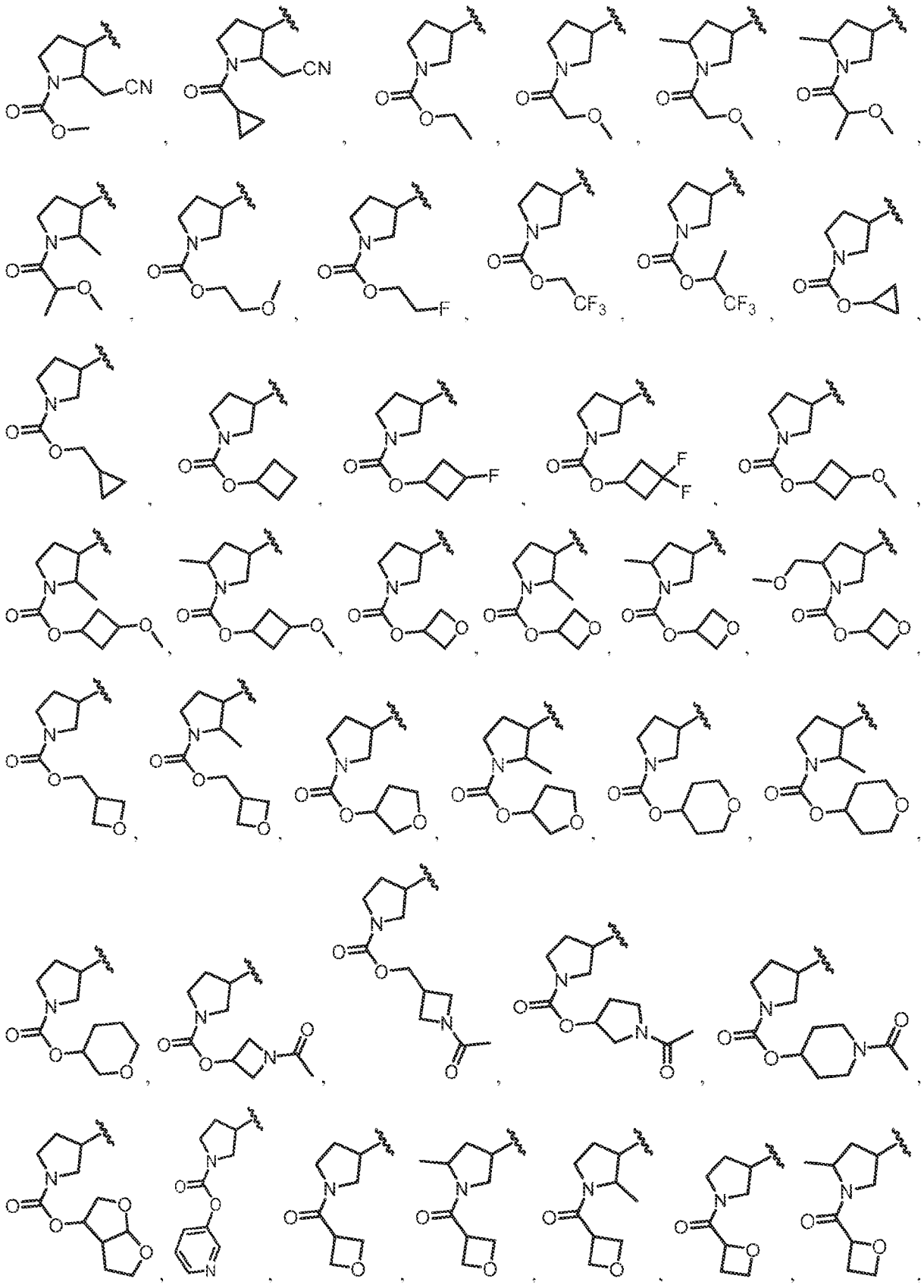
, and , any of which is optionally further substituted with one or more R^{10}.

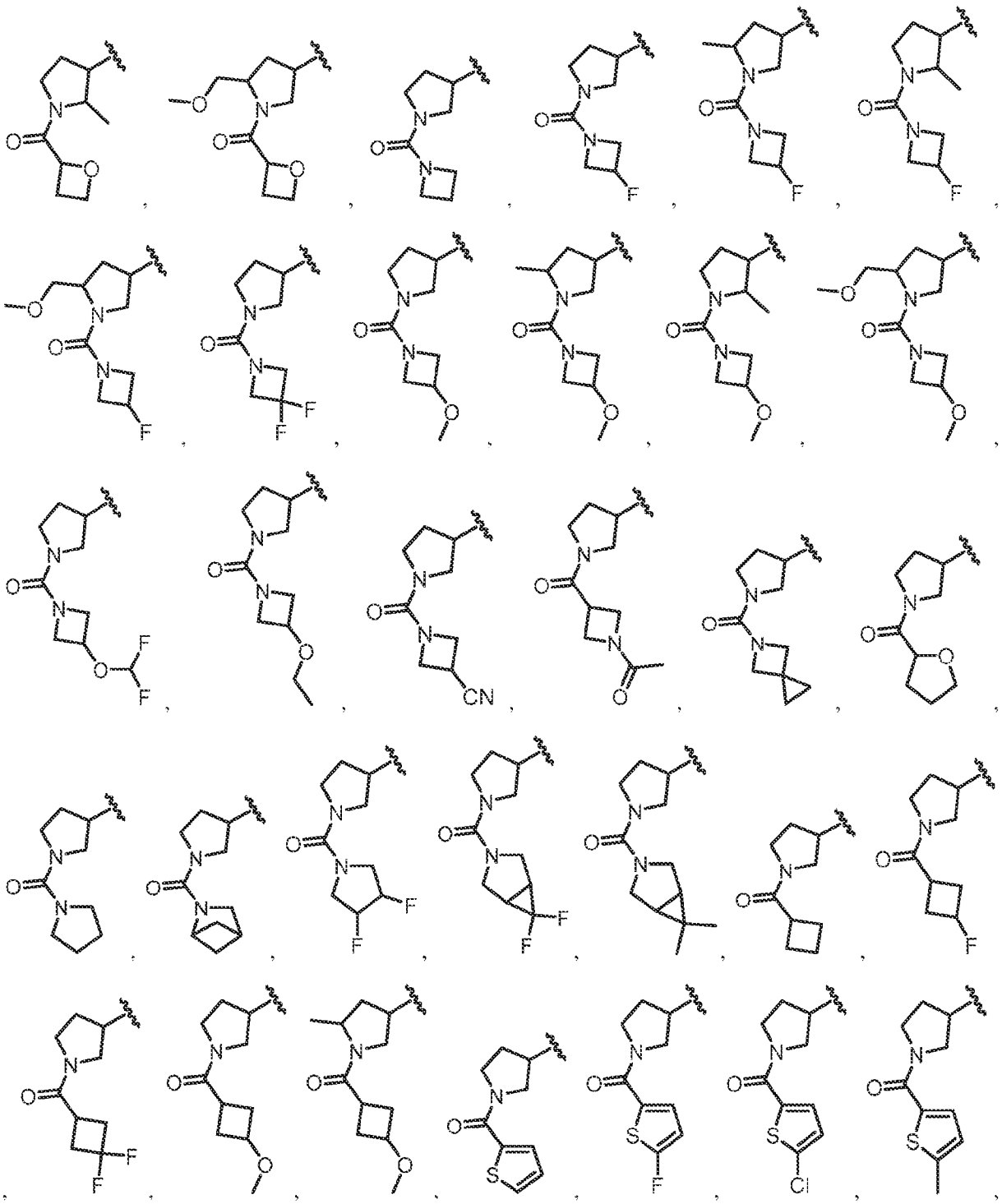
[0190] In some embodiments, for a compound according to Formula II, II', II'', II''-a, II-a, or III, R^3 is selected from:

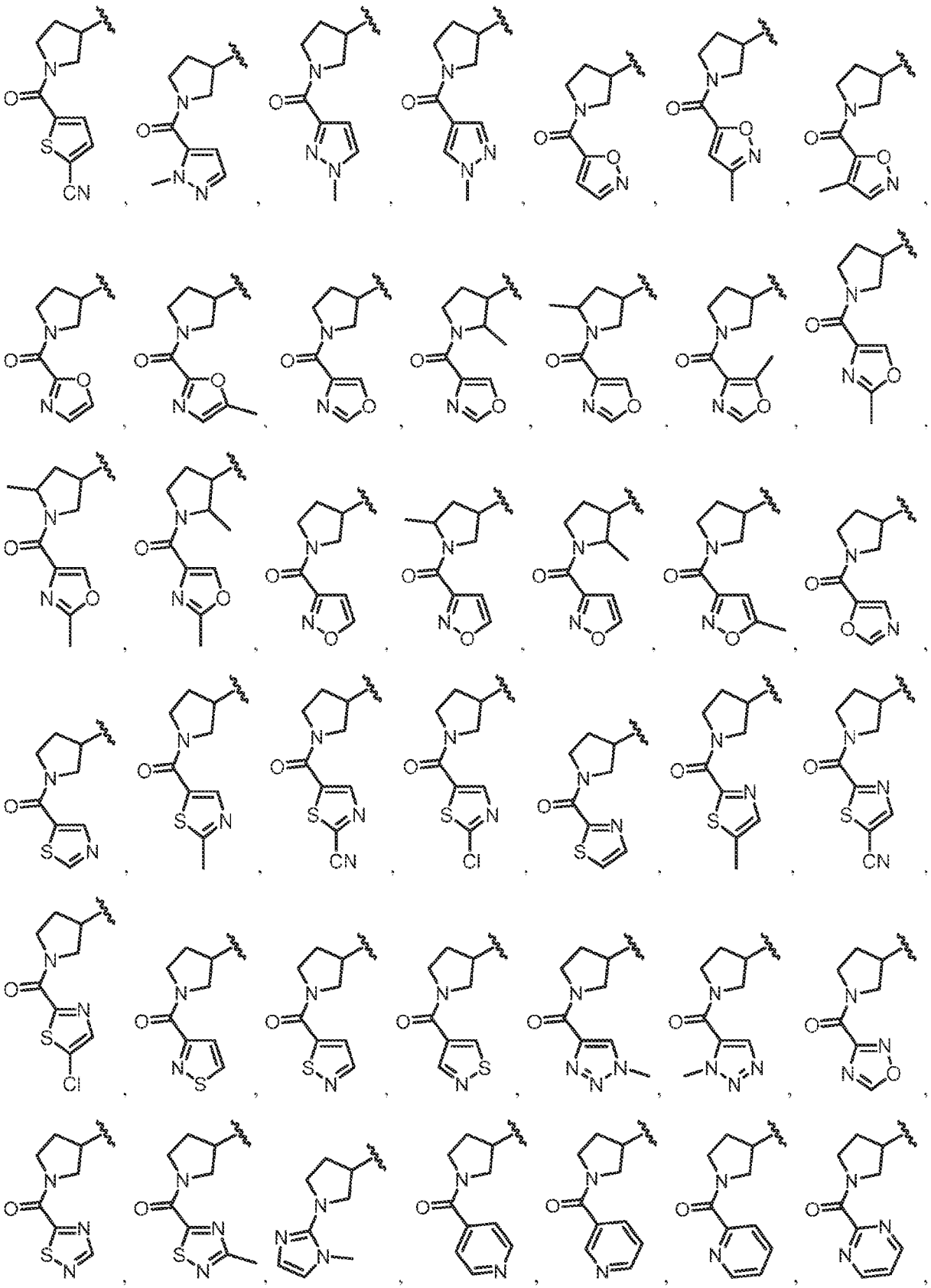


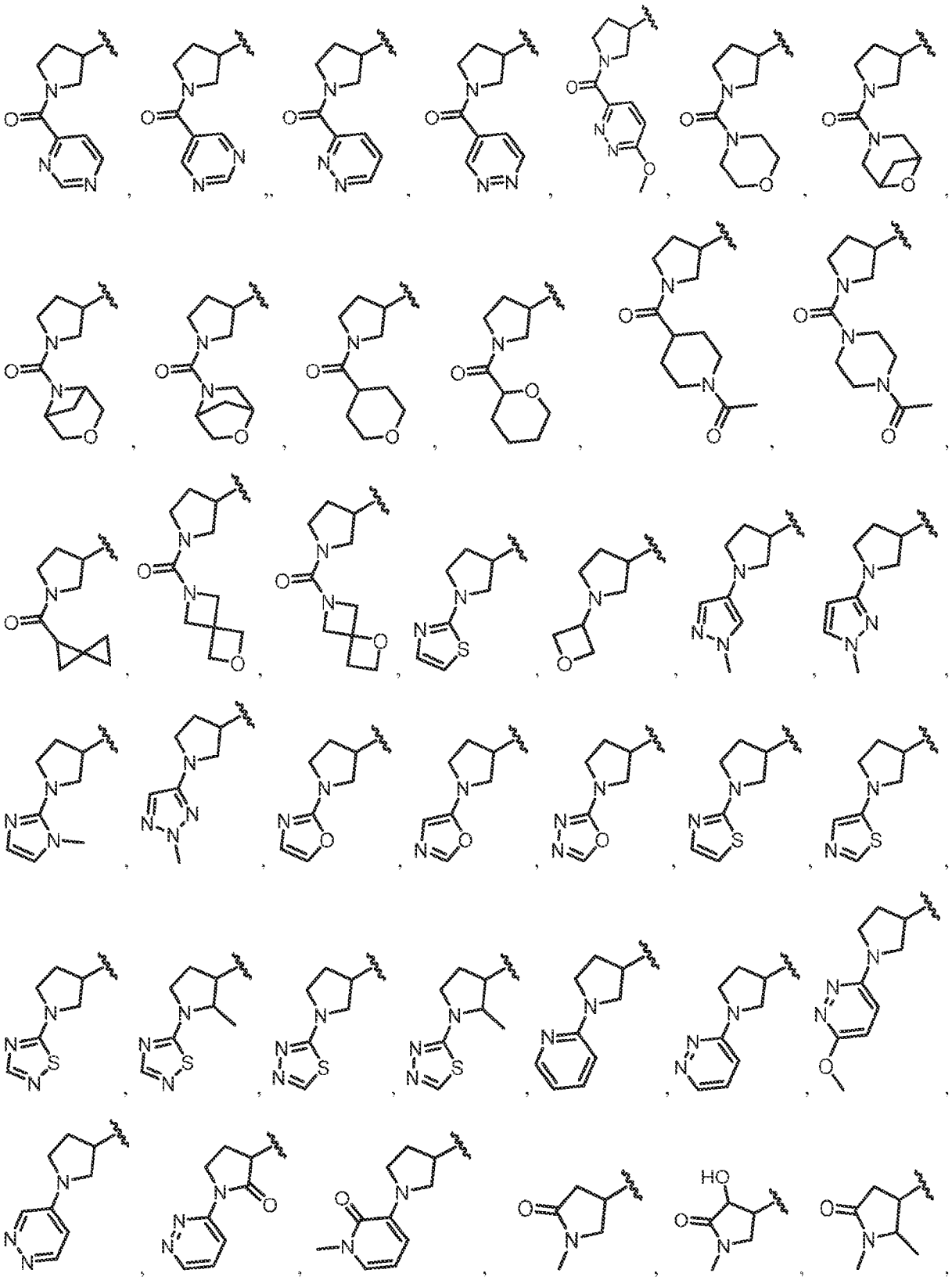


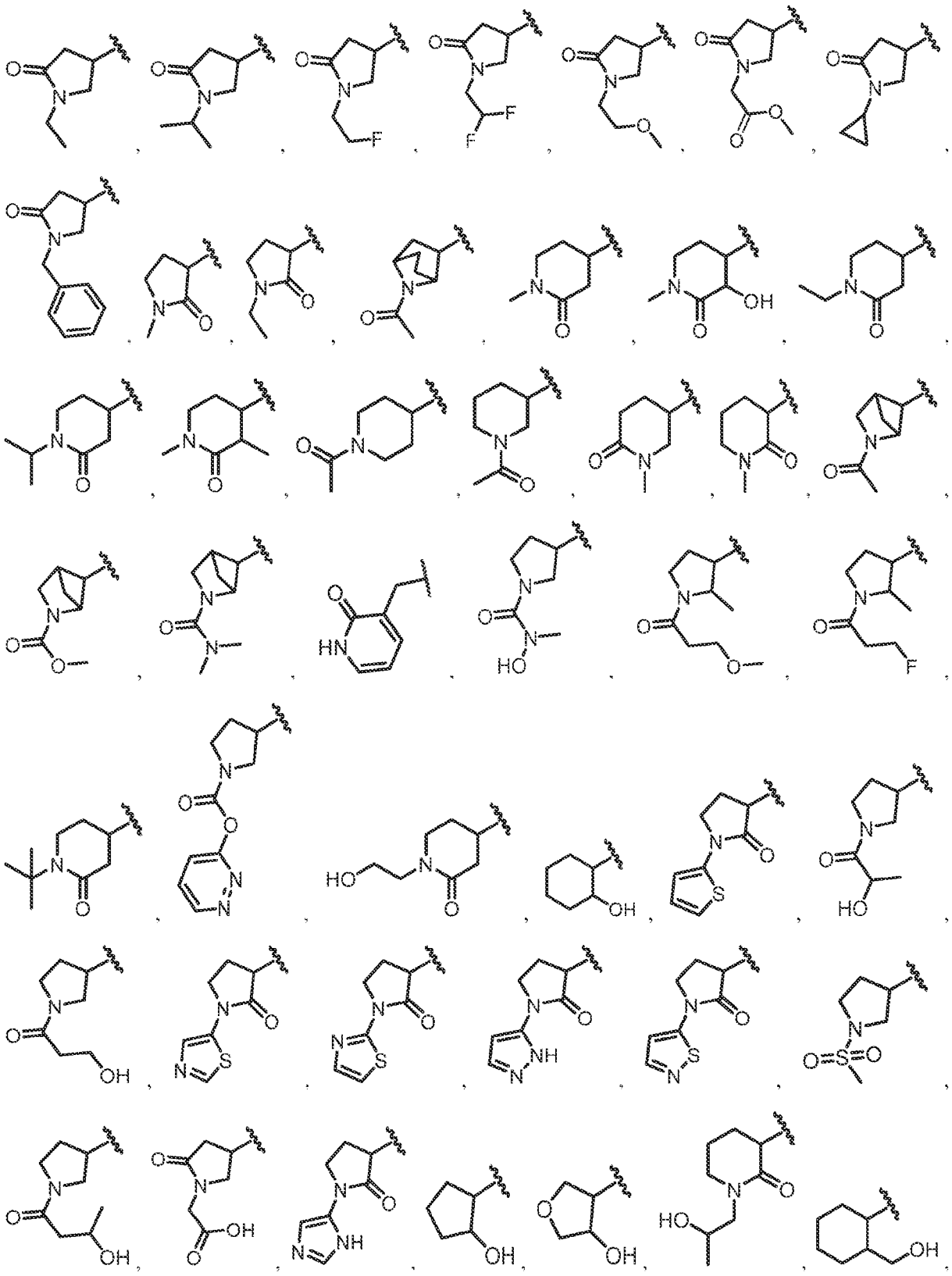


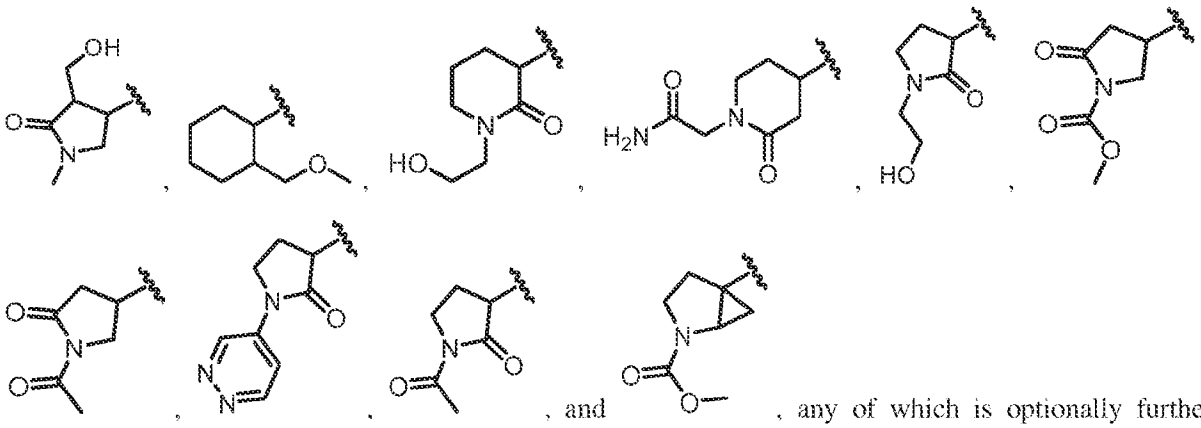






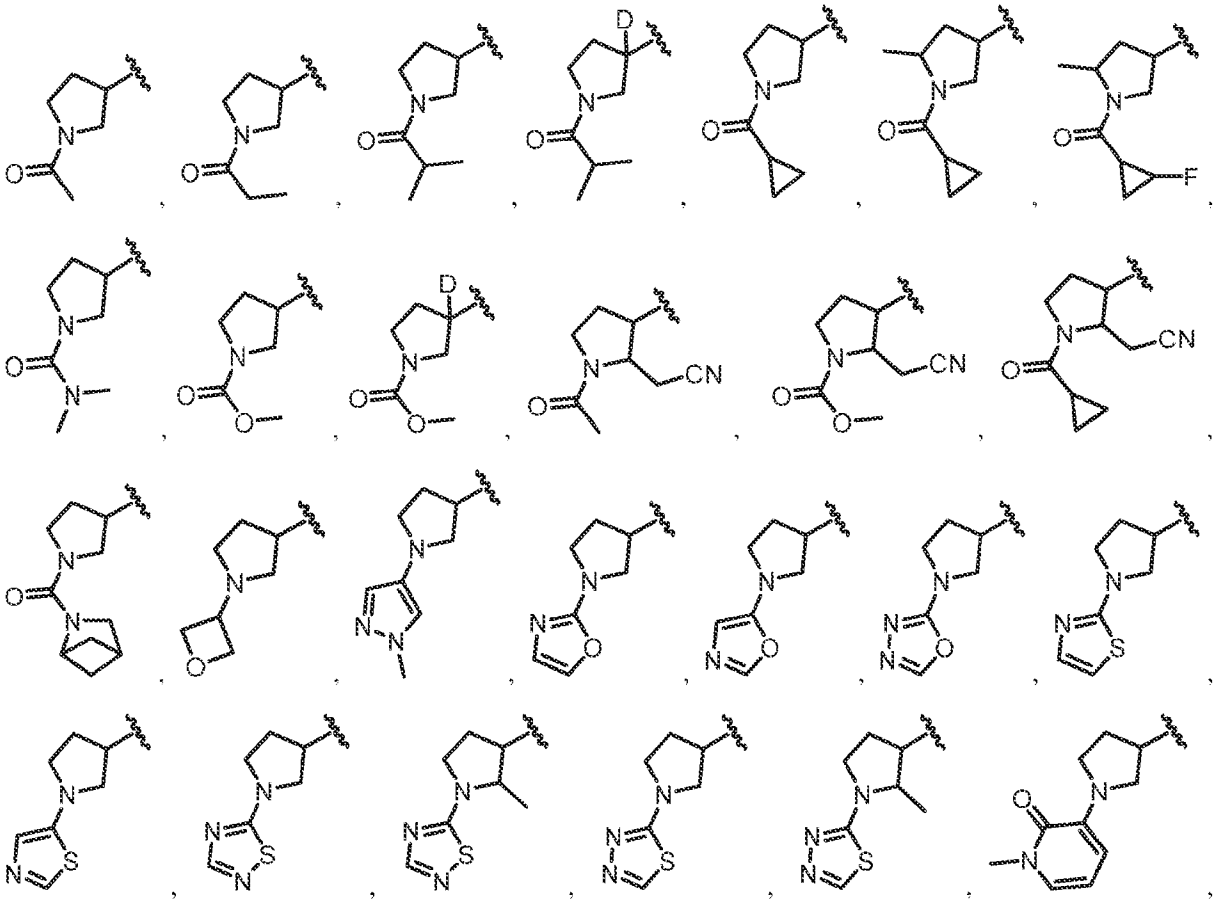


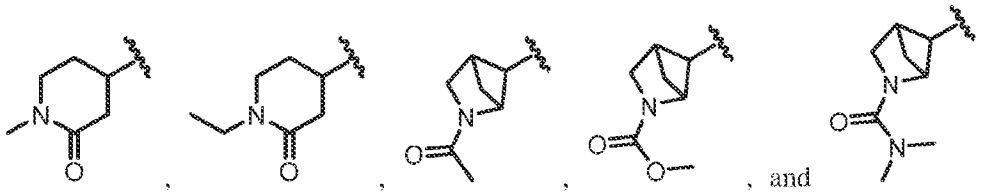




, and , any of which is optionally further substituted with one or more R^{10}.

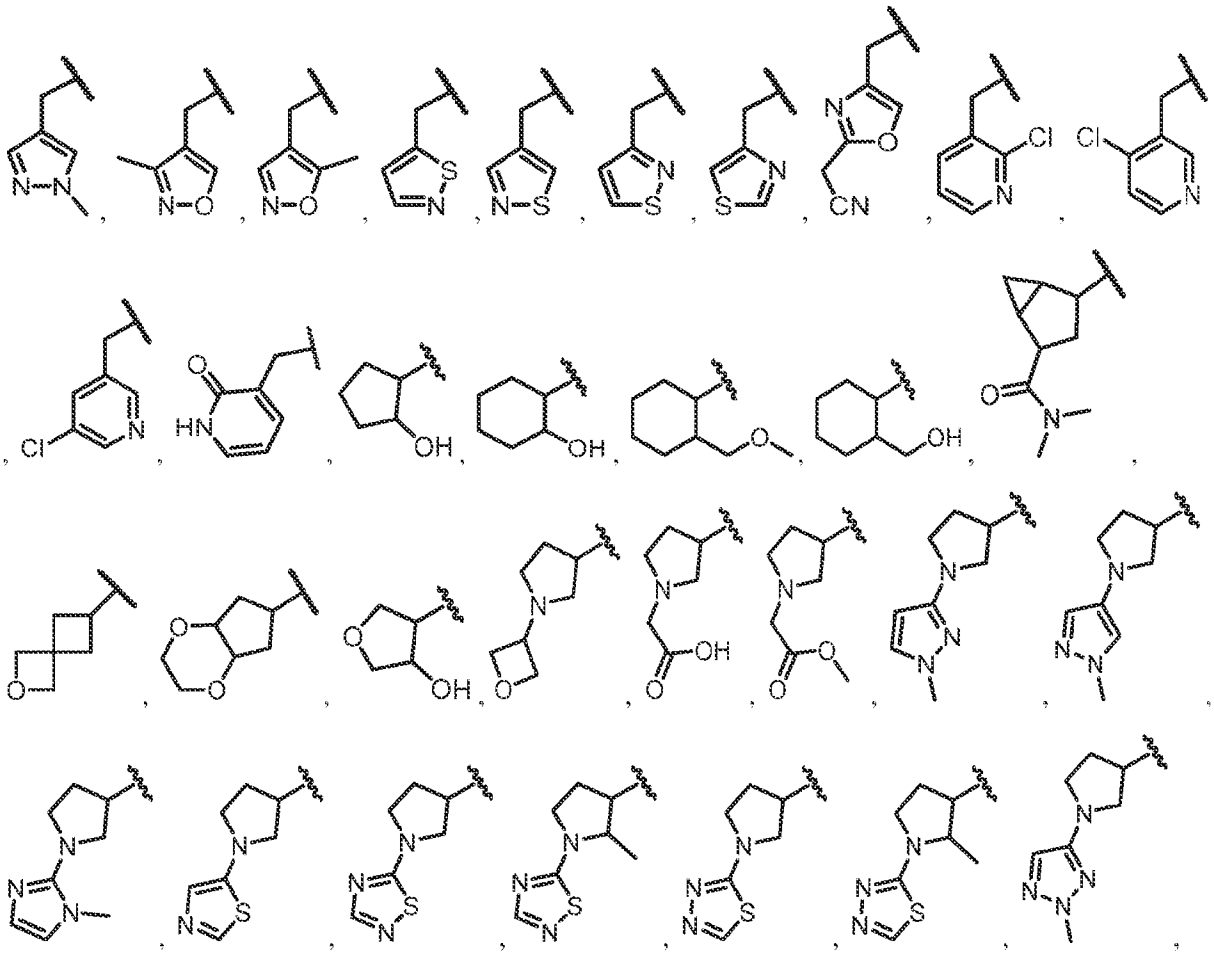
[0191] In some embodiments, for a compound according to Formula II', II-a, or III, R^3 is selected from:

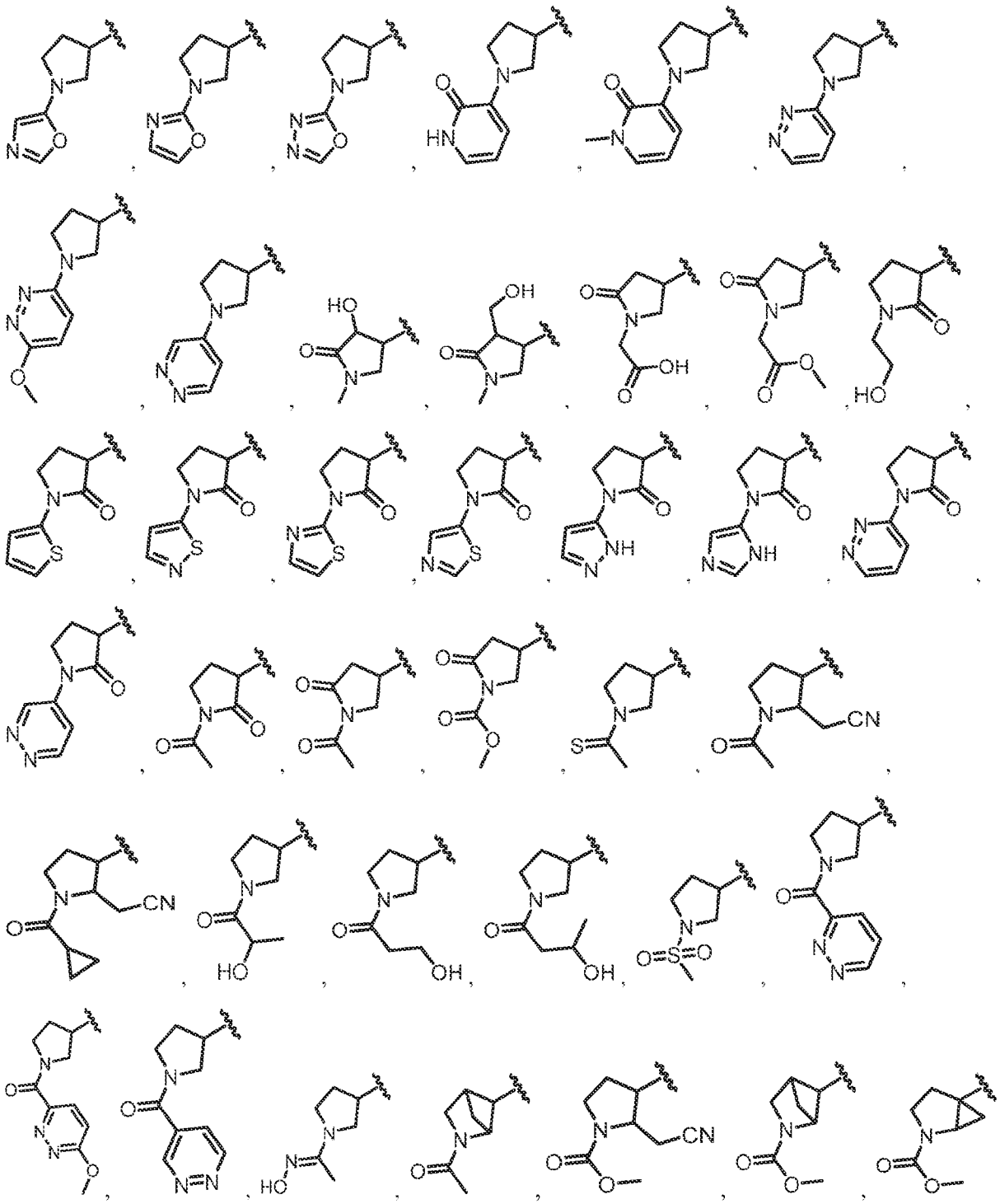


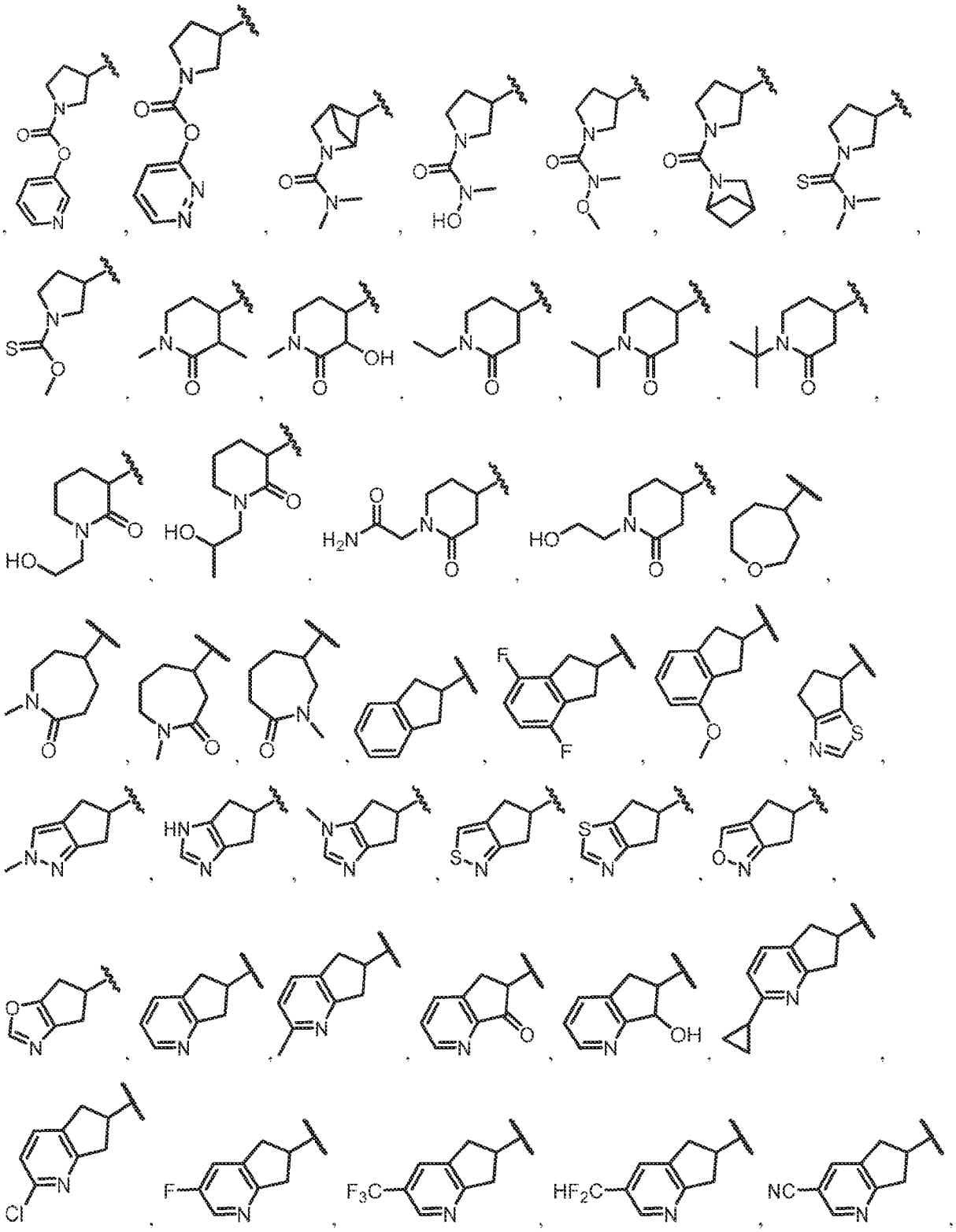


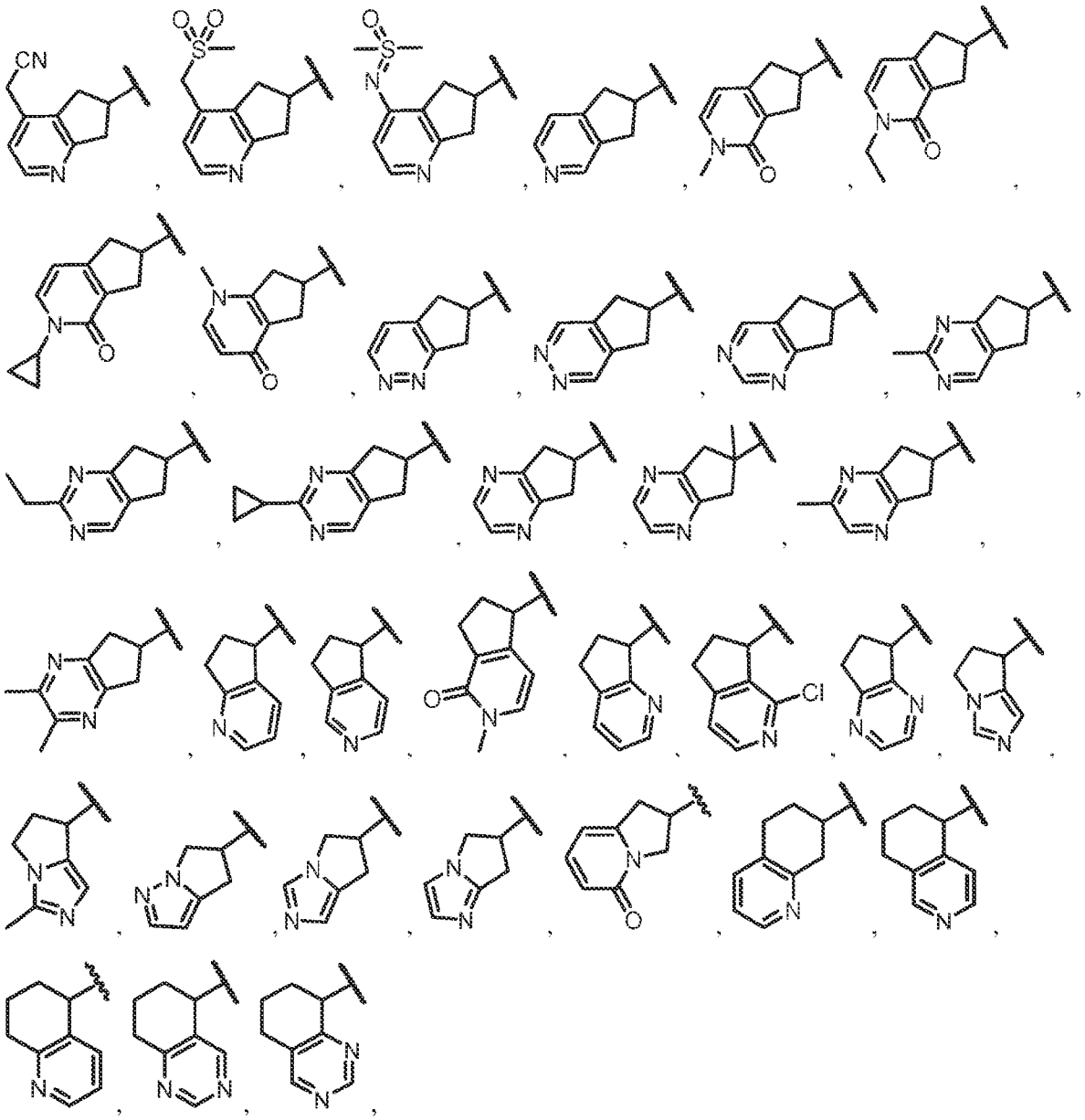
, any of which is optionally further substituted with one or more R^{10}.

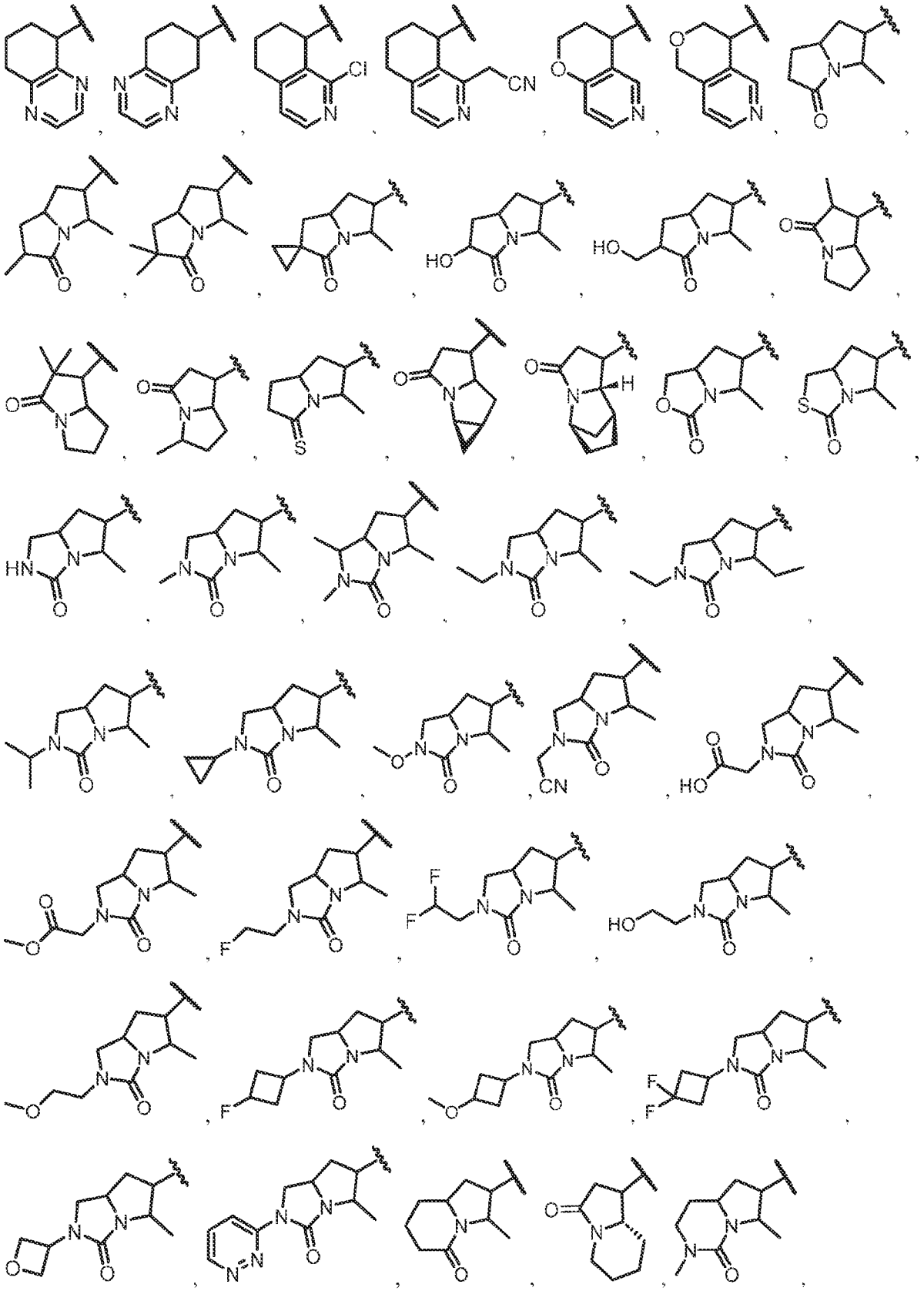
[0192] In some embodiments according to Formula II or Formula III, R^3 is selected from:

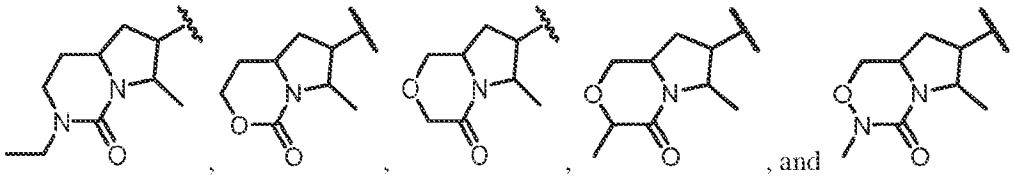






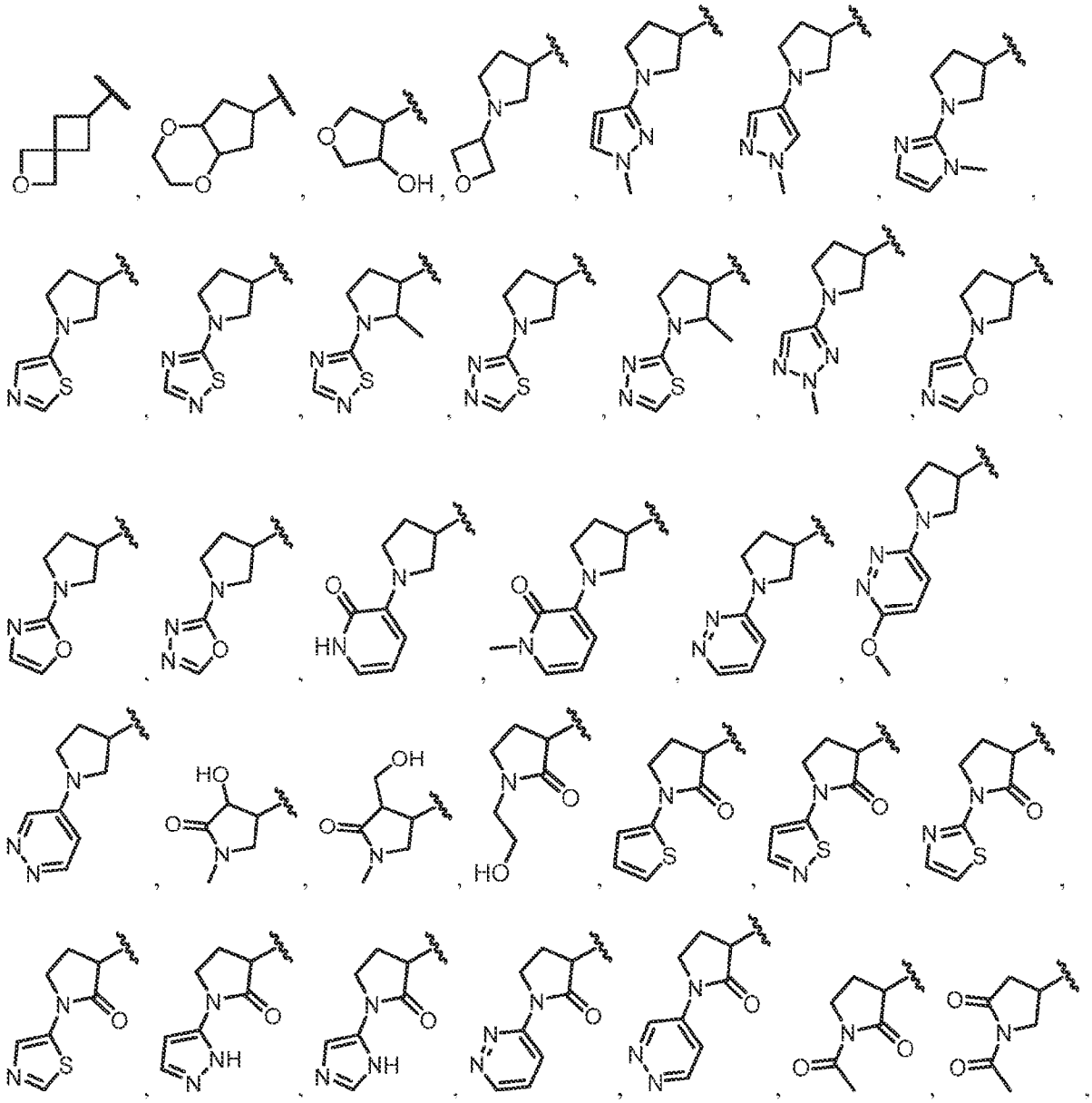


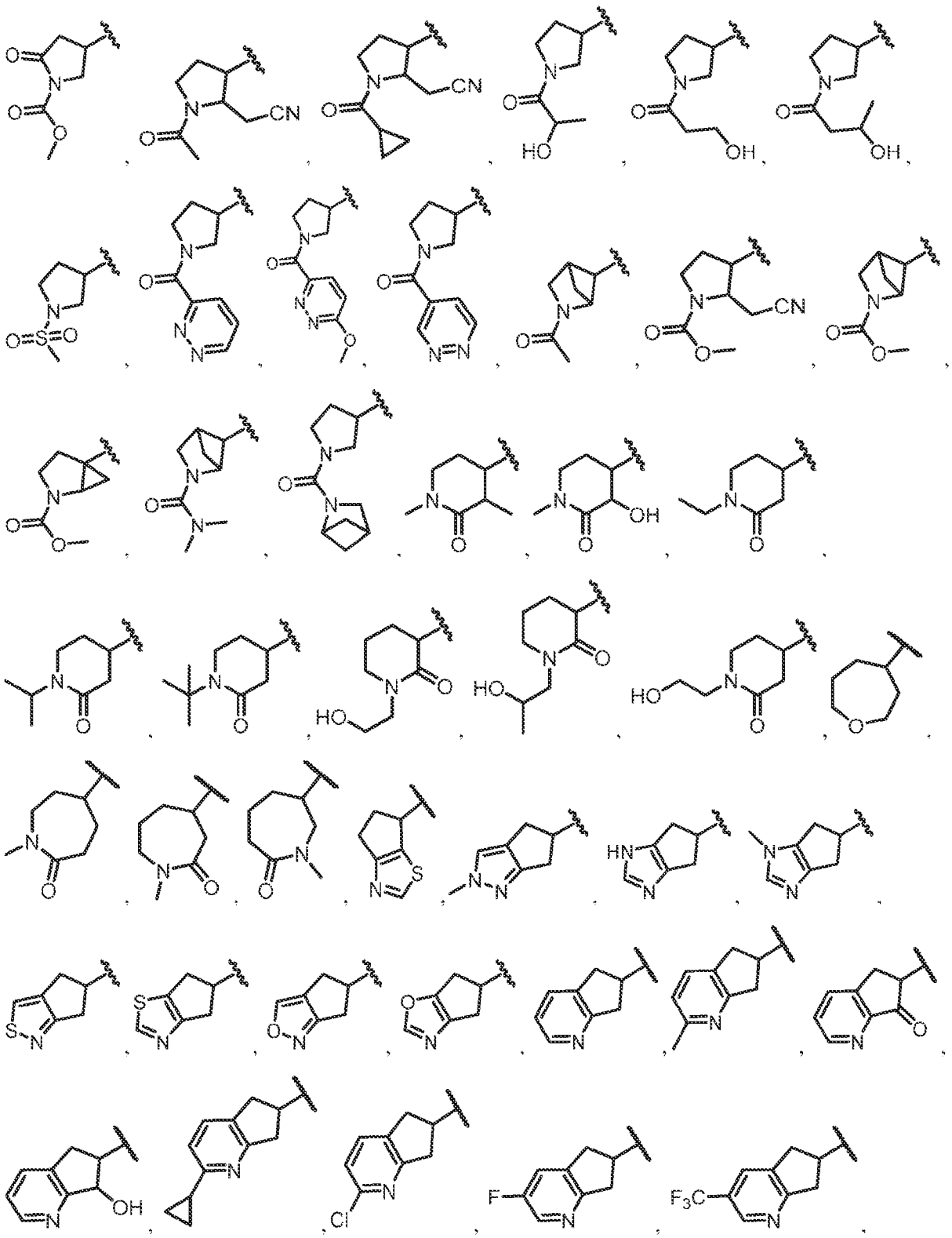


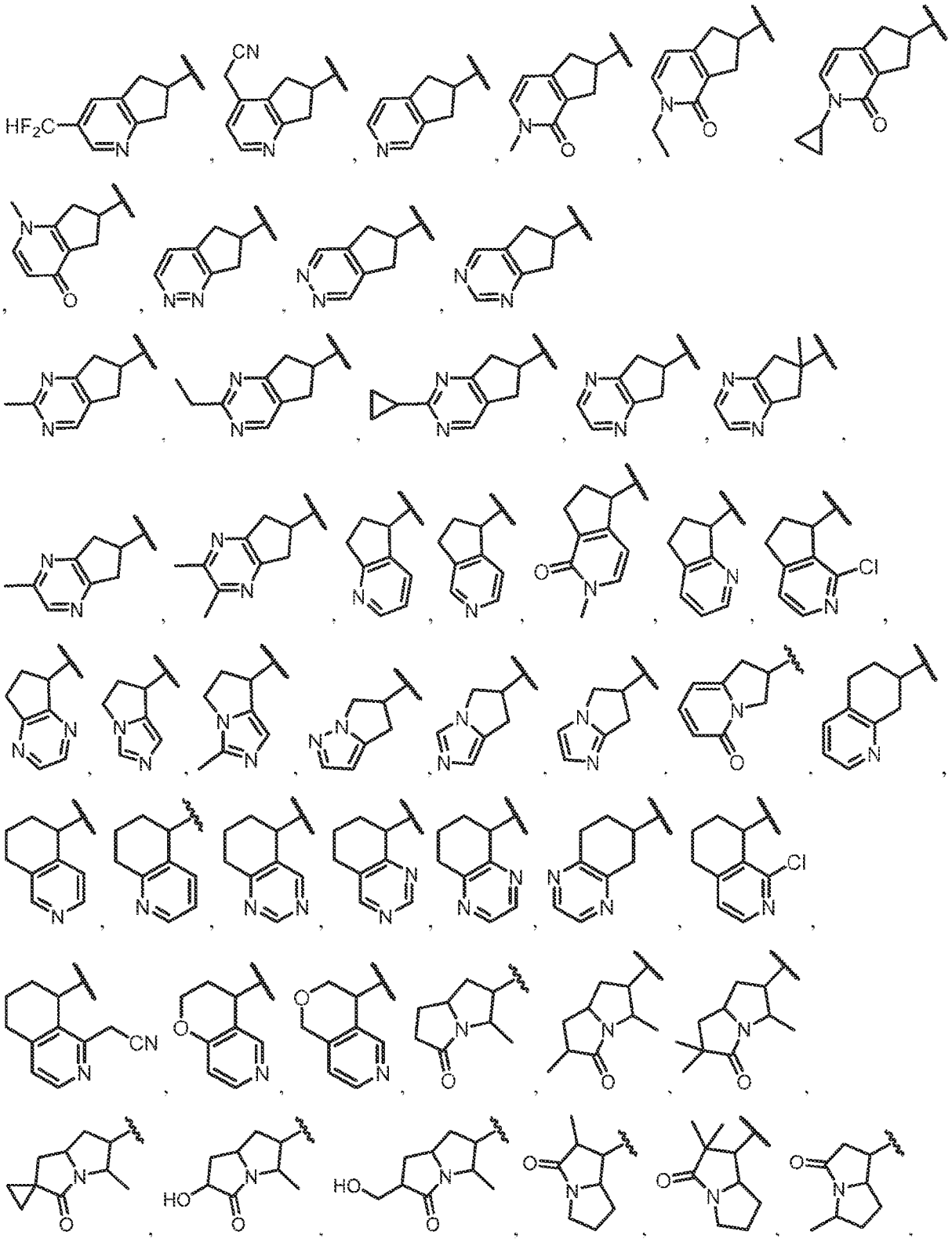


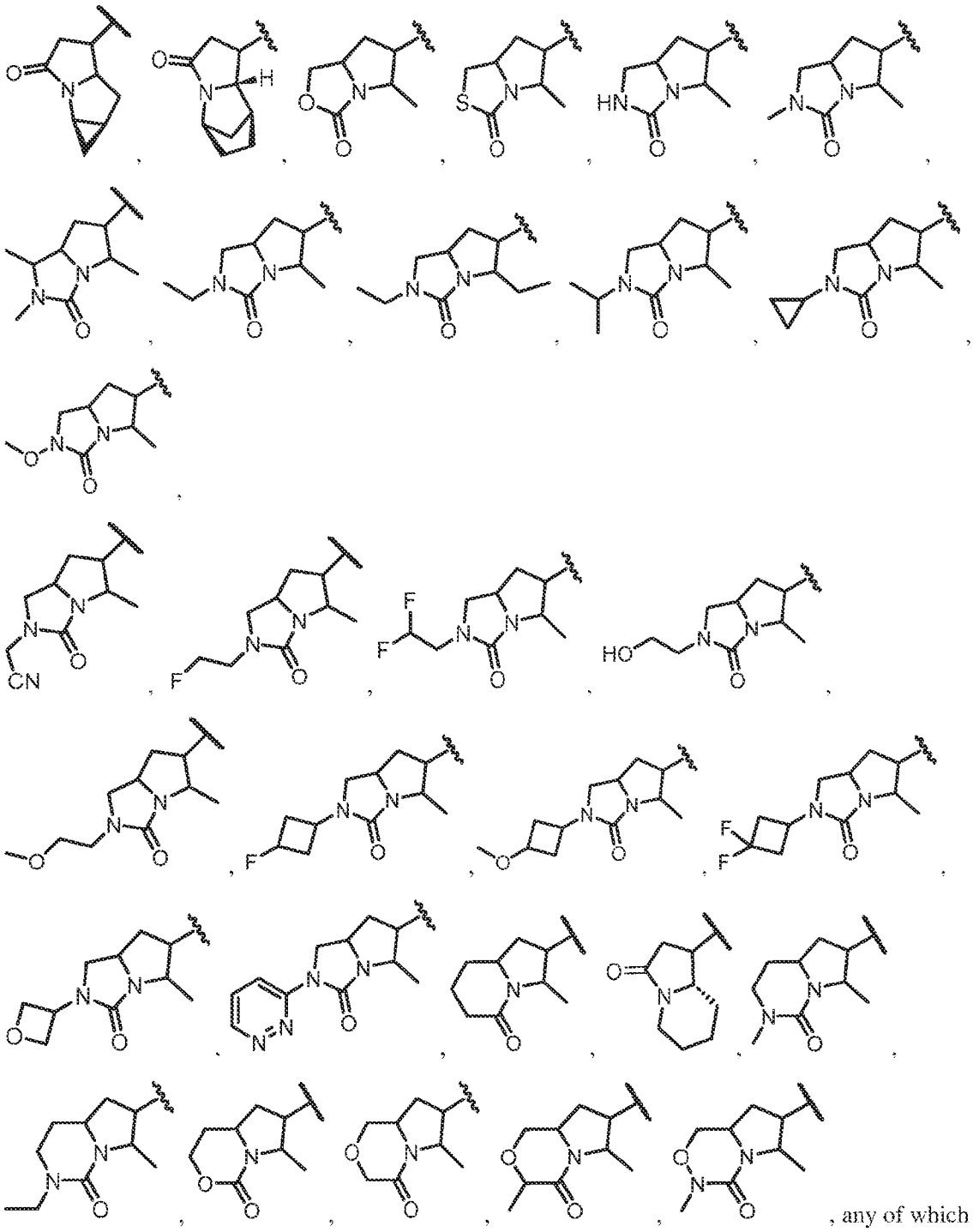
optionally further substituted with one or more R^{10}.

[0193] In some embodiments according to Formula II', R^3 is selected from:



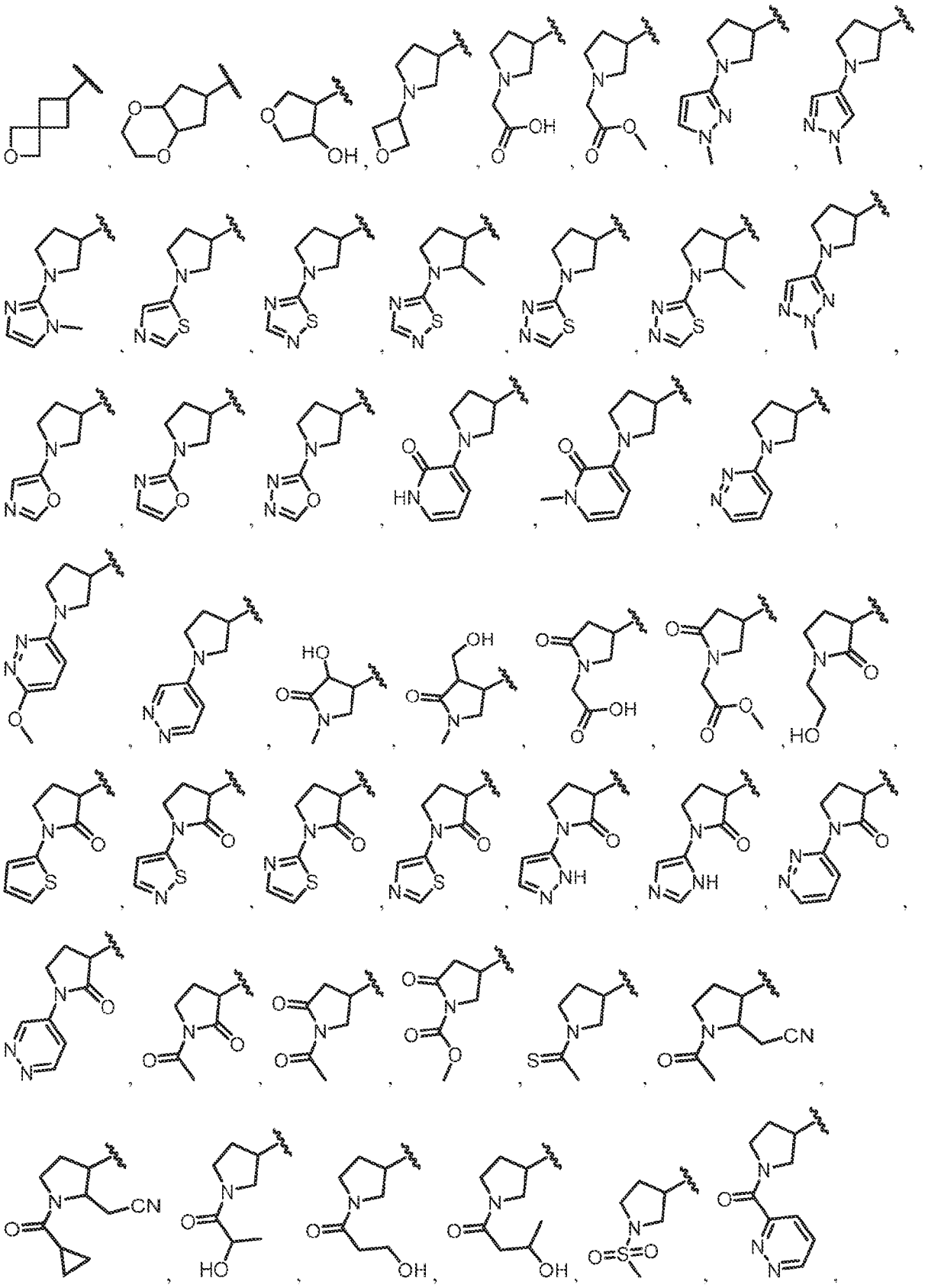


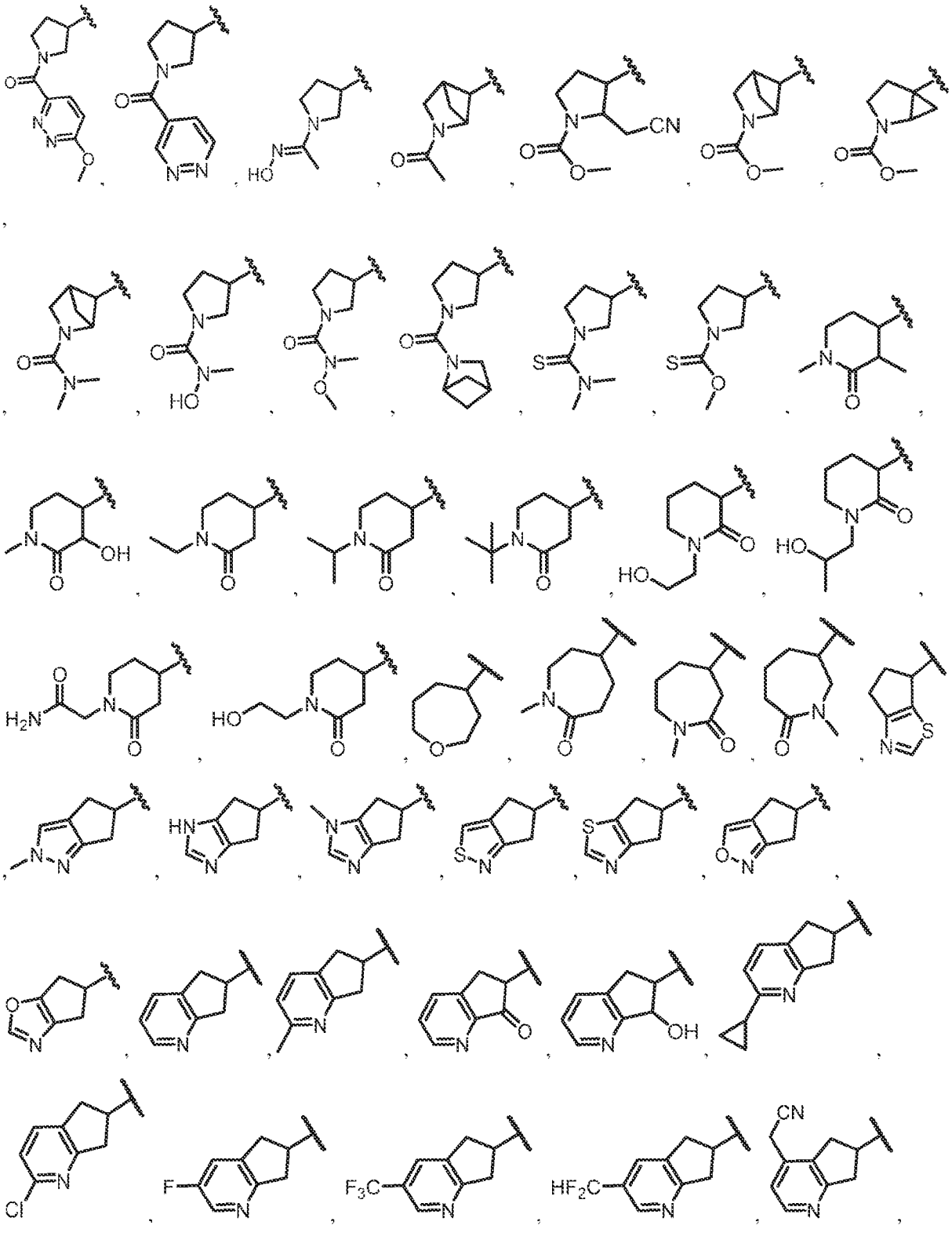


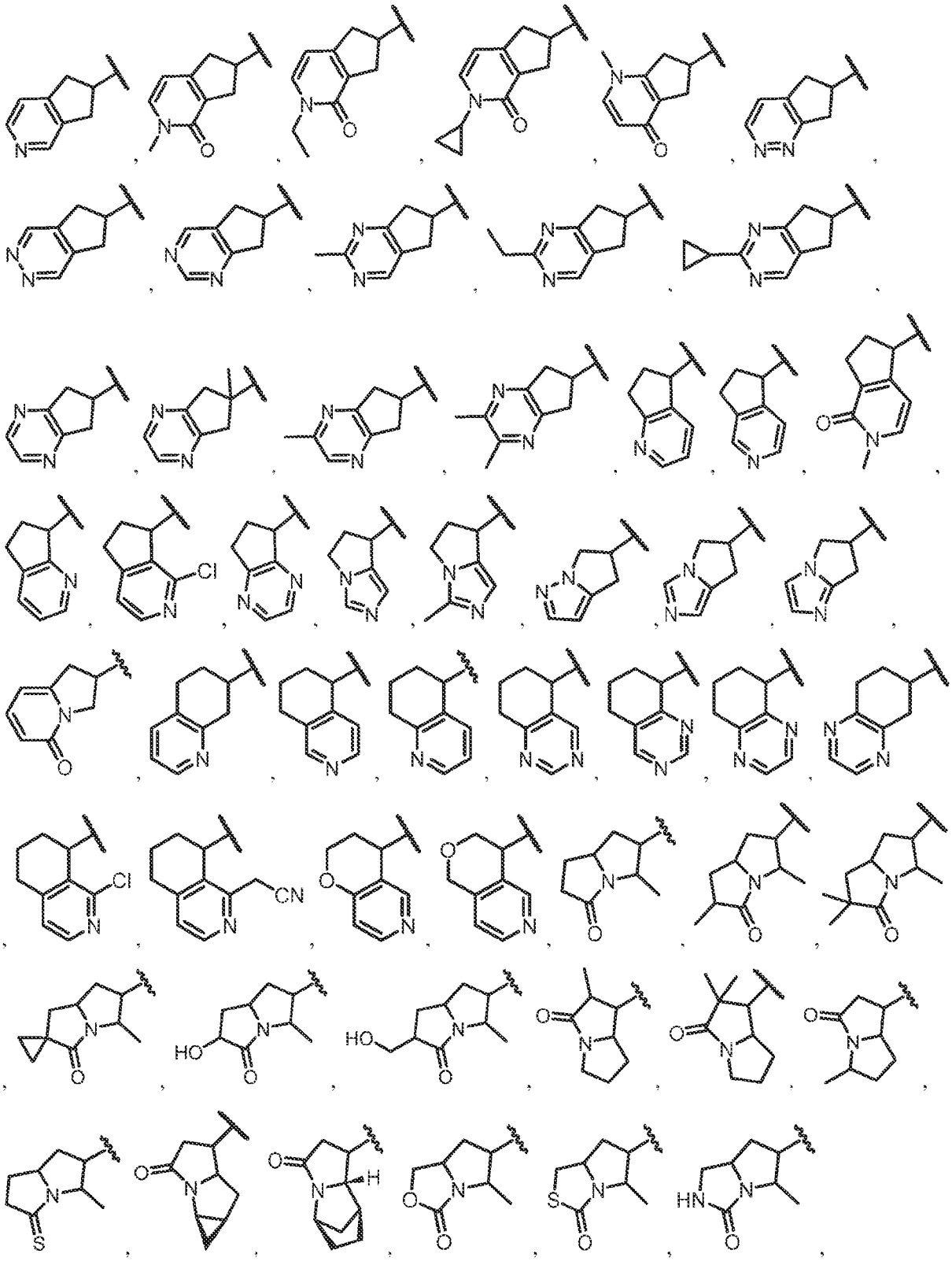


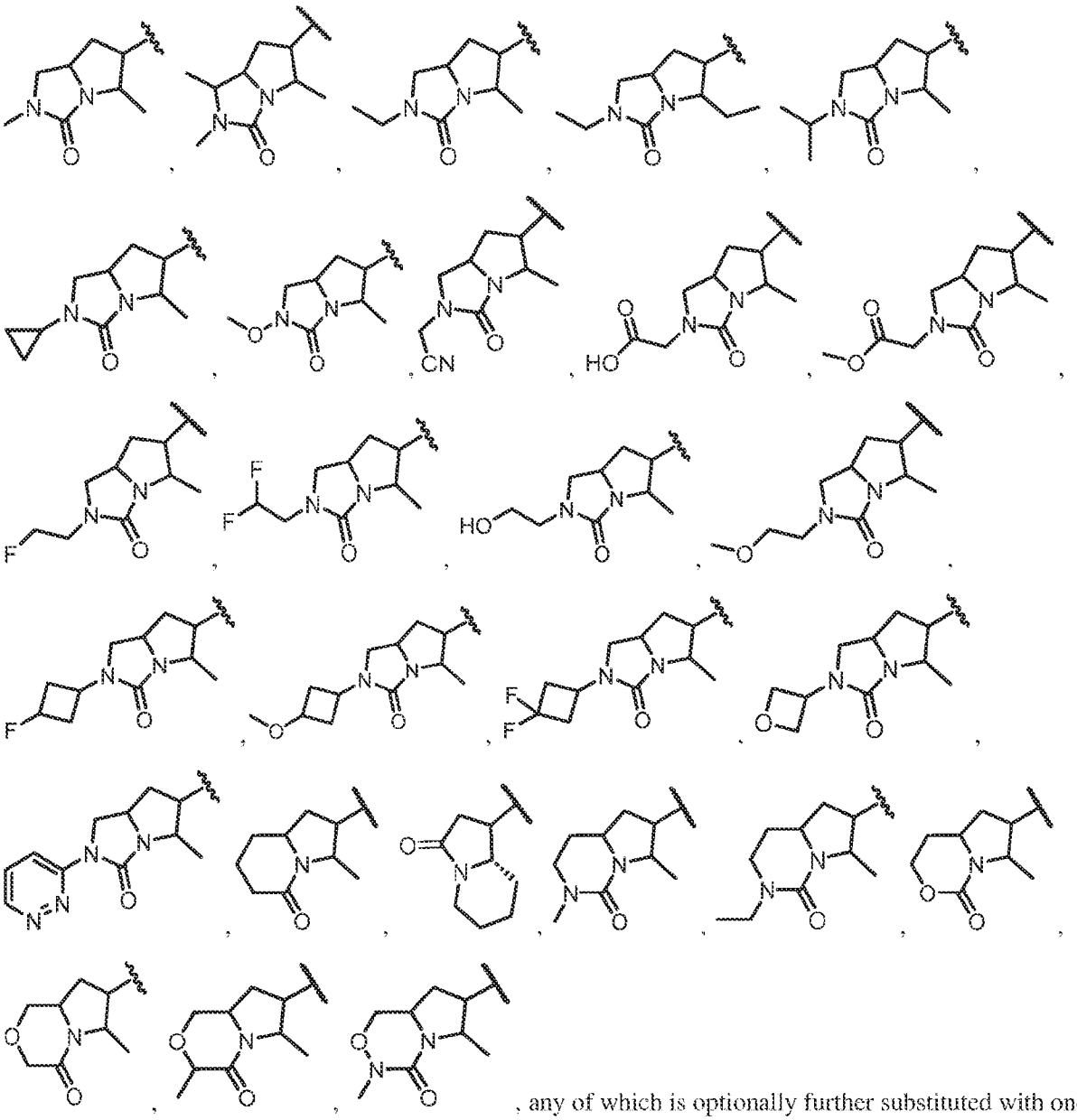
, any of which is optionally further substituted with one or more R^{10}.

[0194] In some embodiments according to Formula II'', R^3 is selected from:



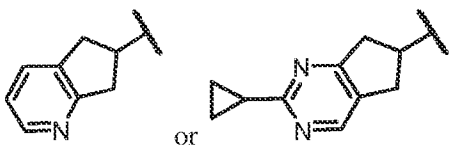






, any of which is optionally further substituted with one or more R^{10}.

[0195] In some embodiments for a compound according to Formula II, II', or II'', R^3 is selected from



, either of which is optionally further substituted with one or more R^{10}.

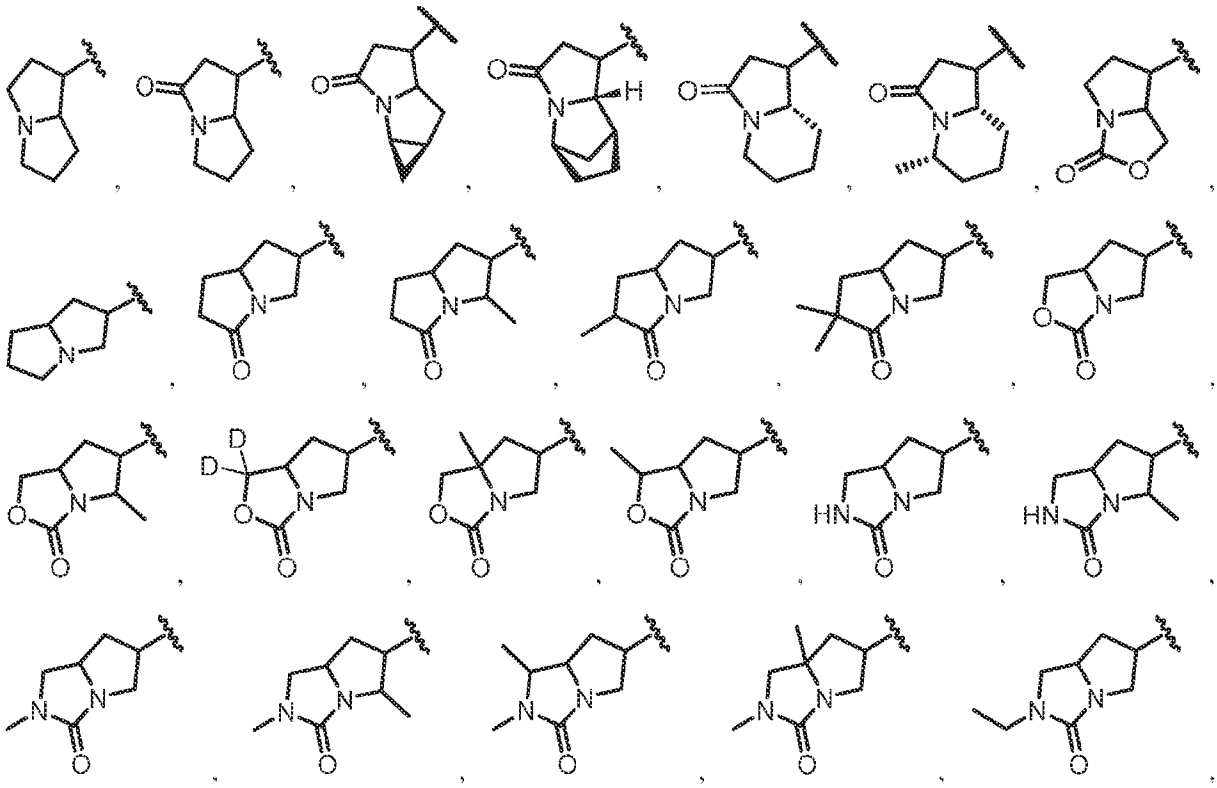
[0196] In some embodiments, for a compound according to Formula II, II', II'', II''-a, or II-a, R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the

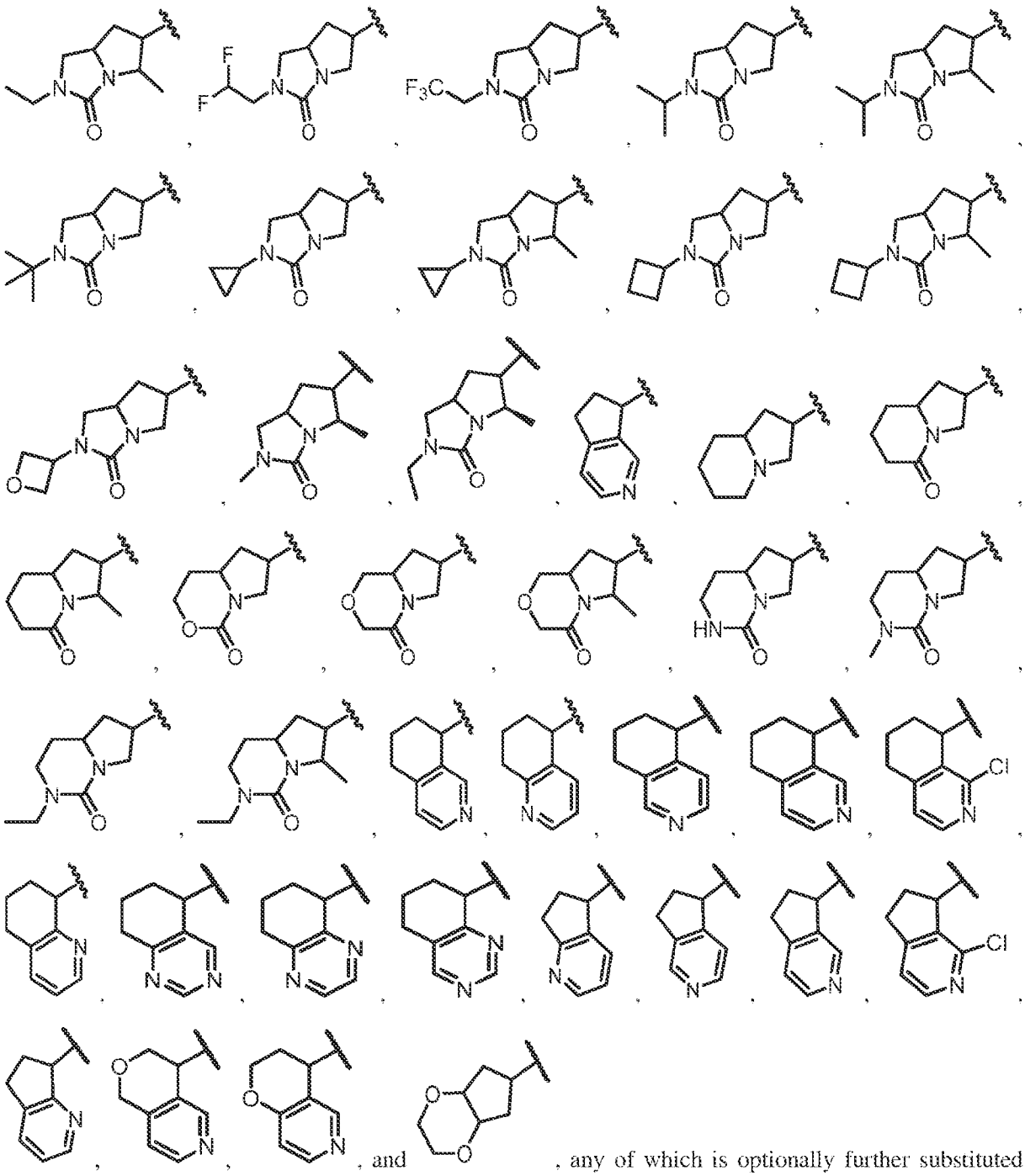
heterocycle is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not comprise an –NH- moiety. In some embodiments, R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) when the heterocycle contains a single ring, the heterocycle does not comprise an –NH- moiety. In some embodiments, R^3 is a 7-10 membered bridged heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the bridged heterocycle is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 is a 7-10 membered bridged heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the bridged heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the bridged heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the bridged heterocycle does not comprise an –NH- moiety. In some embodiments, R^3 is a bridged pyrrolidine that is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 is a bridged pyrrolidine that is unsubstituted or is substituted with one or more R^{10}, provided that the bridged pyrrolidine does not comprise an NH moiety. In some embodiments, R^3 is a bridged pyrrolidine that is substituted with one or more R^{10}, provided that the bridged pyrrolidine does not comprise an NH moiety. In some embodiments, R^3 is a 7-10 membered heterocycle comprising a fused ring system that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 is a 7-10 membered heterocycle comprising a fused ring system that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not comprise an –NH- moiety. In some embodiments, R^3 is a 7-10 membered heterocycle comprising a fused ring system comprising two rings, wherein the heterocycle includes one or more heteroatoms selected from O, S, and N, and the heterocycle is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 is a 7-10 membered heterocycle comprising a fused ring system comprising two rings, wherein the heterocycle includes one or more heteroatoms selected from O, S, and N, and the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not comprise an –NH- moiety. In some embodiments, R^3 comprises a fused ring system comprising two rings, wherein

at least one ring is a 5-membered heterocycle that is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 comprises a fused ring system comprising two rings, wherein at least one ring is a pyrrolidine that is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 comprises a fused ring system comprising two rings, wherein each ring is a 5-membered heterocycle that is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 comprises a fused ring system comprising two rings, wherein one ring is a 5-membered heterocycle that is unsubstituted or is substituted with one or more R^{10} and the second ring is a 6-membered heterocycle that is unsubstituted or is substituted with one or more R^{10}. In some embodiments, R^3 comprises a fused ring system comprising two rings, wherein one ring is a pyrrolidine that is unsubstituted or is substituted with one or more R^{10} and the second ring is a piperidine, oxazinane, oxazolidine, imidazolidine, or pyrrolidine that is unsubstituted or is substituted with one or more R^{10}. In some embodiments, the fused ring system is substituted with at least one R^{10}, wherein the at least one R^{10} is selected from =O and $C_{1\text{-}6}$alkyl, wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{20}.

[0197] In some embodiments, for a compound according to Formula II' or II-a, when R^{10} is $-C(O)N(R^{14})_2$, then at least one R^{14} is not H. In some embodiments, when R^{10} is $-C(O)N(R^{14})_2$, then each R^{14} is $C_{1\text{-}6}$ alkyl (e.g., methyl or ethyl).

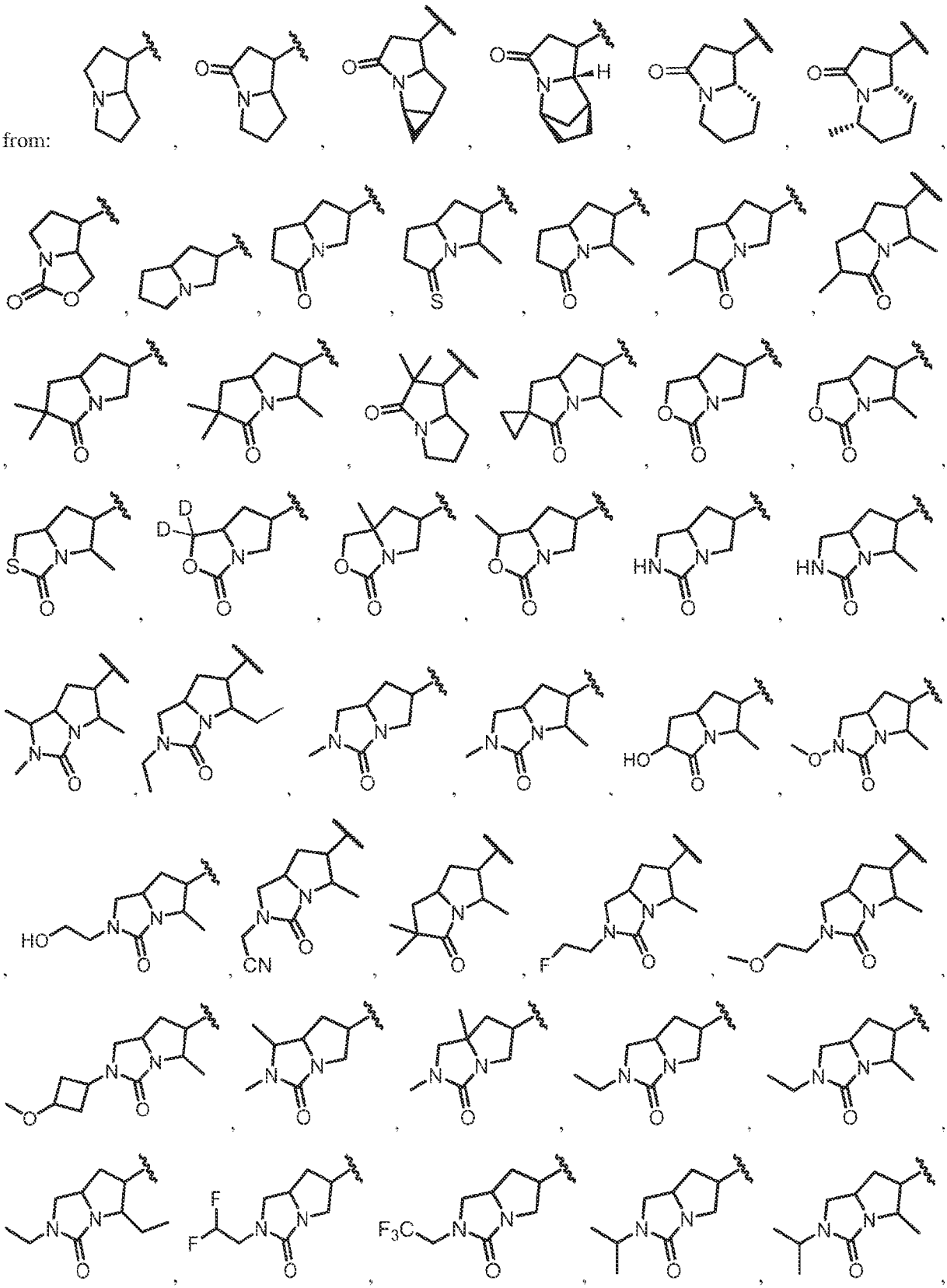
[0198] In some embodiments, for a compound according to Formula II'or II-a, R^3 is selected from:

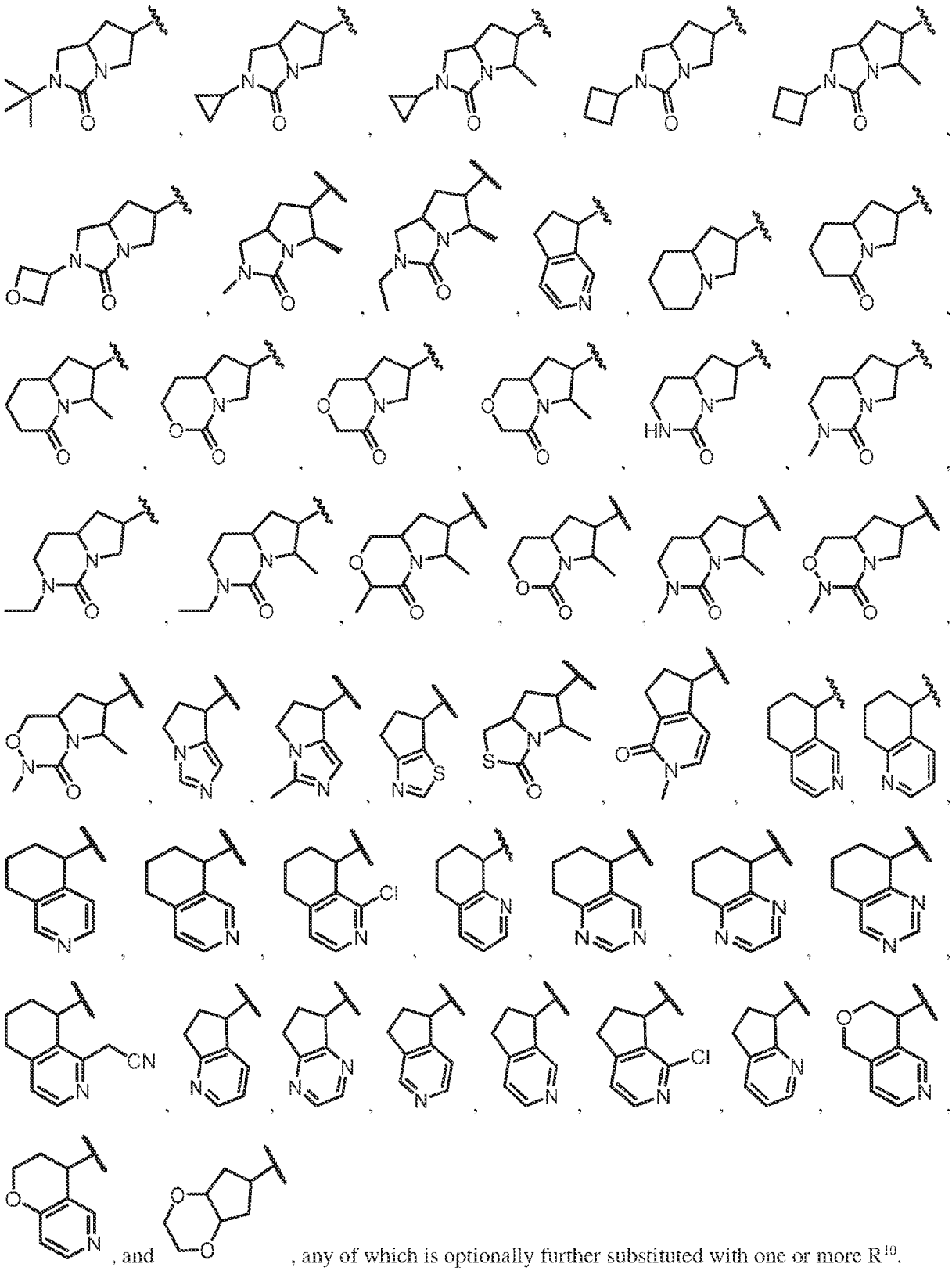




with one or more R^{10}.

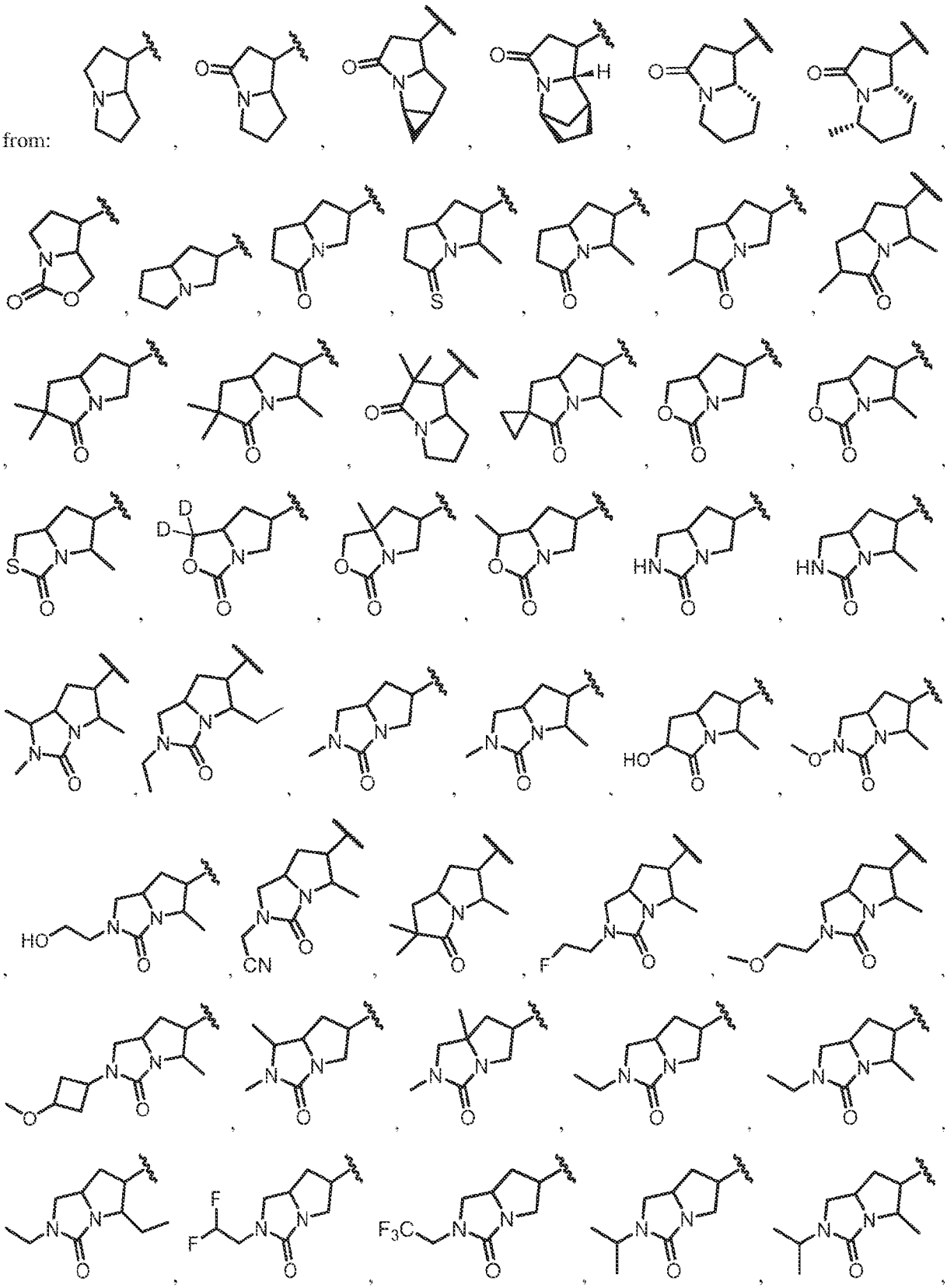
[0199] In some embodiments, for a compound according to Formula II, II', II'', II''-a, or II-a, R^5 is selected from:

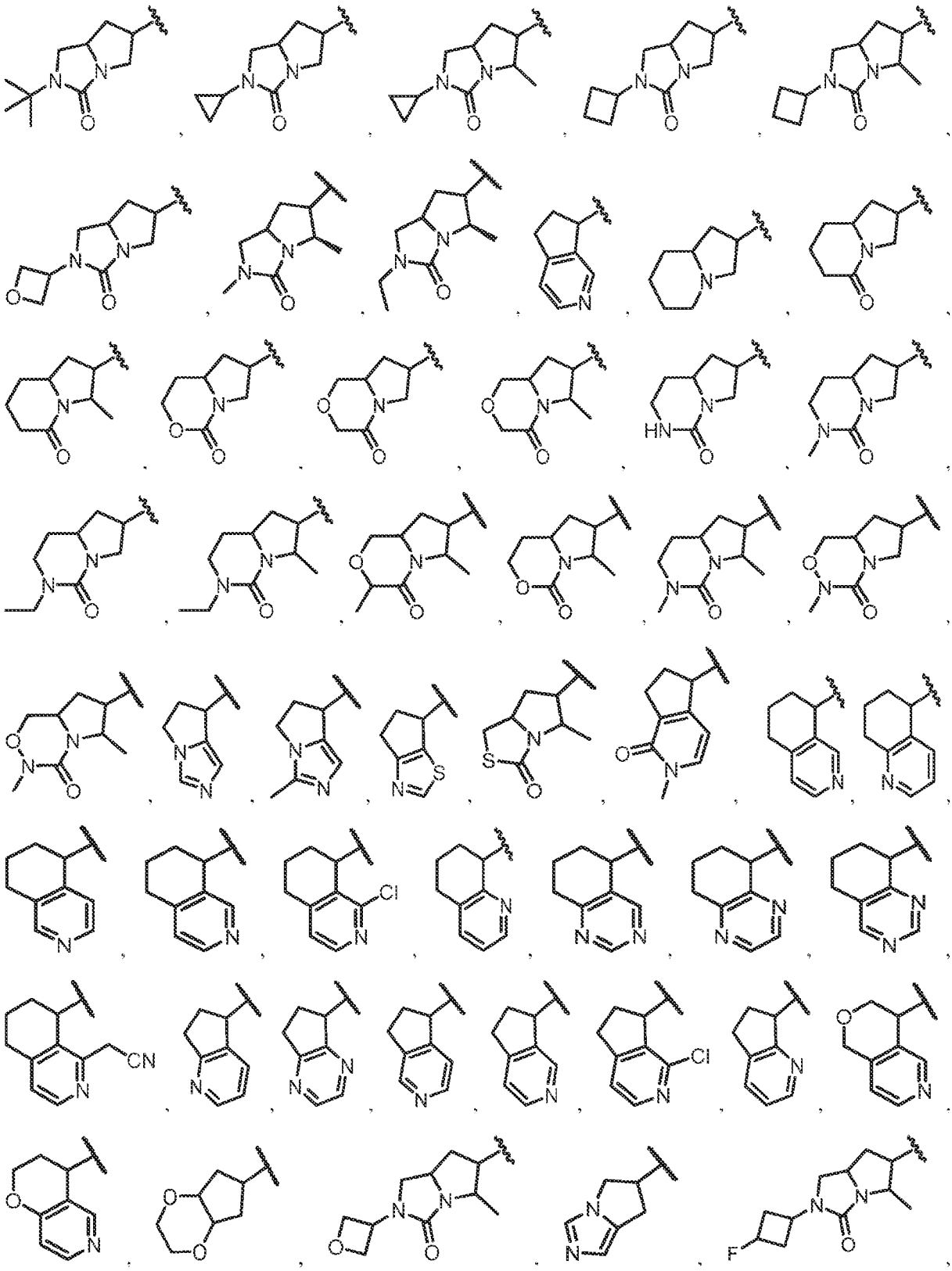


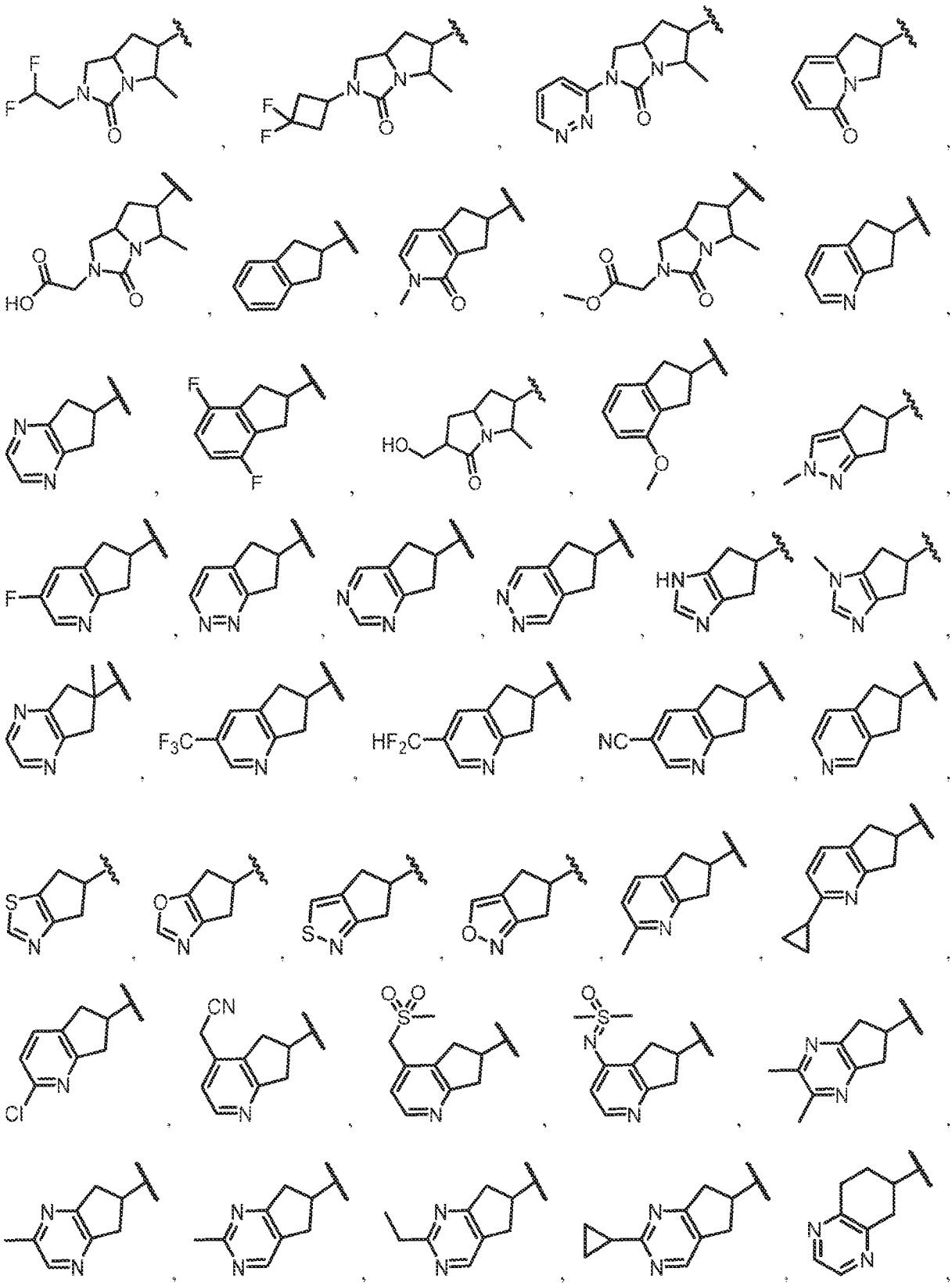


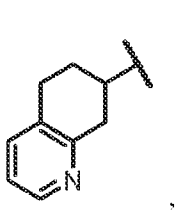
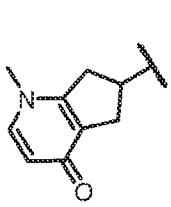
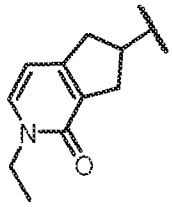
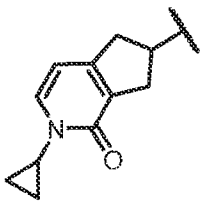
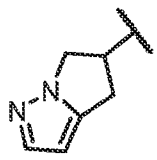
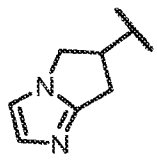
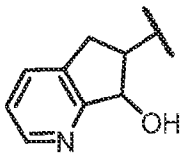
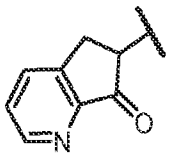
, and , any of which is optionally further substituted with one or more R^{10}.

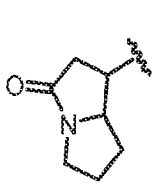
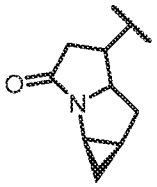
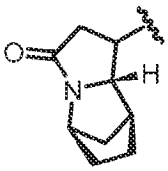
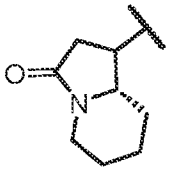
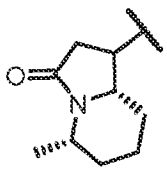
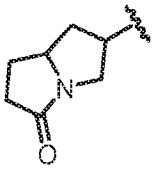
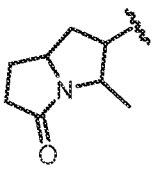
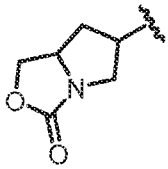
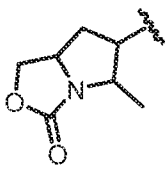
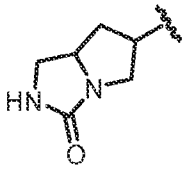
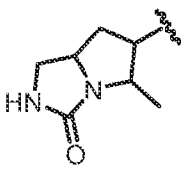
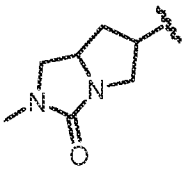
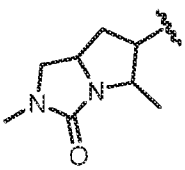
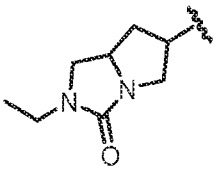
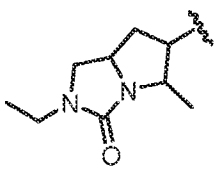
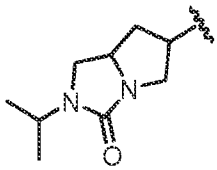
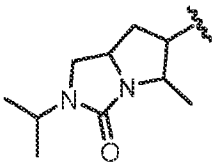
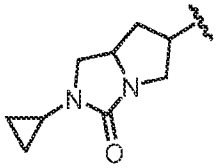
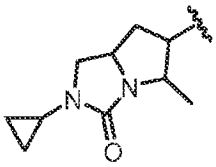
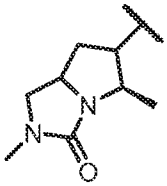
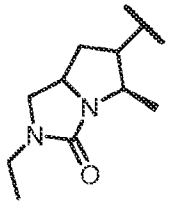
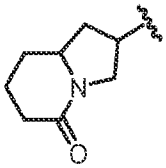
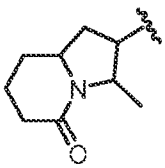
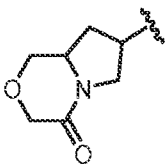
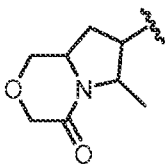
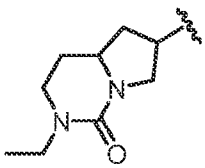
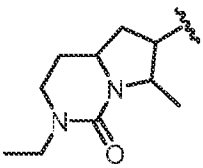
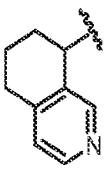
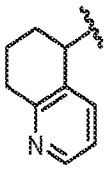
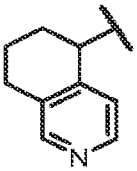
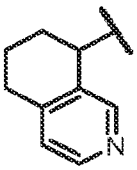
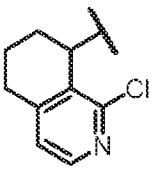
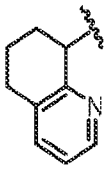
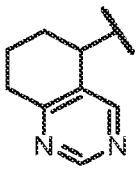
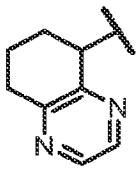
[0200] In some embodiments, for a compound according to Formula II, II', II'', II''-a, or II-a, R^5 is selected from:

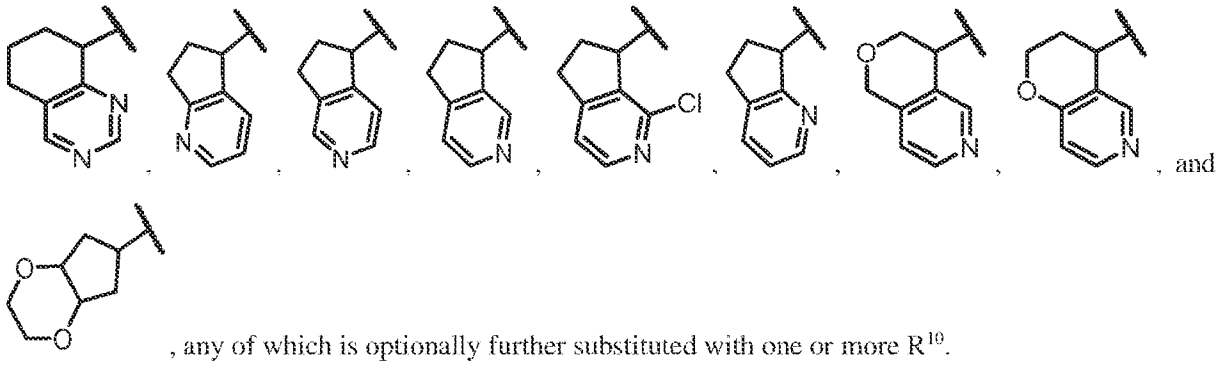






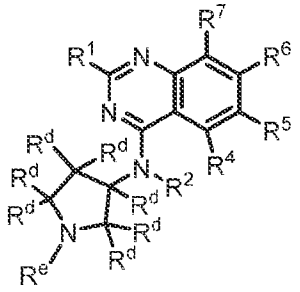







, and  , any of which is optionally further substituted with one or more R^{10}.

[0201] In some embodiments, for a compound according to Formula II, II', II'', II''-a, or II-a, R^3 is selected from: 



































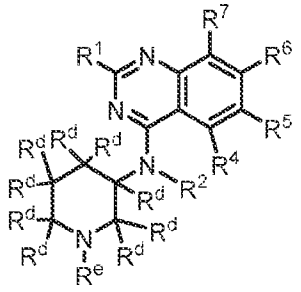


, any of which is optionally further substituted with one or more R^{10}.

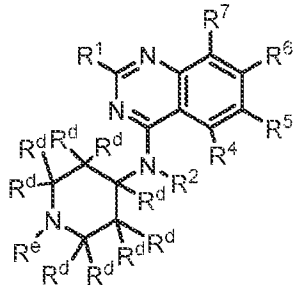
[0202] In some embodiments, the compound is a compound according to Formula IIR', IIU', IIV', or IIZ:



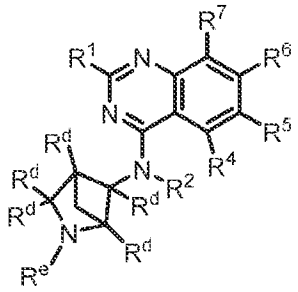
(IIR'),



(IIU'),

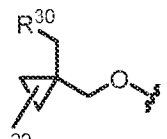


(IIV'), and



(IIZ),

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:



R^1 is selected from H, -OR^8, $(R^{29})_n$, and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2;

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13};

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}$alkylene)CN, $-C(O)(C_{1-6}$alkylene)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}$alkyl), halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^e is selected from $-C(O)(C_{1-6}$alkyl)CN, $-C(O)(C_{1-6}$alkyl)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}$alkylene)(3-6 membered heterocycle), -

$S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

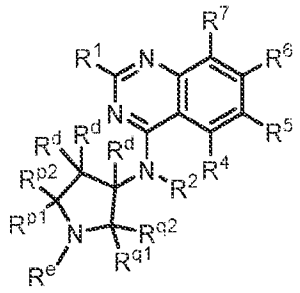
[0203] In some embodiments, the present disclosure provides a compound of Formula IIR', or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIU', or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIV', or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIZ, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0204] In some embodiments, for a compound according to any one of Formulas IIR', IIU', IIV', or IIZ, each R^d is H. In some embodiments, at least one R^d is selected from deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, at least one R^d is selected from $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, at least one R^d is selected from $C_{1-6}alkyl$ that is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

[0205] In some embodiments, for a compound according to any one of Formulas IIR', IIU', IIV', or IIZ, R^e is selected from $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, R^e is selected from $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6

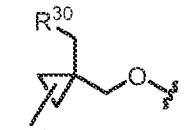
membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, R^e is a 5-6 membered heteroaryl that is unsubstituted or substituted with one or more R^{12} or R^{20}.

[0206] In some embodiments, the compound is a compound according to Formula IIAA':



(IIAA'),

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2;

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13};

each R^d is independently selected from deuterium, H, $-OR^{12}$, =O, $-C(O)(C_{1-6}$alkylene)CN, $-C(O)(C_{1-6}$alkylene)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)$(3-6 membered carbocycle), $-S(O)_2(C_{1-6}$alkyl), halogen, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle or 3-6 membered heterocycle, is unsubstituted or substituted with one or more R^{12} or R^{20}; and

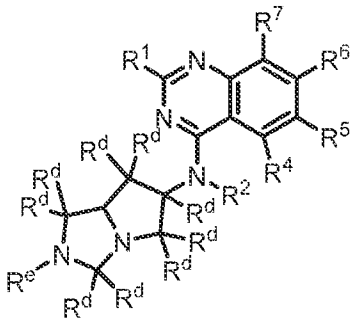
(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

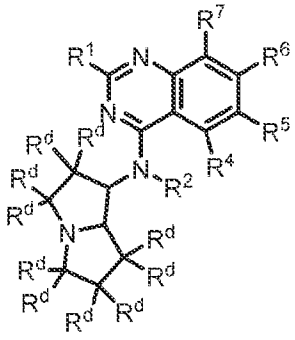
[0207] In some embodiments, the compound is a compound according to Formula IIAA', or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0208] In some embodiments, for a compound according to Formula IIAA', R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d. In some embodiments, R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

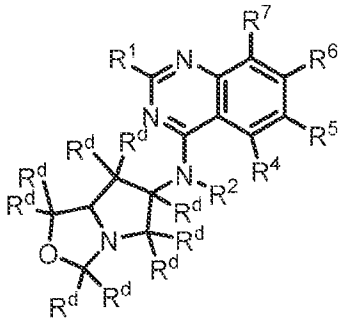
[0209] In some embodiments, the compound is a compound according to Formula IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, or IIJJ:



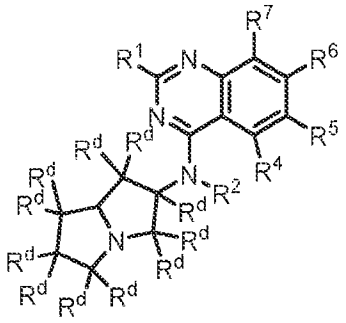
(IIBB),



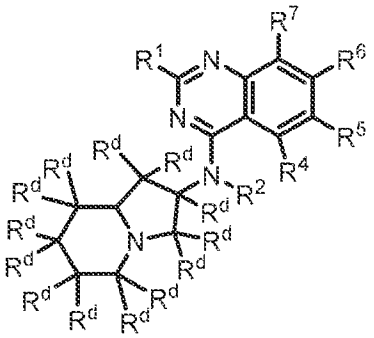
(IICC),



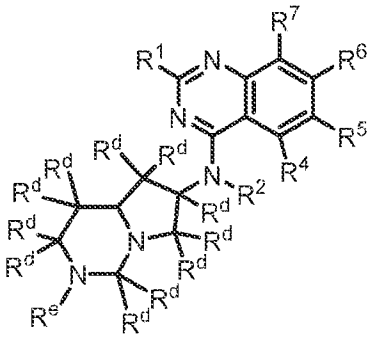
(IIDD),



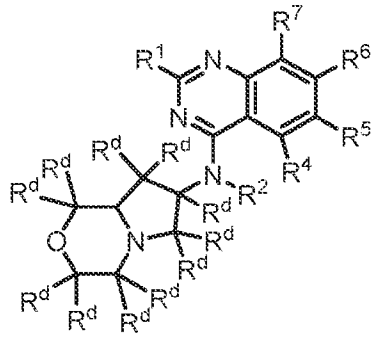
(IIEE),



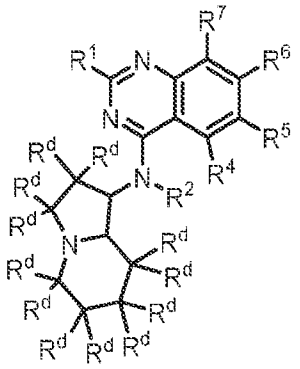
(IIFF),



(IIGG),

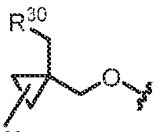


(IIHH), and



(IIJJ),

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2;

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13};

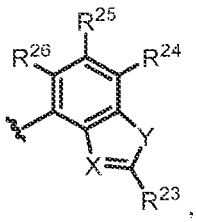
each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}$alkylene)CN, $-C(O)(C_{1-6}$alkylene)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}$alkyl), halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^e, if present, is selected from $-C(O)(C_{1-6}$alkyl)CN, $-C(O)(C_{1-6}$alkyl)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered

carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -$S(O)_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

[0210] In some embodiments, the present disclosure provides a compound of Formula IIBB, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IICC, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIDD, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIEE, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIFF, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIGG, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIHH, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIJJ, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

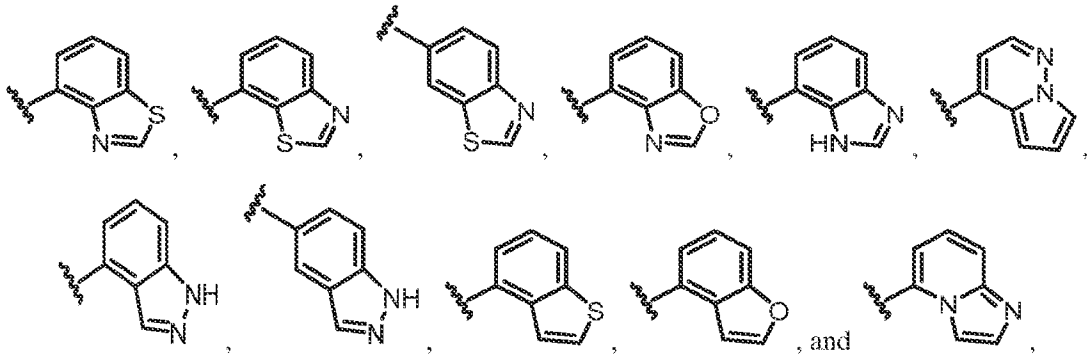
[0211] In some embodiments, for a compound according to any one of Formulas II, II', II'', IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, and IIJJ, R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15}. In some embodiments, R^6 is selected from:



wherein X is selected from N and C-CN; Y is selected from O, S, and Se; R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments, X is C-CN and Y is S. In some embodiments, X is C-CN and Y is O. In some embodiments, X is C-CN and Y is Se. In some embodiments, X is N and Y is S. In some embodiments, X is N and Y is O. In some embodiments, X is N and Y is Se. In some embodiments, X is C-CN, Y is S, and R^{23} is -$N(R^{12})_2$. In some embodiments, X is C-

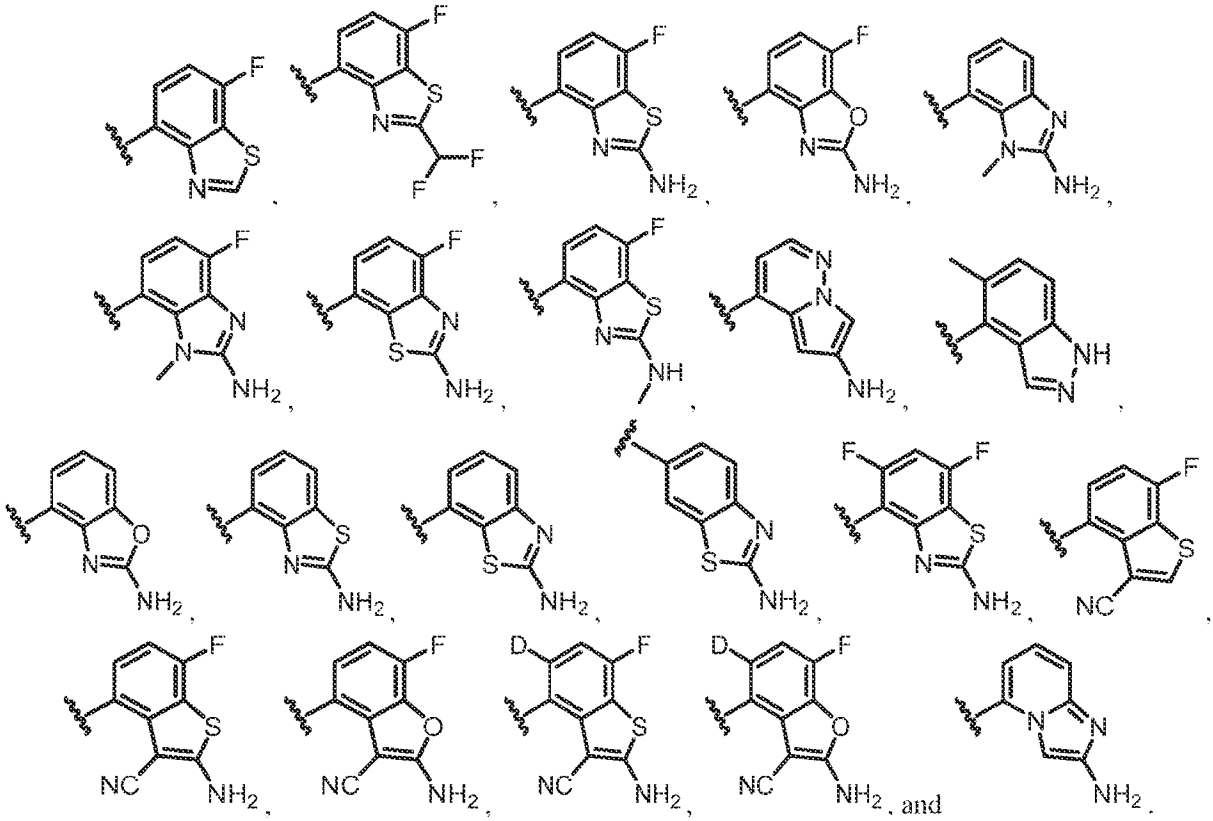
CN, Y is Se, and R^{23} is $-N(R^{12})_2$. In some embodiments, X is C-CN, Y is S, and R^{23} is $-NH_2$. In some embodiments, X is C-CN, Y is Se, and R^{23} is $-NH_2$. In some embodiments, R^{24} is a halogen (e.g., fluoro). In some embodiments, R^{26} is deuterium.

[0212] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, and IIJJ, R^6 is selected from:

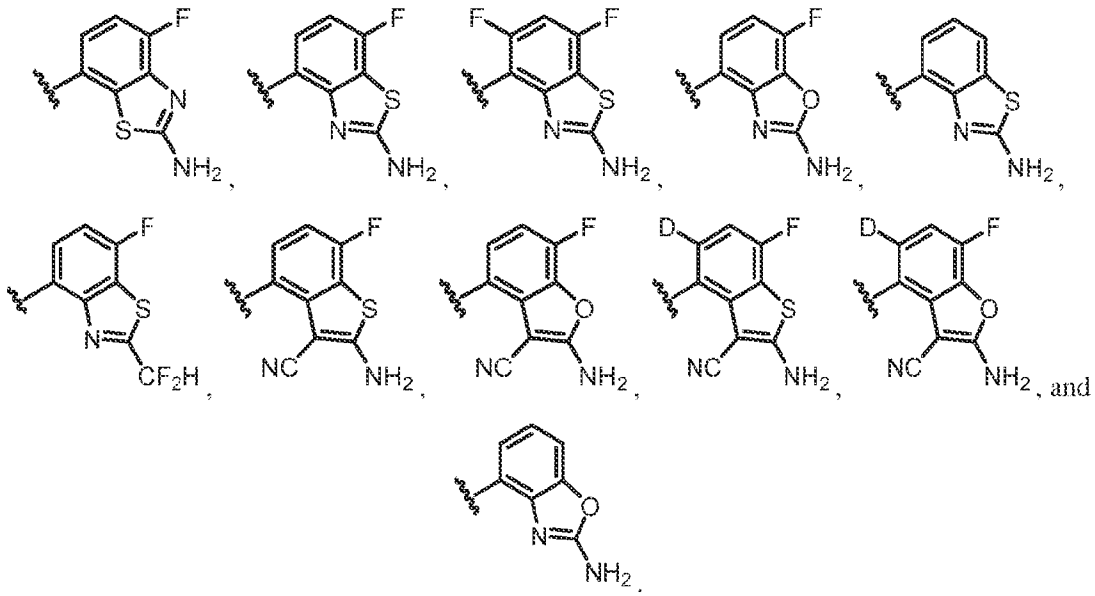

, and

any of which is substituted with one or more R^{15}.

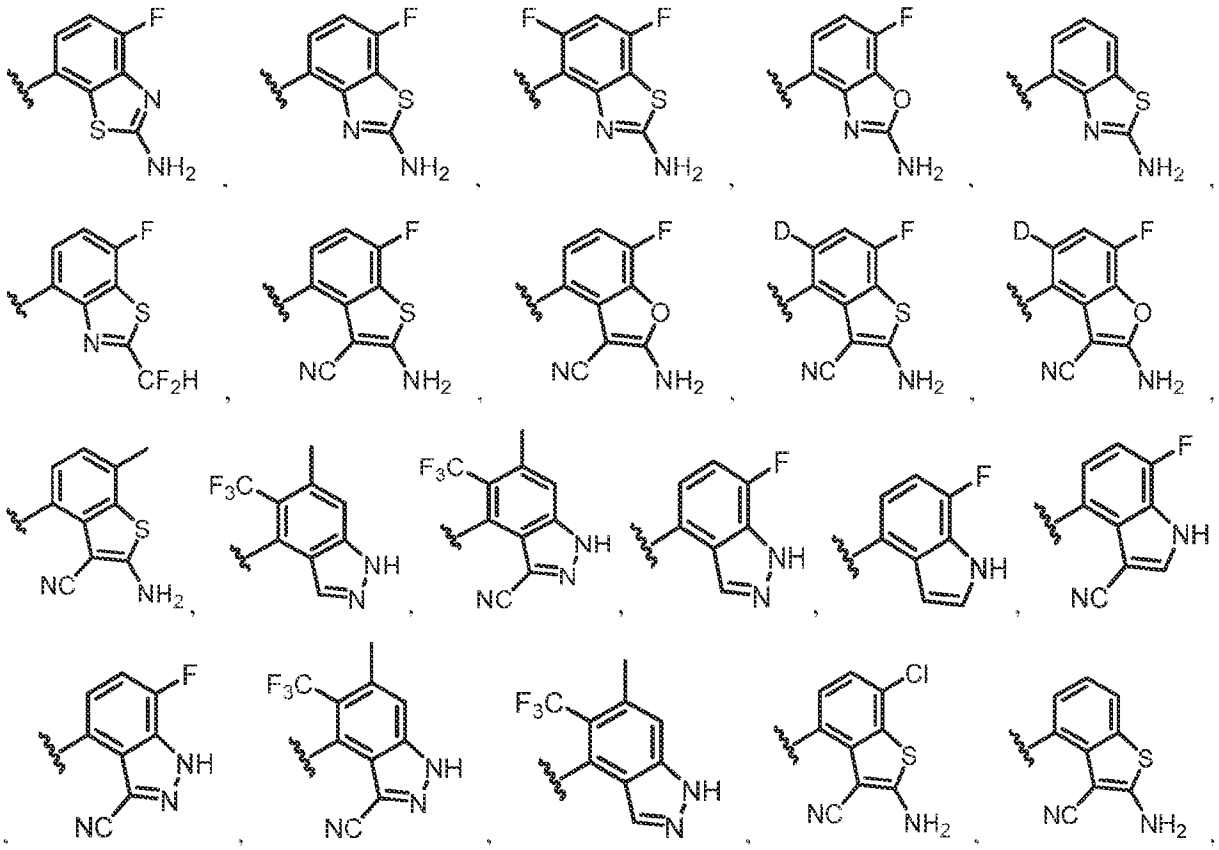
[0213] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, and IIJJ, R^6 is selected from:

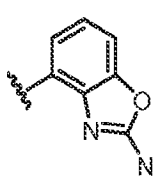

, and

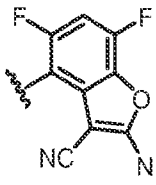
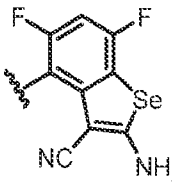
[0214] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, and IIJJ, R^6 is selected from:



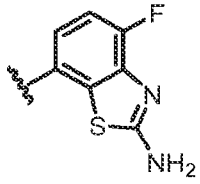
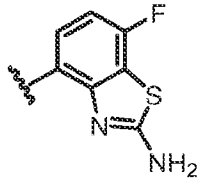
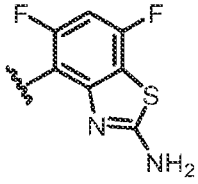
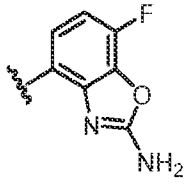
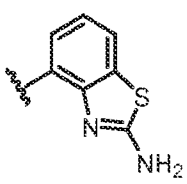
[0215] In some embodiments, for a compound according to Formula II'' or III, R^6 is selected from:





, : , , and . In some embodiments, for a compound according to Formula II or III, R^6 is selected from:

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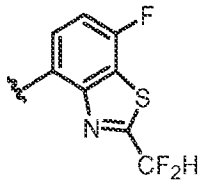
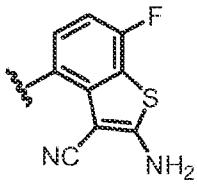
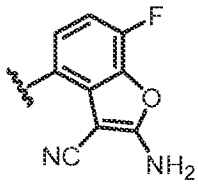
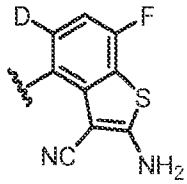
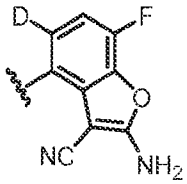

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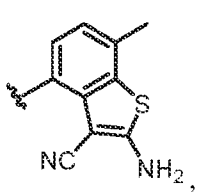
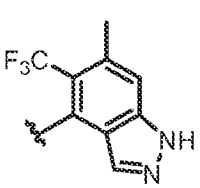
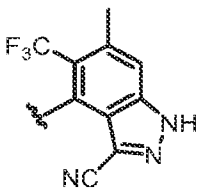
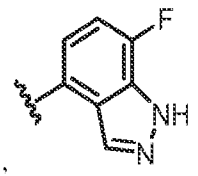
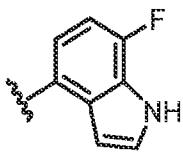
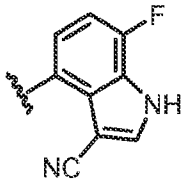

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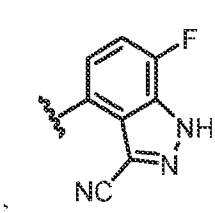
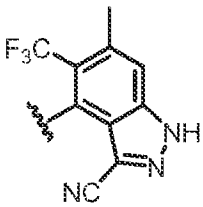
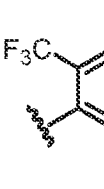
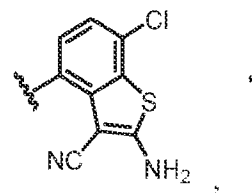
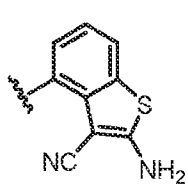

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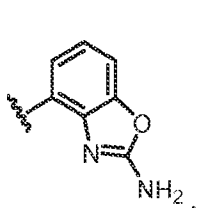
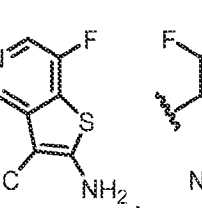
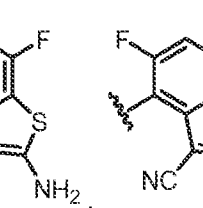
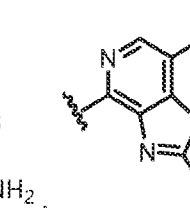
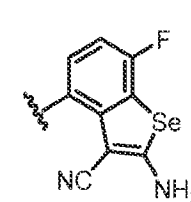

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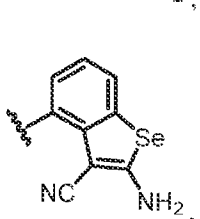
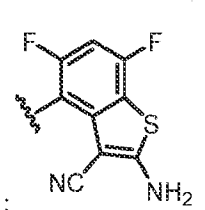
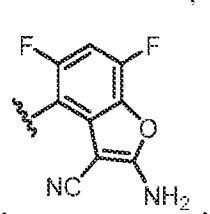
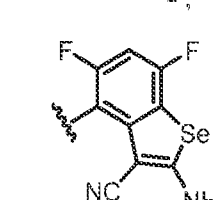
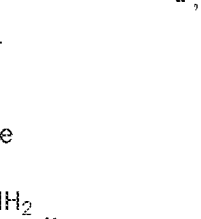

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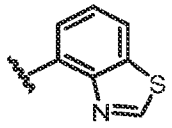
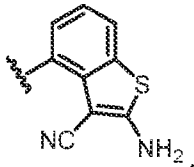
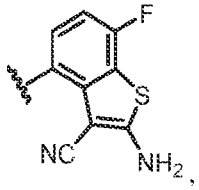
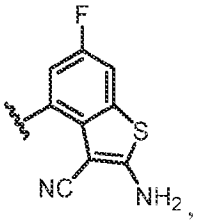
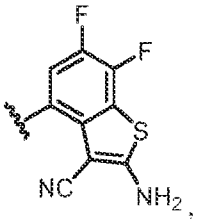
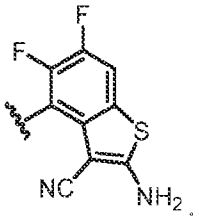
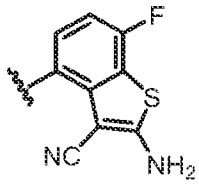
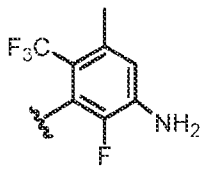
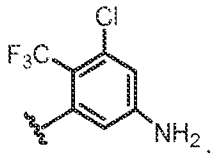
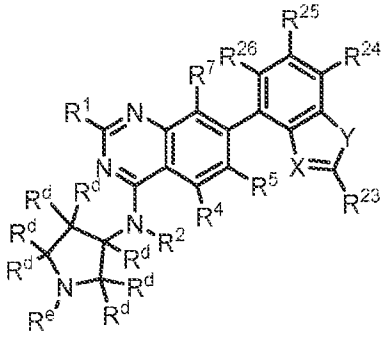
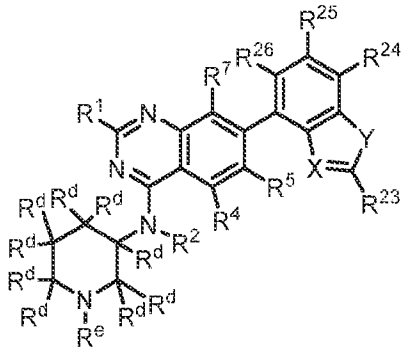
[0216] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, and IIJJ, R^6 is selected from:  , which is substituted with one or more R^{15}. In some embodiments, R^6 is selected from:  ,  ,  ,  , and  . In some embodiments, R^6 is  .

[0217] In some embodiments, for a compound according to Formula II, R^6 is a phenyl optionally substituted with one or more R^{15}. In some embodiments, R^6 is a phenyl optionally substituted with two or more R^{15}. In some embodiments, R^6 is selected from:  or  .

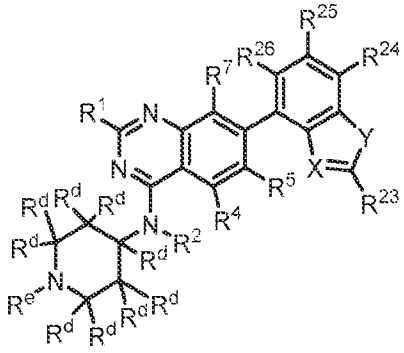
[0218] In some embodiments, the compound is a compound according to Formula IIR1', IIU1', IIV1', or IIZ1:



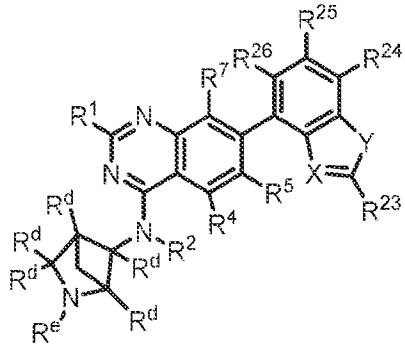
(IIR1'),



(IIU1'),

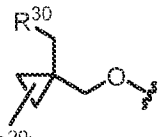


(IIV1'),



(IIZ1),

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:



R^1 is selected from H, $-OR^8$, , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, $C_{1\text{-}6}$alkyl, and a 3-6 membered carbocycle, wherein any $C_{1\text{-}6}$ alkyl is unsubstituted or is substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and $C_{1\text{-}6}$alkyl, wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{13};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from $C_{1\text{-}6}$alkyl;

each R^{12} is independently selected from $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, and H, wherein any $C_{1\text{-}6}$alkyl or $C_{2\text{-}6}$ alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2;

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13};

each R^d is independently selected from H, deuterium, -OR^{12}, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)N$(R^{14})_2$, -C(O)(3-6 membered carbocycle), -S(O)$_2$(C_{1-6}alkyl), halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e is selected from -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N$(R^{14})_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

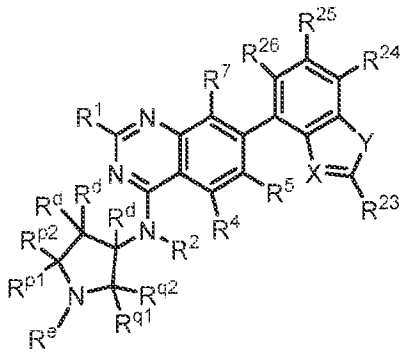
Y is selected from O and S;

R^{23} is selected from -N$(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-N$(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

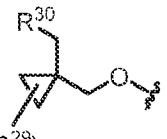
[0219] In some embodiments, the compound is a compound according to Formula IIR1', or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IIU1', or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IIV1', or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IIZ1', or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0220] In some embodiments, the compound is a compound according to Formula IIAA1':



(IIAA1'),

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:



R^1 is selected from H, $-OR^8$, , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2;

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13};

each R^d is independently selected from H, deuterium, -OR^{12}, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -$C(O)N(R^{14})_2$, -$S(O)_2$(C_{1-6}alkyl), a 3-6 membered carbocycle, a 3-6 membered heterocycle, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle or 3-6 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

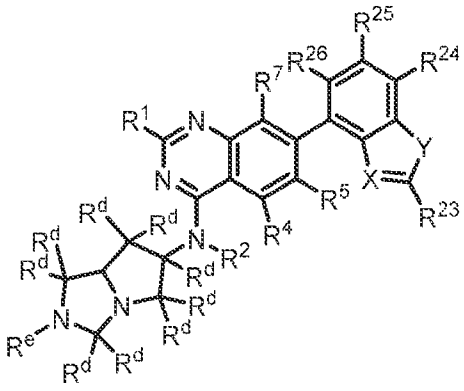
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

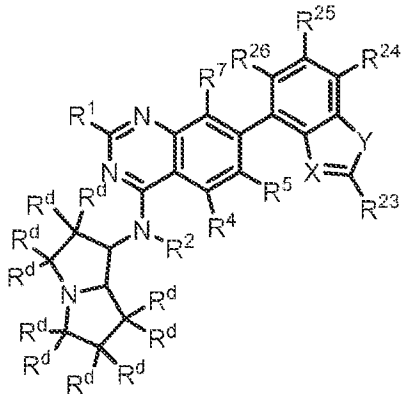
(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

[0221] In some embodiments, the compound is a compound according to Formula IIAA1', or a salt (e.g., pharmaceutically acceptable salt) thereof.

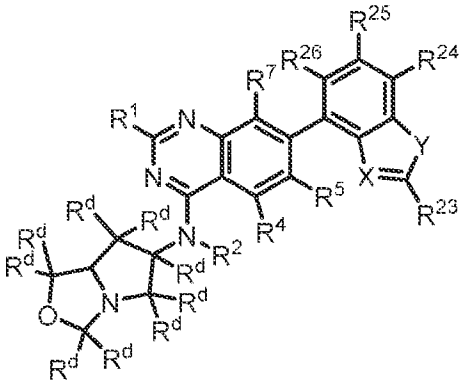
[0222] In some embodiments, the compound is a compound according to Formula IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1:



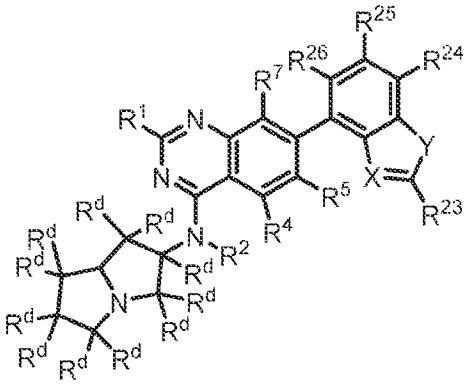
(IIBB1),



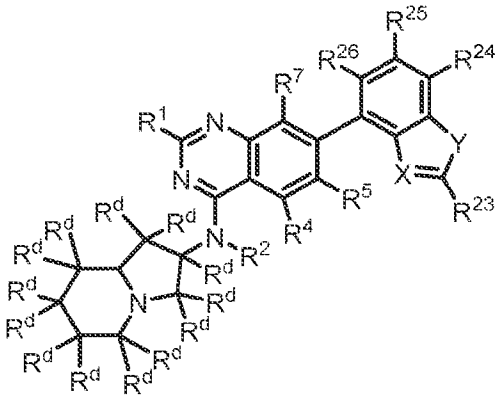
(IICC1),



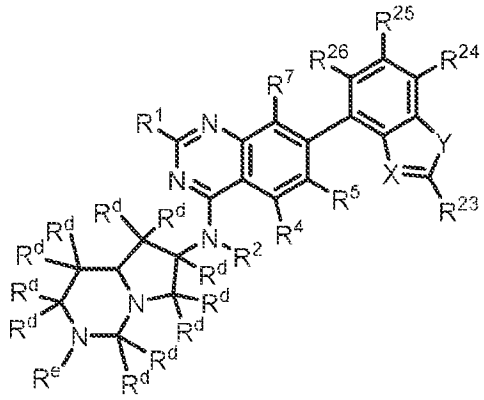
(IIDD1),



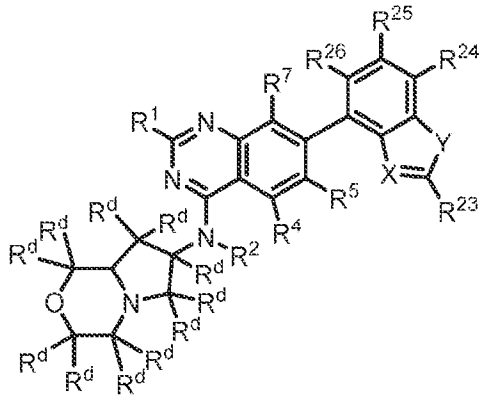
(IIEE1),



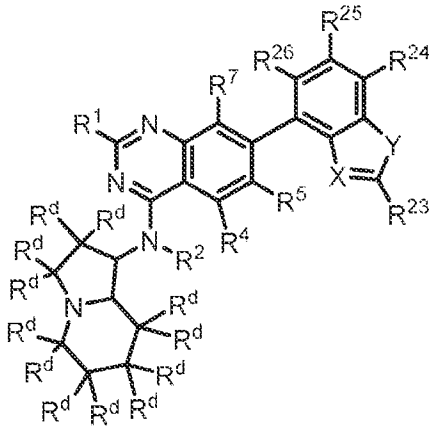
(IIFF1),



(IIGG1),

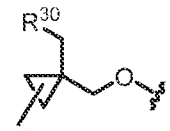


(IIHH1), and



(IIJJ1),

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:



R^1 is selected from H, $-OR^8$, , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2;

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13};

each R^d is independently selected from H, deuterium, -OR^{12}, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)$N(R^{14})_2$, -C(O)(3-6 membered carbocycle), -$S(O)_2$(C_{1-6}alkyl), halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e, if present, is selected from -C(O)(C_{1-6}alkyl)CN, -C(O)(C_{1-6}alkyl)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)$N(R^{14})_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -$S(O)_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

[0223] In some embodiments, the compound is a compound according to Formula IIBB1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IICC1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IIDD1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IIEE1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IIFF1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IIGG1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IIHH1, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the compound is a compound according to Formula IIJJ1, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0224] In some embodiments, for a compound according to any one of Formulas IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, each R^d is H. In some embodiments, at least one R^d is selected from deuterium, $-OR^{12}$, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}$alkyl), halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, at least one R^d is selected from $-OR^{12}$, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}$alkyl), halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, at least one R^d is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

[0225] In some embodiments, for a compound according to any one of Formulas IIBB, IIGG, IIBB1, or IIGG1, R^e is selected from -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6

membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -$S(O)_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, R^e is selected from -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -$S(O)_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, R^e is a 5-6 membered heteroaryl that is unsubstituted or substituted with one or more R^{12} or R^{20}. In some embodiments, R^e is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{20}. In some embodiments, R^e is -C(O)(3-6 membered carbocycle). In some embodiments, R^e is selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), and -C(O)O(C_{1-6}alkyl), wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

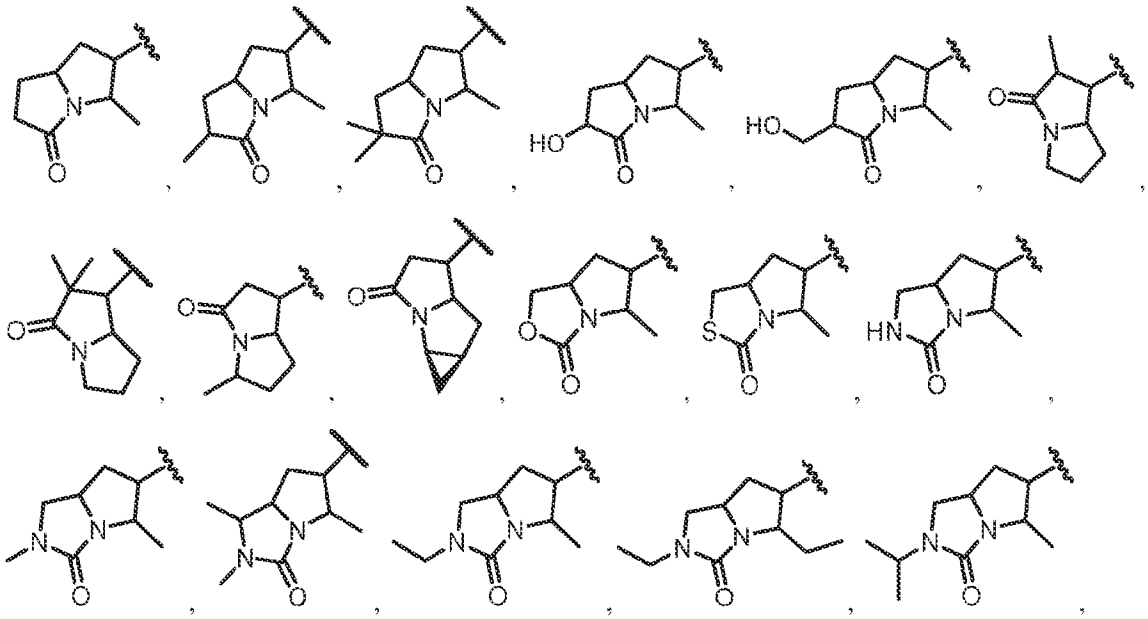
[0226] In some embodiments, for a compound according to any one of Formulas IIR1', IIU1', IIV1', IIZ1, IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, X is C-CN. In some embodiments, Y is S. In some embodiments, R^{23} is -$N(R^{12})_2$. In some embodiments, one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

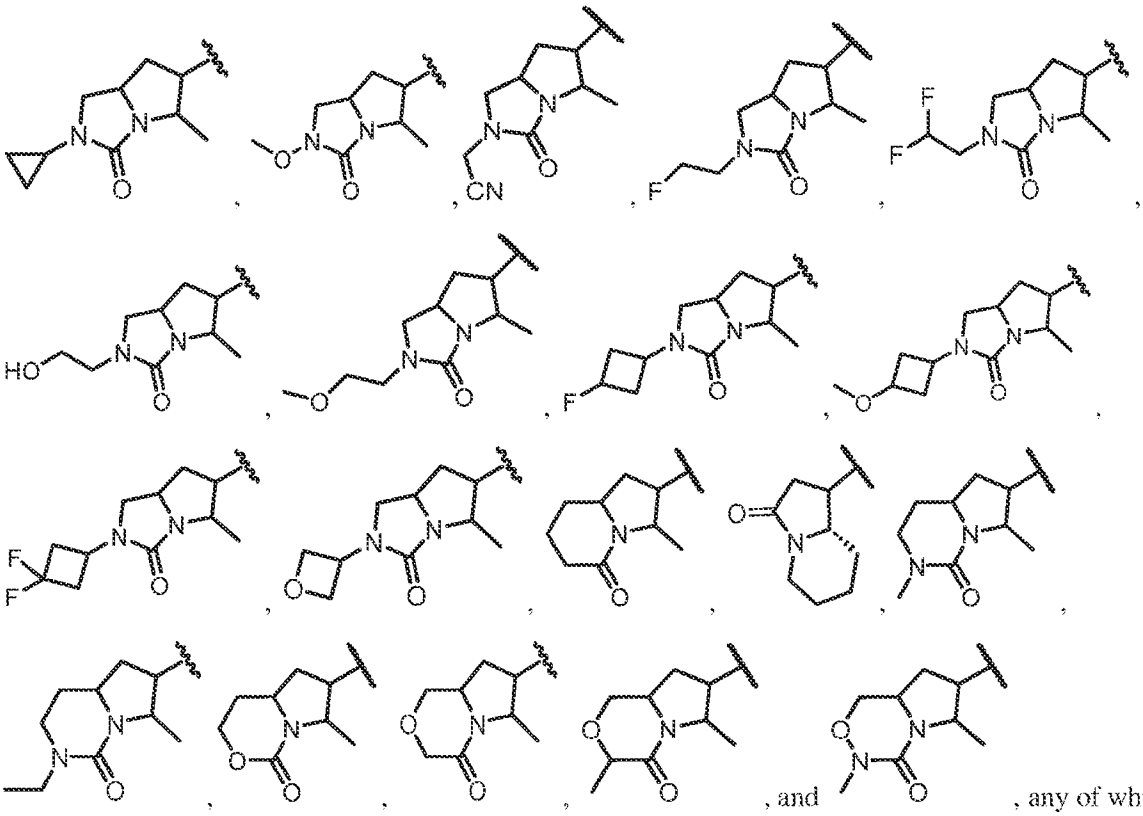
[0227] In some embodiments, for a compound according to any one of Formulas II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^2 is H. In some embodiments, R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^2 is selected from C_{1-6}alkyl that is unsubstituted. In some embodiments, R^2 is selected from C_{1-2}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^2 is selected from C_{1-2}alkyl that is unsubstituted. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl.

[0228] In some embodiments, for a compound according to any one of Formulas II, II', II'', IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^1 is selected from -OR^8. In some embodiments, R^8 is a heterocycle or an alkylheterocycle, wherein any heterocycle contains 4-8 ring atoms and is substituted

with one or more R^a or R^b. In some embodiments, R^8 is a heterocycle that is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, R^8 is an alkylheterocycle that is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, R^8 is $-CH_2$(heterocycle), where the heterocycle is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is a 4-6 membered monocyclic heterocycle having 1-2 heteroatoms independently selected from N, O, and S. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is an 8-membered bicyclic heterocycle having 1-2 heteroatoms independently selected from N, O, and S. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a halogen (e.g., F). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a C_{1-6}alkyl (e.g., methyl). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a $-OR^{12}$ (e.g., $-OCH_3$). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a 3-6 membered carbocycle (e.g., a cyclopropane). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is deuterium.

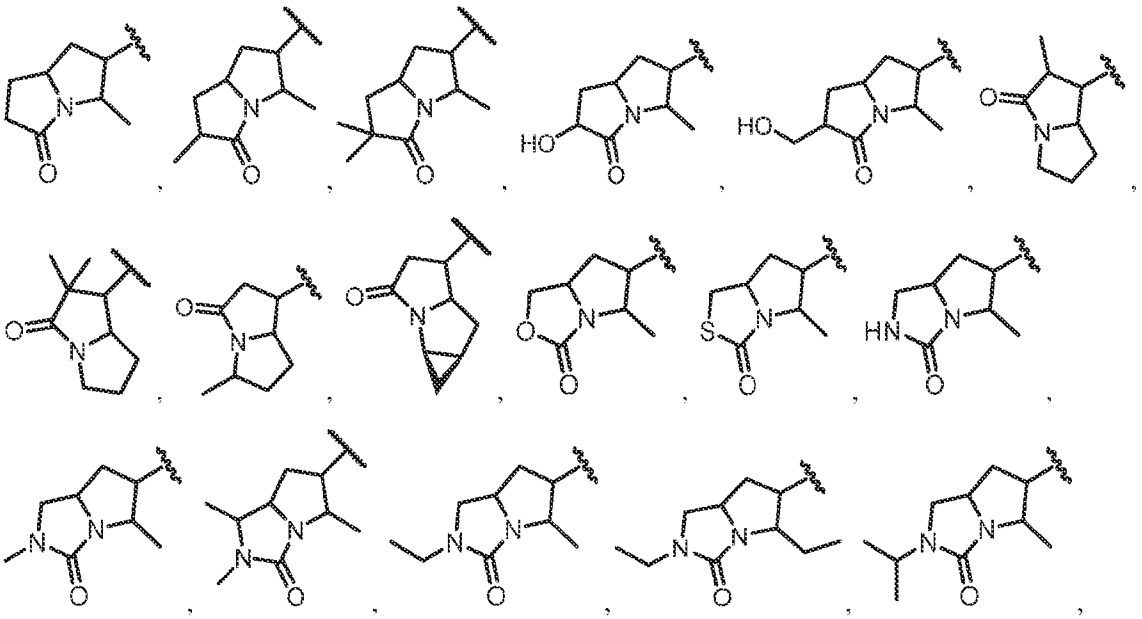
[0229] In some embodiments according to Formula IIAA', R^3 is selected from:

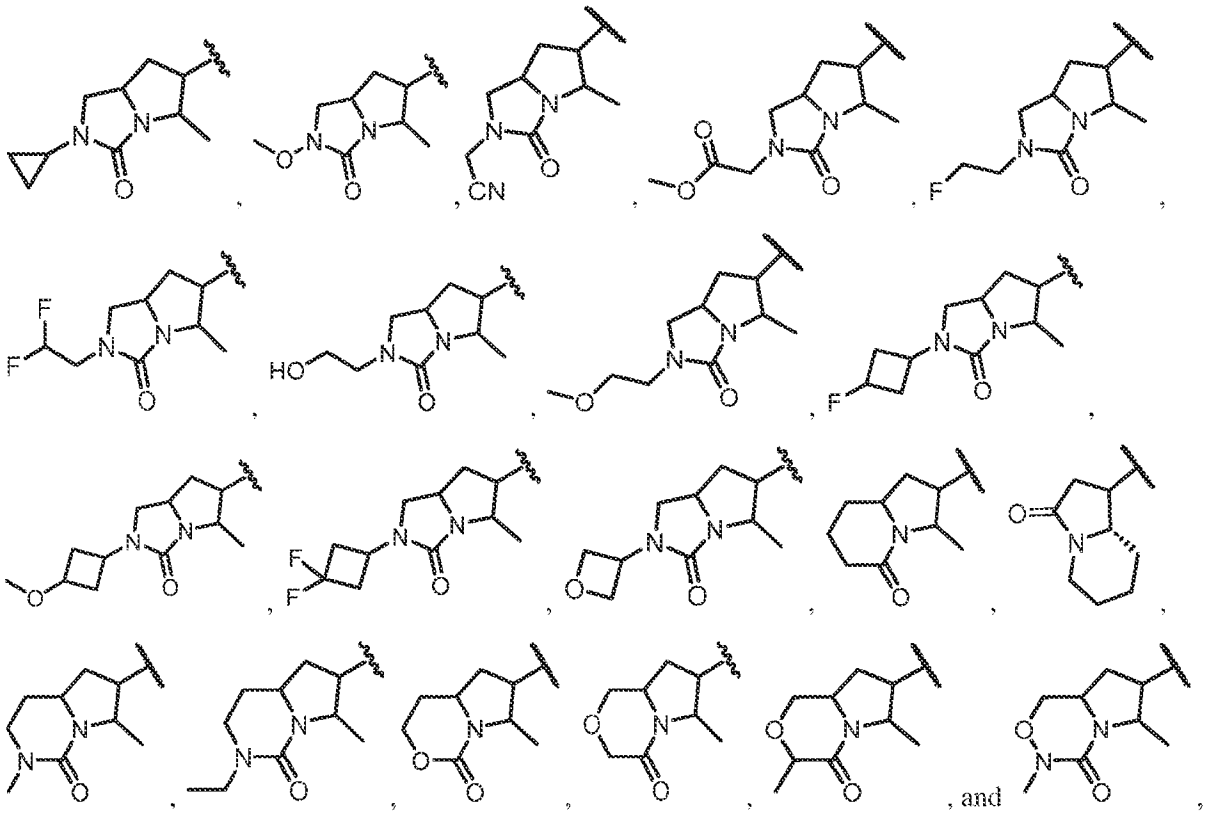




optionally further substituted with one or more R^{10}.

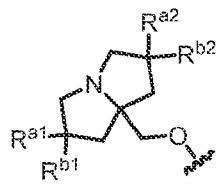
[0230] In some embodiments according to Formula IIAA1', R^3 is selected from:





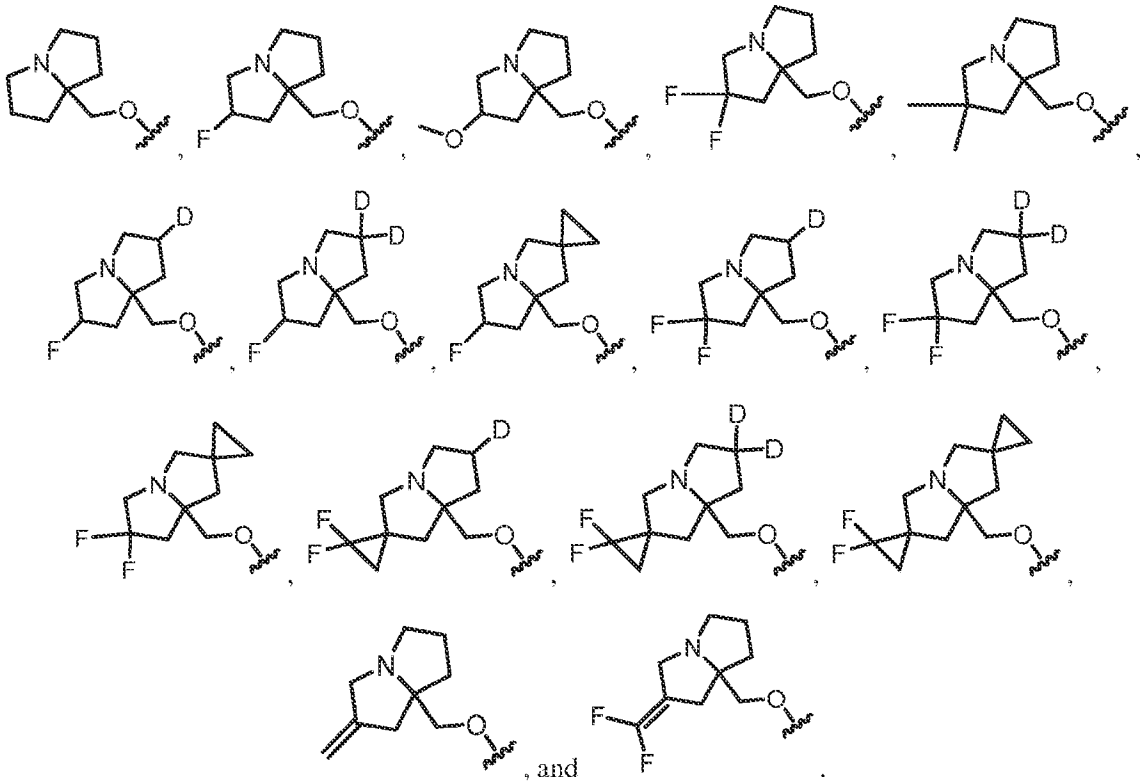
any of which is optionally further substituted with one or more R^{10}.

[0231] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^1 is selected from:

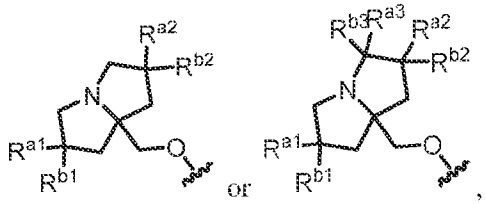


wherein R^{a1}, R^{a2}, R^{b1}, and R^{b2} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H, wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} and R^{b1} can optionally join together to form an exocyclic double bond that is unsubstituted or is substituted by halogen. In some embodiments, R^{a1} and R^{b1} are each independently selected from halogen, C_{1-6}alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} is a halogen. In some embodiments, R^{a1} is F. In some embodiments, R^{a1} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} is methyl. In some embodiments, R^{a1} is $-OC_{1-6}$alkyl. In some embodiments, R^{a1} is H. In

some embodiments, R^{b1} is H. In some embodiments, R^{b1} is a halogen. In some embodiments, R^{b1} is F. In some embodiments, R^{b1} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{b1} is methyl. In some embodiments, each of R^{a1} and R^{b1} is F. In some embodiments, each of R^{a1} and R^{b1} is methyl. In some embodiments, each of R^{a1} and R^{b1} is H. In some embodiments, each of R^{a2} and R^{b2} is H. In some embodiments, one of R^{a1} and R^{b1} is deuterium. In some embodiments, each of R^{a1} and R^{b1} is deuterium. In some embodiments, R^{a2} and R^{b2} join together to form a 3-6 membered carbocycle, such as cyclopropyl. In some embodiments, R^1 is selected from:

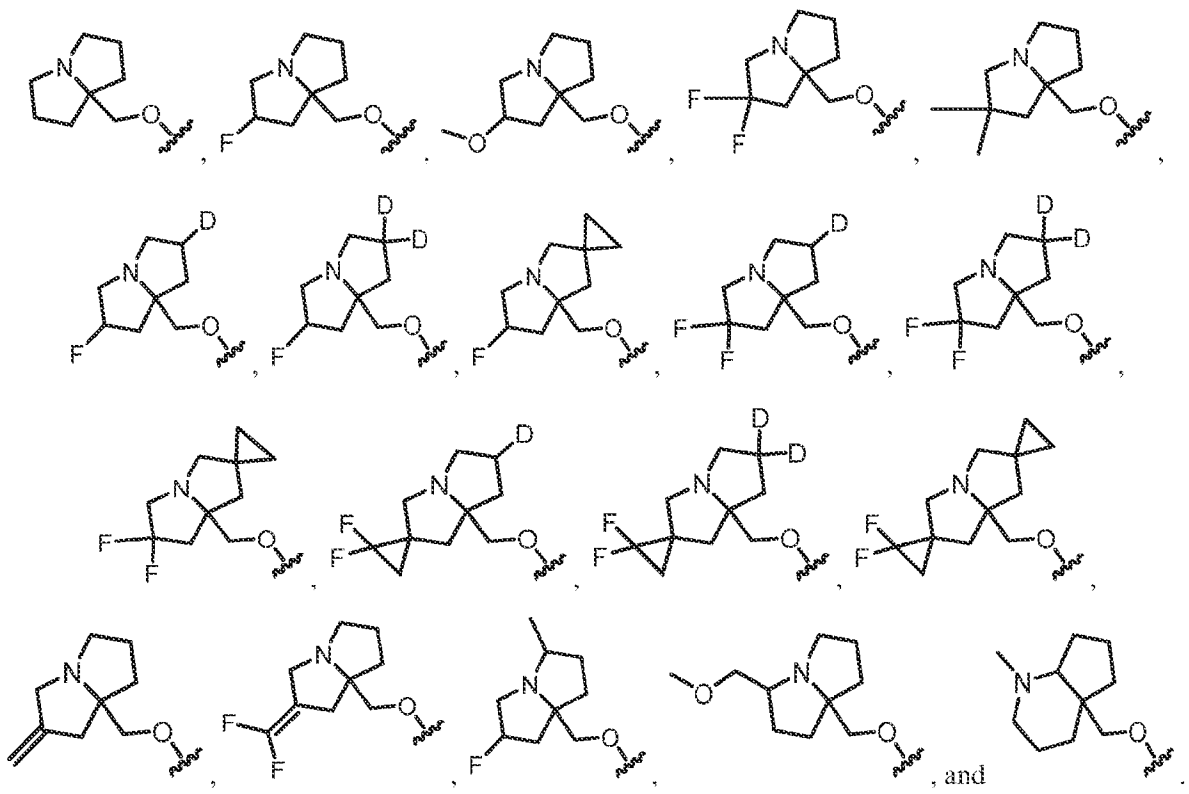


[0232] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^1 is selected from:



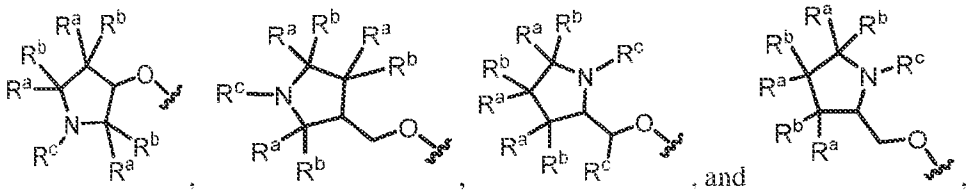
wherein R^{a1}, R^{a2}, R^{b1}, R^{b2}, R^{a3}, and R^{b3} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, , -C_{1-6} heteroalkyl, -OR^{12}, and H, wherein R^{a2} and R^{b2} can optionally join together to

form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} and R^{b1} can optionally join together to form an exocyclic double bond that is unsubstituted or is substituted by halogen. In some embodiments, R^{a1} and R^{b1} are each independently selected from halogen, C_{1-6}alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} is a halogen. In some embodiments, R^{a1} is F. In some embodiments, R^{a1} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} is methyl. In some embodiments, R^{a1} is $-OC_{1-6}$alkyl. In some embodiments, R^{a1} is H. In some embodiments, R^{b1} is H. In some embodiments, R^{b1} is a halogen. In some embodiments, R^{b1} is F. In some embodiments, R^{b1} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{b1} is methyl. In some embodiments, each of R^{a1} and R^{b1} is F. In some embodiments, each of R^{a1} and R^{b1} is methyl. In some embodiments, each of R^{a1} and R^{b1} is H. In some embodiments, each of R^{a2} and R^{b2} is H. In some embodiments, one of R^{a1} and R^{b1} is deuterium. In some embodiments, each of R^{a1} and R^{b1} is deuterium. In some embodiments, R^{a2} and R^{b2} join together to form a 3-6 membered carbocycle, such as cyclopropyl. In some embodiments, R^1 is selected from:

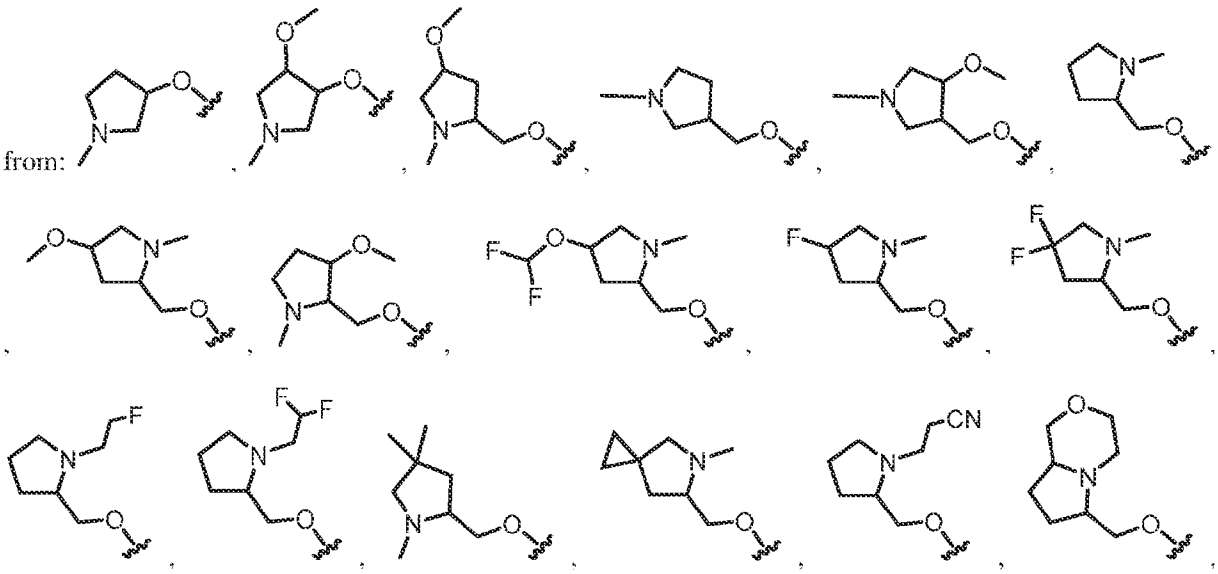


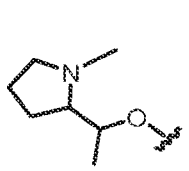
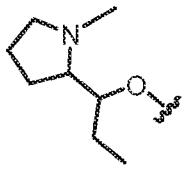
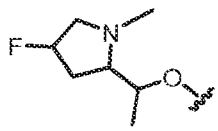
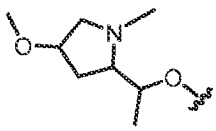
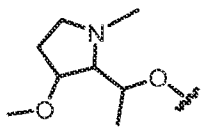
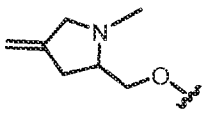
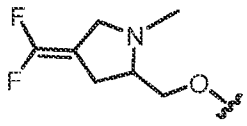
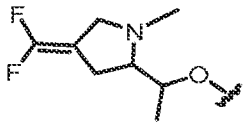
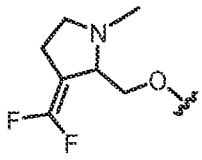
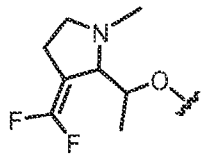
, and .

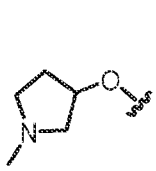
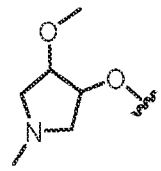
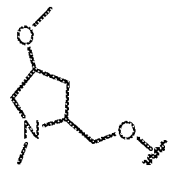
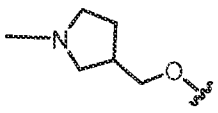
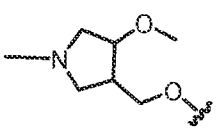
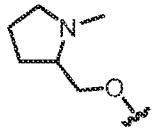
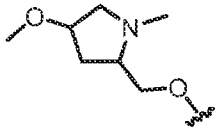
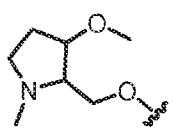
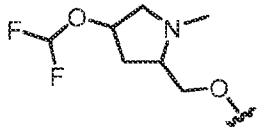
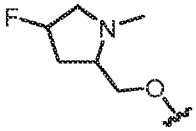
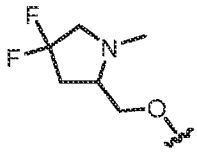
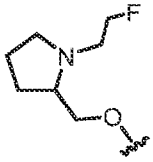
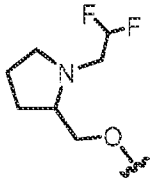
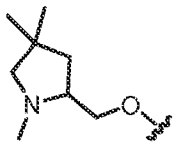
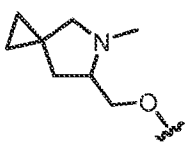
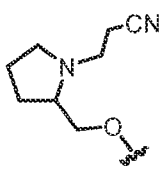
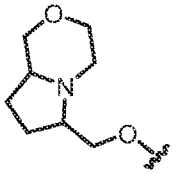
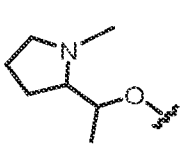
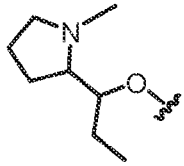
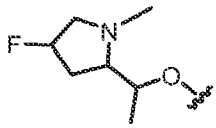
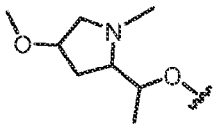
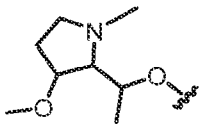
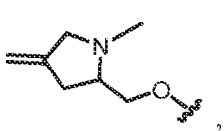
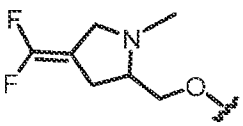
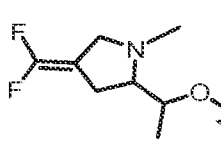
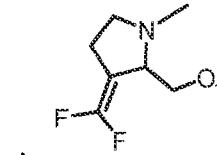
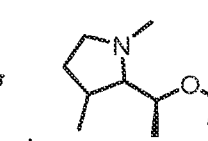
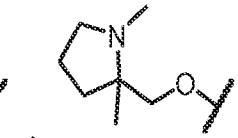
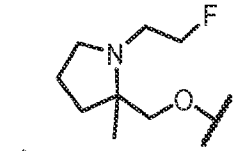
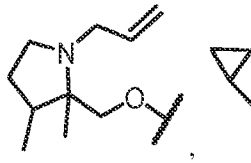
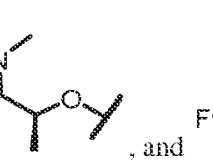
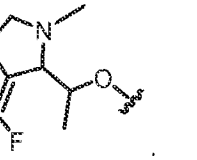
[0233] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^1 is selected from:

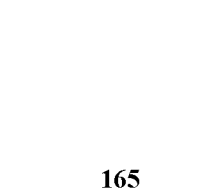


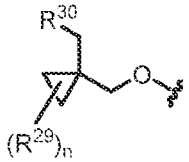
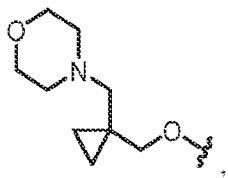
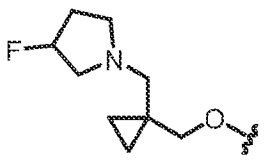
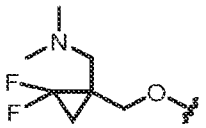
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H; and each R^c is independently selected from C_{1-6} alkyl and H, wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}. In some embodiments, each R^a is H. In some embodiments, each R^b is H. In some embodiments, each R^a and R^b is H. In some embodiments, at least one R^a or R^b is selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, and $-OR^{12}$. In some embodiments, one R^a or R^b is selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, and $-OR^{12}$, and the other R^as and R^bs are H. In some embodiments, one R^a is C_{2-6}alkenyl that is unsubstituted or substituted with one or more R^{13}, and the R^b that is connected to the same atom is absent. In some embodiments, one R^a is C_2alkenyl that is unsubstituted or substituted with one or more R^{13}, and the R^b that is connected to the same atom is absent. In some embodiments, one R^a is C_{2-6}alkenyl that is unsubstituted, and the R^b that is connected to the same atom is absent. In some embodiments, one R^a is C_2alkenyl that is substituted with one or more R^{13}, and the R^b that is connected to the same atom is absent. In some embodiments, the R^c linked to the nitrogen atom is selected from C_{1-6}alkyl. In some embodiments, the R^c linked to the nitrogen atom is selected from methyl. In some embodiments, the R^c that is not linked to the nitrogen atom is H. In some embodiments, the R^c that is not linked to the nitrogen atom is selected from C_{1-6}alkyl. In some embodiments, the R^c that is not linked to the nitrogen atom is methyl. In some embodiments, R^1 is selected from:

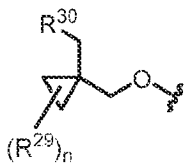











, and  .

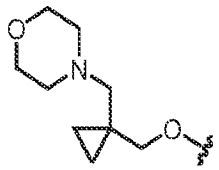
[0234] In some embodiments, R^1 is selected from: 
































, and  .

[0235] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^1 is selected from  , wherein: R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; each R^{28} is independently selected from $C_{1\text{-}6}$alkyl and halogen; and each R^{29} is independently selected from halogen and $C_{1\text{-}6}$alkyl; and n is 0-2. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, at least one R^{29} is halogen. In some embodiments, each R^{29} is independently selected from halogen. In some embodiments, at least one R^{29} is independently selected from $C_{1\text{-}6}$alkyl. In some embodiments, each R^{29} is independently selected from $C_{1\text{-}6}$alkyl. In some embodiments, R^{30} is $N(R^{14})_2$. In some embodiments, R^{30} is $N(CH_3)_2$. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is substituted with one or more R^{28}. In some embodiments, R^1 is selected from:  ,  , and  .

[0236] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^1 is selected from  , wherein: R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; R^{28} is independently selected from $C_{1\text{-}6}$alkyl, $-OR^{12}$, $C_{1\text{-}6}$heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen; and each

R^{29} is independently selected from halogen and C_{1-6}alkyl; and n is 0-2. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, at least one R^{29} is halogen. In some embodiments, each R^{29} is independently selected from halogen. In some embodiments, at least one R^{29} is independently selected from C_{1-6}alkyl. In some embodiments, each R^{29} is independently selected from C_{1-6}alkyl. In some embodiments, R^{30} is $N(R^{14})_2$. In some embodiments, R^{30} is $N(CH_3)_2$. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is substituted with one or more R^{28}. In some embodiments, R^1 is selected from: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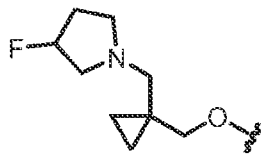
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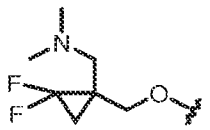
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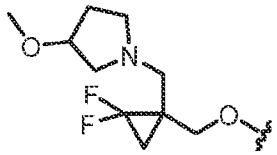
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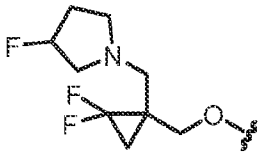
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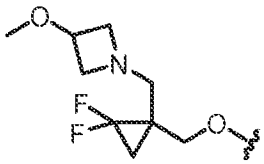
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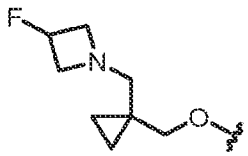
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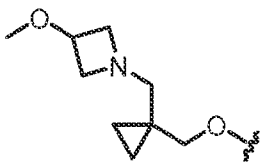
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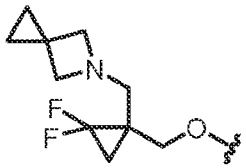
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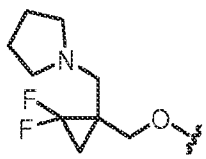
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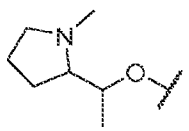
[0237] In some embodiments according to Formula II or III, R^1 is selected from: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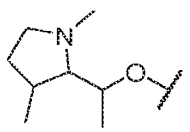
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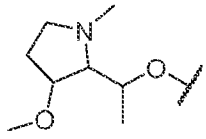
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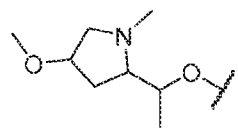
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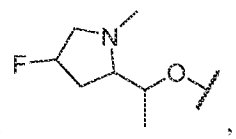
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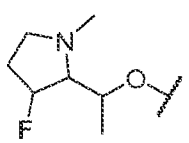
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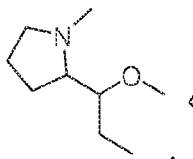
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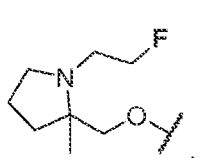
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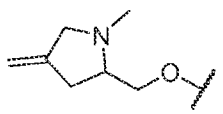
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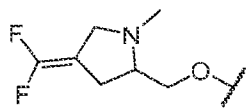
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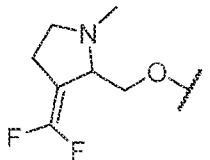
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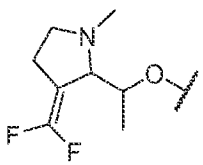
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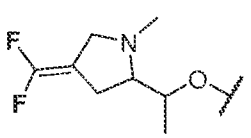
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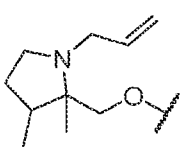
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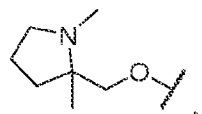
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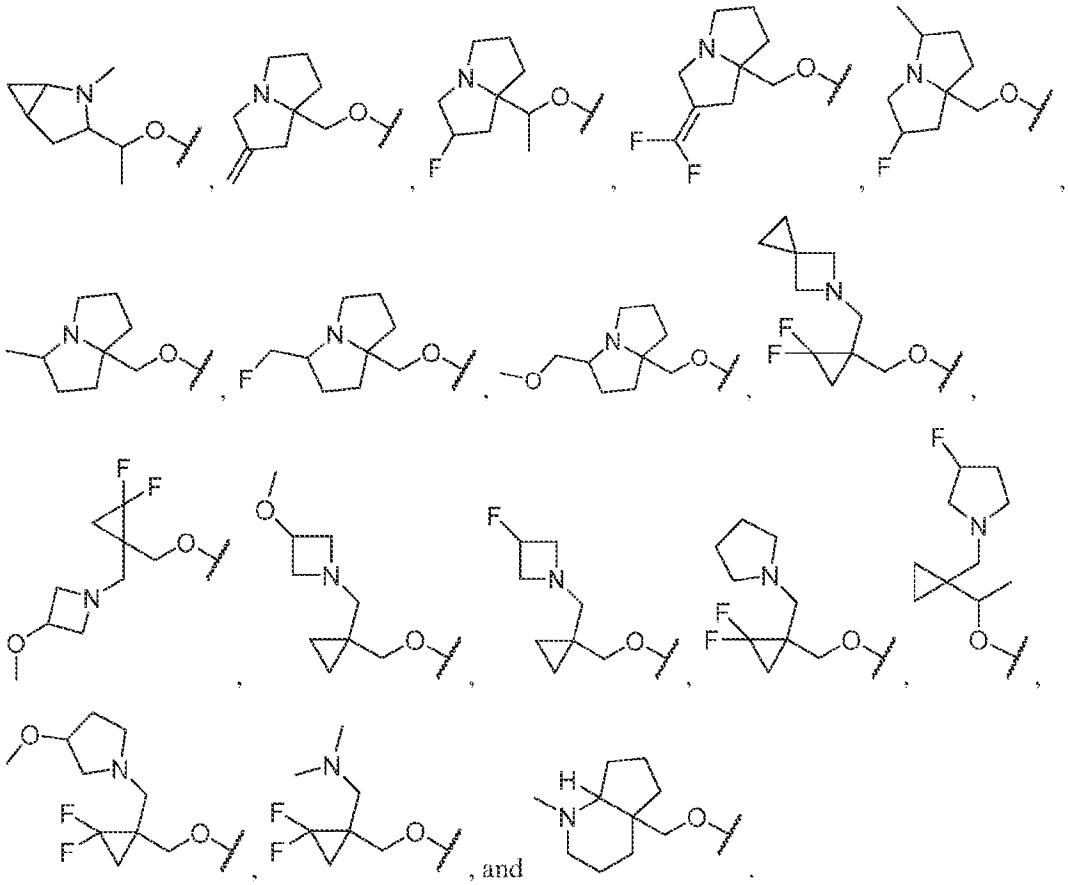
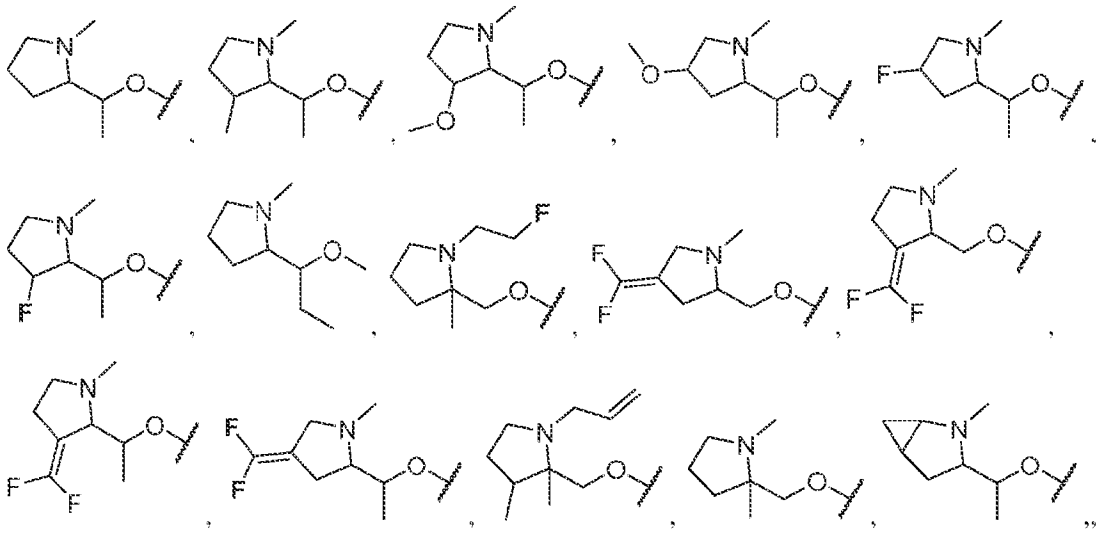


, and

[0238] In some embodiments according to Formula II' or III, R^1 is selected from:



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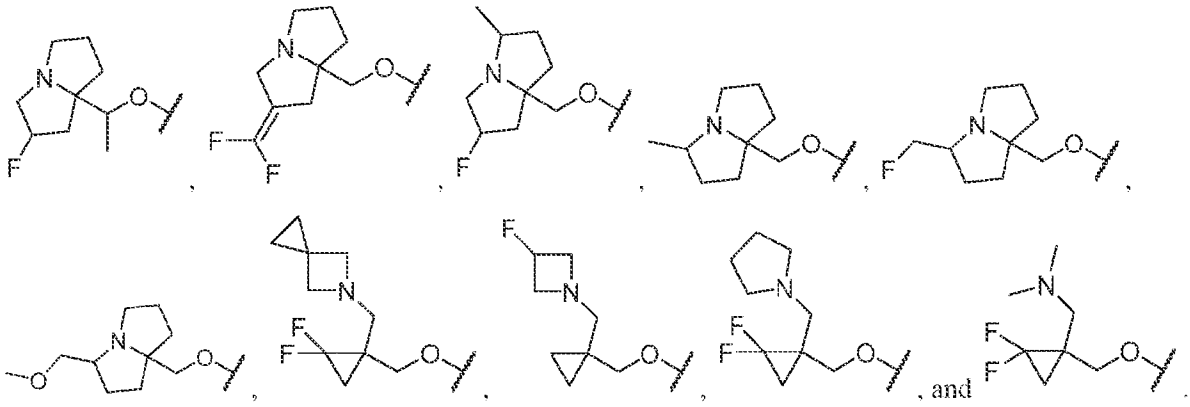
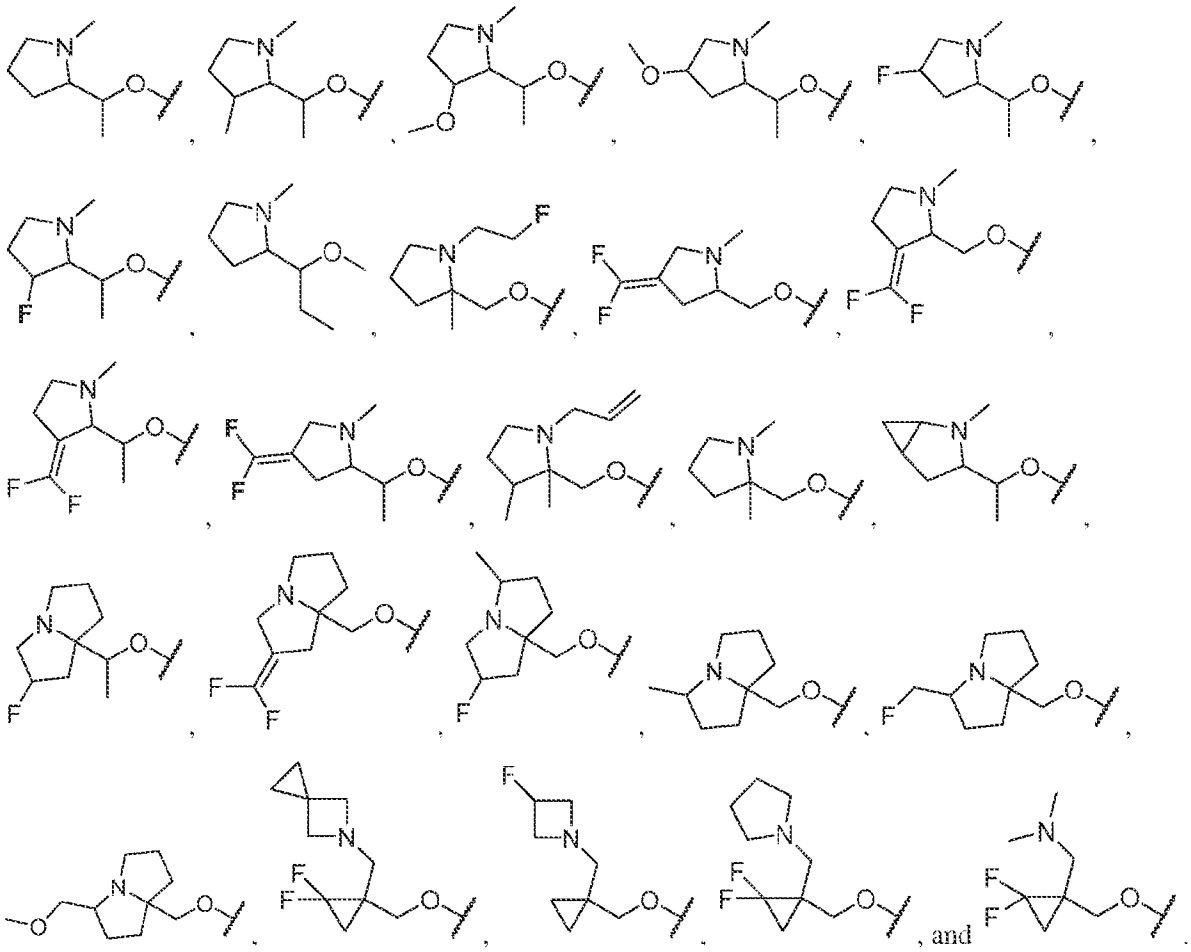
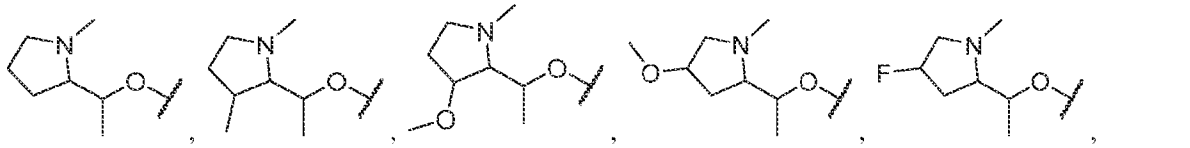
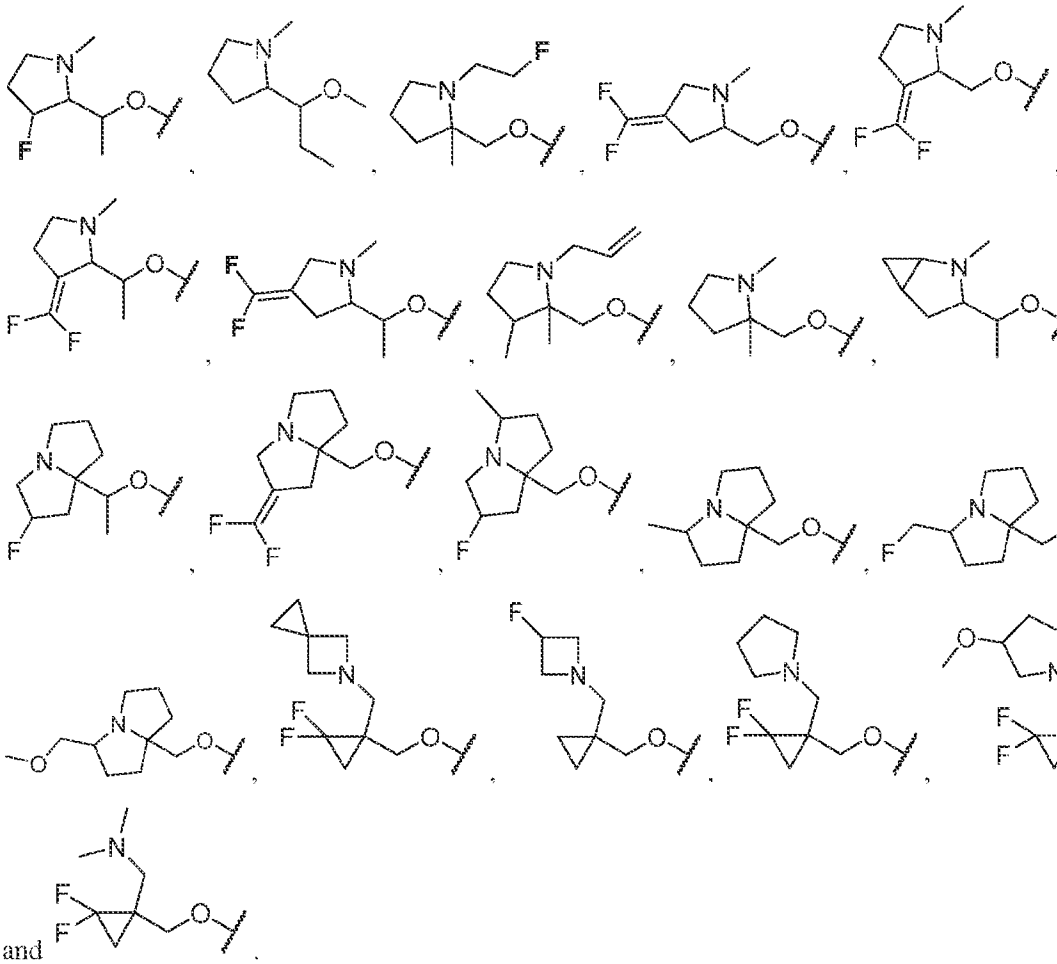


[0239] In some embodiments according to Formula II'' or III, R^1 is selected from:



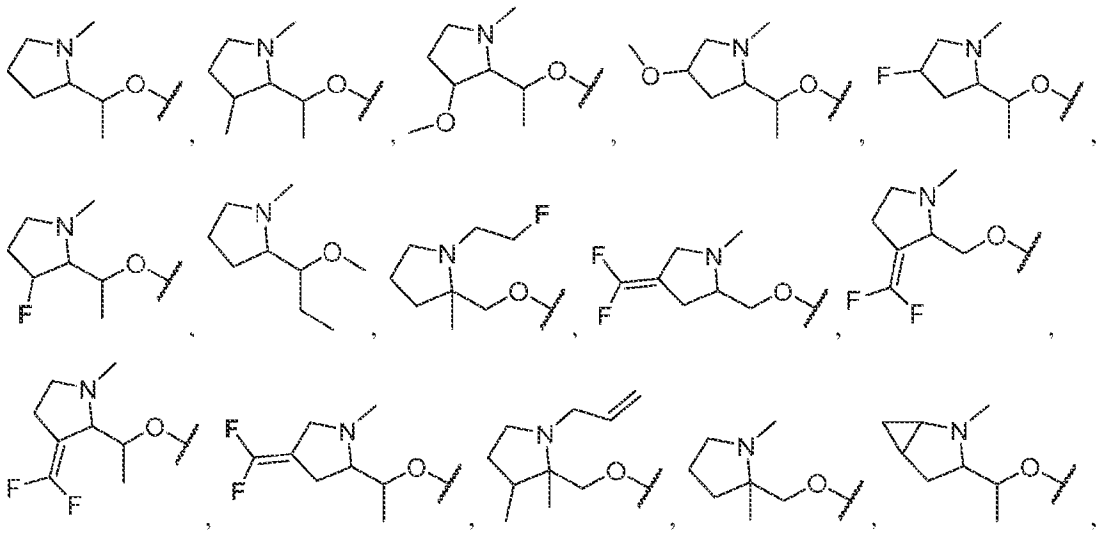
[0240] In some embodiments according to Formula IIAA' or III, R^1 is selected from:

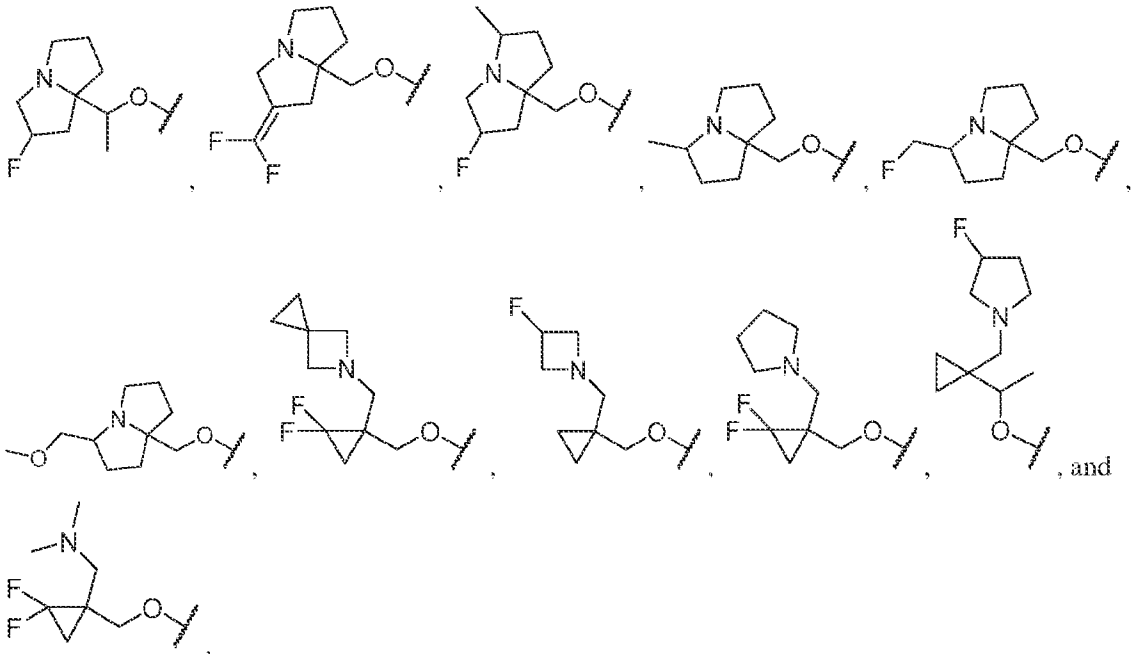




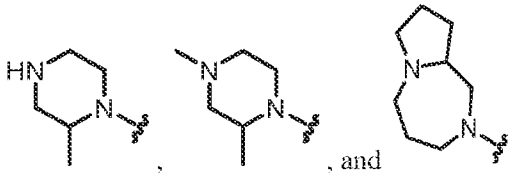
and

[0241] In some embodiments according to Formula IIAA1' or III, R^1 is selected from:





[0242] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl. In some embodiments, R^1 is an unsubstituted heterocycle comprising one or more N atoms. In some embodiments, R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl. In some embodiments, R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl. In some embodiments, R^1 is a monocyclic heterocycle containing one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}. In some embodiments, R^1 is a piperazine that is unsubstituted or substituted with one or more R^{31}. In some embodiments, R^1 is a piperazine that is substituted with one or more R^{31}. In some embodiments, R^1 is a bicyclic heterocycle containing one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}. In some embodiments, R^1 is a 10-membered bicyclic heterocycle containing one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}. In some embodiments, R^1 is a 10-membered bicyclic heterocycle

containing two N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}. In some embodiments, R^1 is selected from:  .

[0243] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^1 is H.

[0244] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^5 is a halogen (e.g., F or Cl). In some embodiments, R^5 is Cl. In some embodiments, R^5 is F. In some embodiments, R^5 is selected from $C_{1\text{-}6}$alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^5 is selected from $C_{1\text{-}6}$alkyl that is unsubstituted. In some embodiments, R^5 is selected from $C_{1\text{-}6}$alkyl that is substituted with one or more R^{13}. In some embodiments, R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$. In some embodiments, R^5 is $-CF_3$. In some embodiments, R^5 is $-OC_{1\text{-}6}$ alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^5 is $-OC_{1\text{-}6}$ alkyl that is substituted with one or more R^{13}. In some embodiments, R^5 is $-OCH_3$ or $-OCF_3$. In some embodiments, R^5 is -CN. In some embodiments, R^5 is H. In some embodiments, R^5 is 5- to 6-membered heteroaryl. In some such embodiments, R^5 is furanyl.

[0245] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, R^7 is F. In some embodiments, R^7 is Cl.

[0246] In some embodiments, for a compound according to any one of Formulas II, II', II'', III, II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1', IIAA1, IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1, the compound is not a compound included in Table 1, or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof.

Table 1.

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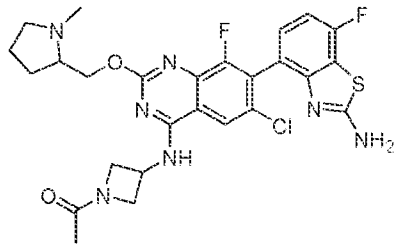
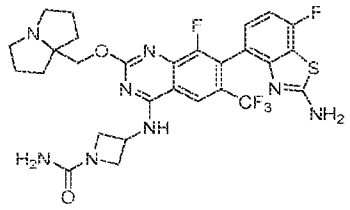
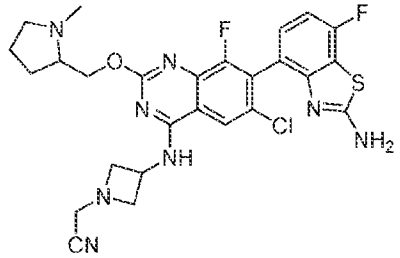
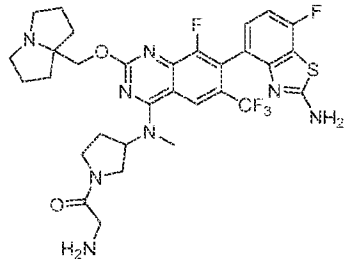
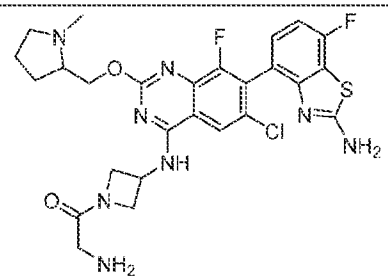
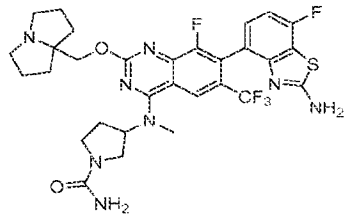
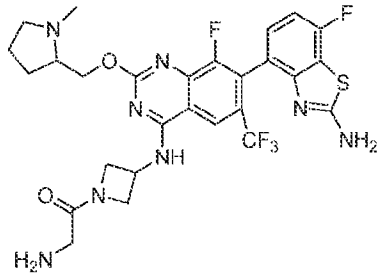
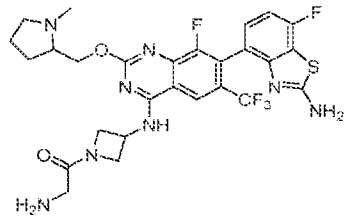
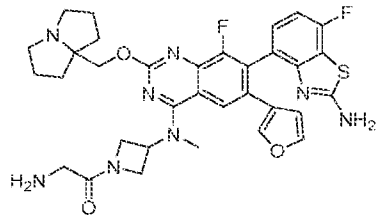
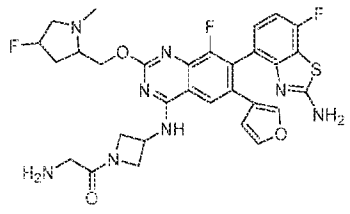
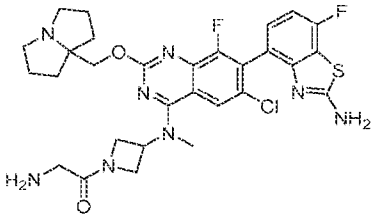
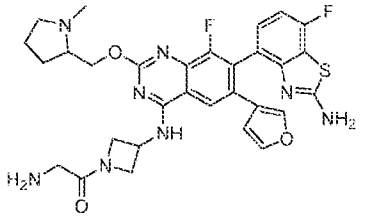
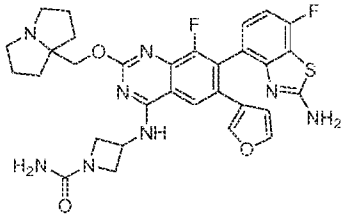
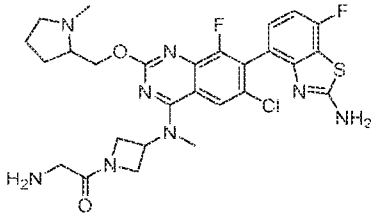
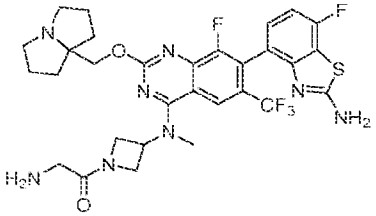
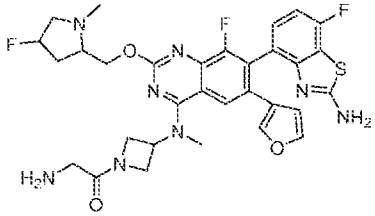
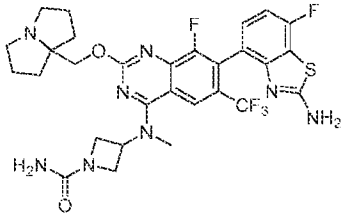
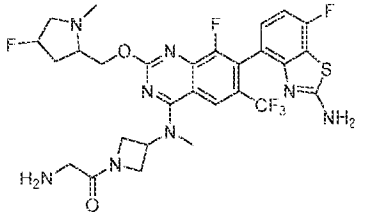
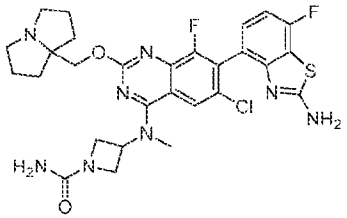
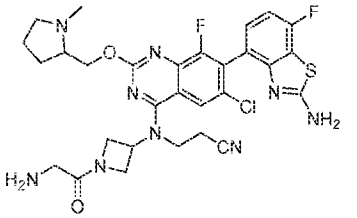
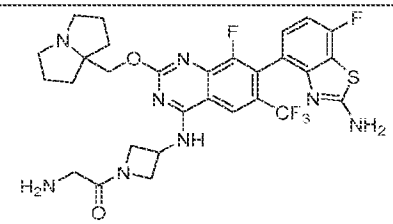
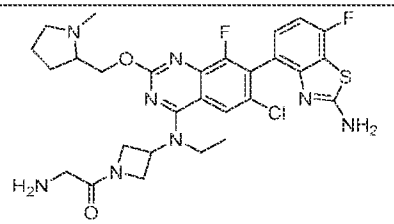
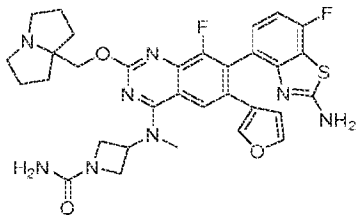
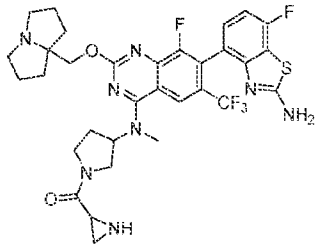
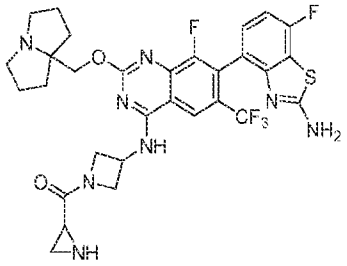
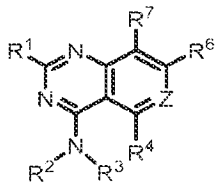
II-67a		II-188	
II-79a		II-276	
II-97a		II-278	
II-114a		II-130	
II-163		II-137	

Compound Number	Structure	Compound Number	Structure
II-164		II-146	
II-167		II-147	
II-171		II-150	
II-173		II-156	
II-182		II-183	
II-187		II-197	

Compound Number	Structure	Compound Number	Structure
II-151		II-230a	
II-235			

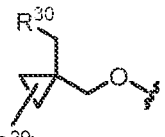
[0247] In another aspect, the present disclosure provides a compound represented by Formula III:



(III)

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

Z is N or C-R^5;

R^1 is selected from H, -OR^8,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated;

R^3 is selected from 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, a 4-10 membered heterocycle, or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10};

or wherein R^2 and R^3 optionally come together to form a 7-9 membered heterocyle, which is optionally substituted with one or more R^{10};

R^4 is H, $-OR^{12}$,or $-N(R^{14})_2$;

R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, $-OC_{1-6}$alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a phenyl, naphthyl, or bicyclic heteroaryl, wherein the phenyl, naphthyl, or bicyclic heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen or H;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl, and C_{1-6}alkyl is optionally deuterated (e.g. $-CH_2-$ or $-CD_2-$);

each R^{10} is independently selected from deuterium, $-OR^{12}$, =O, =S, -CN, $-N=S(=O)Me_2$, $-C(O)(C_{1-6}$alkylene)CN, $-C(O)(C_{1-6}$alkylene)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), $-C(O)O$(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),$-C(O)O(C_{1-6}$alkylene)(3-6 membered heterocycle), $-S(O)_2(C_{1-6}$alkyl), $-C(S)(C_{1-6}$alkyl), $-C(S)O(C_{1-6}$alkyl), $-C(S)N(C_{1-6}$alkyl)$_2$, $-C(=N-OR^{12})(C_{1-6}$ alkyl), $-C(O)N(R^{12})OR^{12}$, halogen, phenyl, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{2-6} alkenyl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, $-OC(O)R^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-8 membered heterocycle, C_{1-6} alkyl, $-OR^{12}$, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, -OH, halogen, $-N(R^{12})_2$, -CN, C_{2-6} alkynyl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), -C(O)OR^{12}, -C(O)$N(R^{12})_2$, -$S(O)_2R^{12}$, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl, -OR^{12}, C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, , , -C_{1-6} heteroalkyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0248] In some embodiments, the present disclosure provides a compound of Formula III, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

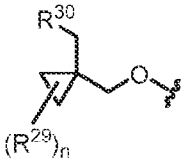
[0249] As described herein, for a compound according to Formula II or III, Z is N or C-R^5.

[0250] In some embodiments of Formula II or III, Z is N.

[0251] In some embodiments of Formula II or III, Z is C-R^5. In some embodiments,of Formula II or III, Z is C-R^5, wherein R^5 is halogen. In some embodiments of Formula II or III, Z is C-R^5, wherein R^5 is Cl. In some embodiments of Formula II or III, Z is C-R^5, wherein R^5 is F. In some embodiments of Formula II or III, Z is C-R^5, wherein R^5 is C_{1-6}alkyl, wherein C_{1-6}alkyl unsubstituted or substituted with one or more R^{13}. In some embodiments of Formula II or III, Z is C-R^5, wherein R^5 is C_{1-2}alkyl, wherein C_{1-2} alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments,of Formula II or III, Z is C-R^5, wherein R^5 is CH_3. In some embodiments of Formula II or III, Z is C-R^5, wherein R^5 is CF_3. In some embodiments of Formula II or III, Z is C-R^5, wherein R^5 is H. In some embodiments of Formula II or III, Z is C-R^5, wherein R^5 is CN.

[0252] In some embodiments of Formula II or III, Z is N or C-R^5, wherein R^5 is selected from halogen, C_{1-2}alkyl, H, and CN, wherein C_{1-2} alkyl is unsubstituted or substituted with one or more R^{13}.

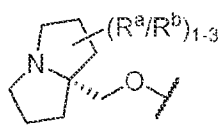
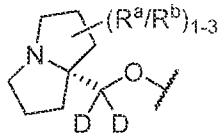
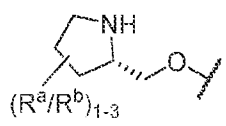
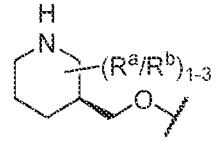
[0253] In some embodiments of Formula II or III, Z is N or C-R^5, wherein R^5 is selected from Cl, F, CH_3, CF_3, H, and CN.

[0254] As described herein, for a compound of Formula II or III, R^1 is selected from H, -OR^8,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}.

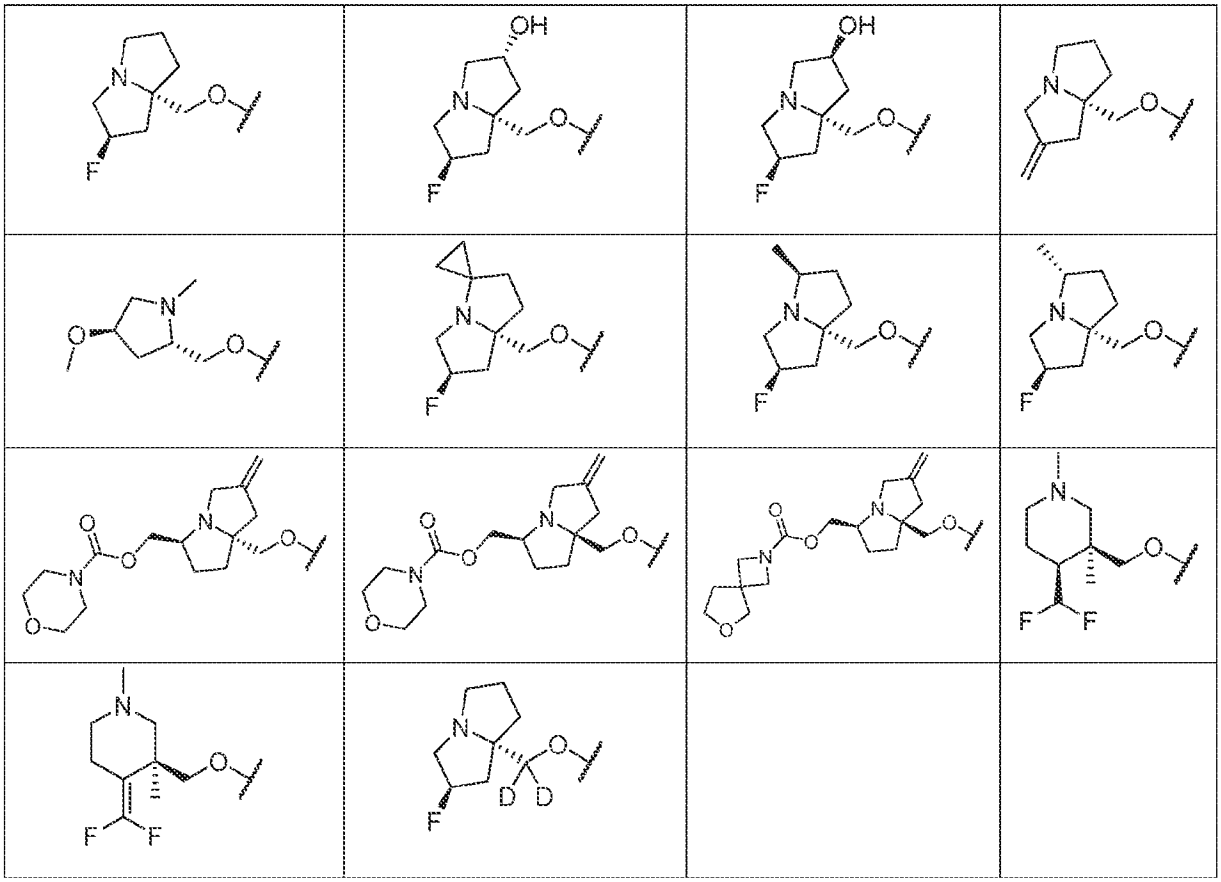
[0255] In some embodiments of Formula II or III, R^1 is H.

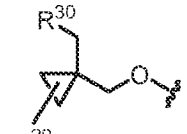
[0256] In some embodiments of Formula II or III, R^1 is -OR^8. In some embodiments of Formula II or III, R^1 is -O(alkylheterocycle), wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl, and C_{1-6}alkyl is optionally deuterated (e.g. -CH_2- or -CD_2-). In some embodiments of Formula II or III, R^1 is -O(alkylheterocycle), wherein any heterocycle comprises 4-9 ring atoms and is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl, and C_{1-6}alkyl is optionally deuterated (e.g. -CH_2- or -CD_2-). In some embodiments of Formula II or III, R^1 is -O(alkylheterocycle), wherein any heterocycle comprises 4-9 ring atoms and is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-2} alkyl, and C_{1-2} alkyl is optionally deuterated (e.g. -CH_2- or -CD_2-). In some embodiments of Formula II or III, R^1 is -O(alkylheterocycle), wherein any heterocycle comprises 4-9 ring atoms and is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-2} alkyl. In some embodiments of Formula II or III, R^1 is -O(alkylheterocycle), wherein any heterocycle comprises 4-9 ring atoms and is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-2} alkyl, and C_{1-2} alkyl is deuterated (e.g. -CD_2-).

[0257] In some embodiments of Formula II or III, R^1 is selected from:

[0258] In some embodiments of Formula II or III, R^1 is selected from:



[0259] In some embodiments of Formula II or III, R^1 is  .

[0260] In some embodiments of Formula II or III, R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}.

[0261] As described herein, for a compound of Formula II or III, R^2 is selected from H, $C_{1\text{-}6}$alkyl, and a 3-6 membered carbocycle, wherein any $C_{1\text{-}6}$ alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated. In some embodiments, R^5 is selected from halogen. In some embodiments, R^5 is Cl. In some embodiments, R^5 is selected from $C_{1\text{-}6}$alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^5 is selected from $C_{1\text{-}6}$alkyl that is substituted with one or more halogen. In some embodiments, R^5 is CF_2H or CF_3. In some embodiments, R^5 is CF_3.

[0262] In some embodiments of Formula II or III, R^2 is H.

[0263] In some embodiments of Formula II or III, R^2 is $C_{1\text{-}6}$alkyl, which is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated. In some embodiments of Formula II or III, R^2 is $C_{1\text{-}2}$ alkyl, which is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated. In some

embodiments of Formula II or III, R^2 is C_{1-6}alkyl. In some embodiments of Formula II or III, R^2 is C_{1-6}alkyl and is deuterated. In some embodiments of Formula II or III, R^2 is C_{1-2}alkyl. In some embodiments of Formula II or III, R^2 is C_{1-2}alkyl and is deuterated. In some embodiments of Formula II or III, R^2 is methyl. In some embodiments of Formula II or III, R^2 is ethyl. In some embodiments of Formula II or III, R^2 is propyl. In some embodiments of Formula II or III, R^2 is deuterated ethyl.

[0264] In some embodiments of Formula II or III, R^2 is a 3-6 membered carbocycle.

[0265] In some embodiments of Formula II or III, R^2 is selected from C_{1-6}alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated. In some embodiments, for a compound according to Formula II or III, R^2 is ethyl (e.g., $-CH_2CH_3$).

[0266] In some embodimentsof Formula II or III, R^2 is selected from methyl ethyl, propyl, and deuterated ethyl.

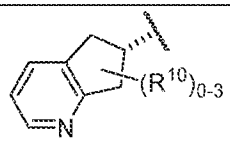
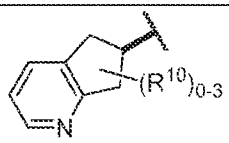
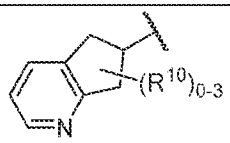
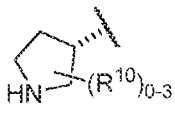
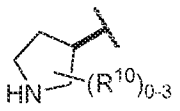
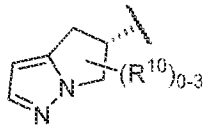
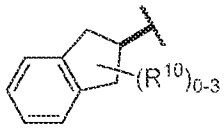
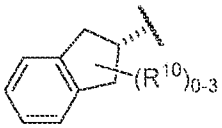
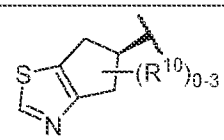
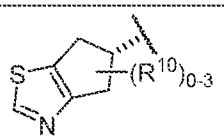
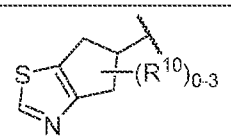
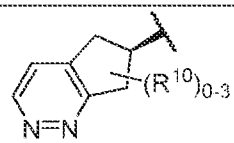
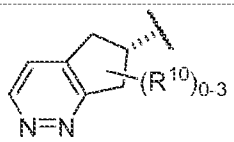
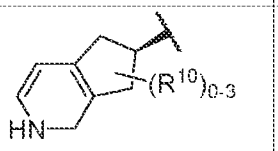
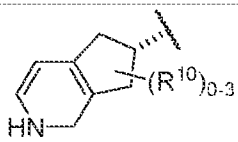
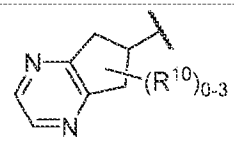
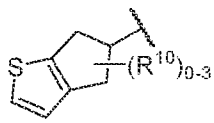
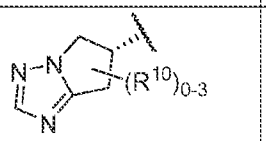
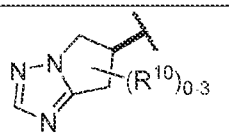
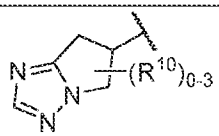
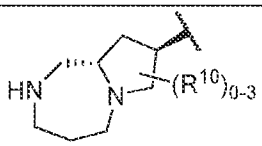
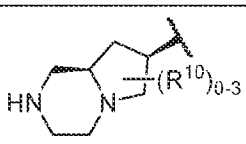
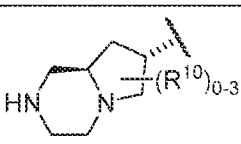
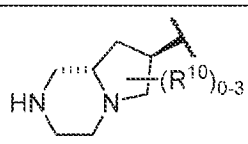
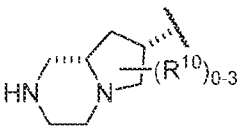
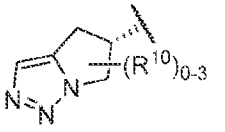
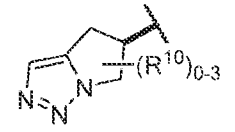
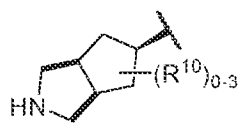
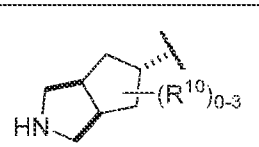
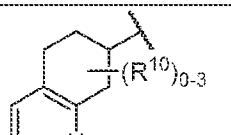
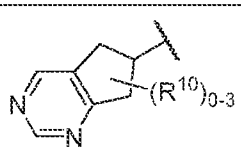
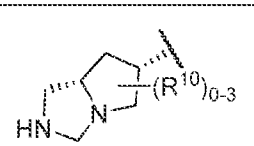
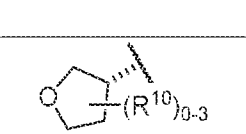
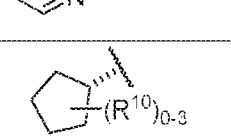
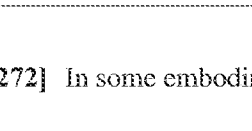
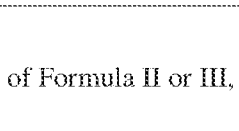
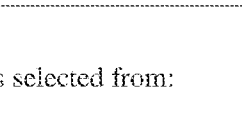
[0267] As described herein, for a compound of Formula II or III, R^3 is selected from 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, a 4-10 membered heterocycle, or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10}.

[0268] In some embodiments of Formula II or III, R^3 is 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10}. In some embodiments of Formula II or III, R^3 is 3- to 6-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10}. In some embodimentsof Formula II or III, R^3 is 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, which is unsubstituted or substituted with one or more R^{10}. In some embodimentsof Formula II or III, R^3 is 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered heterocycle, which is unsubstituted or substituted with one or more R^{10}. In some embodiments of Formula II or III, R^3 is 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered heteroaryl, which is unsubstituted or substituted with one or more R^{10}. In some embodiments, R^2 is ethyl.

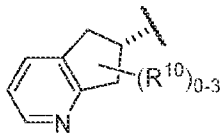
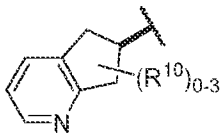
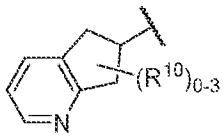
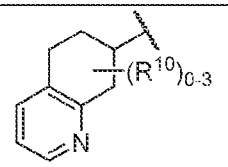
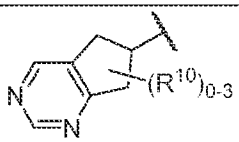
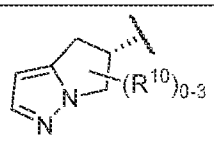
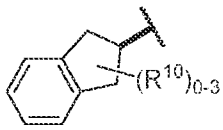
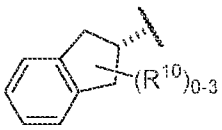
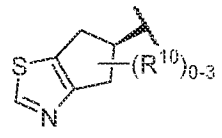
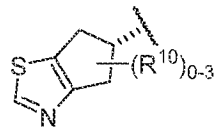
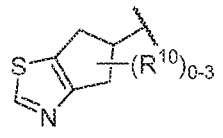
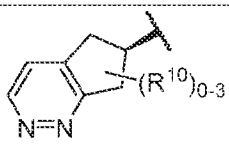
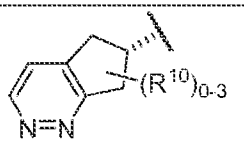
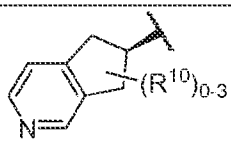
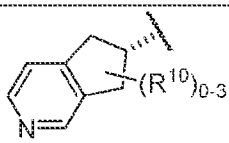
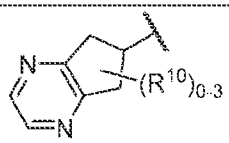
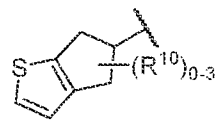
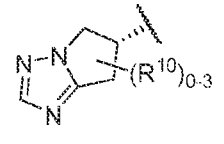
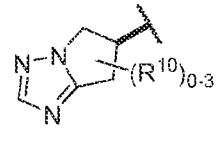
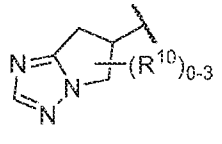
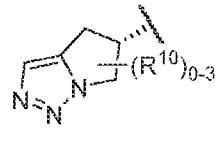
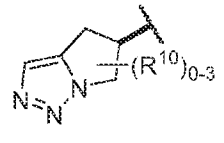
[0269] In some embodiments of Formula II or III, R^3 is a 4-10 membered heterocycle, which is unsubstituted or substituted with one or more R^{10}.

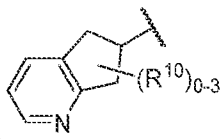
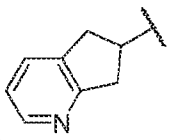
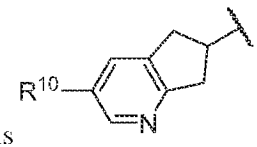
[0270] In some embodiments of Formula II or III, R^3 is -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein a heteroaryl is unsubstituted or substituted with one or more R^{10}.

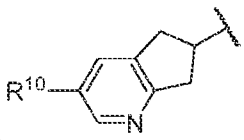
[0271] In some embodiments of Formula II or III, R^3 is selected from:

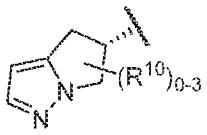
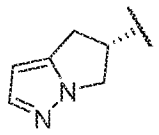
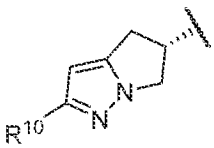
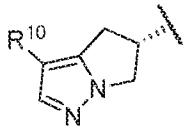
			
			
			
			
			
			
			
			
			
			

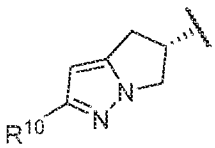
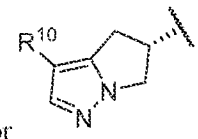
[0272] In some embodiments of Formula II or III, R^3 is selected from:

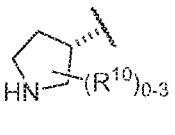
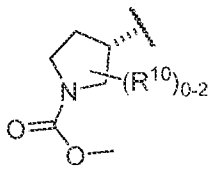
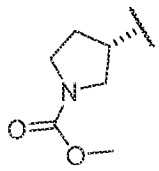
			
			
			
			
			
			

[0273] In some embodiments, for a compound according to Formula II or III, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  .

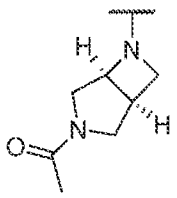
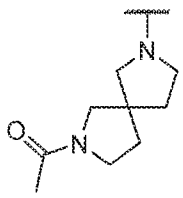
[0274] In some embodiments, R^3 is  , where R^{10} is selected from halogen, $-OR^{12}$, and -CN. R^{10} is selected from F, -CN, and $-OCH_3$.

[0275] In some embodiments, for a compound according to Formula II or III, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  or  .

[0276] In some embodiments, R^3 is  or  , where R^{10} is selected from halogen, $-OR^{12}$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}. In some embodiments, R^{10} is selected from $-CH_3$, $-CF_2H$, $-CH_2F$, -F, $-OCH_3$, and -CN.

[0277] In some embodiments, for a compound according to Formula II or III, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  .

[0278] As described herein, for a compound of Formula II or III, R^2 and R^3 can optionally come together to form a 7-9 membered heterocycle, which is optionally substituted with one or more R^{10}

[0279] In some embodimentsof Formula II or III, R^2 and R^3 optionally come together to form a 7-9 membered heterocycle, which is optionally substituted with $-C(O)(C_{1-6}$alkyl). In some embodimentsof Formula II or III, R^2 and R^3 optionally come together to form  or  .

[0280] As described herein, for a compound of Formula II or III, R^4 is H, $-OR^{12}$,or $-N(R^{14})_2$.

[0281] In some embodiments of Formula II or III, R^4 is H.

[0282] In some embodiments of Formula II or III, R^4 is $-OR^{12}$. In some embodiments of Formula II or III, R^4 is $-O(C_{1-6}$ alkyl). In some embodiments, for a compound according to Formula II or III, R^4 is $-O(C_{1-2}$ alkyl). In some embodiments of Formula II or III, R^4 is $-OCH_3$.

[0283] In some embodiments of Formula II or III, R^4 is $-N(R^{14})_2$. In some embodiments of Formula II or III, R^4 is $-N(C_{1-6}$ alkyl$)_2$. In some embodiments of Formula II or III, R^4 is $-N(C_{1-2}$ alkyl$)_2$. In some embodiments of Formula II or III, R^4 is $-N(CH_3)_2$.

[0284] In some embodimentsof Formula II or III, R^4 is H, $-OCH_3$, or $-N(CH_3)_2$.

[0285] As described herein, for a compound of Formula II or III, R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, $-OC_{1-6}$alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

[0286] In some embodimentsof Formula II or III, R^5 is halogen. In some embodimentsof Formula II or III, R^5 is fluoro. In some embodimentsof Formula II or III, R^5 is chloro.

[0287] In some embodimentsof Formula II or III, R^5 is -CN.

[0288] In some embodimentsof Formula II or III, R^5 is 5- to 6-membered heteroaryl.

[0289] In some embodimentsof Formula II or III, R^5 is $-OC_{1-6}$alkyl.

[0290] In some embodimentsof Formula II or III, R^5 is C_{1-6}alkyl, which is unsubstituted or substituted with one or more R^{13}. In some embodimentsof Formula II or III, R^5 is C_{1-2} alkyl, which is unsubstituted or substituted with one or more R^{13}. In some embodimentsof Formula II or III, R^5 is $-CH_3$. In some embodimentsof Formula II or III, R^5 is $-CF_3$.

[0291] In some embodimentsof Formula II or III, R^5 is H.

[0292] In some embodimentsof Formula II or III, R^5 is selected from halogen, -CN, C_{1-2} alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

[0293] In some embodimentsof Formula II or III, R^5 is selected from fluoro, chloro, -CN, $-CH_3$, $-CF_3$, and H.

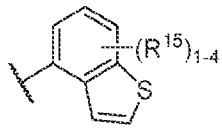
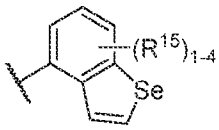
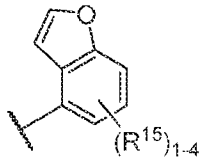
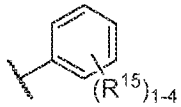
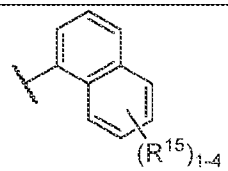
[0294] As described herein, for a compound of Formula II or III, R^6 is a phenyl, naphthyl, or bicyclic heteroaryl, wherein the phenyl, naphthyl, or bicyclic heteroaryl is substituted with one or more R^{15}. In some embodimentsof Formula II or III, R^6 is a phenyl or a bicyclic heteroaryl, wherein the phenyl or bicyclic heteroaryl is substituted with one or more R^{15}.

[0295] In some embodimentsof Formula II or III, R^6 is a phenyl, wherein the phenyl is substituted with one or more R^{15}.

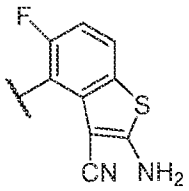
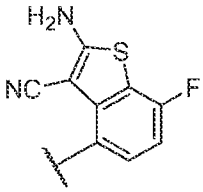
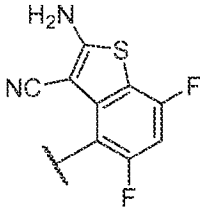
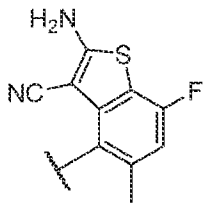
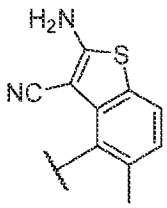
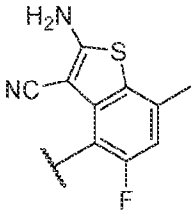
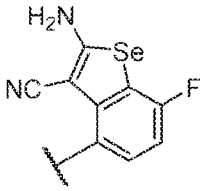
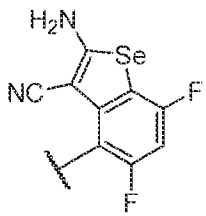
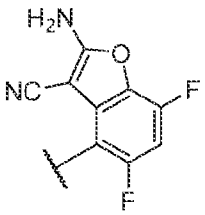
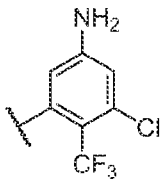
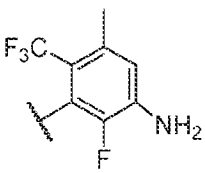
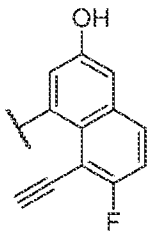
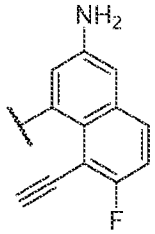
[0296] In some embodimentsof Formula II or III, R^6 is a naphthyl, wherein the naphthyl is substituted with one or more R^{15}.

[0297] In some embodimentsof Formula II or III, R^6 is a bicyclic heteroaryl, wherein the bicyclic heteroaryl is substituted with one or more R^{15}.

[0298] In some embodimentsof Formula II or III, R^6 is selected from:

[0299] In some embodimentsof Formula II or III, R^6 is selected from:

[0300] As described herein, for a compound of Formula II or III, R^7 is selected from halogen or H.

[0301] In some embodiments of Formula II or III, R^7 is H.

[0302] In some embodiments of Formula II or III, R^7 is halogen. In some embodiments of Formula II or III, R^7 is fluoro.

[0303] In some embodiments of Formula II or III, R^7 is H or fluoro.

[0304] As described herein, for a compound of Formula II or III, R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl, and C_{1-6}alkyl is optionally deuterated (e.g. $-CH_2-$ or $-CD_2-$). In some embodiments of Formula II or III, R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl.

[0305] In some embodiments of Formula II or III, R^8 is a heterocycle, wherein any heterocycle comprises 4-9 ring atoms and is substituted with one or more R^a or R^b.

[0306] In some embodiments of Formula II or III, R^8 is an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl, and C_{1-6}alkyl is optionally deuterated (e.g. $-CH_2-$ or $-CD_2-$). In some embodiments of Formula II or III, R^8 is an alkylheterocycle wherein any heterocycle comprises 4-9 ring atoms and is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-2} alkyl, and C_{1-2} alkyl is optionally deuterated (e.g. $-CH_2-$ or $-CD_2-$). In some embodiments of Formula II or III, R^8 is an alkylheterocycle wherein any heterocycle comprises 4-9 ring atoms and is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-2} alkyl. In some embodiments of Formula II or III, R^8 is an alkylheterocycle wherein any heterocycle comprises 4-9 ring atoms and is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-2} alkyl, and C_{1-2} alkyl is deuterated (e.g. $-CD_2-$).

[0307] As described herein, for a compound of Formula II or III, each R^{10} is independently selected from deuterium, $-OR^{12}$, =O, =S, -CN, $-N=S(=O)Me_2$, $-C(O)(C_{1-6}$alkylene)CN, $-C(O)(C_{1-6}$alkylene)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),$-C(O)O(C_{1-6}$alkylene)(3-6 membered heterocycle), $-S(O)_2(C_{1-6}$alkyl), $-C(S)(C_{1-6}$alkyl), $-C(S)O(C_{1-6}$alkyl), $-C(S)N(C_{1-6}$alkyl$)_2$, -C(=N-

OR^{12})(C_{1-6} alkyl), -C(O)N(R^{12})OR^{12}, halogen, phenyl, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{2-6} alkenyl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle. In some embodiments of Formula II or III, each R^{10} is independently selected from deuterium, -OR^{12}, =O, =S, -CN, -N=S(=O)Me_2, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),-C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), -C(S)(C_{1-6}alkyl), -C(S)O(C_{1-6}alkyl), -C(S)N(C_{1-6}alkyl)$_2$, -C(=N-OR^{12})(C_{1-6} alkyl), -C(O)N(R^{12})OR^{12}, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle.

[0308] In some embodiments of Formula II or III, each R^{10} is independently -OR^{12}. In some embodiments of Formula II or III, each R^{10} is independently -O(C_{1-6} alkyl). In some embodiments of Formula II or III, each R^{10} is independently -O(C_{1-2} alkyl). In some embodiments of Formula II or III, each R^{10} is independently -OCH_3.

[0309] In some embodiments of Formula II or III, each R^{10} is independently =O.

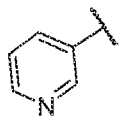
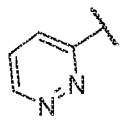
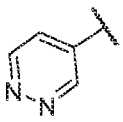
[0310] In some embodiments of Formula II or III, each R^{10} is independently =S.

[0311] In some embodiments of Formula II or III, each R^{10} is independently -CN.

[0312] In some embodiments of Formula II or III, each R^{10} is independently -C(O)O(C_{1-6}alkyl), wherein C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}. In some embodiments, for a compound according to Formula II or III, each R^{10} is independently -C(O)O(C_{1-2}alkyl), wherein C_{1-2} alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}. In some embodiments of Formula II or III, each R^{10} is independently -C(O)OCH_3. In some embodiments of Formula II or III, each R^{10} is independently -C(O)O(CD_3).

[0313] In some embodiments of Formula II or III, each R^{10} is independently halogen. In some embodiments of Formula II or III, each R^{10} is independently fluoro. In some embodiments of Formula II or III, each R^{10} is independently chloro.

[0314] In some embodiments of Formula II or III, each R^{10} is independently phenyl.

[0315] In some embodiments of Formula II or III, each R^{10} is independently a 5-6 membered heteroaryl. In some embodiments of Formula II or III, each R^{10} is independently  ,  , or  .

[0316] In some embodiments of Formula II or III, each R^{10} is independently a 3-6 membered carbocycle. In some embodiments of Formula II or III, each R^{10} is independently cyclopropyl or cyclobutyl.

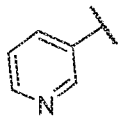
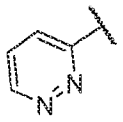
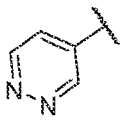
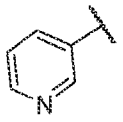
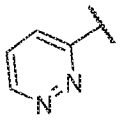
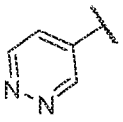
[0317] In some embodiments of Formula II or III, each R^{10} is independently C_{2-6} alkenyl. In some embodiments of Formula II or III, each R^{10} is independently C_2 alkenyl.

[0318] In some embodiments of Formula II or III, each R^{10} is independently C_{1-6}alkyl, which is optionally deuterated and is unsubstituted or substituted with one or more R^{20}. In some embodiments of Formula II or III, each R^{10} is independently C_{1-2}alkyl, which is optionally deuterated and is unsubstituted or substituted with one or more R^{20}. In some embodiments of Formula II or III, each R^{10} is independently C_{1-2}alkyl, which is substituted with one or more R^{20}. In some embodiments of Formula II or III, each R^{10} is independently methyl. In some embodiments of Formula II or III, each R^{10} is independently ethyl. In some embodiments of Formula II or III, each R^{10} is independently $-CH_2OH$. In some embodiments of Formula II or III, each R^{10} is independently $-CH_2OCH_3$. In some embodiments of Formula II or III, each R^{10} is independently $-CHF_2$. In some embodiments of Formula II or III, each R^{10} is independently $-CH_2F$.

[0319] In some embodiments of Formula II or III, two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle. In some embodiments of Formula II or III, two R^{10}s join together to form, together with the atom to which they are attached, a cyclopropyl ring.

[0320] In some embodiments of Formula II or III, each R^{10} is independently selected from $-OR^{12}$, =O, =S, -CN, $-C(O)O(C_{1-6}alkyl)$, halogen, phenyl, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, C_{2-6} alkenyl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle. In some embodiments of Formula II or III, each R^{10} is independently selected from $-OR^{12}$, =O, =S, -CN, $-C(O)O(C_{1-6}alkyl)$, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally

deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle.

[0321] In some embodiments of Formula II or III, each R^{10} is independently selected from $-OCH_3$, =O, =S, -CN, $-C(O)OCH_3$, $-C(O)OCD_3$, fluoro, chloro, phenyl,    , cyclopropyl, cyclobutyl, C_2 alkenyl, methyl, ethyl, $-CH_2OH$, $-CH_2OCH_3$, $-CHF_2$, $-CH_2F$, wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a cyclopropyl ring. In some embodiments, for a compound according to Formula II or III, each R^{10} is independently selected from $-OCH_3$, =O, =S, -CN, $-C(O)OCH_3$, $-C(O)OCD_3$, fluoro, chloro,    , cyclopropyl, cyclobutyl, methyl, ethyl, $-CH_2OH$, $-CH_2OCH_3$, $-CHF_2$, $-CH_2F$, wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a cyclopropyl ring.

[0322] As described herein, for a compound of Formula II or III, each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13}.

[0323] In some embodiments of Formula II or III, each R^{12} is independently C_{1-6} alkyl, which is unsubstituted or substituted with one or more R^{13}. In some embodiments of Formula II or III, each R^{12} is independently C_{1-2} alkyl, which is unsubstituted or substituted with one or more R^{13}. In some embodiments of Formula II or III, each R^{12} is independently methyl.

[0324] In some embodiments of Formula II or III, each R^{12} is independently C_{2-6} alkenyl, which is unsubstituted or substituted with one or more R^{13}.

[0325] In some embodiments of Formula II or III, each R^{12} is independently H.

[0326] In some embodiments of Formula II or III, each R^{12} is independently selected from C_{1-6} alkyl and H.

[0327] In some embodiments of Formula II or III, each R^{12} is independently selected from methyl and H.

[0328] As described herein, for a compound of Formula II or III, each R^{13} is independently selected from $-OR^{14}$, $-OC(O)R^{14}$, -CN, $-N(R^{14})_2$, and halogen. In some embodiments, of Formula II or III, each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen.

[0329] In some embodiments of Formula II or III, each R^{13} is independently selected from $-OR^{14}$.

[0330] In some embodiments of Formula II or III, each R^{13} is independently selected from -OC(O)R^{14}. In some embodiments of Formula II or III, each R^{13} is independently -OC(O)(3-8 membered heterocycle).

[0331] In some embodiments of Formula II or III, each R^{13} is independently selected from -CN.

[0332] In some embodiments of Formula II or III, each R^{13} is independently selected from -N(R^{14})$_2$.

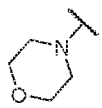
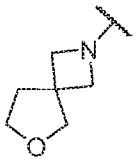
[0333] In some embodiments of Formula II or III, each R^{13} is independently selected from halogen. In some embodiments of Formula II or III, each R^{13} is fluoro.

[0334] In some embodiments of Formula II or III, each R^{13} is independently selected from -OC(O)R^{14} and halogen. In some embodiments of Formula II or III, each R^{13} is independently selected from –OC(O)(3-8 membered heterocycle) and fluoro.

[0335] In some embodiments of Formula II or III, each R^{13} is independently selected from -OC(O)R^{14}, -CN, and halogen. In some embodiments of Formula II or III, each R^{13} is independently selected from –OC(O)(3-8 membered heterocycle), CN, and fluoro.

[0336] As described herein, each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-8 membered heterocycle, C_{1-6} alkyl, -OR^{12}, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated. In some embodiments of Formula II or III, each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, -OR^{12}, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated.

[0337] In some embodiments of Formula II or III, each R^{14} is a 3-6 membered carbocycle.

[0338] In some embodiments of Formula II or III, each R^{14} is a 3-8 membered heterocycle. In some embodiments of Formula II or III, each R^{14} is  . In some embodiments ofFormula II or III, each R^{14} is  . In some embodiments of Formula II or III, each R^{14} is a 3-6 membered heterocycle.

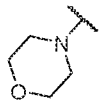
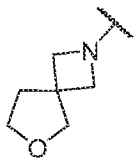
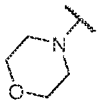
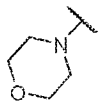
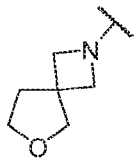
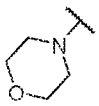
[0339] In some embodiments of Formula II or III, each R^{14} is C_{1-6} alkyl, which is optionally deuterated. In some embodiments of Formula II or III, each R^{14} is C_{1-2} alkyl, which is optionally deuterated. In some embodiments of Formula II or III, each R^{14} is C_{1-2} alkyl. In some embodiments of Formula II or III, each R^{14} is methyl.

[0340] In some embodiments of Formula II or III, each R^{14} is -OR^{12}.

[0341] In some embodiments of Formula II or III, each R^{14} is C_{2-6} alkenyl.

[0342] In some embodiments of Formula II or III, each R^{14} is H.

[0343] In some embodiments of Formula II or III, each R^{14} is independently selected from a 3-8 membered heterocycle and C_{1-2} alkyl. In some embodiments of Formula II or III, each R^{14} is independently selected from a 3-8 membered heterocycle, H, and C_{1-2} alkyl. In some embodiments of Formula II or III, each R^{14} is independently selected from a 3-6 membered heterocycle and C_{1-2} alkyl. In some embodiments of Formula II or III, each R^{14} is independently selected from a 3-6 membered heterocycle, H, and C_{1-2} alkyl.

[0344] In some embodiments, for a compound according to Formula II or III, each R^{14} is independently selected from  ,  , methyl, and H. In some embodiments of Formula II or III, each R^{14} is independently selected from  , H, and methyl. In some embodiments of Formula II or III, each R^{14} is independently selected from  ,  , and methyl. In some embodiments of Formula II or III, each R^{14} is independently selected from  and methyl.

[0345] As described herein, for a compound of Formula II or III, each R^{15} is independently selected from deuterium, -OH, halogen, $-N(R^{12})_2$, -CN, C_{2-6} alkynyl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments of Formula II or III, each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

[0346] In some embodiments of Formula II or III, each R^{15} is independently deuterium.

[0347] In some embodiments of Formula II or III, each R^{15} is independently -OH.

[0348] In some embodiments of Formula II or III, each R^{15} is independently halogen. In some embodiments of Formula II or III, each R^{15} is independently fluoro. In some embodiments of Formula II or III, each R^{15} is independently chloro.

[0349] In some embodiments of Formula II or III, each R^{15} is independently $-N(R^{12})_2$. In some embodiments of Formula II or III, each R^{15} is independently $-NH_2$.

[0350] In some embodiments of Formula II or III, each R^{15} is independently -CN.

[0351] In some embodiments of Formula II or III, each R^{15} is independently C_{2-6} alkynyl. In some embodiments of Formula II or III, each R^{15} is independently C_2 alkynyl.

[0352] In some embodiments of Formula II or III, each R^{15} is independently C_{1-6}alkyl, which is unsubstituted or substituted with one or more R^{13}. In some embodiments of Formula II or III, each R^{15} is independently C_{1-2} alkyl, which is unsubstituted or substituted with one or more R^{13}. In some embodiments of Formula II or III, each R^{15} is independently methyl. In some embodiments of Formula II or III, each R^{15} is independently $-CF_3$.

[0353] In some embodiments of Formula II or III, each R^{15} is independently selected from -OH, halogen, $-N(R^{12})_2$, -CN, C_{2-6} alkynyl, and C_{1-2}alkyl, wherein any C_{1-2}alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments ofFormula II or III, each R^{15} is independently selected from halogen, $-N(R^{12})_2$, -CN, and C_{1-2}alkyl, wherein any C_{1-2}alkyl is unsubstituted or substituted with one or more R^{13}.

[0354] In some embodiments of Formula II or III, each R^{15} is independently selected from -OH, fluoro, chloro, $-NH_2$, -CN, C_2 alkynyl, methyl, and $-CF_3$. In some embodiments of Formula II or III, each R^{15} is independently selected from fluoro, chloro, $-NH_2$, -CN, methyl, and $-CF_3$.

[0355] As described herein, for a compound of Formula II or III, each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$baloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), $-C(O)OR^{12}$, $-C(O)N(R^{12})_2$, $-S(O)_2R^{12}$, a 3-6 membered carbocycle, phenyl, and halogen.

[0356] In some embodiments of Formula II or III, each R^{20} is independently halogen. In some embodiments of Formula II or III, each R^{20} is independently fluoro.

[0357] In some embodiments of Formula II or III, each R^{20} is independently -OH.

[0358] In some embodiments of Formula II or III, each R^{20} is independently $-OC_{1-6}$alkyl. In some embodiments of Formula II or III, each R^{20} is independently $-OC_{1-2}$ alkyl. In some embodiments of Formula II or III, each R^{20} is independently $-OCH_3$.

[0359] In some embodiments of Formula II or III, each R^{20} is independently selected from -OH, $-OCH_3$, and fluoro.

[0360] In some embodiments of Formula II or III, each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, and halogen.

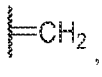
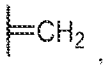
[0361] As described herein, for a compound of Formula II or III, each R^{31} is selected from C_{1-6} alkyl. In some embodiments of Formula II or III, each R^{31} is selected from C_{1-2} alkyl.

[0362] As described herein, for a compound of Formula II or III, n is 0-2. In some embodiments n is 0-1. In some embodiments n is 1-2. In some embodiments n is 0 or 2.

[0363] In some embodiments n is 0.

[0364] In some embodiments n is 1.

[0365] In some embodiments n is 2.

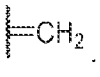
[0366] As described herein, for a compound of Formula II or III, R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl,  , , $-C_{1-6}$ heteroalkyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}. In some embodiments, of Formula II or III, R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl,  , $-C_{1-6}$ heteroalkyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

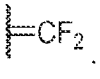
[0367] In some embodiments of Formula II or III, R^a and R^b are each independently deuterium.

[0368] In some embodiments of Formula II or III, R^a and R^b are each independently halogen. In some embodiments of Formula II or III, R^a and R^b are each independently fluoro.

[0369] In some embodiments of Formula II or III, R^a and R^b are each independently C_{1-6} alkyl, which is unsubstituted or is substituted with one or more R^{13}. In some embodiments of Formula II or III, R^a and R^b are each independently C_{1-2} alkyl, which is unsubstituted or is substituted with one or more R^{13}. In some embodiments, of Formula II or III, R^a and R^b are each independently C_{1-2} alkyl, which is substituted with $-OC(O)R^{14}$. In some embodiments of Formula II or III, R^a and R^b are each independently C_{1-2} alkyl, which is substituted with -OC(O)(3-8 membered heterocycle). In some embodiments of Formula II or III, R^a and R^b are each independently $-CF_2H$. In some embodiments of Formula II or III, R^a and R^b are each independently methyl.

[0370] In some embodiments of Formula II or III, R^a and R^b are each independently C_{2-6} alkenyl, which is unsubstituted or is substituted with one or more R^{13}.

[0371] In some embodiments of Formula II or III, R^a and R^b are each independently  .

[0372] In some embodiments of Formula II or III, R^a and R^b are each independently  .

[0373] In some embodiments, of Formula II or III, R^a and R^b are each independently-C_{1-6} heteroalkyl.

[0374] In some embodiments of Formula II or III, R^a and R^b are each independently a 3-6 membered carbocycle.

[0375] In some embodiments of Formula II or III, R^a and R^b are each independently -OR^{12}. In some embodiments of Formula II or III, R^a and R^b are each independently -OH. In some embodiments, of Formula II or III, R^a and R^b are each independently -OCH_3.

[0376] In some embodiments of Formula II or III, R^a and R^b are each independently H.

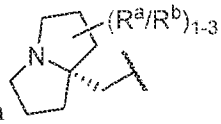
[0377] In some embodiments of Formula II or III, R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle which is unsubstituted or is substituted with one or more R^{13}. In some embodiments of Formula II or III, R^a and R^b optionally join together to form a 3-6 membered carbocycle. In some embodiments of Formula II or III, R^a and R^b optionally join together to form a cyclopropyl ring.

[0378] In some embodiments of Formula II or III, R^a and R^b are each independently selected from halogen, C_{1-2} alkyl, , , and -OR^{12}, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-2}alkyl is unsubstituted or is substituted with one or more R^{13}. In some embodiments of Formula II or III, R^a and R^b are each independently selected from halogen, C_{1-2} alkyl, , and -OR^{12}, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-2}alkyl is unsubstituted or is substituted with one or more R^{13}.

[0379] In some embodiments of Formula II or III, R^a and R^b are each independently selected from fluoro, -OC(O)(3-8 membered heterocycle), -CF_2H, methyl, , , -OH, and-OCH_3, wherein an R^a and R^b optionally join together to form a cyclopropyl ring. In some embodiments of Formula II or III, R^a and R^b are each independently selected from fluoro, -CF_2H, methyl, , -OH, and-OCH_3, wherein an R^a and R^b optionally join together to form a cyclopropyl ring.

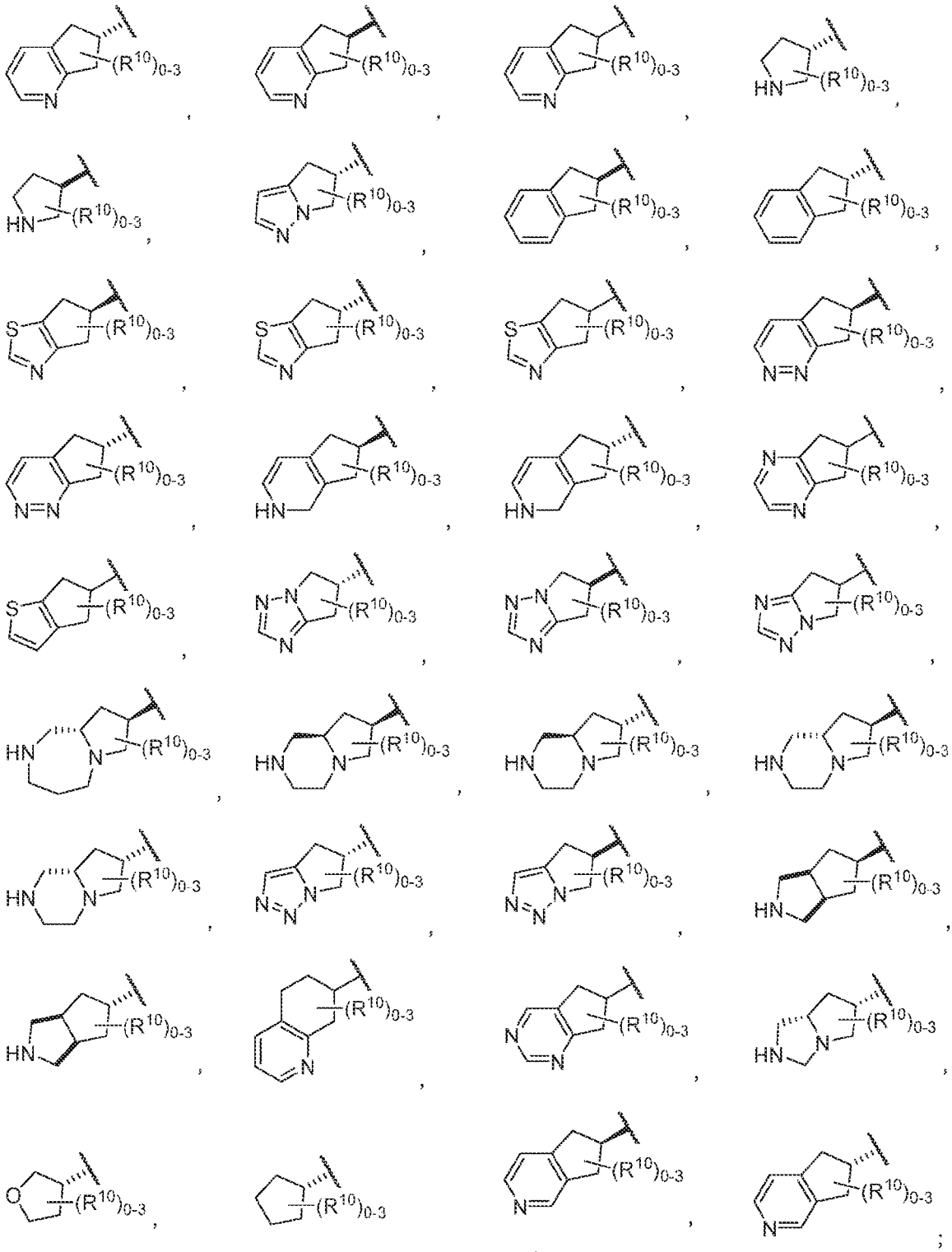
[0380] In some embodiments, for a compound according to Formula III, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof:

Z is C-R^5;

R^1 is selected from  ;

R^2 is selected from C_{1-6}alkyl;

R^3 is selected from:

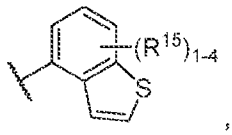
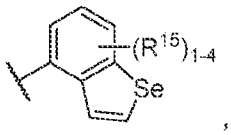
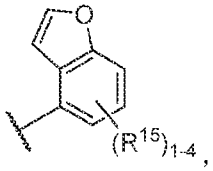
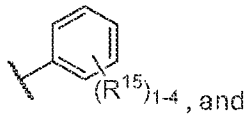


and

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is selected from: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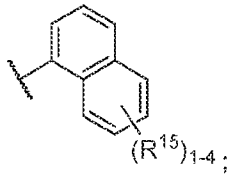
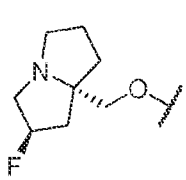
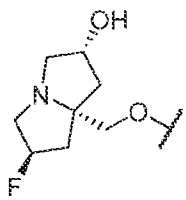
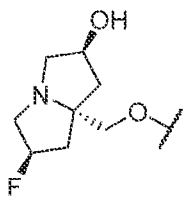
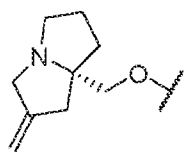
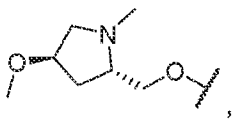
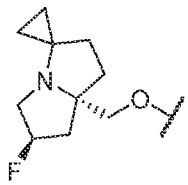
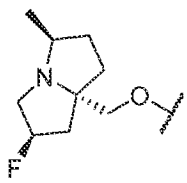
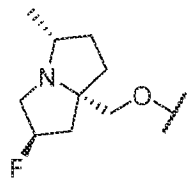
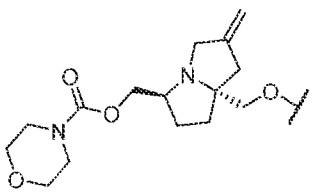
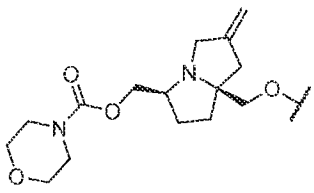
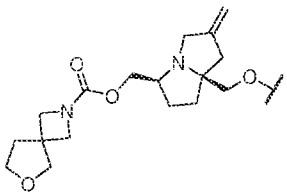
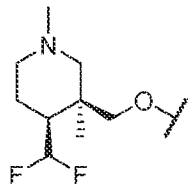
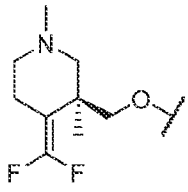

;

R^7 is selected from halogen.

[0381] In some embodiments, for a compound according to Formula III, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof:

Z is C-R^5;

R^1 is selected from: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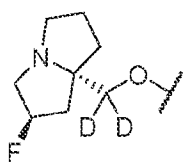
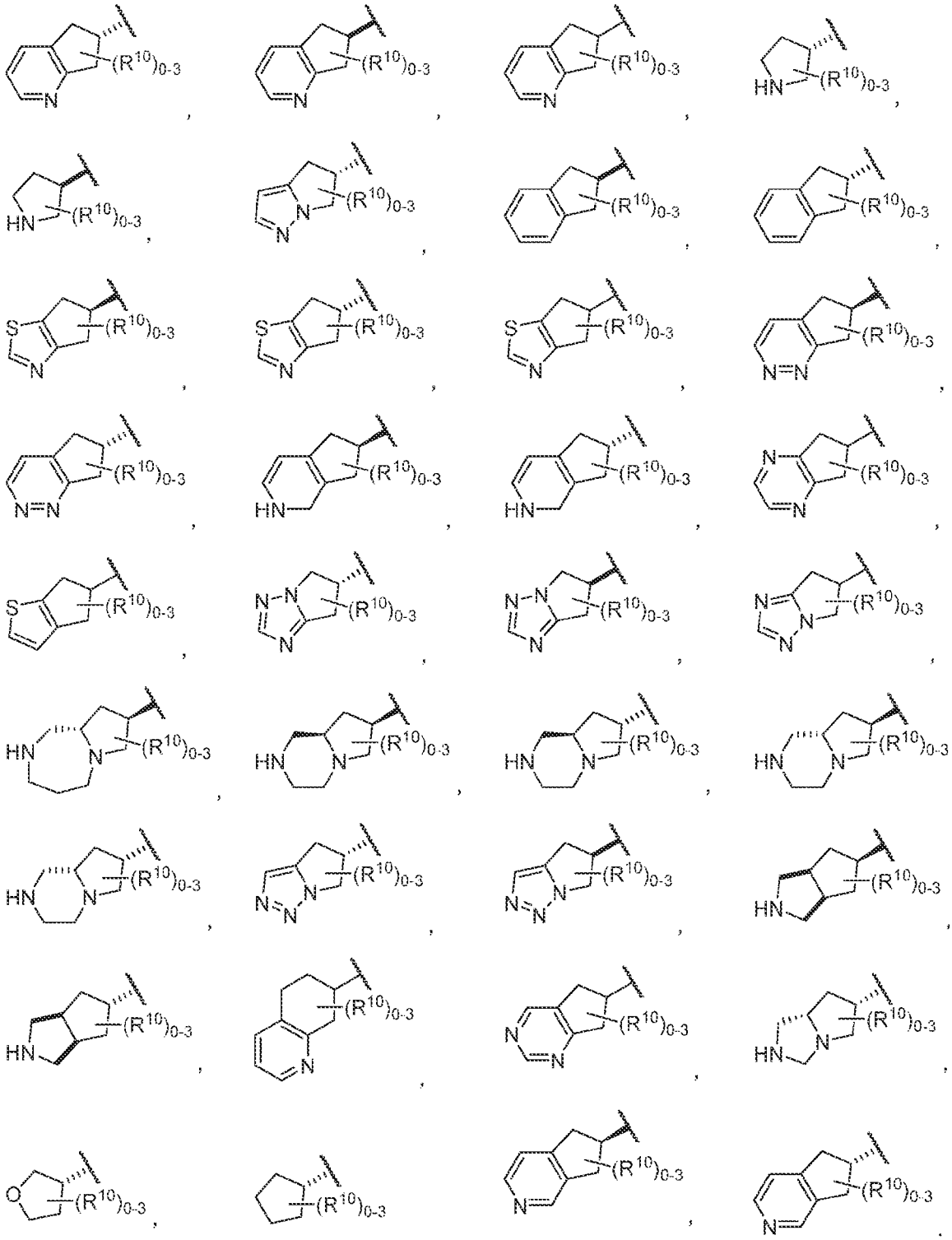

;

R^2 is selected from $C_{1\text{-}6}$alkyl;

R^3 is selected from:

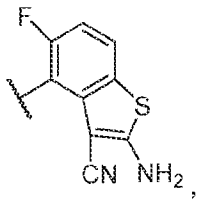


and

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is selected from: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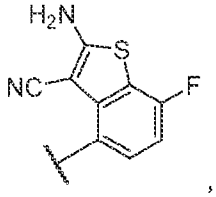
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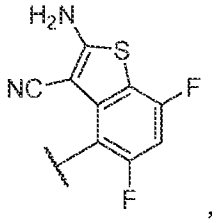
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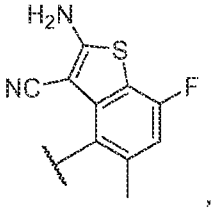
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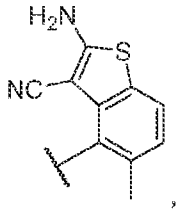
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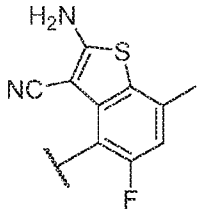
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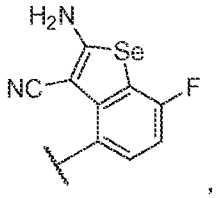
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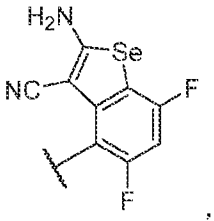
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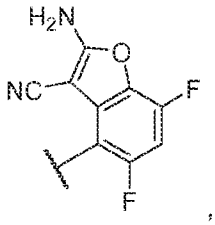
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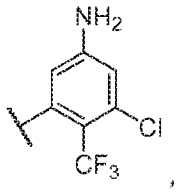
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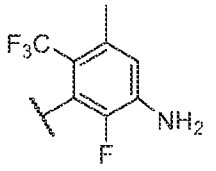
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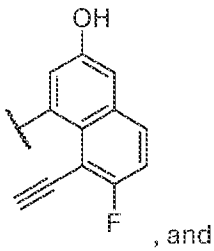
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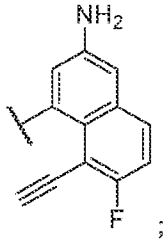
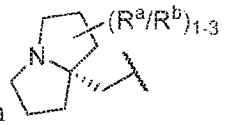

; and

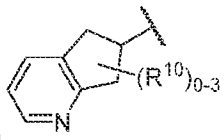
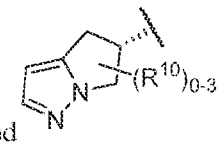
R^7 is selected from halogen.

[0382] In some embodiments, for a compound according to Formula III, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof:

Z is C-R^5;

R^1 is selected from 
;

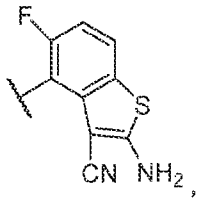
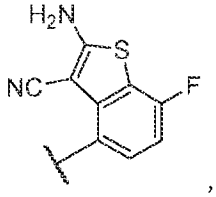
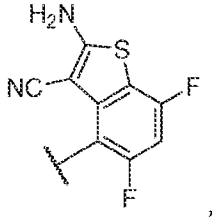
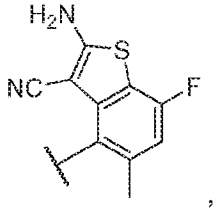
R^2 is selected from CH_3- and CH_3CH_2-;

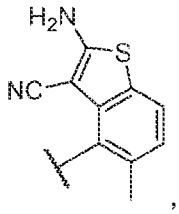
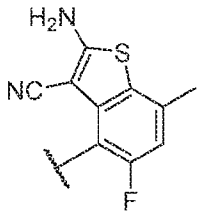
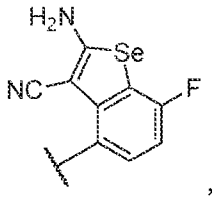
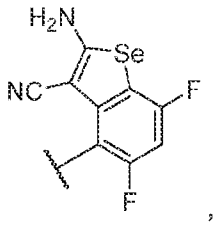
R^3 is selected from  and  ;

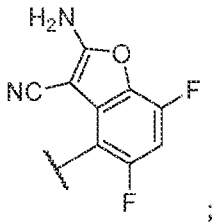
R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is selected from:

 ,  ,  ,  ,

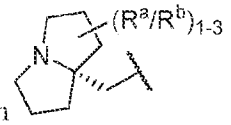
 ,  ,  ,  , and

 ;

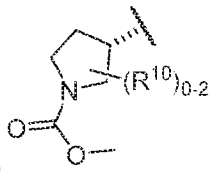
R^7 is selected from halogen.

[0383] In some embodiments, for a compound according to Formula III, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof:

Z is C-R^5;

R^1 is selected from  ;

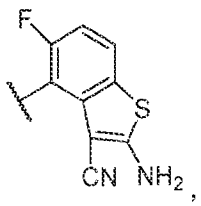
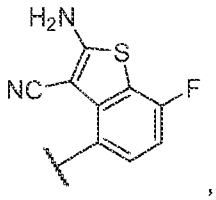
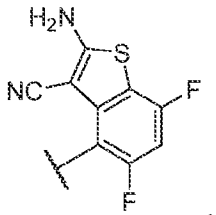
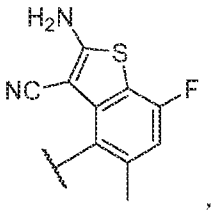
R^2 is selected from CH_3- and CH_3CH_2-;

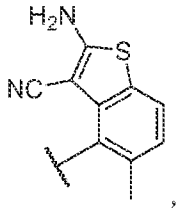
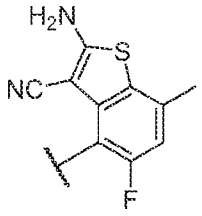
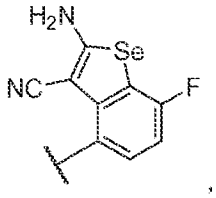
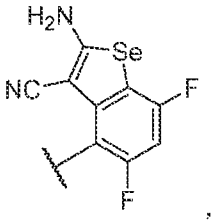
R^3 is selected from  ;

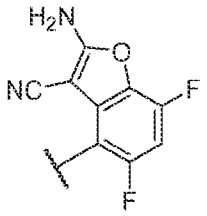
R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

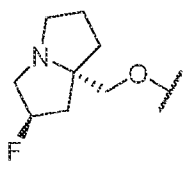
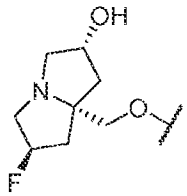
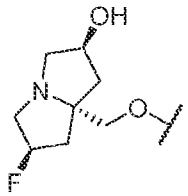
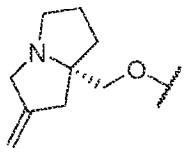
R^6 is selected from:

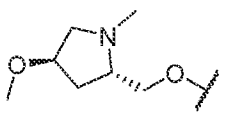
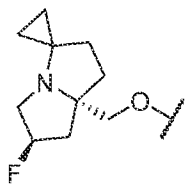
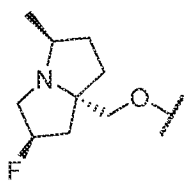
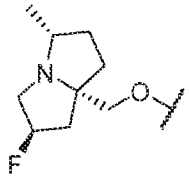
 ,  ,  ,  ,

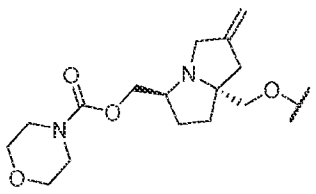
 ,  ,  ,  , and

and  ;

R^7 is selected from halogen. In some embodiments, R^1 is selected from:

 ,  ,  ,  ,

 ,  ,  ,  ,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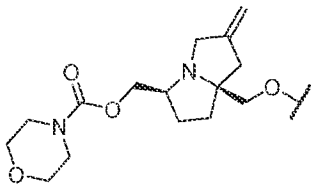
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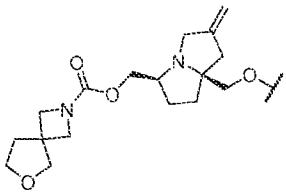
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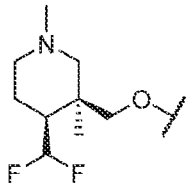
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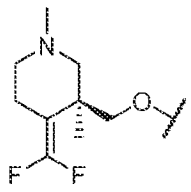
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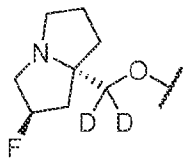
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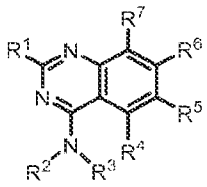
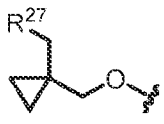
[0384] In another aspect, the present disclosure provides a compound represented by Formula IV:


(IV)

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from $-OR^8$ and  ;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from C_{1-6}alkyl that is substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20},

and any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, and halogen;

R^{27} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen; and

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle.

[0385] In some embodiments, the present disclosure provides a compound of Formula IV or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0386] In some embodiments, the present disclosure provides a compound of Formula IV, wherein:

R^1 is selected from $-OR^8$;

R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from C_{1-6}alkyl that is substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from a 3-6 membered heterocycle and a 5-6 membered heteroaryl, wherein any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13};

each R^{12} is independently selected from C_{1-6} alkyl and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

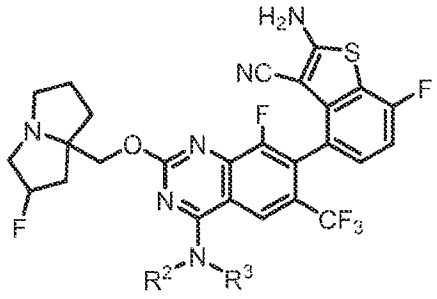
each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl and H;

each R^{15} is independently selected from halogen, $-N(R^{12})_2$, and -CN; and

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle.

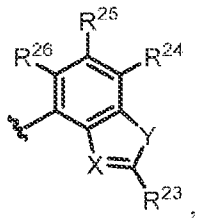
[0387] In some embodiments, the present disclosure provides a compound of Formula IV-a:



(IV-a)

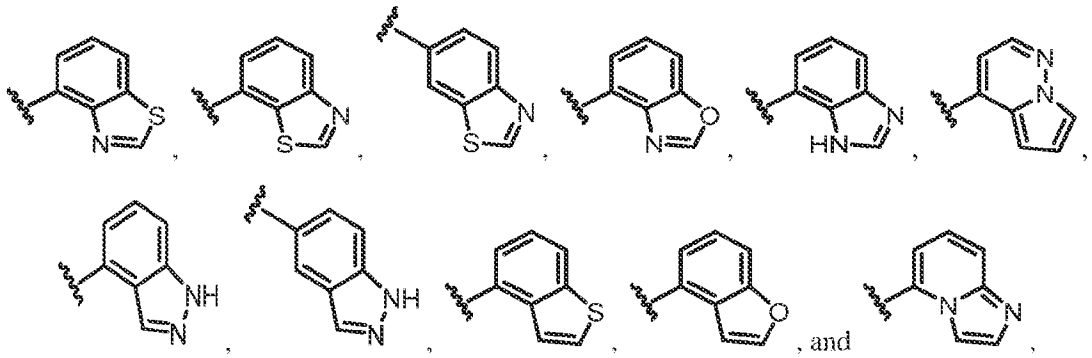
or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein R^2 and R^3 are as defined for Formula IV above and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IV-a, or a salt (e.g., pharmaceutically acceptable salt) thereof.

[0388] In some embodiments, for a compound according to Formula IV, R^6 is selected from:



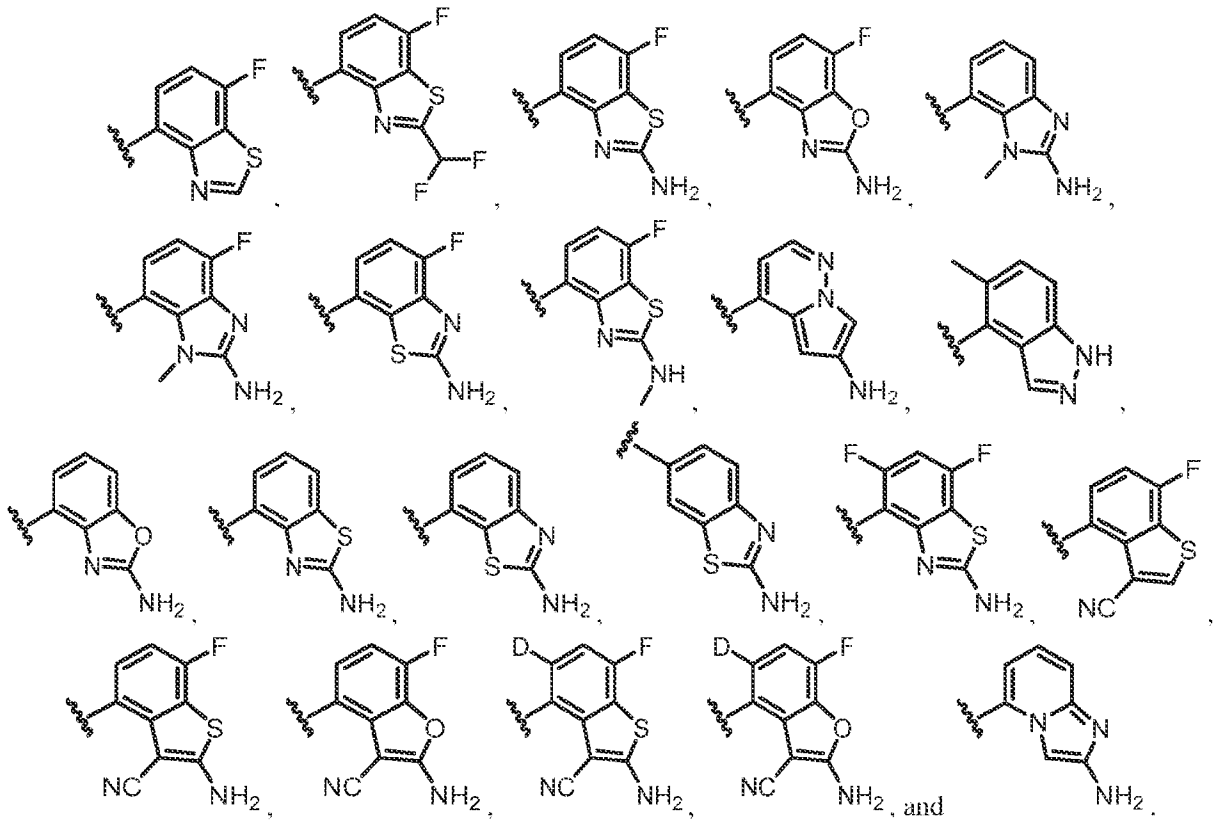
wherein X is selected from N and C-CN; Y is selected from O and S; R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments, X is C-CN and Y is S. In some embodiments, X is C-CN and Y is O. In some embodiments, X is N and Y is S. In some embodiments, X is N and Y is O. In some embodiments, X is C-CN, Y is S, and R^{23} is $-N(R^{12})_2$. In some embodiments, X is C-CN, Y is S, and R^{23} is $-NH_2$. In some embodiments, R^{24} is halogen (e.g., fluoro). In some embodiments, R^{26} is deuterium.

[0389] In some embodiments, for a compound according to Formula IV, R^6 is selected from:

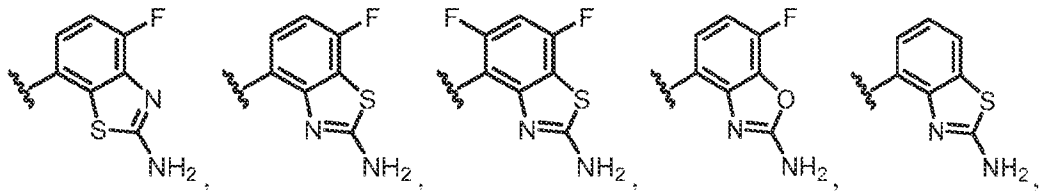


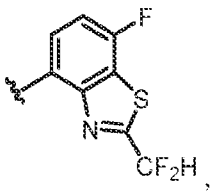
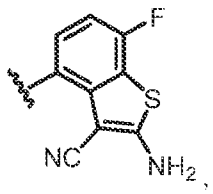
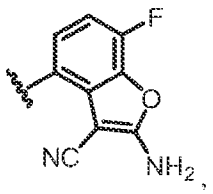
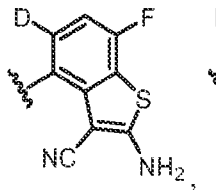
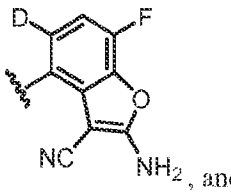
any of which is substituted with one or more R^{15}.

[0390] In some embodiments, for a compound according to Formula IV, R^6 is selected from:



[0391] In some embodiments, for a compound according to Formula IV, R^6 is selected from:

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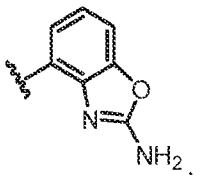
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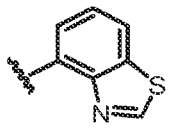
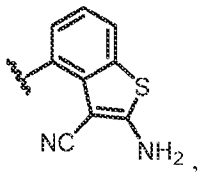
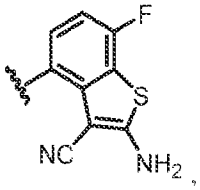
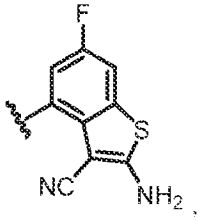
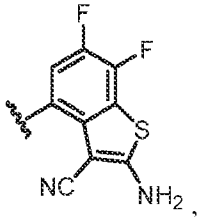
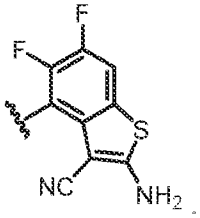
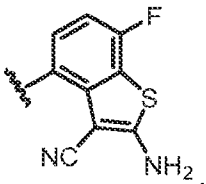
[0392] In some embodiments, for a compound according to Formula IV, R^6 is selected from:

, which is substituted with one or more R^{15}. In some embodiments, R^6 is selected from:




, and

. In some embodiments, R^6 is

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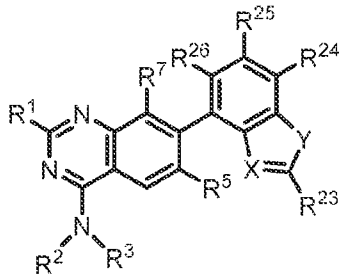
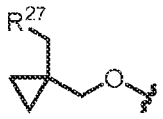
[0393] In some embodiments, the compound is a compound according to Formula IVB:



(IVB)

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from $-OR^8$ and

;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from C_{1-6}alkyl that is substituted with one or more R^{10};

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, and halogen;

R^{27} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen; and

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle.

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

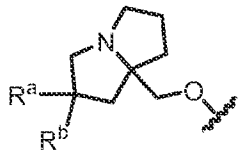
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

[0394] In some embodiments, the present disclosure provides a compound of Formula IVB or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0395] In some embodiments, for a compound of Formula IV or IVB, R^1 is selected from $-OR^8$, wherein R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring

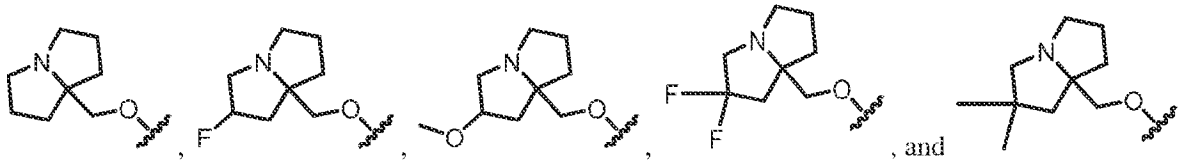
atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6} alkyl. In some embodiments, R^8 is a heterocycle or an alkylheterocycle, wherein any heterocycle contains 4-8 ring atoms and is substituted with one or more R^a or R^b. In some embodiments, R^8 is a heterocycle that is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, R^8 is an alkylheterocycle that is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, R^8 is -CH_2(heterocycle), where the heterocycle is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is a 4-6 membered monocyclic heterocycle having 1-2 heteroatoms independently selected from N, O, and S. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is an 8-membered bicyclic heterocycle having 1-2 heteroatoms independently selected from N, O, and S. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a halogen (e.g., F). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a C_{1-6}alkyl (e.g., methyl). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a -OR^{12} (e.g., -OCH_3).

[0396] In some embodiments, for a compound of Formula IV or IVB, R^1 is selected from:



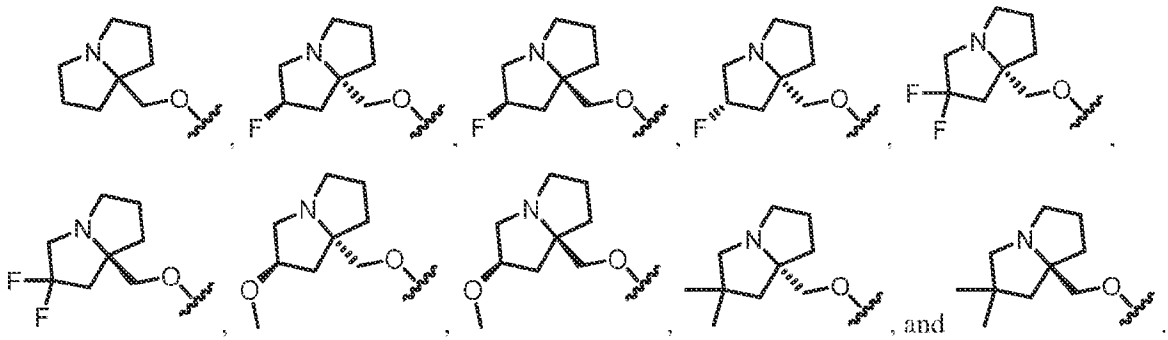
,

wherein R^a and R^b are each independently selected from halogen, C_{1-6}alkyl, -OR^{12}, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^a is a halogen. In some embodiments, R^a is F. In some embodiments, R^a is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^a is methyl. In some embodiments, R^a is -OC_{1-6}alkyl. In some embodiments, R^a is H. In some embodiments, R^b is H. In some embodiments, R^b is a halogen. In some embodiments, R^b is F. In some embodiments, R^b is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^b is methyl. In some embodiments, each of R^a and R^b is F. In some embodiments, each of R^a and R^b is methyl. In some embodiments, R^1 is selected from:

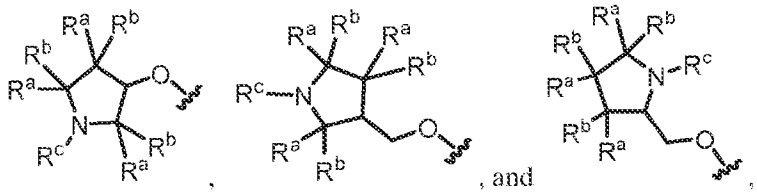


, and .

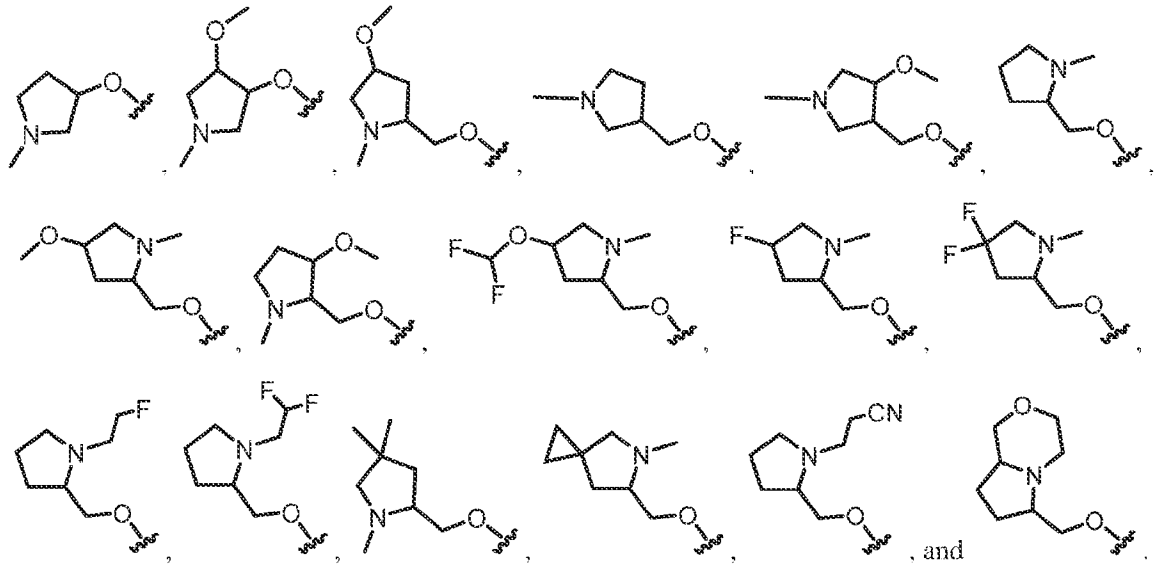
[0397] In some embodiments, for a compound of Formula IV or IVB, R^1 is selected from:



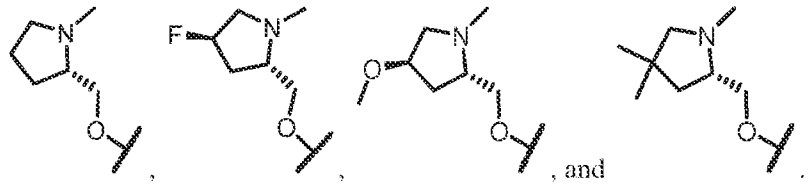
[0398] In some embodiments, for a compound of Formula IV or IVB, R^1 is selected from:



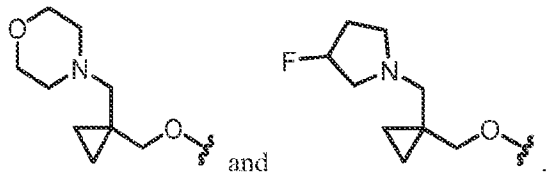
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and R^c is selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle. In some embodiments, each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and R^c is selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b attached to the same carbon atom join together to form a 3-6 membered carbocycle. In some embodiments, each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and wherein an R^a and R^c join together to form a 3-6 membered heterocycle. In some embodiments, each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and R^c is selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13}. In some embodiments, one R^a or R^b is selected from halogen, C_{1-6} alkyl, and $-OR^{12}$, and the other R^a and R^b groups are H. In some embodiments, one R^a or R^b is halogen (e.g., F). In some embodiments, two R^a groups, two R^b groups, or an R^a and an R^b are halogen (e.g., F). In some embodiments, one R^a or R^b is $-OR^{12}$ (e.g., $-OCH_3$ or $-OCHF_2$). In some embodiments, one R^a or R^b is C_{1-6} alkyl (e.g., methyl). In some embodiments, two R^a groups, two R^b groups, or an R^a and an R^b are C_{1-6} alkyl (e.g., methyl). In some embodiments, R^c is selected from $-CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CH_2CN$. In some embodiments, an R^a and R^b join together to form a 3-6 membered carbocycle, such as a cyclopropane. In some embodiments, an R^a and R^b attached to the same carbon atom join together to form a 3-6 membered carbocycle, such as a cyclopropane. In some embodiments, an R^a and R^c join together to form a 3-6 membered heterocycle. In some embodiments, R^1 is selected from:



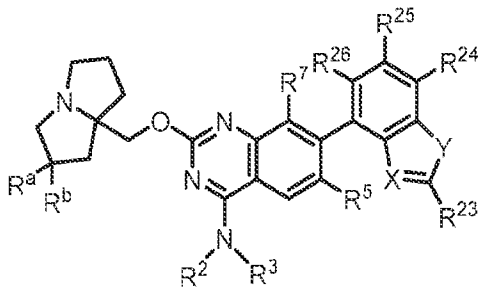
[0399] In some embodiments, for a compound of Formula IV or IVB, R^1 is selected from:



[0400] In some embodiments, for a compound of Formula IV or IVB, R^1 is selected from:



[0401] In some embodiments, the compound is a compound according to Formula IVC,



(IVC),

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{15};

R^3 is selected from C_{1-6}alkyl that is substituted with one or more R^{16};

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^7 is selected from halogen;

each R^{10} is independently selected from a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, and halogen;

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, -OR^{12}, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, -OR^{12}, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

[0402] In some embodiments, the present disclosure provides a compound of Formula IVC or a salt (e.g., a pharmaceutically acceptable salt) thereof.

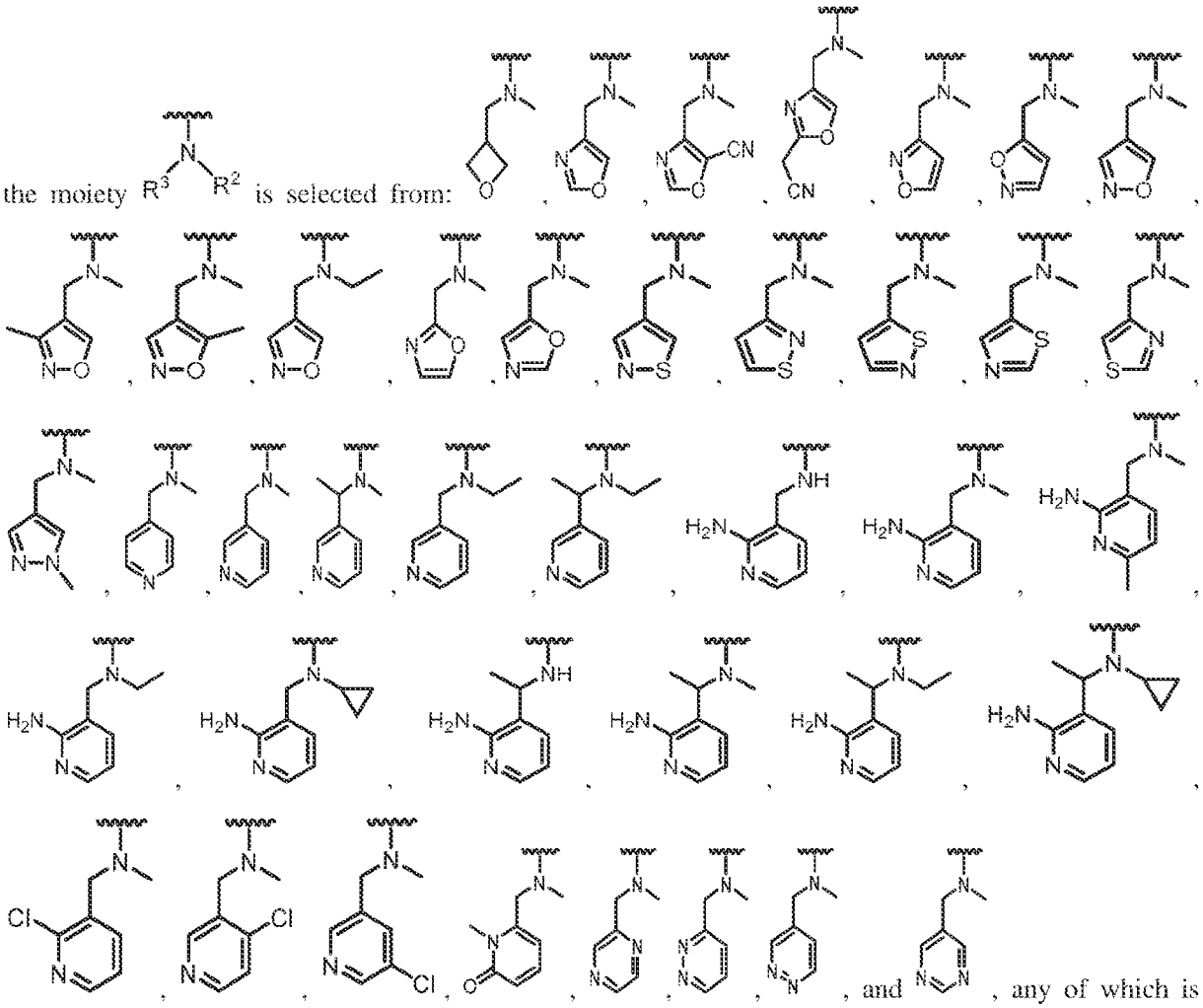
[0403] In some embodiments, for a compound according to Formula IVC, R^a is a halogen. In some embodiments, R^a is F. In some embodiments, R^a is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^a is methyl. In some embodiments, R^a is -OC_{1-6}alkyl. In some embodiments, R^a is H. In some embodiments, R^b is H. In some embodiments, R^b is a halogen. In some embodiments, R^b is F. In some embodiments, R^b is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^b is methyl. In some embodiments, each of R^a and R^b is F. In some embodiments, each of R^a and R^b is methyl.

[0404] In some embodiments, for a compound according to Formula IVB or IVC, X is C-CN and Y is S. In some embodiments, X is C-CN and Y is O. In some embodiments, X is N and Y is S. In some embodiments, X is N and Y is O. In some embodiments, R^{23} is selected from -$N(R^{12})_2$. In some embodiments, R^{23} is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^{23} is selected from C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or

substituted with one or more R^{13}. In some embodiments, X is C-CN, Y is S, and R^{23} is $-N(R^{12})_2$. In some embodiments, X is C-CN, Y is S, and R^{23} is $-NH_2$. In some embodiments, at least one of R^{24}, R^{25}, and R^{26} are independently selected from deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments, at least one of R^{24}, R^{25}, and R^{26} are independently selected from halogen. In some embodiments, X is C-CN, Y is S, R^{23} is selected from $-N(R^{12})_2$, and at least one of R^{24}, R^{25}, and R^{26} are independently selected from halogen. In some embodiments, X is C-CN, Y is S, R^{23} is $-N(R^{12})_2$, and R^{24} is a halogen (e.g., F). In some embodiments, X is C-CN, Y is S, R^{23} is $-N(R^{12})_2$, and one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F). In some embodiments, R^{26} is deuterium.

[0405] In some embodiments, for a compound according to any one of Formulas IV, IV-a, IVB, or IVC, R^2 is H. In some embodiments, R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^2 is selected from C_{1-6}alkyl that is unsubstituted. In some embodiments, R^2 is selected from C_{1-6}alkyl that is substituted with one or more R^{13}. In some embodiments, R^2 is selected from C_{1-2}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^2 is selected from C_{1-2}alkyl that is unsubstituted. In some embodiments, R^2 is selected from C_{1-2}alkyl that is substituted with one or more R^{13}. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl. In some embodiments, R^2 is a 3-6 membered carbocycle (e.g., a cyclopropane).

[0406] In some embodiments, for a compound according to any one of Formula IV, IV-a, IVB, and IVC, R^3 is selected from C_{1-3}alkyl that is substituted with one or more R^{10}. In some embodiments, R^3 is selected from C_{1-3}alkyl that is substituted with one or more R^{10}, wherein each R^{10} is independently selected from a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 5-6 membered heteroaryl or 3-6 membered heterocycle is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^3 is C_{1-3}alkyl that is substituted with a 3-6 membered heterocycle that is unsubstituted or substituted with one or more =O, R^{12}, or R^{13}. In some embodiments, R^3 is C_{1-3}alkyl that is substituted with a 5-6 membered heteroaryl that is unsubstituted or substituted with one or more =O, R^{12}, or R^{13}. In some embodiments, R^3 is C_{2-3}alkyl that is substituted with a 5-6 membered heteroaryl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^3 is C_{1-3}alkyl that is substituted with an oxazole, isoxazole, thiazole, isothiazole, pyrazole, pyridine, pyrazine, pyridazine, or pyrimidine that is unsubstituted or substituted with one or more =O, R^{12}, or R^{13}. In some embodiments, R^3 is C_{2-3}alkyl that is substituted with a pyridine that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^3 is C_{2-3}alkyl that is substituted with a pyridine that is substituted with one or more R^{13}.

[0407] In some embodiments, for a compound according to any one of Formula IV, IV-a, IVB, and IVC, the moiety is selected from:  , any of which is optionally further substituted with one or more R^{10}.

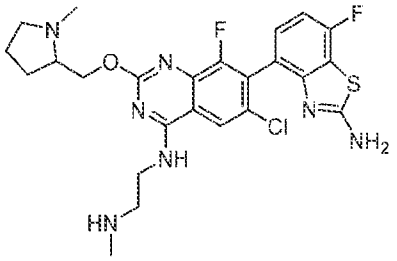
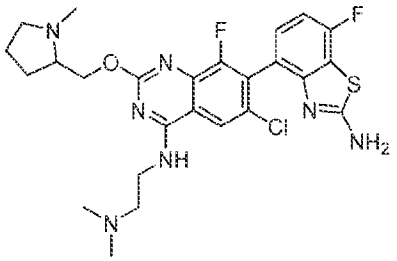
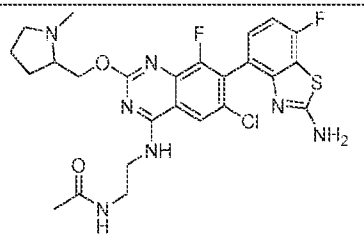
[0408] In some embodiments, for a compound according to any one of Formula IV, IVB, and IVC, R^5 is a halogen (e.g., F or Cl). In some embodiments, R^5 is Cl. In some embodiments, R^5 is F. In some embodiments, R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^5 is selected from C_{1-2}alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^5 is selected from C_{1-6}alkyl that is unsubstituted, such as methyl or ethyl. In some embodiments, R^5 is selected from C_{1-6}alkyl that is substituted with one or more halogens or -CN. In some embodiments, R^5 is C_{1-6}alkyl that is substituted with one or more halogens, such as one or more fluorines. In some embodiments, R^5 is $-CF_3$. In some embodiments, R^5 is $-CHF_2$. In some embodiments, R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$. In some embodiments, R^5 is selected from $-CH_3$, $-CH_2CH_3$, $-CF_2H$, $-CF_3$, $-CF_2CH_3$, and $-CH_2CN$. In some embodiments, R^5 is C_{1-6}alkyl that is substituted with one or

more R^{13}, wherein each R^{13} is independently selected from $-OR^{14}$, -CN, and $-N(R^{14})_2$. In some embodiments, R^5 is $-CH_2CN$.

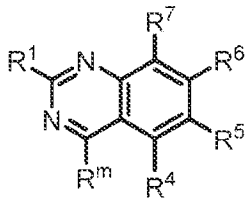
[0409] In some embodiments, for a compound according to any one of Formulas IV, IVB, and IVC, R^7 is Cl. In some embodiments, R^7 is F.

[0410] In some embodiments, for a compound of any one of Formulas IV, IV-a, IVB, and IVC, the compound is not a compound included in Table 2, or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof.

Table 2.

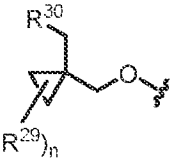
Compound Number	Structure	Compound Number	Structure
IV-70a		IV-75a	
IV-76a			

[0411] In another aspect, the present disclosure provides a compound represented by Formula V':



(V')

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:



R^1 is selected from -OR^8, , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^m is selected from hydrogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, -$N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

n is 0-2;

each R^{31} is selected from C_{1-6} alkyl; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

[0412] In some embodiments, the present disclosure provides a compound of Formula V' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0413] In some embodiments, the present disclosure provides a compound of Formula V', wherein:

R^1 is selected from -OR^8;

R^m is H;

R^4 is H;

R^5 is C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl, wherein the heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is an alkylheterocycle, wherein the heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of the alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

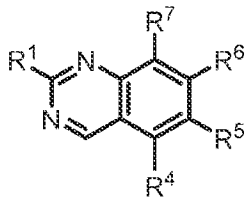
each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from halogen, -$N(R^{12})_2$, and -CN; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

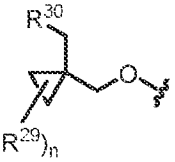
[0414] In some embodiments, for a compound according to Formula V', R^m is hydrogen. In some embodiments, R^m is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^m is C_{1-6}alkyl that is unsubstituted. In some embodiments, R^m is methyl that is unsubstituted. In some embodiments, R^m is C_{1-6}alkyl that is substituted with one or more R^{13}.

[0415] In some embodiments, the compound is a compound according to Formula VA':



(VA')

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

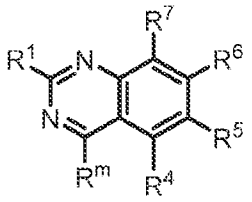
n is 0-2;

each R^{31} is selected from C_{1-6} alkyl; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

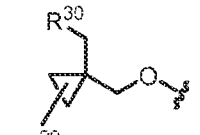
[0416] In some embodiments, the present disclosure provides a compound of Formula VA' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0417] In some embodiments, the compound is a compound according to Formula VB':



(VB')

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^m is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

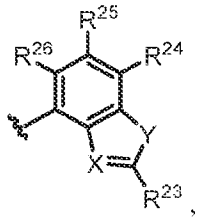
n is 0-2;

each R^{31} is selected from C_{1-6} alkyl; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

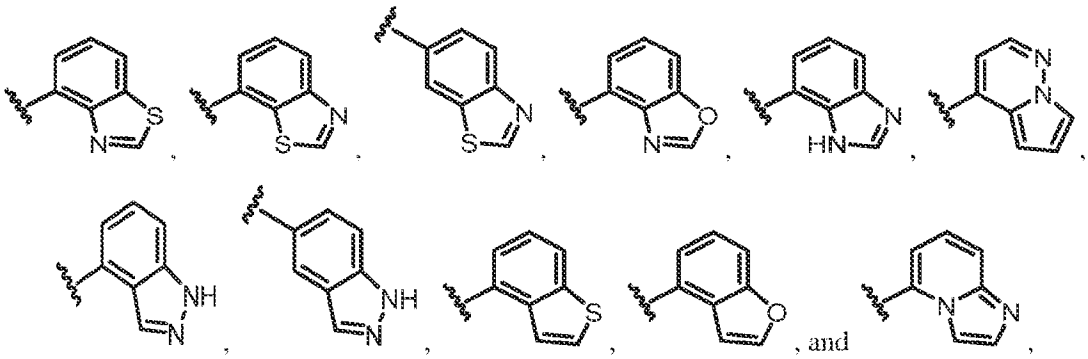
[0418] In some embodiments, the present disclosure provides a compound of Formula VB' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0419] In some embodiments, for a compound according to any one of Formulas V', VA', and VB', R^6 is selected from:



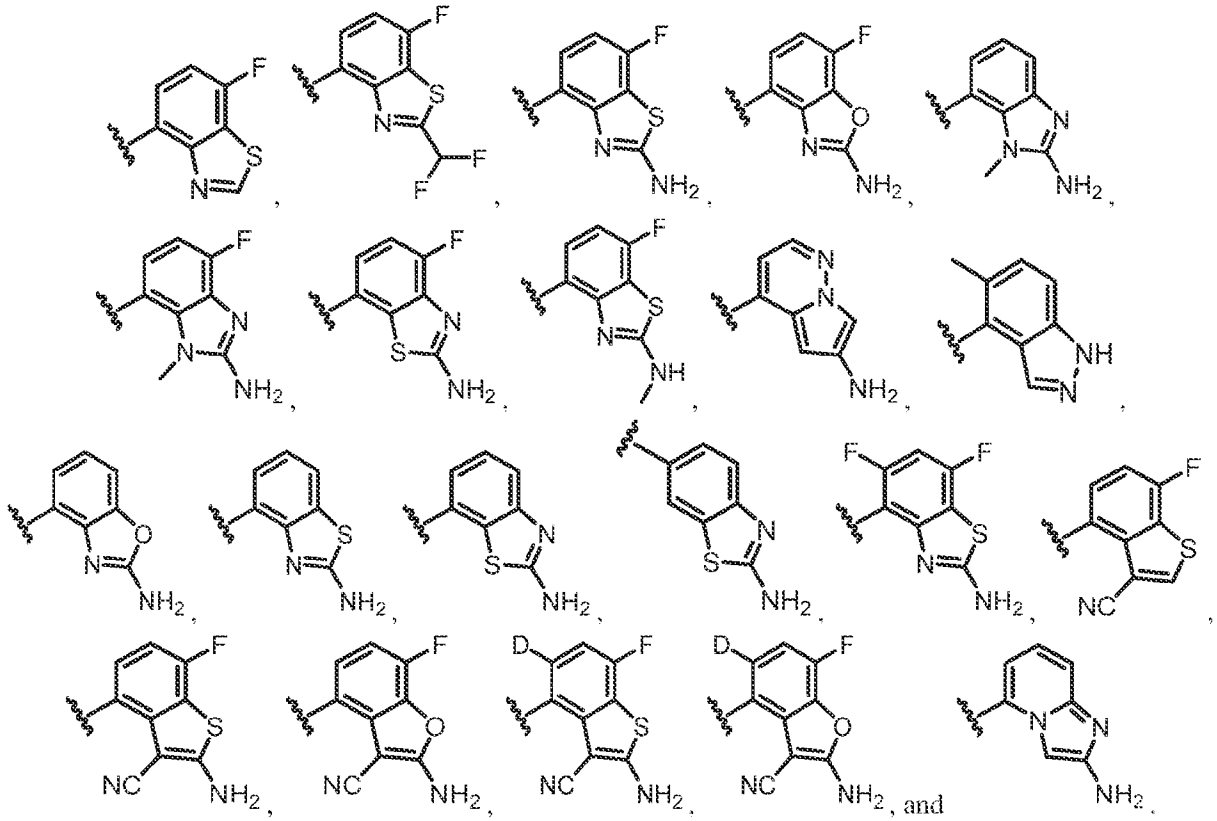
wherein X is selected from N and C-CN; Y is selected from O and S; R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments, X is C-CN and Y is S. In some embodiments, X is C-CN and Y is O. In some embodiments, X is N and Y is S. In some embodiments, X is N and Y is O. In some embodiments, X is C-CN, Y is S, and R^{23} is $-N(R^{12})_2$. In some embodiments, X is C-CN, Y is S, and R^{23} is $-NH_2$. In some embodiments, R^{24} is halogen (e.g., fluoro). In some embodiments, R^{26} is deuterium.

[0420] In some embodiments, for a compound according to any one of Formulas V', VA', and VB', R^6 is selected from:

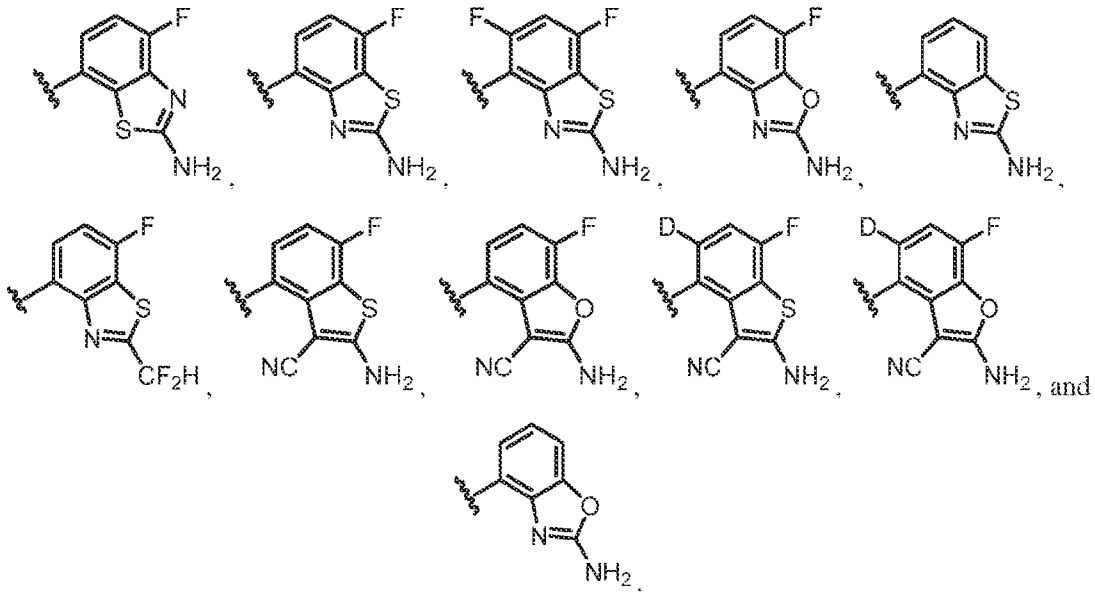


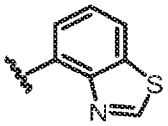
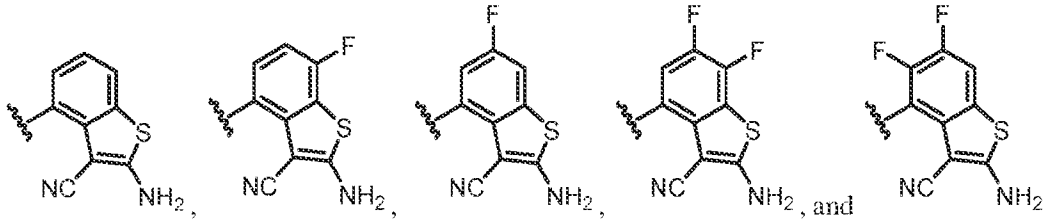
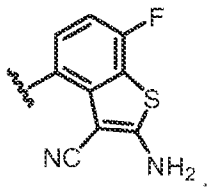
any of which is substituted with one or more R^{15}.

[0421] In some embodiments, for a compound according to any one of Formulas V', VA', and VB', R^6 is selected from:

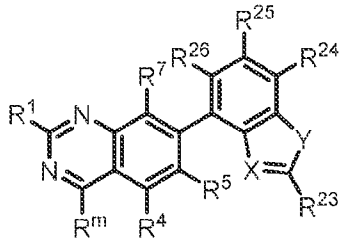


[0422] In some embodiments, for a compound according to any one of Formulas V', VA', and VB', R^6 is selected from:



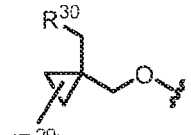
[0423] In some embodiments, for a compound according to any one of Formulas V', VA', and VB', R^6 is selected from:  , which is substituted with one or more R^{15}. In some embodiments, R^6 is selected from:  . In some embodiments, R^6 is  .

[0424] In some embodiments, the compound is a compound according to Formula VC':



(VC')

or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, wherein:

R^1 is selected from -OR^8,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^m is selected from hydrogen and $C_{1\text{-}6}$alkyl, wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and $C_{1\text{-}6}$alkyl, wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{13};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

n is 0-2;

each R^{31} is selected from C_{1-6} alkyl;

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

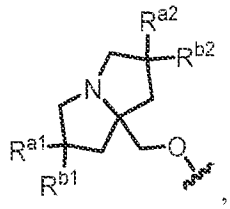
[0425] In some embodiments, the present disclosure provides a compound of Formula VC' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0426] In some embodiments, for a compound of Formula VC', X is C-CN and Y is S. In some embodiments, X is C-CN and Y is O. In some embodiments, X is N and Y is S. In some embodiments, X is N and Y is O. In some embodiments, R^{23} is selected from $-N(R^{12})_2$. In some embodiments, R^{23} is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^{23} is selected from C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments, X is C-CN, Y is S, and R^{23} is $-N(R^{12})_2$. In some embodiments, at least one of R^{24}, R^{25}, and R^{26} are independently selected from deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}. In some embodiments, at least one of R^{24}, R^{25},

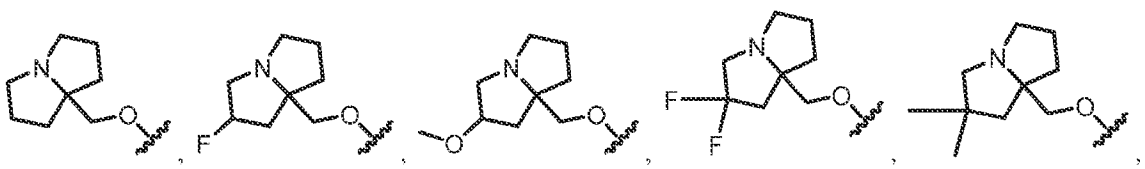
and R^{26} are independently selected from halogen. In some embodiments, X is C-CN, Y is S, R^{23} is selected from -$N(R^{12})_2$, and at least one of R^{24}, R^{25}, and R^{26} are independently selected from halogen. In some embodiments, X is C-CN, Y is S, and R^{23} is -NH_2. In some embodiments, X is C-CN, Y is S, R^{23} is -$N(R^{12})_2$, and R^{24} is a halogen (e.g., F). In some embodiments, X is C-CN, Y is S, R^{23} is -$N(R^{12})_2$, and one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F). In some embodiments, R^{26} is deuterium.

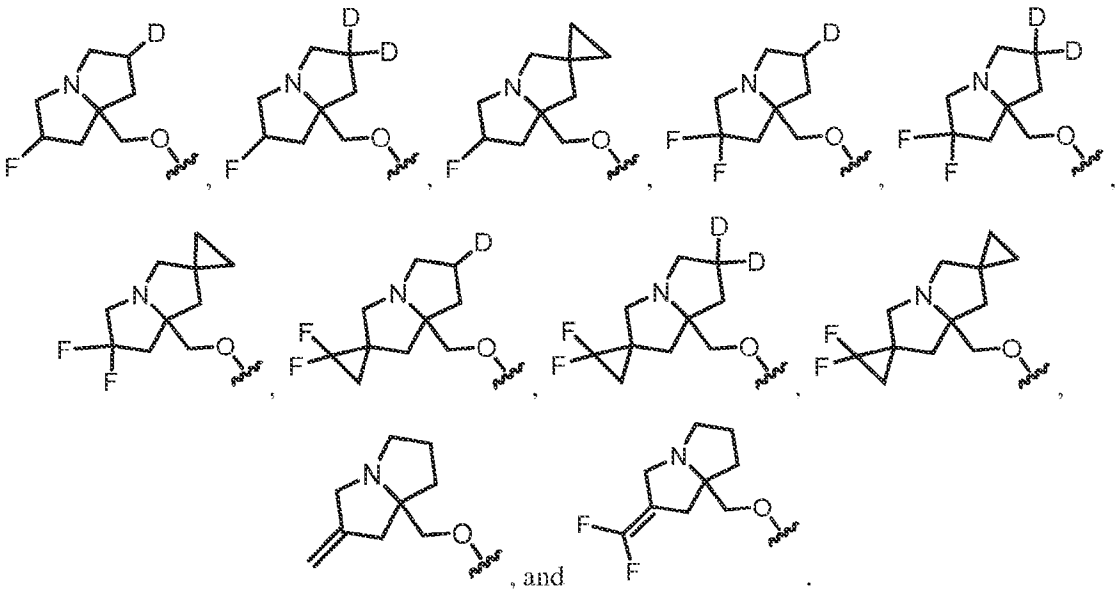
[0427] In some embodiments, for a compound of any one of Formulas V', VA', VB', and VC', R^1 is selected from -OR^8, wherein R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6} alkyl. In some embodiments, R^8 is a heterocycle or an alkylheterocycle, wherein any heterocycle contains 4-8 ring atoms and is substituted with one or more R^a or R^b. In some embodiments, R^8 is a heterocycle that is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, R^8 is an alkylheterocycle that is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, R^8 is –CH_2(heterocycle), where the heterocycle is unsubstituted or substituted with one or more R^a or R^b. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is a 4-6 membered monocyclic heterocycle having 1-2 heteroatoms independently selected from N, O, and S. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is an 8-membered bicyclic heterocycle having 1-2 heteroatoms independently selected from N, O, and S. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a halogen (e.g., F). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a C_{1-6}alkyl (e.g., methyl). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a -OR^{12} (e.g., -OCH_3). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a 3-6 membered carbocycle (e.g., a cyclopropane). In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is deuterium. In some embodiments, a heterocycle or a heterocycle of an alkylheterocycle is substituted with one or more R^a or R^b, wherein the one or more R^a or R^b is a C_{2-6}alkenyl (e.g., C_2alkenyl).

[0428] In some embodiments, for a compound of any one of Formulas V', VA', VB', and VC', R^1 is selected from:

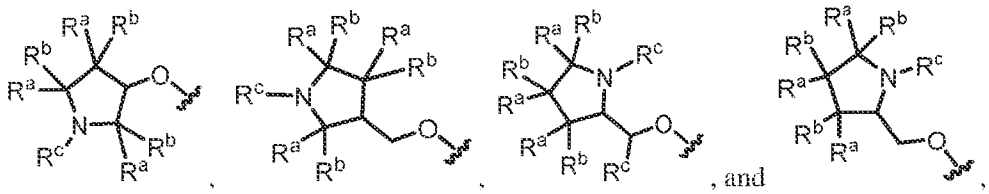


wherein R^{a1}, R^{a2}, R^{b1}, and R^{b} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H or are absent, wherein (i) R^{a2} and R^{b2} or (ii) R^{a1} and R^{b1} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} and/or R^{a2} is a halogen. In some embodiments, R^{a1} and/or R^{a2} is F. In some embodiments, R^{a1} and/or R^{a2} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{a1} and/or R^{a2} is methyl. In some embodiments, R^{a1} and/or R^{a2} is $-OC_{1-6}$alkyl. In some embodiments, R^{a1} and/or R^{a2} is H. In some embodiments, R^{b1} and/or R^{b2} is H. In some embodiments, R^{b1} and/or R^{b2} is a halogen. In some embodiments, R^{b1} and/or R^{b2} is F. In some embodiments, R^{b1} and/or R^{b2} is C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{b1} and/or R^{b2} is methyl. In some embodiments, one of R^{a1} and R^{b1} is F and the other is H. In some embodiments, each of R^{a1} and R^{b1} is F. In some embodiments, one of R^{a1} and R^{b1} is $-OC_{1-6}$alkyl and the other is H. In some embodiments, each of R^{a1} and R^{b1} is H. In some embodiments, each of R^{a2} and R^{b2} is H. In some embodiments, each of R^{a2} and R^{b2} is methyl. In some embodiments, R^{a2} and/or R^{b2} is D. In some embodiments, each of R^{a2} and R^{b2} is D. In some embodiments, R^{a2} and R^{b2} join together to form a 3-6 membered carbocycle (e.g., cyclopropane), which carbocycle is optionally substituted with one or more R^{13}. In some embodiments, R^{a1} and R^{b1} join together to form a 3-6 membered carbocycle (e.g., cyclopropane). In some embodiments, R^{a2} and R^{b2} join together to form a 3-6 membered carbocycle (e.g., cyclopropane). In some embodiments, R^{b1} is absent and R^{a1} is C_{2-6}alkenyl that is unsubstituted or is substituted with one or more R^{13}. In some embodiments, R^{b1} is absent and R^{a1} is C_{2-6}alkenyl that is unsubstituted. In some embodiments, R^{b1} is absent and R^{a1} is C_{2-6}alkenyl that is substituted with one or more R^{13}. In some embodiments, R^{1} is selected from:



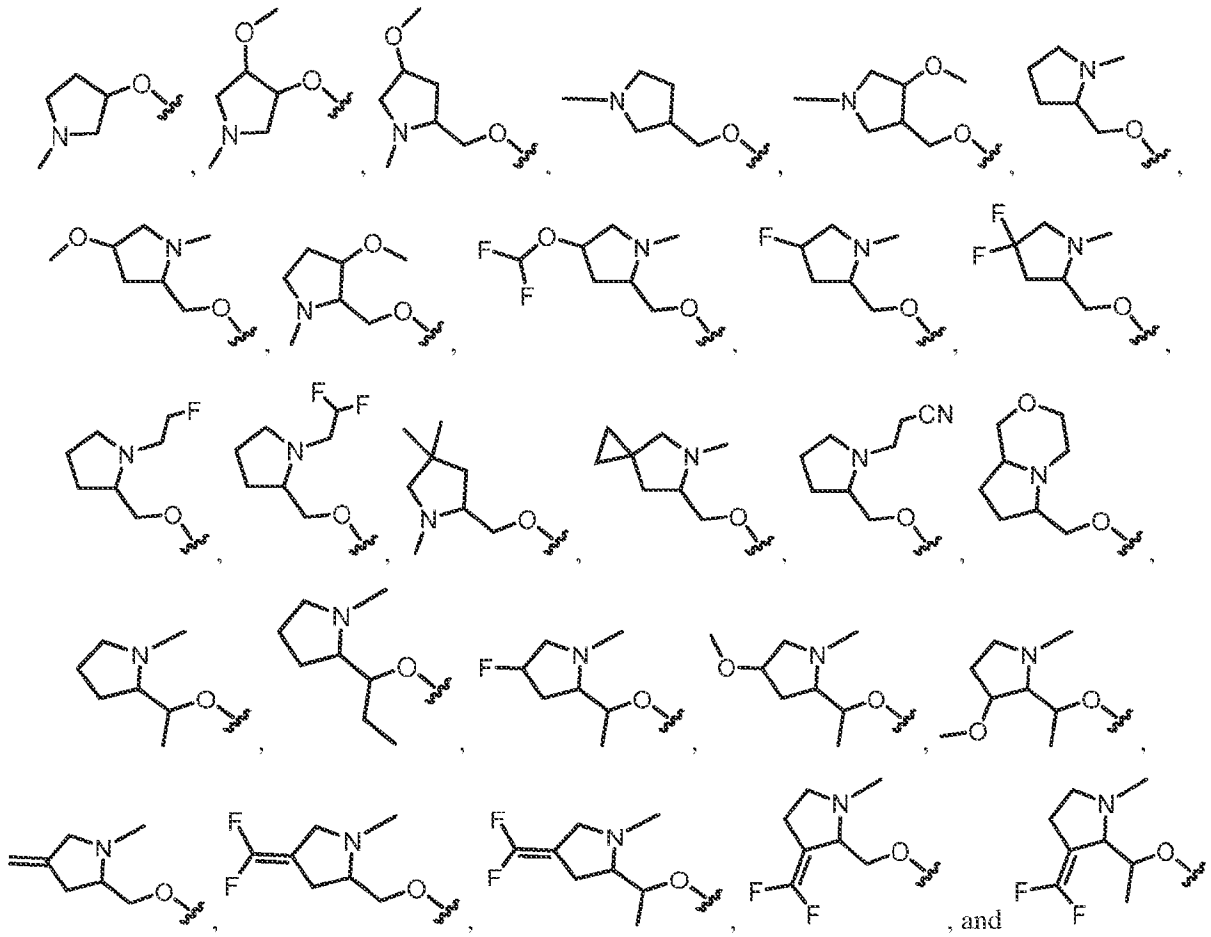


[0429] In some embodiments, for a compound of any one of Formulas V', VA', VB', and VC', R^1 is selected from:



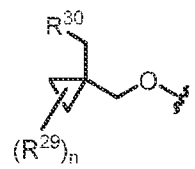
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H; and each R^c is selected from H and C_{1-6} alkyl, wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}. In some embodiments, each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and R^c is selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b attached to the same carbon atom join together to form a 3-6 membered carbocycle. In some embodiments, each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and wherein an R^a and R^c join together to form a 3-6 membered heterocycle. In some embodiments, each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and R^c is selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13}. In some embodiments, one R^a or R^b is selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, and $-OR^{12}$, and the other R^a and R^b groups are H. In some embodiments, at least one R^a or R^b is halogen (e.g., F). In some embodiments, one R^a or R^b is halogen (e.g., F). In some embodiments, two R^a groups, two R^b groups, or an R^a and an R^b are halogen (e.g., F). In some embodiments, one R^a or R^b is $-OR^{12}$ (e.g., $-OCH_3$ or $-OCHF_2$). In some embodiments, one R^a or R^b is C_{1-6}

alkyl (e.g., methyl). In some embodiments, two R^a groups, two R^b groups, or an R^a and an R^b are C_{1-6} alkyl (e.g., methyl). In some embodiments, R^c is selected from $-CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CH_2CN$. In some embodiments, one R^a is selected from C_{2-6}alkenyl that is unsubstituted or substituted with one or more R^{13}, and the R^b connected to the same atom is absent. In some embodiments, an R^a and R^b join together to form a 3-6 membered carbocycle, such as a cyclopropane. In some embodiments, an R^a and R^b attached to the same carbon atom join together to form a 3-6 membered carbocycle, such as a cyclopropane. In some embodiments, an R^a and R^c join together to form a 3-6 membered heterocycle. In some embodiments, R^1 is selected from:

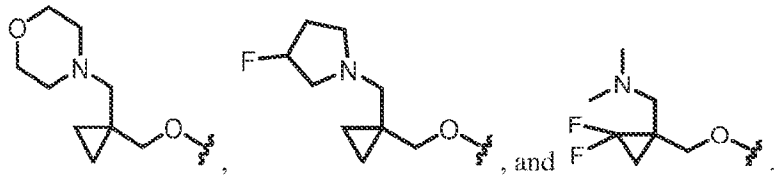

, and

.

[0430] In some embodiments, for a compound of any one of Formulas V', VA', VB', and VC', R^1 is selected from:

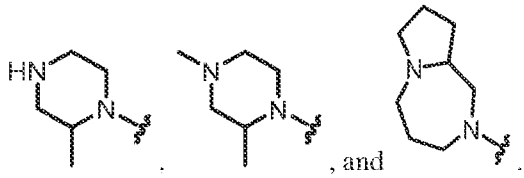

.

wherein R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; each R^{28} is independently selected from C_{1-6}alkyl and halogen; n is 0-2; and each R^{29} is independently selected from halogen and C_{1-6}alkyl. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted. In some embodiments, R^{30} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is substituted with one or more R^{28}. In some embodiments, R^{30} is a 6-membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}. In some embodiments, R^{30} is a 5-membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}. In some embodiments, R^{30} is $N(R^{14})_2$. In some embodiments, R^{30} is $N(C_{1-6}alkyl)_2$. In some embodiments, R^{30} is $N(CH_3)_2$. In some embodiments, at least one R^{29} is a halogen such as F. In some embodiments, R^1 is selected from:



, and .

[0431] In some embodiments, for a compound of any one of Formulas V', VA', VB', and VC', R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl. In some embodiments, R^1 is a 3-12 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl. In some embodiments, R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl. In some embodiments, R^1 is a 6-membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl. In some embodiments, R^1 is a piperazine that is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl. In some embodiments, R^1 is selected from:



[0432] In some embodiments, for a compound of any one of Formulas V', VA', VB', and VC', R^5 is a halogen (e.g., F or Cl). In some embodiments, R^5 is Cl. In some embodiments, R^5 is F. In some embodiments, R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^5 is selected from C_{1-2}alkyl that is unsubstituted or substituted with one or more R^{13}. In some embodiments, R^5 is selected from C_{1-6}alkyl that is unsubstituted, such as methyl or ethyl. In some embodiments, R^5 is selected from C_{1-6}alkyl that is substituted with one or more halogens or -CN. In some embodiments, R^5 is C_{1-6}alkyl that is substituted with one or more halogens, such as one or more fluorines. In some embodiments, R^5 is $-CF_3$. In some embodiments, R^5 is $-CHF_2$. In some embodiments, R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$. In some embodiments, R^5 is selected from $-CH_3$, $-CH_2CH_3$, $-CF_2H$, $-CF_3$, $-CF_2CH_3$, and $-CH_2CN$. In some embodiments, R^5 is C_{1-6}alkyl that is substituted with one or more R^{13}, wherein each R^{13} is independently selected from $-OR^{14}$, -CN, and $-N(R^{14})_2$. In some embodiments, R^5 is $-CH_2CN$.

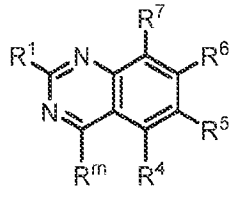
[0433] In some embodiments, for a compound of any one of Formulas V', VA', VB', and VC', R^7 is Cl. In some embodiments, R^7 is F.

[0434] Also provided herein are embodiments wherein any embodiment described herein may be combined with any one or more of these embodiments, provided the combination is not mutually exclusive. As used herein, two embodiments are "mutually exclusive" when one is defined to be something which is different than the other. For example, an embodiment wherein two groups combine to form a ring is mutually exclusive with an embodiment in which one group is ethyl and the other group is hydrogen. Similarly, an embodiment wherein one group is CH_2 is mutually exclusive with an embodiment wherein the same group is NH.

EXEMPLARY EMBODIMENTS

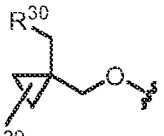
[0435] Among other things, the present disclosure provides the following Example Embodiments:

1. A compound represented by Formula A:



(A)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^m is selected from H and $-NR^2R^3$;

R^2 is selected from C_{1-6}alkyl;

R^3 is selected from a 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, $-N(R^{12})_2$, and -CN;

each R^{20} is independently selected from =O, -CN, and halogen;

each R^{28} is independently selected from halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

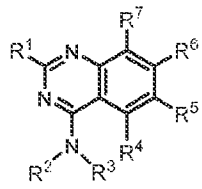
R^{30} is selected from $-N(R^{12})_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

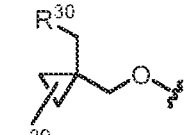
R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-4} alkenyl, and $-OR^{12}$, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

2. The compound of Embodiment 1, wherein the compound is a compound represented by Formula B:



(B)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^2 is selected from C_{1-6}alkyl;

R^3 is selected from a 4-10 membered heterocycle or $-(C_{1-6}$ alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl, wherein the heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, -N(R^{12})$_2$, and -CN;

each R^{20} is independently selected from =O, -CN, and halogen;

each R^{28} is independently selected from halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

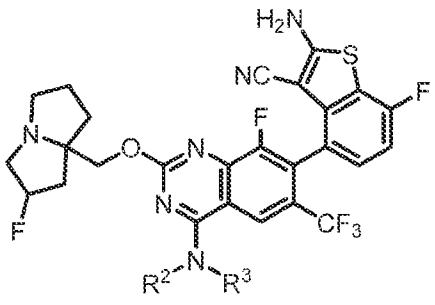
R^{30} is selected from -N(R^{12})$_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, C_{2-4} alkenyl, and -OR^{12}, wherein any C_{1-6}alkyl or C_{2-4} alkenyl is unsubstituted or is substituted with one or more R^{13}.

3. The compound of Embodiment 2, wherein the compound is of Formula B-a:



(B-a) or a salt (e.g., pharmaceutically acceptable salt) thereof.

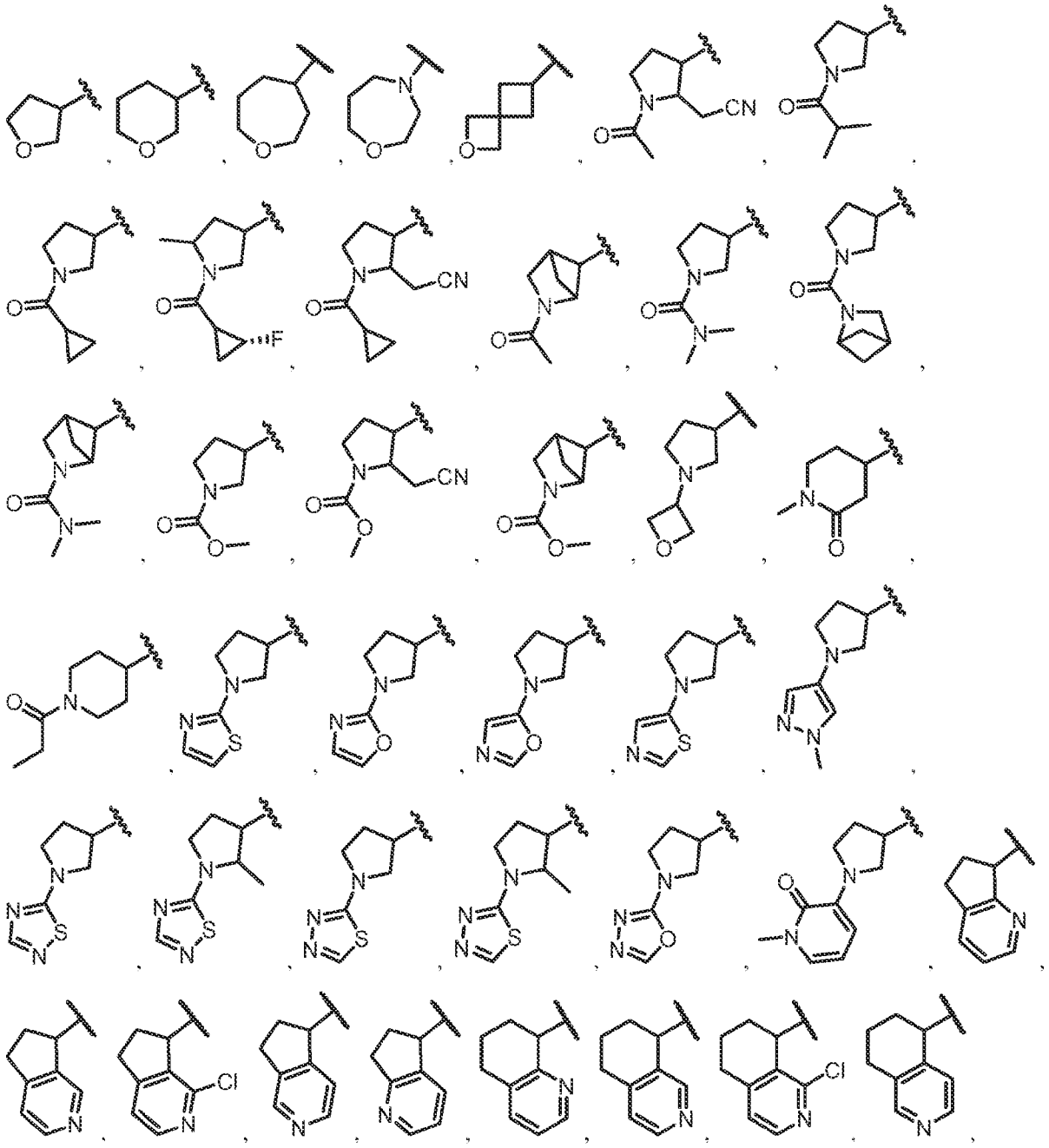
4. The compound of any one of Embodiments 1-3, wherein R^3 is a 4-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N.
5. The compound of Embodiment 4, wherein R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.
6. The compound of Embodiment 4, wherein R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}.
7. The compound of any one of Embodiments 1-6, wherein R^3 is a pyrrolidine that is substituted with 0-4 R^{10}.
8. The compound of any one of Embodiments 1-6, wherein R^3 is a pyrrolidine that is substituted with 0-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}.
9. The compound of any one of Embodiments 1-6, wherein R^3 is a 4-6 membered heterocycle that is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, and each R^{10} is independently selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.
10. The compound of any one of Embodiments 1-4, wherein R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N.
11. The compound of Embodiment 10, wherein R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.
12. The compound of Embodiment 10 or 11, wherein R^3 is an 8-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.
13. The compound of Embodiment 10 or 11, wherein R^3 is a 9-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.
14. The compound of Embodiment 10 or 11, wherein R^3 is a 10-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.
15. The compound of any one of Embodiments 12-14, wherein R^{10} is selected from =O, C_{1-6}alkyl, a 3-6 membered carbocycle, and halogen.

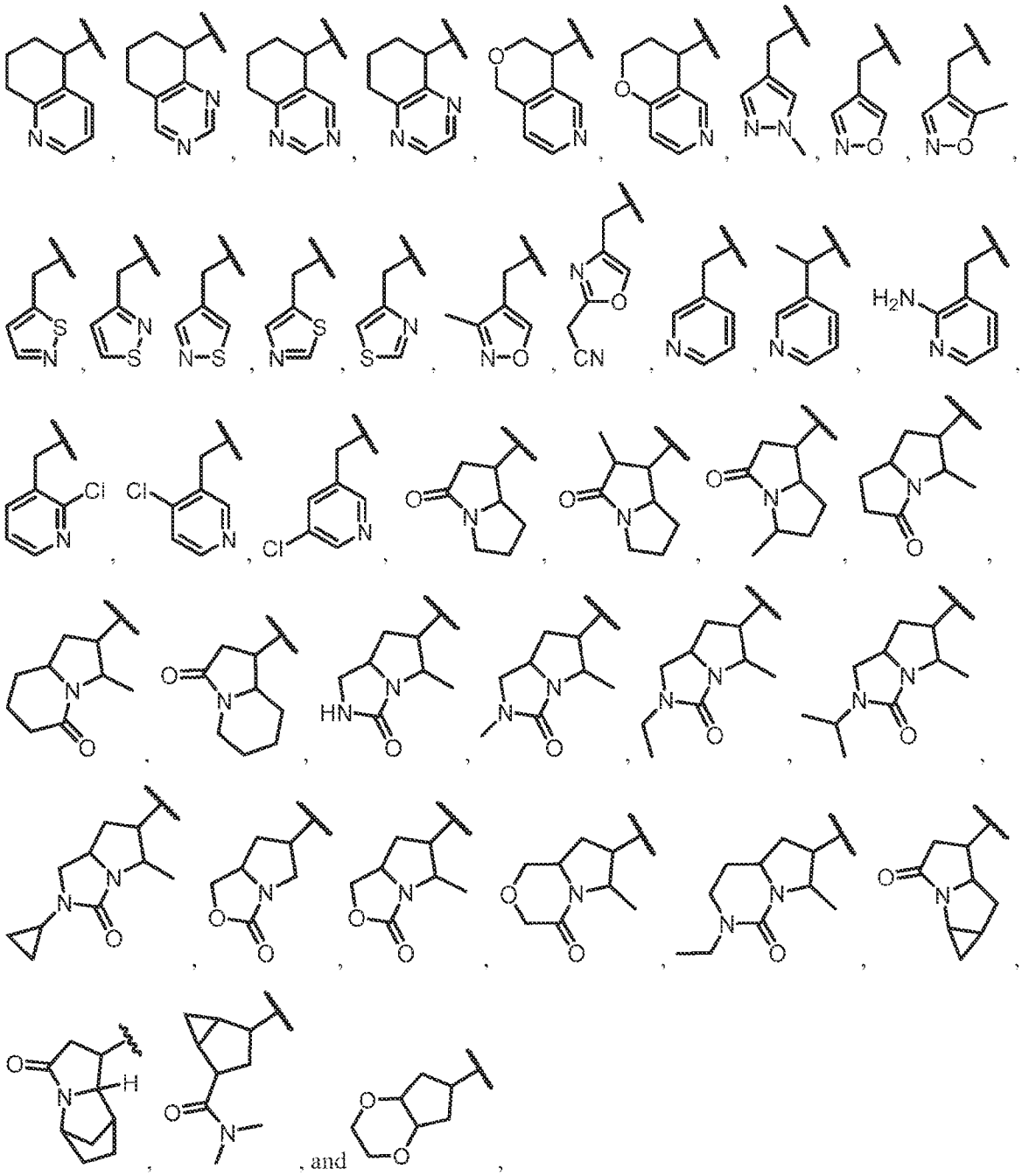
16. The compound of any one of Embodiments 1-3, wherein R^3 is -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}.

17. The compound of Embodiment 16, wherein R^3 is -CH_2(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}.

18. The compound of Embodiment 17, wherein R^{10} is selected from halogen and C_{1-6}alkyl, wherein the C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}.

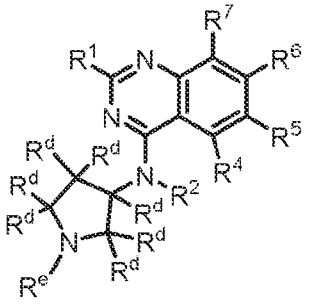
19. The compound of any one of Embodiments 1-18, wherein R^3 is selected from:

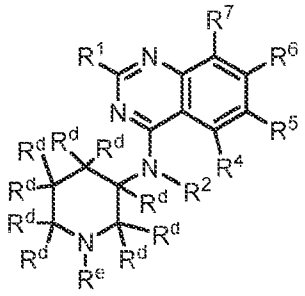


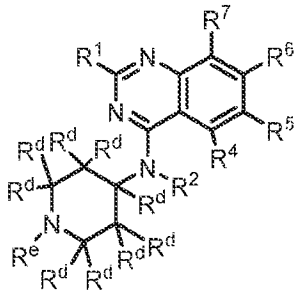


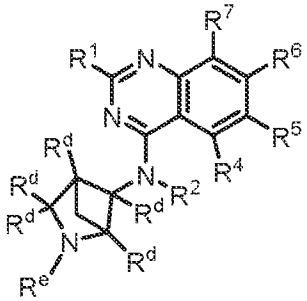
any of which is optionally further substituted with one or more R^{10}.

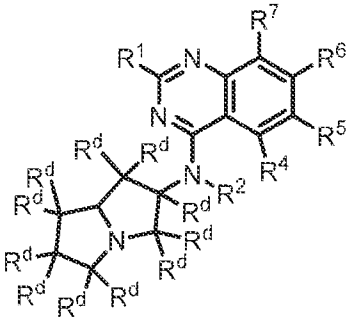
20. The compound of any one of Embodiments 1-19, wherein the compound is a compound according to Formula BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM:


(BA),


(BB),


(BC),


(BD),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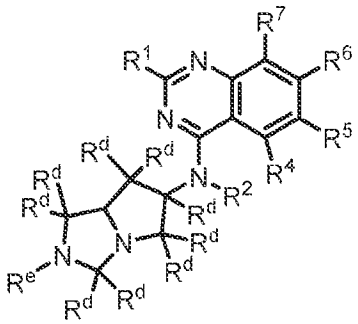
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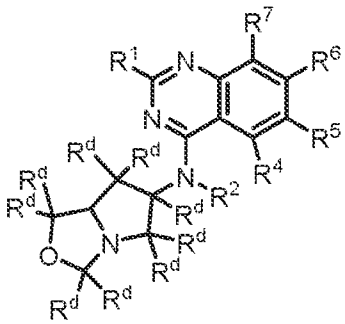
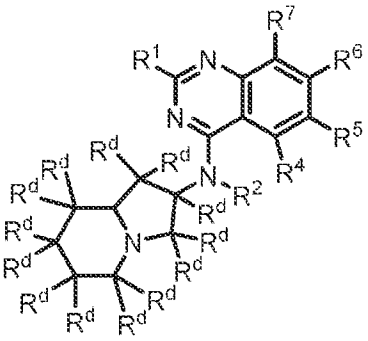
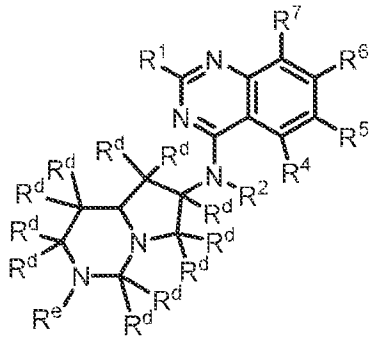
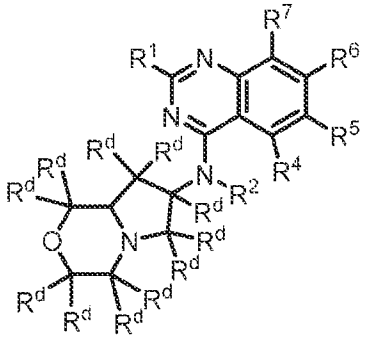

(BG),



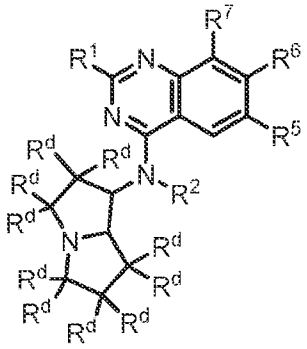
(BH),



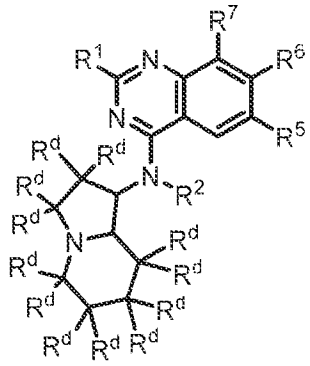
(BI),



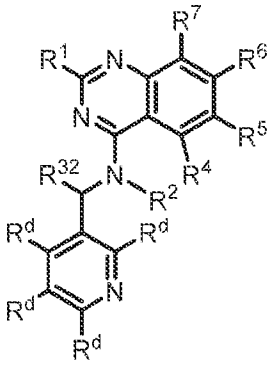
(BJ),



(BK),



(BL),



and (BM),

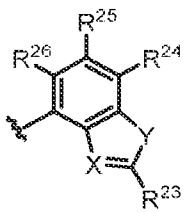
or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^{32}, if present, is selected from H and $C_{1\text{-}5}$alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and $C_{1\text{-}6}$alkyl, wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{20}; and

R^e, if present, is selected from H, -C(O)($C_{1\text{-}6}$alkyl), -C(O)O($C_{1\text{-}6}$alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and $C_{1\text{-}6}$alkyl, wherein any $C_{1\text{-}6}$alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

21. The compound of Embodiment 20, wherein the compound is a compound according to Formula BA, or a salt (e.g., pharmaceutically acceptable salt) thereof.
22. The compound of Embodiment 20, wherein the compound is a compound according to Formula BB, or a salt (e.g., pharmaceutically acceptable salt) thereof.
23. The compound of Embodiment 20, wherein the compound is a compound according to Formula BC, or a salt (e.g., pharmaceutically acceptable salt) thereof.
24. The compound of Embodiment 20, wherein the compound is a compound according to Formula BD, or a salt (e.g., pharmaceutically acceptable salt) thereof.
25. The compound of Embodiment 20, wherein the compound is a compound according to Formula BE, or a salt (e.g., pharmaceutically acceptable salt) thereof.
26. The compound of Embodiment 20, wherein the compound is a compound according to Formula BF, or a salt (e.g., pharmaceutically acceptable salt) thereof.
27. The compound of Embodiment 20, wherein the compound is a compound according to Formula BG, or a salt (e.g., pharmaceutically acceptable salt) thereof.
28. The compound of Embodiment 20, wherein the compound is a compound according to Formula BH, or a salt (e.g., pharmaceutically acceptable salt) thereof.
29. The compound of Embodiment 20, wherein the compound is a compound according to Formula BI, or a salt (e.g., pharmaceutically acceptable salt) thereof.
30. The compound of Embodiment 20, wherein the compound is a compound according to Formula BJ, or a salt (e.g., pharmaceutically acceptable salt) thereof.
31. The compound of Embodiment 20, wherein the compound is a compound according to Formula BK, or a salt (e.g., pharmaceutically acceptable salt) thereof.
32. The compound of Embodiment 20, wherein the compound is a compound according to Formula BL, or a salt (e.g., pharmaceutically acceptable salt) thereof.
33. The compound of Embodiment 20, wherein the compound is a compound according to Formula BM, or a salt (e.g., pharmaceutically acceptable salt) thereof.
34. The compound of any one of Embodiments 1-33, wherein (i) when R^3 includes a heterocycle or heteroaryl containing a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle or heteroaryl does not comprise an –NH- moiety.
35. The compound of any one of Embodiments 1, 2, or 4-34, wherein R^6 is selected from:



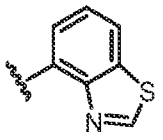
, wherein:

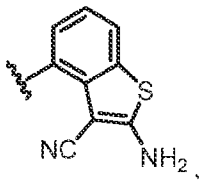
X is selected from N and C-CN;

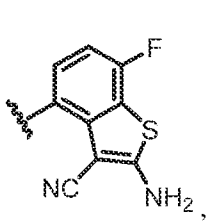
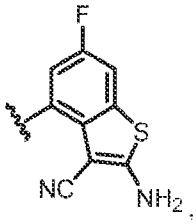
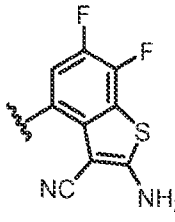
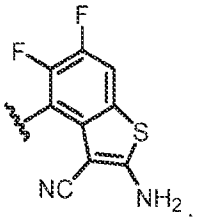
Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

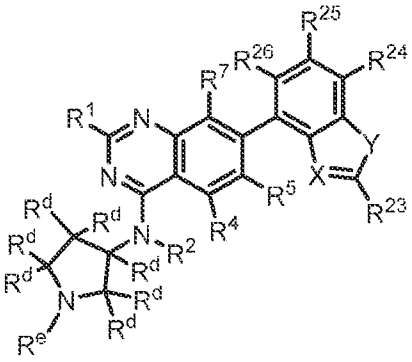
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

36. The compound of Embodiment 35, wherein R^6 is selected from:  , which is substituted with one or more R^{15}.

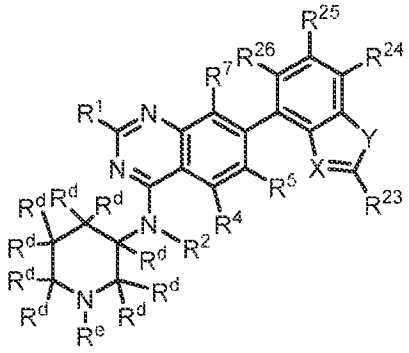
37. The compound of Embodiment 36, wherein R^6 is selected from:  ,

 ,  ,  , and  .

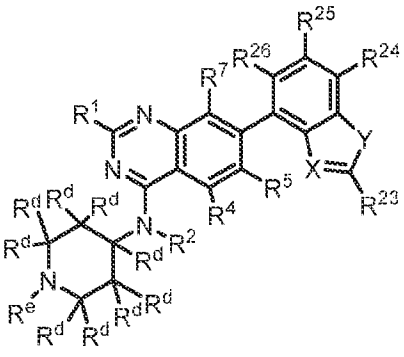
38. The compound of any one of Embodiments 1, 2, or 4-37, wherein the compound is a compound according to Formula BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1:



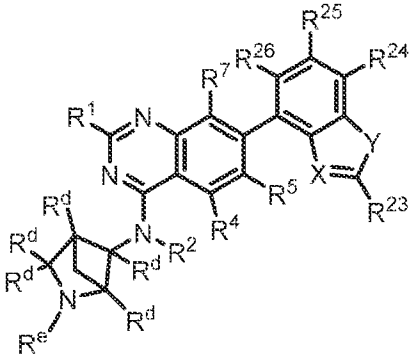
(BA1),



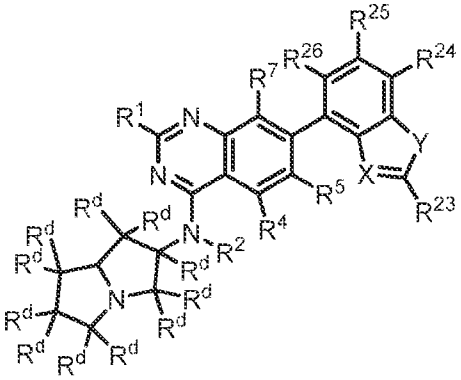
(BB1),



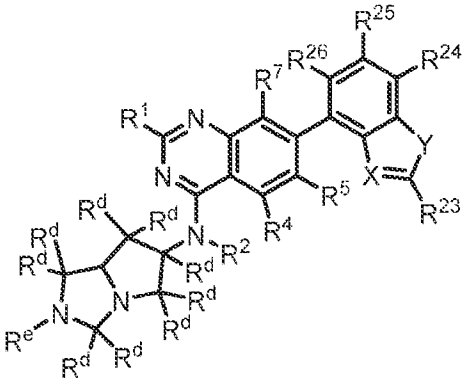
(BC1),



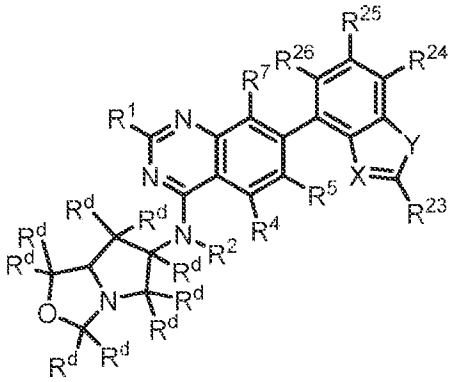
(BD1),



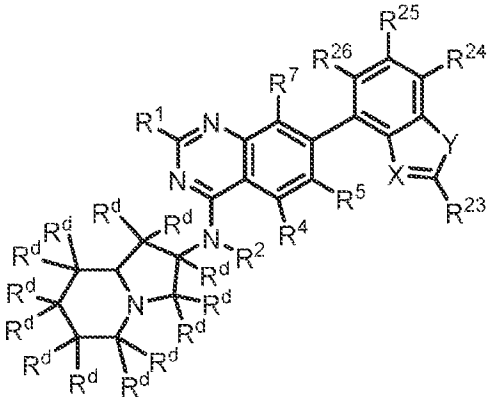
(BE1),



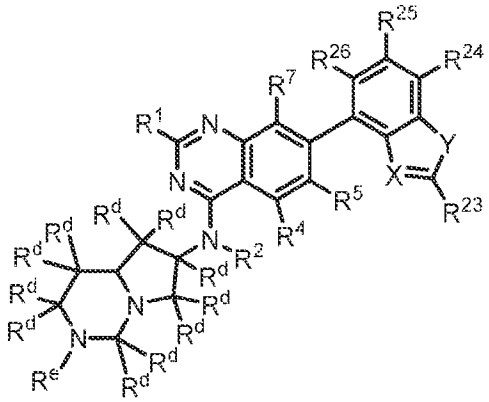
(BF1),



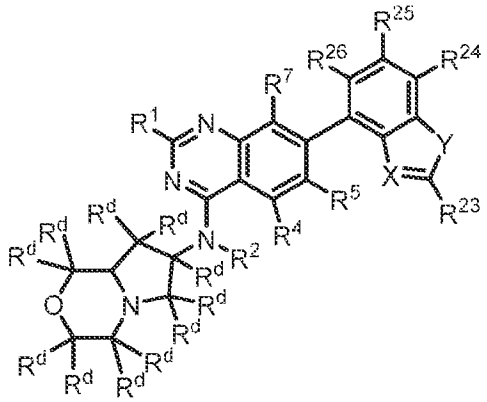
(BG1),



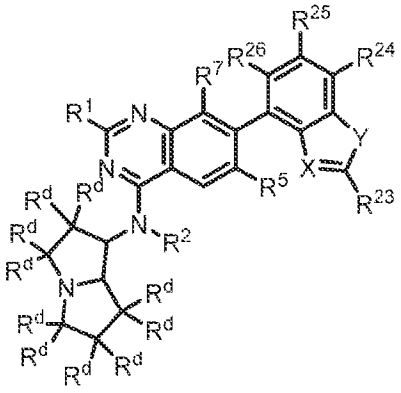
(BH1),



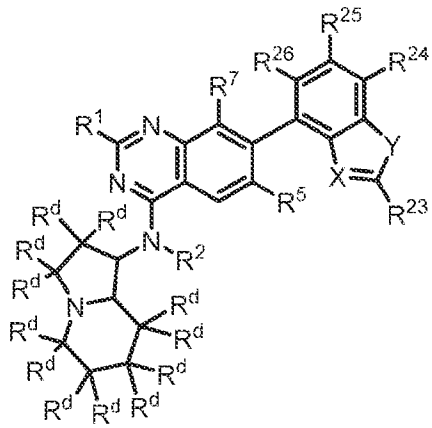
(BI1),



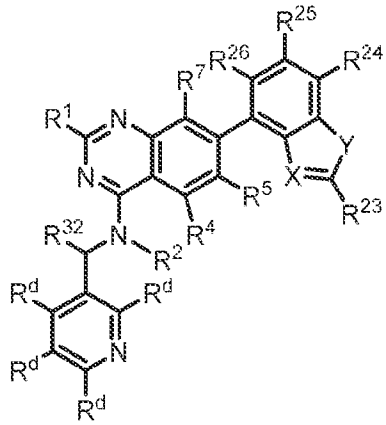
(BJ1),



(BK1),



(BL1), and



(BM1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^{32}, if present, is selected from H and C_{1-5}alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

R^e, if present, is selected from -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-}

$_{6}$alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is C-CN;

Y is S;

R^{23} is selected from $-N(R^{12})_2$; and

R^{24}, R^{25}, and R^{26} are independently selected from H and halogen.

39. The compound of any one of Embodiments 35-38, wherein one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

40. The compound of any one of Embodiments 20-39, wherein R^e is -C(O)(3-6 membered carbocycle).

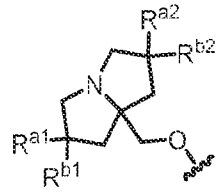
41. The compound of any one of Embodiments 20-39, wherein R^e is selected from $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), and $-C(O)O(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

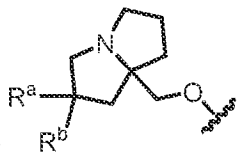
42. The compound of any one of Embodiments 20-41, wherein each R^d is H.

43. The compound of any one of Embodiments 1-42, wherein R^2 is H.

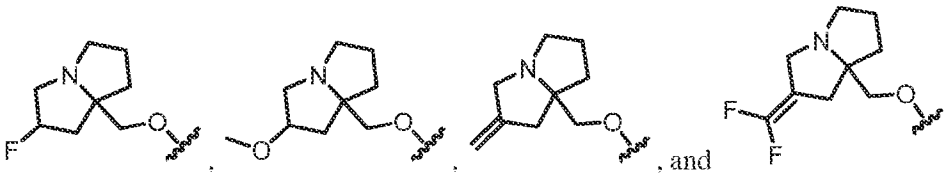
44. The compound of any one of Embodiments 1-42, wherein R^2 is selected from C_{1-2}alkyl.

45. The compound of any one of Embodiments 1, 2, or 4-44, wherein R^1 is selected from $-OR^8$.

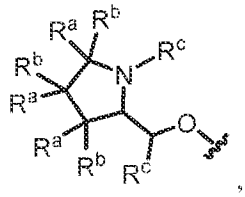
46. The compound of Embodiment 45, wherein R^1 is selected from:  , wherein R^{a1}, R^{a2}, R^{b1}, and R^{b2} are each independently selected from deuterium, halogen, $-OR^{12}$, and H, wherein R^{a1} and R^{b1} can optionally join together to form a exocyclic double bond that is unsubstituted or is substituted by halogen.

47. The compound of Embodiment 46, wherein R^1 is selected from:  , wherein R^a and R^b are each independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen.

48. The compound of Embodiment 47, wherein R^1 is selected from:

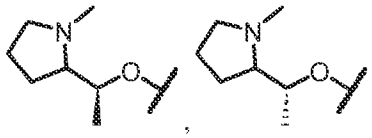


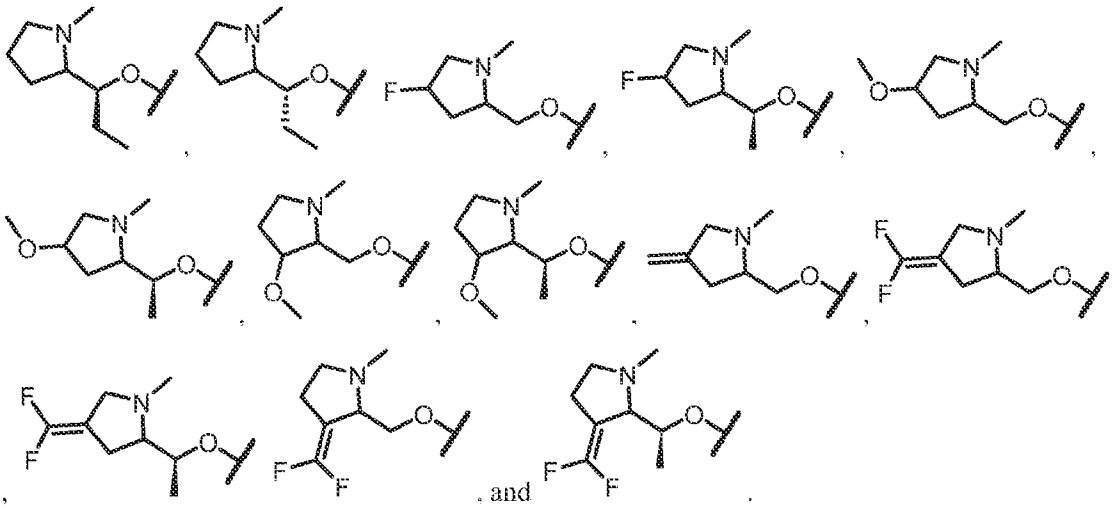
49. The compound of Embodiment 45, wherein R^1 is:



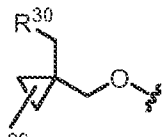
wherein each R^a and R^b is independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H; and each R^c is independently selected from H and C_{1-6} alkyl, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen.

50. The compound of Embodiment 49, wherein R^1 is selected from:



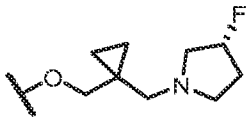
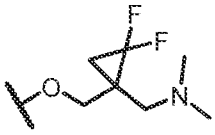
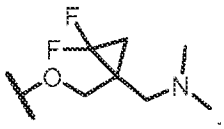


51. The compound of any one of Embodiments 1, 2, or 4-44, wherein R^1 is



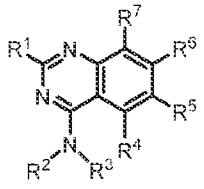
.

52. The compound of Embodiment 51, wherein R^1 is selected from .

 ,  , and  .

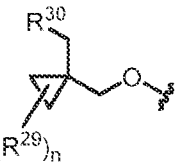
53. The compound of any one of Embodiments 1, 2, or 4-52, wherein R^5 is $-CF_3$.

54. A compound represented by Formula II':



(II')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}$alkylene)CN, $-C(O)(C_{1-6}$alkylene)OH, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}$alkylene)(3-6 membered heterocycle), $-S(O)_2(C_{1-6}$alkyl), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, -$N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

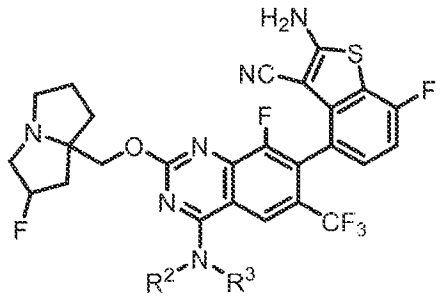
each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

55. The compound of Embodiment 54, wherein R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, or (ii) the heterocycle does not comprise an –NH- moiety.

56. The compound of Embodiment 54 or 55, wherein the compound is of Formula II-a:



(II-a)

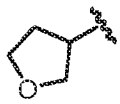
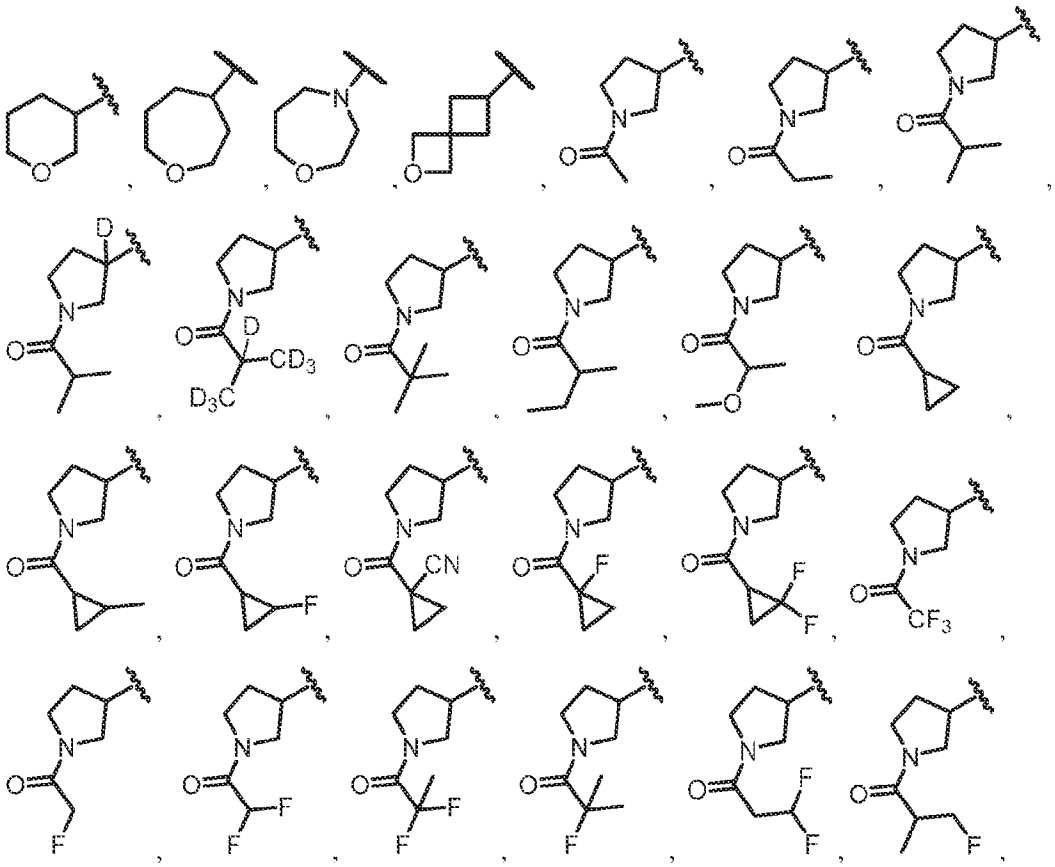
or a salt (e.g., pharmaceutically acceptable salt) thereof.

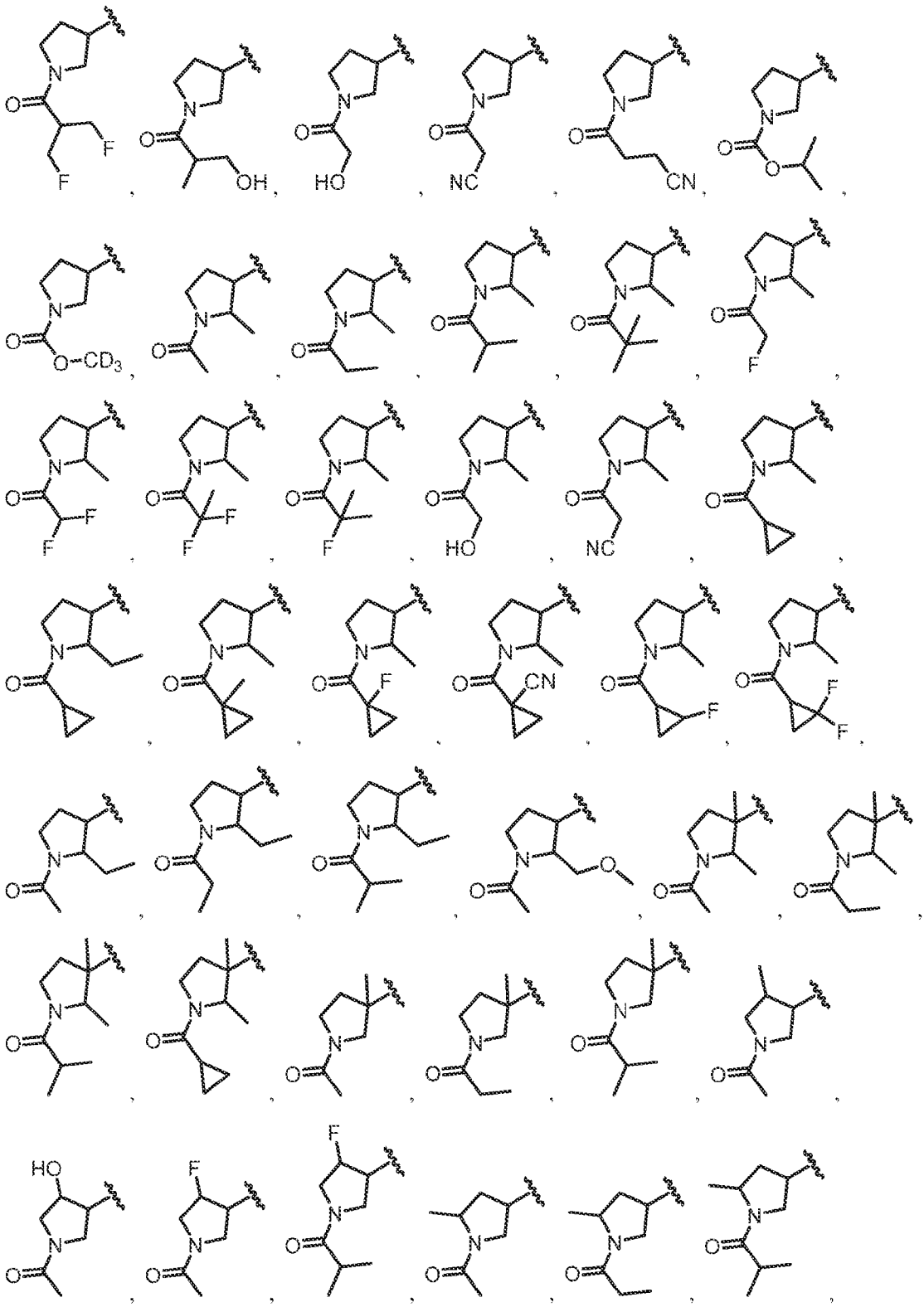
57. The compound of any one of Embodiments 54-56, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N.

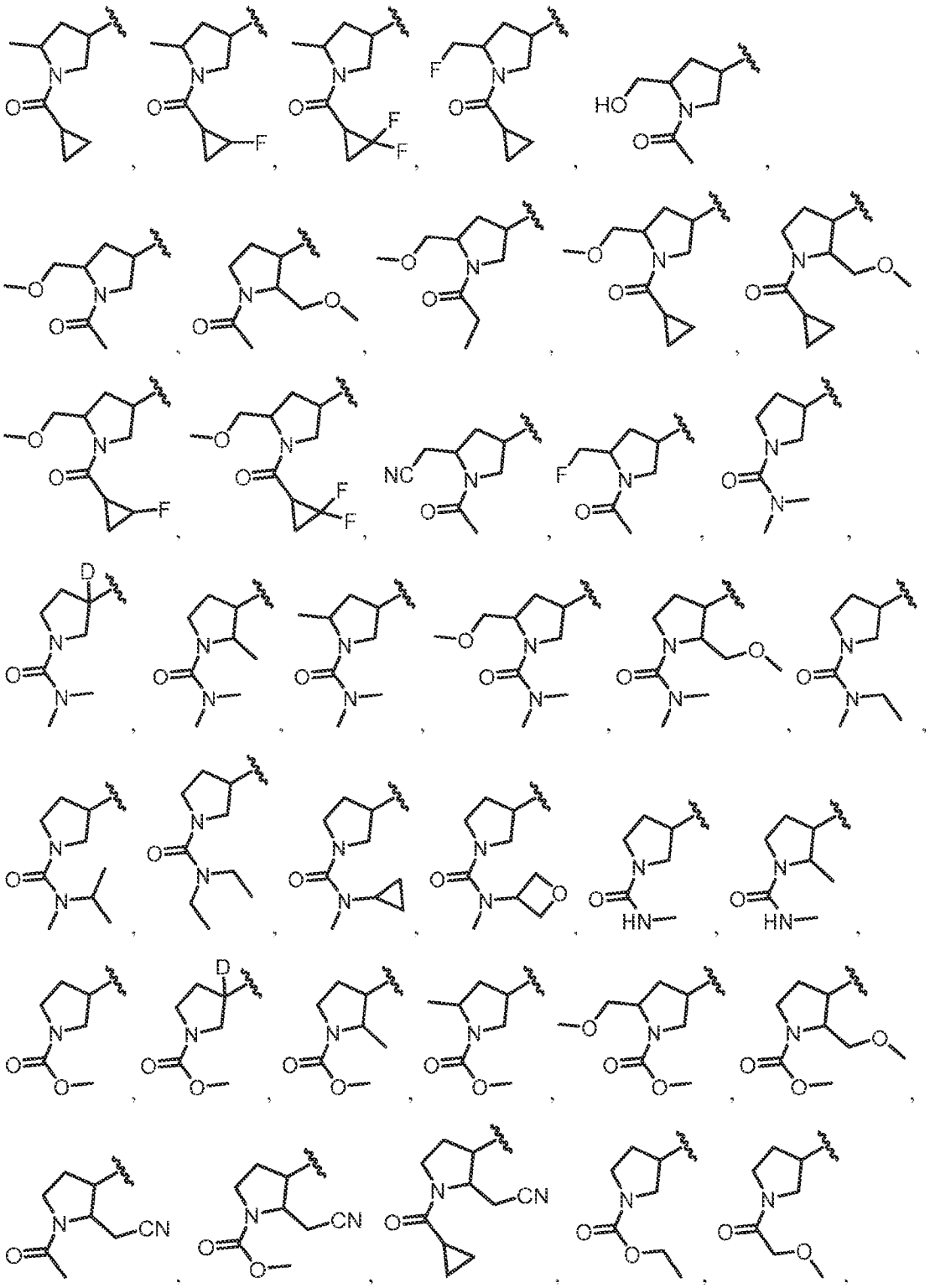
58. The compound of Embodiment 57, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}.

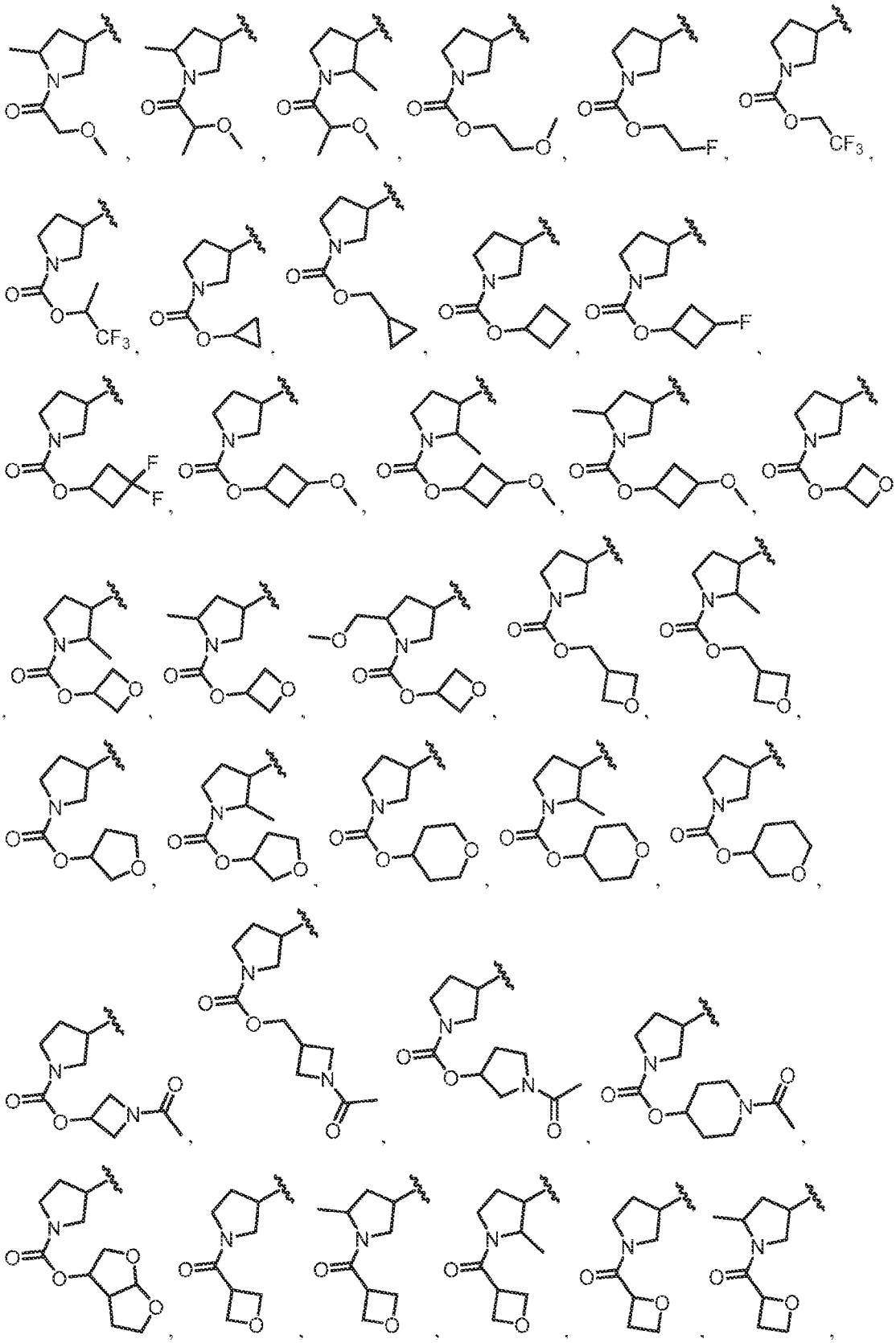
59. The compound of any one of Embodiments 54-58, wherein R^3 is a pyrrolidine that is substituted with 1-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}.

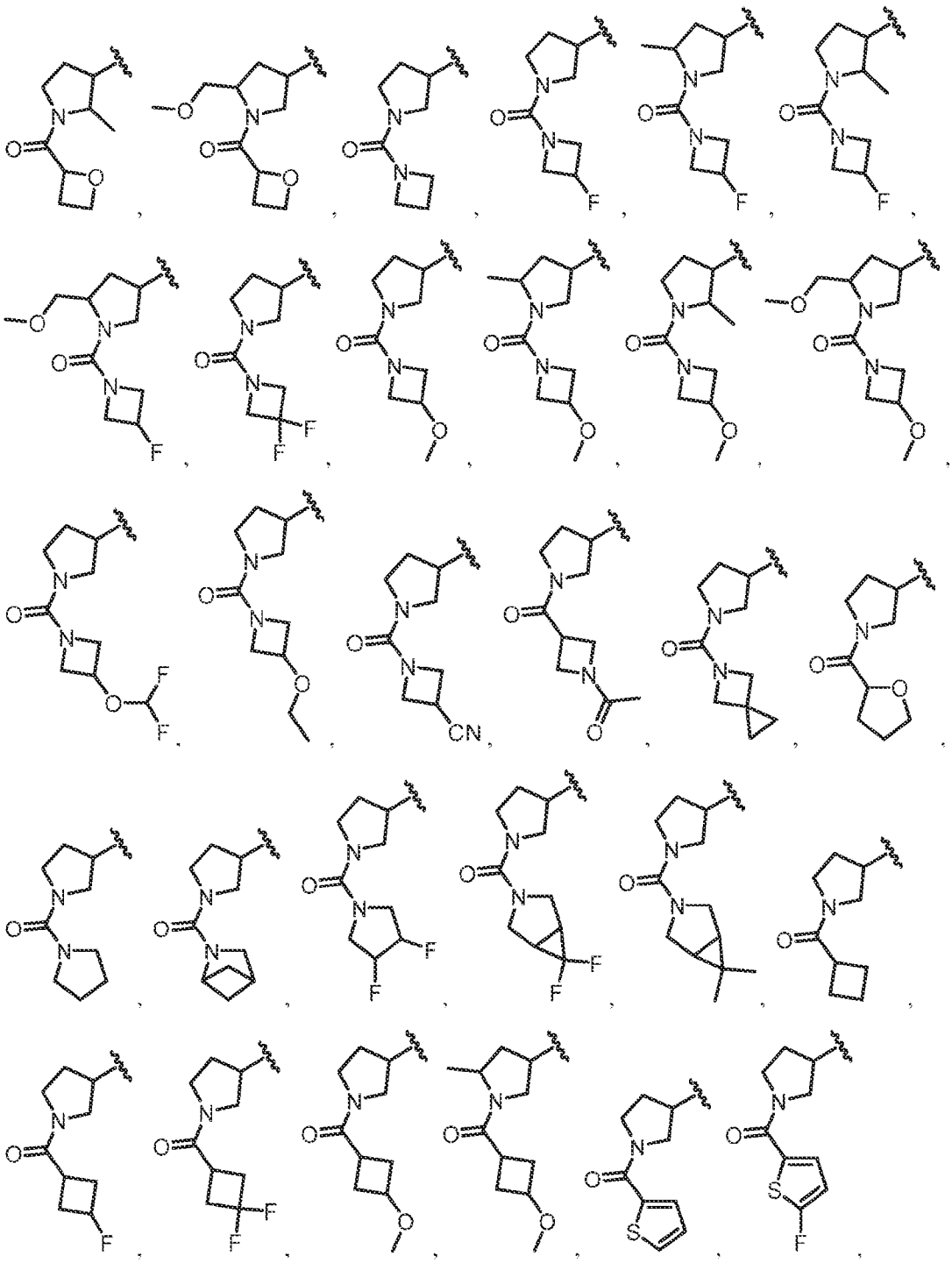
60. The compound of Embodiment 59, wherein each R^{10} is independently selected from deuterium, -C(O)N(R^{14})$_2$, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 3-6 membered heterocycle, a 5-6 membered heteroaryl, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

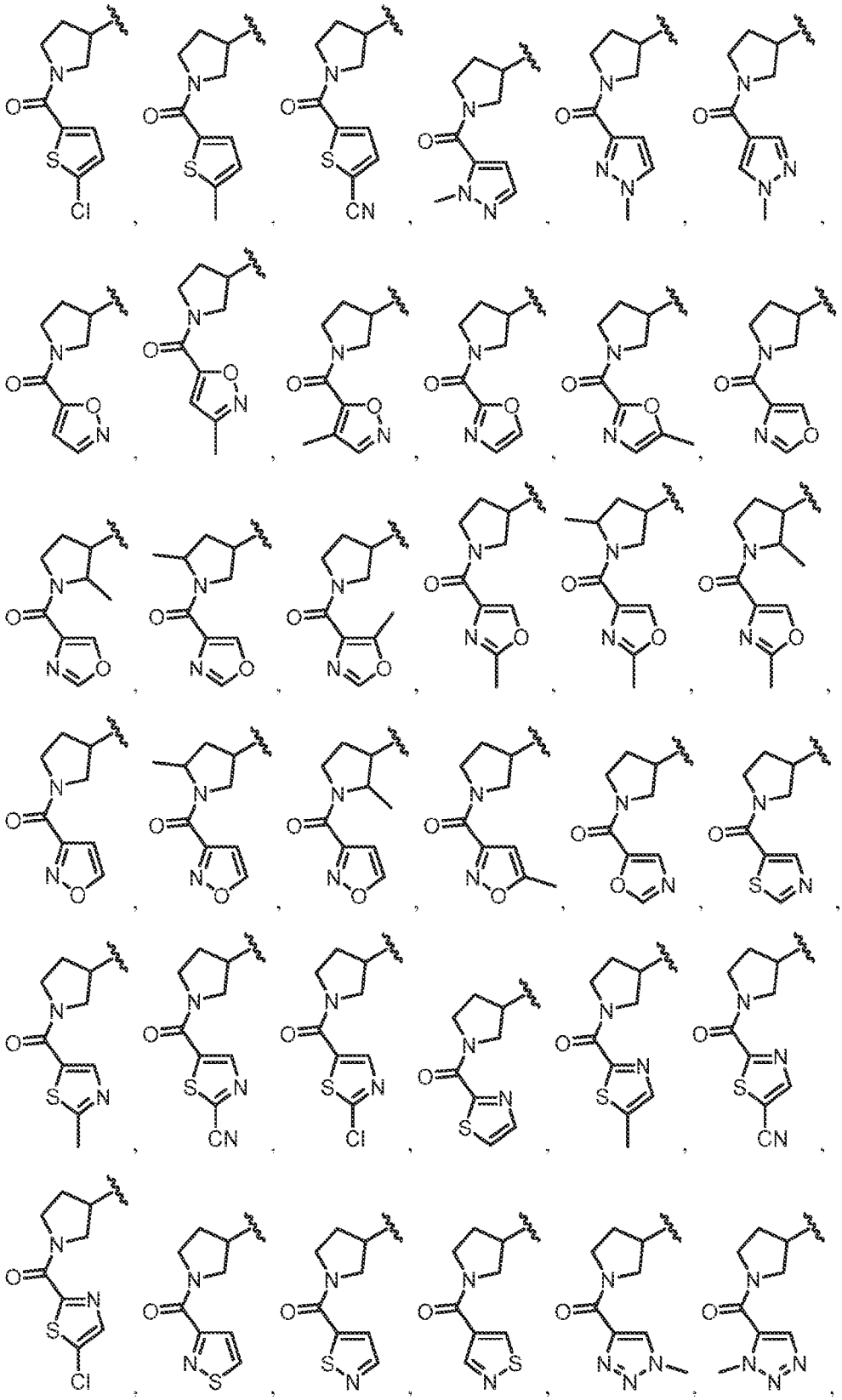
61. The compound of any one of Embodiments 54-60, wherein R^3 is selected from:  , 

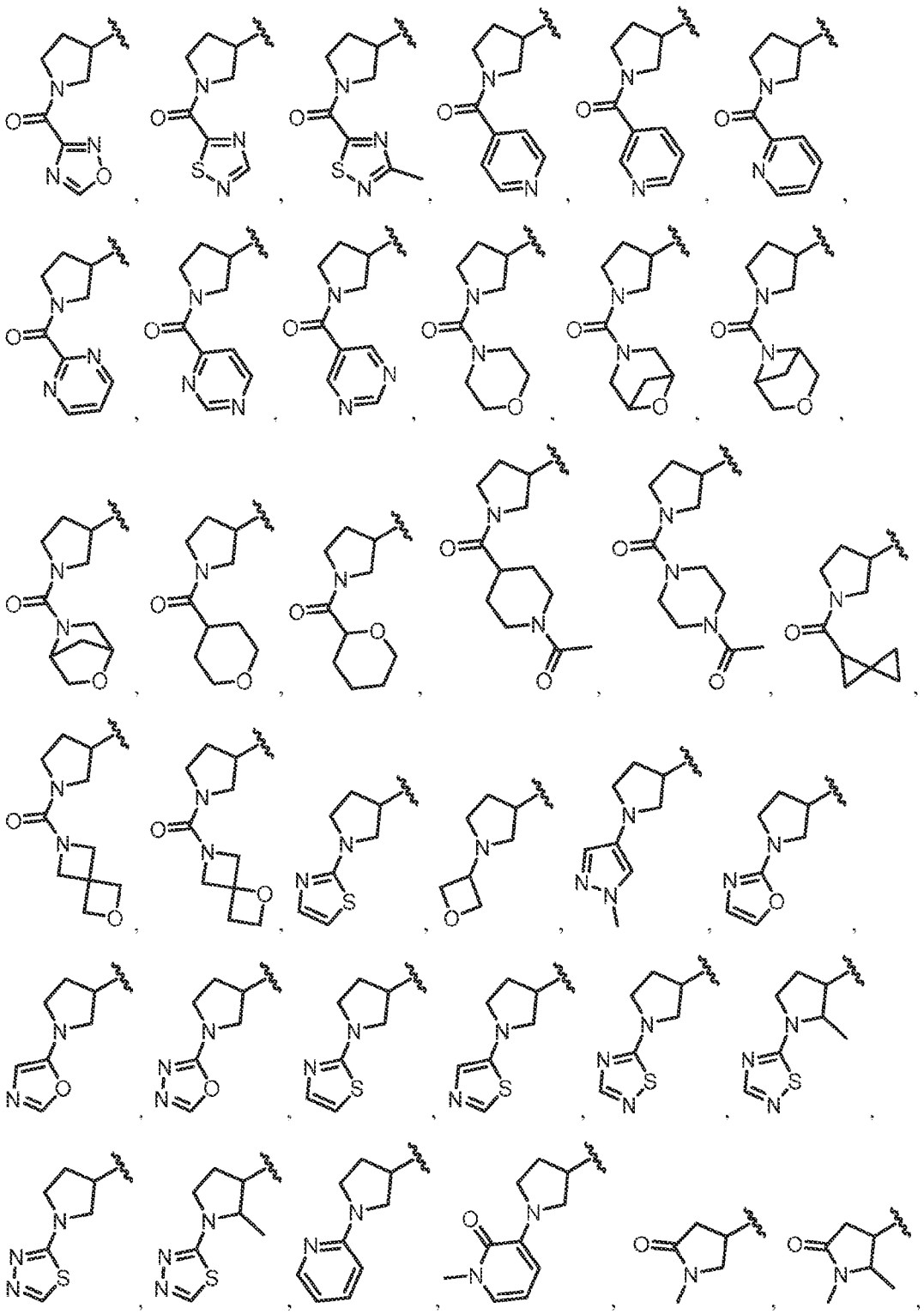


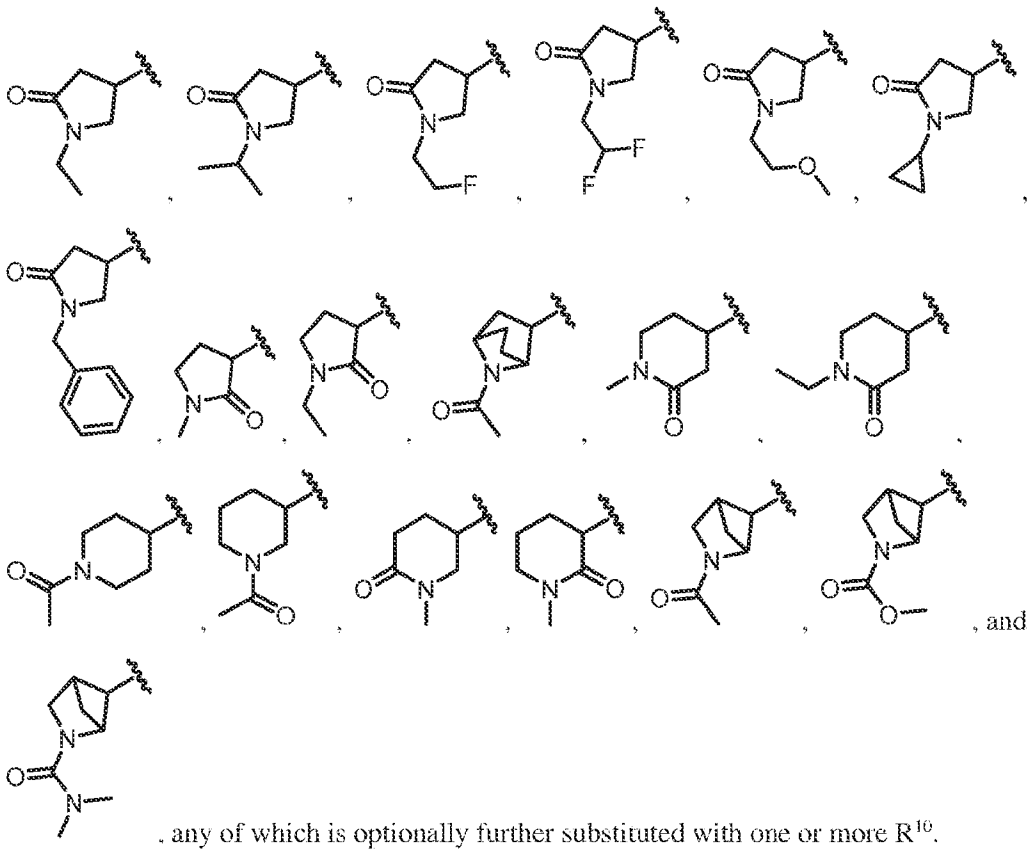






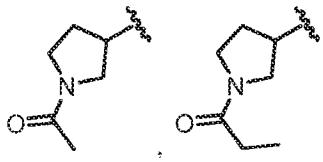


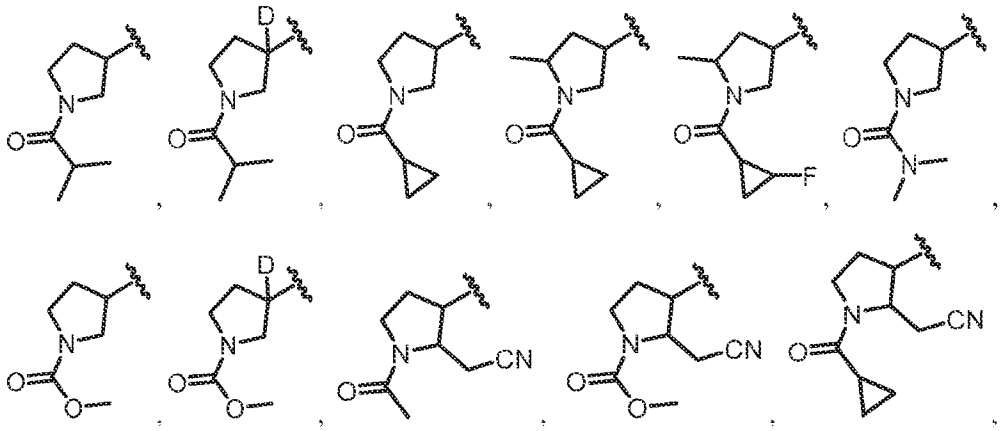


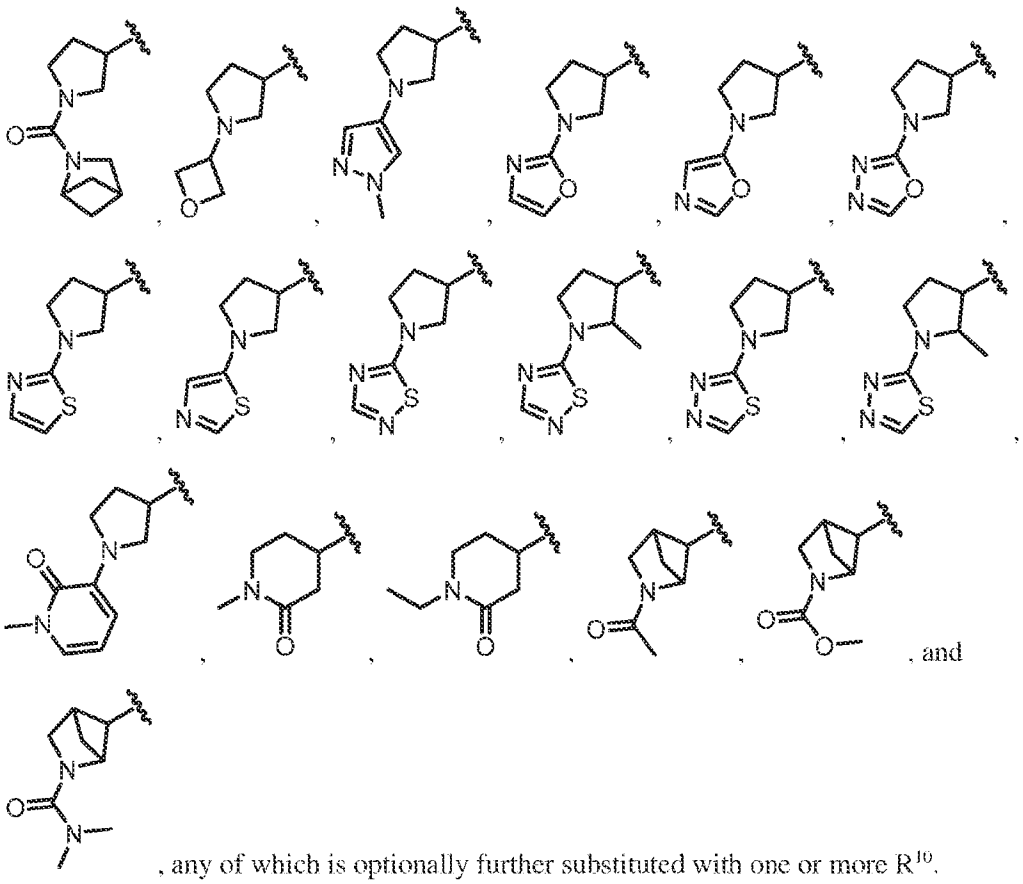


, any of which is optionally further substituted with one or more R^{10}.

62. The compound of Embodiment 61, wherein R^3 is selected from:







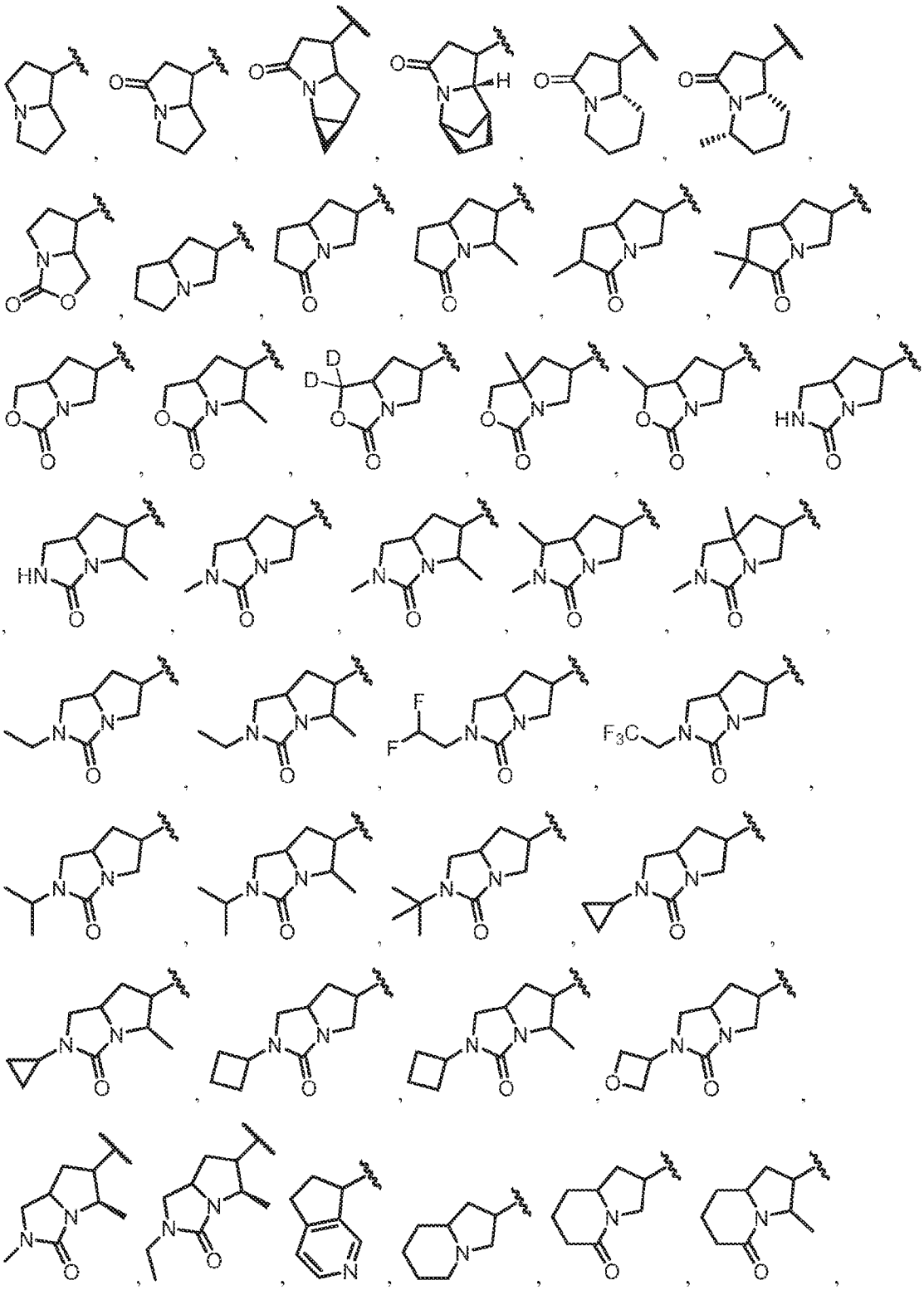
, any of which is optionally further substituted with one or more R^{10}.

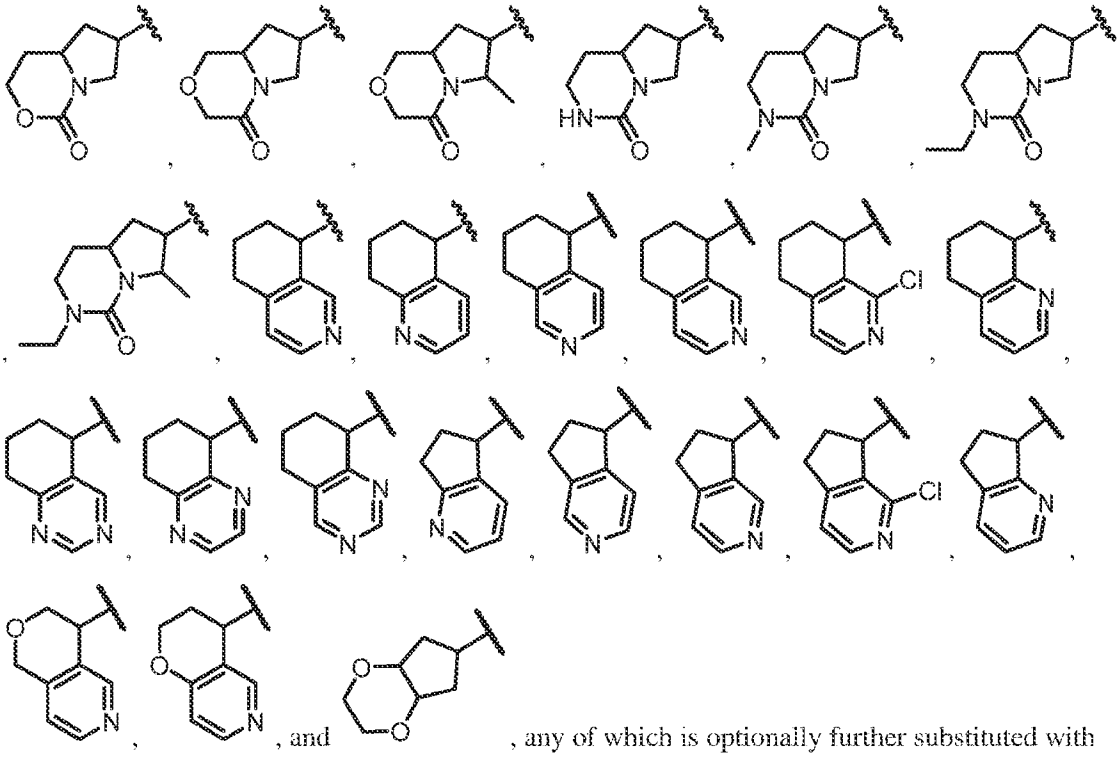
63. The compound of any one of Embodiments 54-56, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

64. The compound of Embodiment 63, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not comprise an –NH- moiety.

65. The compound of Embodiment 63 or 64, wherein R^3 is a 7-10 membered heterocycle comprising a fused ring system that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

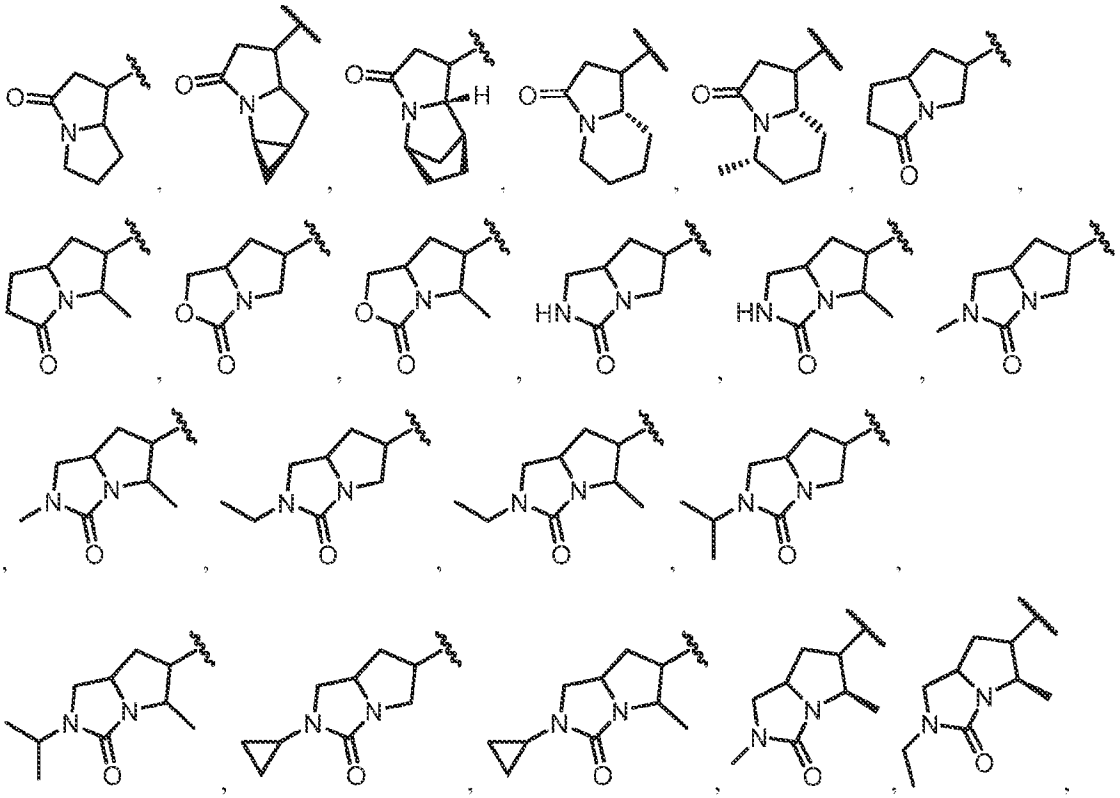
66. The compound of any one of Embodiments 54-56 and 63-65, wherein R^3 is selected from:

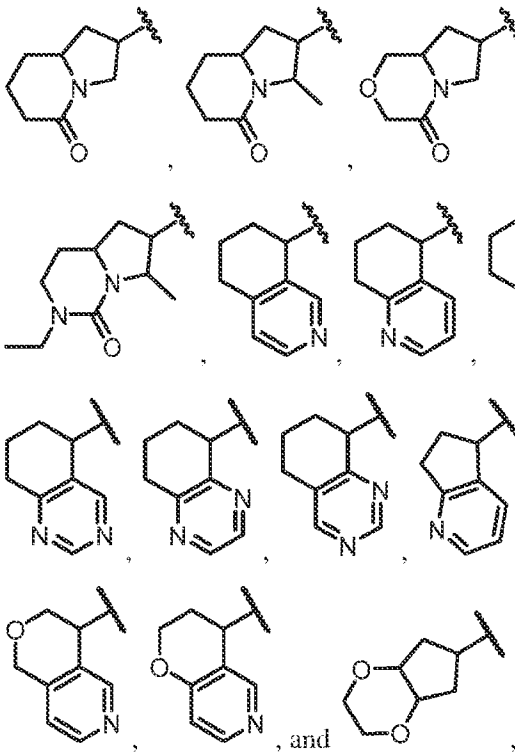




, and , any of which is optionally further substituted with one or more R^{10}.

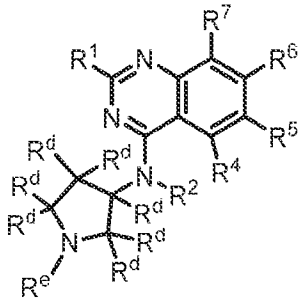
67. The compound of Embodiment 66, wherein R^3 is selected from:



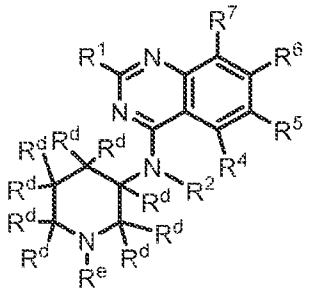


, any of which is optionally further substituted with one or more R^{10}.

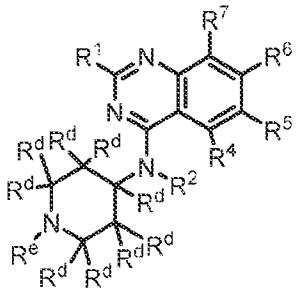
68. The compound of any one of Embodiments 54, 55, and 57-67, wherein the compound is a compound according to Formula IIR', IIU', IIV', or IIZ:



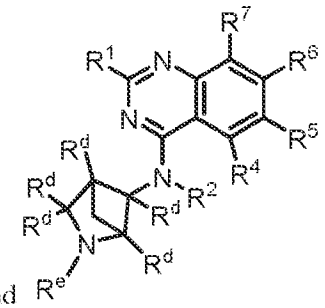
(IIR'),



(IIU'),



(IIV'),



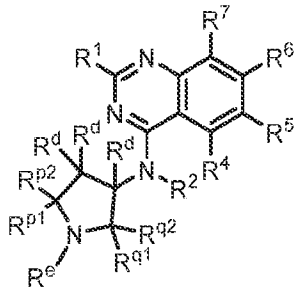
and (IIZ),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^e is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

69. The compound of any one of Embodiments 54, 55, and 57-67, wherein the compound is a compound according to Formula IIAA':



(IIAA'),

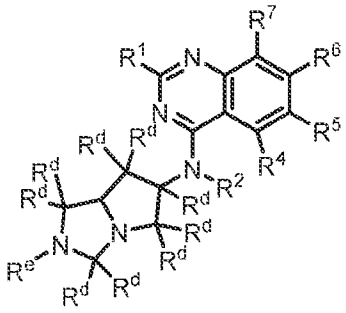
or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from deuterium, H, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle or 3-6 membered heterocycle, is unsubstituted or substituted with one or more R^{12} or R^{20}; and

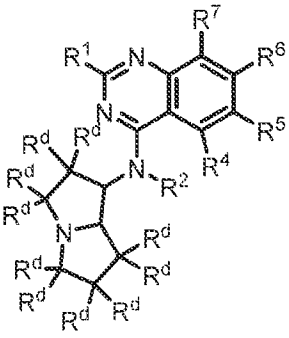
(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

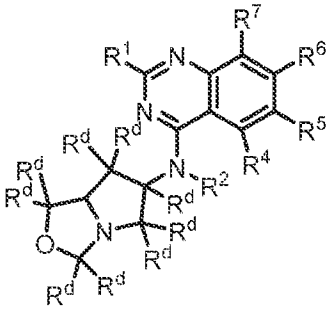
70. The compound of any one of Embodiments 54, 55 and 69, wherein the compound is a compound according to Formula IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, or IIKK:



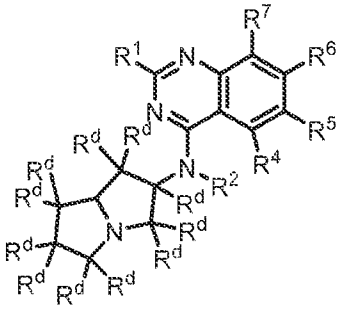
(IIBB),



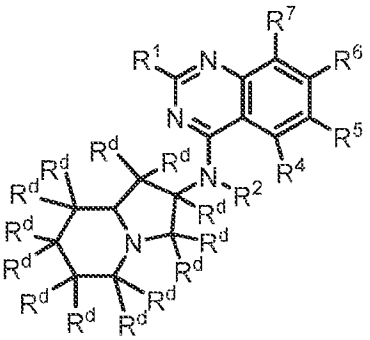
(IICC),



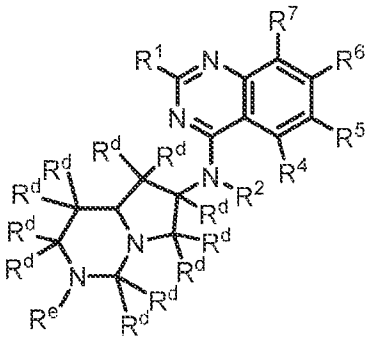
(IIDD),



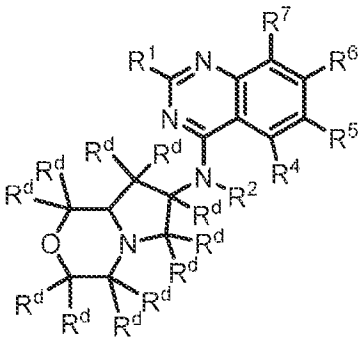
(IIEE),



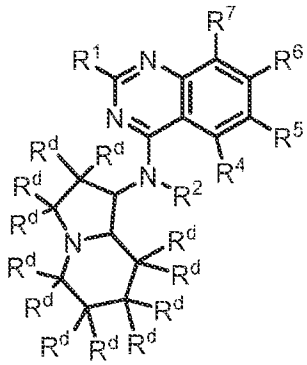
(IIFF),



(IIGG),



(IIHH), and



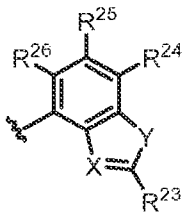
(IIJJ),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, -OR^{12}, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -S(O)$_2$(C_{1-6}alkyl), halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^c, if present, is selected from -C(O)(C_{1-6}alkyl)CN, -C(O)(C_{1-6}alkyl)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

71. The compound of any one of Embodiments 54, 55, and 57-70, wherein R^6 is selected from:



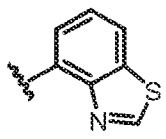
, wherein:

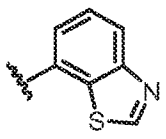
X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -N(R^{12})$_2$, C_{1-6}alkyl, and C_{1-6}alkyl-N(R^{14})$_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

72. The compound of Embodiment 71, wherein R^6 is selected from: 

, 

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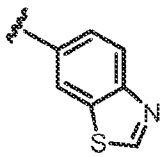
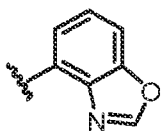
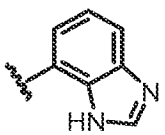
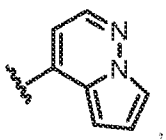
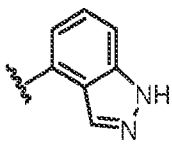
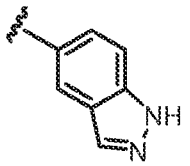


, 

, 

, 

, 

, 

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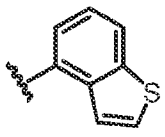
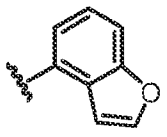
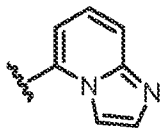
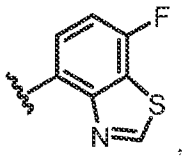
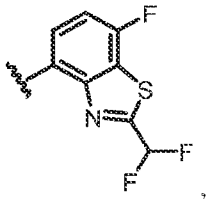
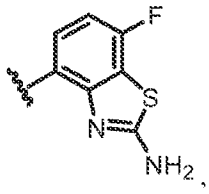
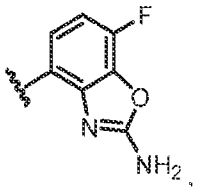
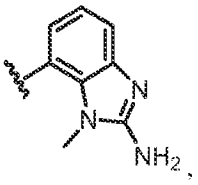
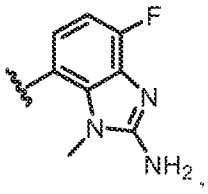
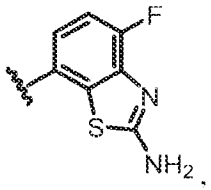
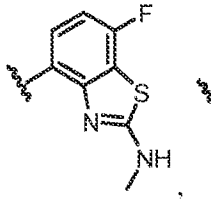
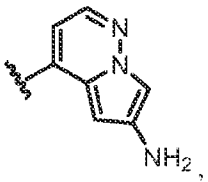
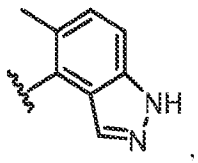
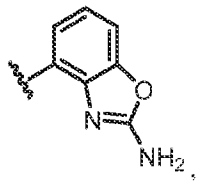
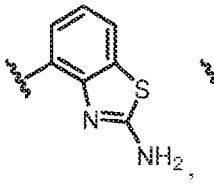
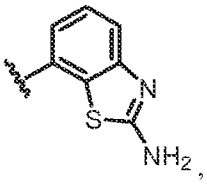
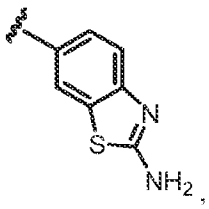
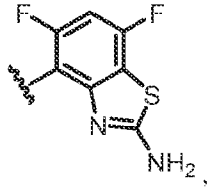
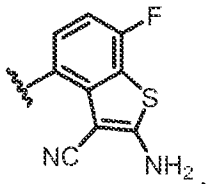
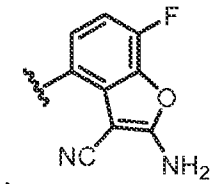
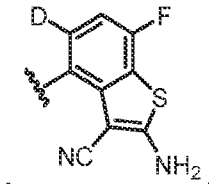
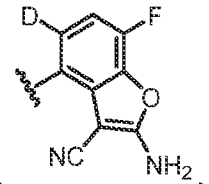
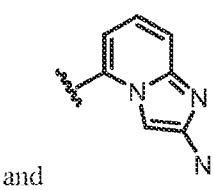
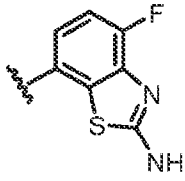



, and , any of which is substituted with one or more R^{15}.

73. The compound of Embodiment 71 or 72, wherein R^6 is selected from:  ,

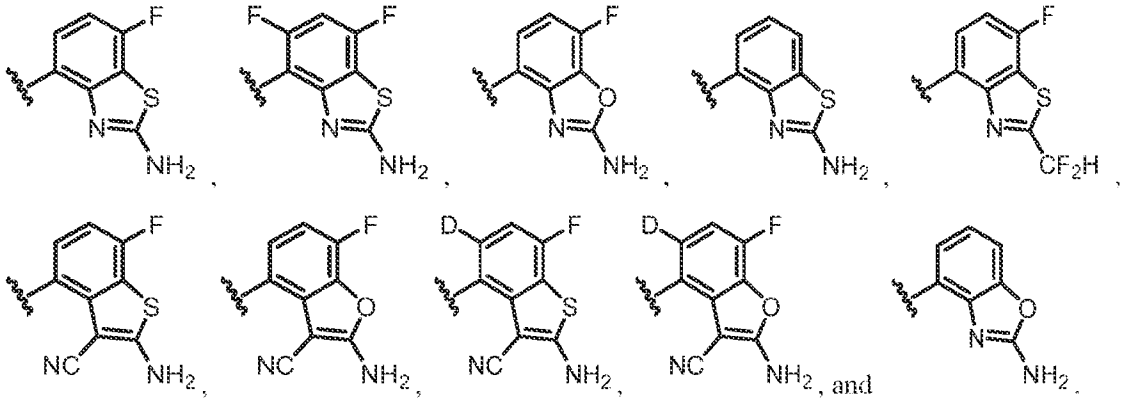















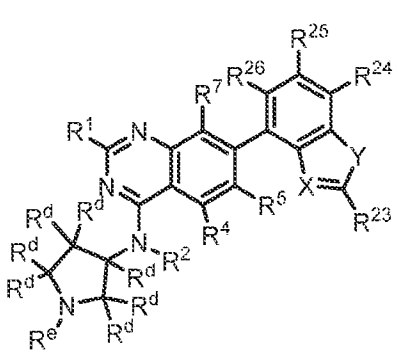
, and .



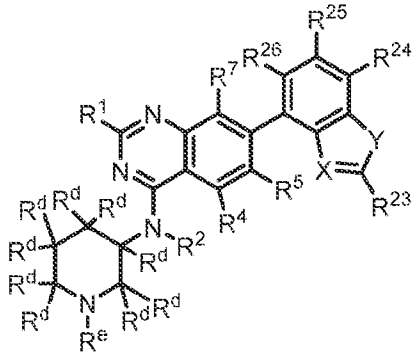
74. The compound of any one of Embodiments 71-73, wherein R^6 is selected from:



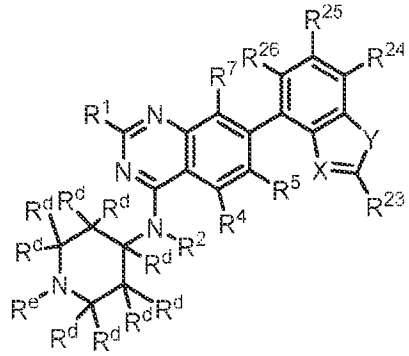
75. The compound of any one of Embodiments 54, 55, and 57-70, wherein the compound is a compound according to Formula IIR1', IIU1', IIV1', or IIZ1:



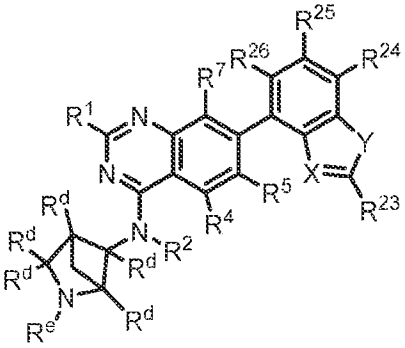
(IIR1'),



(IIU1'),



(IIV1'),



(IIZ1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is

unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e is selected from -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

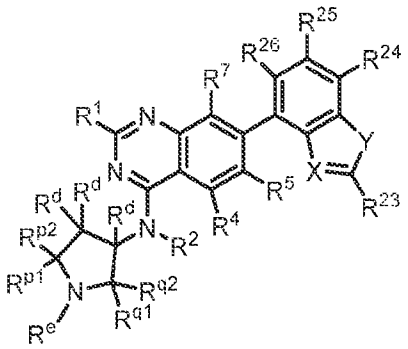
X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -N(R^{12})$_2$, C_{1-6}alkyl, and C_{1-6}alkyl-N(R^{14})$_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

76. The compound of any one of Embodiments 54, 55, and 57-70, wherein the compound is a compound according to Formula IIAA1':



(IIAA1'),

or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, -OR^{12}, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)N(R^{14})$_2$, -S(O)$_2$(C_{1-6}alkyl), a 3-6 membered carbocycle, a 3-6 membered heterocycle, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle or 3-6 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

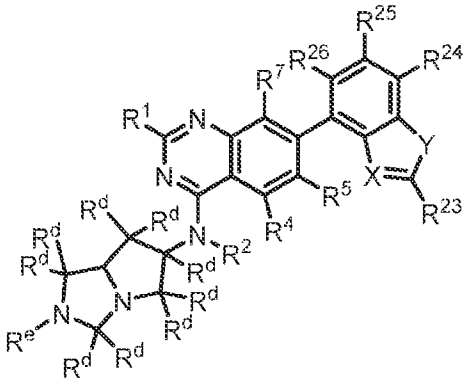
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

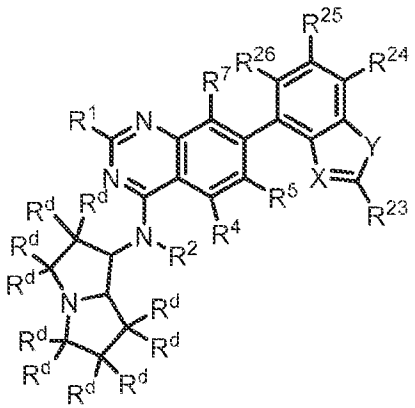
(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

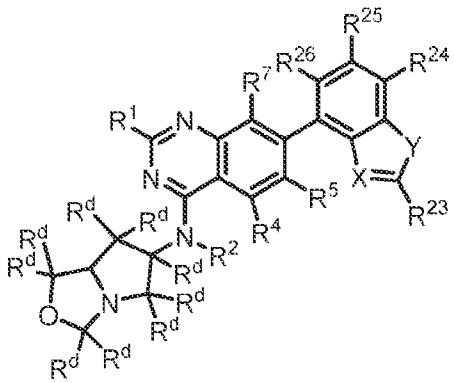
77. The compound of Embodiment 76, wherein the compound is a compound according to Formula IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, or IIKK1:



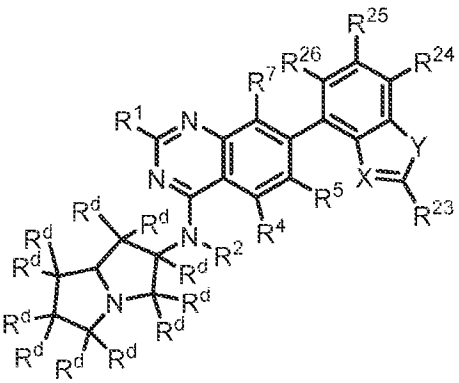
(IIBB1),



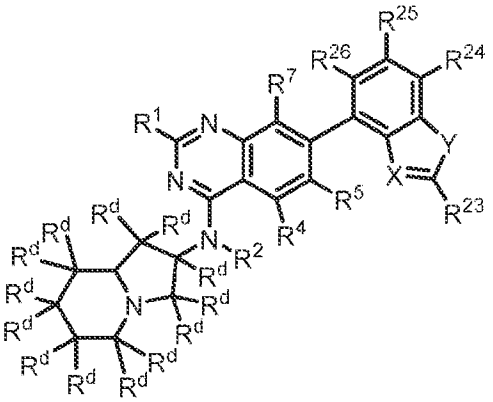
(IICC1),



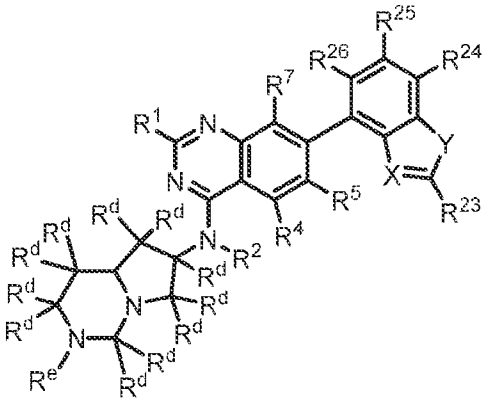
(IIDD1),



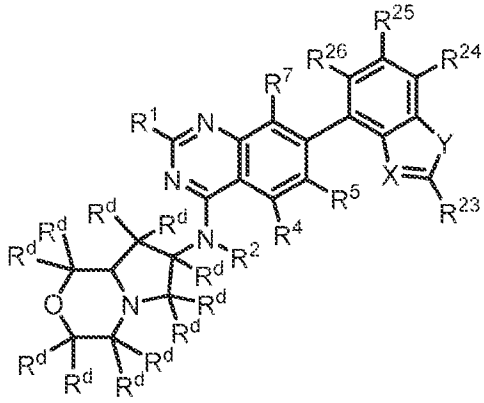
(IIEE1),



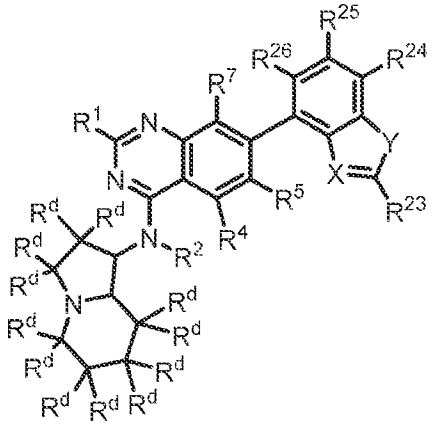
(IIFF1),



(IIGG1),



(IIHH1), and



(IIJJ1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e, if present, is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

78. The compound of any one of Embodiments 75-77, wherein X is C-CN, Y is S, and R^{23} is -$N(R^{12})_2$.

79. The compound of any one of Embodiments 75-78, wherein one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

80. The compound of any one of Embodiments 68-79, wherein R^e is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{20}.

81. The compound of any one of Embodiments 68-79, wherein R^e is -C(O)(3-6 membered carbocycle).

82. The compound of any one of Embodiments 68-79, wherein R^e is selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), and -C(O)O(C_{1-6}alkyl), wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

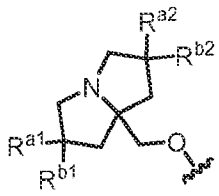
83. The compound of any one of Embodiments 68-82, wherein each R^d is H.

84. The compound of any one of Embodiments 54-83, wherein R^2 is H.

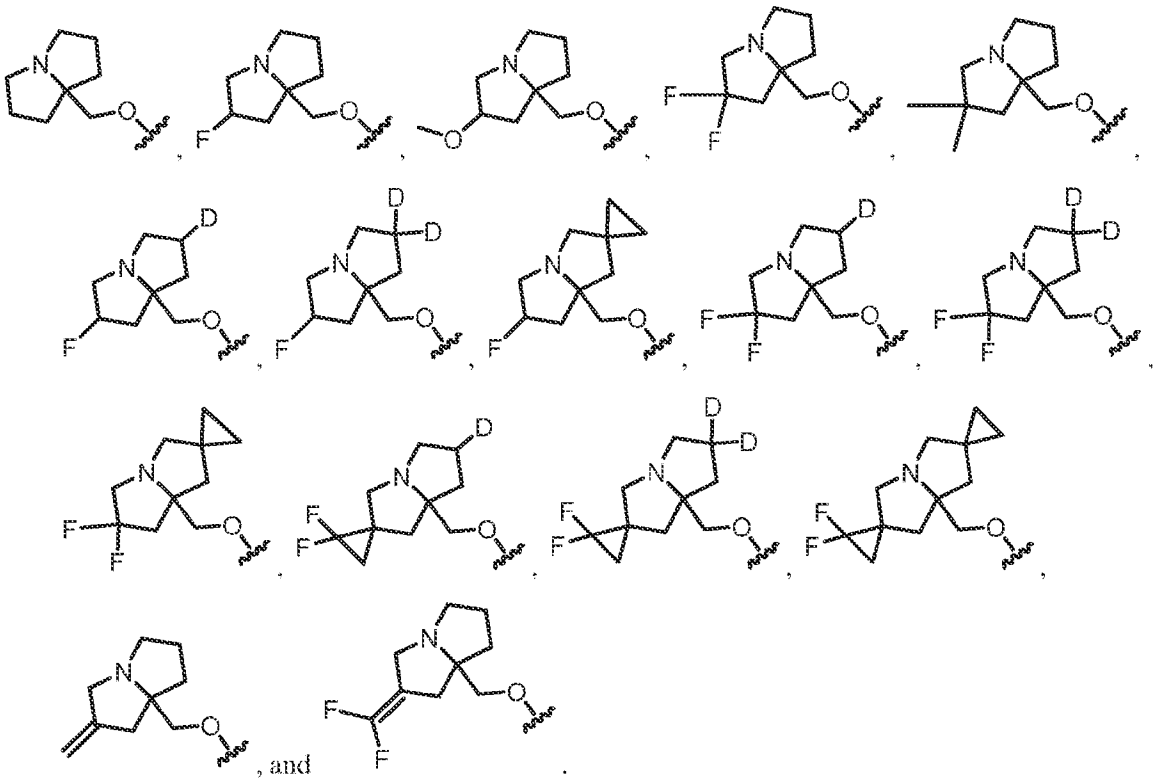
85. The compound of any one of Embodiments 54-84, wherein R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}.

86. The compound of Embodiment 85, wherein R^2 is selected from C_{1-2}alkyl.

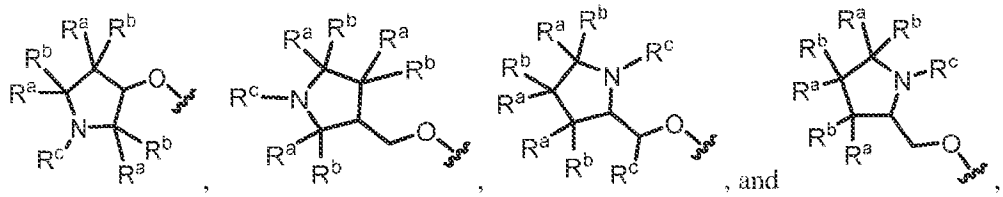
87. The compound of any one of Embodiments 54, 55, and 57-86, wherein R^1 is selected from -OR^8.

88. The compound of Embodiment 87, wherein R^1 is selected from:  , wherein R^{a1}, R^{a2}, R^{b1}, and R^{b2} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, -OR^{12}, and H, wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}.

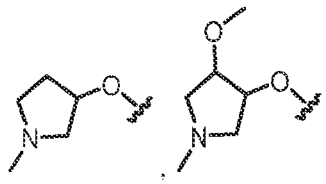
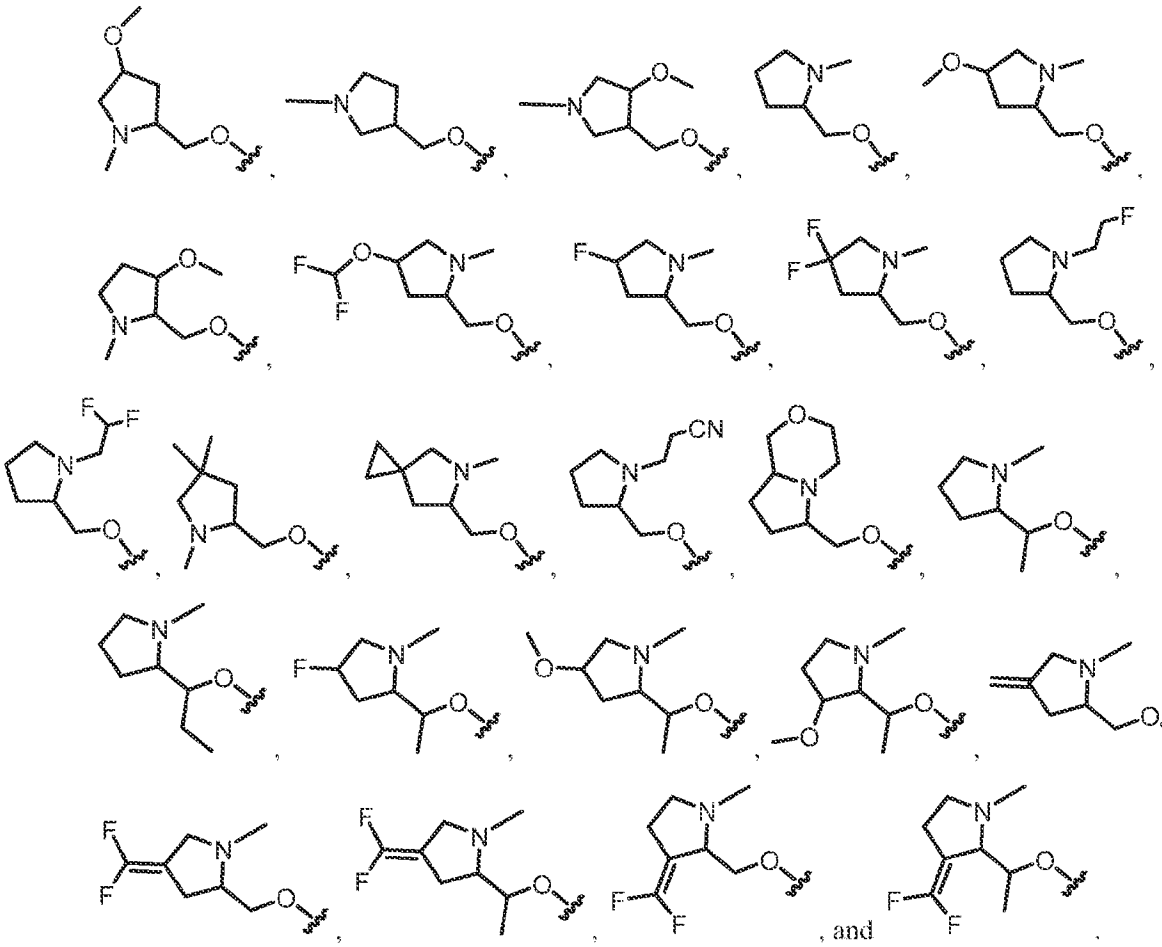
89. The compound of Embodiment 88, wherein R^1 is selected from:

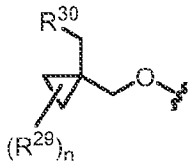


90. The compound of Embodiment 87, wherein R^1 is selected from:



wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H; and each R^c is independently selected from C_{1-6} alkyl and H, wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

91. The compound of Embodiment 90, wherein R^1 is selected from:  ,  , and .

92. The compound of any one of Embodiments 54, 55, and 57-86, wherein R^1 is selected from  , wherein:

each R^{28} is independently selected from $C_{1\text{-}6}$alkyl and halogen; and

each R^{29} is independently selected from halogen and $C_{1\text{-}6}$alkyl;

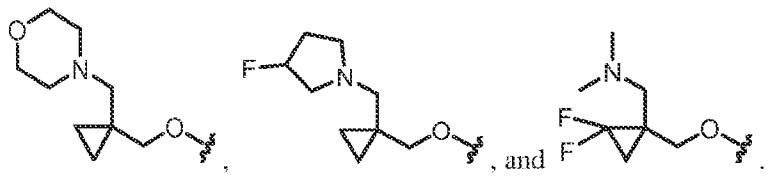
R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; and

n is 0-2.

93. The compound of Embodiment 92, wherein R^{30} is $N(R^{14})_2$.

94. The compound of Embodiment 92 or 93, wherein at least one R^{29} is a halogen such as F.

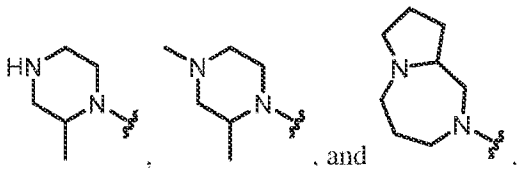
95. The compound of any one of Embodiments 92-94, wherein R^1 is selected from:



96. The compound of any one of Embodiments 54-86, wherein R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

97. The compound of Embodiment 96, wherein R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

98. The compound of Embodiment 96 or 97, wherein R^1 is selected from:



99. The compound of any one of Embodiments 54, 55, and 57-86, wherein R^1 is H.

100. The compound of any one of Embodiments 54, 55, and 57-99, wherein R^5 is a halogen (e.g., F or Cl).

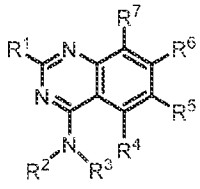
101. The compound of any one of Embodiments 54, 55, and 57-99, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

102. The compound of Embodiment 101, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

103. The compound of Embodiment 102, wherein R^5 is $-CF_3$.

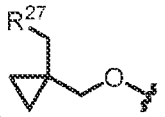
104. The compound of any one of Embodiments 54-103, wherein the compound is a not a compound included in Table 1.

105. A compound represented by Formula IV:



(IV)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from $-OR^8$ and  ;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from C_{1-6}alkyl that is substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

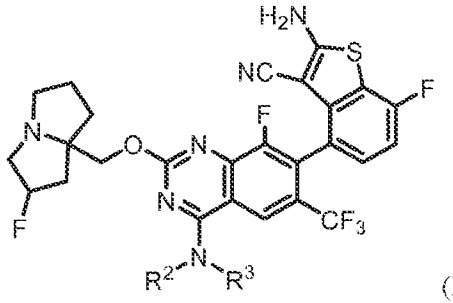
each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, and halogen;

R^{27} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen; and

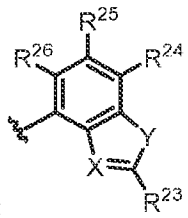
R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle.

106. The compound of Embodiment 105, wherein the compound is of Formula IV-a:



(IV-a)

or a salt (e.g., pharmaceutically acceptable salt) thereof.



107. The compound of Embodiment 105, wherein R^6 is selected from: , wherein:

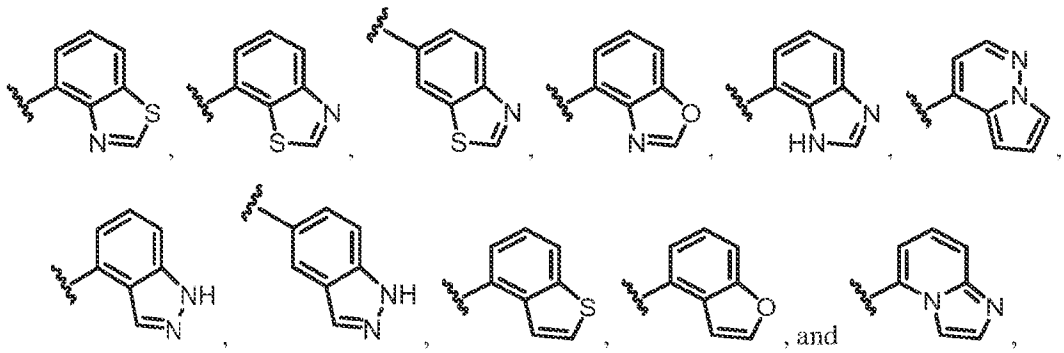
X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

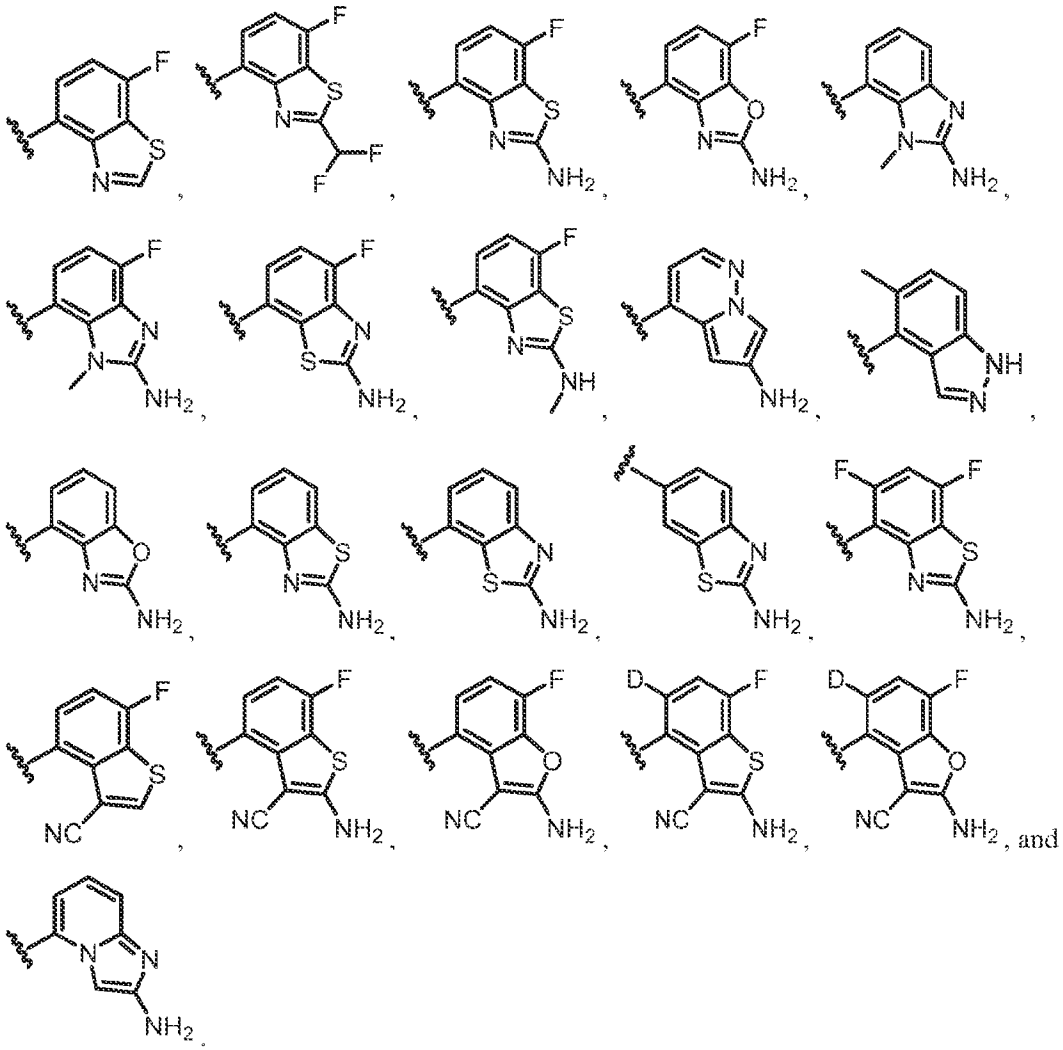
108. The compound of Embodiment 105 or Embodiment 107, wherein R^6 is selected from:



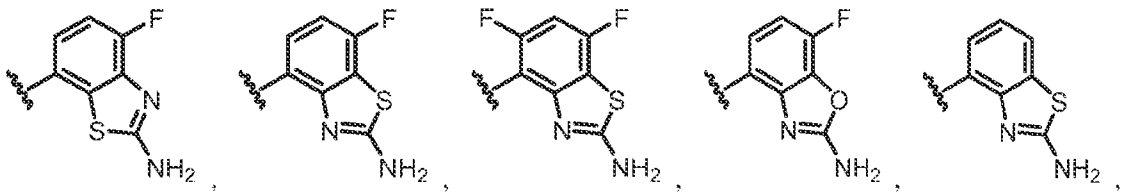
, and

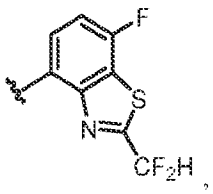
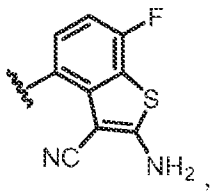
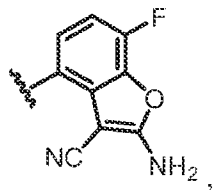
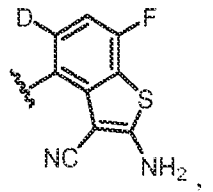
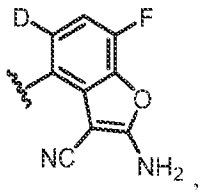
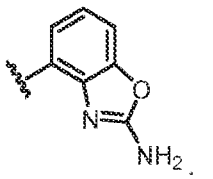
any of which is substituted with one or more R^{15}.

109. The compound of any one of Embodiments 105, and 107-108, wherein R^6 is selected from:

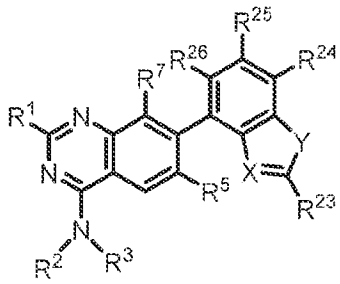


110. The compound of any one of Embodiments 105, and 107-109, wherein R^6 is selected from:








and


111. The compound of Embodiment 105, wherein the compound is a compound according to Formula IVB:


(IVB),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

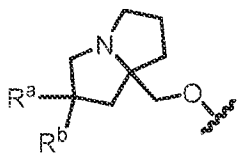
X is selected from N and C-CN;

Y is selected from O and S;

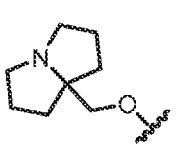
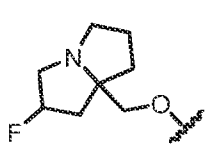
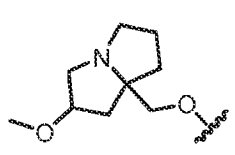
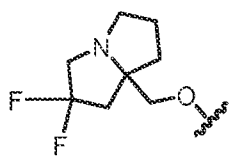
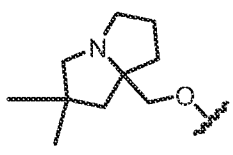
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

112. The compound of any one of Embodiments 105, and 107-111, wherein R^1 is selected from $-OR^8$.

113. The compound of Embodiment 112, wherein R^1 is selected from:  , wherein R^a and R^b are each independently selected from halogen, C_{1-6}alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}.

114. The compound of Embodiment 113, wherein R^1 is selected from:





, and

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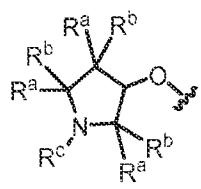
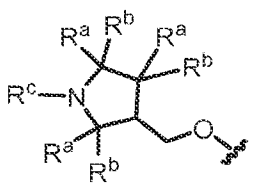
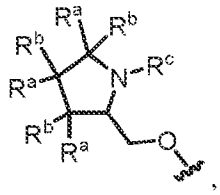
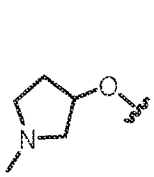
115. The compound of Embodiment 112, wherein R^1 is selected from:



, and

,

wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and R^c is selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle.

116. The compound of Embodiment 115, wherein R^1 is selected from:

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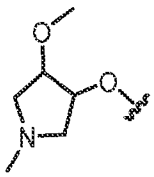
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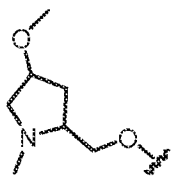
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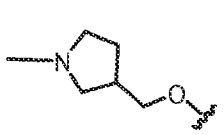
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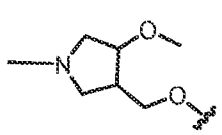
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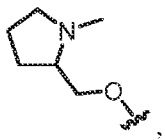
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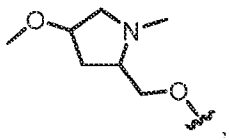
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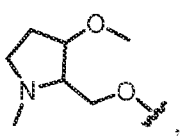
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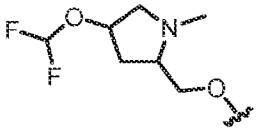
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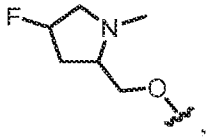
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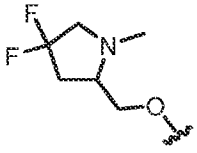
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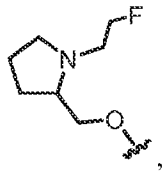
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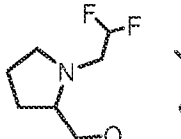
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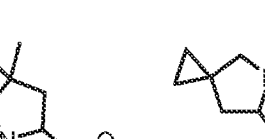
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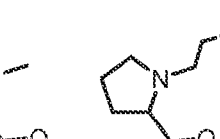
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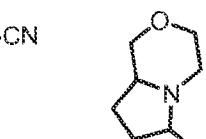
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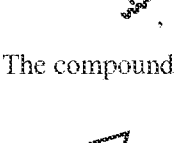
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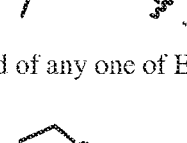
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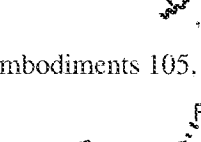
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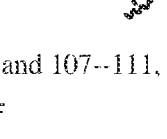
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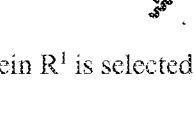
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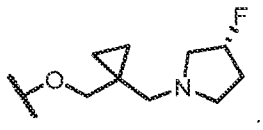
117. The compound of any one of Embodiments 105, and 107--111, wherein R^1 is selected from

and

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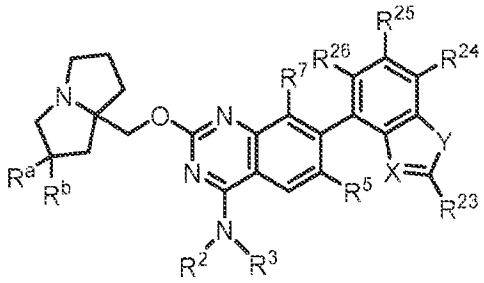
118. The compound of Embodiment 105, wherein the compound is a compound according to Formula IVC:



(IVC),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

119. The compound of Embodiment 118, wherein R^a is a halogen (e.g., F).

120. The compound of Embodiment 118 or 119, wherein R^b is H.

121. The compound of any one of Embodiments 111-120, wherein X is C-CN, Y is S, and R^{23} is selected from $-N(R^{12})_2$.

122. The compound of any one of Embodiments 111-121, wherein at least one of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

123. The compound of any one of Embodiments 105-122, wherein R^3 is selected from C_{1-3}alkyl that is substituted with one or more R^{10}.

124. The compound of Embodiment 123, wherein each R^{10} is independently selected from 3-6 membered heterocycle and a 5-6 membered heteroaryl, wherein any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13}.

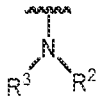
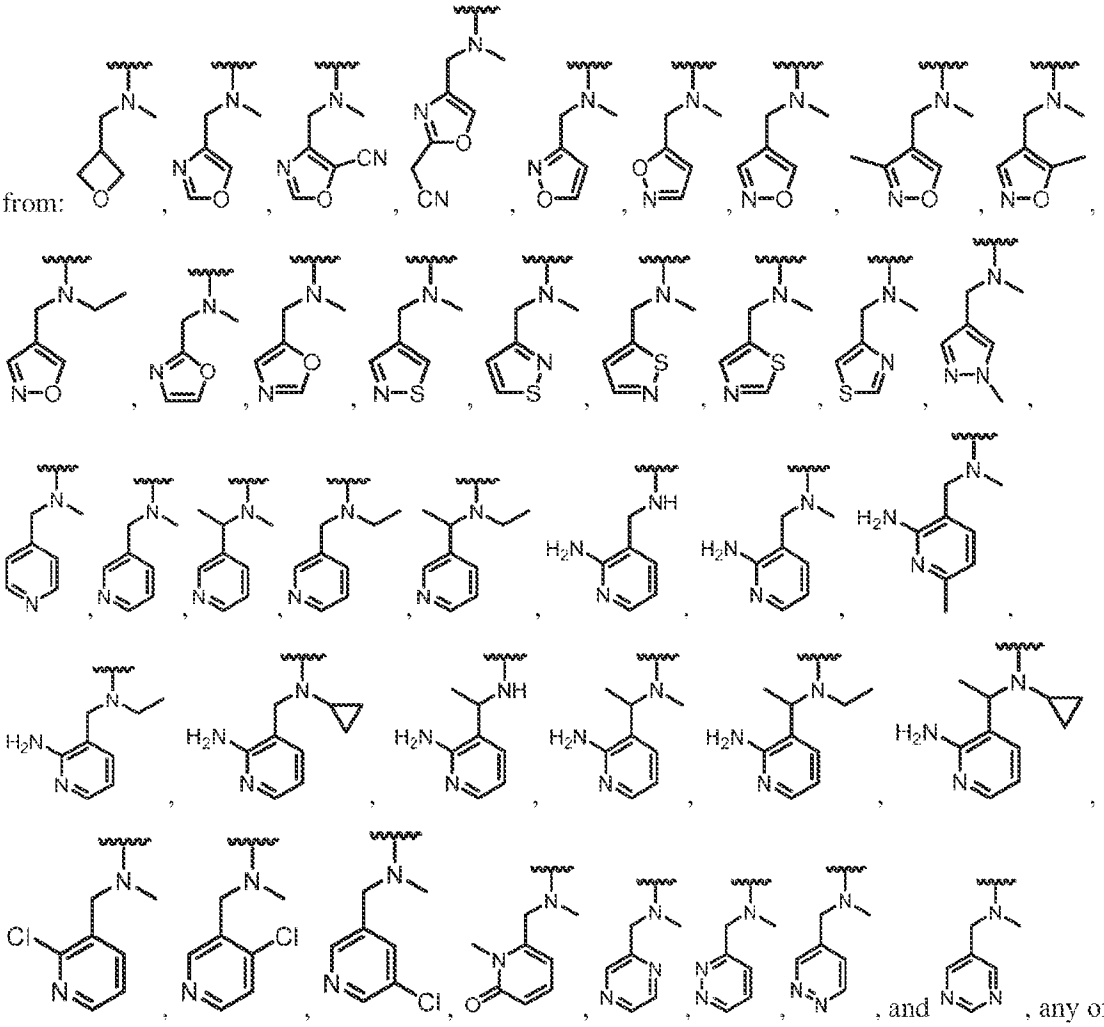
125. The compound of Embodiment 124, wherein each R^{10} is independently selected from thiazole, oxazole, isoxazole, isothiazole, pyrazole, and pyridine, any of which is unsubstituted or substituted with one or more R^{12}, or R^{13}.

126. The compound of any one of Embodiments 105-125, wherein R^2 is H.

127. The compound of any one of Embodiments 105-125, wherein R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}.

128. The compound of Embodiment 127, wherein R^2 is selected from C_{1-3}alkyl that is unsubstituted.

129. The compound of any one of Embodiments 105-125, wherein R^2 is a 3-6 membered carbocycle.

130. The compound of any one of Embodiments 105-122, wherein the moiety  is selected from:  , and , any of which is optionally further substituted with one or more R^{10}.

131. The compound of any one of Embodiments 105, and 107-130, wherein R^5 is a halogen (e.g., F or Cl).

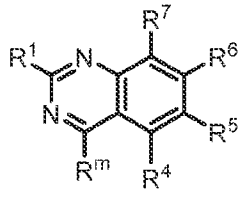
132. The compound of any one of Embodiments 105, and 107-130, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

133. The compound of Embodiment 132, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

134. The compound of Embodiment 133, wherein R^5 is $-CF_3$.

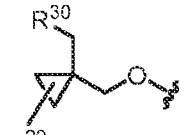
135. The compound of any one of Embodiments 105, and 107-134, wherein R^7 is F.

136. A compound represented by Formula V':



(V')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^m is selected from hydrogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

n is 0-2;

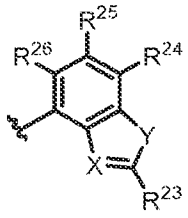
each R^{31} is selected from C_{1-6} alkyl; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

137. The compound of Embodiment 136, wherein R^m is hydrogen.

138. The compound of Embodiment 136, wherein R^m is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

139. The compound of Embodiment 138, wherein R^m is methyl that is unsubstituted.

140. The compound of any one of Embodiments 136-139, wherein R^6 is  , wherein:

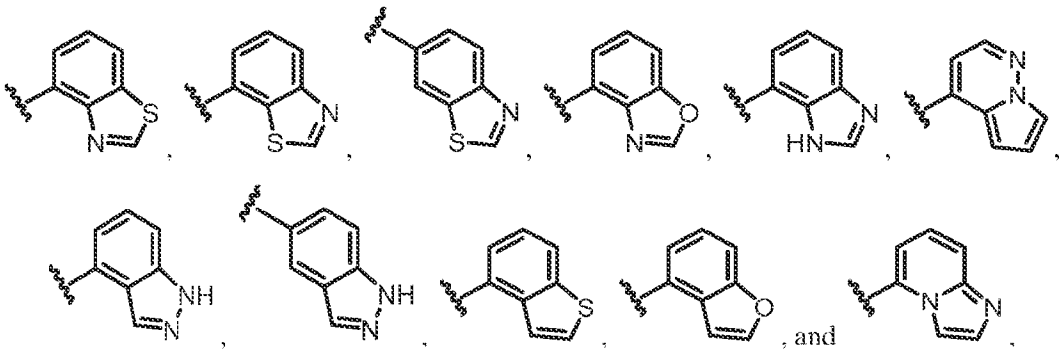
X is selected from N and C-CN;

Y is selected from O and S;

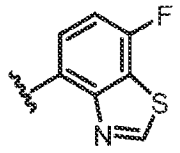
R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

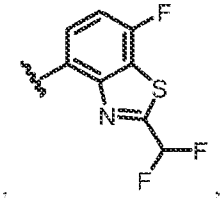
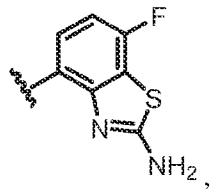
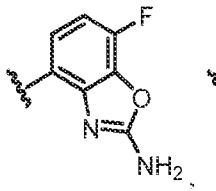
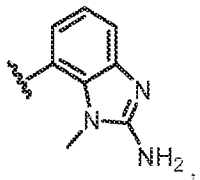
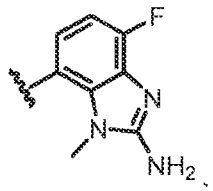
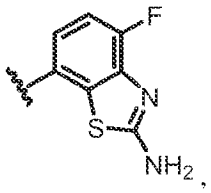
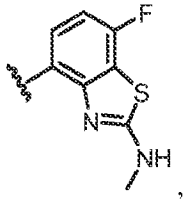
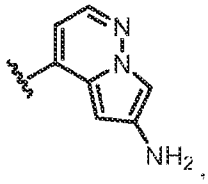
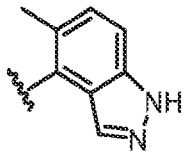
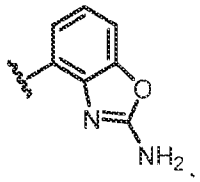
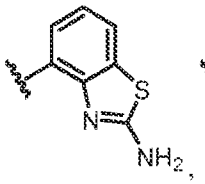
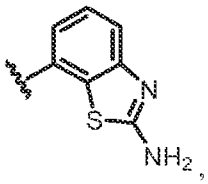
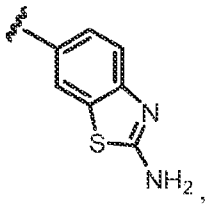
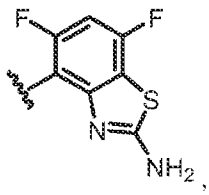
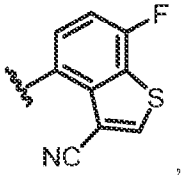
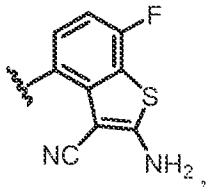
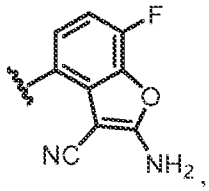
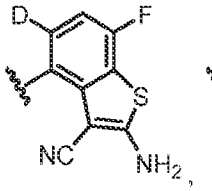
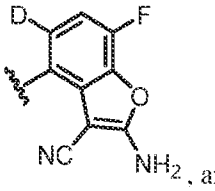
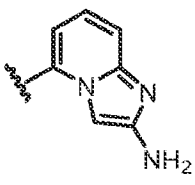
141. The compound of any one of Embodiments 136-140, wherein R^6 is selected from:



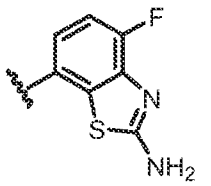
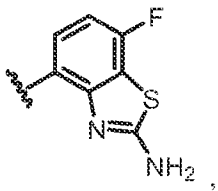
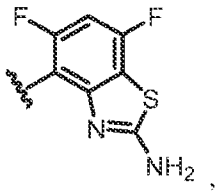
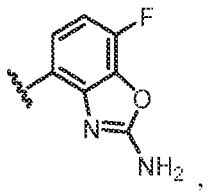
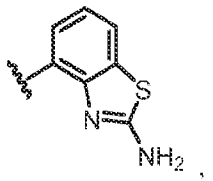
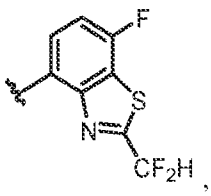
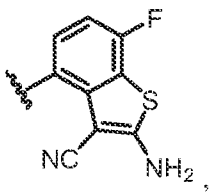
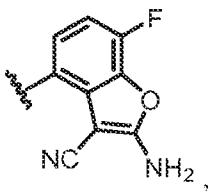
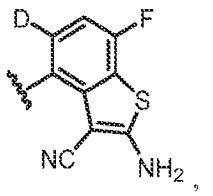
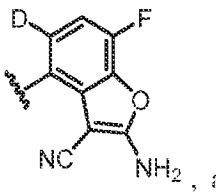
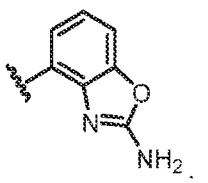
any of which is substituted with one or more R^{15}.



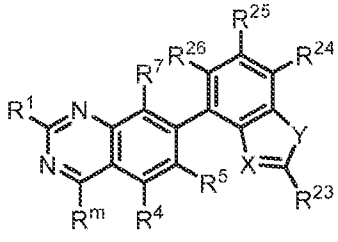
142. The compound of any one of Embodiments 136-141, wherein R^6 is selected from:

143. The compound of any one of Embodiments 136-142, wherein R^6 is selected from:

144. The compound of any one of Embodiments 136-140, wherein the compound is a compound of Formula VC':



(VC')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

X is selected from N and C-CN;

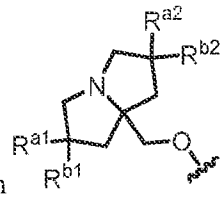
Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

145. The compound of any one of Embodiments 140-144, wherein X is C-CN, Y is S, R^{23} is $-N(R^{12})_2$, and one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

146. The compound of any one of Embodiments 136-145, wherein R^1 is selected from $-OR^8$.

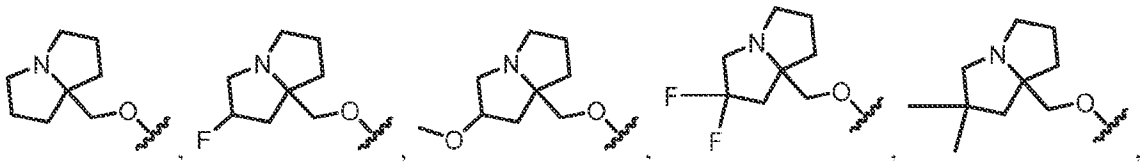
147. The compound of Embodiment 146, wherein R^1 is selected from  , wherein:

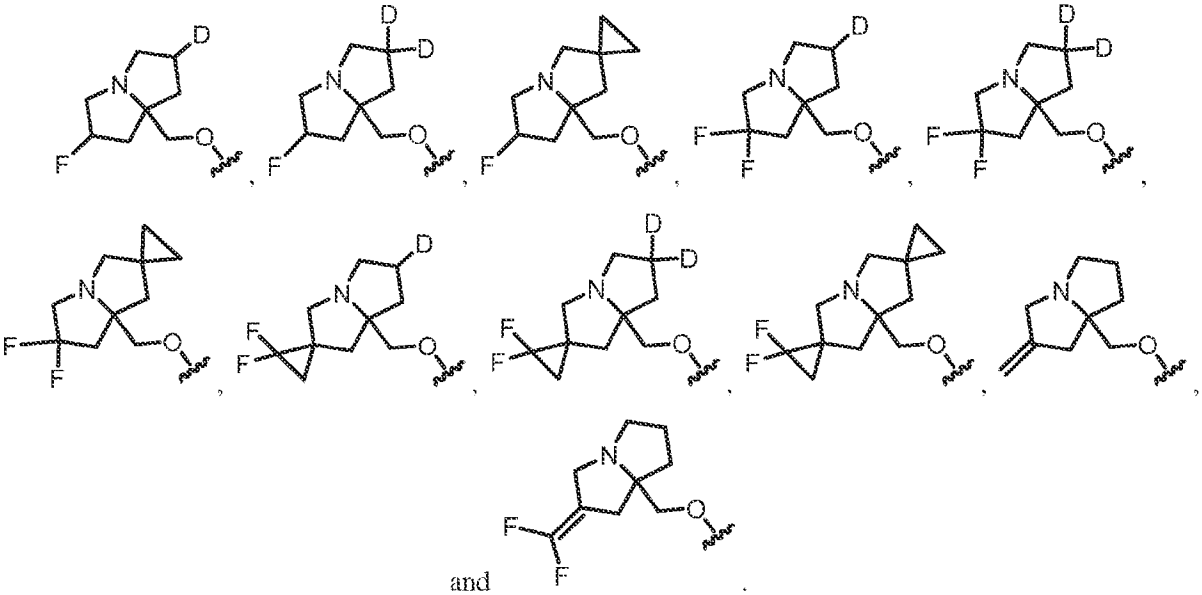
R^{a1}, R^{a2}, R^{b1}, and R^b are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H or are absent,

wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and

wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}.

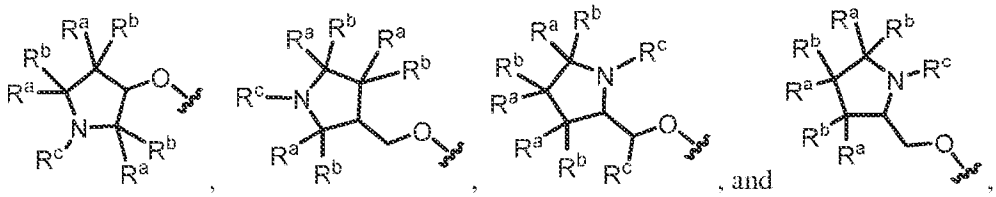
148. The compound of Embodiment 147, wherein R^1 is selected from:





and

149. The compound of Embodiment 146, wherein R^1 is selected from:



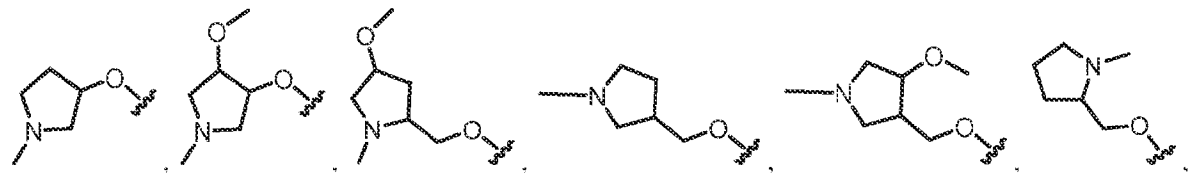
, and

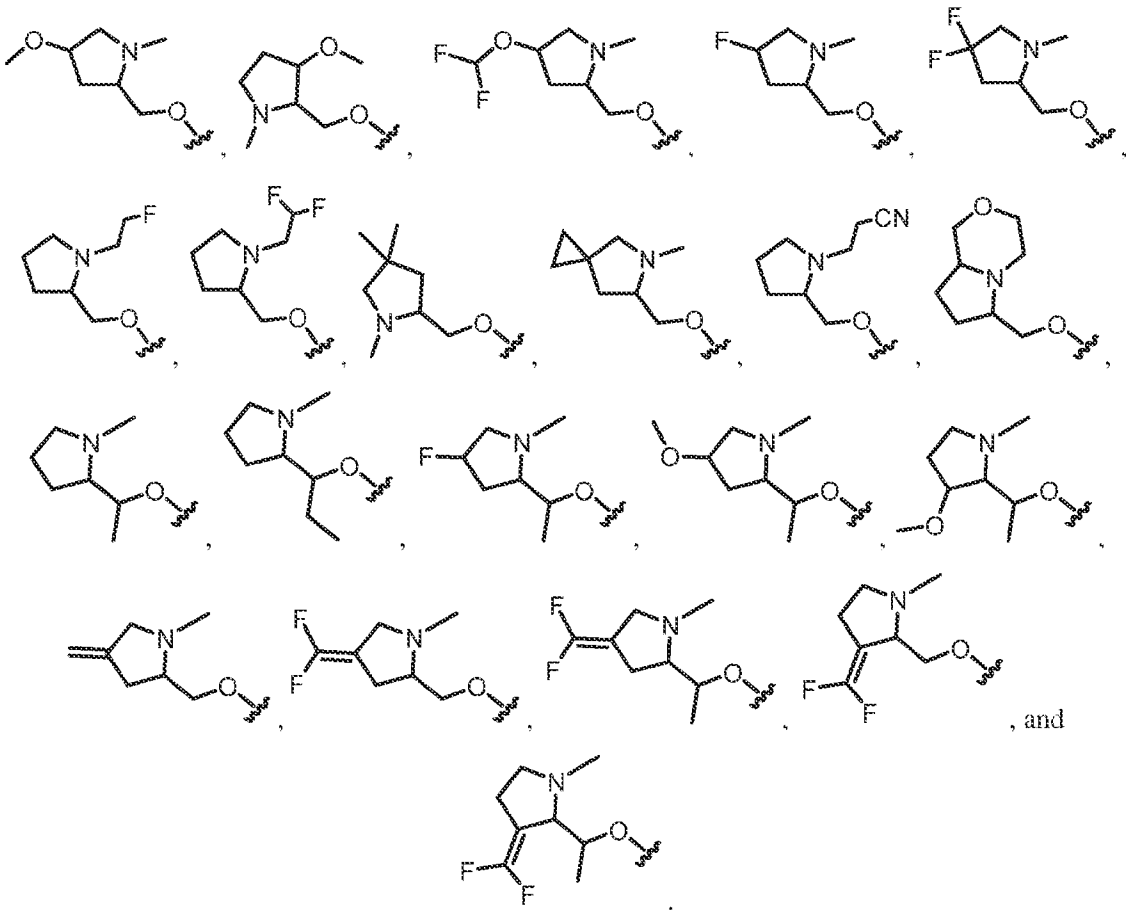
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H; and each R^c is independently selected from H and C_{1-6} alkyl,

wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and

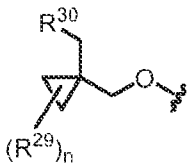
wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

150. The compound of Embodiment 149, wherein R^1 is selected from:





[0436] 151. The compound of any one of Embodiments 136-145, wherein R^1 is selected from



, wherein:

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

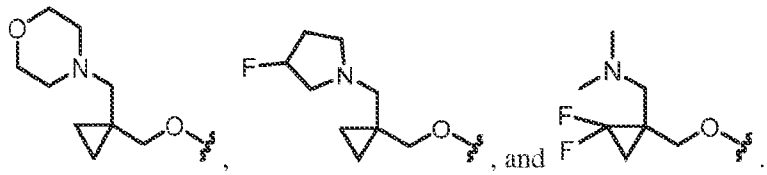
R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; and

n is 0-2.

152. The compound of Embodiment 151, wherein R^{30} is $N(R^{14})_2$.

153. The compound of Embodiment 151 or 152, wherein at least one R^{29} is a halogen such as F.

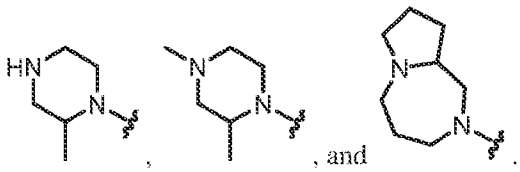
154. The compound of any one of Embodiments 151-153, wherein R^1 is selected from:



155. The compound of any one of Embodiments 136-145, wherein R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

156. The compound of Embodiment 155, wherein R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

157. The compound of Embodiment 156, wherein R^1 is selected from:



158. The compound of any one of Embodiments 136-157, wherein R^5 is a halogen (e.g., F or Cl).

159. The compound of any one of Embodiments 136-157, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

160. The compound of Embodiment 159, wherein R^5 is selected from C_{1-6}alkyl that is substituted with one or more halogens or -CN.

161. The compound of Embodiment 160, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

162. The compound of Embodiment 161, wherein R^5 is $-CF_3$.

163. The compound of any one of Embodiments 136-162, wherein R^7 is F.

164. A compound shown in Table 3, or a salt (e.g., pharmaceutically acceptable salt) thereof.

165. A pharmaceutical composition comprising a compound of any one of Embodiments 1-164, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable excipient.

166. A compound of any one of Embodiments 1-164, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use as a medicament.

167. The compound of Embodiment 166, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

168. The compound of Embodiment 167, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

169. The compound of Embodiment 167, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

170. The compound of any one of Embodiments 166-169, wherein the medicament is useful in the prevention or treatment of a cancer.

171. The compound of Embodiment 170, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

172. A compound of any one of Embodiments 1-164, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the treatment of a disease, disorder, or condition.

173. The compound of Embodiment 172, wherein the disease, disorder, or condition is a cancer.

174. The compound of Embodiment 173, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

175. The compound of any one of Embodiments 172-174, wherein the compound is used in the treatment of a disease, disorder, or condition in a subject in need thereof.

176. A compound of any one of Embodiments 1-164, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the manufacture of a medicament.

177. The compound of Embodiment 176, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

178. The compound of Embodiment 177, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

179. The compound of Embodiment 177 or 178, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

180. The compound of any one of Embodiments 176-179, wherein the medicament is useful in the treatment of a cancer.

181. The compound of Embodiment 180, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

182. A method, comprising administering a therapeutically effective amount of a compound of any one of Embodiments 1-164, or a salt (e.g., pharmaceutically acceptable salt) thereof, to a subject in need thereof.

183. The method of Embodiment 182, wherein the subject has a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

184. The method of Embodiment 183, wherein the disease, disorder, or condition is ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

185. The method of Embodiment 183 or 184, wherein the disease, disorder, or condition is ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

186. The method of any one of Embodiments 182-185, wherein the subject has a cancer.

187. The method of Embodiment 186, wherein the subject was previously diagnosed with the cancer.

188. The method of Embodiment 186 or 187, wherein the subject has previously undergone a treatment regimen for the cancer.

189. The method of any one of Embodiments 186-188, wherein the subject has previously entered remission from the cancer.

190. The method of any one of Embodiments 186-189, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

191. The method of any one of Embodiments 182-190, wherein the compound, or the salt thereof, is administered in combination with an additional therapeutic agent.

192. The use of a compound of any one of Embodiments 1-164, or a salt (e.g., pharmaceutically acceptable salt) thereof, for the manufacture of a medicament for the treatment of a cancer.

193. The use of Embodiment 192, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

194. A method, comprising contacting a KRAS protein with a compound of any one of Embodiments 1-164, or a salt (e.g., pharmaceutically acceptable salt) thereof.

195. The method of Embodiment 194, wherein contacting the KRAS protein with the compound modulates KRAS.

196. The method of Embodiment 194 or 195, wherein the KRAS protein has a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation.

197. The method of Embodiment 194 or 195, wherein the KRAS protein is a wild-type KRAS protein, including wild-type amplified KRAS.

198. The method of any one of Embodiments 194-197, wherein the KRAS protein is in an active (GTP-bound) state.

199. The method of any one of Embodiments 194-197, wherein the KRAS protein is in an inactive (GDP-bound) state.

200. The method of any one of Embodiments 194-199, wherein the KRAS protein is located within a cell.

201. The method of Embodiment 200, wherein the cell is located within a subject.

202. The method of Embodiment 201, wherein the subject is a human.

203. The method of Embodiment 201 or 202, wherein the subject has a cancer.

204. The method of Embodiment 203, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

205. A method of inhibiting the function of a wild-type KRAS protein, including wild-type amplified KRAS, or a KRAS protein having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, comprising contacting the KRAS protein with a compound of any one of Embodiments 1-164, or a salt (e.g., pharmaceutically acceptable salt) thereof.

206. The method of Embodiment 205, wherein the KRAS protein is a wild-type KRAS protein, including wild-type amplified KRAS.

207. The method of Embodiment 205, wherein the KRAS protein has a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation.

208. The method of Embodiment207, wherein the KRAS protein has a G12D, G12V, or G12R mutation.

209. The method of any one of Embodiments 205-208, wherein the KRAS protein is in an active (GTP-bound) state.

210. The method of any one of Embodiments 205-208, wherein the KRAS protein is in an inactive (GDP-bound) state.

211. The method of any one of Embodiments 205-210, wherein the KRAS protein is located within a cell.

212. The method of Embodiment 211, wherein the cell is located within a subject.

213. The method of Embodiment 212, wherein the subject is a human.

214. The method of Embodiment 212 or 213, wherein the subject has a cancer.

215. The method of Embodiment 214, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

216. A compound capable of inhibiting a wild-type KRAS protein, including wild-type amplified KRAS, or a KRAS protein having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation in both its active (GTP-bound) and inactive (GDP-bound) state.

217. The compound of Embodiment 216, wherein the compound:

(i) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, 1 μM< $IC_{50} \leq 10$ μM, or 10 μM< IC_{50} in the assay of Biological Example 1 (e.g., a protein:protein interaction (PPI) Homogenous Time Resolved Fluorescence (HTRF) analysis of 50 nM Avi-KRAS G12D (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12C (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12V (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS WT (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), and/or 75 nM 3xFLAG-RAF1 RBD (51-131)-Avi; and/or

(ii) has $IC_{50} \leq 0.1$ μM, or IC_{50}>0.1 μM in the assay of Biological Example 2 or 4 (e.g., cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iii) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or IC_{50} >1 μM in the assay of Biological Example 3 (cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iv) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or IC_{50} >1 μM in the assay of Biological Example 4 (cell-based pERK HTRF assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080); and/or

(v) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or IC_{50} >1 μM in the assay of Biological Example 5 (3D Cell viability assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080).

218. The compound of Embodiment 217, wherein the compound:

(i) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or 1 μM< $IC_{50} \leq 10$ μM in the assay of Biological Example 1 (e.g., a protein:protein interaction (PPI) Homogenous Time Resolved Fluorescence (HTRF) analysis of 50 nM Avi-KRAS G12D (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12C (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12V (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS WT (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), and/or 75 nM 3xFLAG-RAF1 RBD (51-131)-Avi; and/or

(ii) has $IC_{50} \leq 0.1$ μM in the assay of Biological Example 2 or 4 (e.g., cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iii) has $IC_{50} \leq 0.1$ μM or 0.1 μM< $IC_{50} \leq 1$ μM in the assay of Biological Example 3 (cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iv) has $IC_{50} \leq 0.1$ μM or 0.1 μM< $IC_{50} \leq 1$ μM in the assay of Biological Example 4 (cell-based pERK HTRF assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080); and/or

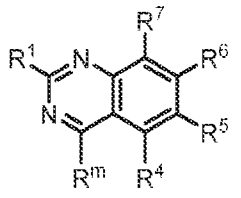
(v) has $IC_{50} \leq 0.1$ μM or 0.1 μM< $IC_{50} \leq 1$ μM in the assay of Biological Example 5 (3D Cell viability assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080).

219. The compound of any one of Embodiments 216-218, wherein the compound is capable of irreversibly binding the KRAS protein.

220. The compound of any one of Embodiments 216-218, wherein the compound is capable of reversibly binding the KRAS protein.

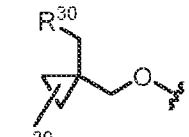
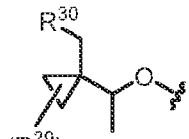
221. The compound of any one of Embodiments 216-220, wherein the compound is a compound according to any one of Embodiments 1-164.

222. A compound represented by Formula A:



(A')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from H, $-OR^8$,  ,  , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^m is selected from H and $-NR^2R^3$;

R^2 is selected from C_{1-6}alkyl which is optionally deuterated;

R^3 is selected from a C_{1-6}alkyl, 3- to 6-membered cycloalkyl optionally fused to a 5- or 6-membered heterocycle or heteroaryl, 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10}, or

R^2 and R^3, together with the atom they attach to, form a 4- to 10-membered heterocycle optionally substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, -N(R^{12})$_2$, and -CN;

each R^{20} is independently selected from =O, -CN, -CN, -OR^{12}, and halogen;

each R^{28} is independently selected from halogen,-OR^{12}, C_{1-6}alkyl, and C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13};

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

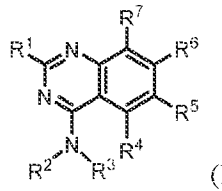
R^{30} is selected from -N(R^{12})$_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

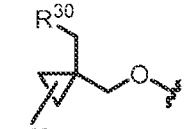
R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-4} alkenyl, , -OR^{12}, a 4- to 10-membered heterocycle, and a 4- to 10-membered aryl, wherein any 4- to 10-membered heterocycle or 4- to 10-membered aryl is optionally substituted with one or more R^{28}, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

223. The compound of Embodiment 222, wherein the compound is a compound represented by Formula B:



(B)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^2 is selected from C_{1-6}alkyl;

R^3 is selected from a 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl, wherein the heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, $-N(R^{12})_2$, and -CN;

each R^{20} is independently selected from =O, -CN, and halogen;

each R^{28} is independently selected from halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

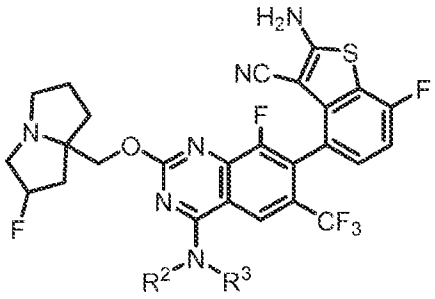
R^{30} is selected from $-N(R^{12})_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, C_{2-4} alkenyl, and $-OR^{12}$, wherein any C_{1-6}alkyl or C_{2-4} alkenyl is unsubstituted or is substituted with one or more R^{13}.

224. The compound of Embodiment 223, wherein the compound is of Formula B-a:



(B-a) or a salt (e.g., pharmaceutically acceptable salt) thereof.

225. The compound of any one of Embodiments 222-224, wherein R^3 is a 4-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N.

226. The compound of Embodiment 225, wherein R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

227. The compound of Embodiment 225, wherein R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}.

228. The compound of any one of Embodiments 222-227, wherein R^3 is a pyrrolidine that is substituted with 0-4 R^{10}.

229. The compound of any one of Embodiments 222-227, wherein R^3 is a pyrrolidine that is substituted with 0-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}.

230. The compound of any one of Embodiments 222-227, wherein R^3 is a 4-6 membered heterocycle that is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, and each R^{10} is independently selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

231. The compound of any one of Embodiments 222-225, wherein R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N.

232. The compound of Embodiment 231, wherein R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

233. The compound of Embodiment 231 or 232, wherein R^3 is an 8-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

234. The compound of Embodiment 231 or 232, wherein R^3 is a 9-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

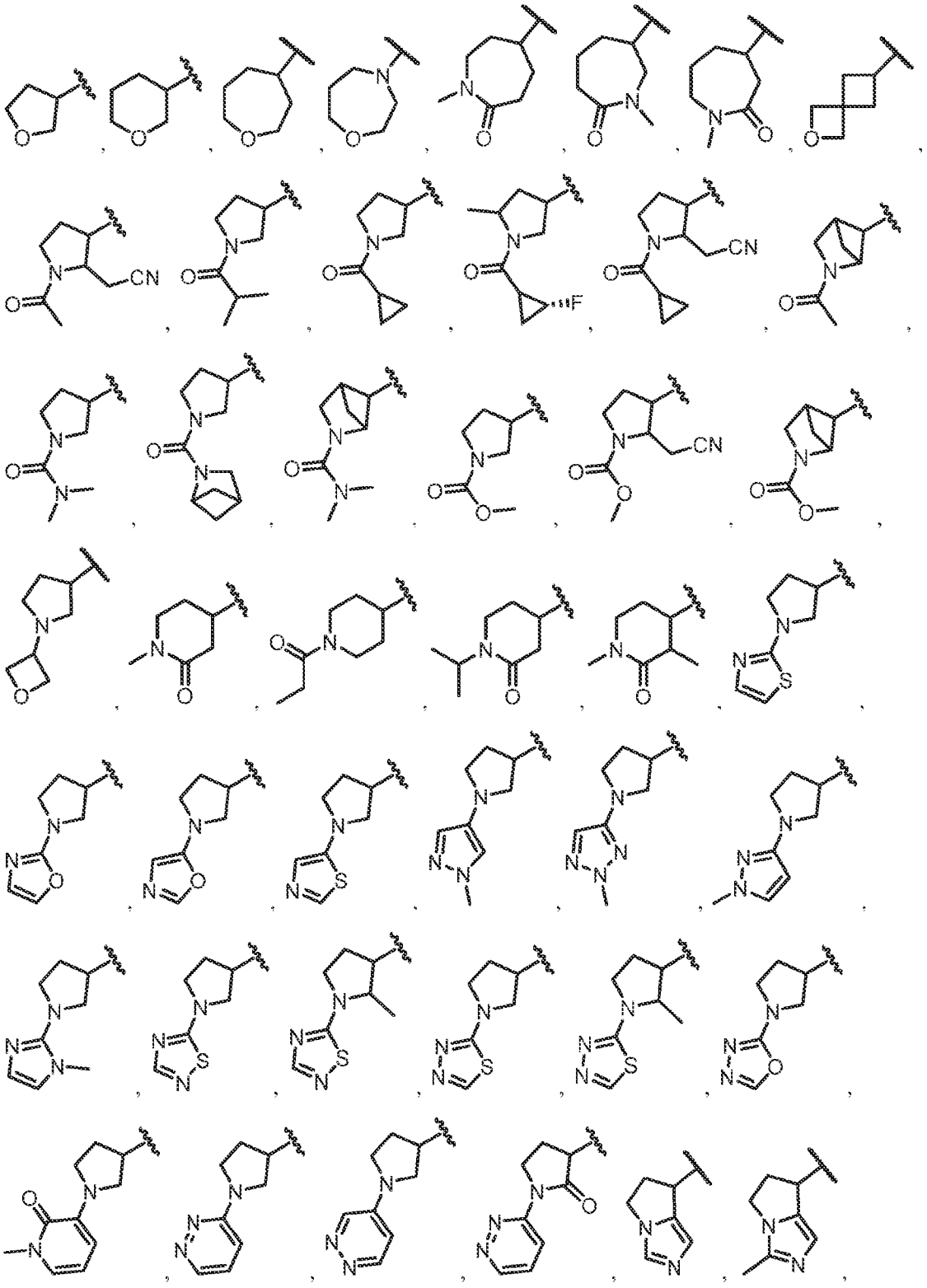
235. The compound of Embodiment 231 or 232, wherein R^3 is a 10-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

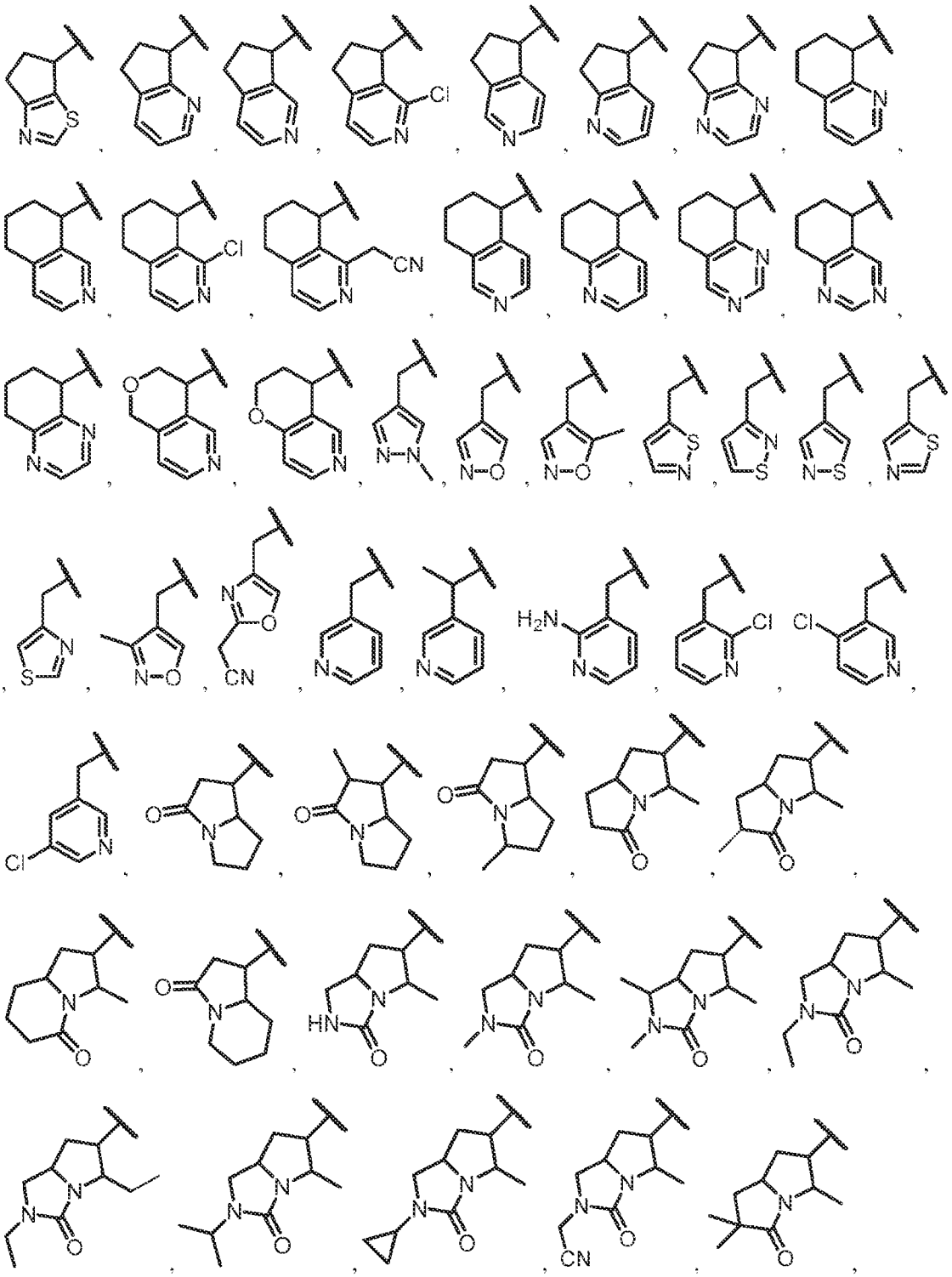
236. The compound of any one of Embodiments 233-235, wherein R^{10} is selected from =O, C_{1-6}alkyl, a 3-6 membered carbocycle, and halogen.

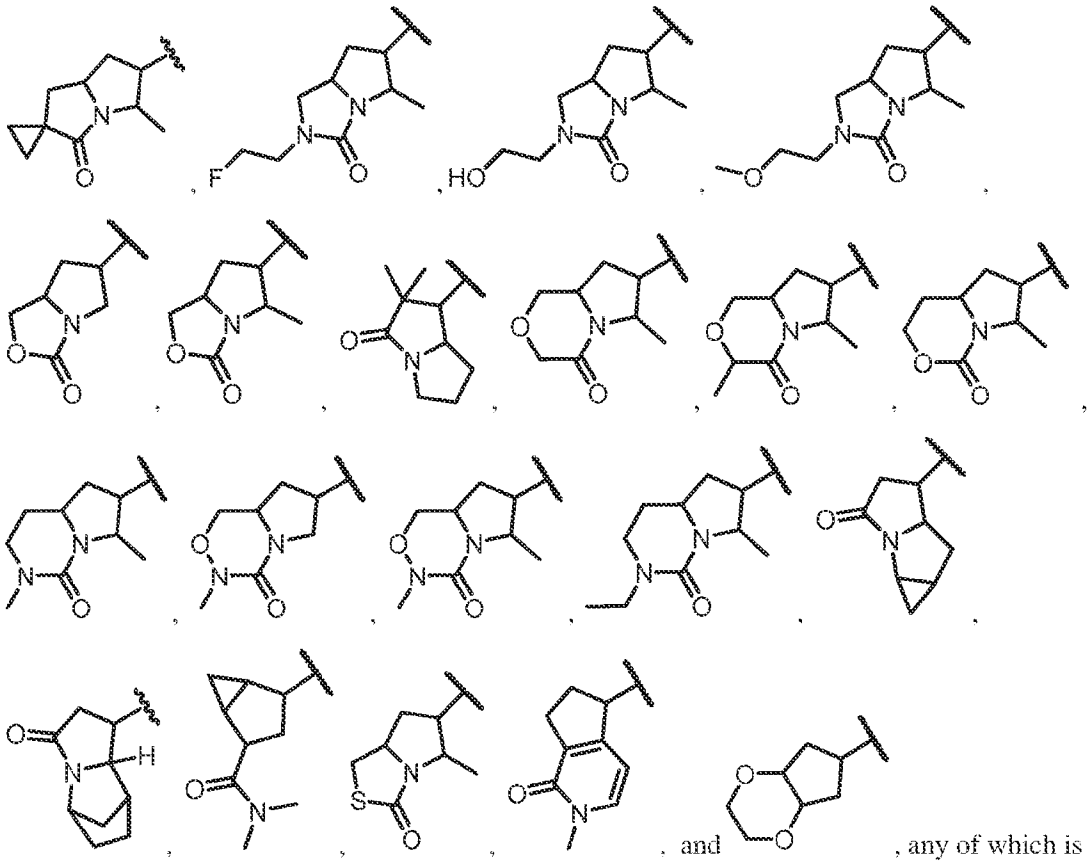
237. The compound of any one of Embodiments 222-224, wherein R^3 is -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}.

238. The compound of Embodiment 237, wherein R^3 is -CH_2(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}.

239. The compound of Embodiment 238, wherein R^{10} is selected from halogen and C_{1-6}alkyl, wherein the C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}.

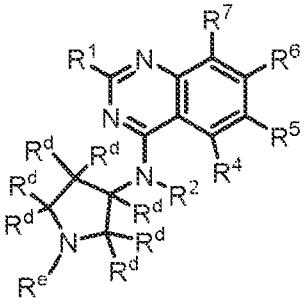
240. The compound of any one of Embodiments 222-239, wherein R^3 is selected from: $-CH_3$, , 



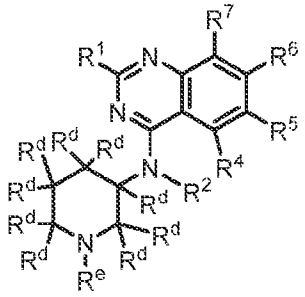


optionally further substituted with one or more R^{10}.

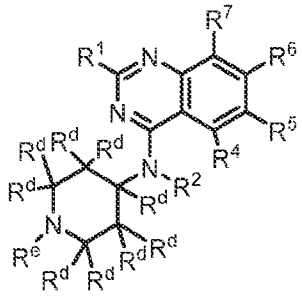
241. The compound of any one of Embodiments 222-240, wherein the compound is a compound according to Formula BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM:



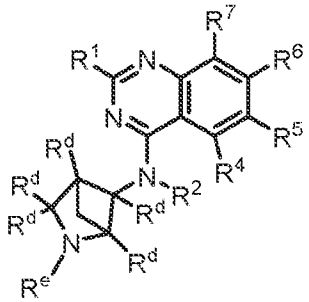
(BA),



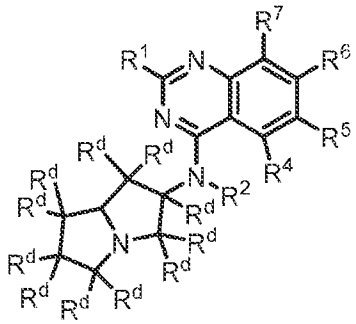
(BB),



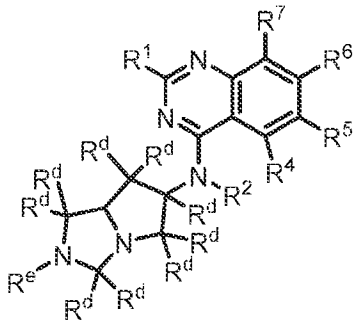
(BC),



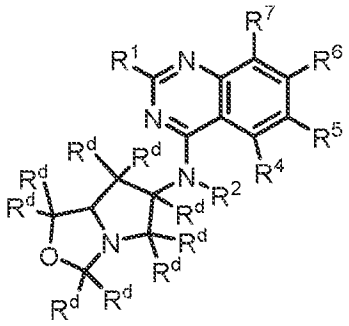
(BD),



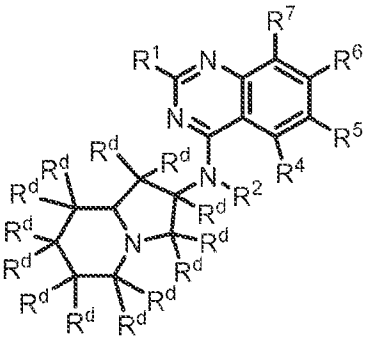
(BE),



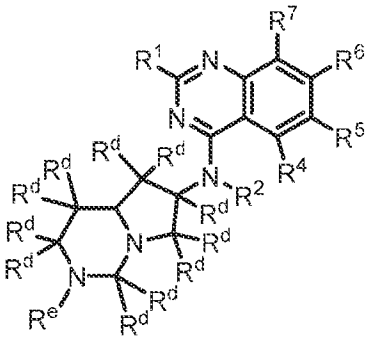
(BF),



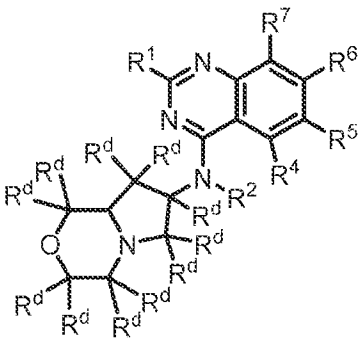
(BG),



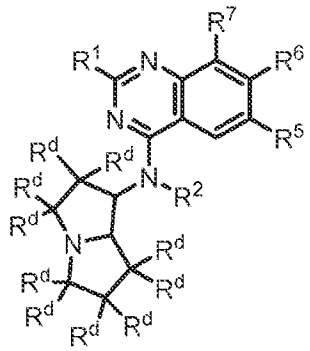
(BH),



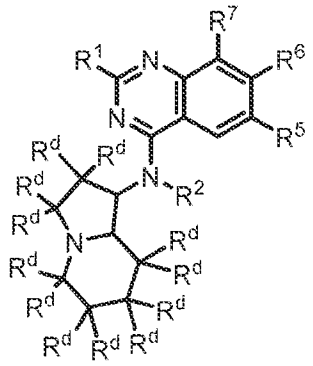
(BI),



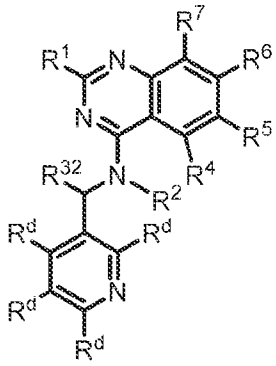
(BJ),



(BK),



(BL),



and (BM),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^{32}, if present, is selected from H and $C_{1\text{-}5}$alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and $C_{1\text{-}6}$alkyl, wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{20}; and

R^c, if present, is selected from H, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

242. The compound of Embodiment 241, wherein the compound is a compound according to Formula BA, or a salt (e.g., pharmaceutically acceptable salt) thereof.

243. The compound of Embodiment 241, wherein the compound is a compound according to Formula BB, or a salt (e.g., pharmaceutically acceptable salt) thereof.

244. The compound of Embodiment 241, wherein the compound is a compound according to Formula BC, or a salt (e.g., pharmaceutically acceptable salt) thereof.

245. The compound of Embodiment 241, wherein the compound is a compound according to Formula BD, or a salt (e.g., pharmaceutically acceptable salt) thereof.

246. The compound of Embodiment 241, wherein the compound is a compound according to Formula BE, or a salt (e.g., pharmaceutically acceptable salt) thereof.

247. The compound of Embodiment 241, wherein the compound is a compound according to Formula BF, or a salt (e.g., pharmaceutically acceptable salt) thereof.

248. The compound of Embodiment 241, wherein the compound is a compound according to Formula BG, or a salt (e.g., pharmaceutically acceptable salt) thereof.

249. The compound of Embodiment 241, wherein the compound is a compound according to Formula BH, or a salt (e.g., pharmaceutically acceptable salt) thereof.

250. The compound of Embodiment 241, wherein the compound is a compound according to Formula BI, or a salt (e.g., pharmaceutically acceptable salt) thereof.

251. The compound of Embodiment 241, wherein the compound is a compound according to Formula BJ, or a salt (e.g., pharmaceutically acceptable salt) thereof.

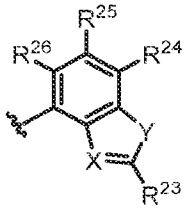
252. The compound of Embodiment 241, wherein the compound is a compound according to Formula BK, or a salt (e.g., pharmaceutically acceptable salt) thereof.

253. The compound of Embodiment 241, wherein the compound is a compound according to Formula BL, or a salt (e.g., pharmaceutically acceptable salt) thereof.

254. The compound of Embodiment 241, wherein the compound is a compound according to Formula BM, or a salt (e.g., pharmaceutically acceptable salt) thereof.

255. The compound of any one of Embodiments 222-254, wherein (i) when R^3 includes a heterocycle or heteroaryl containing a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle or heteroaryl does not comprise an –NH- moiety.

256. The compound of any one of Embodiments 222, 223, or 225-255, wherein R^6 is selected from:



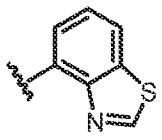
, wherein:

X is selected from N and C-CN;

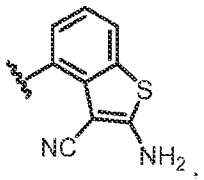
Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

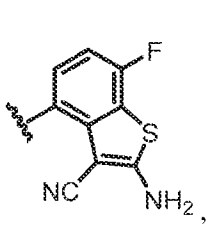
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

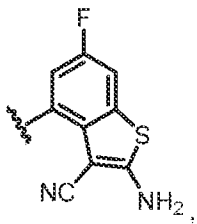
257. The compound of Embodiment 256, wherein R^6 is selected from: 

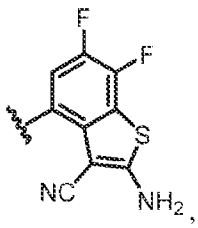
, which is substituted with one or more R^{15}.

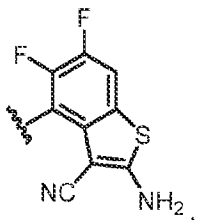
258. The compound of Embodiment 257, wherein R^6 is selected from: 

,



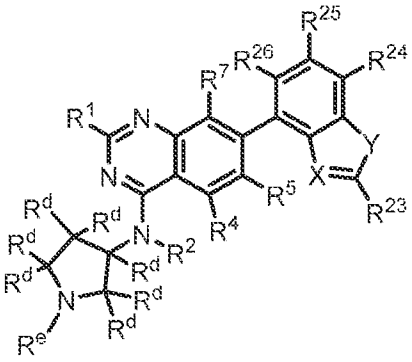
, 

, 

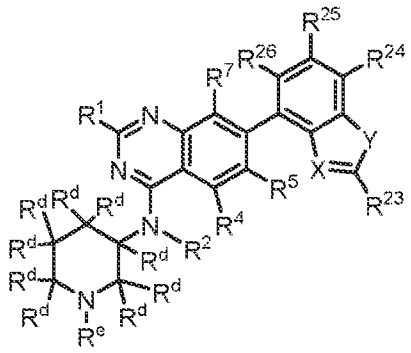
, and 

.

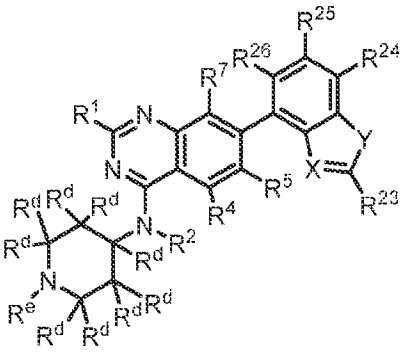
259. The compound of any one of Embodiments 222, 223, or 225-258, wherein the compound is a compound according to Formula BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1:



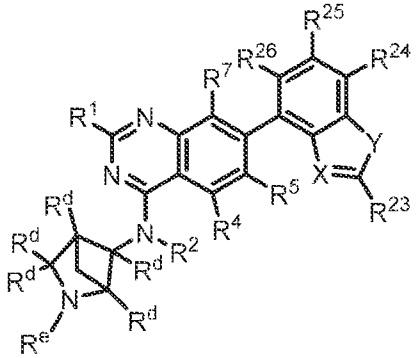
(BA1),



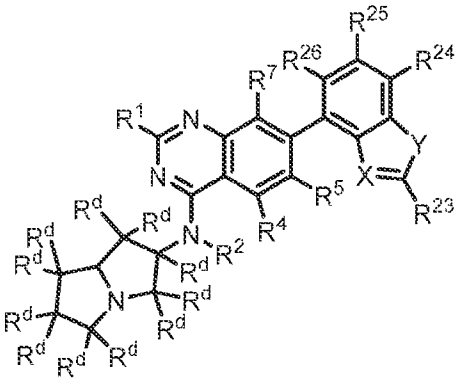
(BB1),



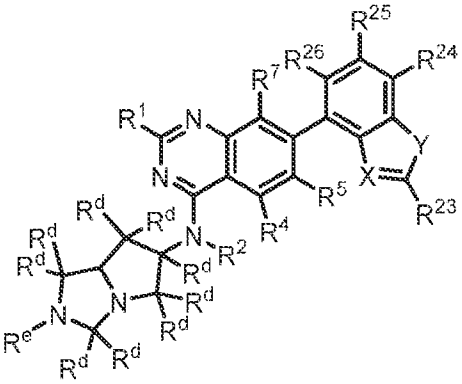
(BC1),



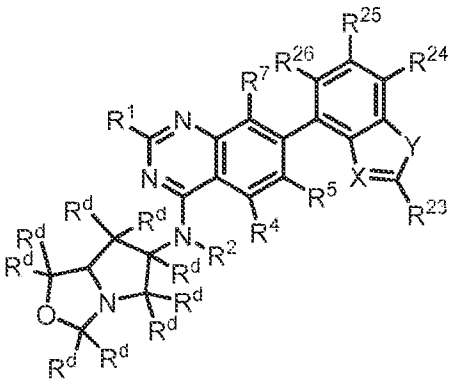
(BD1),



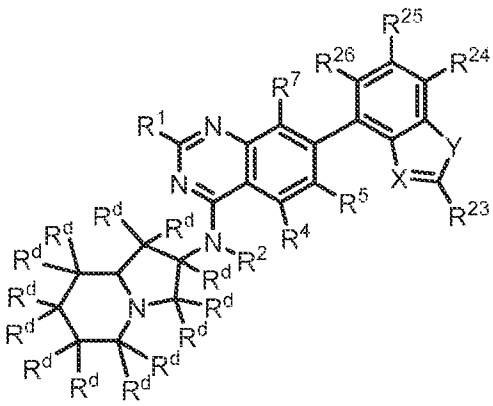
(BE1),



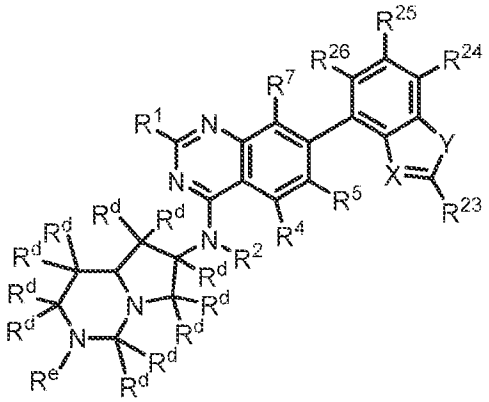
(BF1),



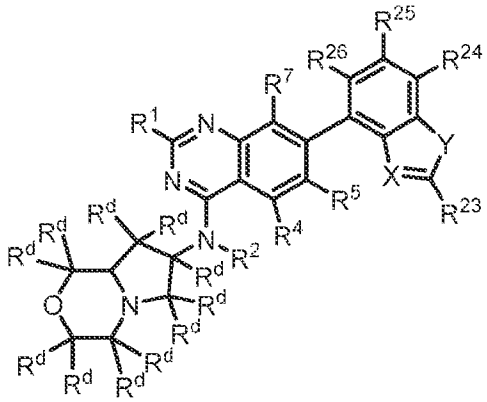
(BG1),



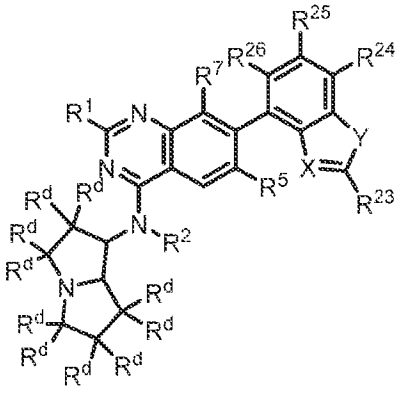
(BH1),



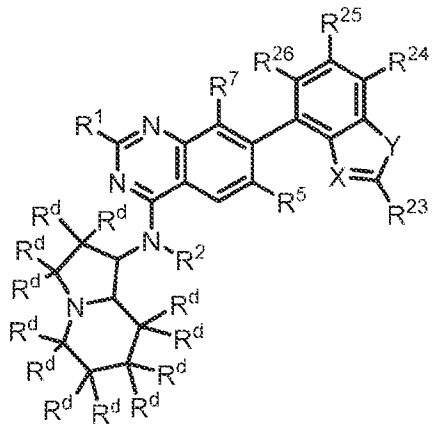
(BI1),



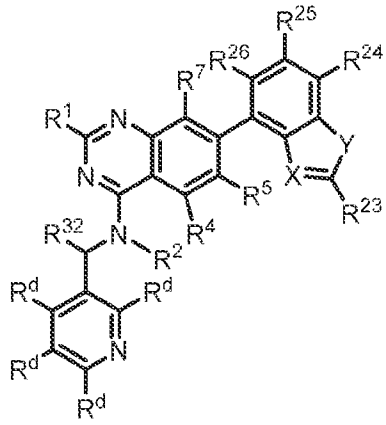
(BJ1),



(BK1),



(BL1), and



(BM1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^{32}, if present, is selected from H and C_{1-5}alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

R^e, if present, is selected from -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-}

$_{6}$alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is C-CN;

Y is S;

R^{23} is selected from $-N(R^{12})_2$; and

R^{24}, R^{25}, and R^{26} are independently selected from H and halogen.

260. The compound of any one of Embodiments 256-259, wherein one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

261. The compound of any one of Embodiments 241-260, wherein R^e is -C(O)(3-6 membered carbocycle).

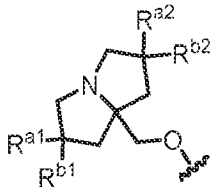
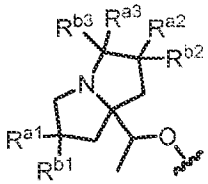
262. The compound of any one of Embodiments 241-260, wherein R^e is selected from -C(O)(C_{1-6}alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), and -C(O)O(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

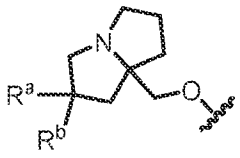
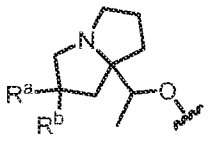
263. The compound of any one of Embodiments 241-262, wherein each R^d is H.

264. The compound of any one of Embodiments 222-263, wherein R^2 is H.

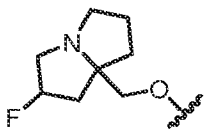
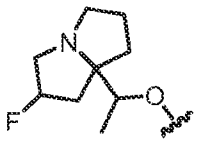
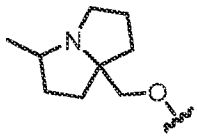
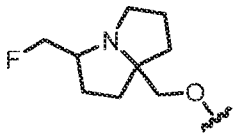
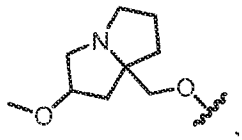
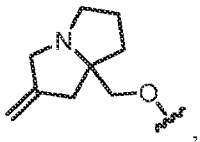
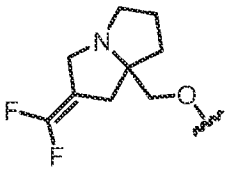
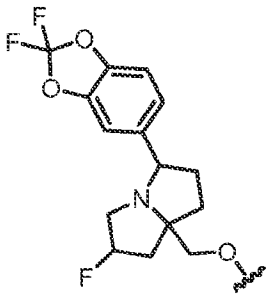
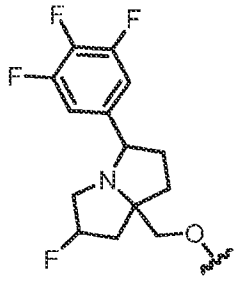
265. The compound of any one of Embodiments 222-263, wherein R^2 is selected from C_{1-2}alkyl.

266. The compound of any one of Embodiments 222, 223, or 225-265, wherein R^1 is selected from $-OR^8$.

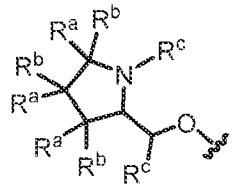
267. The compound of Embodiment 266, wherein R^1 is selected from:  or  , wherein R^{a1}, R^{a2}, R^{b1}, R^{b2}, R^{a3}, and R^{b3} are each independently selected from deuterium, halogen, $-OR^{12}$, a 4- to 10-membered heterocycle, and a 4- to 10-membered aryl, wherein any 4- to 10-membered heterocycle or 4- to 10-membered aryl is optionally substituted with one or more R^{28}, and H, wherein R^{a1} and R^{b1} can optionally join together to form a exocyclic double bond that is unsubstituted or is substituted by halogen.

268. The compound of Embodiment 267, wherein R^1 is selected from:  or  , wherein R^a and R^b are each independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen.

269. The compound of Embodiment 268, wherein R^1 is selected from:

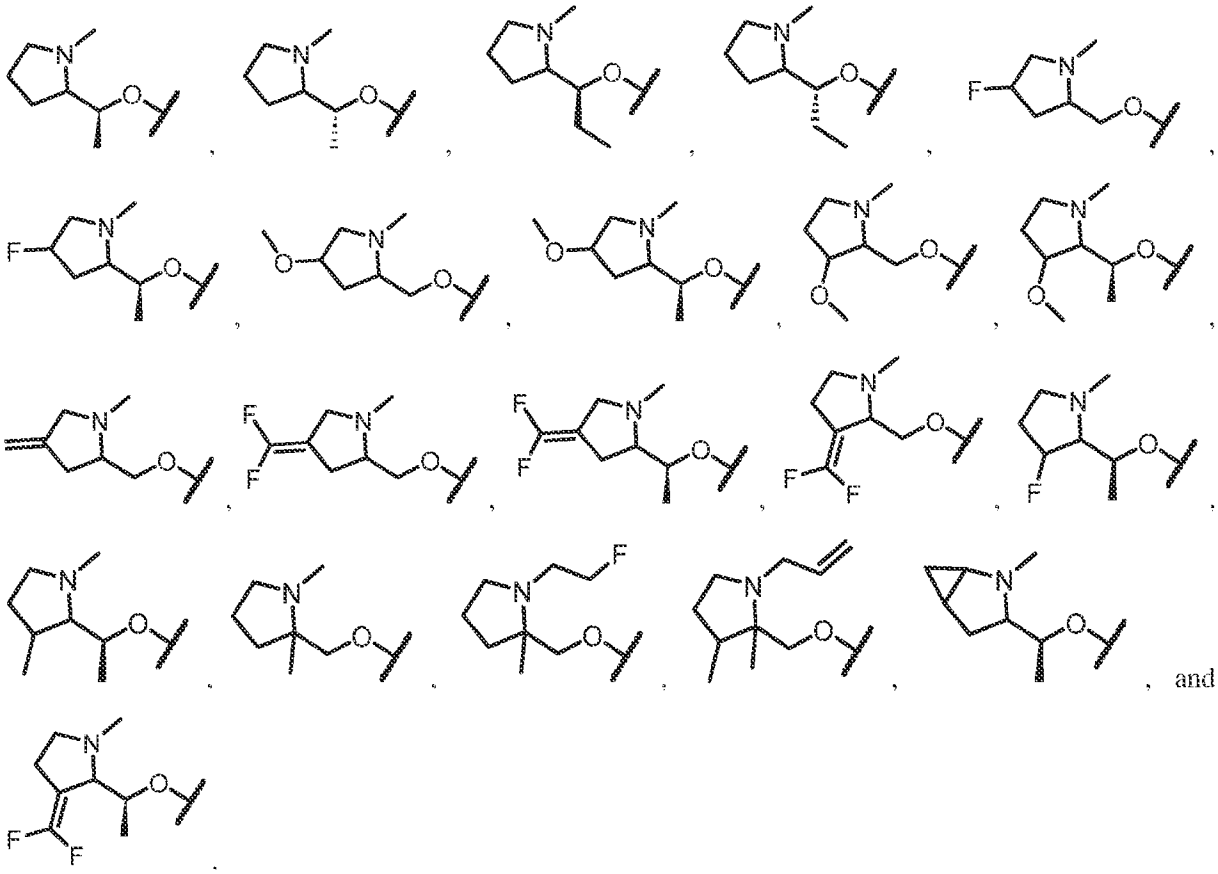
 ,  ,  ,  ,  ,  ,  ,  and  .

270. The compound of Embodiment 266, wherein R^1 is:

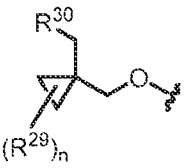
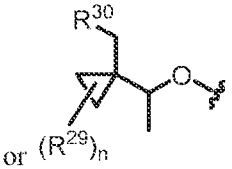
 ,

wherein each R^a and R^b is independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H; and each R^c is independently selected from H and C_{1-6} alkyl, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen.

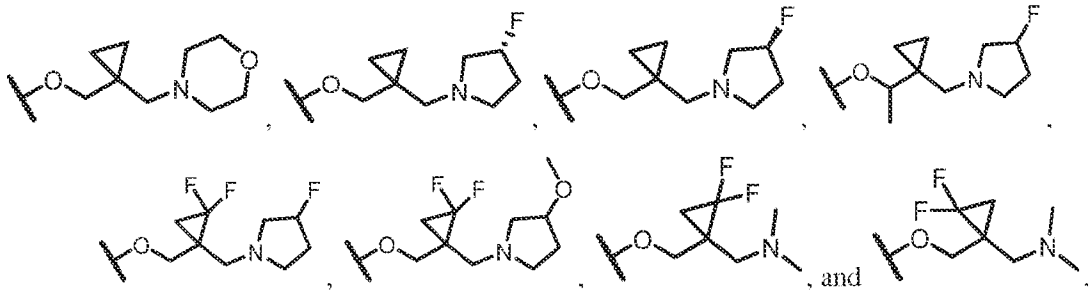
271. The compound of Embodiment 270, wherein R^1 is selected from:



and

272. The compound of any one of Embodiments 222, 223, or 225-265, wherein R^1 is  or  .

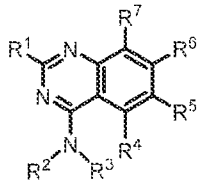
273. The compound of Embodiment 272, wherein R^1 is selected from



and

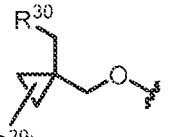
274. The compound of any one of Embodiments 222, 223, or 225-273, wherein R^5 is $-CF_3$.

275. A compound represented by Formula II':



(II'')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, $-OC_{1-6}$alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen or H;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, $-OR^{12}$, =O, =S, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, $-C(S)(C_{1-6}alkyl)$, $-C(S)O(C_{1-6}alkyl)$, $-C(S)N(C_{1-6}alkyl)_2$, $-C(=N-OR^{12})(C_{1-6}$ alkyl), $-C(O)N(R^{12})OR^{12}$, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally

join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, $-OC_{1-6}$ alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), $-C(O)OR^{12}$, $-C(O)N(R^{12})_2$, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

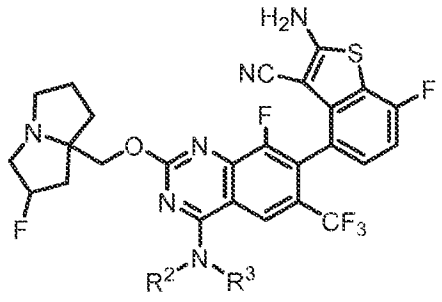
each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

276. The compound of Embodiment 275, wherein R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, or (ii) the heterocycle does not comprise an –NH- moiety.

277. The compound of Embodiment 275 or 276, wherein the compound is of Formula II-a:



(II-a)

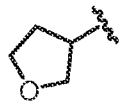
or a salt (e.g., pharmaceutically acceptable salt) thereof.

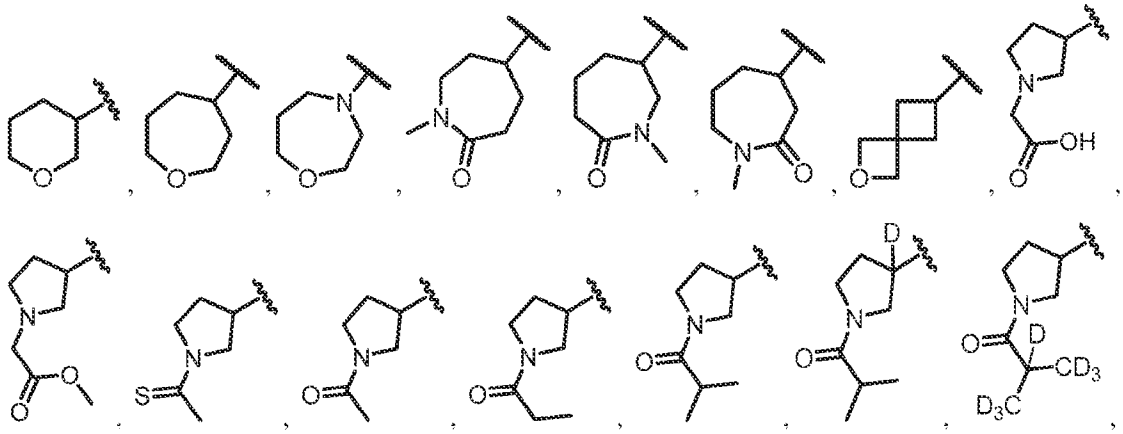
278. The compound of any one of Embodiments 275-277, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N.

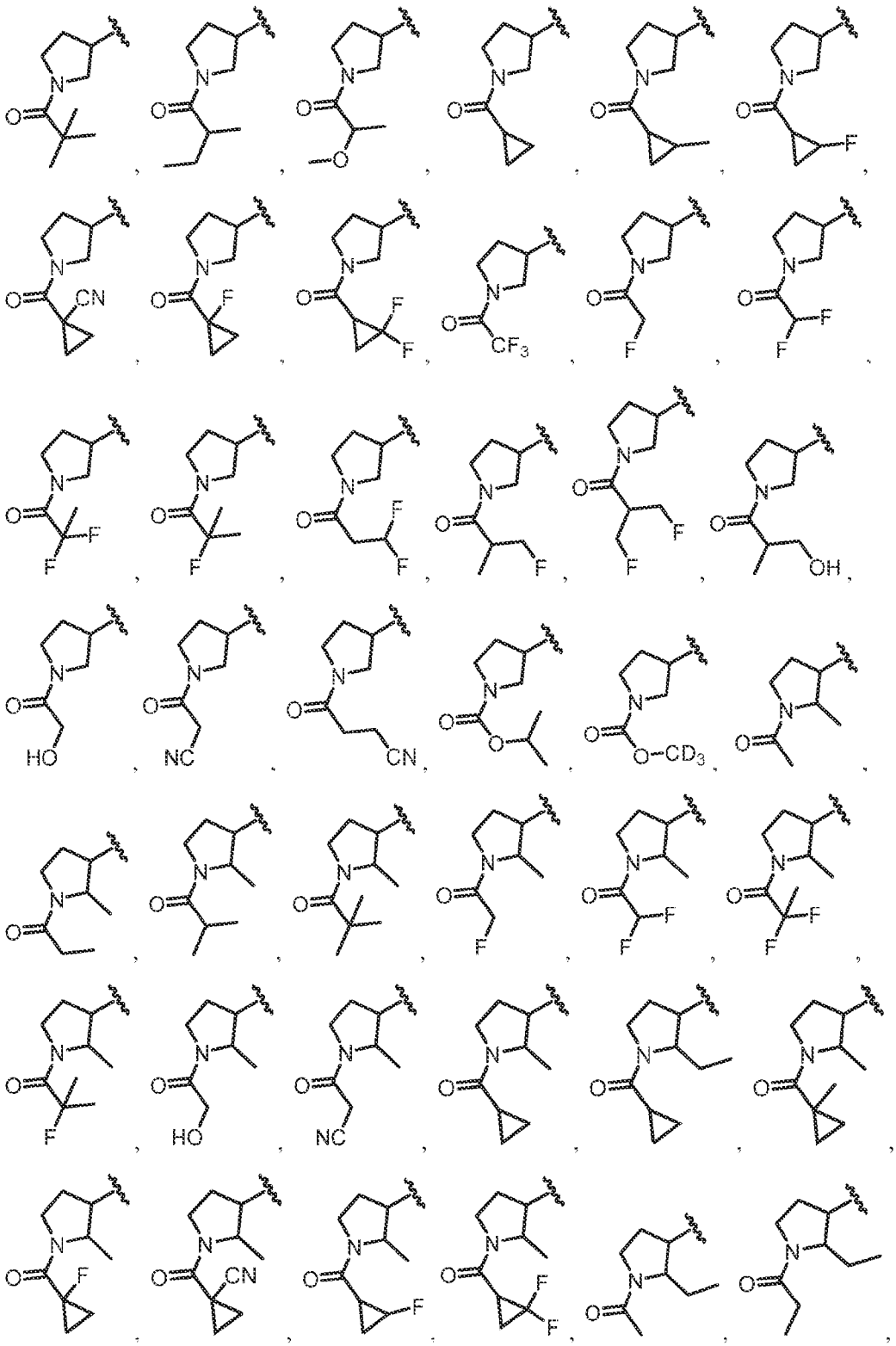
279. The compound of Embodiment 278, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}.

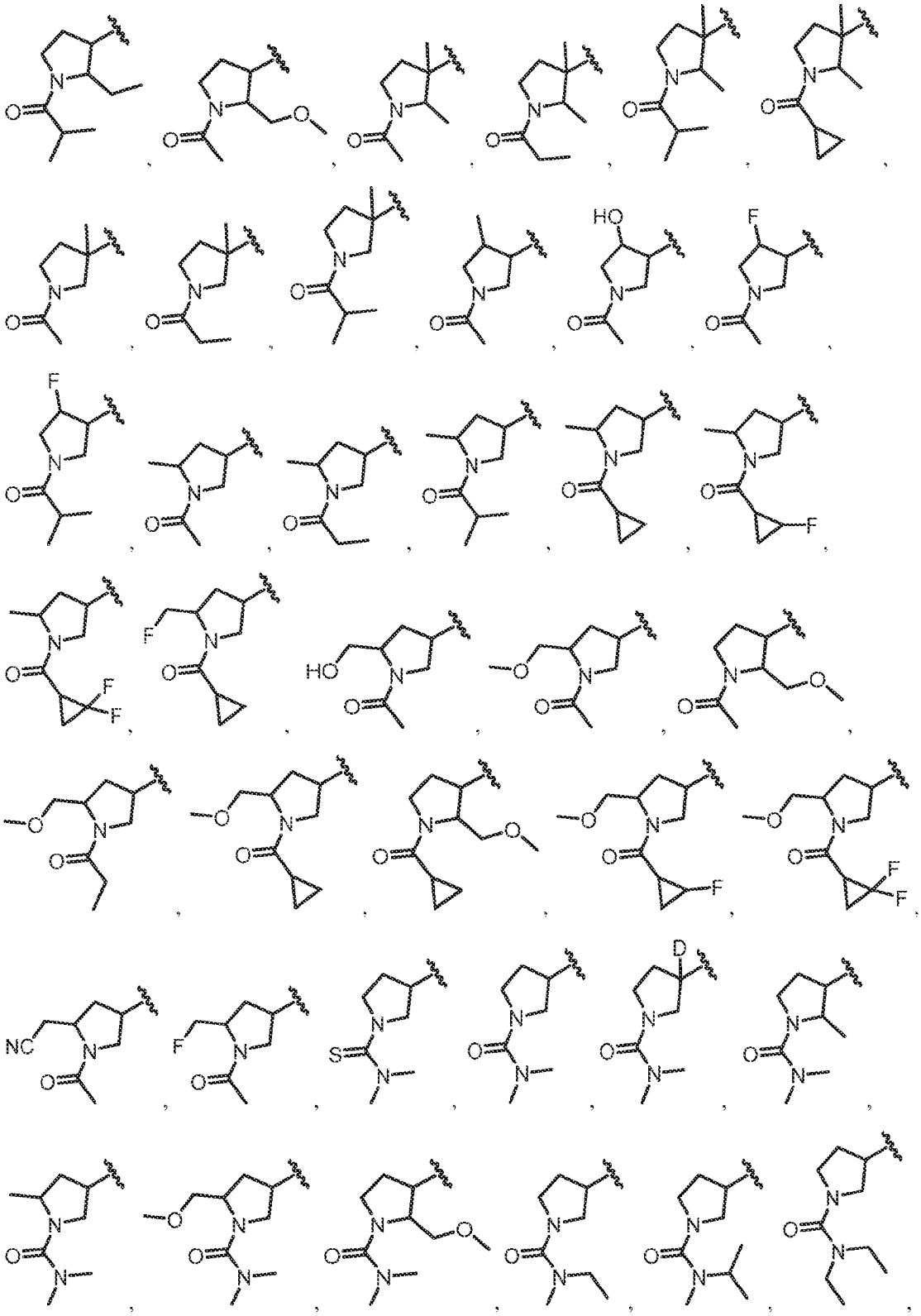
280. The compound of any one of Embodiments 275-279, wherein R^3 is a pyrrolidine that is substituted with 1-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}.

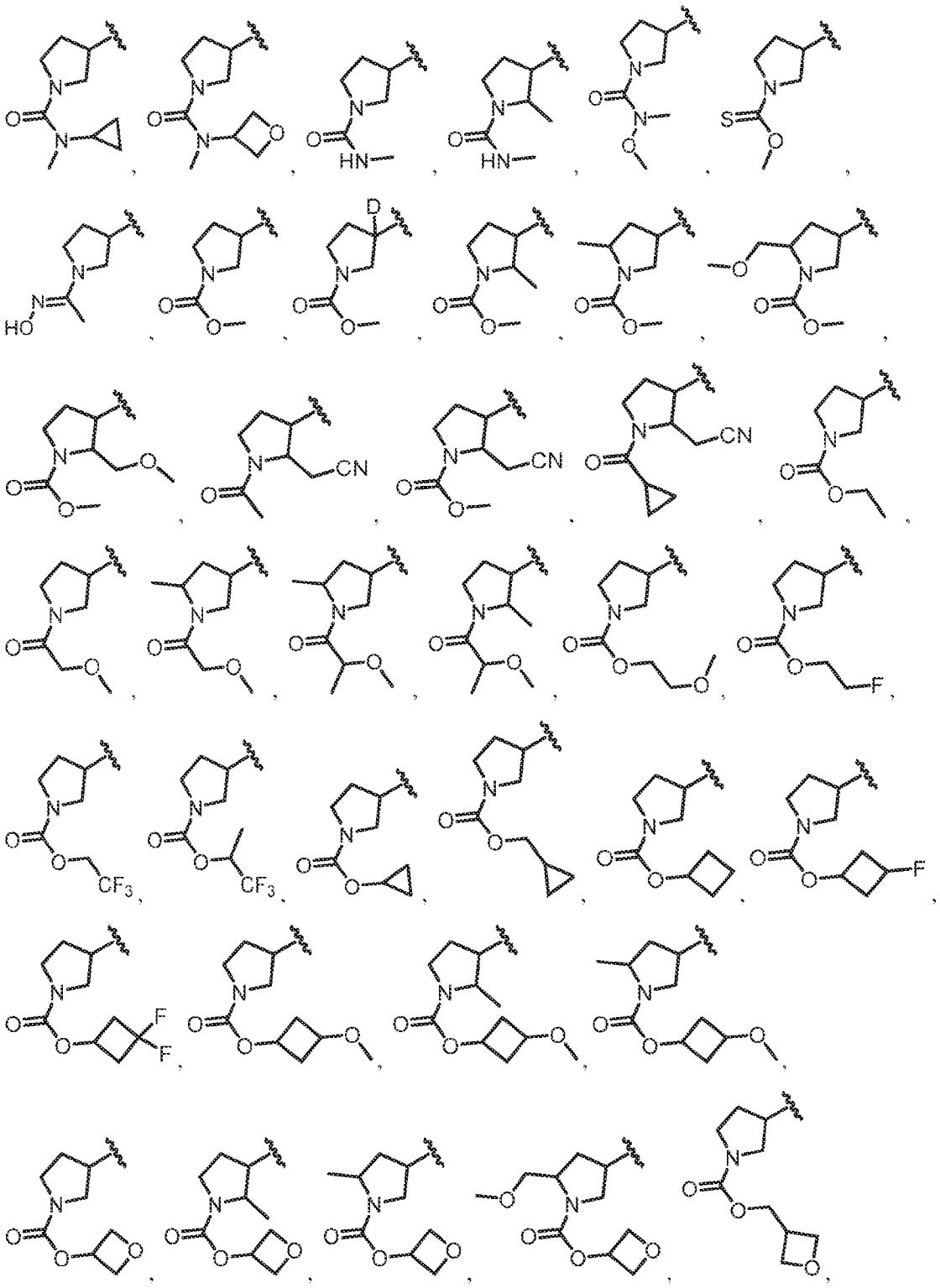
281. The compound of Embodiment 280, wherein each R^{10} is independently selected from deuterium, -C(O)N(R^{14})$_2$, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 3-6 membered heterocycle, a 5-6 membered heteroaryl, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

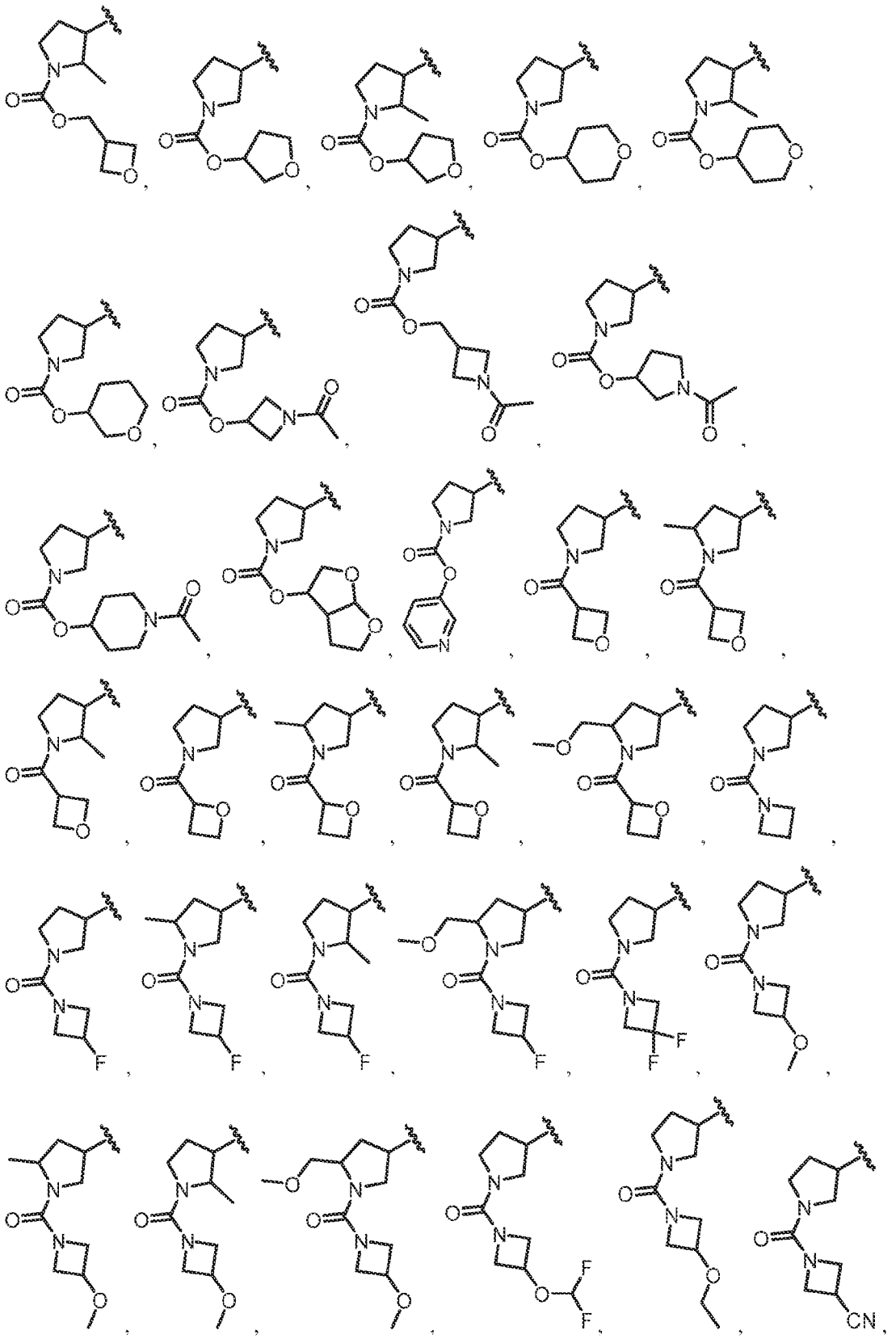
282. The compound of any one of Embodiments 222-281, wherein R^3 is selected from:  ,

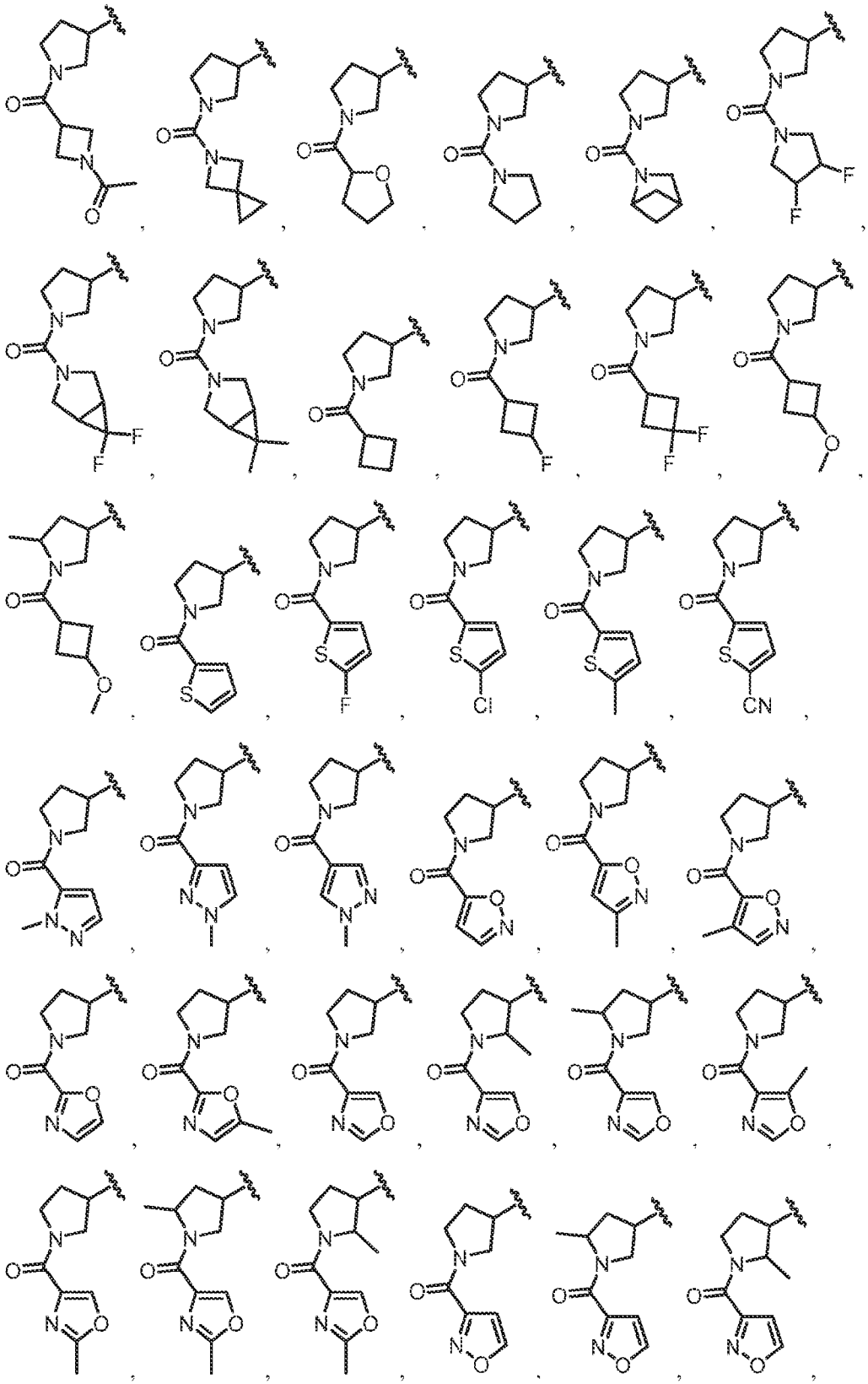


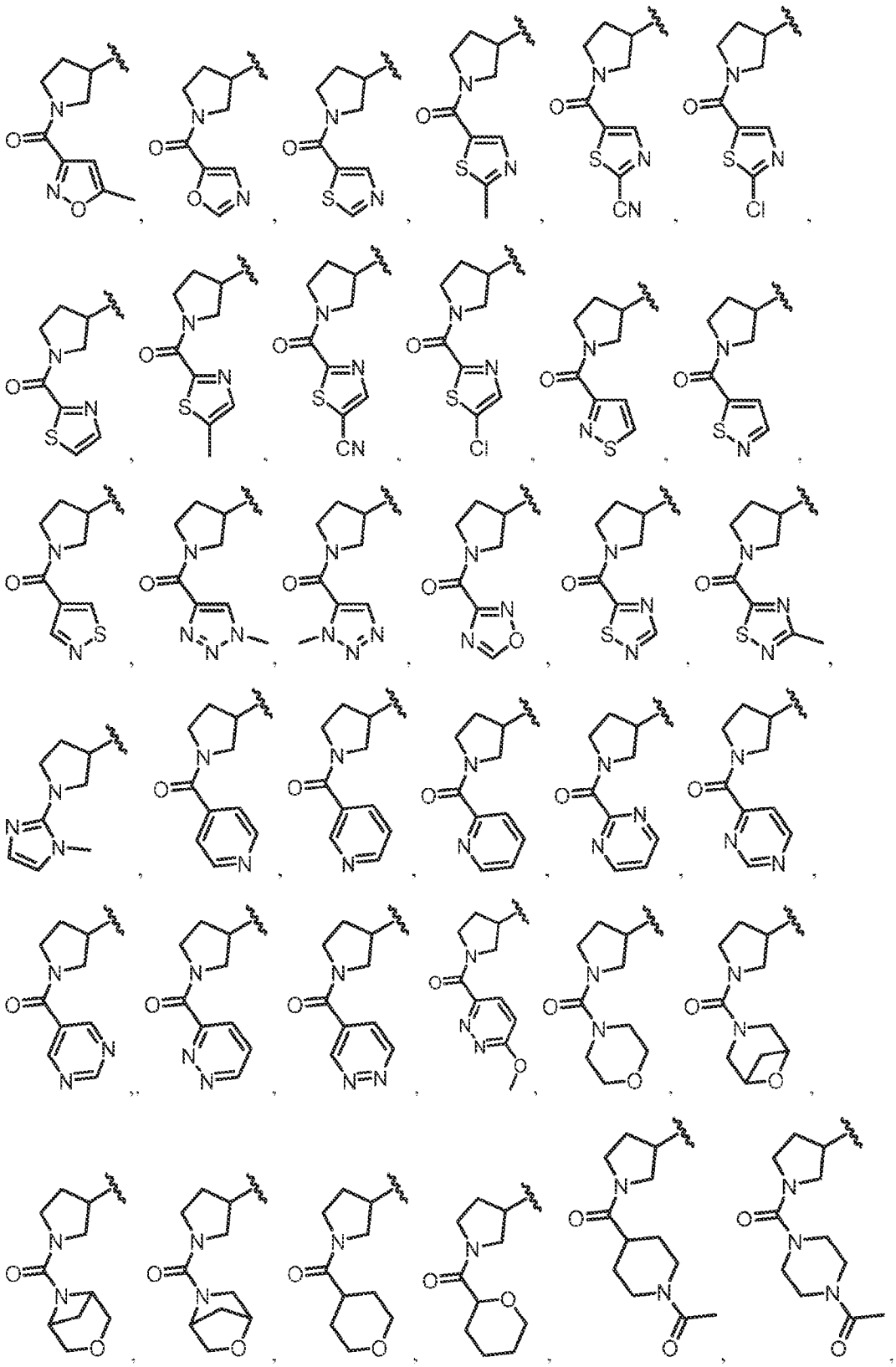


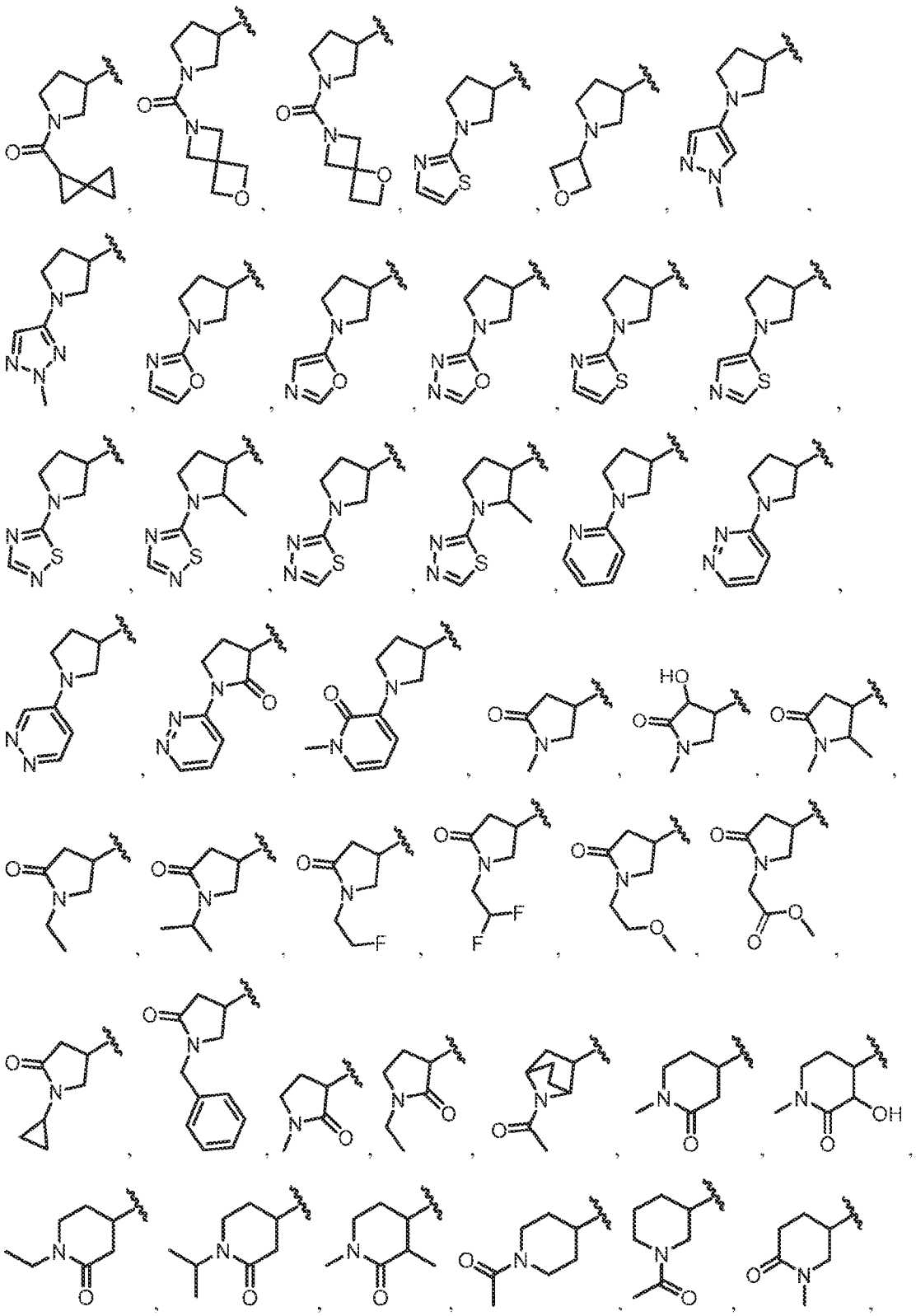


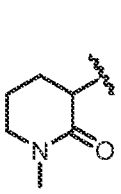
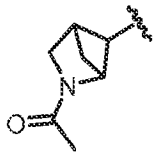
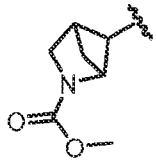
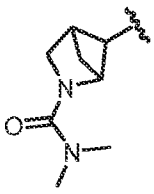


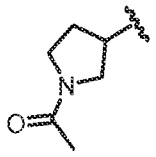
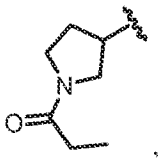


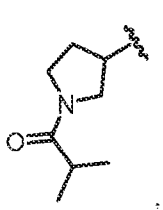
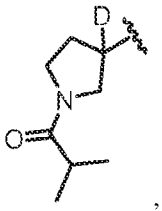
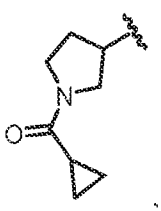
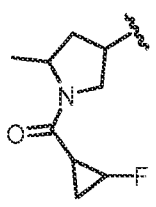
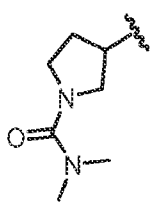


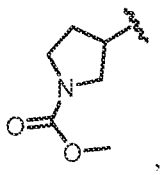
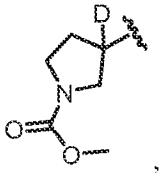
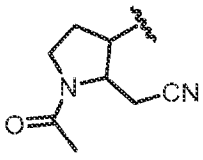
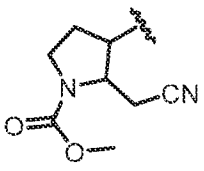
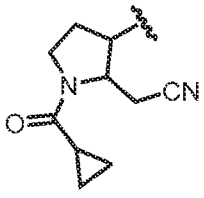


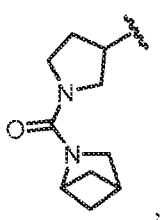
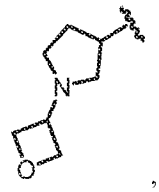
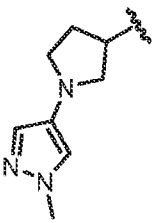
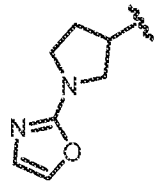
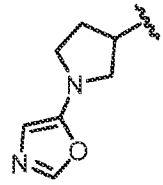
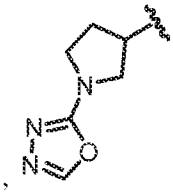


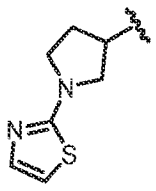
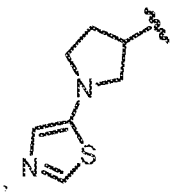
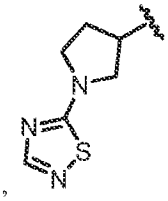
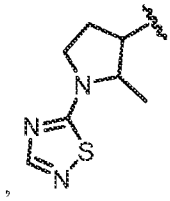
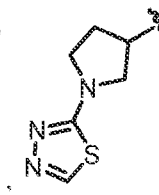
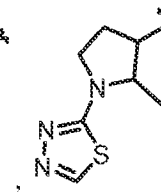
 ,  ,  , and  , any of which is optionally further substituted with one or more R^{10}.

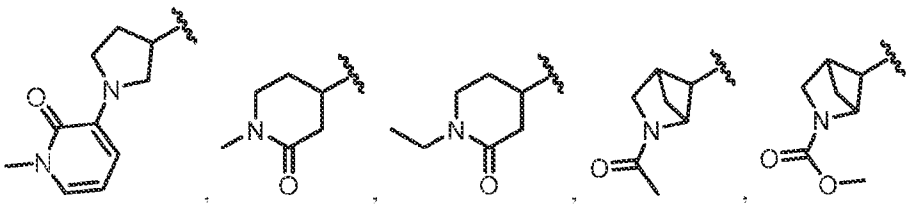
283. The compound of Embodiment 282, wherein R^3 is selected from:  ,  ,

 ,  ,  , ,  ,  ,

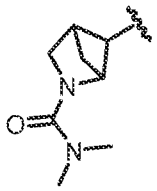
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,



, and



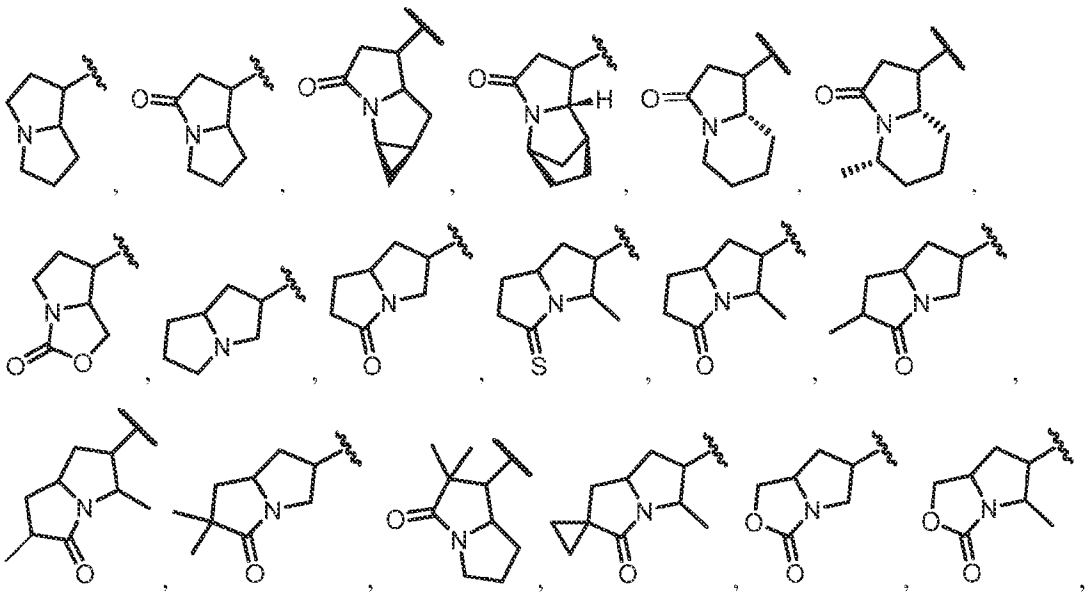
, any of which is optionally further substituted with one or more R^{10}.

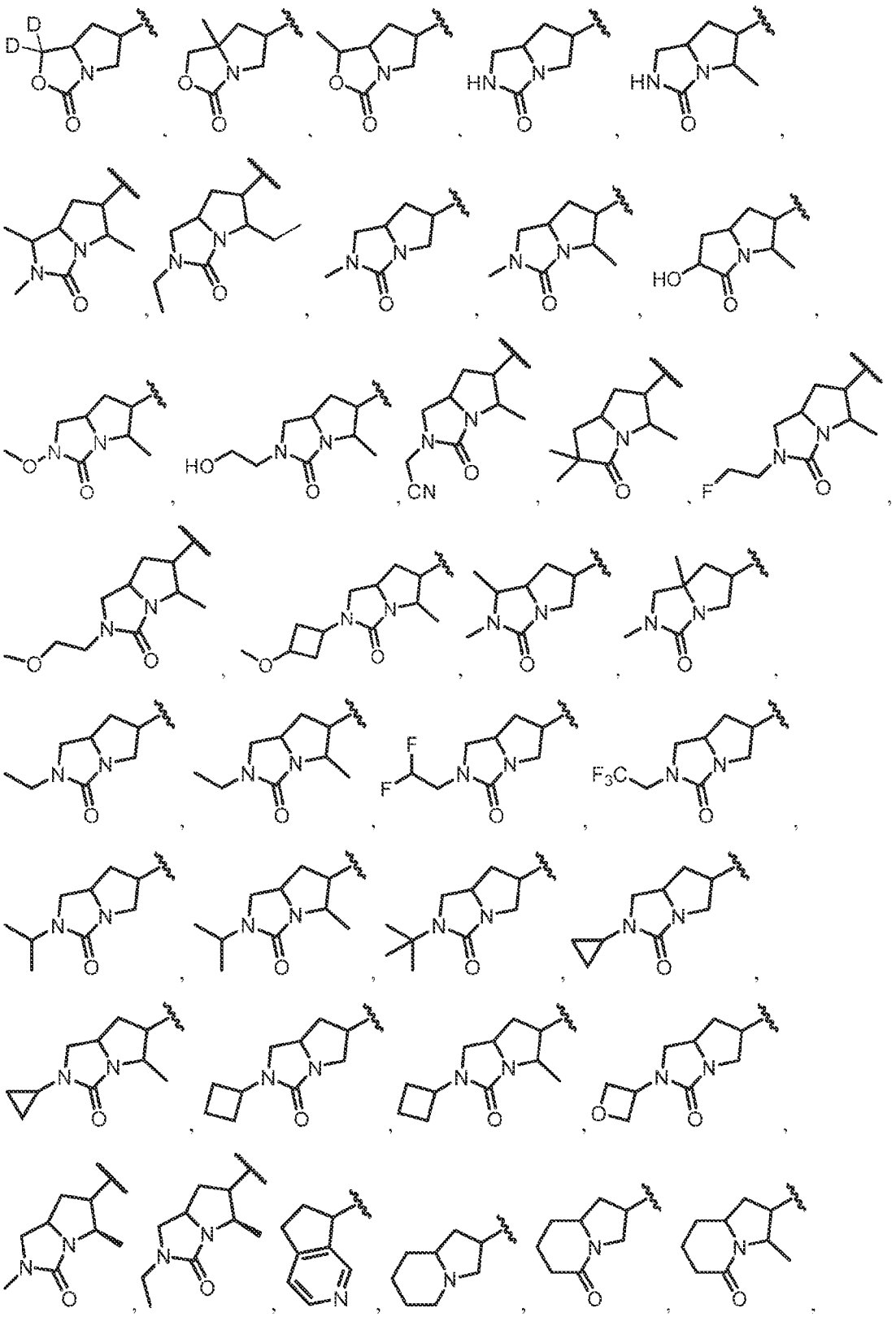
284. The compound of any one of Embodiments 275-277, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

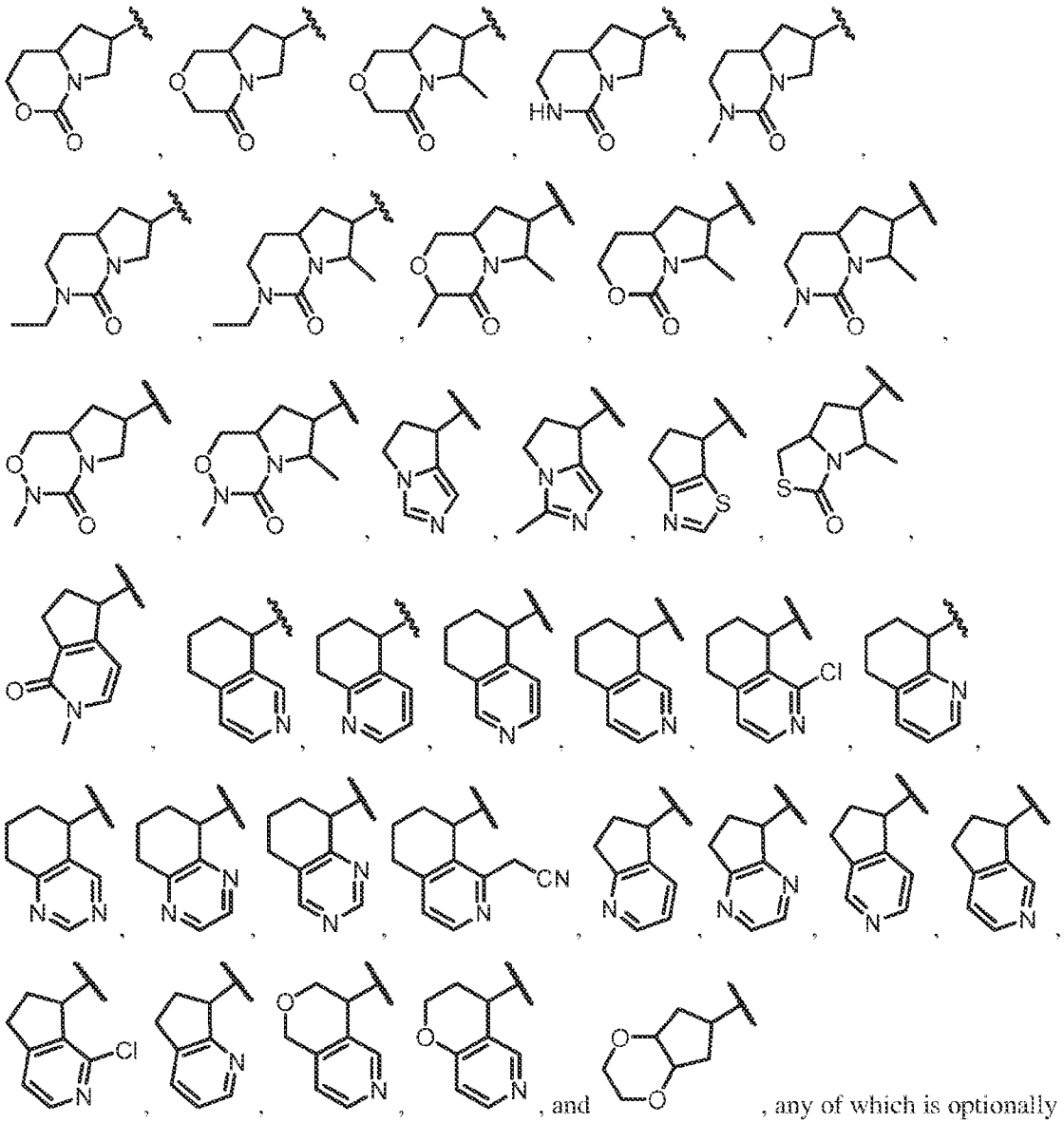
285. The compound of Embodiment 284, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not comprise an –NH- moiety.

286. The compound of Embodiment 284 or 285, wherein R^3 is a 7-10 membered heterocycle comprising a fused ring system that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

287. The compound of any one of Embodiments 275-277 and 284-286, wherein R^3 is selected from:

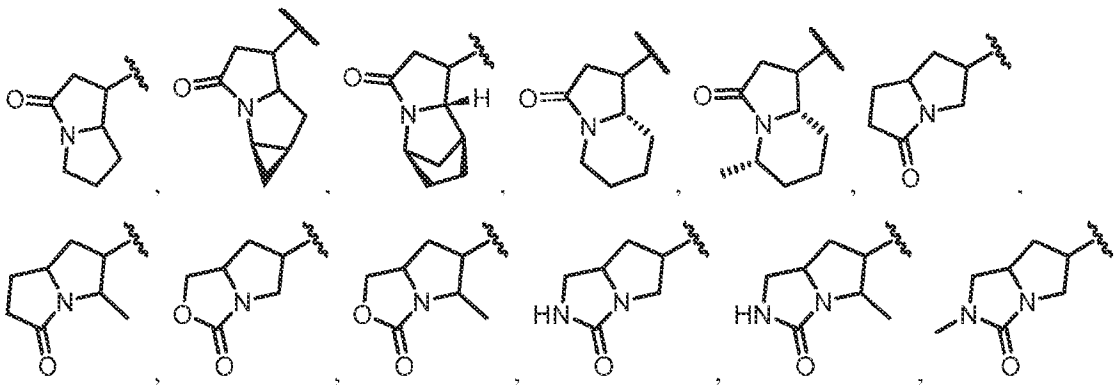


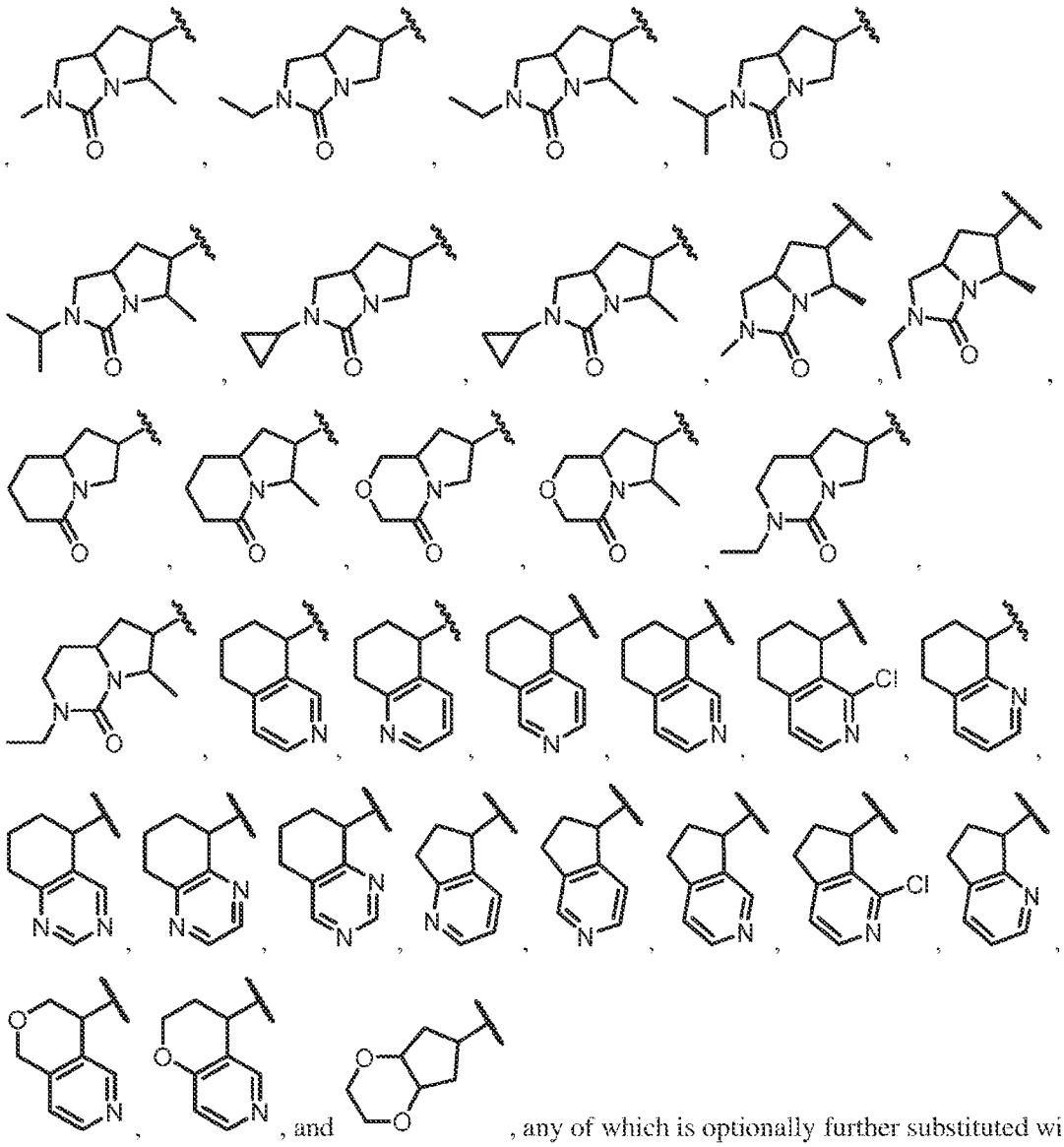




, and , any of which is optionally further substituted with one or more R^{10}.

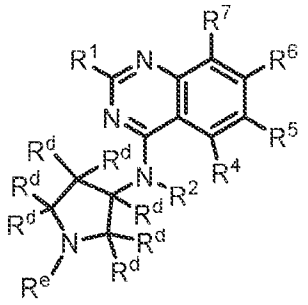
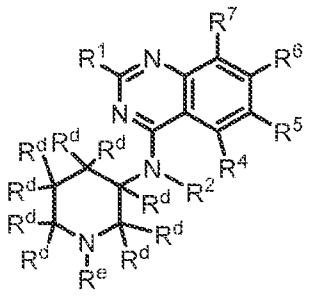
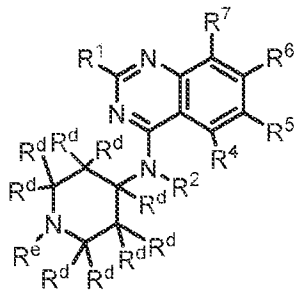
288. The compound of Embodiment 287, wherein R^3 is selected from:

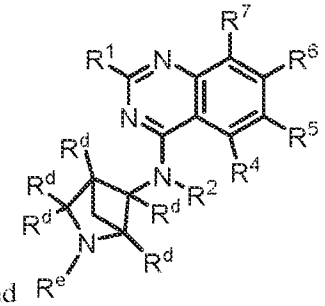




, any of which is optionally further substituted with one or more R^{10}.

289. The compound of any one of Embodiments 275, 276, and 278-288, wherein the compound is a compound according to Formula IIR', IIU', IIV', or IIZ:


(IIR'),

(IIU'),

(IIV'),

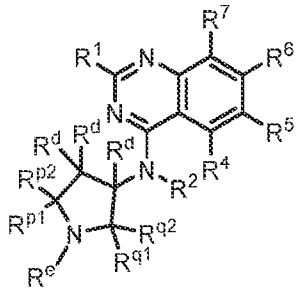

and
(IIZ),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^e is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

290. The compound of any one of Embodiments 275, 276, and 278-288, wherein the compound is a compound according to Formula IIAA':



(IIAA'),

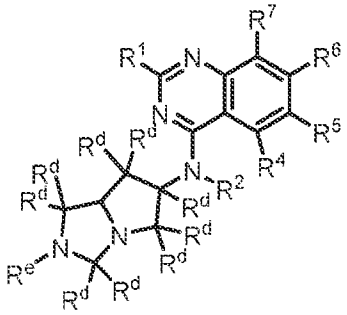
or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from deuterium, H, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)$(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle or 3-6 membered heterocycle, is unsubstituted or substituted with one or more R^{12} or R^{20}; and

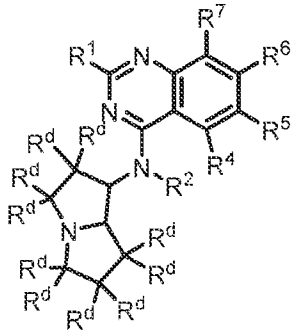
(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

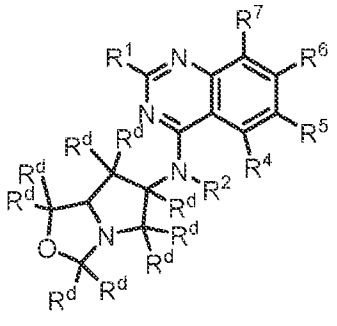
291. The compound of any one of Embodiments 275, 276 and 290, wherein the compound is a compound according to Formula IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, or IIJJ:



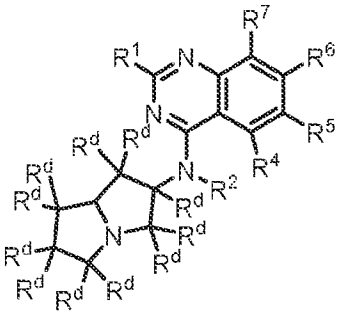
(IIBB),



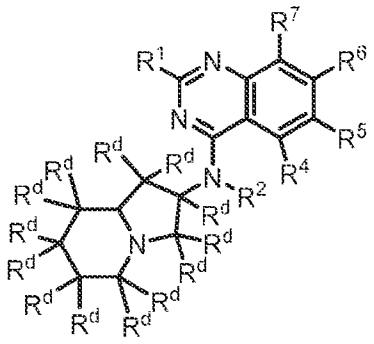
(IICC),



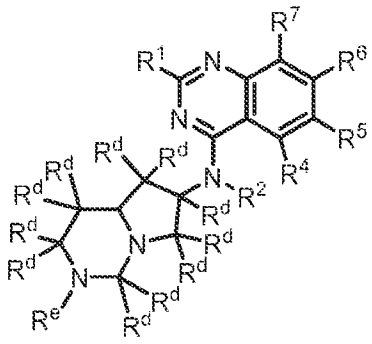
(IIDD),



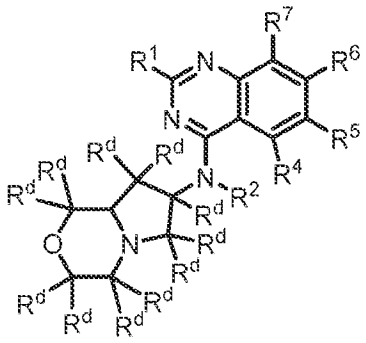
(IIEE),



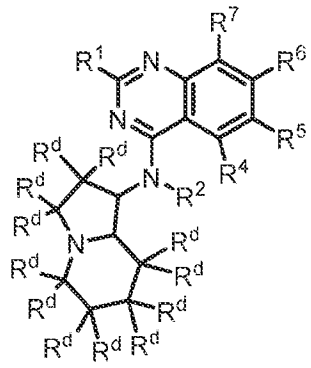
(IIFF),



(IIGG),



(IIHH), and



(IIJJ),

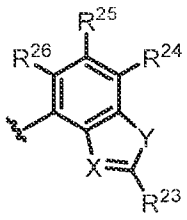
or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^e, if present, is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or

substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

292. The compound of any one of Embodiments 275, 276, and 278-291, wherein R^6 is selected from:

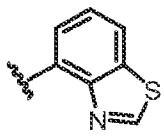
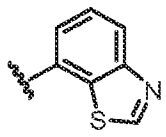
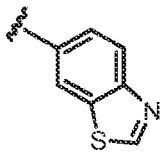
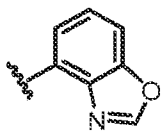
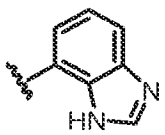
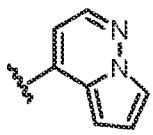
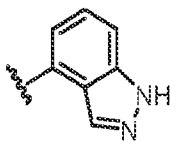
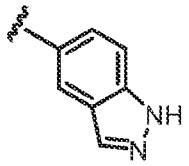
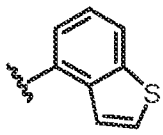
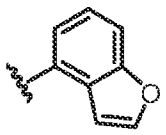
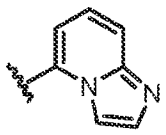

, wherein:

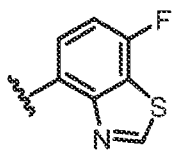
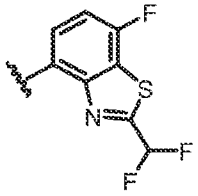
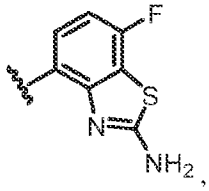
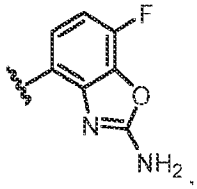
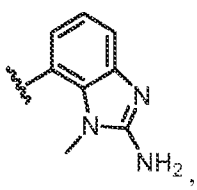
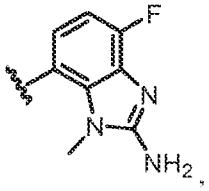
X is selected from N and C-CN;

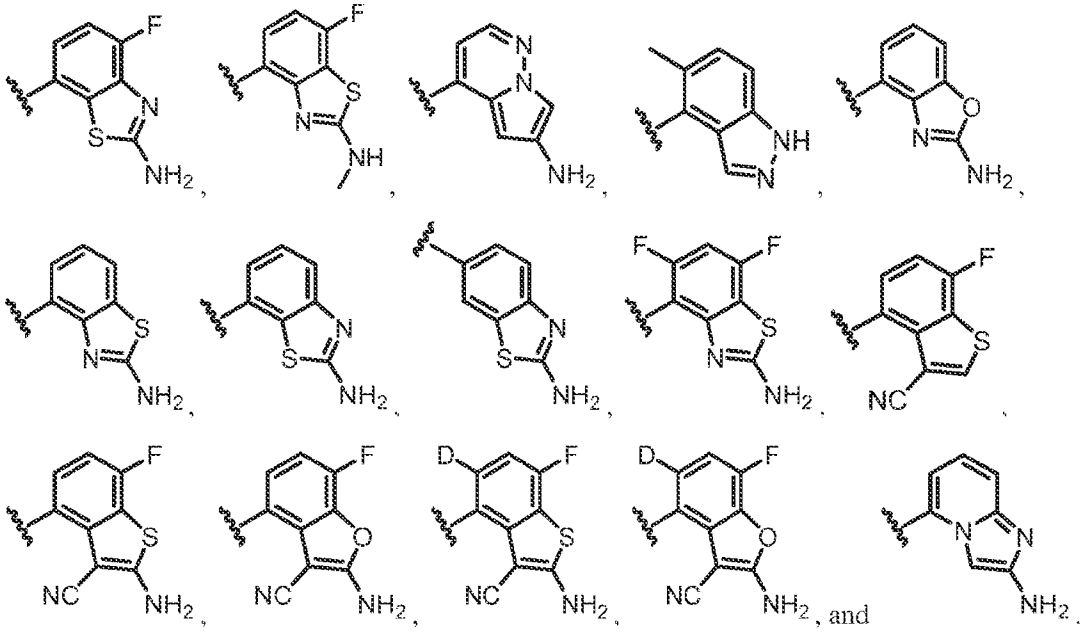
Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

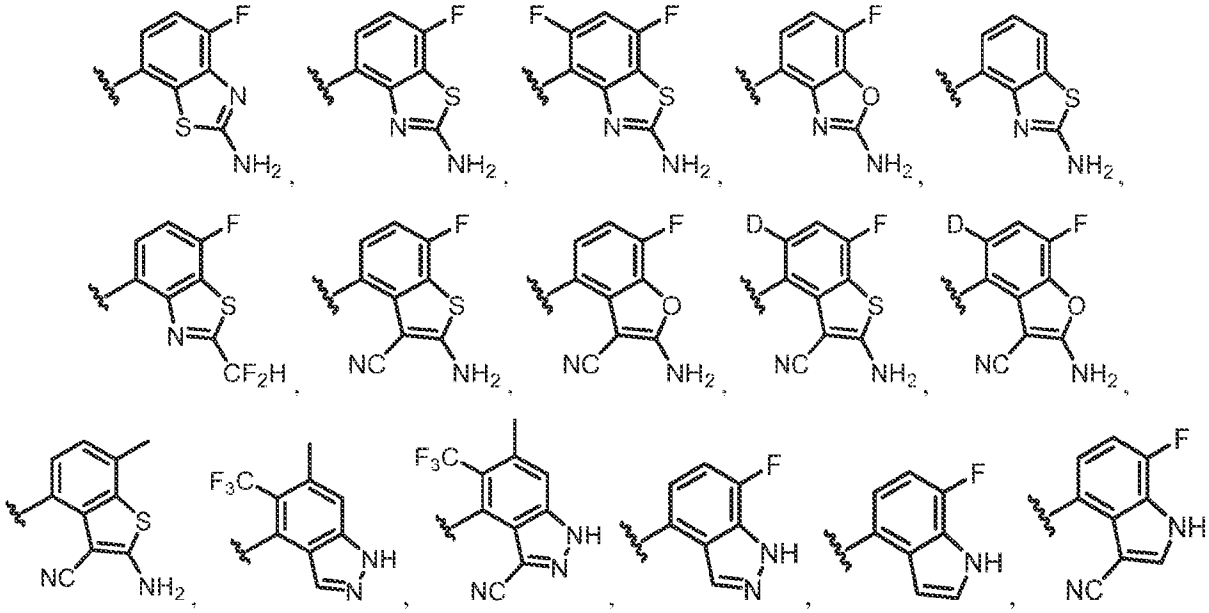
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

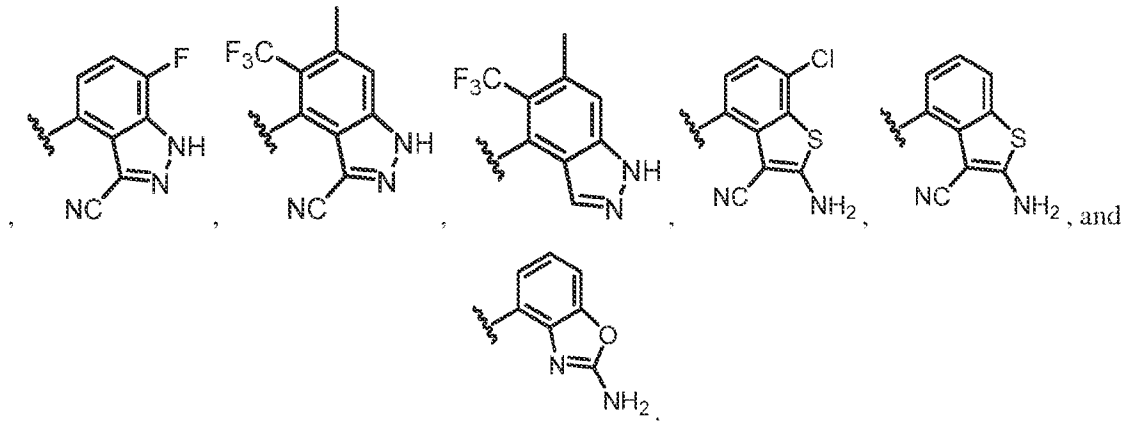
293. The compound of Embodiment 292, wherein R^6 is selected from:  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , any of which is substituted with one or more R^{15}.

294. The compound of Embodiment 292 or 293, wherein R^6 is selected from:  ,  ,  ,  ,  ,  .

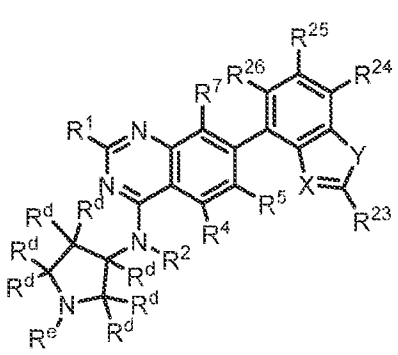


295. The compound of any one of Embodiments 292-294, wherein R^6 is selected from:

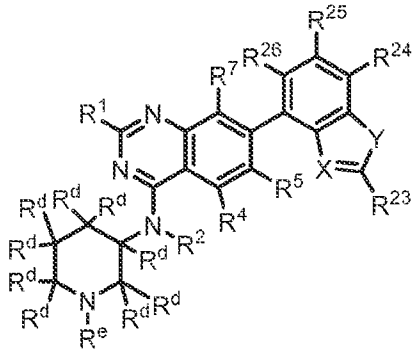




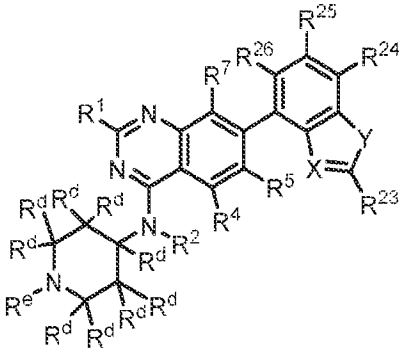
296. The compound of any one of Embodiments 275, 276, and 278-291, wherein the compound is a compound according to Formula IIR1', IIU1', IIV1', or IIZ1:



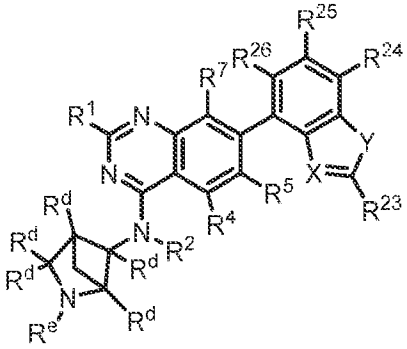
(IIR1'),



(IIU1'),



(IIV1'),



(IIZ1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e is selected from $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8

membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

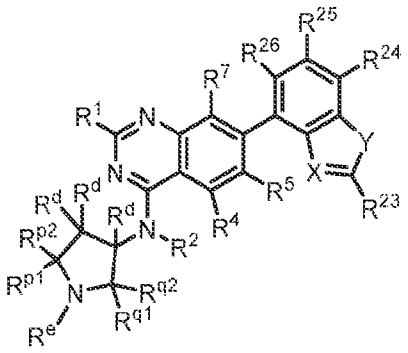
X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -N(R^{12})$_2$, C_{1-6}alkyl, and C_{1-6}alkyl-N(R^{14})$_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

297. The compound of any one of Embodiments 275, 276, and 278-291, wherein the compound is a compound according to Formula IIAA1':



(IIAA1'),

or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, -OR^{12}, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)N(R^{14})$_2$, -S(O)$_2$(C_{1-6}alkyl), a 3-6 membered carbocycle, a 3-6 membered heterocycle, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle or 3-6 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

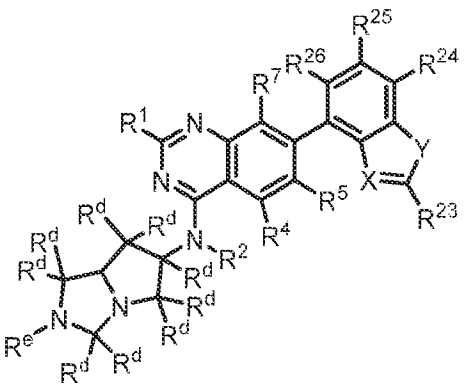
R^{23} is selected from -N(R^{12})$_2$, C_{1-6}alkyl, and C_{1-6}alkyl-N(R^{14})$_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

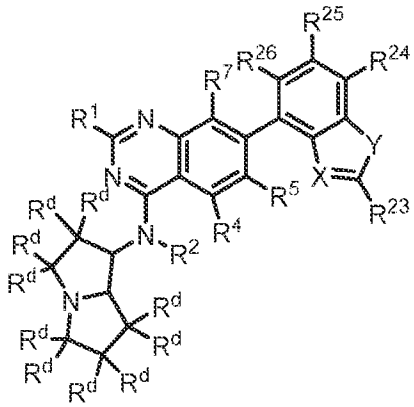
(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

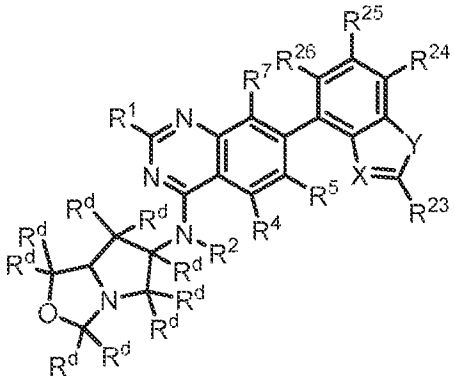
298. The compound of Embodiment 297, wherein the compound is a compound according to Formula IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1:



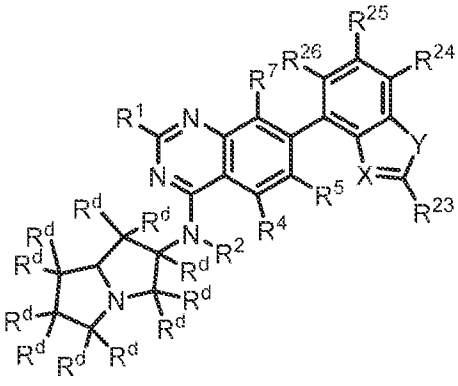
(IIBB1),



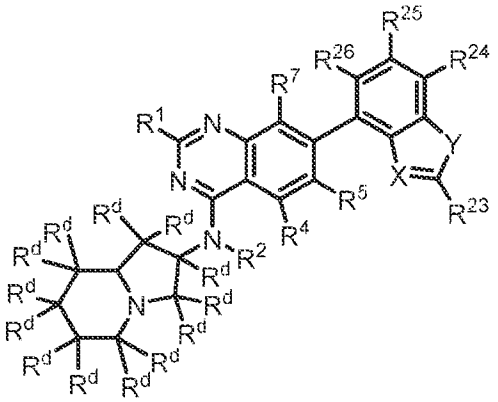
(IICC1),



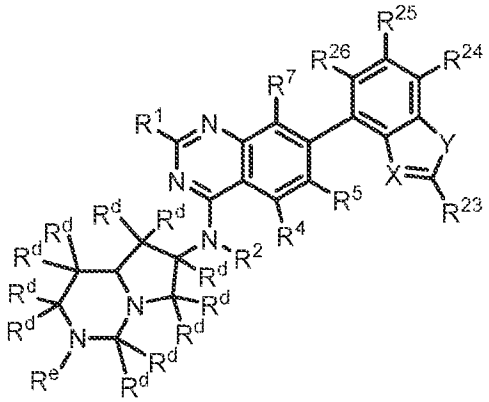
(IIDD1),



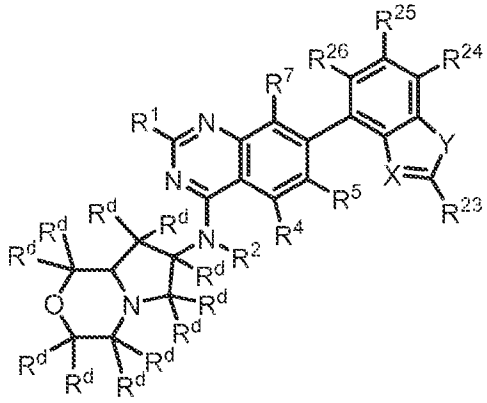
(IIEE1),



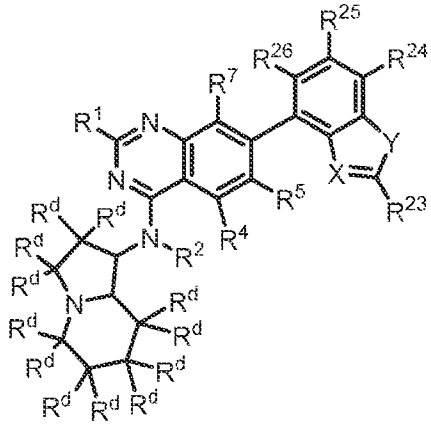
(IIFF1),



(IIGG1),



(IIHH1), and



(IIJJ1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e, if present, is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

299. The compound of any one of Embodiments 296-298, wherein X is C-CN, Y is S, and R^{23} is -$N(R^{12})_2$.

300. The compound of any one of Embodiments 296-299, wherein one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

301. The compound of any one of Embodiments 289-300, wherein R^e is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{20}.

302. The compound of any one of Embodiments 289-300, wherein R^e is -C(O)(3-6 membered carbocycle).

303. The compound of any one of Embodiments 289-300, wherein R^e is selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), and -C(O)O(C_{1-6}alkyl), wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

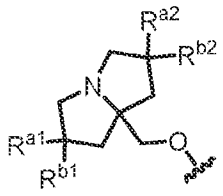
304. The compound of any one of Embodiments 289-303, wherein each R^d is H.

305. The compound of any one of Embodiments 275-304, wherein R^2 is H.

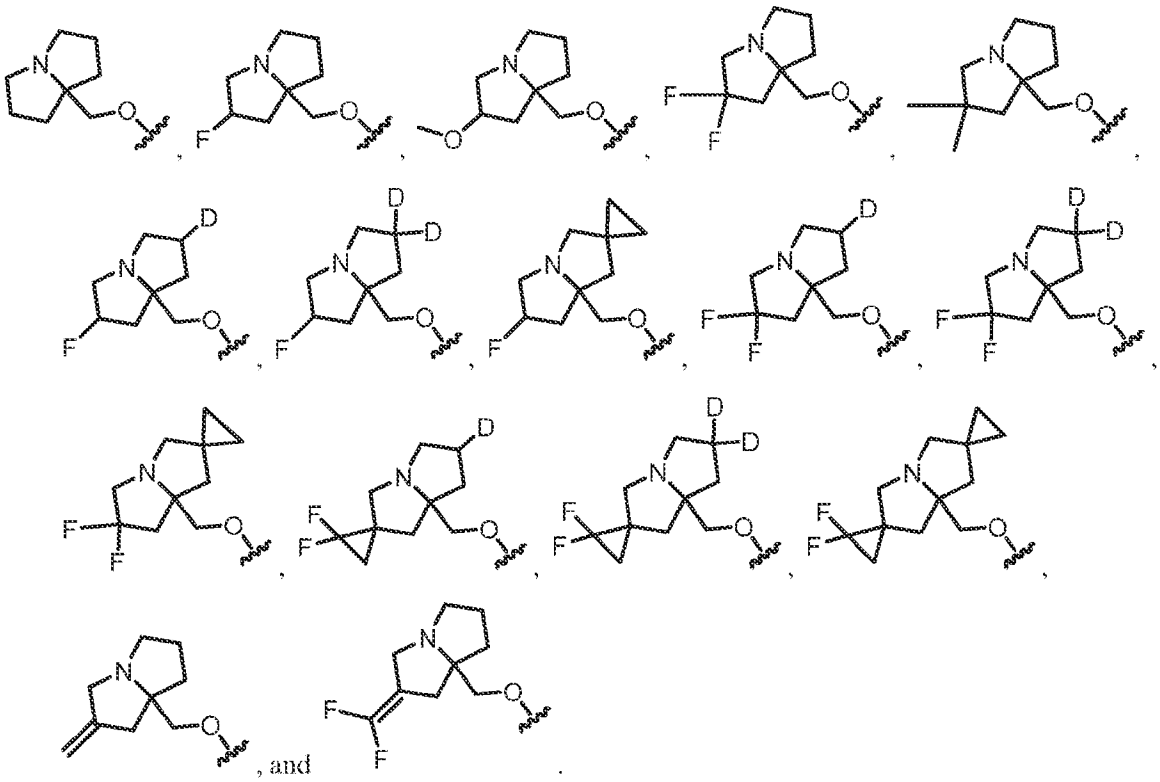
306. The compound of any one of Embodiments 275-305, wherein R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}.

307. The compound of Embodiment 306, wherein R^2 is selected from C_{1-2}alkyl.

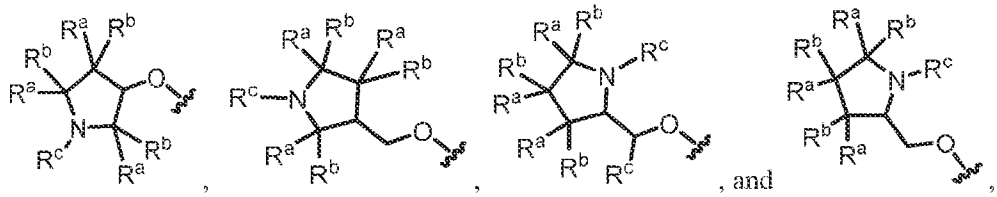
308. The compound of any one of Embodiments 275, 276, and 278-307, wherein R^1 is selected from -OR^8.

309. The compound of Embodiment 308, wherein R^1 is selected from:  , wherein R^{a1}, R^{a2}, R^{b1}, and R^{b2} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, -OR^{12}, and H, wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}.

310. The compound of Embodiment 309, wherein R^1 is selected from:

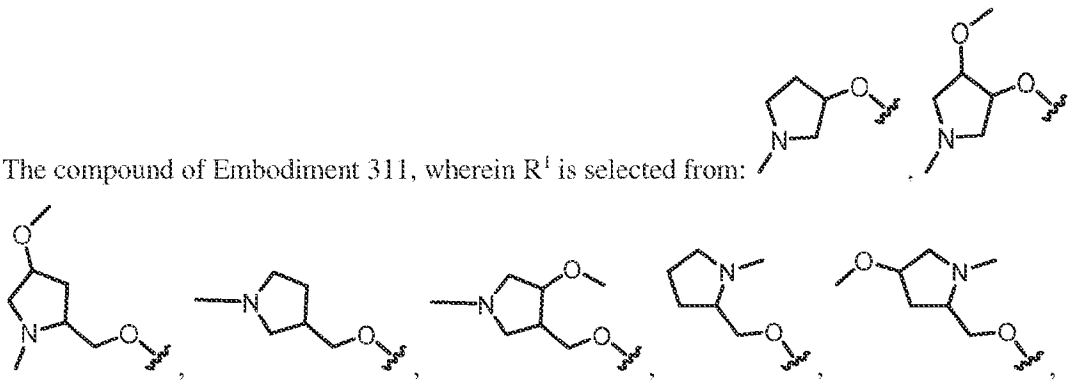


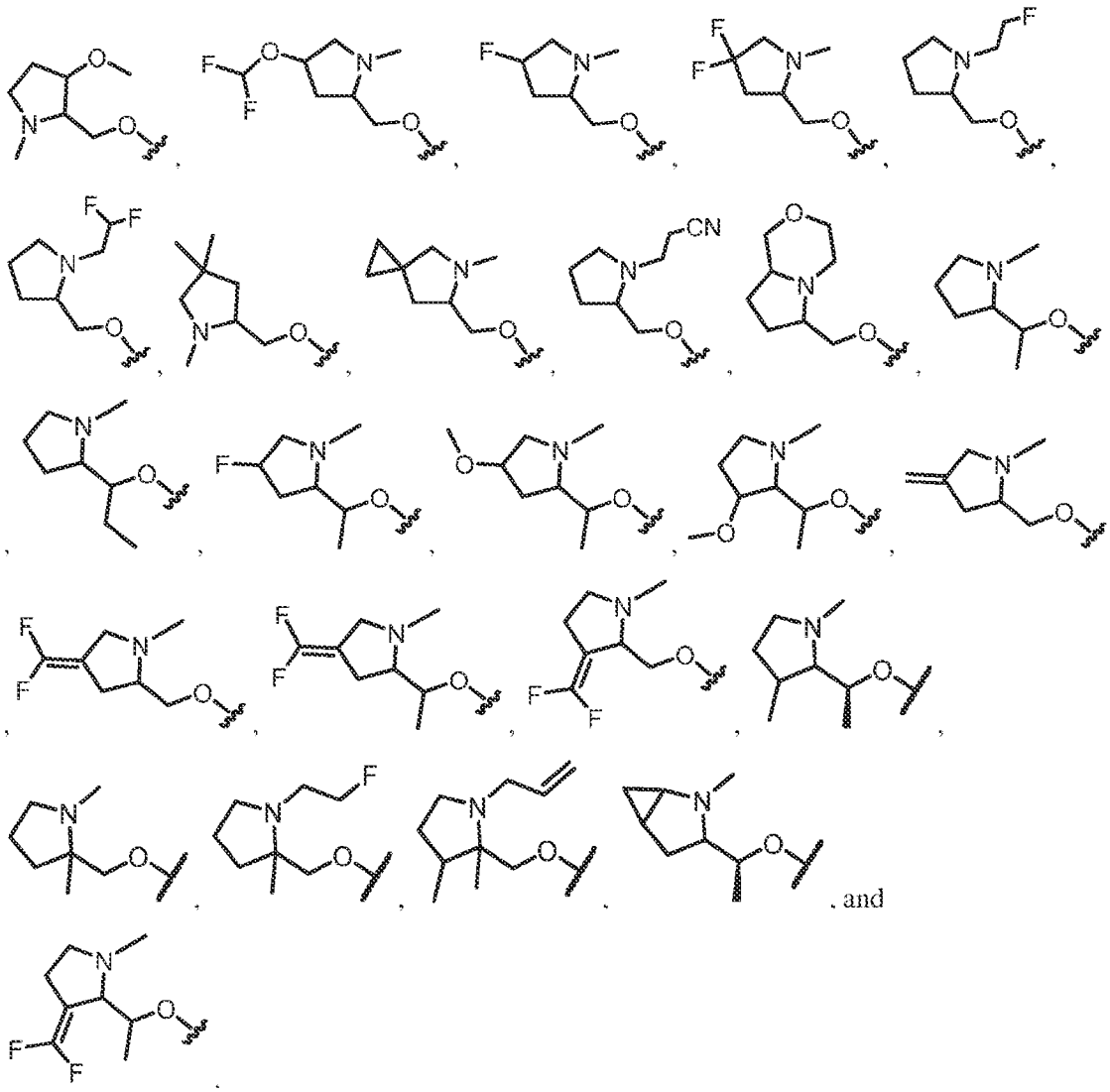
311. The compound of Embodiment 308, wherein R^1 is selected from:



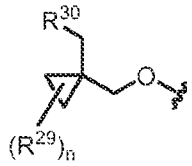
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H; and each R^c is independently selected from C_{1-6} alkyl and H, wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

312. The compound of Embodiment 311, wherein R^1 is selected from:





313. The compound of any one of Embodiments 275, 276, and 278-307, wherein R^1 is selected from



, wherein:

each R^{28} is independently selected from C_{1-6}alkyl and halogen; and

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

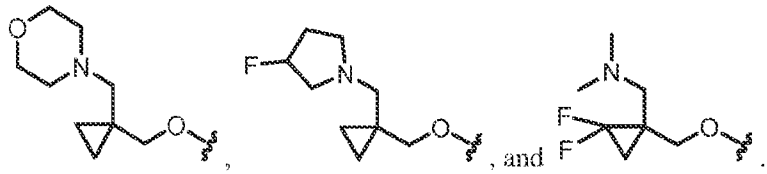
R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; and

n is 0-2.

314. The compound of Embodiment 313, wherein R^{30} is $N(R^{14})_2$.

315. The compound of Embodiment 313 or 314, wherein at least one R^{29} is a halogen such as F.

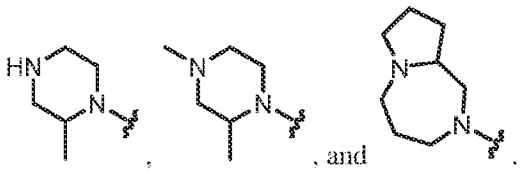
316. The compound of any one of Embodiments 313-315, wherein R^1 is selected from:



317. The compound of any one of Embodiments 275-307, wherein R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

318. The compound of Embodiment 317, wherein R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

319. The compound of Embodiment 317 or 318, wherein R^1 is selected from:



320. The compound of any one of Embodiments 275, 276, and 278-307, wherein R^1 is H.

321. The compound of any one of Embodiments 275, 276, and 278-320, wherein R^5 is a halogen (e.g., F or Cl).

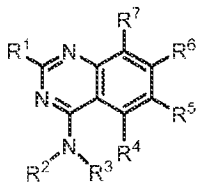
322. The compound of any one of Embodiments 275, 276, and 278-320, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

323. The compound of Embodiment 322, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

324. The compound of Embodiment 323, wherein R^5 is $-CF_3$.

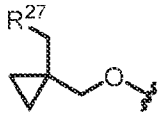
325. The compound of any one of Embodiments 275-324, wherein the compound is a not a compound included in Table 1.

326. A compound represented by Formula IV:



(IV)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from $-OR^8$ and  ;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from C_{1-6}alkyl that is substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

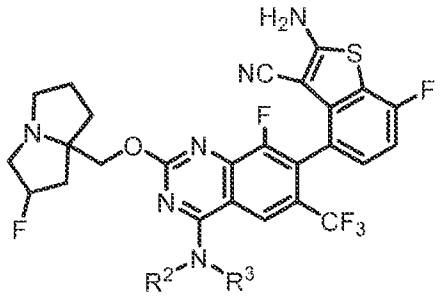
each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, and halogen;

R^{27} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen; and

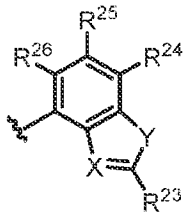
R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle.

327. The compound of Embodiment 326, wherein the compound is of Formula IV-a:



(IV-a)

or a salt (e.g., pharmaceutically acceptable salt) thereof.



328. The compound of Embodiment 1326, wherein R^6 is selected from: , wherein:

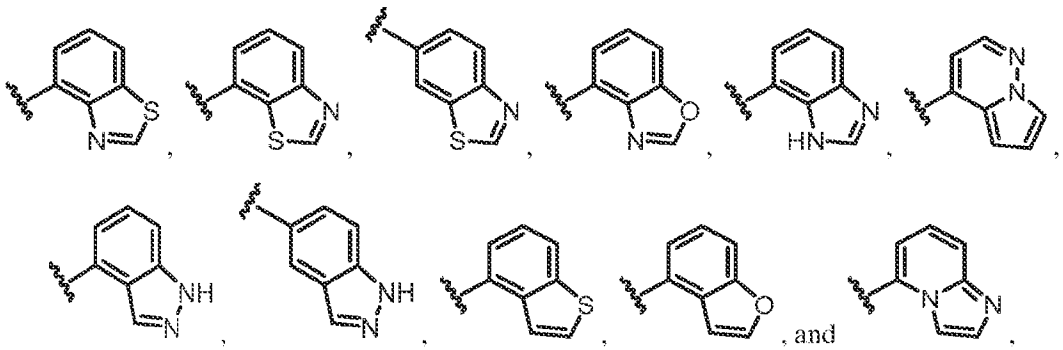
X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

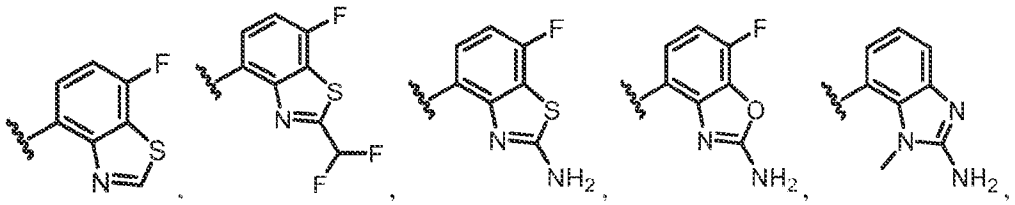
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

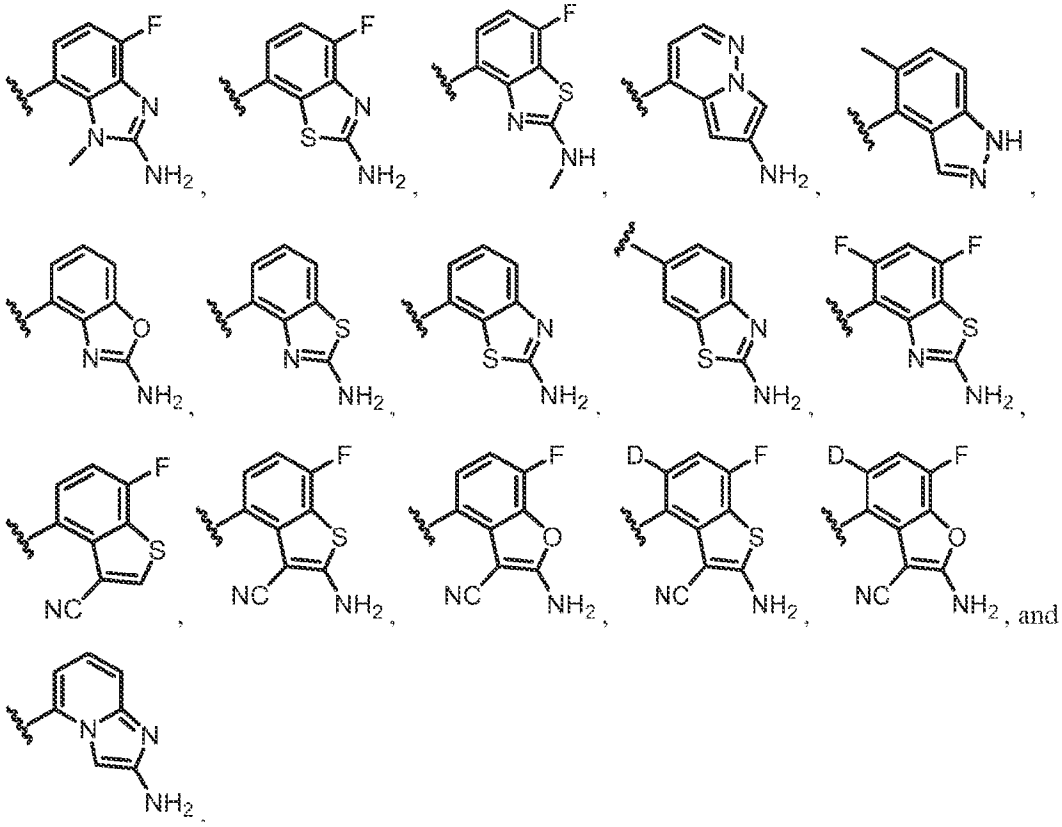
329. The compound of Embodiment 326 or Embodiment 328, wherein R^6 is selected from:



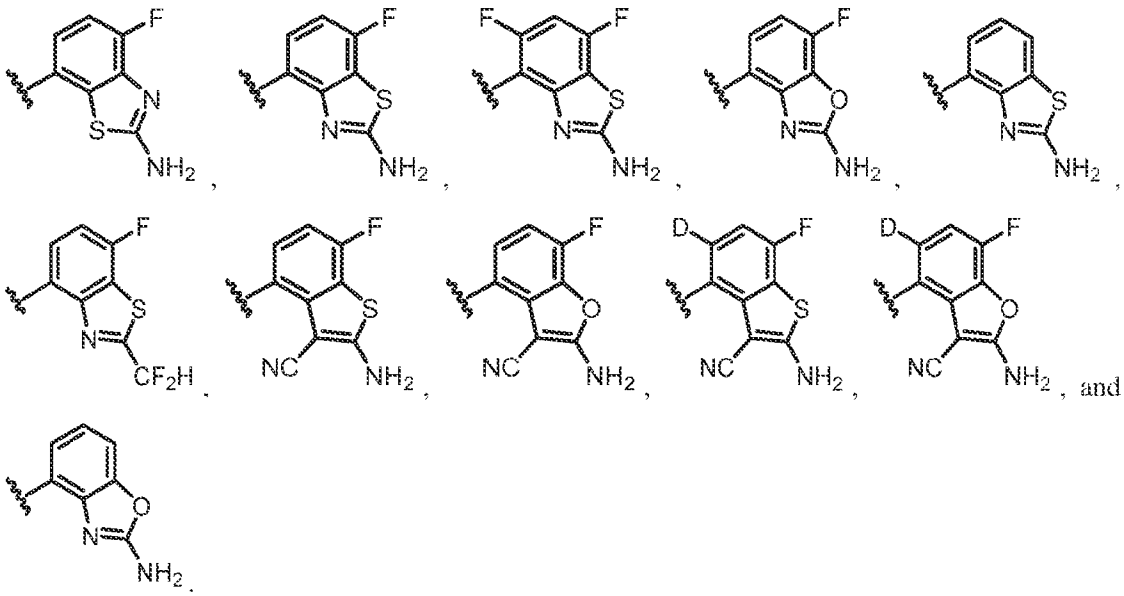
any of which is substituted with one or more R^{15}.

330. The compound of any one of Embodiments 326, and 328-329, wherein R^6 is selected from:

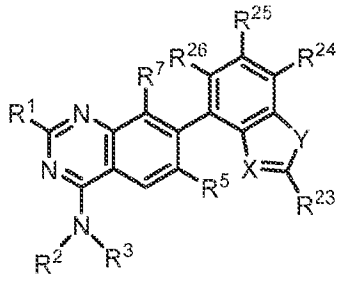




331. The compound of any one of Embodiments 326, and 328-330, wherein R^6 is selected from:



332. The compound of Embodiment 326, wherein the compound is a compound according to Formula IVB:



(IVB),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

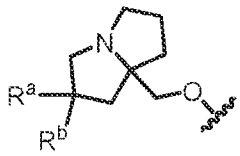
X is selected from N and C-CN;

Y is selected from O and S;

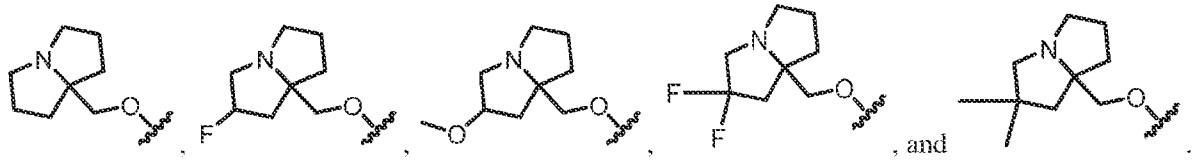
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

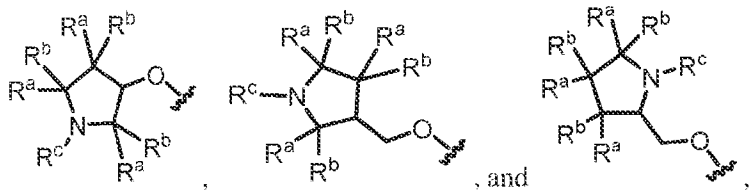
333. The compound of any one of Embodiments 326, and 328-332, wherein R^1 is selected from $-OR^8$.

334. The compound of Embodiment 333, wherein R^1 is selected from:  , wherein R^a and R^b are each independently selected from halogen, C_{1-6}alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}.

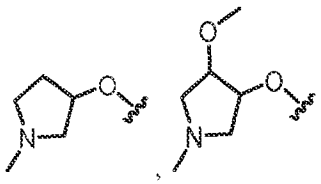
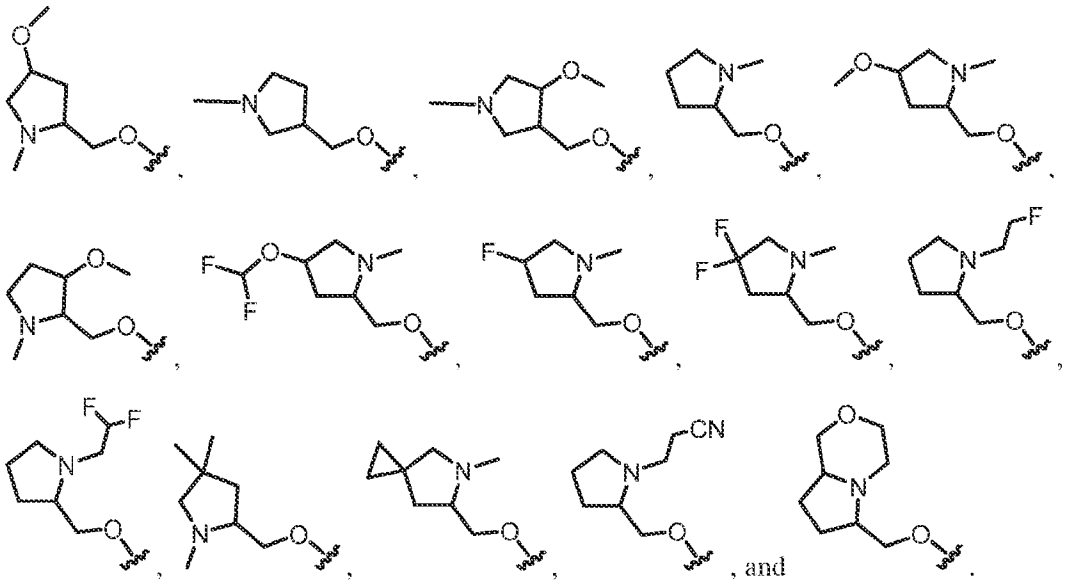
335. The compound of Embodiment 334, wherein R^1 is selected from:



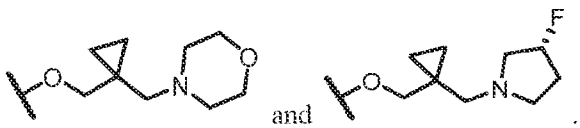
336. The compound of Embodiment 333, wherein R^1 is selected from:



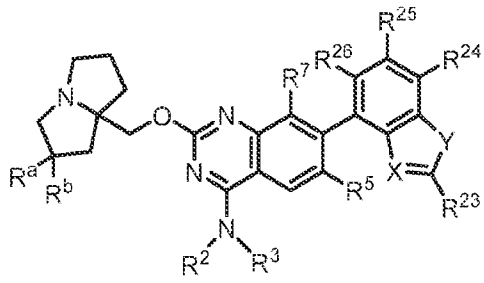
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and R^c is selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle.

337. The compound of Embodiment 336, wherein R^1 is selected from:  ,  , and .

338. The compound of any one of Embodiments 326, and 328-332, wherein R^1 is selected from

 and .

339. The compound of Embodiment 326, wherein the compound is a compound according to Formula IVC:



(IVC),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -N(R^{12})$_2$, C_{1-6}alkyl, and C_{1-6}alkyl-N(R^{14})$_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, -OR^{12}, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

340. The compound of Embodiment 339, wherein R^a is a halogen (e.g., F).

341. The compound of Embodiment 339 or 340, wherein R^b is H.

342. The compound of any one of Embodiments 332-341, wherein X is C-CN, Y is S, and R^{23} is selected from -N(R^{12})$_2$.

343. The compound of any one of Embodiments 332-342, wherein at least one of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

344. The compound of any one of Embodiments 326-343, wherein R^3 is selected from C_{1-3}alkyl that is substituted with one or more R^{10}.

345. The compound of Embodiment 344, wherein each R^{10} is independently selected from 3-6 membered heterocycle and a 5-6 membered heteroaryl, wherein any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13}.

346. The compound of Embodiment 345, wherein each R^{10} is independently selected from thiazole, oxazole, isoxazole, isothiazole, pyrazole, and pyridine, any of which is unsubstituted or substituted with one or more R^{12}, or R^{13}.

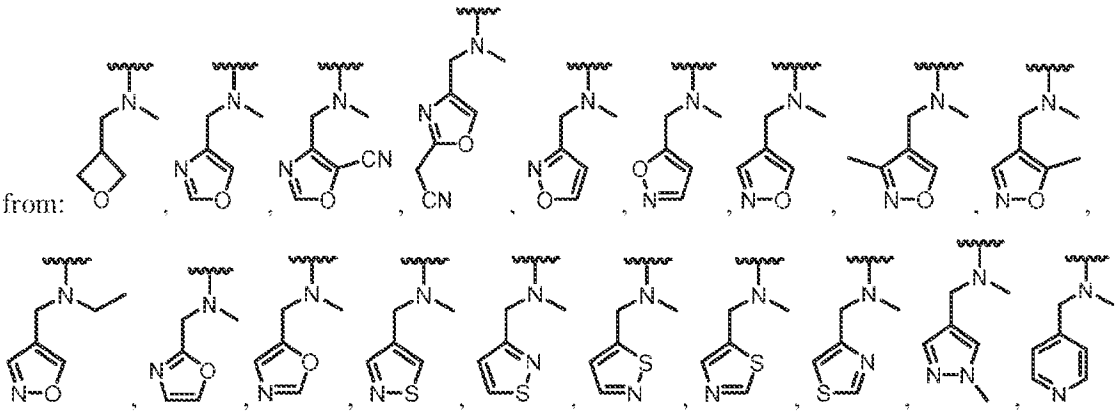
347. The compound of any one of Embodiments 326-346, wherein R^2 is H.

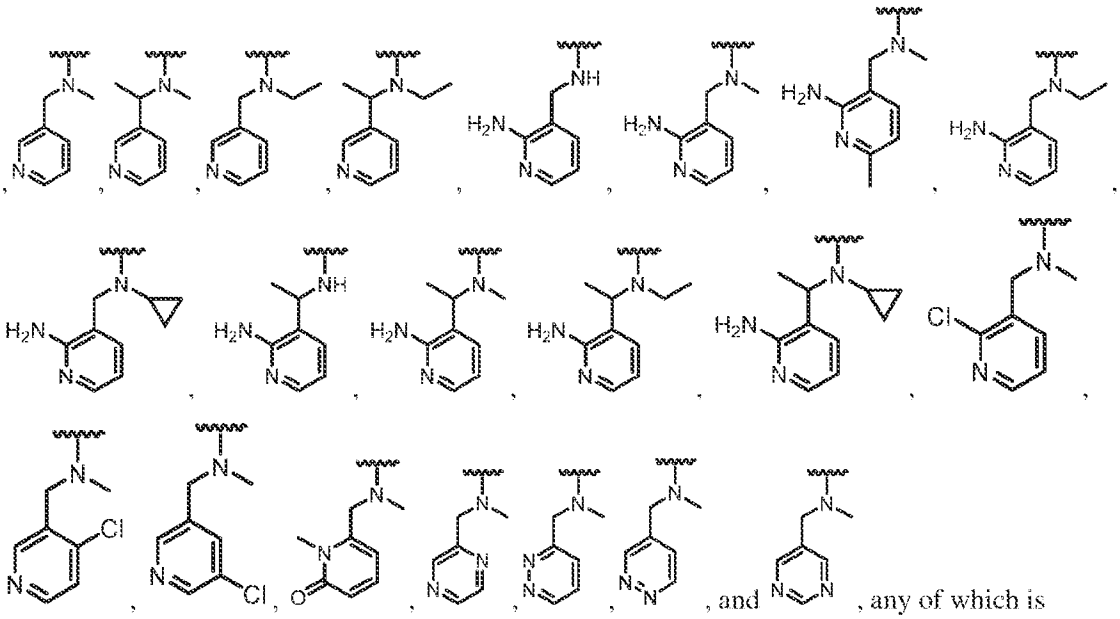
348. The compound of any one of Embodiments 326-346, wherein R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}.

349. The compound of Embodiment 348, wherein R^2 is selected from C_{1-2}alkyl that is unsubstituted.

350. The compound of any one of Embodiments 326-346, wherein R^2 is a 3-6 membered carbocycle.

351. The compound of any one of Embodiments 326-343, wherein the moiety is selected from:





optionally further substituted with one or more R^{10}.

352. The compound of any one of Embodiments 326, and 328-351, wherein R^5 is a halogen (e.g., F or Cl).

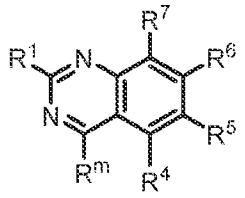
353. The compound of any one of Embodiments 326, and 328-351, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

354. The compound of Embodiment 353, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

355. The compound of Embodiment 354, wherein R^5 is $-CF_3$.

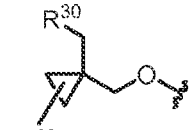
356. The compound of any one of Embodiments 326, and 328-355, wherein R^7 is F.

357. A compound represented by Formula V':



(V')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^m is selected from hydrogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

n is 0-2;

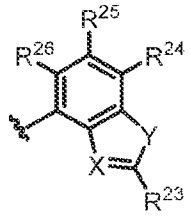
each R^{31} is selected from C_{1-6} alkyl; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

358. The compound of Embodiment 357, wherein R^m is hydrogen.

359. The compound of Embodiment 357, wherein R^m is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

360. The compound of Embodiment 359, wherein R^m is methyl that is unsubstituted.



361. The compound of any one of Embodiments 357-360, wherein R^6 is , wherein:

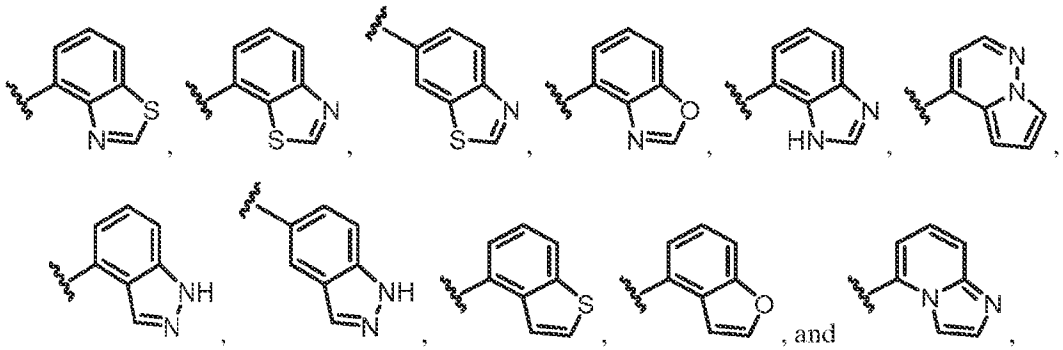
X is selected from N and C-CN;

Y is selected from O and S;

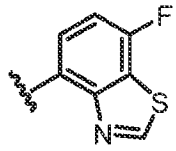
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

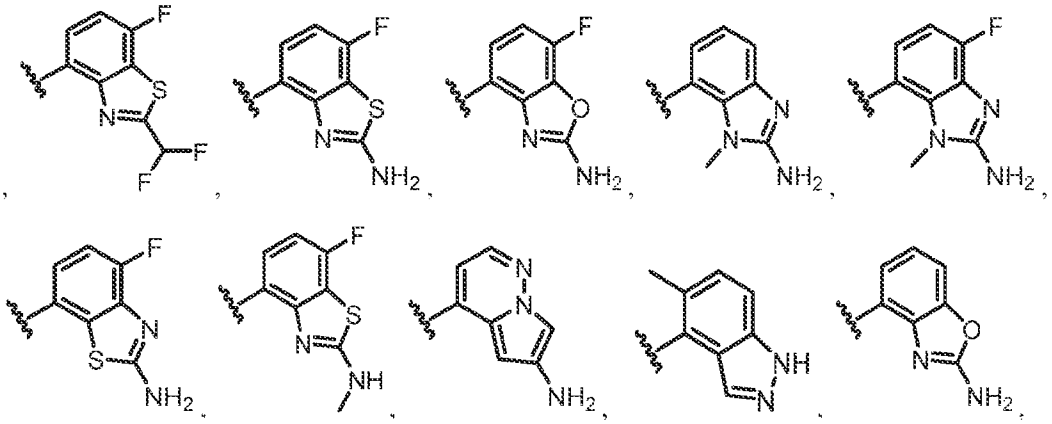
362. The compound of any one of Embodiments 357-361, wherein R^6 is selected from:

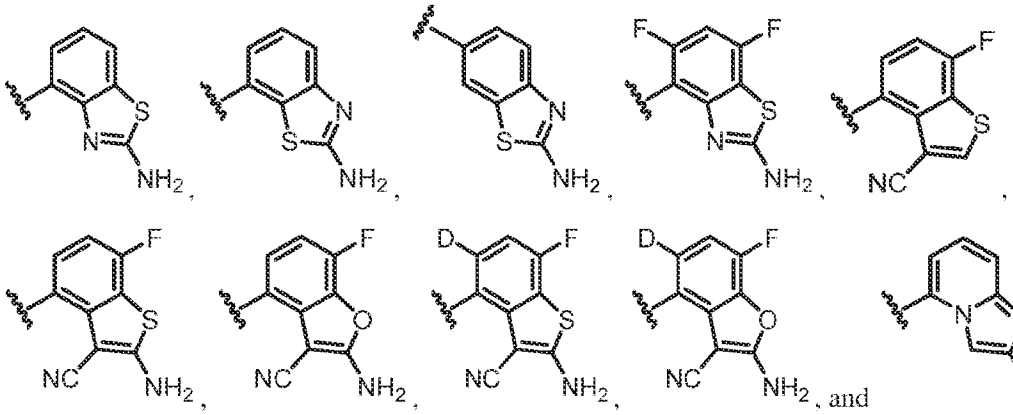


any of which is substituted with one or more R^{15}.

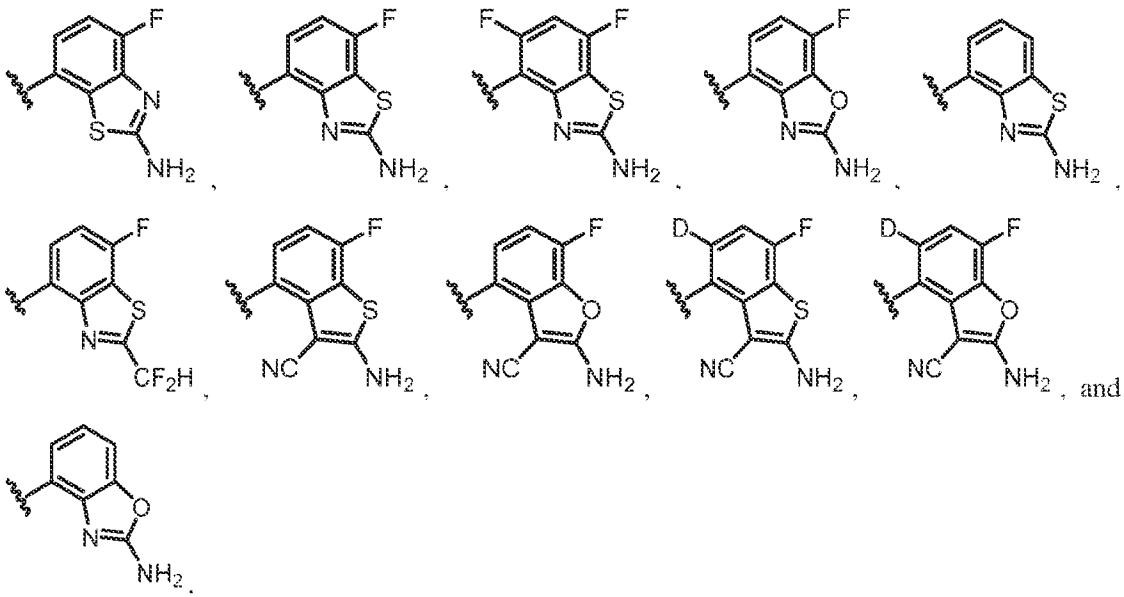


363. The compound of any one of Embodiments 357-362, wherein R^6 is selected from:

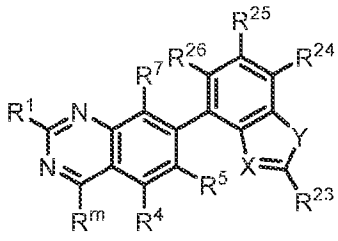




364. The compound of any one of Embodiments 357-363, wherein R^6 is selected from:



365. The compound of any one of Embodiments 357-361, wherein the compound is a compound of Formula VC':



(VC')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

X is selected from N and C-CN;

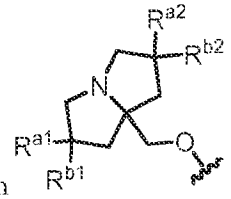
Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

366. The compound of any one of Embodiments 361-365, wherein X is C-CN, Y is S, R^{23} is $-N(R^{12})_2$, and one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

367. The compound of any one of Embodiments 357-366, wherein R^1 is selected from $-OR^8$.

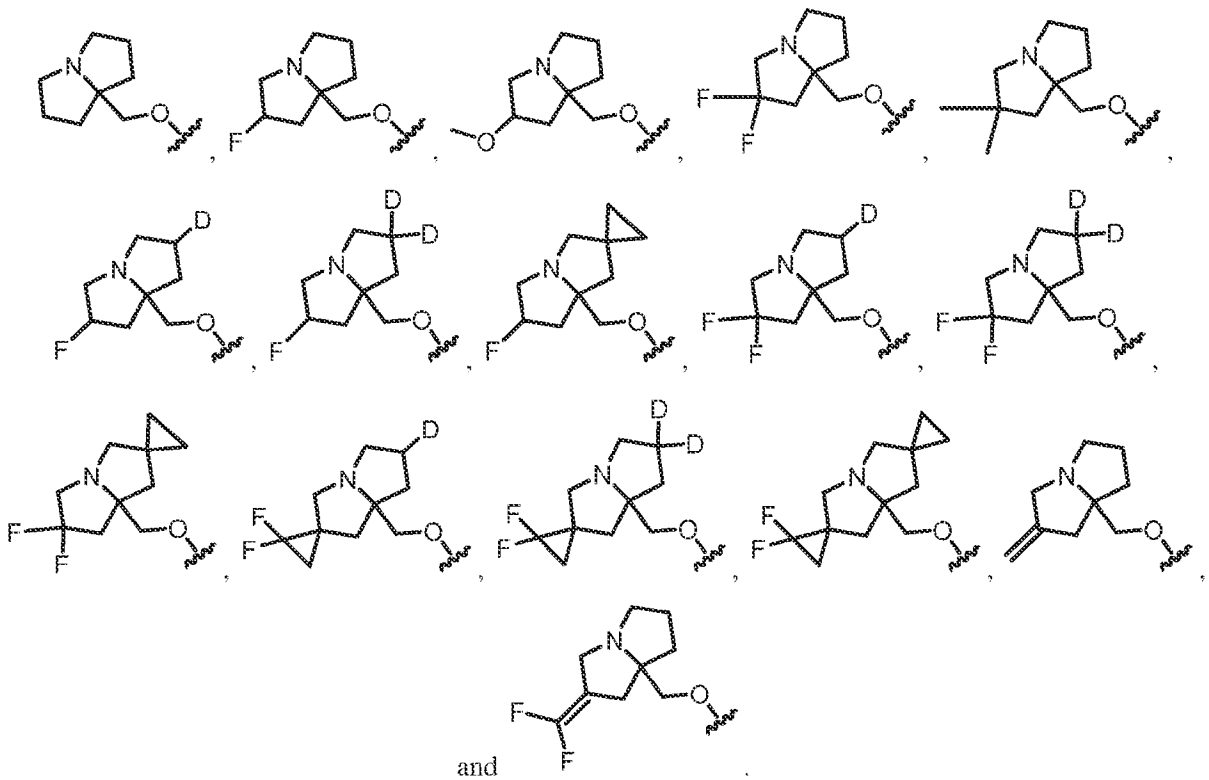
368. The compound of Embodiment 367, wherein R^1 is selected from  , wherein:

R^{a1}, R^{a2}, R^{b1}, and R^b are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H or are absent,

wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and

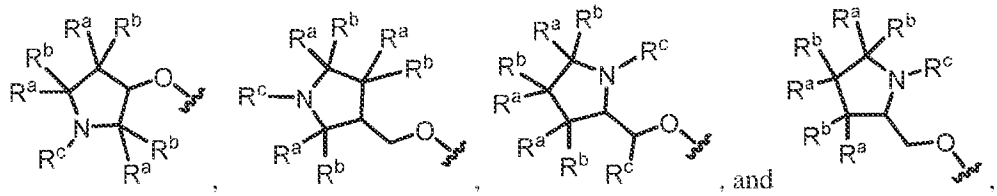
wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}.

369. The compound of Embodiment 368, wherein R^1 is selected from:



and .

370. The compound of Embodiment 367, wherein R^1 is selected from:

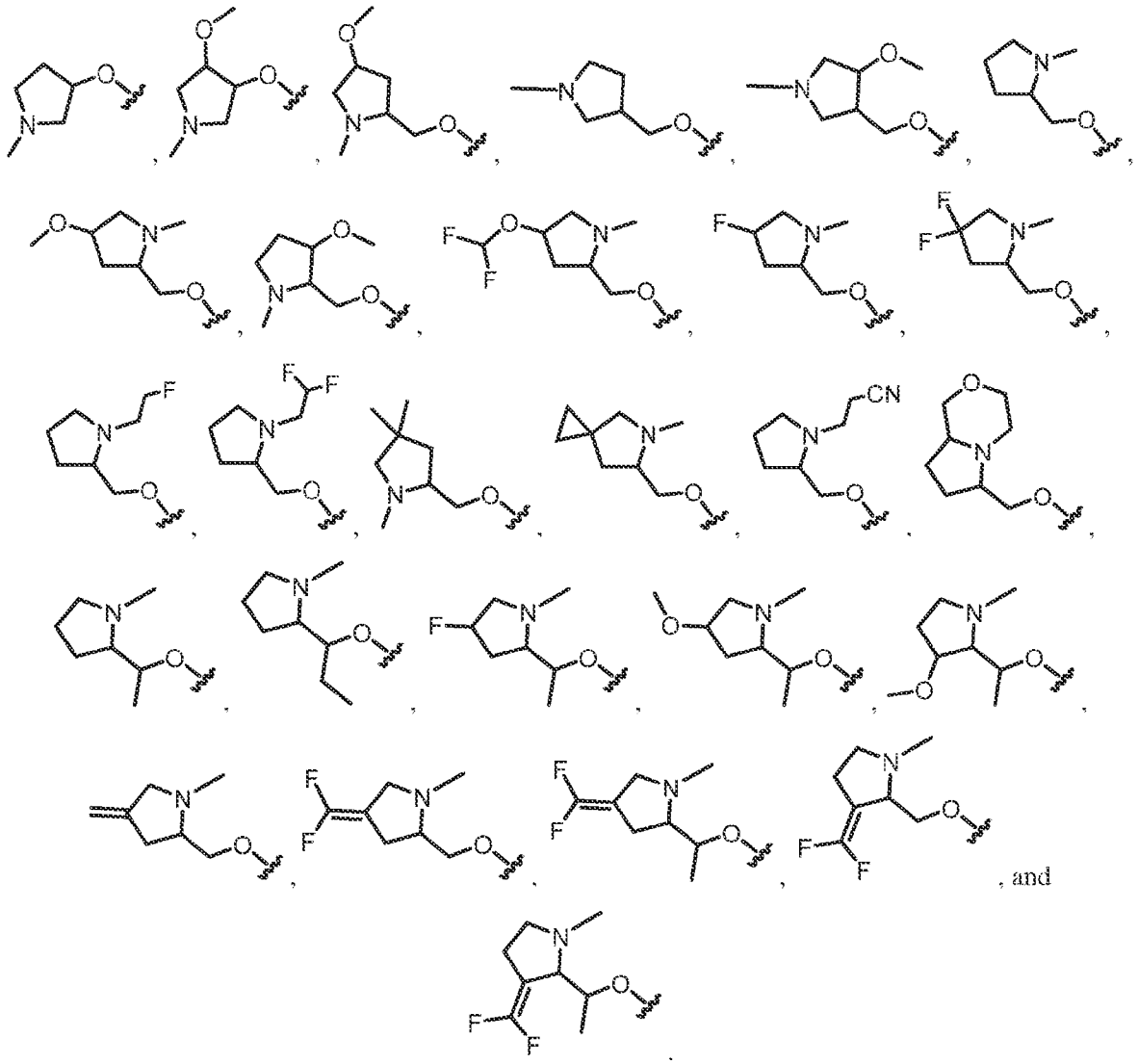


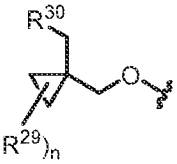
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H; and each R^c is independently selected from H and C_{1-6} alkyl,

wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and

wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

371. The compound of Embodiment 370, wherein R^1 is selected from:



372. The compound of any one of Embodiments 357-366, wherein R^1 is selected from  , wherein:

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

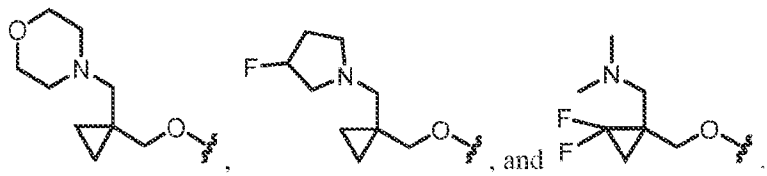
R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; and

n is 0-2.

373. The compound of Embodiment 372, wherein R^{30} is $N(R^{14})_2$.

374. The compound of Embodiment 372 or 373, wherein at least one R^{29} is a halogen such as F.

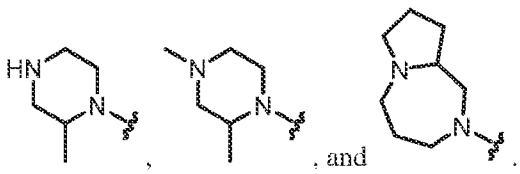
375. The compound of any one of Embodiments 372-374, wherein R^1 is selected from:



376. The compound of any one of Embodiments 357-366, wherein R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

377. The compound of Embodiment 376, wherein R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

378. The compound of Embodiment 377, wherein R^1 is selected from:



379. The compound of any one of Embodiments 357-378, wherein R^5 is a halogen (e.g., F or Cl).

380. The compound of any one of Embodiments 357-378, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

381. The compound of Embodiment 380, wherein R^5 is selected from C_{1-6}alkyl that is substituted with one or more halogens or -CN.

382. The compound of Embodiment 381, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

383. The compound of Embodiment 382, wherein R^5 is $-CF_3$.

384. The compound of any one of Embodiments 357-383, wherein R^7 is F.

385. A compound shown in Table 3 or Table 3a, or a salt (e.g., pharmaceutically acceptable salt) thereof.

386. A pharmaceutical composition comprising a compound of any one of Embodiments 222-384, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable excipient.

387. A compound of any one of Embodiments 222-384, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use as a medicament.

388. The compound of Embodiment 387, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

389. The compound of Embodiment 388, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

390. The compound of Embodiment 388, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

391. The compound of any one of Embodiments 387-390, wherein the medicament is useful in the prevention or treatment of a cancer.

392. The compound of Embodiment 391, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

393. A compound of any one of Embodiments 222-385, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the treatment of a disease, disorder, or condition.

394. The compound of Embodiment 393, wherein the disease, disorder, or condition is a cancer.

395. The compound of Embodiment 394, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

396. The compound of any one of Embodiments 393-395, wherein the compound is used in the treatment of a disease, disorder, or condition in a subject in need thereof.

397. A compound of any one of Embodiments 222-385, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the manufacture of a medicament.

398. The compound of Embodiment 397, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a

Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

399. The compound of Embodiment 398, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

400. The compound of Embodiment 398 or 399, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

401. The compound of any one of Embodiments 397-400, wherein the medicament is useful in the treatment of a cancer.

402. The compound of Embodiment 401, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

403. A method, comprising administering a therapeutically effective amount of a compound of any one of Embodiments 222-385, or a salt (e.g., pharmaceutically acceptable salt) thereof, to a subject in need thereof.

404. The method of Embodiment 403, wherein the subject has a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

405. The method of Embodiment 404, wherein the disease, disorder, or condition is ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

406. The method of Embodiment 404 or 405, wherein the disease, disorder, or condition is ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

407. The method of any one of Embodiments 403-406, wherein the subject has a cancer.

408. The method of Embodiment 407, wherein the subject was previously diagnosed with the cancer.

409. The method of Embodiment 407 or 408, wherein the subject has previously undergone a treatment regimen for the cancer.

410. The method of any one of Embodiments 407-409, wherein the subject has previously entered remission from the cancer.

411. The method of any one of Embodiments 407-410, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

412. The method of any one of Embodiments 403-411, wherein the compound, or the salt thereof, is administered in combination with an additional therapeutic agent.

413. The use of a compound of any one of Embodiments 222-385, or a salt (e.g., pharmaceutically acceptable salt) thereof, for the manufacture of a medicament for the treatment of a cancer.

414. The use of Embodiment 413, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

415. A method, comprising contacting a KRAS protein with a compound of any one of Embodiments 222-385, or a salt (e.g., pharmaceutically acceptable salt) thereof.

416. The method of Embodiment 415, wherein contacting the KRAS protein with the compound modulates KRAS.

417. The method of Embodiment 415 or 416, wherein the KRAS protein has a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation.

418. The method of Embodiment 415 or 416, wherein the KRAS protein is a wild-type KRAS protein, including wild-type amplified KRAS.

419. The method of any one of Embodiments 415-418, wherein the KRAS protein is in an active (GTP-bound) state.

420. The method of any one of Embodiments 415-418, wherein the KRAS protein is in an inactive (GDP-bound) state.

421. The method of any one of Embodiments 415-420, wherein the KRAS protein is located within a cell.

422. The method of Embodiment 421, wherein the cell is located within a subject.

423. The method of Embodiment 422, wherein the subject is a human.

424. The method of Embodiment 422 or 423, wherein the subject has a cancer.

425. The method of Embodiment 424, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

426. A method of inhibiting the function of a wild-type KRAS protein, including wild-type amplified KRAS, or a KRAS protein having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, comprising contacting the KRAS protein with a compound of any one of Embodiments 222-385, or a salt (e.g., pharmaceutically acceptable salt) thereof.

427. The method of Embodiment 426, wherein the KRAS protein is a wild-type KRAS protein, including wild-type amplified KRAS.

428. The method of Embodiment 426, wherein the KRAS protein has a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation.

429. The method of Embodiment 428, wherein the KRAS protein has a G12D, G12V, or G12R mutation.

430. The method of any one of Embodiments 426-429, wherein the KRAS protein is in an active (GTP-bound) state.

431. The method of any one of Embodiments 426-429, wherein the KRAS protein is in an inactive (GDP-bound) state.

432. The method of any one of Embodiments 426-431, wherein the KRAS protein is located within a cell.

433. The method of Embodiment 432, wherein the cell is located within a subject.

434. The method of Embodiment 433, wherein the subject is a human.

435. The method of Embodiment 433 or 434, wherein the subject has a cancer.

436. The method of Embodiment 435, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

437. A compound capable of inhibiting a wild-type KRAS protein, including wild-type amplified KRAS, or a KRAS protein having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation in both its active (GTP-bound) and inactive (GDP-bound) state.

438. The compound of Embodiment 437, wherein the compound:

(i) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, 1 μM< $IC_{50} \leq 10$ μM, or 10 μM< IC_{50} in the assay of Biological Example 1 (e.g., a protein:protein interaction (PPI) Homogenous Time Resolved Fluorescence (HTRF) analysis of 50 nM Avi-KRAS G12D (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12C (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12V (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS WT (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), and/or 75 nM 3xFLAG-RAF1 RBD (51-131)-Avi; and/or

(ii) has $IC_{50} \leq 0.1$ μM, or $IC_{50} > 0.1$ μM in the assay of Biological Example 2 or 4 (e.g., cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iii) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or $IC_{50} > 1$ μM in the assay of Biological Example 3 (cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iv) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or $IC_{50} > 1$ μM in the assay of Biological Example 4 (cell-based pERK HTRF assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080); and/or

(v) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or $IC_{50} > 1$ μM in the assay of Biological Example 5 (3D Cell viability assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080).

439. The compound of Embodiment 438, wherein the compound:

(i) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or 1 μM< $IC_{50} \leq 10$ μM in the assay of Biological Example 1 (e.g., a protein:protein interaction (PPI) Homogenous Time Resolved Fluorescence (HTRF) analysis of 50 nM Avi-KRAS G12D (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12C (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12V (amino acids 2-169)

GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS WT (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), and/or 75 nM 3xFLAG-RAF1 RBD (51-131)-Avi; and/or

(ii) has IC_{50} ≤0.1 μM in the assay of Biological Example 2 or 4 (e.g., cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iii) has IC_{50} ≤0.1 μM or 0.1 μM< IC_{50} ≤1 μM in the assay of Biological Example 3 (cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iv) has IC_{50} ≤0.1 μM or 0.1 μM< IC_{50} ≤1 μM in the assay of Biological Example 4 (cell-based pERK HTRF assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080); and/or

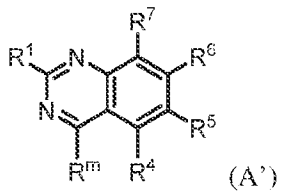
(v) has IC_{50} ≤0.1 μM or 0.1 μM< IC_{50} ≤1 μM in the assay of Biological Example 5 (3D Cell viability assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080).

440. The compound of any one of Embodiments 437-439, wherein the compound is capable of irreversibly binding the KRAS protein.

441. The compound of any one of Embodiments 437-439, wherein the compound is capable of reversibly binding the KRAS protein.

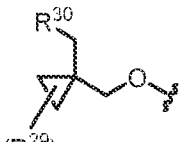
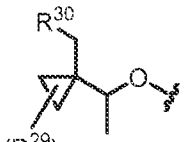
442. The compound of any one of Embodiments 437-441, wherein the compound is a compound according to any one of Embodiments 222-385.

443. A compound represented by Formula A:



(A')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from H, $-OR^8$,  ,  , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^m is selected from H and $-NR^2R^3$;

R^2 is selected from C_{1-6}alkyl which is optionally deuterated;

R^3 is selected from a C_{1-6}alkyl, 3- to 6-membered cycloalkyl optionally fused to a 5- or 6-membered heterocycle or heteroaryl, 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6

membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10}, or

R^2 and R^3, together with the atom they attach to, form a 4- to 10-membered heterocycle optionally substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, -N(R^{12})$_2$, and -CN;

each R^{20} is independently selected from =O, -CN, -CN, -OR^{12}, and halogen;

each R^{28} is independently selected from halogen,-OR^{12}, C_{1-6}alkyl, and C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13};

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

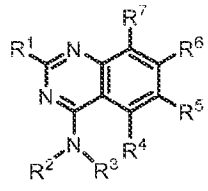
R^{30} is selected from -N(R^{12})$_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

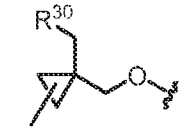
R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-4} alkenyl, , $-OR^{12}$, a 4- to 10-membered heterocycle, and a 4- to 10-membered aryl, wherein any 4- to 10-membered heterocycle or 4- to 10-membered aryl is optionally substituted with one or more R^{28}, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

444. The compound of Embodiment 443, wherein the compound is a compound represented by Formula B:



(B)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^2 is selected from C_{1-6}alkyl;

R^3 is selected from a 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl, wherein the heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered

heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, $-N(R^{12})_2$, and -CN;

each R^{20} is independently selected from =O, -CN, and halogen;

each R^{28} is independently selected from halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

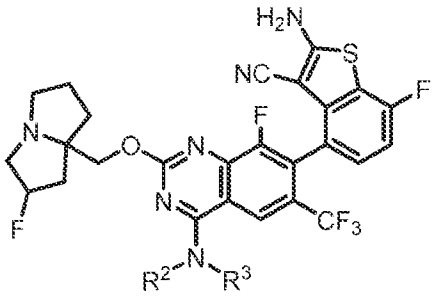
R^{30} is selected from $-N(R^{12})_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, C_{2-4} alkenyl, and $-OR^{12}$, wherein any C_{1-6}alkyl or C_{2-4} alkenyl is unsubstituted or is substituted with one or more R^{13}.

445. The compound of Embodiment 444, wherein the compound is of Formula B-a:



(B-a) or a salt (e.g., pharmaceutically acceptable salt) thereof.

446. The compound of any one of Embodiments 443-445, wherein R^3 is a 4-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N.

447. The compound of Embodiment 446, wherein R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

448. The compound of Embodiment 446, wherein R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10},

provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}.

449. The compound of any one of Embodiments 443-448, wherein R^3 is a pyrrolidine that is substituted with 0-4 R^{10}.

450. The compound of any one of Embodiments 443-448, wherein R^3 is a pyrrolidine that is substituted with 0-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}.

451. The compound of any one of Embodiments 443-448, wherein R^3 is a 4-6 membered heterocycle that is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, and each R^{10} is independently selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

452. The compound of any one of Embodiments 443-446, wherein R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N.

453. The compound of Embodiment 452, wherein R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

454. The compound of Embodiment 452 or 453, wherein R^3 is an 8-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

455. The compound of Embodiment 452 or 453, wherein R^3 is a 9-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

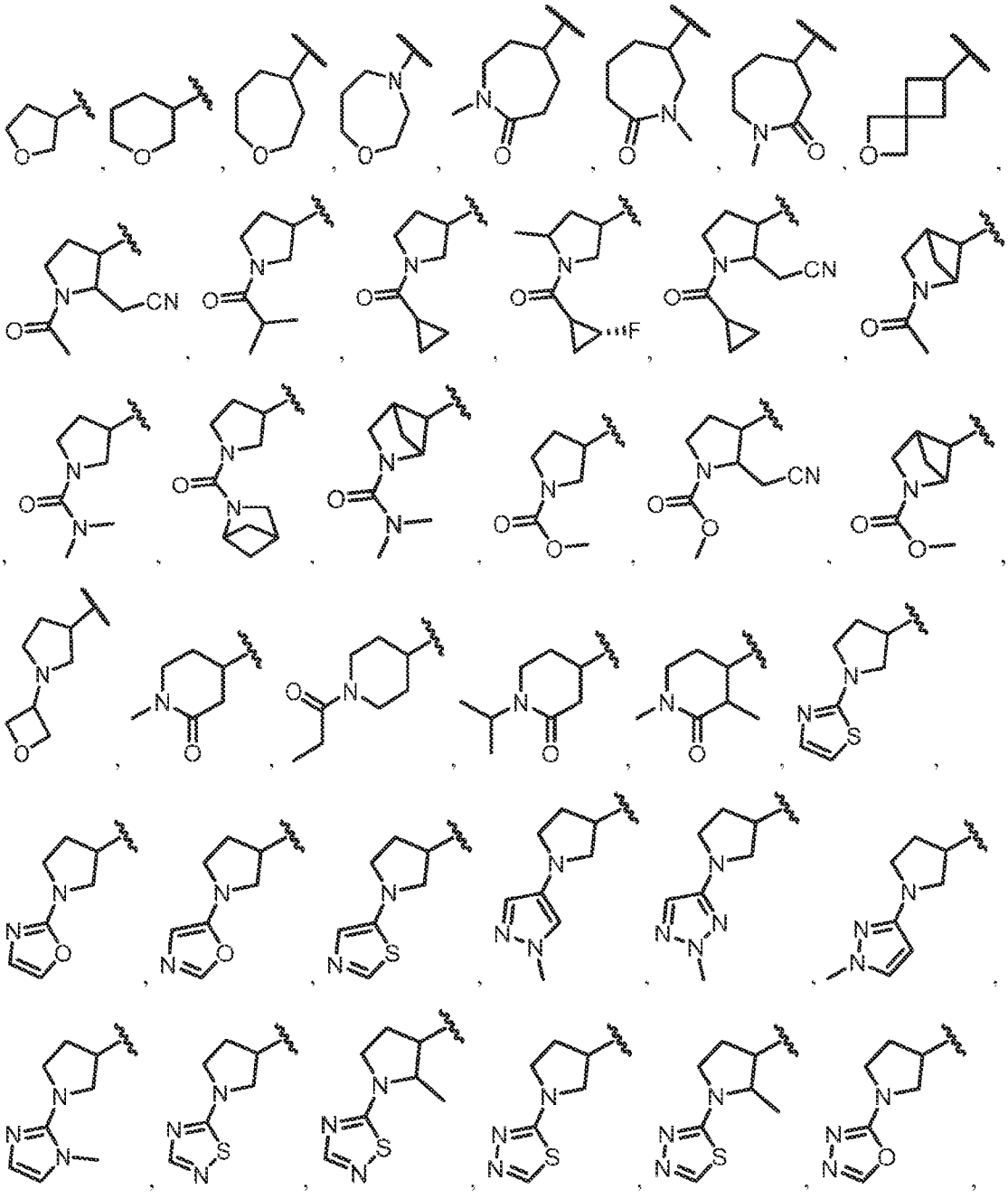
456. The compound of Embodiment 452 or 453, wherein R^3 is a 10-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

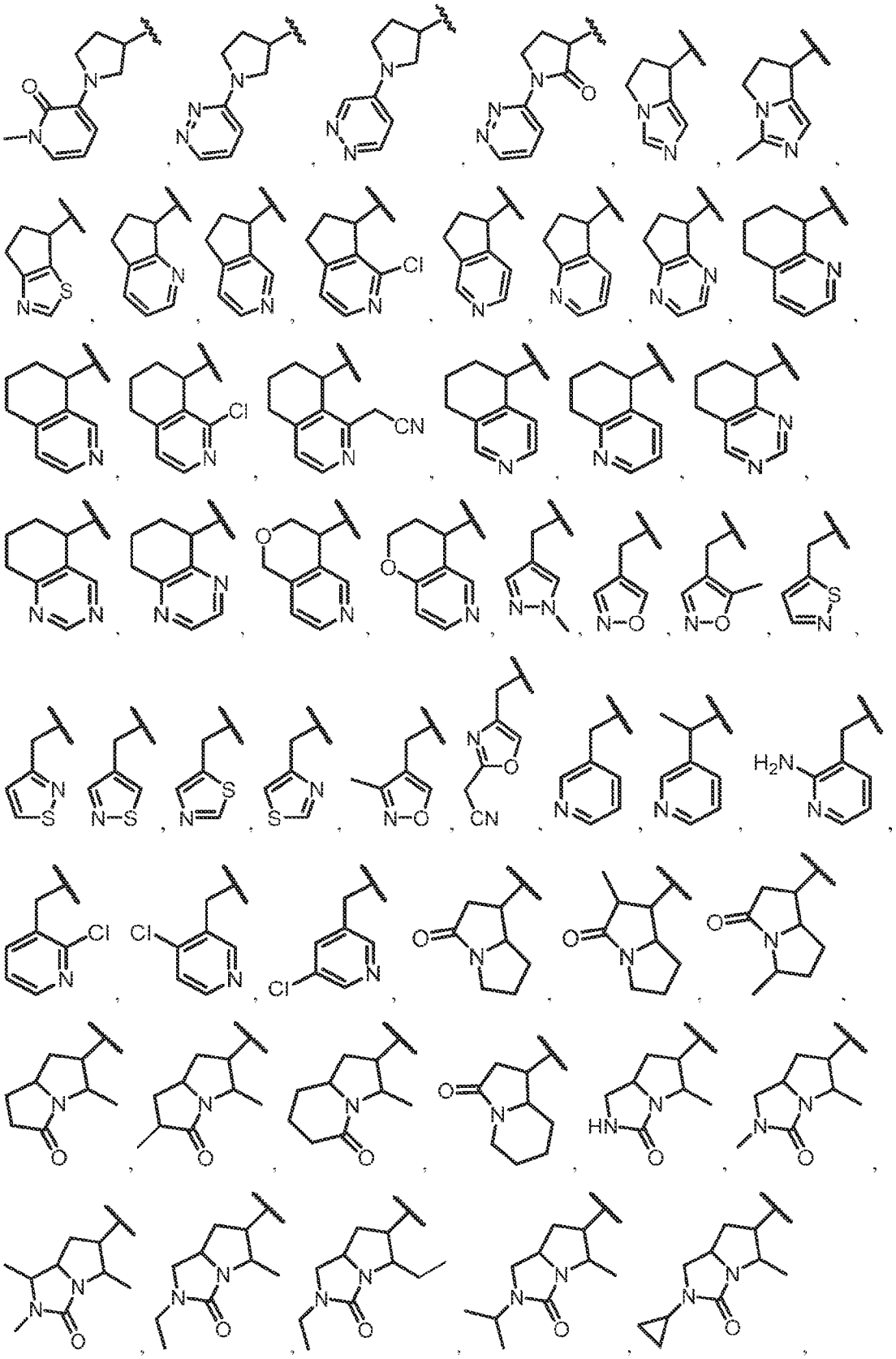
457. The compound of any one of Embodiments 454-456, wherein R^{10} is selected from =O, C_{1-6}alkyl, a 3-6 membered carbocycle, and halogen.

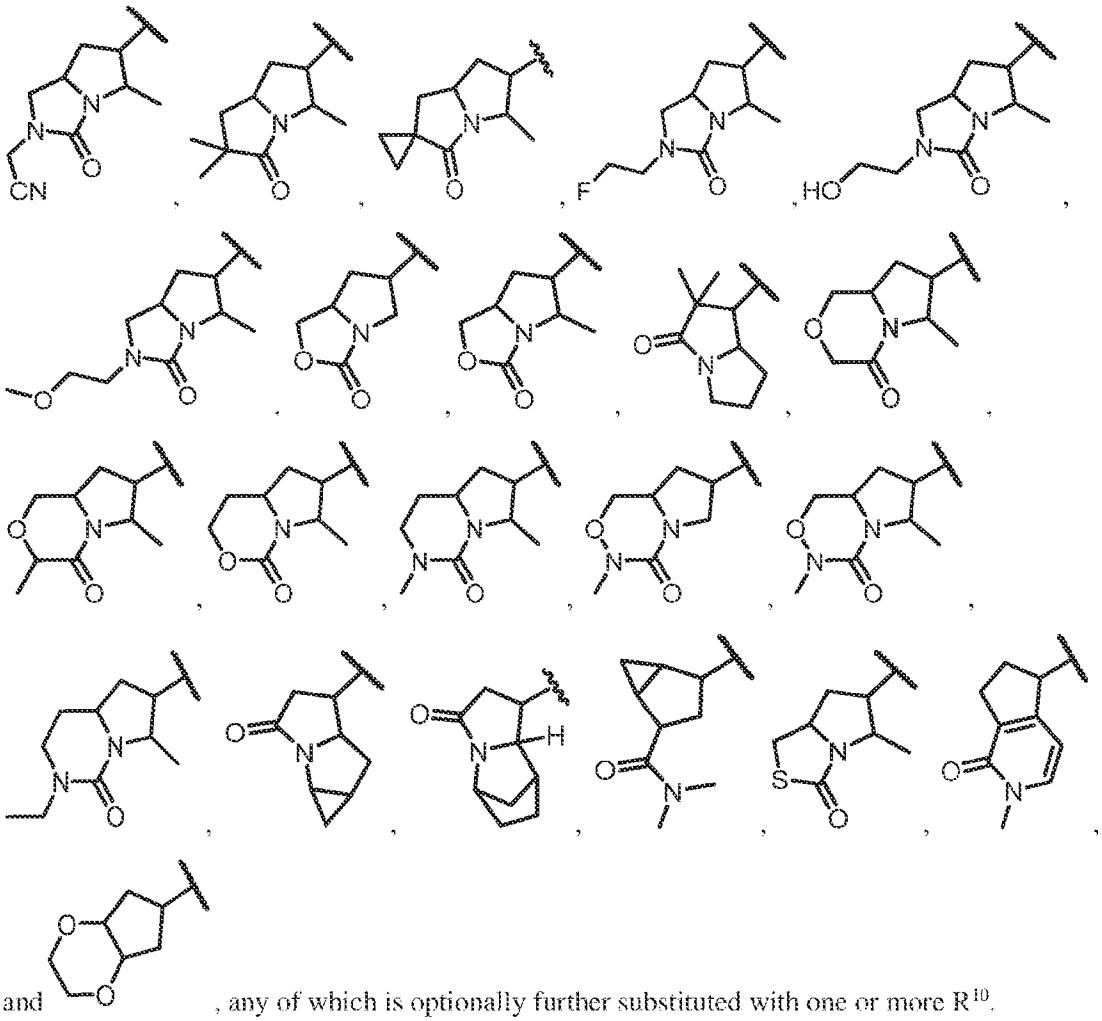
458. The compound of any one of Embodiments 443-445, wherein R^3 is -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}.

459. The compound of Embodiment 458, wherein R^3 is -CH_2(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}.

460. The compound of Embodiment 459, wherein R^{10} is selected from halogen and C_{1-6}alkyl, wherein the C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}.

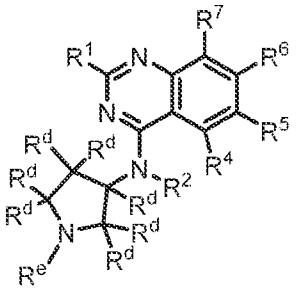
461. The compound of any one of Embodiments 443-460, wherein R^3 is selected from: $-CH_3$, , 



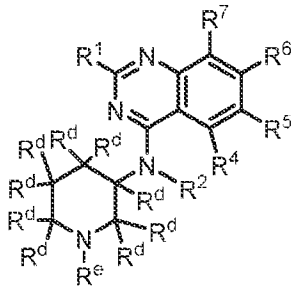


and , any of which is optionally further substituted with one or more R^{10}.

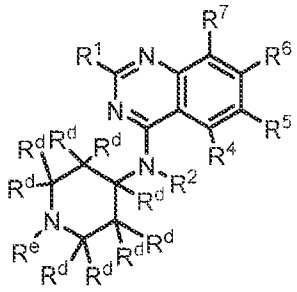
462. The compound of any one of Embodiments 443-461, wherein the compound is a compound according to Formula BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM:



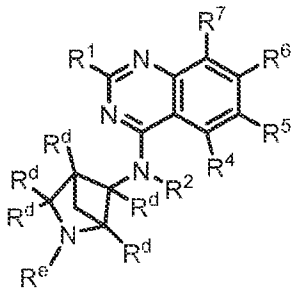
(BA),



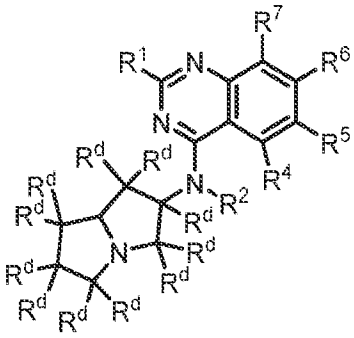
(BB),



(BC),



(BD),



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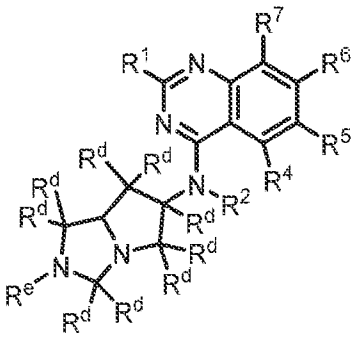

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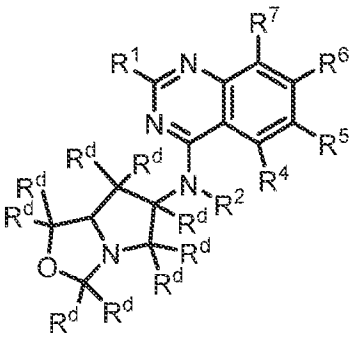
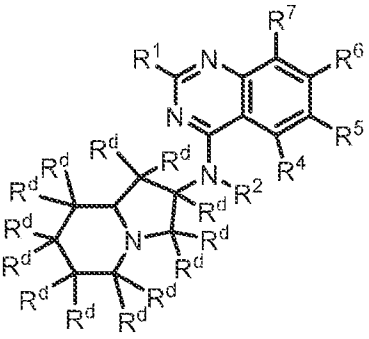
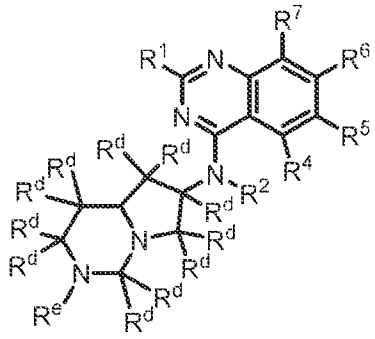


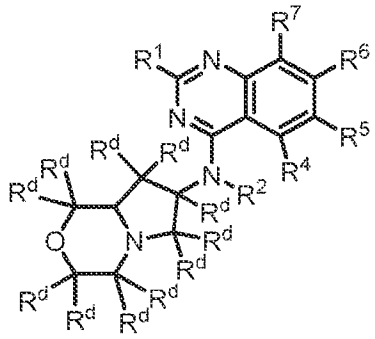
(BG),



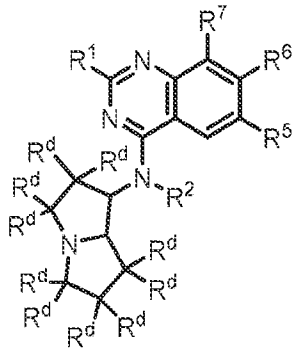
(BH),



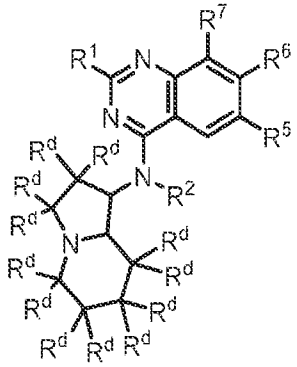
(BI),



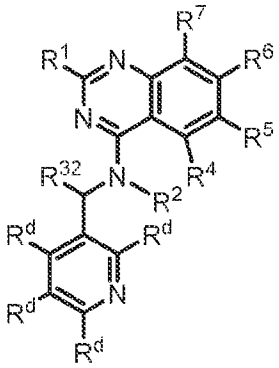
(BJ),



(BK),



(BL),



and (BM),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^{32}, if present, is selected from H and C_{1-5}alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}; and

R^e, if present, is selected from H, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

463. The compound of Embodiment 462, wherein the compound is a compound according to Formula BA, or a salt (e.g., pharmaceutically acceptable salt) thereof.

464. The compound of Embodiment 462, wherein the compound is a compound according to Formula BB, or a salt (e.g., pharmaceutically acceptable salt) thereof.

465. The compound of Embodiment 462, wherein the compound is a compound according to Formula BC, or a salt (e.g., pharmaceutically acceptable salt) thereof.

466. The compound of Embodiment 462, wherein the compound is a compound according to Formula BD, or a salt (e.g., pharmaceutically acceptable salt) thereof.

467. The compound of Embodiment 462, wherein the compound is a compound according to Formula BE, or a salt (e.g., pharmaceutically acceptable salt) thereof.

468. The compound of Embodiment 462, wherein the compound is a compound according to Formula BF, or a salt (e.g., pharmaceutically acceptable salt) thereof.

469. The compound of Embodiment 462, wherein the compound is a compound according to Formula BG, or a salt (e.g., pharmaceutically acceptable salt) thereof.

470. The compound of Embodiment 462, wherein the compound is a compound according to Formula BH, or a salt (e.g., pharmaceutically acceptable salt) thereof.

471. The compound of Embodiment 462, wherein the compound is a compound according to Formula BI, or a salt (e.g., pharmaceutically acceptable salt) thereof.

472. The compound of Embodiment 462, wherein the compound is a compound according to Formula BJ, or a salt (e.g., pharmaceutically acceptable salt) thereof.

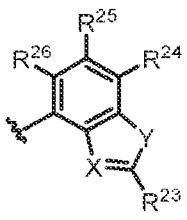
473. The compound of Embodiment 462, wherein the compound is a compound according to Formula BK, or a salt (e.g., pharmaceutically acceptable salt) thereof.

474. The compound of Embodiment 462, wherein the compound is a compound according to Formula BL, or a salt (e.g., pharmaceutically acceptable salt) thereof.

475. The compound of Embodiment 462, wherein the compound is a compound according to Formula BM, or a salt (e.g., pharmaceutically acceptable salt) thereof.

476. The compound of any one of Embodiments 443-475, wherein (i) when R^3 includes a heterocycle or heteroaryl containing a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle or heteroaryl does not comprise an –NH- moiety.

477. The compound of any one of Embodiments 443, 444, or 446-476, wherein R^6 is selected from:



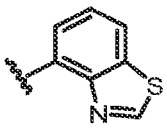
, wherein:

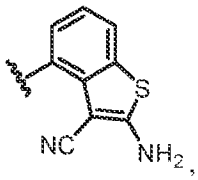
X is selected from N and C-CN;

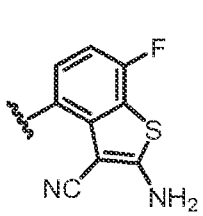
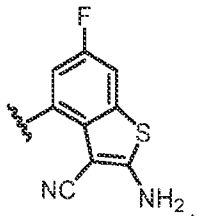
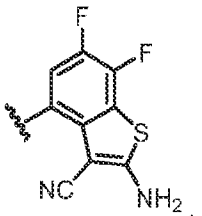
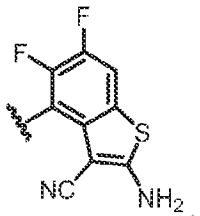
Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

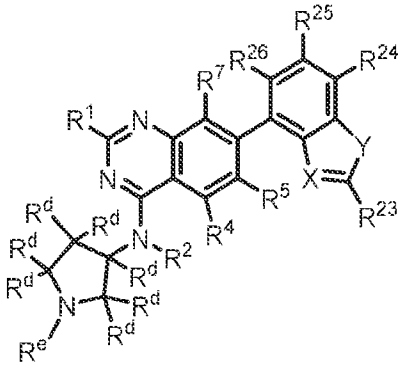
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

478. The compound of Embodiment 477, wherein R^6 is selected from:  , which is substituted with one or more R^{15}.

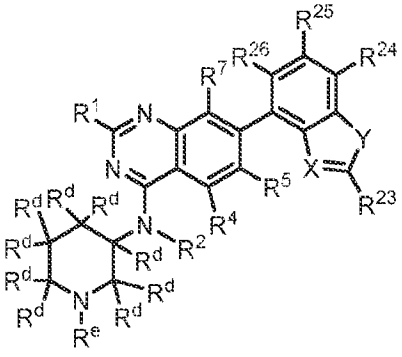
479. The compound of Embodiment 478, wherein R^6 is selected from:  ,

 ,  ,  , and  .

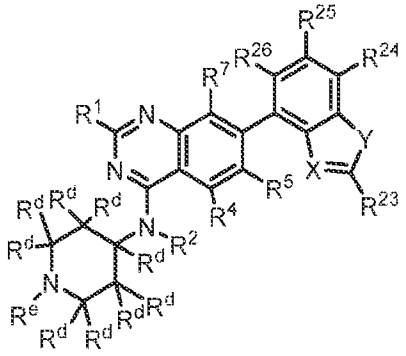
480. The compound of any one of Embodiments 443, 444, or 446-479, wherein the compound is a compound according to Formula BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1:



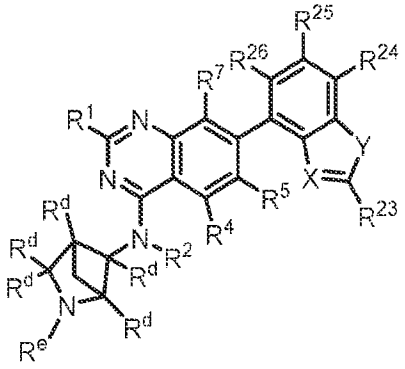
(BA1),



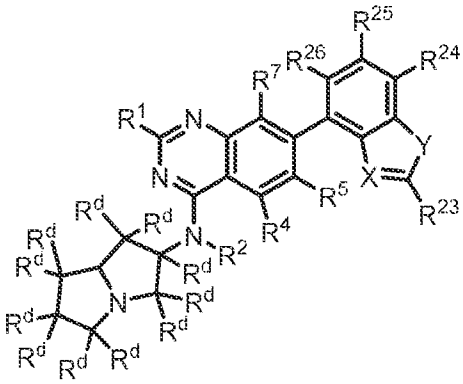
(BB1),



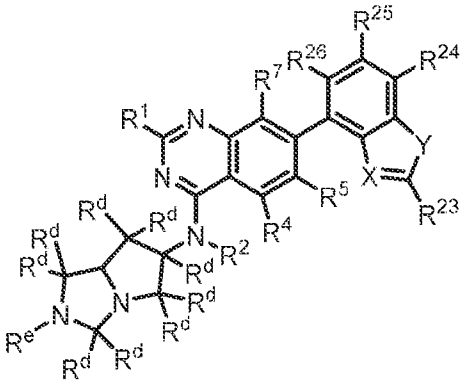
(BC1),



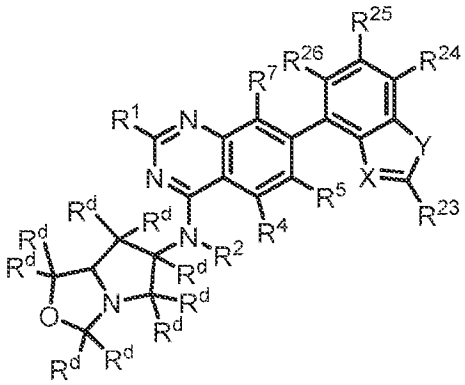
(BD1),



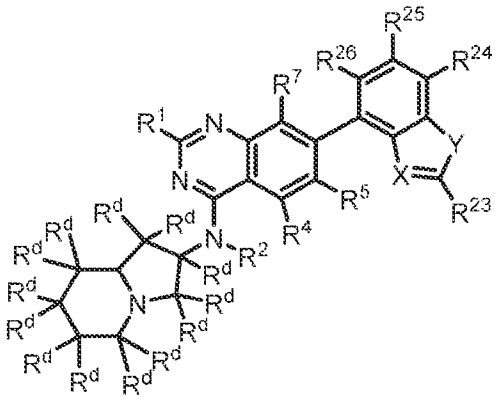
(BE1),



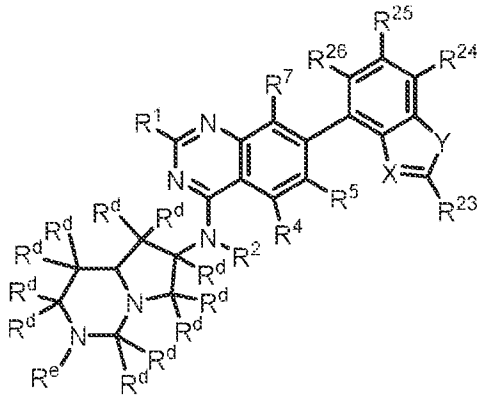
(BF1),



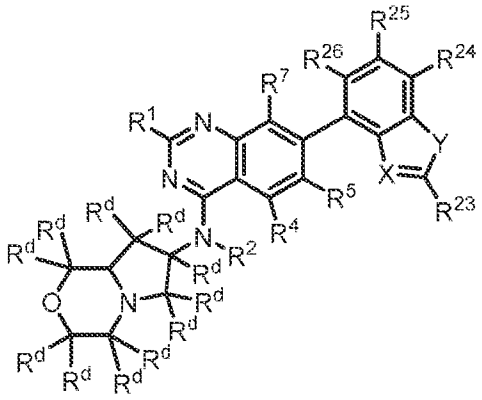
(BG1),



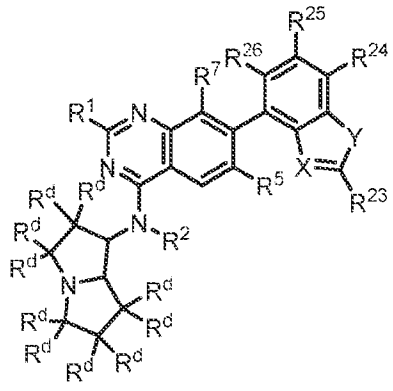
(BH1),



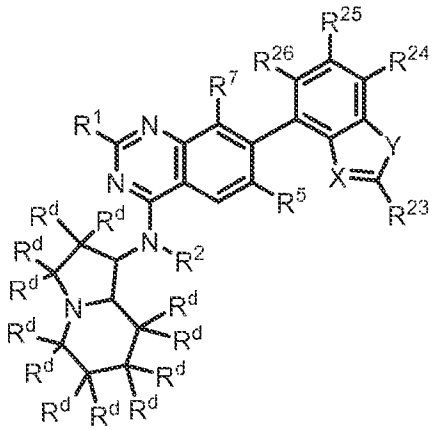
(BI1),



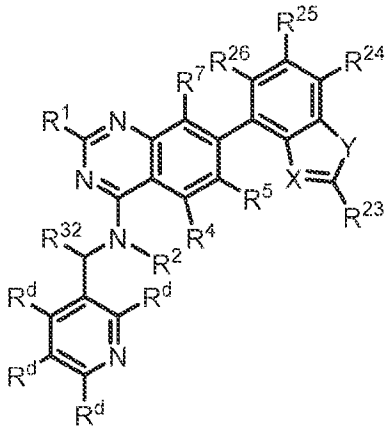
(BJ1),



(BK1),



(BL1), and



(BM1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^{32}, if present, is selected from H and C_{1-5}alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

R^c, if present, is selected from -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-}

$_{6}$alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is C-CN;

Y is S;

R^{23} is selected from $-N(R^{12})_2$; and

R^{24}, R^{25}, and R^{26} are independently selected from H and halogen.

481. The compound of any one of Embodiments 477-480, wherein one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

482. The compound of any one of Embodiments 462-481, wherein R^e is -C(O)(3-6 membered carbocycle).

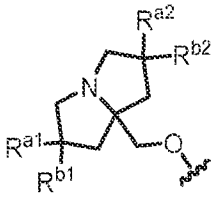
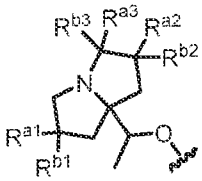
483. The compound of any one of Embodiments 462-481, wherein R^e is selected from -C(O)(C_{1-6}alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), and -C(O)O(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

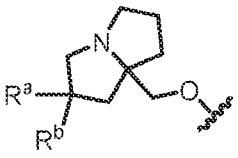
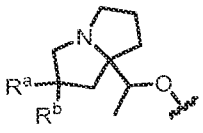
484. The compound of any one of Embodiments 462-483, wherein each R^d is H.

485. The compound of any one of Embodiments 443-484, wherein R^2 is H.

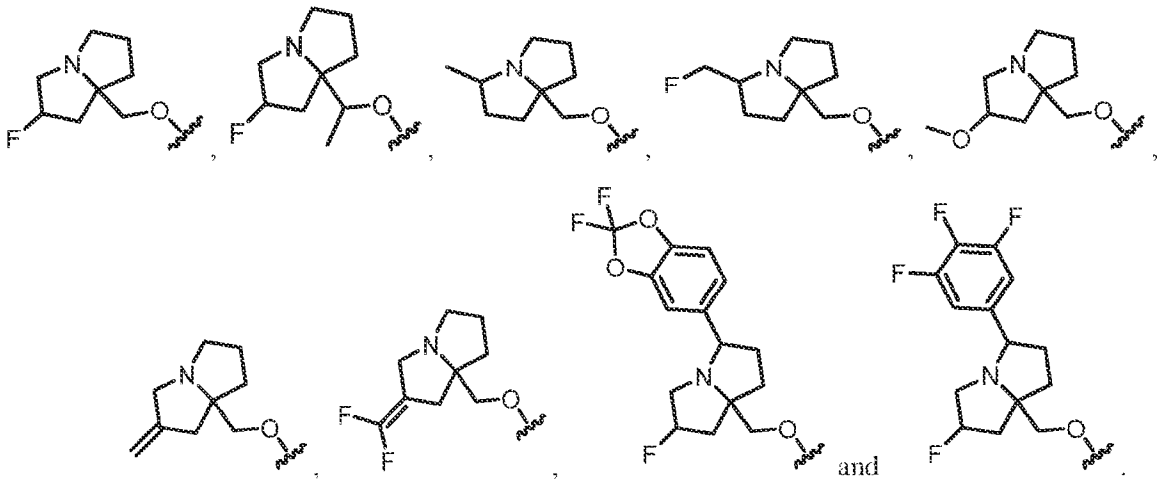
486. The compound of any one of Embodiments 443-484, wherein R^2 is selected from C_{1-2}alkyl.

487. The compound of any one of Embodiments 443, 444, or 446-486, wherein R^1 is selected from $-OR^8$.

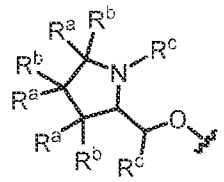
488. The compound of Embodiment 487, wherein R^1 is selected from:  or  , wherein R^{a1}, R^{a2}, R^{b1}, R^{b2}, R^{a3}, and R^{b3} are each independently selected from deuterium, halogen, $-OR^{12}$, a 4- to 10-membered heterocycle, and a 4- to 10-membered aryl, wherein any 4- to 10-membered heterocycle or 4- to 10-membered aryl is optionally substituted with one or more R^{28}, and H, wherein R^{a1} and R^{b1} can optionally join together to form a exocyclic double bond that is unsubstituted or is substituted by halogen.

489. The compound of Embodiment 488, wherein R^1 is selected from:  or  , wherein R^a and R^b are each independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen.

490. The compound of Embodiment 489, wherein R^1 is selected from:

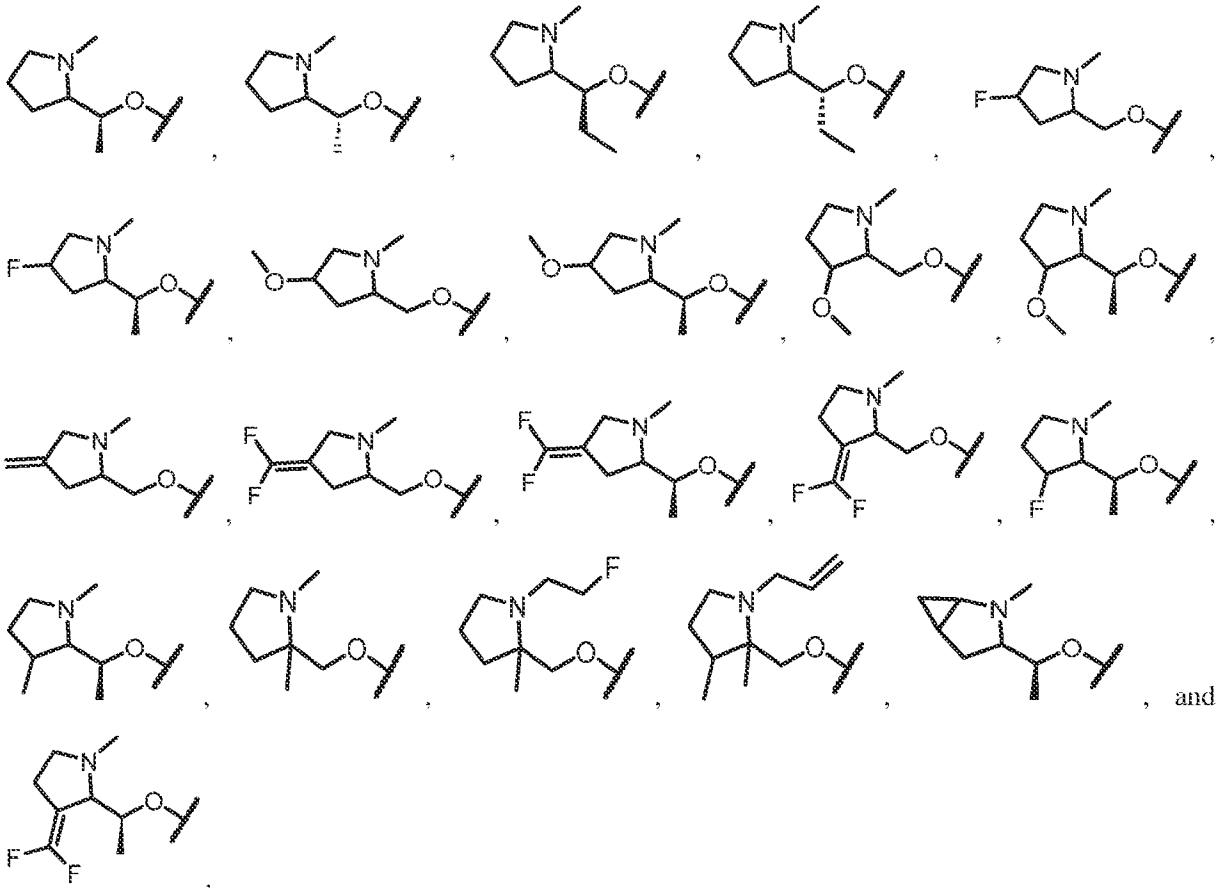


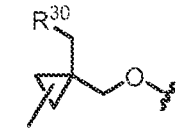
491. The compound of Embodiment 487, wherein R^1 is:



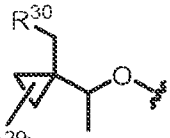
wherein each R^a and R^b is independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H; and each R^c is independently selected from H and C_{1-6} alkyl, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen.

492. The compound of Embodiment 491, wherein R^1 is selected from:



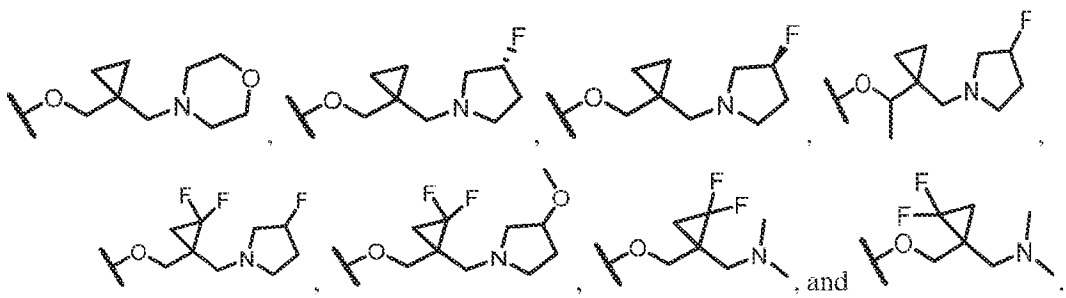


493. The compound of any one of Embodiments 443, 444, or 446-486, wherein R^1 is



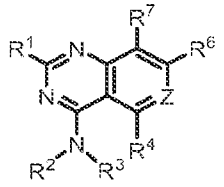
or .

494. The compound of Embodiment 493, wherein R^1 is selected from



495. The compound of any one of Embodiments 443, 444, or 446-494, wherein R^5 is $-CF_3$.

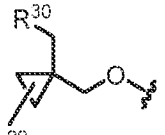
496. A compound represented by Formula II:



(II)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

Z is N or C-R^5;

R^1 is selected from H, -OR^8,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated;

R^3 is selected from 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, a 4-10 membered heterocycle, or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, -OC_{1-6}alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a phenyl or a bicyclic heteroaryl, wherein the phenyl or bicyclic heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen or H;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, -OR^{12}, =O, =S, -CN, -$NSOMe_2$, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),-C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -$S(O)_2$(C_{1-6}alkyl), -C(S)(C_{1-6}alkyl), -C(S)O(C_{1-6}

$_{6}$alkyl), -C(S)N(C_{1-6}alkyl)$_2$, -C(=N-OR^{12})(C_{1-6} alkyl), -C(O)N(R^{12})OR^{12}, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -N(R^{14})$_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, -OR^{12}, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, -N(R^{12})$_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), -C(O)OR^{12}, -C(O)N(R^{12})$_2$, -S(O)$_2$R^{12}, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl, -OR^{12}, C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is N(R^{12})$_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

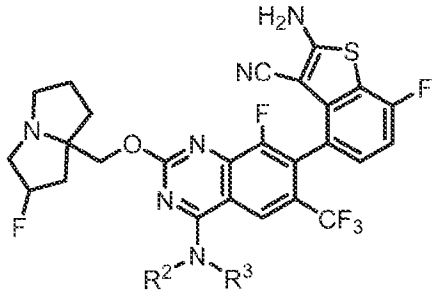
each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, ,-C_{1-6} heteroalkyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

497. The compound of Embodiment 496, wherein R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, or (ii) the heterocycle does not comprise an –NH- moiety.

498. The compound of Embodiment 496 or 497, wherein the compound is of Formula II-a:



(II-a)

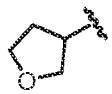
or a salt (e.g., pharmaceutically acceptable salt) thereof.

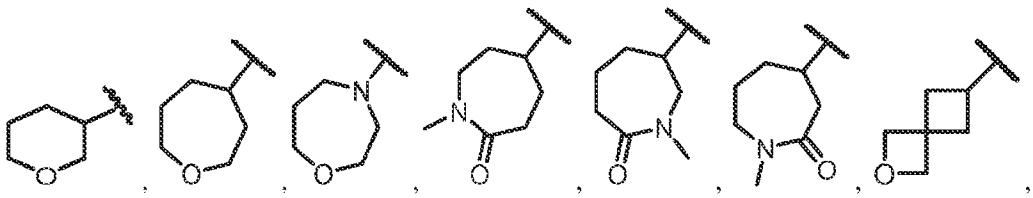
499. The compound of any one of Embodiments 496-498, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N.

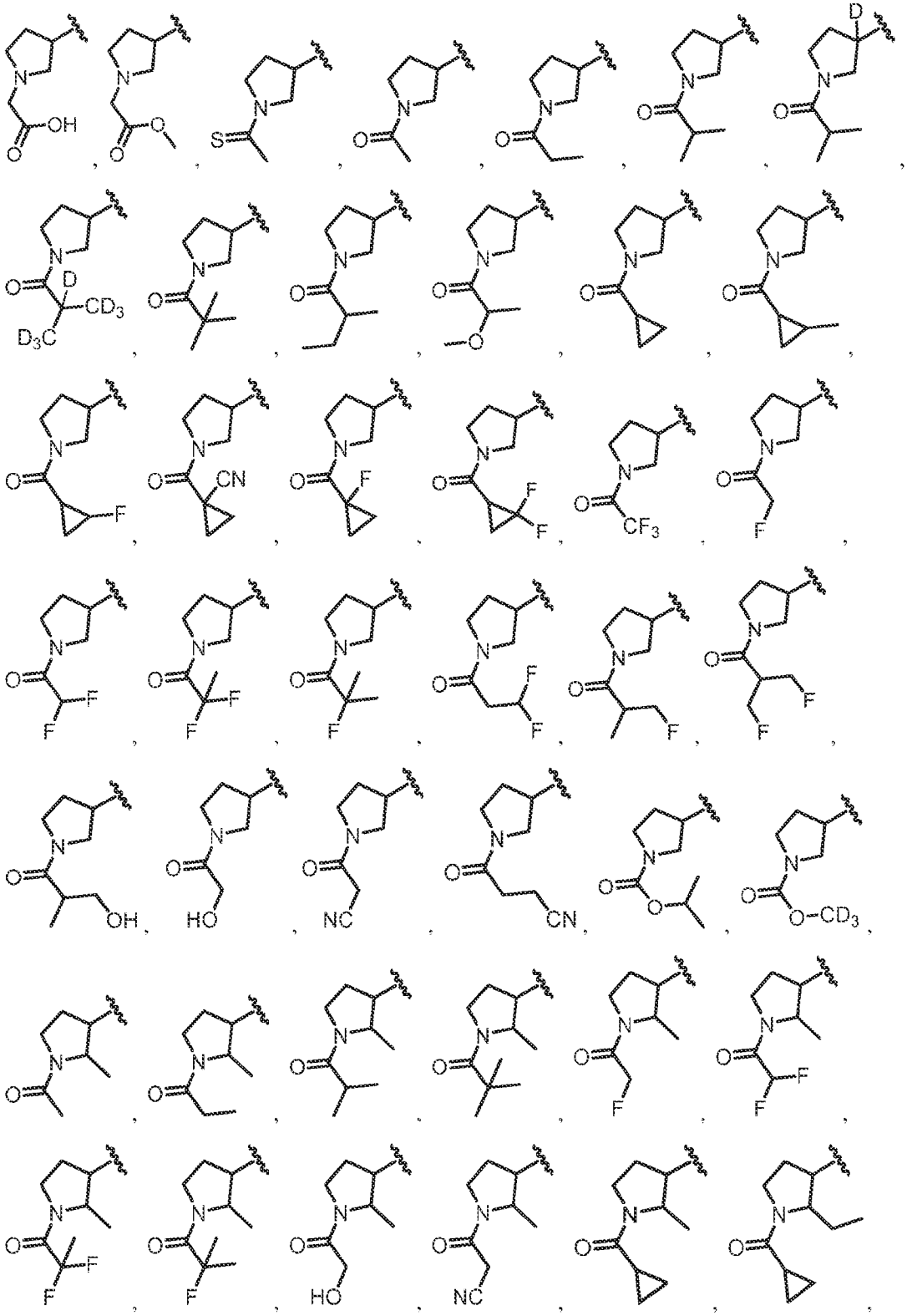
500. The compound of Embodiment 499, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}.

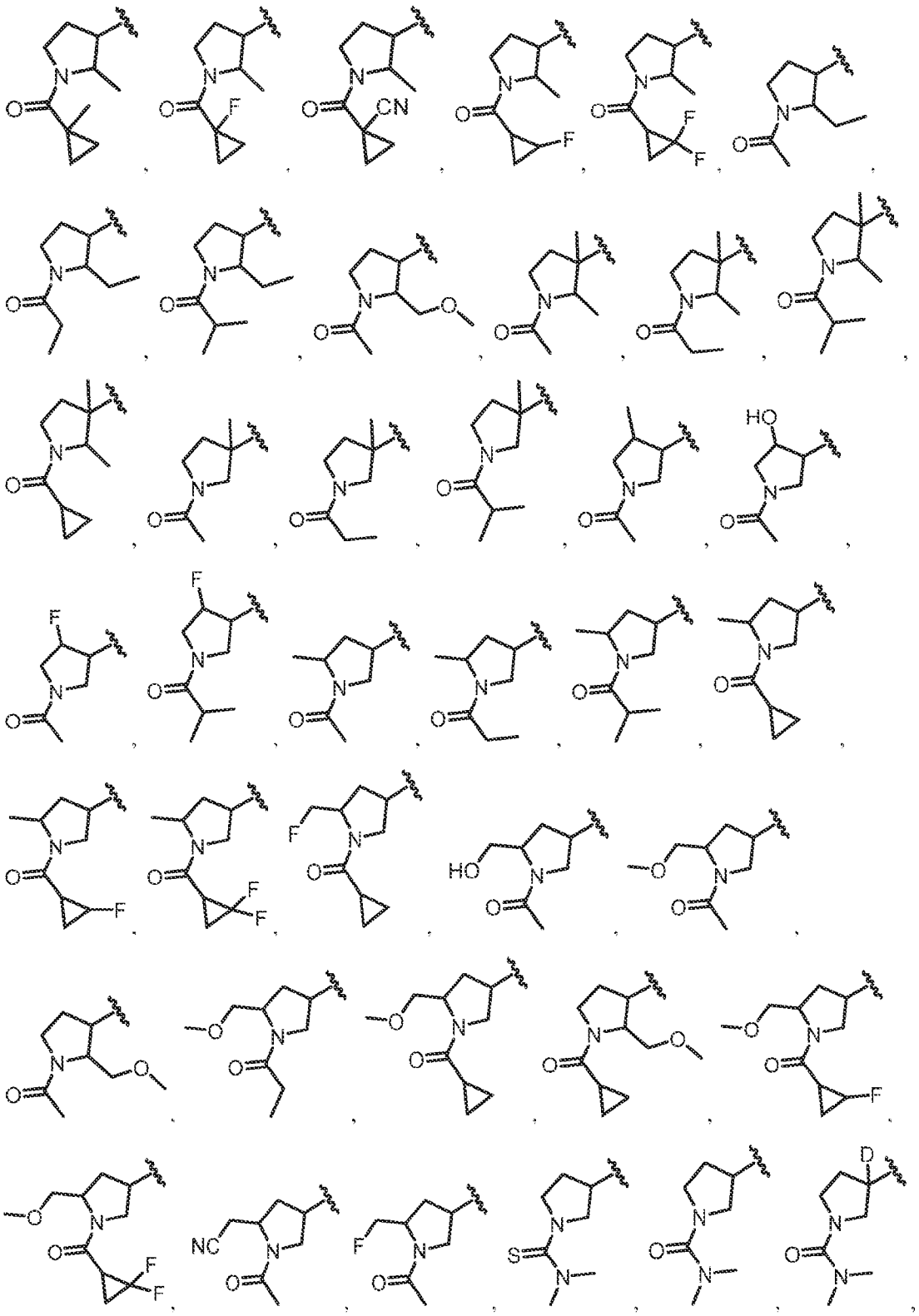
501. The compound of any one of Embodiments 496-500, wherein R^3 is a pyrrolidine that is substituted with 1-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}.

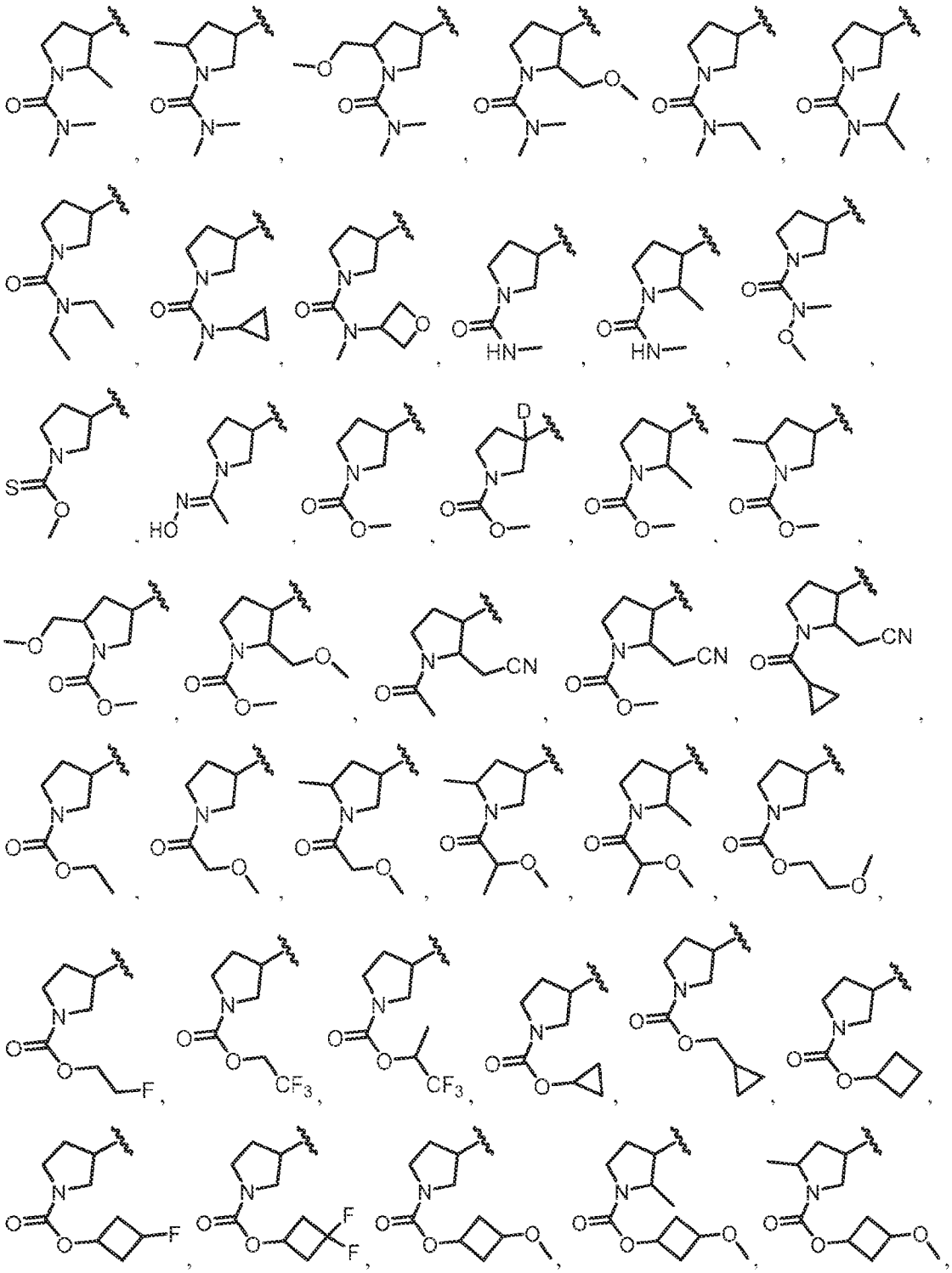
502. The compound of Embodiment 501, wherein each R^{10} is independently selected from deuterium, -C(O)N(R^{14})$_2$, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 3-6 membered heterocycle, a 5-6 membered heteroaryl, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

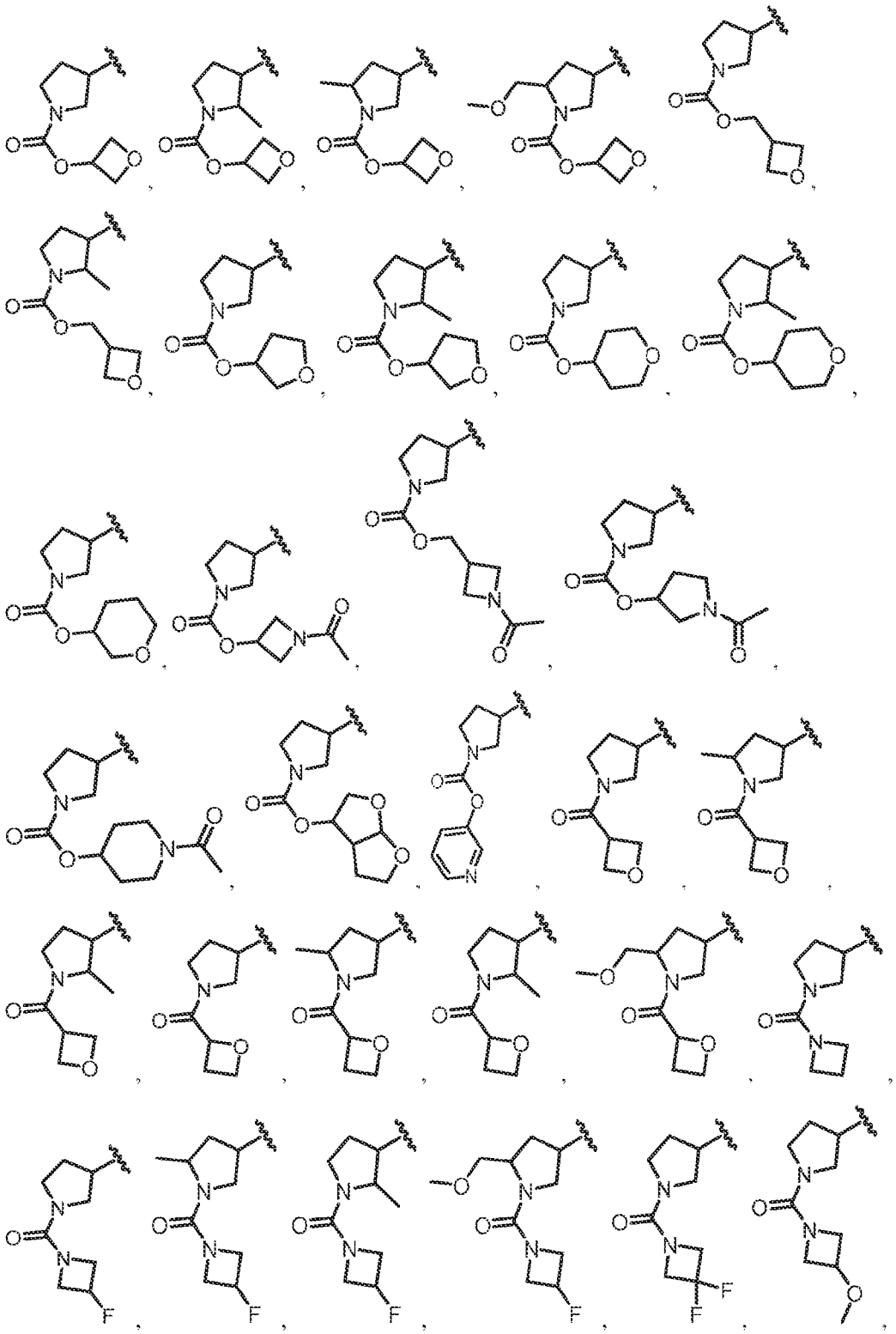
503. The compound of any one of Embodiments 496-502, wherein R^3 is selected from:  ,

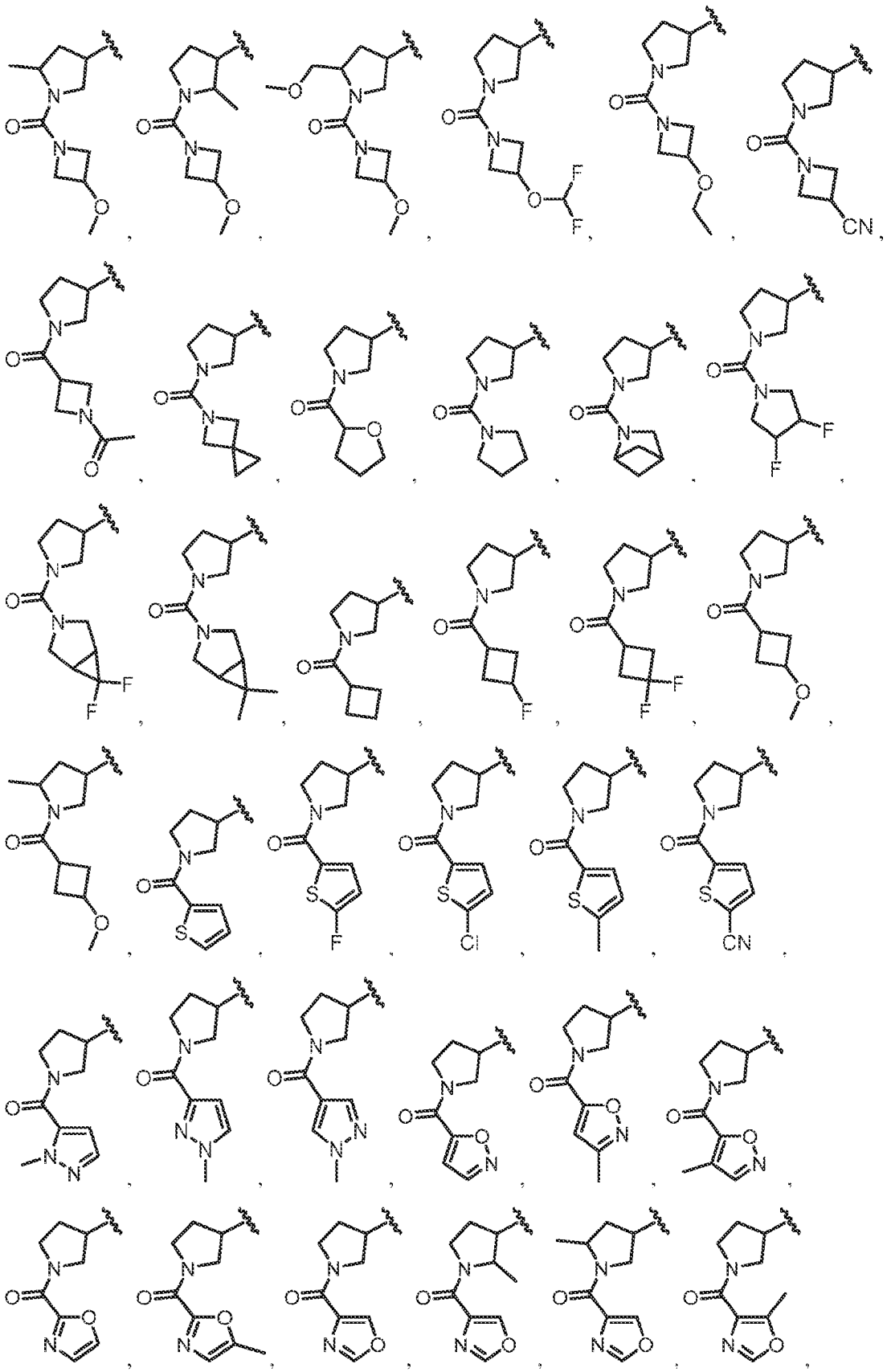


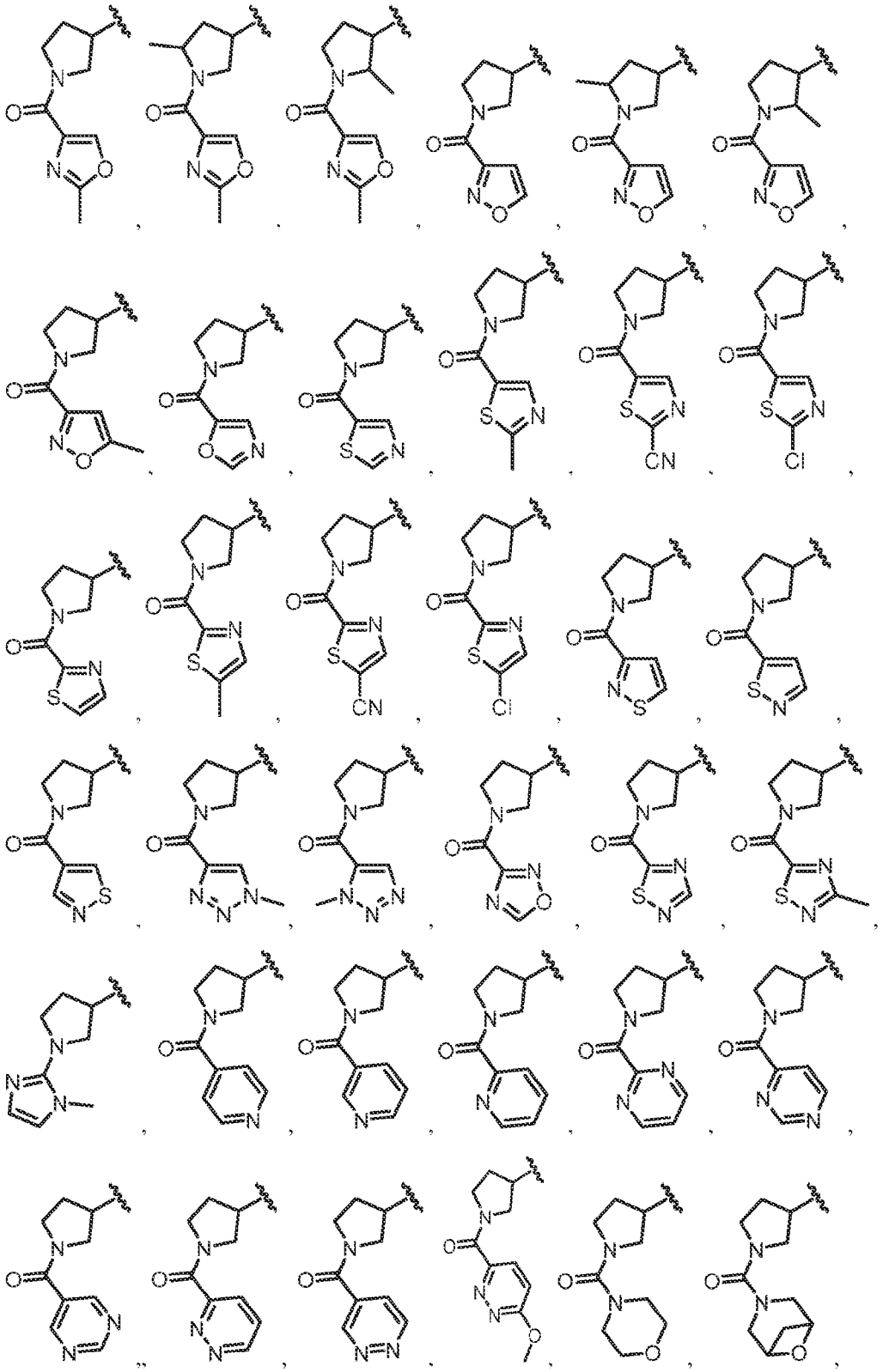


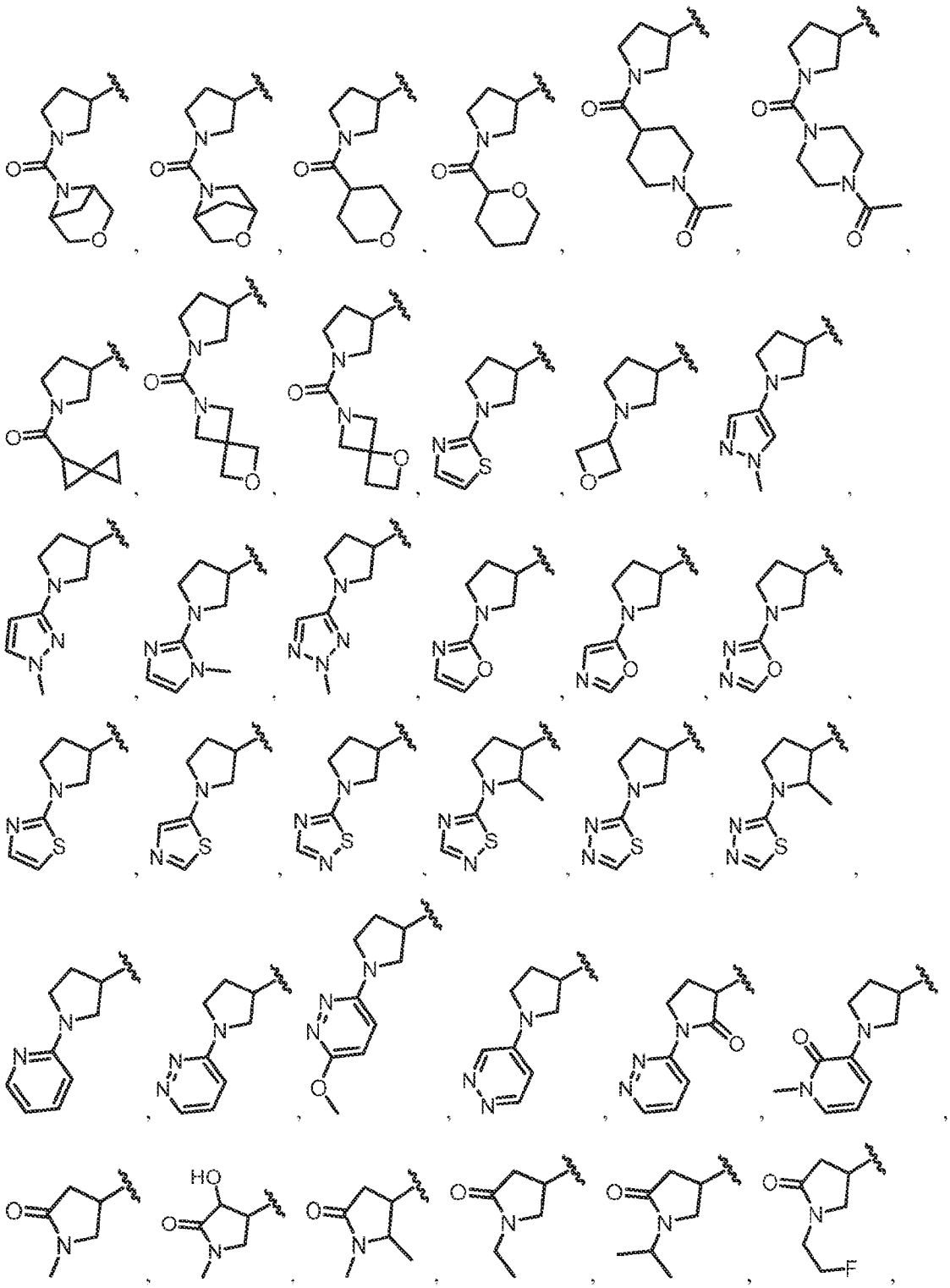


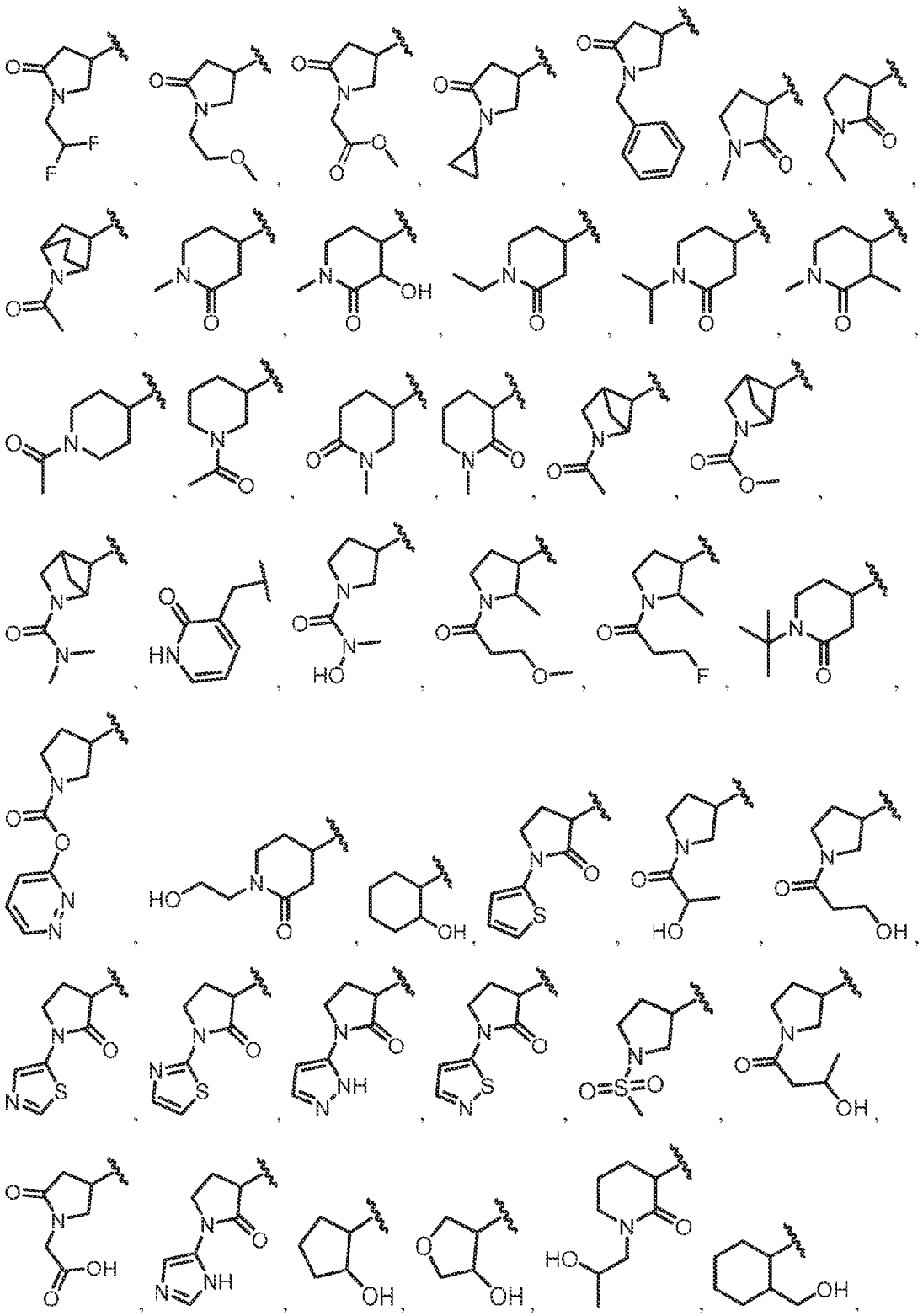


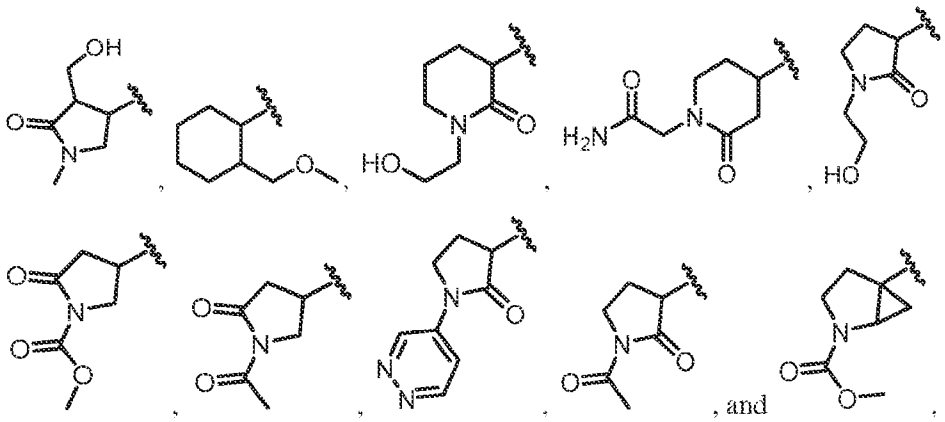






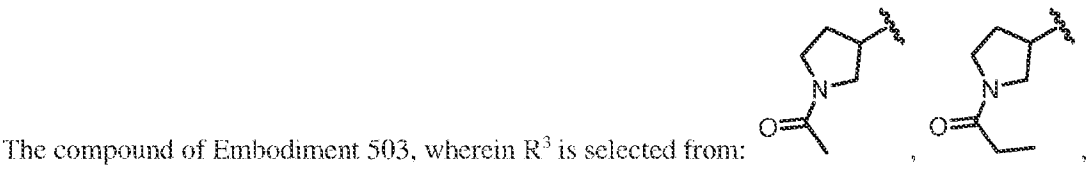


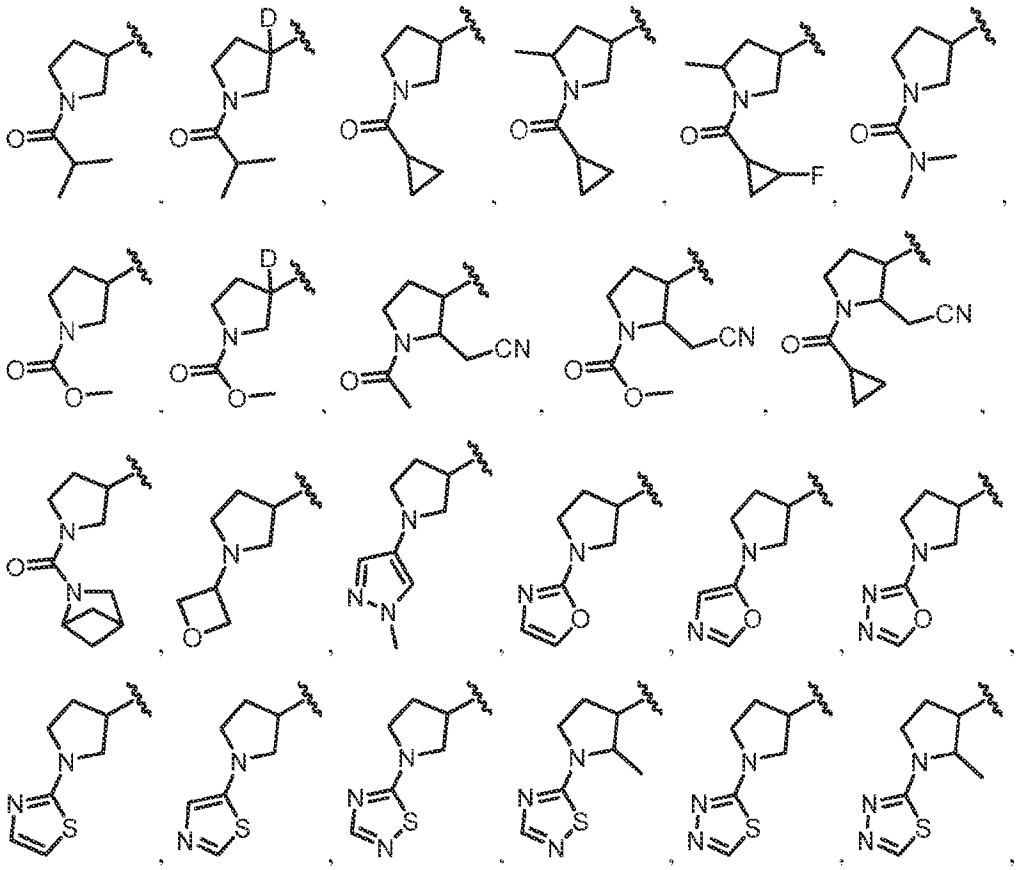


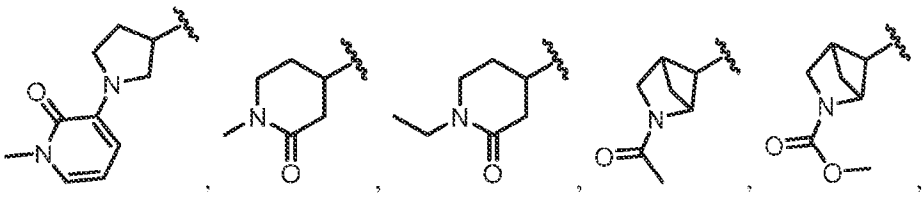


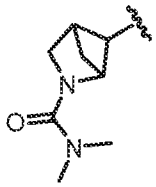
optionally further substituted with one or more R^{10}.

504. The compound of Embodiment 503, wherein R^3 is selected from:






, and

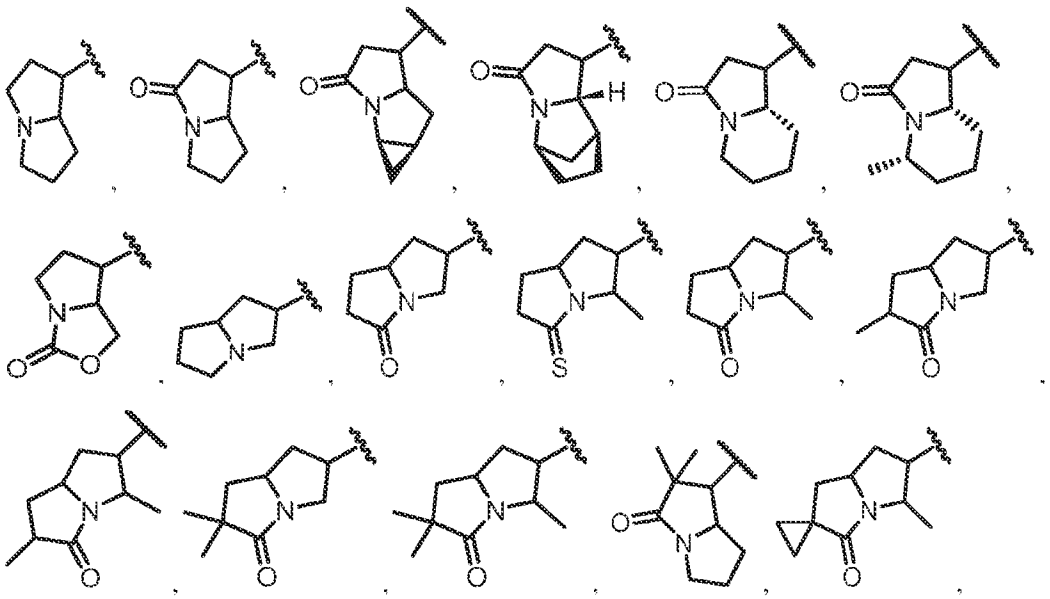

, any of which is optionally further substituted with one or more R^{10}.

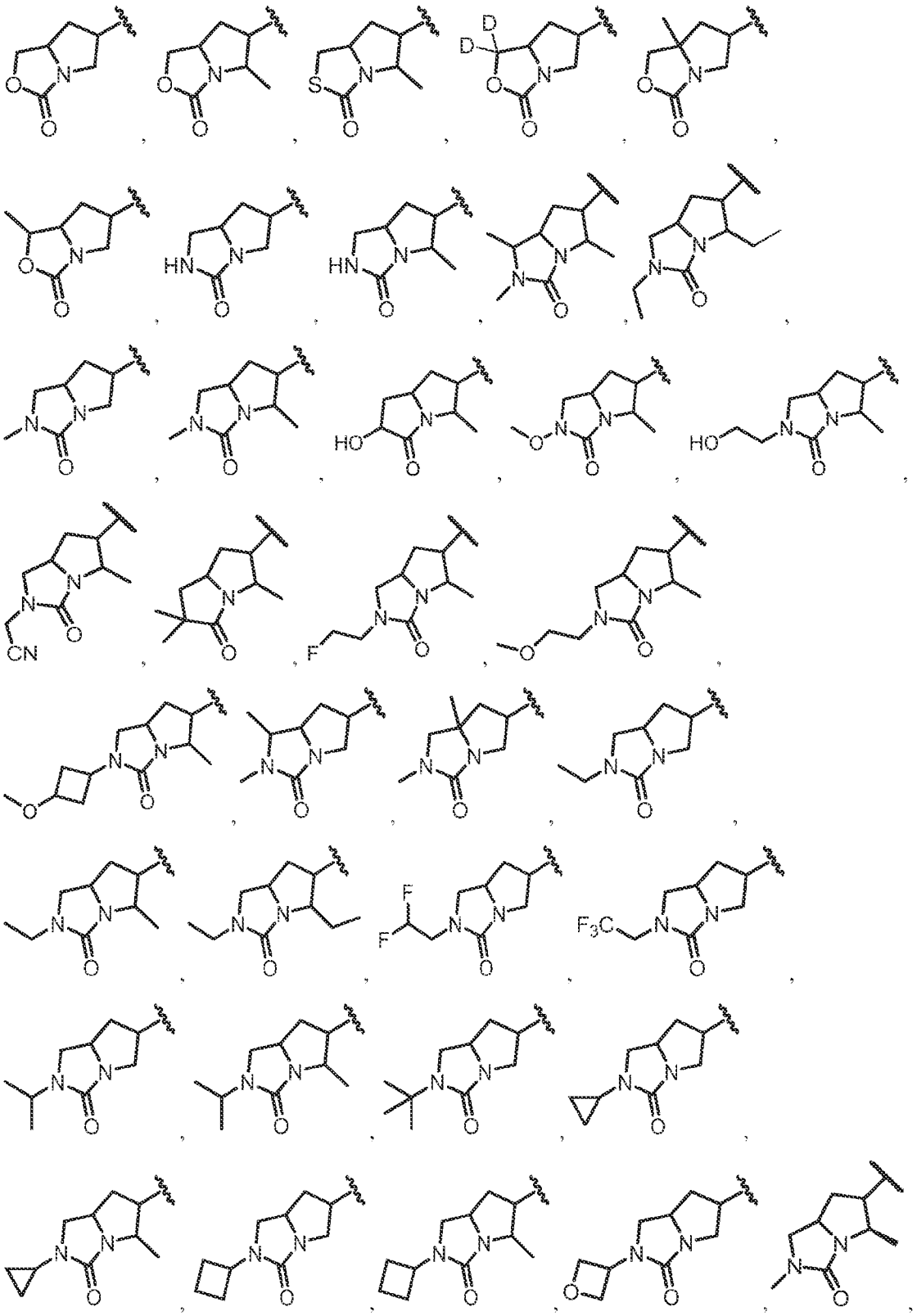
505. The compound of any one of Embodiments 496-498, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

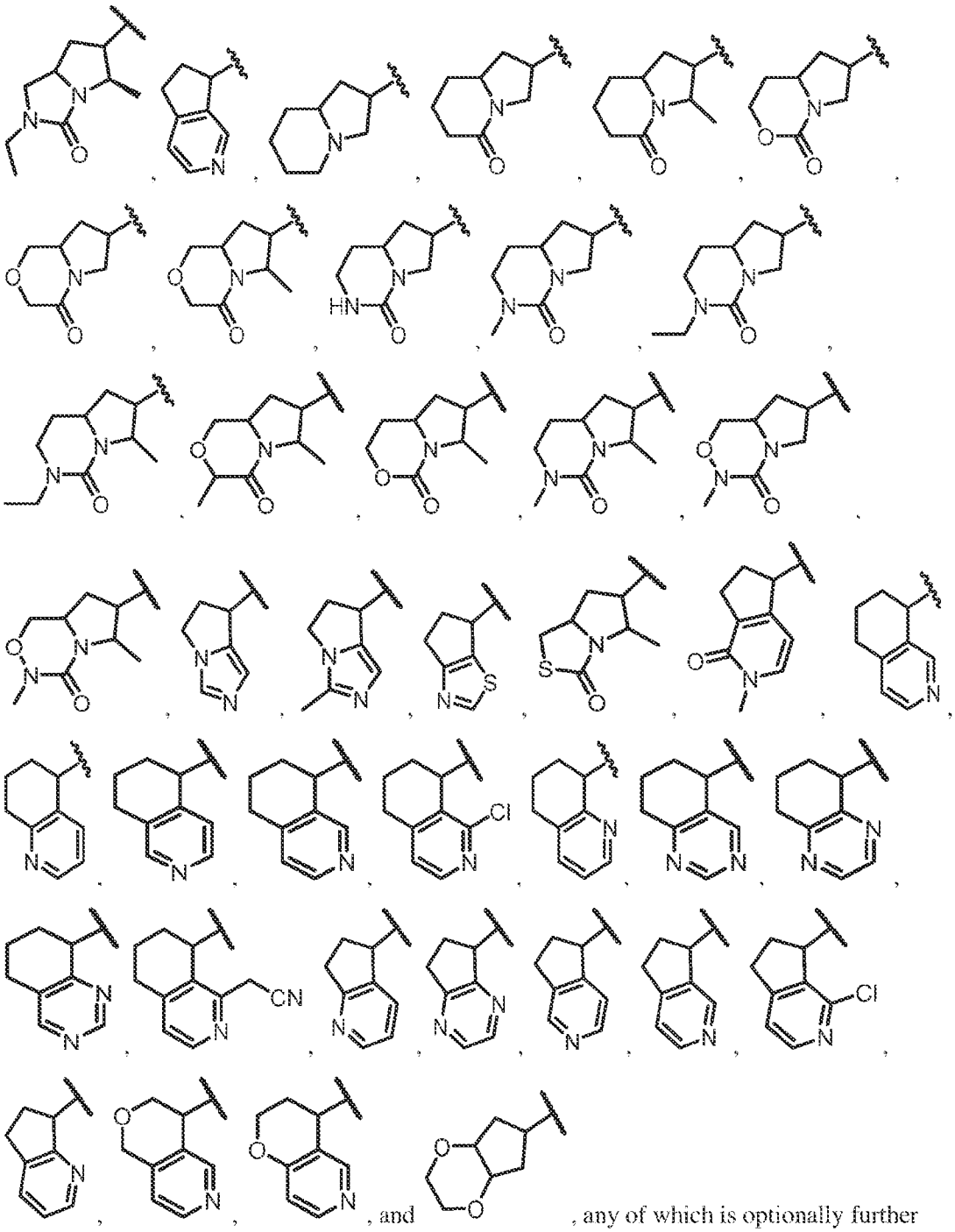
506. The compound of Embodiment 505, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not comprise an –NH- moiety.

507. The compound of Embodiment 505 or 506, wherein R^3 is a 7-10 membered heterocycle comprising a fused ring system that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

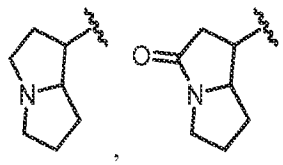
508. The compound of any one of Embodiments 496-498 and 505-507, wherein R^3 is selected from:

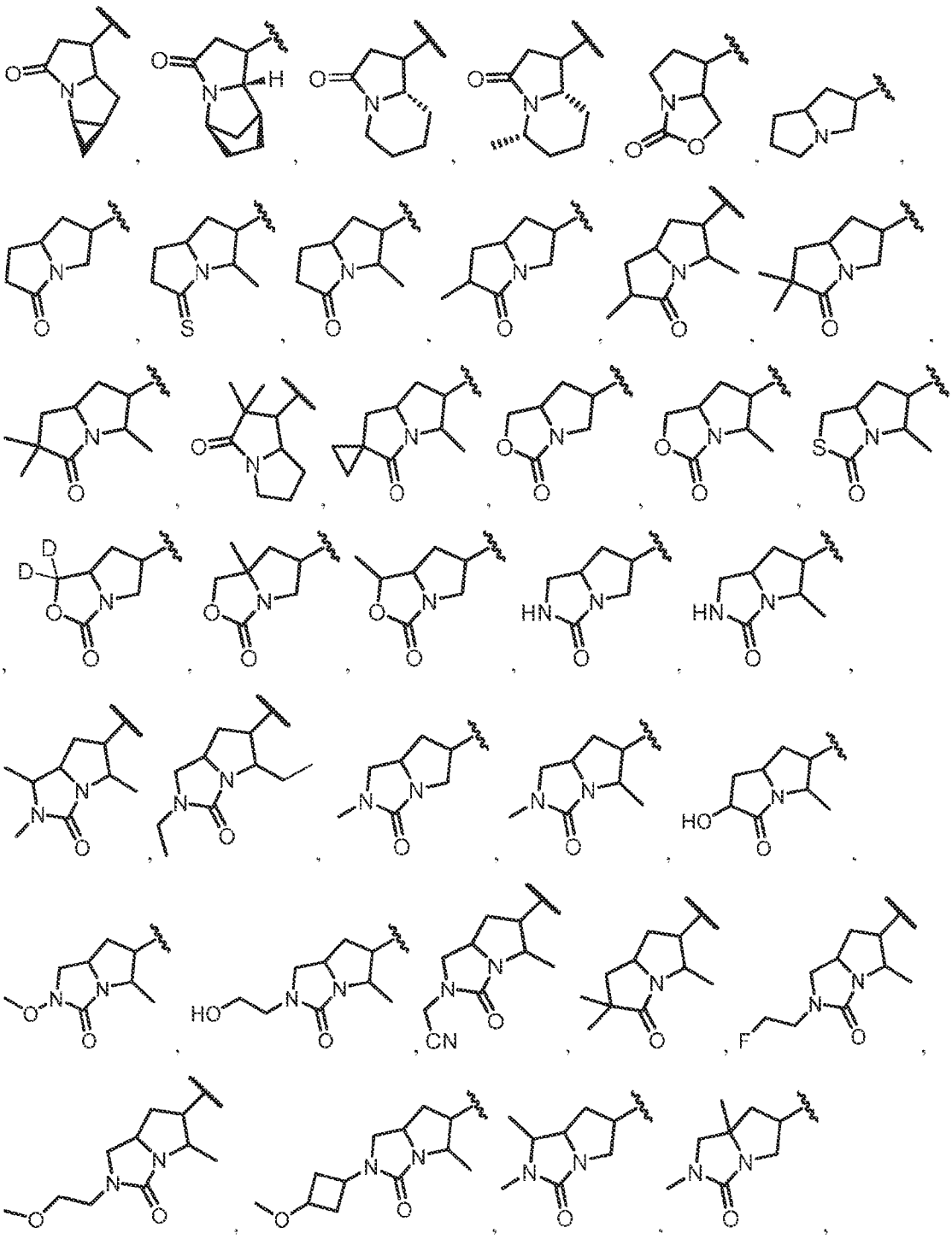


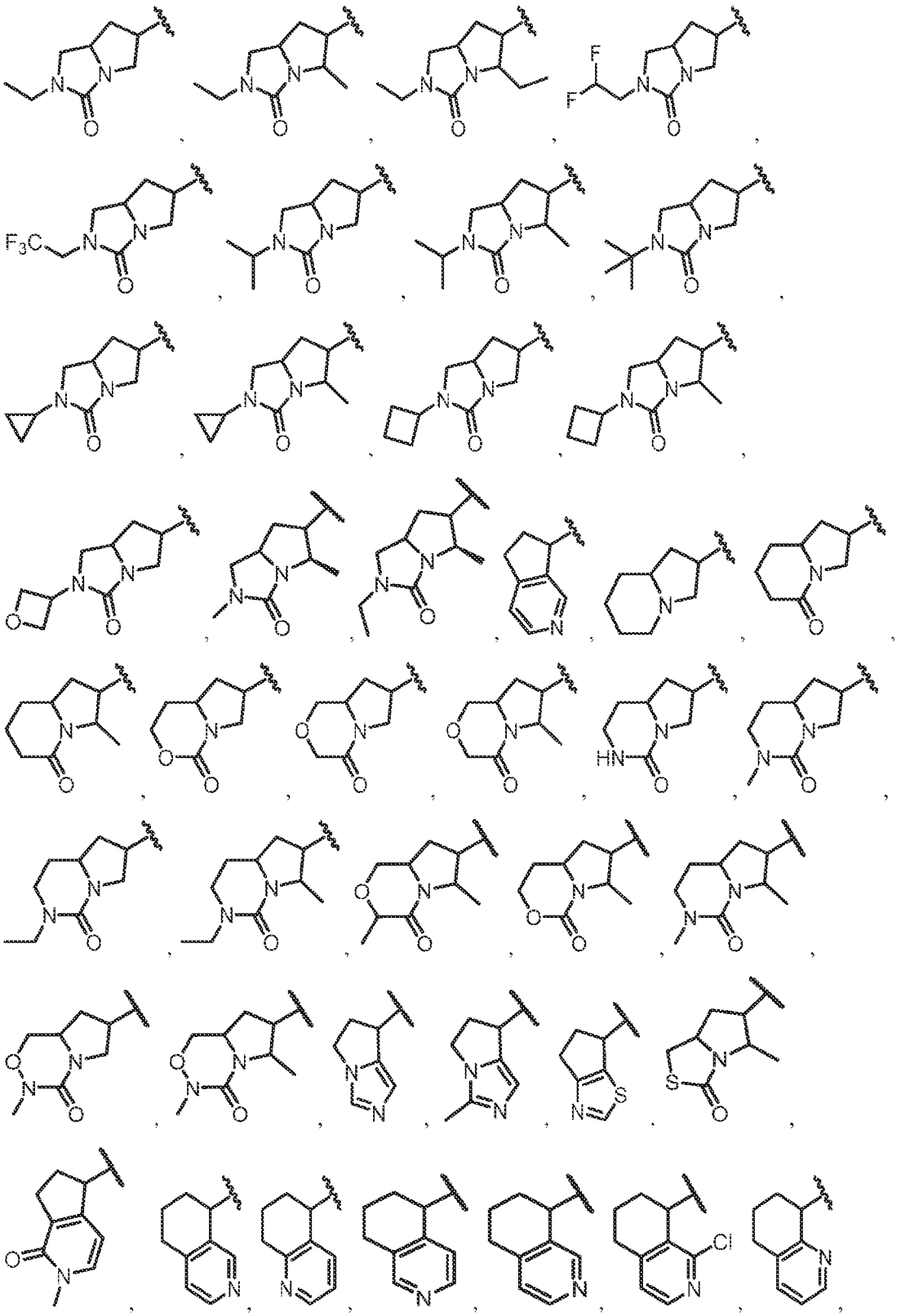


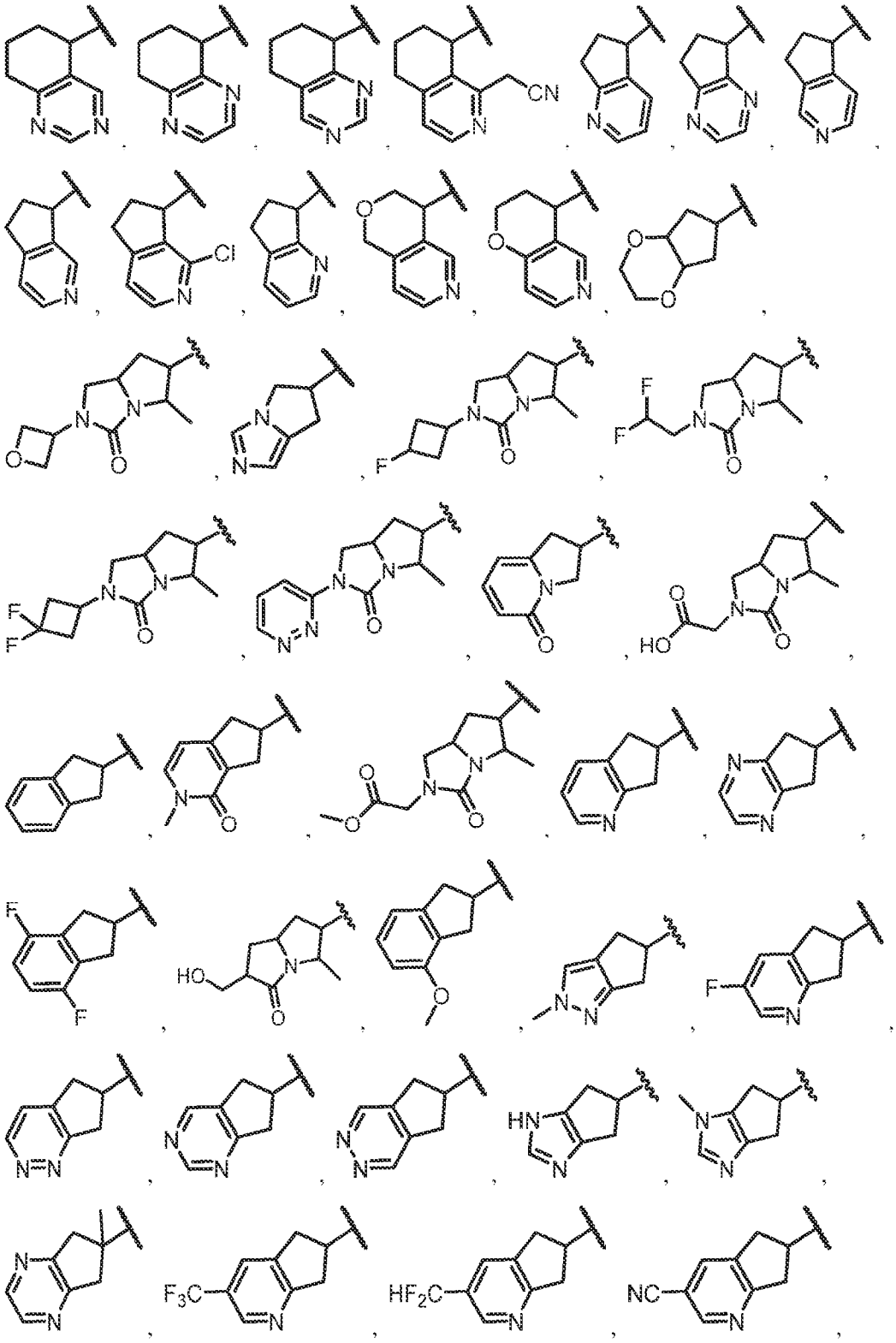


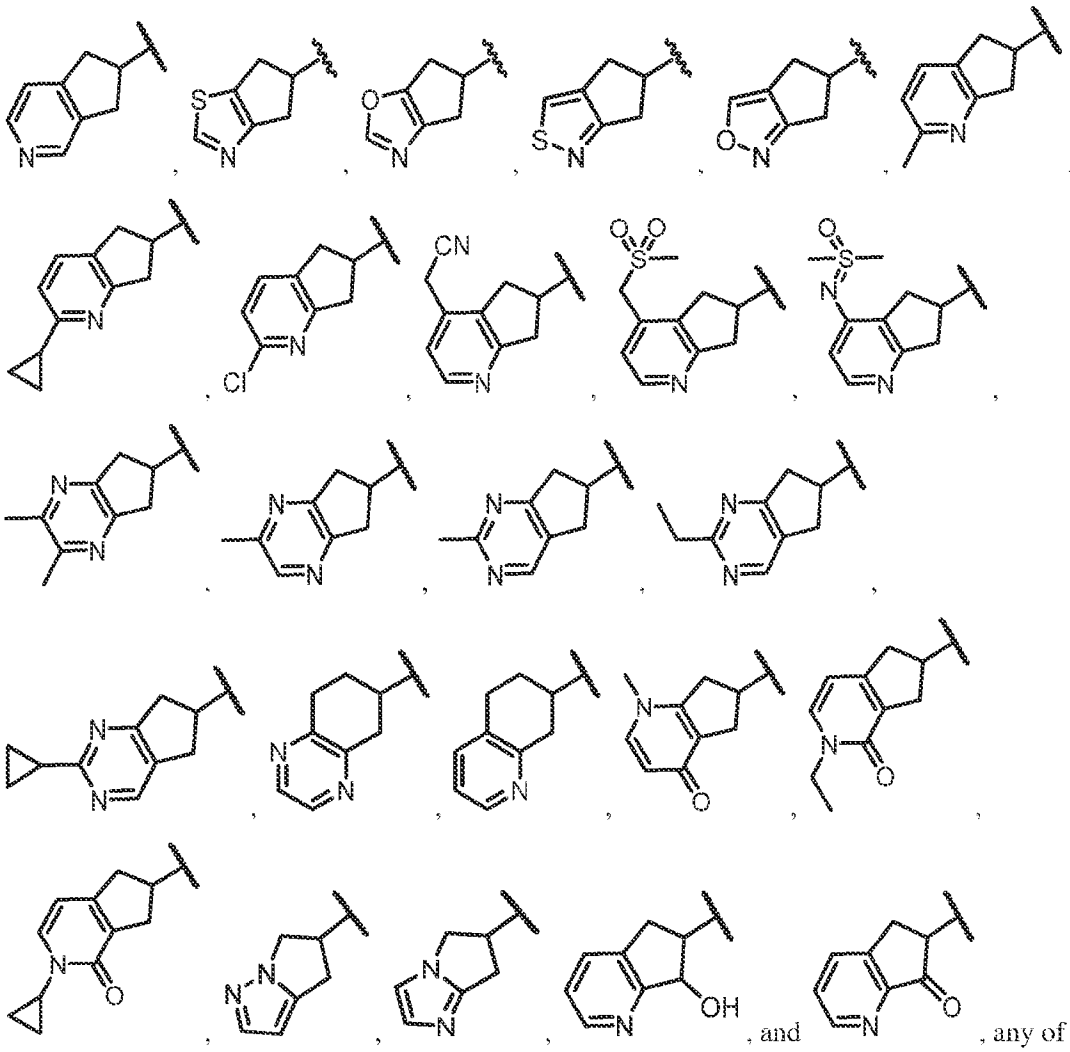
substituted with one or more R^{10}.

509. The compound of Embodiment 508, wherein R^3 is selected from: 



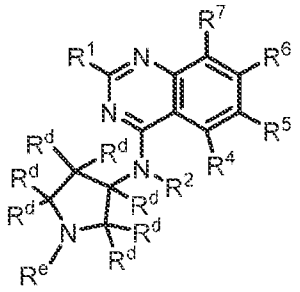
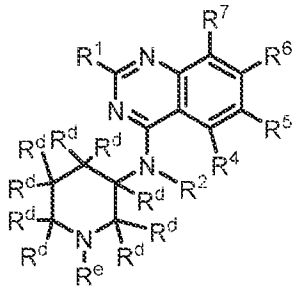
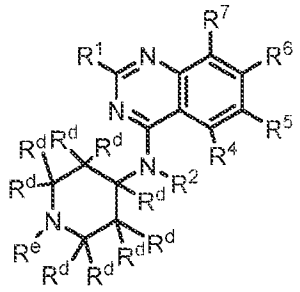
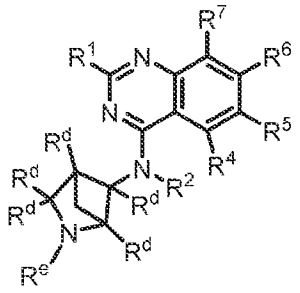






which is optionally further substituted with one or more R^{10}.

510. The compound of any one of Embodiments 496, 497, and 499-509, wherein the compound is a compound according to Formula IIR', IIU', IIV', or IIZ:

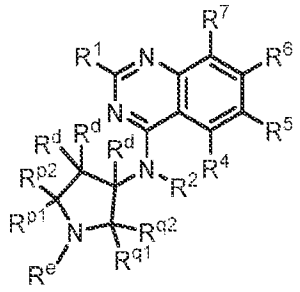

(IIR'),

(IIU'),

(IIV'), and

(IIZ),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^e is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

511. The compound of any one of Embodiments 496, 497, and 499-509, wherein the compound is a compound according to Formula IIAA':



(IIAA'),

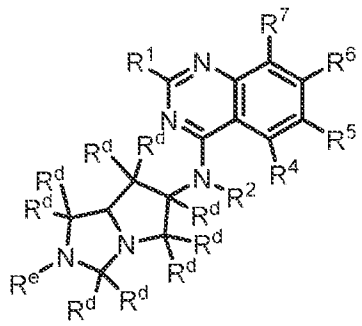
or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from deuterium, H, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)$(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle or 3-6 membered heterocycle, is unsubstituted or substituted with one or more R^{12} or R^{20}; and

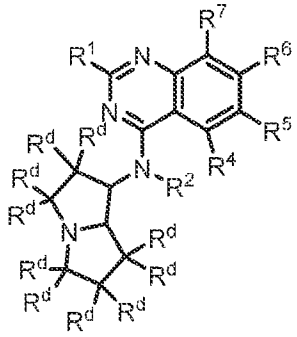
(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

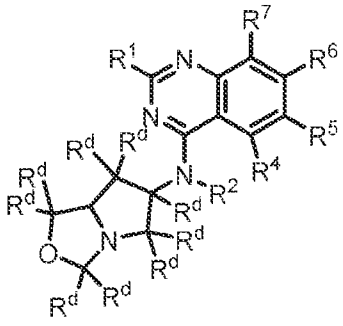
512. The compound of any one of Embodiments 496, 497 and 511, wherein the compound is a compound according to Formula IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, or IIJJ:



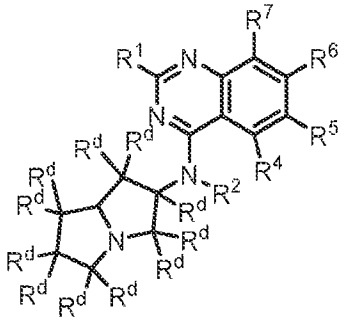
(IIBB),



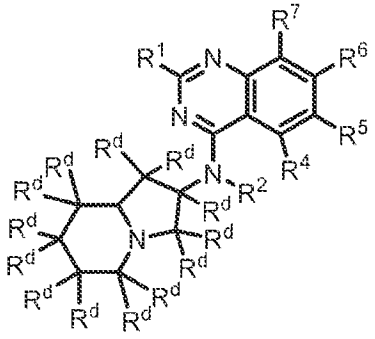
(IICC),



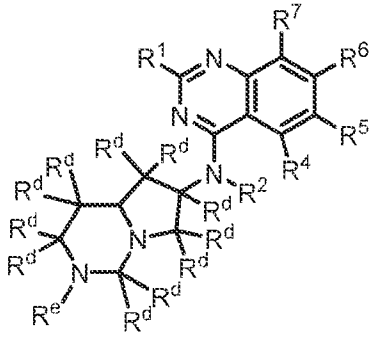
(IIDD),



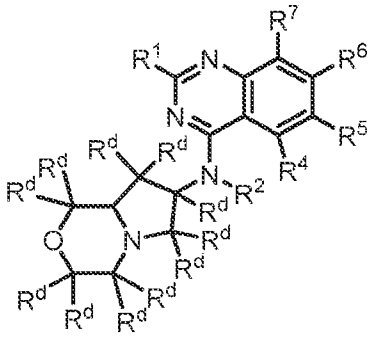
(IIEE),



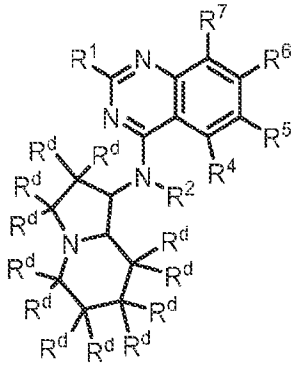
(IIFF),



(IIGG),



(IIHH), and



(IIJJ),

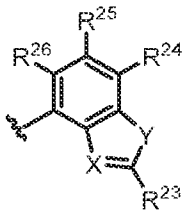
or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^e, if present, is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or

substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

513. The compound of any one of Embodiments 496, 497, and 499-512, wherein R^6 is selected from:

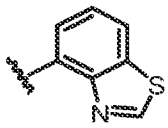
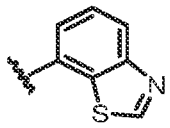
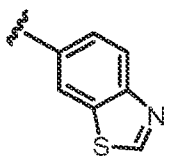
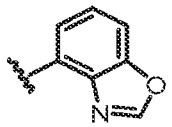
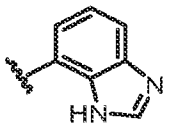
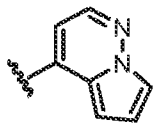
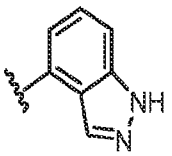
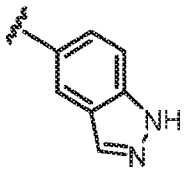
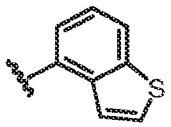
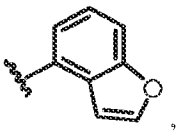
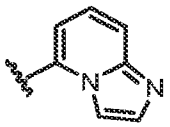

, wherein:

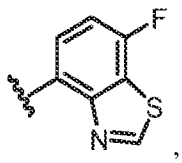
X is selected from N and C-CN;

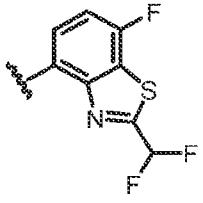
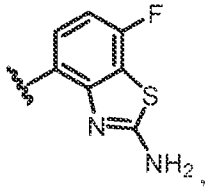
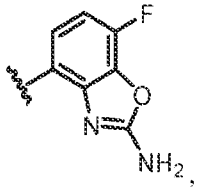
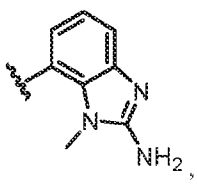
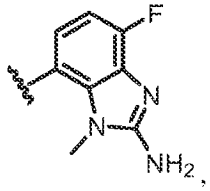
Y is selected from O and S;

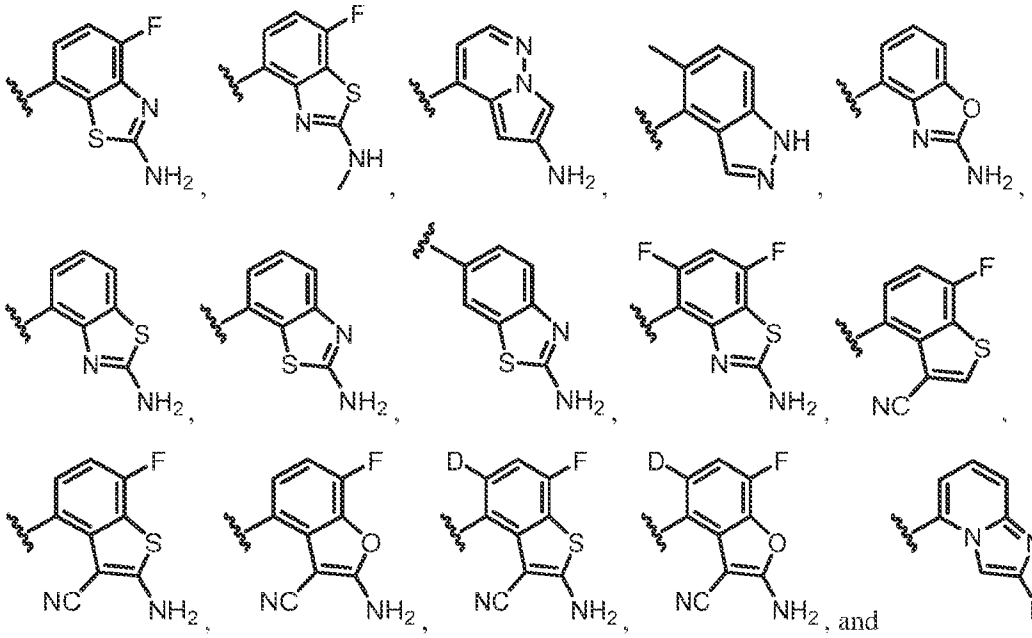
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

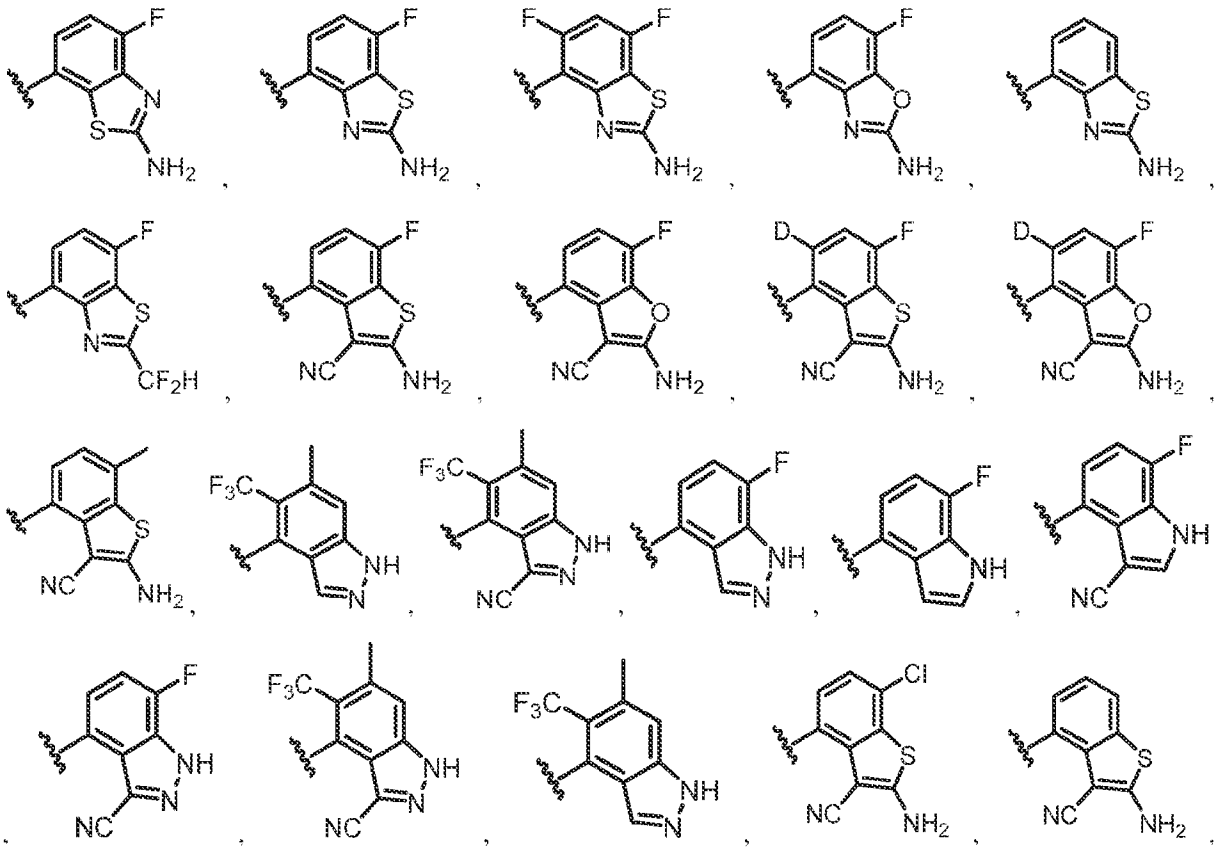
514. The compound of Embodiment 513, wherein R^6 is selected from:  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , any of which is substituted with one or more R^{15}.

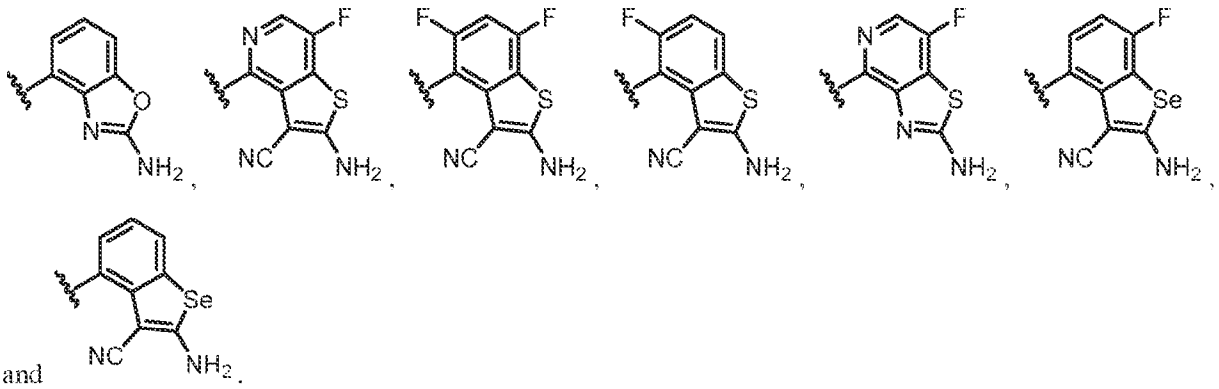
515. The compound of Embodiment 513 or 514, wherein R^6 is selected from:  ,

 ,  ,  ,  ,  ,



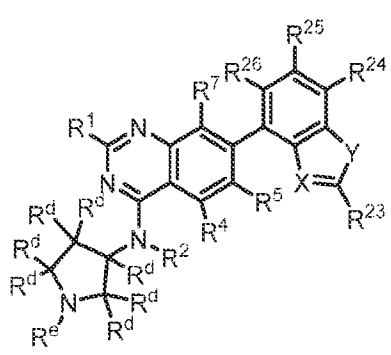
516. The compound of any one of Embodiments 513-515, wherein R^6 is selected from:



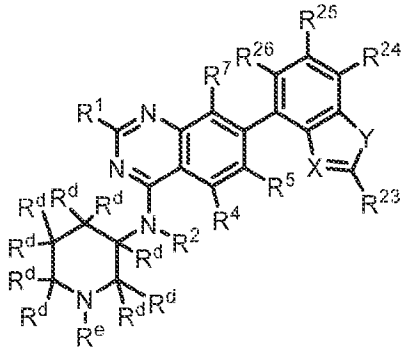


and

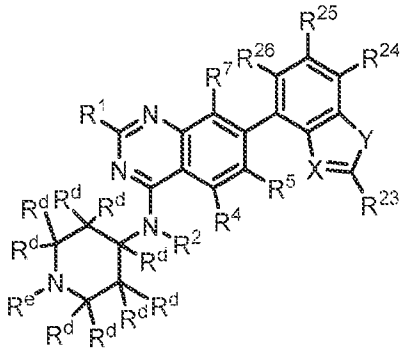
517. The compound of any one of Embodiments 496, 497, and 499-512, wherein the compound is a compound according to Formula IIR1', IIU1', IIV1', or IIZ1:



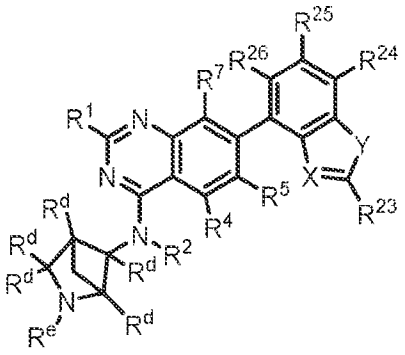
(IIR1'),



(IIU1'),



(IIV1'),



(IIZ1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e is selected from $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered

carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

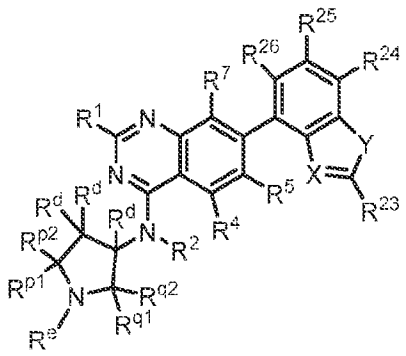
X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -N(R^{12})$_2$, C_{1-6}alkyl, and C_{1-6}alkyl-N(R^{14})$_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

518. The compound of any one of Embodiments 496, 497, and 499-512, wherein the compound is a compound according to Formula IIAA1':



(IIAA1'),

or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, -OR^{12}, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), -C(O)N(R^{14})$_2$, -S(O)$_2$(C_{1-6}alkyl), a 3-6 membered carbocycle, a 3-6 membered heterocycle, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle or 3-6 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

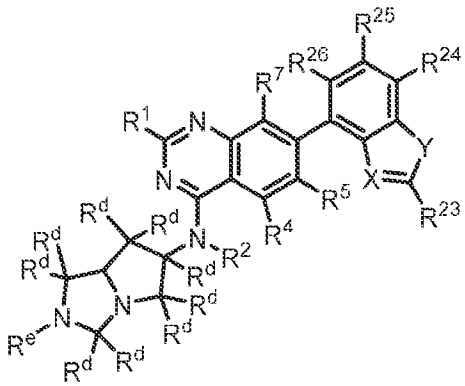
R^{23} is selected from -N(R^{12})$_2$, C_{1-6}alkyl, and C_{1-6}alkyl-N(R^{14})$_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

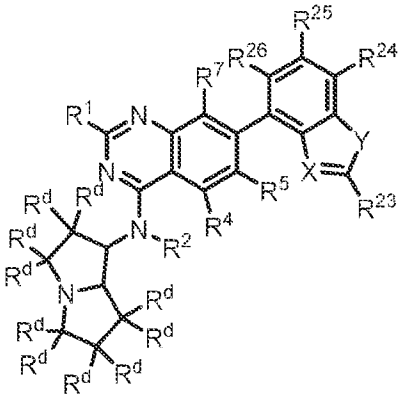
(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

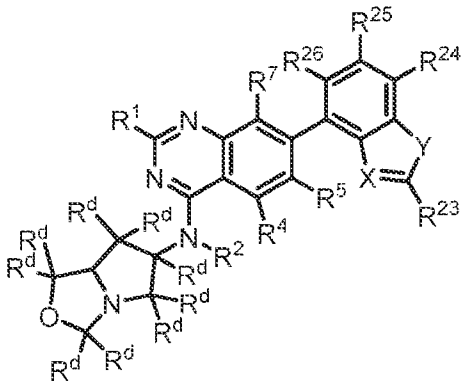
519. The compound of Embodiment 518, wherein the compound is a compound according to Formula IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1:



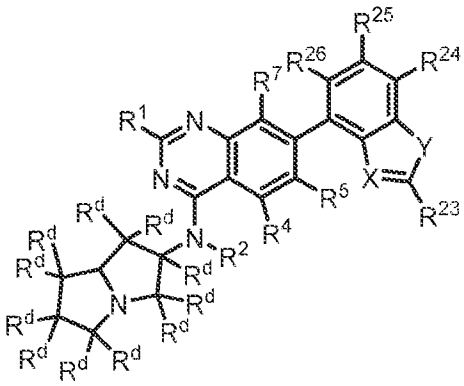
(IIBB1),



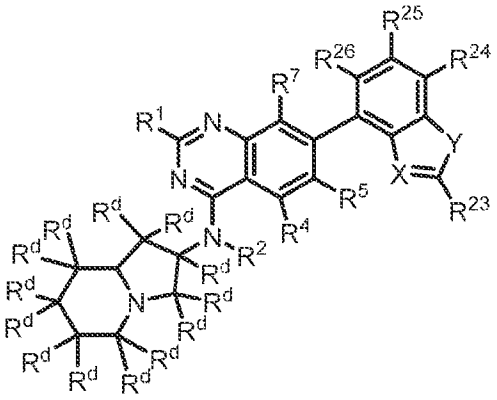
(IICC1),



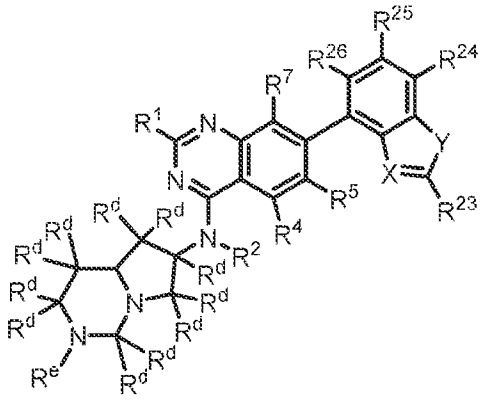
(IIDD1),



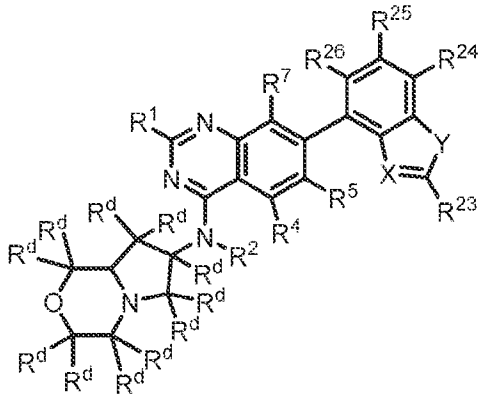
(IIEE1),



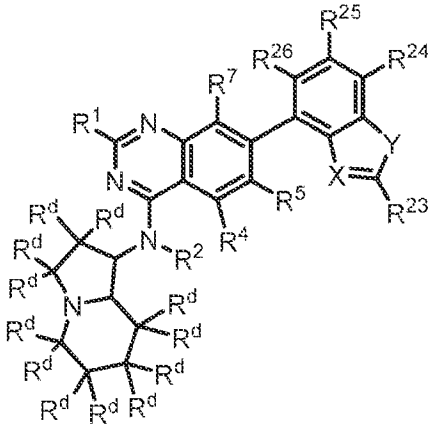
(IIFF1),



(IIGG1),



(IIHH1), and



(IIJJ1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e, if present, is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

520. The compound of any one of Embodiments 517-519, wherein X is C-CN, Y is S, and R^{23} is -$N(R^{12})_2$.

521. The compound of any one of Embodiments 517-520, wherein one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

522. The compound of any one of Embodiments 510-521, wherein R^e is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{20}.

523. The compound of any one of Embodiments 510-521, wherein R^e is -C(O)(3-6 membered carbocycle).

524. The compound of any one of Embodiments 510-521, wherein R^e is selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), and -C(O)O(C_{1-6}alkyl), wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

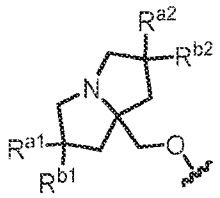
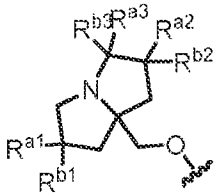
525. The compound of any one of Embodiments 510-524, wherein each R^d is H.

526. The compound of any one of Embodiments 496-525, wherein R^2 is H.

527. The compound of any one of Embodiments 496-526, wherein R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}.

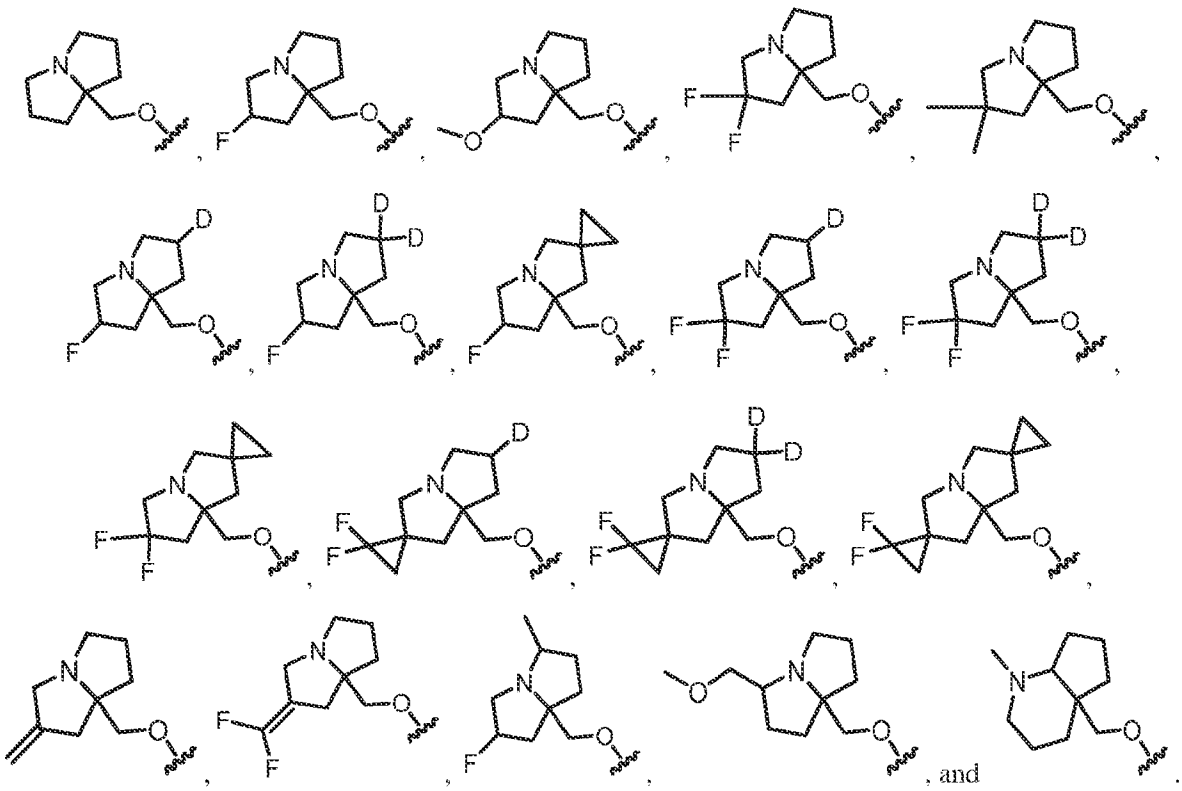
528. The compound of Embodiment 527, wherein R^2 is selected from C_{1-2}alkyl.

529. The compound of any one of Embodiments 496, 497, and 499-528, wherein R^1 is selected from -OR^8.

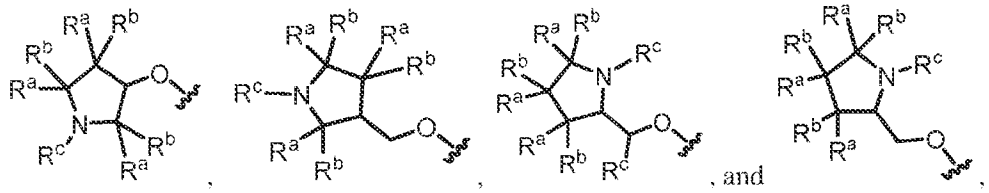
530. The compound of Embodiment 529, wherein R^1 is selected from:  , or  , R^{a1}, R^{a2}, R^{b1}, R^{b2}, R^{a3}, and R^{b3} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, , -C_{1-6} heteroalkyl, -OR^{12}, and H, wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-}

$_{6}$alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}.

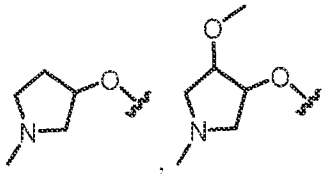
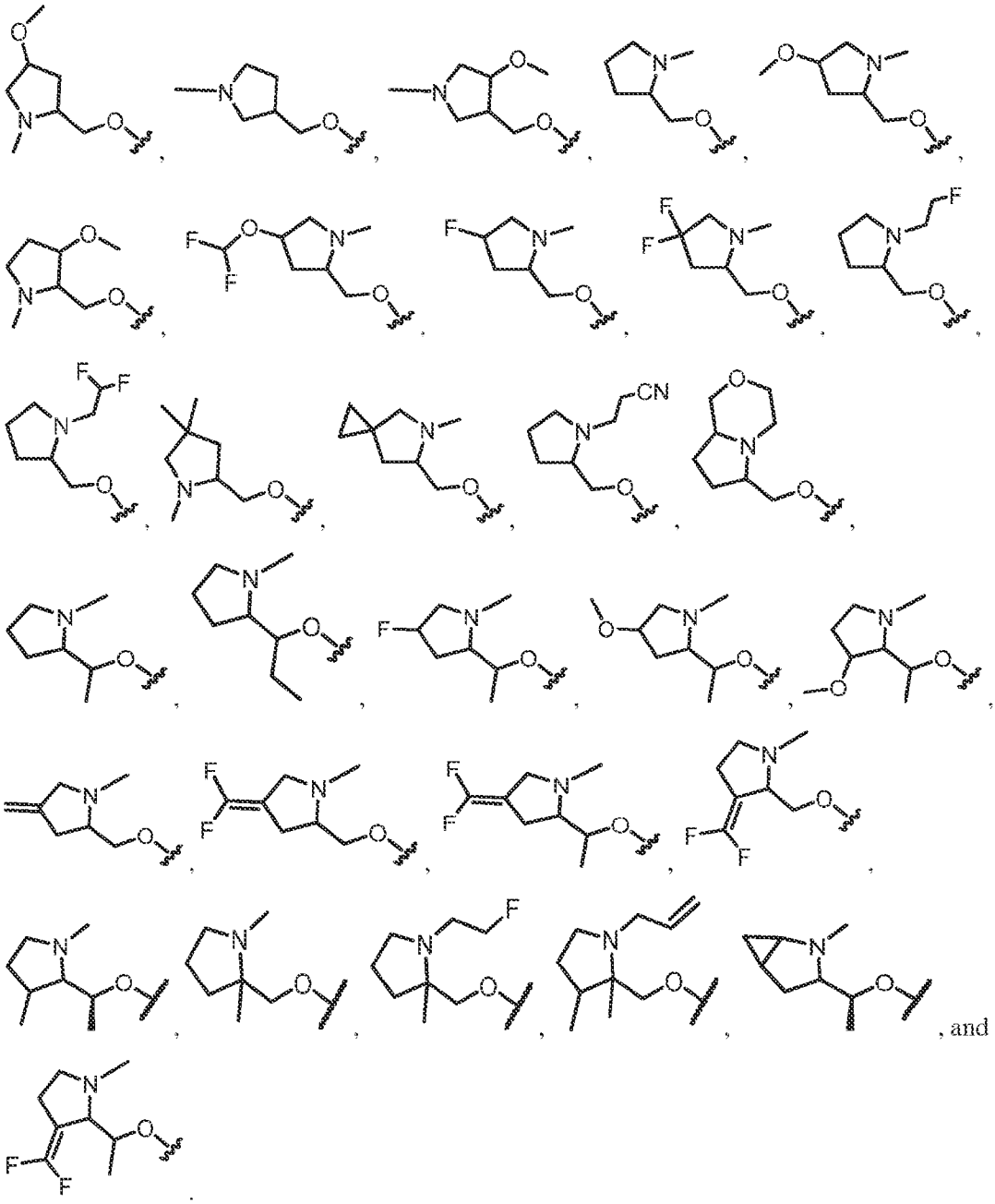
531. The compound of Embodiment 530, wherein R^1 is selected from:



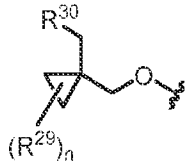
532. The compound of Embodiment 529, wherein R^1 is selected from:



wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, -OR^{12}, and H; and each R^c is independently selected from C_{1-6} alkyl and H, wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

533. The compound of Embodiment 532, wherein R^1 is selected from:  ,  , and .

534. The compound of any one of Embodiments 496, 497, and 499-528, wherein R^1 is selected from



, wherein:

each R^{28} is independently selected from C_{1-6}alkyl and halogen; and

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

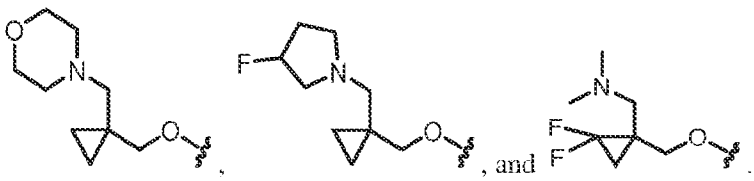
R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; and

n is 0-2.

535. The compound of Embodiment 534, wherein R^{30} is $N(R^{14})_2$.

536. The compound of Embodiment 534 or 535, wherein at least one R^{29} is a halogen such as F.

537. The compound of any one of Embodiments 534-536, wherein R^1 is selected from:

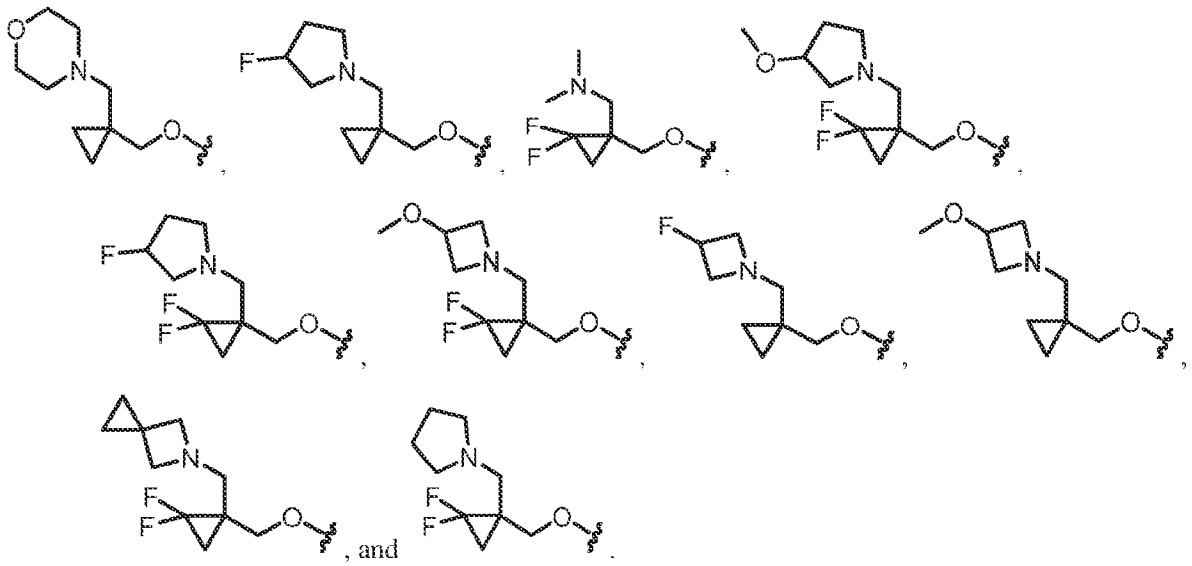


, and .

538. The compound of any one of Embodiments 496-528, wherein R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

539. The compound of Embodiment 538, wherein R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

540. The compound of Embodiment 538 or 539, wherein R^1 is selected from:



, and

541. The compound of any one of Embodiments 496, 497, and 499-528, wherein R^1 is H.

542. The compound of any one of Embodiments 496, 497, and 499-541, wherein R^5 is a halogen (e.g., F or Cl).

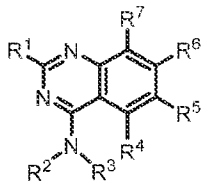
543. The compound of any one of Embodiments 496, 497, and 499-541, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

544. The compound of Embodiment 543, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

545. The compound of Embodiment 544, wherein R^5 is $-CF_3$.

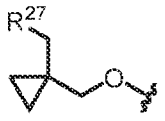
546. The compound of any one of Embodiments 496-545, wherein the compound is a not a compound included in Table 1.

547. A compound represented by Formula IV:



(IV)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from $-OR^8$ and  ;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13};

R^3 is selected from C_{1-6}alkyl that is substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, -$N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

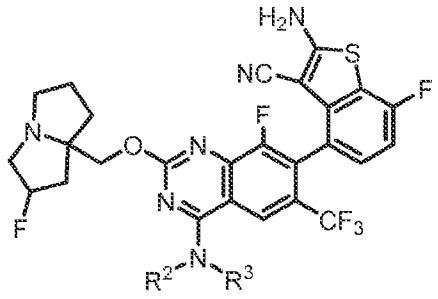
each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -CN, -NH_2, -NHC_{1-6}alkyl, and halogen;

R^{27} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen; and

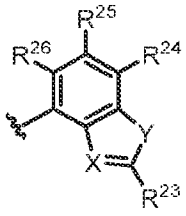
R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, -OR^{12}, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle.

548. The compound of Embodiment 547, wherein the compound is of Formula IV-a:



(IV-a)

or a salt (e.g., pharmaceutically acceptable salt) thereof.



549. The compound of Embodiment 547, wherein R^6 is selected from: , wherein:

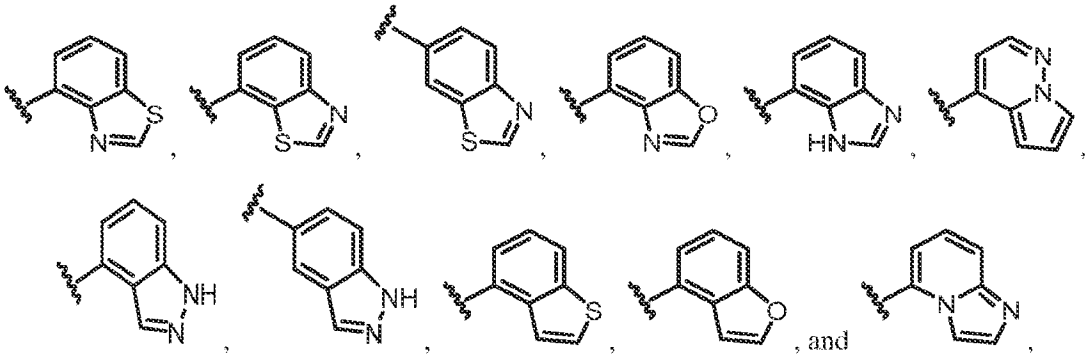
X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

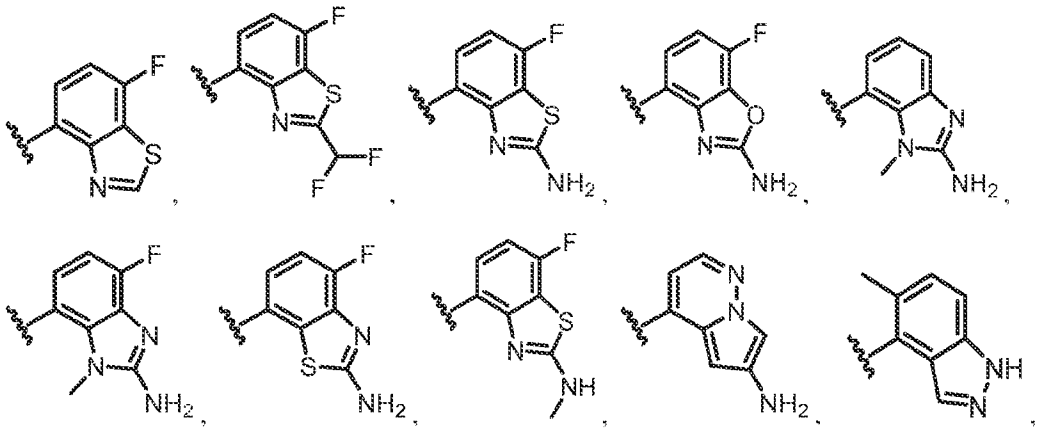
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

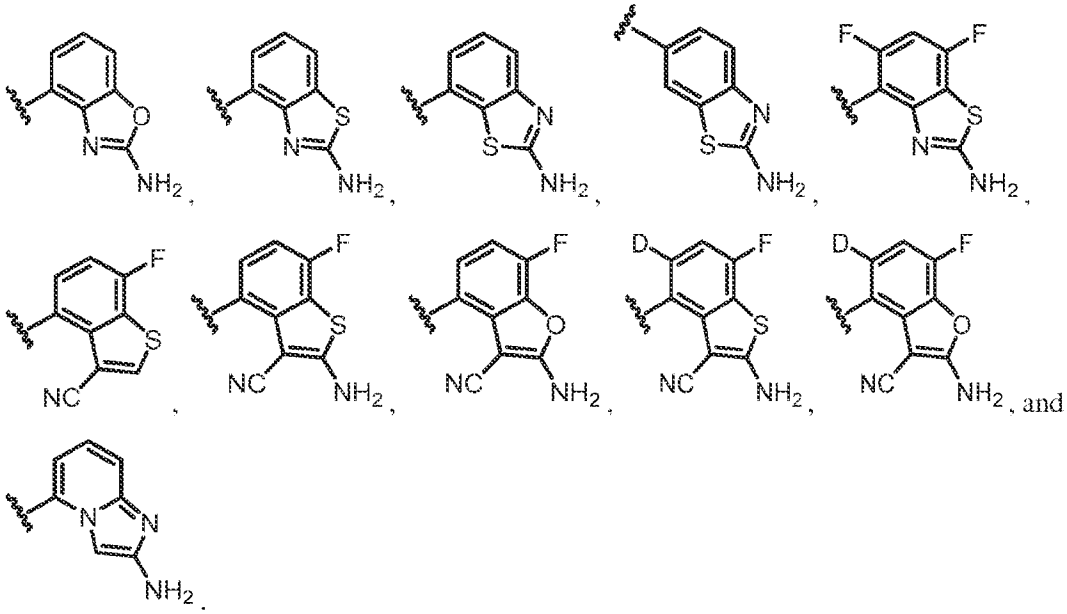
550. The compound of Embodiment 547 or Embodiment 549, wherein R^6 is selected from:



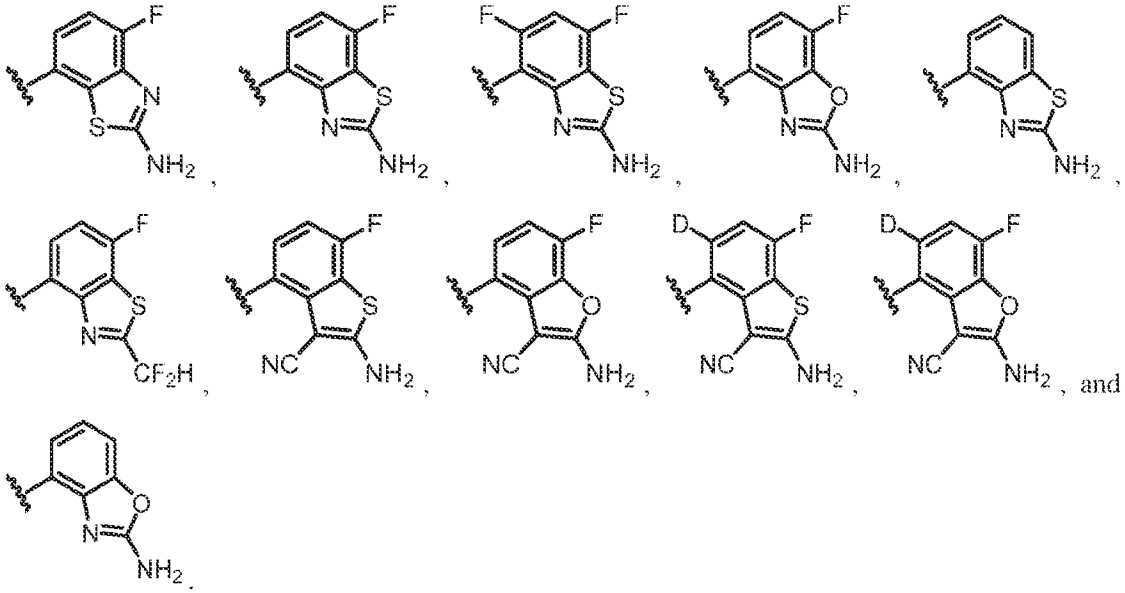
any of which is substituted with one or more R^{15}.

551. The compound of any one of Embodiments 547, and 549-550, wherein R^6 is selected from:

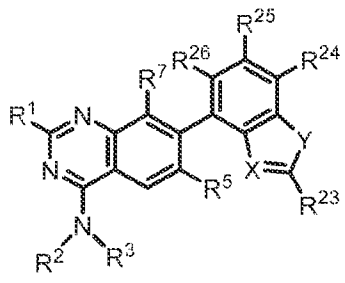




552. The compound of any one of Embodiments 547, and 549-555, wherein R^6 is selected from:



553. The compound of Embodiment 547, wherein the compound is a compound according to Formula IVB:



(IVB),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

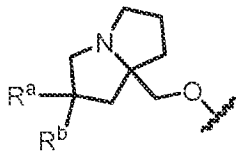
X is selected from N and C-CN;

Y is selected from O and S;

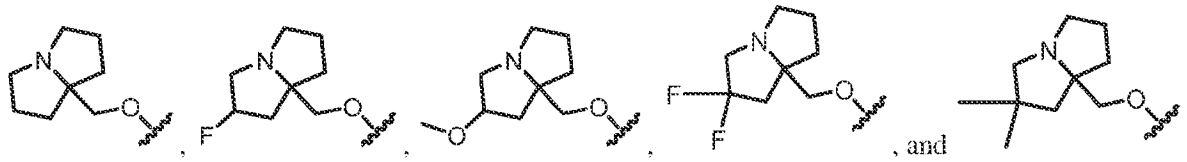
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

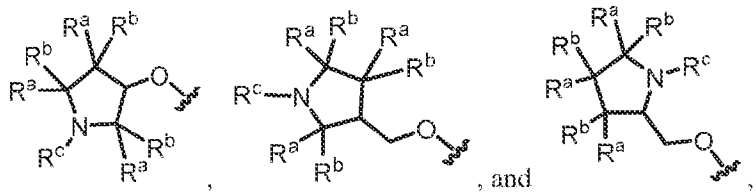
554. The compound of any one of Embodiments 547, and 549-553, wherein R^1 is selected from $-OR^8$.

555. The compound of Embodiment 554, wherein R^1 is selected from:  , wherein R^a and R^b are each independently selected from halogen, C_{1-6}alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}.

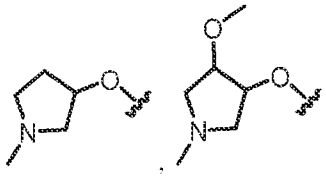
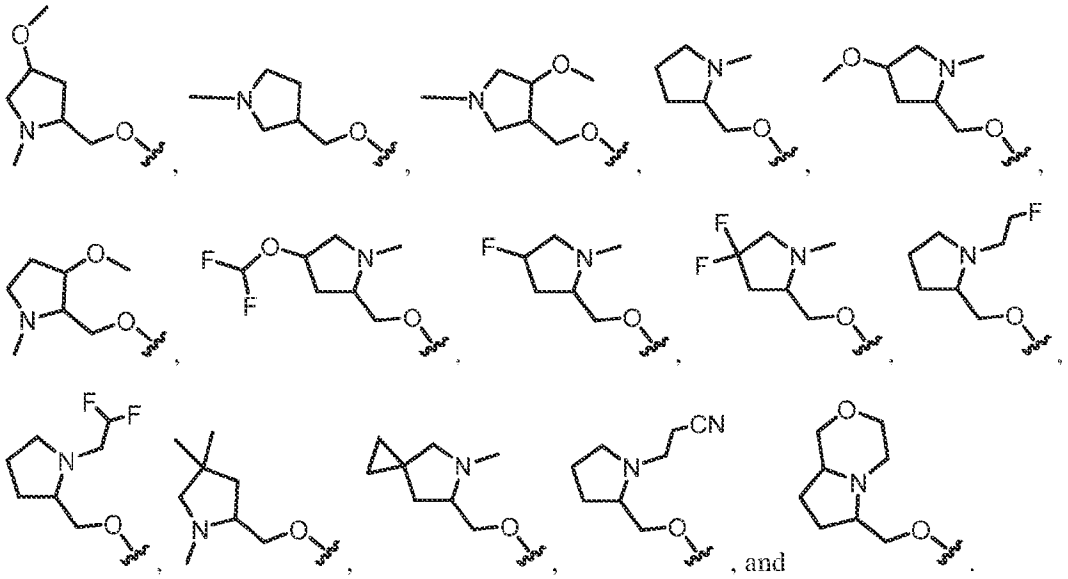
556. The compound of Embodiment 555, wherein R^1 is selected from:

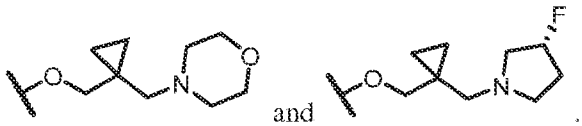


557. The compound of Embodiment 554, wherein R^1 is selected from:

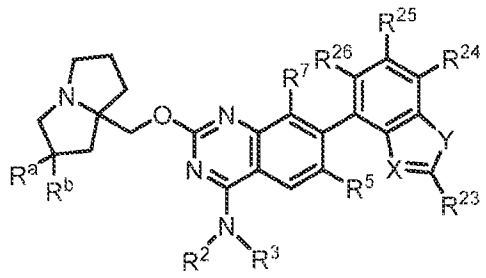


wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and R^c is selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle.

558. The compound of Embodiment 557, wherein R^1 is selected from:  ,  , and .

559. The compound of any one of Embodiments 547, and 549-553, wherein R^1 is selected from  .

560. The compound of Embodiment 547, wherein the compound is a compound according to Formula IVC:


(IVC),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, -OR^{12}, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

561. The compound of Embodiment 560, wherein R^a is a halogen (e.g., F).

562. The compound of Embodiment 560 or 561, wherein R^b is H.

563. The compound of any one of Embodiments 553-562, wherein X is C-CN, Y is S, and R^{23} is selected from -$N(R^{12})_2$.

564. The compound of any one of Embodiments 553-562, wherein at least one of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

565. The compound of any one of Embodiments 547-564, wherein R^3 is selected from C_{1-3}alkyl that is substituted with one or more R^{10}.

566. The compound of Embodiment 565, wherein each R^{10} is independently selected from 3-6 membered heterocycle and a 5-6 membered heteroaryl, wherein any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13}.

567. The compound of Embodiment 566, wherein each R^{10} is independently selected from thiazole, oxazole, isoxazole, isothiazole, pyrazole, and pyridine, any of which is unsubstituted or substituted with one or more R^{12}, or R^{13}.

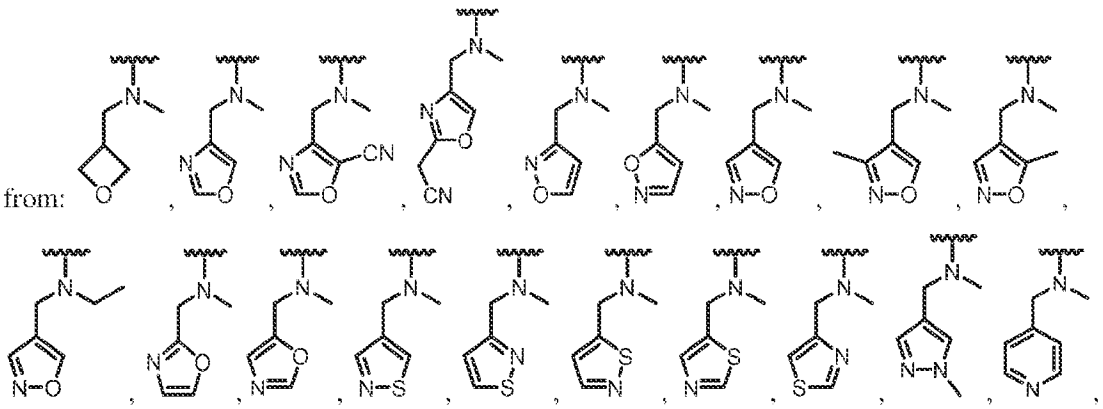
568. The compound of any one of Embodiments 547-567, wherein R^2 is H.

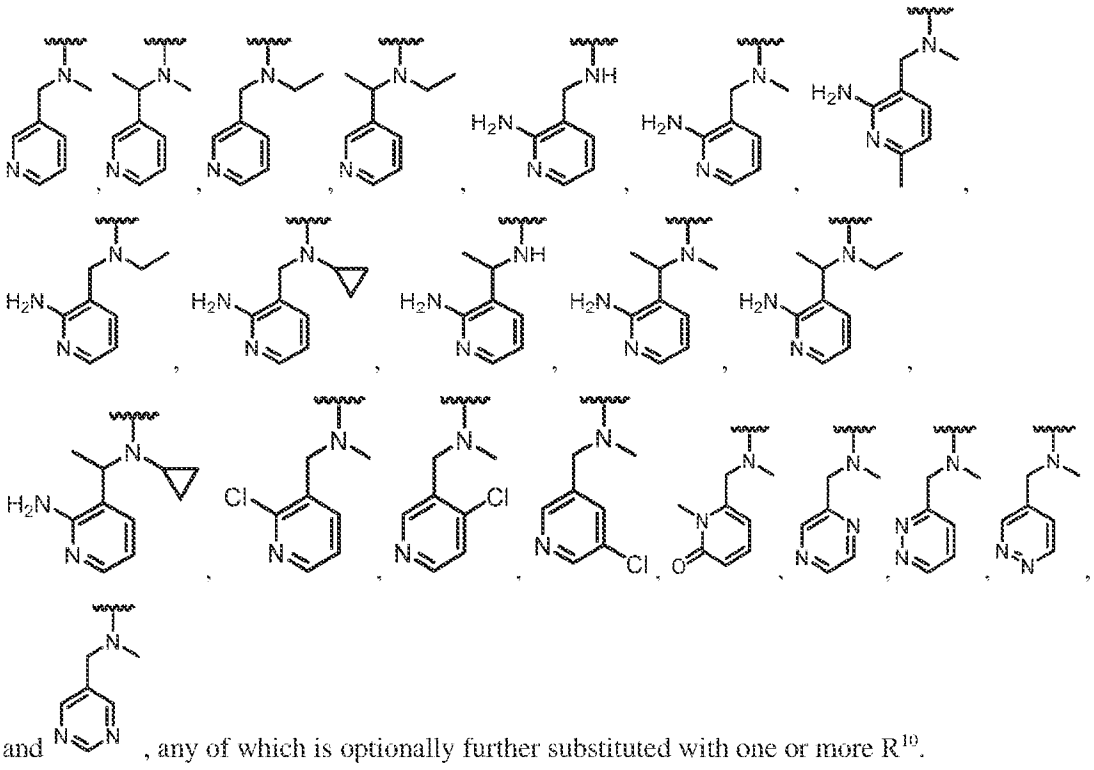
569. The compound of any one of Embodiments 547-567, wherein R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}.

570. The compound of Embodiment 569, wherein R^2 is selected from C_{1-2}alkyl that is unsubstituted.

571. The compound of any one of Embodiments 547-567, wherein R^2 is a 3-6 membered carbocycle.

572. The compound of any one of Embodiments 547-564, wherein the moiety is selected from:





and , any of which is optionally further substituted with one or more R^{10}.

573. The compound of any one of Embodiments 547, and 549-572, wherein R^5 is a halogen (e.g., F or Cl).

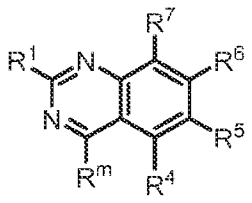
574. The compound of any one of Embodiments 547, and 549-572, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

575. The compound of Embodiment 574, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

576. The compound of Embodiment 575, wherein R^5 is $-CF_3$.

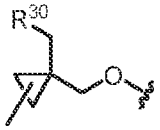
577. The compound of any one of Embodiments 547, and 549-576, wherein R^7 is F.

578. A compound represented by Formula V':



(V')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:



R^1 is selected from -OR^8, , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^m is selected from hydrogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, -$N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

n is 0-2;

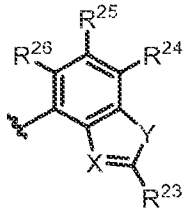
each R^{31} is selected from C_{1-6} alkyl; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

579. The compound of Embodiment 578, wherein R^m is hydrogen.

580. The compound of Embodiment 578, wherein R^m is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

581. The compound of Embodiment 580, wherein R^m is methyl that is unsubstituted.

582. The compound of any one of Embodiments 578-581, wherein R^6 is  , wherein:

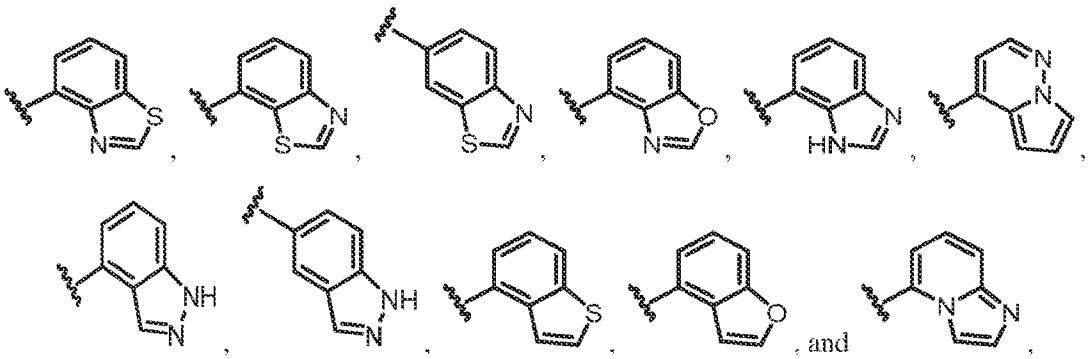
X is selected from N and C-CN;

Y is selected from O and S;

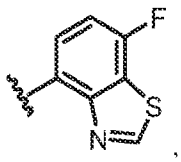
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

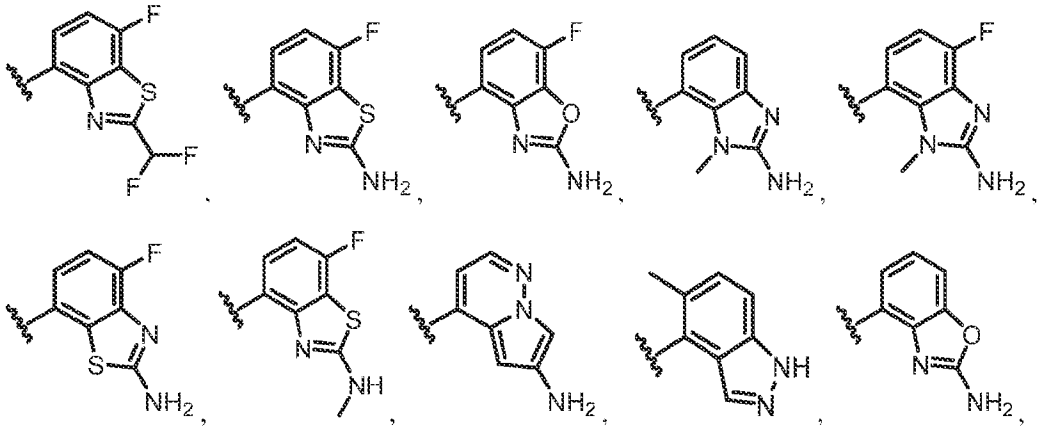
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

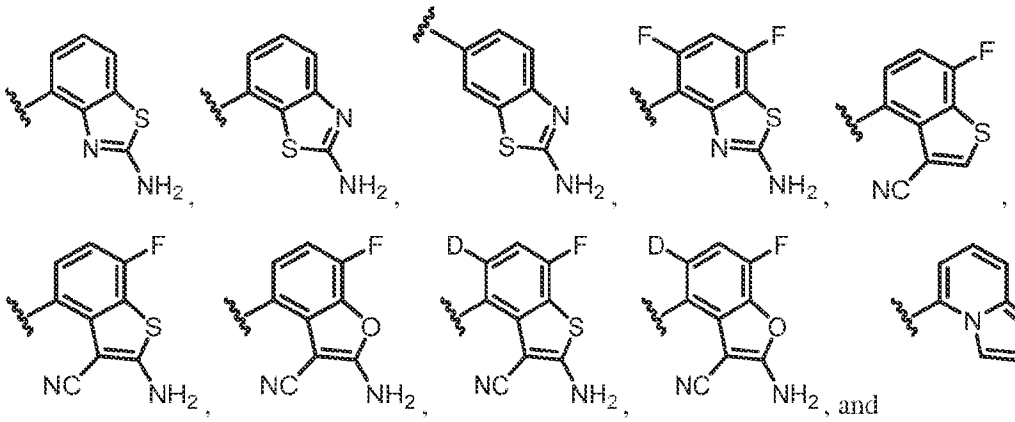
583. The compound of any one of Embodiments 578-582, wherein R^6 is selected from:



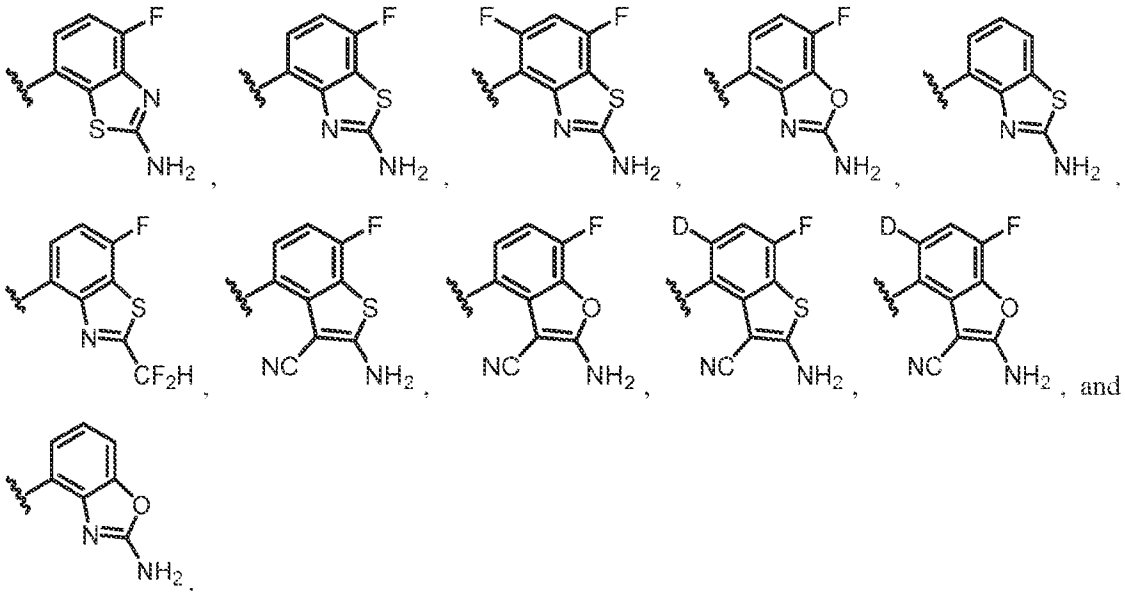
any of which is substituted with one or more R^{15}.

584. The compound of any one of Embodiments 578-583, wherein R^6 is selected from:  ,

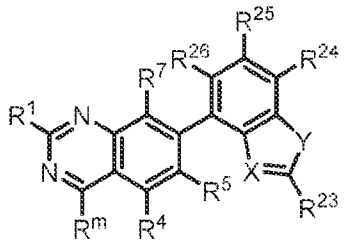




585. The compound of any one of Embodiments 578-584, wherein R^6 is selected from:



586. The compound of any one of Embodiments 578-582, wherein the compound is a compound of Formula VC':



(VC')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

X is selected from N and C-CN;

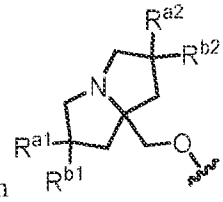
Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

587. The compound of any one of Embodiments 582-586, wherein X is C-CN, Y is S, R^{23} is $-N(R^{12})_2$, and one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

588. The compound of any one of Embodiments 578-587, wherein R^1 is selected from $-OR^8$.

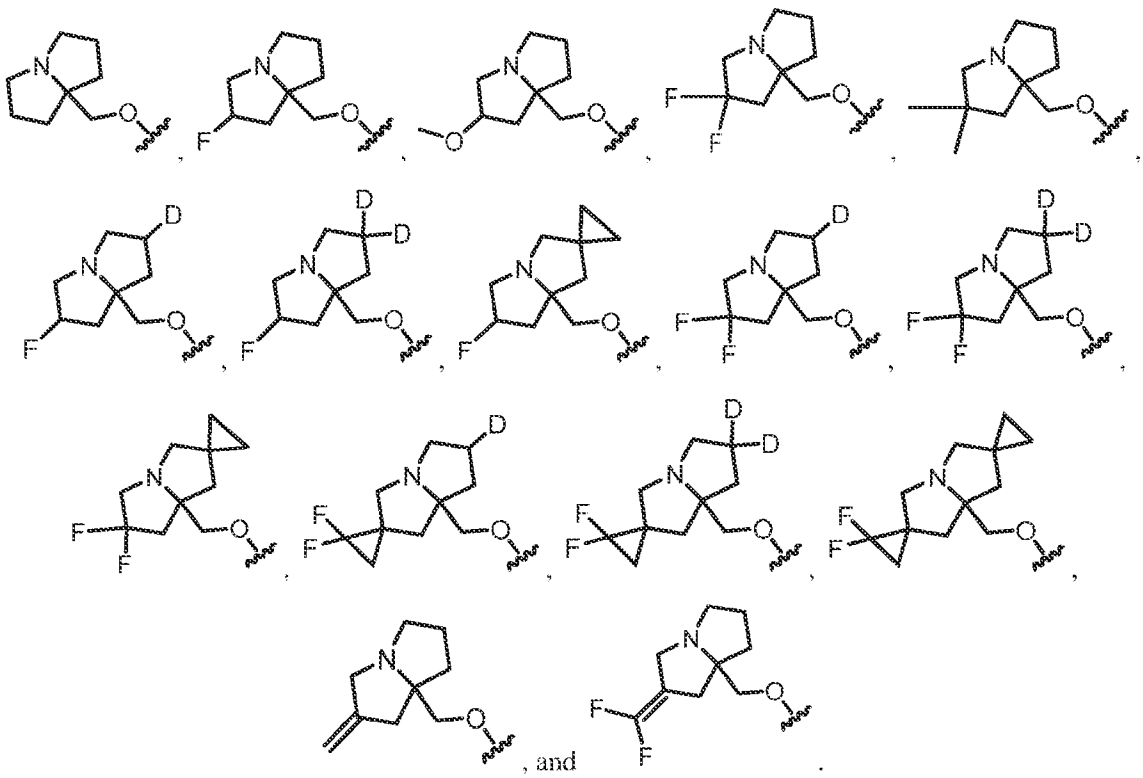
589. The compound of Embodiment 588, wherein R^1 is selected from  , wherein:

R^{a1}, R^{a2}, R^{b1}, and R^{b} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H or are absent,

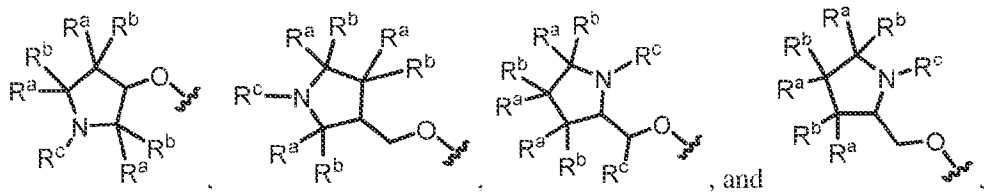
wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and

wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}.

590. The compound of Embodiment 589, wherein R^1 is selected from:



591. The compound of Embodiment 588, wherein R^1 is selected from:

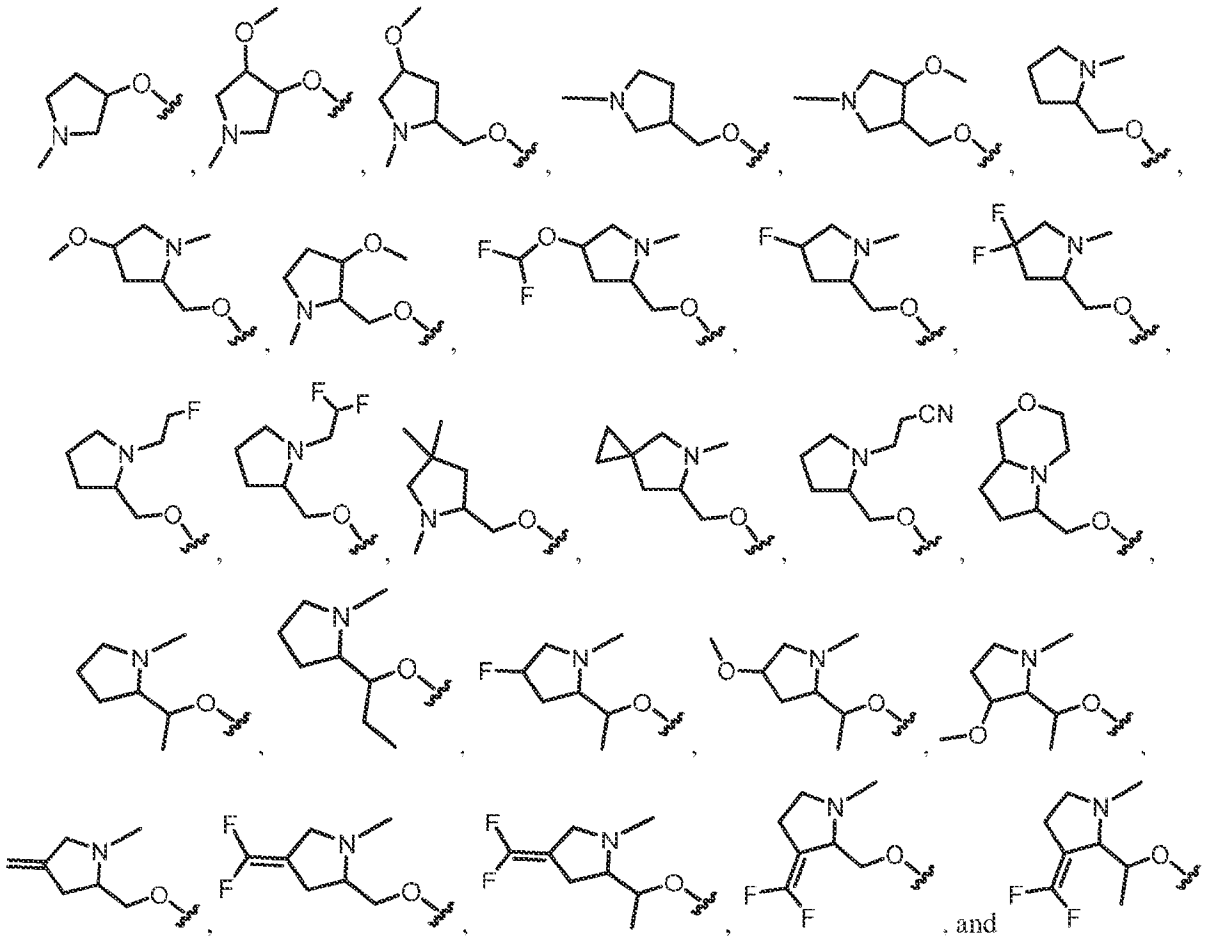


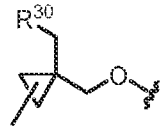
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H; and each R^c is independently selected from H and C_{1-6} alkyl,

wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and

wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

592. The compound of Embodiment 591, wherein R^1 is selected from:



593. The compound of any one of Embodiments 578-587, wherein R^1 is selected from 
, wherein:

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

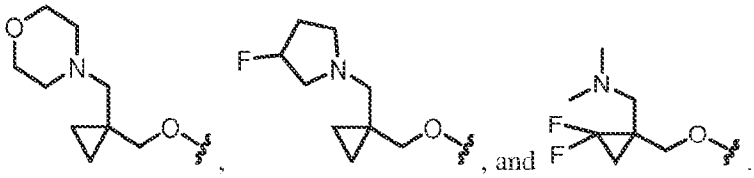
R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; and

n is 0-2.

594. The compound of Embodiment 593, wherein R^{30} is $N(R^{14})_2$.

595. The compound of Embodiment 593 or 594, wherein at least one R^{29} is a halogen such as F.

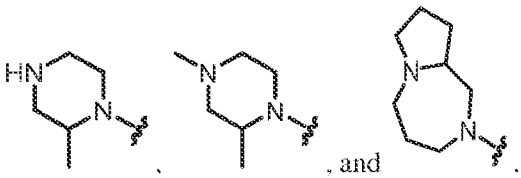
596. The compound of any one of Embodiments 593-595, wherein R^1 is selected from:



597. The compound of any one of Embodiments 578-587, wherein R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

598. The compound of Embodiment 597, wherein R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

599. The compound of Embodiment 598, wherein R^1 is selected from:



600. The compound of any one of Embodiments 578-599, wherein R^5 is a halogen (e.g., F or Cl).

601. The compound of any one of Embodiments 578-599, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

602. The compound of Embodiment 601, wherein R^5 is selected from C_{1-6}alkyl that is substituted with one or more halogens or -CN.

603. The compound of Embodiment 602, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

604. The compound of Embodiment 603, wherein R^5 is $-CF_3$.

605. The compound of any one of Embodiments 578-604, wherein R^7 is F.

606. A compound shown in Table 3 or Table 3a, or a salt (e.g., pharmaceutically acceptable salt) thereof.

607. A pharmaceutical composition comprising a compound of any one of Embodiments 443-606, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable excipient.

608. A compound of any one of Embodiments 443-606, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use as a medicament.

609. The compound of Embodiment 608, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

610. The compound of Embodiment 609, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

611. The compound of Embodiment 609, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

612. The compound of any one of Embodiments 608-611, wherein the medicament is useful in the prevention or treatment of a cancer.

613. The compound of Embodiment 612, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

614. A compound of any one of Embodiments 443-606, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the treatment of a disease, disorder, or condition.

615. The compound of Embodiment 614, wherein the disease, disorder, or condition is a cancer.

616. The compound of Embodiment 615, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

617. The compound of any one of Embodiments 614-616, wherein the compound is used in the treatment of a disease, disorder, or condition in a subject in need thereof.

618. A compound of any one of Embodiments 443-606, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the manufacture of a medicament.

619. The compound of Embodiment 618, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a

Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

620. The compound of Embodiment 619, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

621. The compound of Embodiment 619 or 620, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

622. The compound of any one of Embodiments 618-621, wherein the medicament is useful in the treatment of a cancer.

623. The compound of Embodiment 622, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

624. A method, comprising administering a therapeutically effective amount of a compound of any one of Embodiments 443-606, or a salt (e.g., pharmaceutically acceptable salt) thereof, to a subject in need thereof.

625. The method of Embodiment 624, wherein the subject has a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

626. The method of Embodiment 625, wherein the disease, disorder, or condition is ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

627. The method of Embodiment 625 or 626, wherein the disease, disorder, or condition is ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

628. The method of any one of Embodiments 624-627, wherein the subject has a cancer.

629. The method of Embodiment 628, wherein the subject was previously diagnosed with the cancer.

630. The method of Embodiment 628 or 629, wherein the subject has previously undergone a treatment regimen for the cancer.

631. The method of any one of Embodiments 628-630, wherein the subject has previously entered remission from the cancer.

632. The method of any one of Embodiments 628-631, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

633. The method of any one of Embodiments 624-632, wherein the compound, or the salt thereof, is administered in combination with an additional therapeutic agent.

634. The use of a compound of any one of Embodiments 443-606, or a salt (e.g., pharmaceutically acceptable salt) thereof, for the manufacture of a medicament for the treatment of a cancer.

635. The use of Embodiment 634, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

636. A method, comprising contacting a KRAS protein with a compound of any one of Embodiments 443-606, or a salt (e.g., pharmaceutically acceptable salt) thereof.

637. The method of Embodiment 636, wherein contacting the KRAS protein with the compound modulates KRAS.

638. The method of Embodiment 636 or 637, wherein the KRAS protein has a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation.

639. The method of Embodiment 636 or 637, wherein the KRAS protein is a wild-type KRAS protein, including wild-type amplified KRAS.

640. The method of any one of Embodiments 636-639, wherein the KRAS protein is in an active (GTP-bound) state.

641. The method of any one of Embodiments 636-639, wherein the KRAS protein is in an inactive (GDP-bound) state.

642. The method of any one of Embodiments 636-641, wherein the KRAS protein is located within a cell.

643. The method of Embodiment 642, wherein the cell is located within a subject.

644. The method of Embodiment 643, wherein the subject is a human.

645. The method of Embodiment 643 or 644, wherein the subject has a cancer.

646. The method of Embodiment 645, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

647. A method of inhibiting the function of a wild-type KRAS protein, including wild-type amplified KRAS, or a KRAS protein having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, comprising contacting the KRAS protein with a compound of any one of Embodiments 443-606, or a salt (e.g., pharmaceutically acceptable salt) thereof.

648. The method of Embodiment 647, wherein the KRAS protein is a wild-type KRAS protein, including wild-type amplified KRAS.

649. The method of Embodiment 647, wherein the KRAS protein has a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation.

650. The method of Embodiment 649, wherein the KRAS protein has a G12D, G12V, or G12R mutation.

651. The method of any one of Embodiments 647-650, wherein the KRAS protein is in an active (GTP-bound) state.

652. The method of any one of Embodiments 647-650, wherein the KRAS protein is in an inactive (GDP-bound) state.

653. The method of any one of Embodiments 647-652, wherein the KRAS protein is located within a cell.

654. The method of Embodiment 653, wherein the cell is located within a subject.

655. The method of Embodiment 654, wherein the subject is a human.

656. The method of Embodiment 654 or 655, wherein the subject has a cancer.

657. The method of Embodiment 656, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, esophageal adenocarcinoma, gastroesophageal junction cancer, invasive ductal carcinoma, and lung cancer.

658. A compound capable of inhibiting a wild-type KRAS protein, including wild-type amplified KRAS, or a KRAS protein having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation in both its active (GTP-bound) and inactive (GDP-bound) state.

659. The compound of Embodiment 658, wherein the compound:

(i) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, 1 μM< $IC_{50} \leq 10$ μM, or 10 μM< IC_{50} in the assay of Biological Example 1 (e.g., a protein:protein interaction (PPI) Homogenous Time Resolved Fluorescence (HTRF) analysis of 50 nM Avi-KRAS G12D (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12C (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12V (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS WT (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), and/or 75 nM 3xFLAG-RAF1 RBD (51-131)-Avi; and/or

(ii) has $IC_{50} \leq 0.1$ μM, or $IC_{50} > 0.1$ μM in the assay of Biological Example 2 or 4 (e.g., cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iii) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or $IC_{50} > 1$ μM in the assay of Biological Example 3 (cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iv) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or $IC_{50} > 1$ μM in the assay of Biological Example 4 (cell-based pERK HTRF assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080); and/or

(v) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or $IC_{50} > 1$ μM in the assay of Biological Example 5 (3D Cell viability assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080).

660. The compound of Embodiment 659, wherein the compound:

(i) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, or 1 μM< $IC_{50} \leq 10$ μM in the assay of Biological Example 1 (e.g., a protein:protein interaction (PPI) Homogenous Time Resolved Fluorescence (HTRF) analysis of 50 nM Avi-KRAS G12D (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12C (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12V (amino acids 2-169)

GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS WT (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), and/or 75 nM 3xFLAG-RAF1 RBD (51-131)-Avi; and/or

(ii) has $IC_{50} \leq 0.1$ μM in the assay of Biological Example 2 or 4 (e.g., cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iii) has $IC_{50} \leq 0.1$ μM or $0.1\ \mu M < IC_{50} \leq 1$ μM in the assay of Biological Example 3 (cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iv) has $IC_{50} \leq 0.1$ μM or $0.1\ \mu M < IC_{50} \leq 1$ μM in the assay of Biological Example 4 (cell-based pERK HTRF assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080); and/or

(v) has $IC_{50} \leq 0.1$ μM or $0.1\ \mu M < IC_{50} \leq 1$ μM in the assay of Biological Example 5 (3D Cell viability assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080).

661. The compound of any one of Embodiments 658-660, wherein the compound is capable of irreversibly binding the KRAS protein.

662. The compound of any one of Embodiments 658-660, wherein the compound is capable of reversibly binding the KRAS protein.

663. The compound of any one of Embodiments 658-662, wherein the compound is a compound according to any one of Embodiments 443-606.

[0437] In some embodiments of any of the preceding aspects, the compound is a compound included in Table 3, Table 3a, Table 3b, or Table 3c, or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof. In some embodiments, the compound is a compound included in Table 3, Table 3a, Table 3b, or Table 3c, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[0438] Also provided herein is a compound selected from Table 3 Table 3a, Table 3b, or Table 3c, or any of the Examples provided herein, or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof. In some embodiments, the present disclosure provides a compound selected from Table 3 Table 3a, Table 3b, or Table 3c, or any of the Examples provided herein, or a salt thereof.

[0439] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of interacting with a residue at the 12 and/or 13 and/or 61 position of the KRAS protein (e.g., a glutamine, histidine, cysteine, valine, aspartic acid, serine, alanine, arginine, or glycine residue). In some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of non-covalently interacting with a residue at the 12 and/or 13 and/or 61 position of the KRAS protein (e.g., a glutamine, histidine,

cysteine, valine, aspartic acid, serine, alanine, arginine, or glycine residue), such as via one or more van der Waals, hydrogen bonding, ionic, or other interactions.

[0440] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12C mutation relative to KRAS having other residues at the 12 position of the P loop, such as arginine(R), glycine (G), valine (V), serine (S), alanine (A), and aspartic acid (D). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater selectivity for KRAS having a G12C mutation relative to KRAS having other residues at the 12 position of the P loop, such as arginine (R), glycine (G), valine (V), serine (S), alanine (A), and aspartic acid (D). In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12C mutation relative to wild-type KRAS. For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12C mutation relative to wild-type KRAS. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12C mutation relative to other forms of RAS (e.g., HRAS and NRAS). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12C mutation relative to another form of RAS (e.g., HRAS or NRAS), such as an HRAS or NRAS protein having a G12C mutation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding to a KRAS protein having a G12C mutation and one or more additional mutations, such as a mutation at codon 13 (to, e.g., D or C) or codon 61.

[0441] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12R mutation relative to KRAS having other residues at the 12 position of the P loop, such as cysteine (C), glycine (G), valine (V), serine (S), alanine (A), and aspartic acid (D). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater selectivity for KRAS having a G12R mutation relative to KRAS having other residues at the 12 position of the P loop, such as cysteine

(C), glycine (G), valine (V), serine (S), alanine (A), and aspartic acid (D). In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12R mutation relative to wild-type KRAS. For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12R mutation relative to wild-type KRAS. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12R mutation relative to other forms of RAS (e.g., HRAS and NRAS). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12R mutation relative to another form of RAS (e.g., HRAS or NRAS), such as an HRAS or NRAS protein having a G12R mutation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding to a KRAS protein having a G12R mutation and one or more additional mutations, such as a mutation at codon 13 (to, e.g., D or C) or codon 61.

[0442] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12V mutation relative to KRAS having other residues at the 12 position of the P loop, such as cysteine (C), glycine (G), arginine (R), serine (S), alanine (A), and aspartic acid (D). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater selectivity for KRAS having a G12V mutation relative to KRAS having other residues at the 12 position of the P loop, such as cysteine (C), glycine (G), arginine (R), serine (S), alanine (A), and aspartic acid (D). In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12V mutation relative to wild-type KRAS. For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12V mutation relative to wild-type KRAS. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12V mutation relative to other forms of RAS (e.g., HRAS and NRAS). For example, in some embodiments, a compound provided

herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12V mutation relative to another form of RAS (e.g., HRAS or NRAS), such as an HRAS or NRAS protein having a G12V mutation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding to a KRAS protein having a G12V mutation and one or more additional mutations, such as a mutation at codon 13 (to, e.g., D or C) or codon 61.

[0443] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12S mutation relative to KRAS having other residues at the 12 position of the P loop, such as cysteine (C), glycine (G), arginine (R), valine (V), alanine (A), and aspartic acid (D). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater selectivity for KRAS having a G12S mutation relative to KRAS having other residues at the 12 position of the P loop, such as cysteine (C), glycine (G), arginine (R), valine (V), alanine (A), and aspartic acid (D). In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12S mutation relative to wild-type KRAS. For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12S mutation relative to wild-type KRAS. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12S mutation relative to other forms of RAS (e.g., HRAS and NRAS). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12S mutation relative to another form of RAS (e.g., HRAS or NRAS), such as an HRAS or NRAS protein having a G12S mutation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding to a KRAS protein having a G12S mutation and one or more additional mutations, such as a mutation at codon 13 (to, e.g., D or C) or codon 61.

[0444] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12A mutation

relative to KRAS having other residues at the 12 position of the P loop, such as cysteine (C), glycine (G), arginine (R), valine (V), serine (S), and aspartic acid (D). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater selectivity for KRAS having a G12A mutation relative to KRAS having other residues at the 12 position of the P loop, such as cysteine (C), glycine (G), arginine (R), valine (V), serine (S), and aspartic acid (D). In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12A mutation relative to wild-type KRAS. For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12A mutation relative to wild-type KRAS. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12A mutation relative to other forms of RAS (e.g., HRAS and NRAS). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12A mutation relative to another form of RAS (e.g., HRAS or NRAS), such as an HRAS or NRAS protein having a G12A mutation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding to a KRAS protein having a G12A mutation and one or more additional mutations, such as a mutation at codon 13 (to, e.g., D or C) or codon 61.

[0445] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12D mutation relative to KRAS having other residues at the 12 position of the P loop, such as cysteine (C), glycine (G), arginine (R), valine (V), serine (S), and alanine (A). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater selectivity for KRAS having a G12D mutation relative to KRAS having other residues at the 12 position of the P loop, such as cysteine (C), glycine (G), arginine (R), valine (V), serine (S), and alanine (A). In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12D mutation relative to wild-type KRAS. For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic

form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12D mutation relative to wild-type KRAS. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G12D mutation relative to other forms of RAS (e.g., HRAS and NRAS). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G12D mutation relative to another form of RAS (e.g., HRAS or NRAS), such as an HRAS or NRAS protein having a G12D mutation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding to a KRAS protein having a G12D mutation and one or more additional mutations, such as a mutation at codon 13 (to, e.g., D or C) or codon 61.

[0446] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G13D mutation relative to KRAS having other residues at the 13 position of the P loop, such as cysteine (C), glycine (G), arginine (R), valine (V), serine (S), and alanine (A). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater selectivity for KRAS having a G13D mutation relative to KRAS having other residues at the 13 position of the P loop, such as cysteine (C), glycine (G), arginine (R), valine (V), serine (S), and alanine (A). In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G13D mutation relative to wild-type KRAS. For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G13D mutation relative to wild-type KRAS. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a G13D mutation relative to other forms of RAS (e.g., HRAS and NRAS). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a G13D mutation relative to another form of RAS (e.g., HRAS or NRAS), such as an HRAS or NRAS protein having a G13D mutation. In some embodiments of any of the preceding aspects, a compound provided

herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding to a KRAS protein having a G13D mutation and one or more additional mutations, such as a mutation at codon 12 (to, e.g., D, C, A, S, V, or R) or codon 61.

[0447] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a Q61H mutation relative to KRAS having other residues at the 61 position of the P loop, such as glutamine (Q). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater selectivity for KRAS having a Q61H mutation relative to KRAS having other residues at the 61 position of the P loop, such as glutamine (Q). In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a Q61H mutation relative to wild-type KRAS. For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a Q61H mutation relative to wild-type KRAS. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, binds selectively to KRAS having a Q61H mutation relative to other forms of RAS (e.g., HRAS and NRAS). For example, in some embodiments, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, demonstrates at least 1.5, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100-fold, or greater binding selectivity for KRAS having a Q61H mutation relative to another form of RAS (e.g., HRAS or NRAS), such as an HRAS or NRAS protein having a Q61H mutation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of binding to a KRAS protein having a Q61H mutation and one or more additional mutations, such as a mutation at codon 12 (to, e.g., D, C, A, S, V, or R) or codon 13 (to, e.g., D).

[0448] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of selectively binding a KRAS protein in an active (GTP-bound) conformation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of selectively binding a KRAS protein in an inactive (GDP-bound) conformation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, is capable of selectively binding a KRAS protein in both active (GTP-bound) and

inactive (GDP-bound) conformations. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, has higher selectivity for a KRAS protein in its active (GTP-bound) conformation than in its inactive (GDP-bound) conformation. In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, has higher selectivity for a KRAS protein in its inactive (GDP-bound) conformation than in its active (GTP-bound) conformation.

[0449] In some embodiments of any of the preceding aspects, a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, comprises enriched levels of one or more isotopes. For example, in some embodiments, provided compounds comprise enriched levels of deuterium (D). In some embodiments, R^8 is an alkylheterocycle, wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl, and C_{1-6}alkyl is optionally deuterated (e.g. $-CH_2-$ or $-CD_2-$).. Various technologies are available for incorporating enriched levels of various isotopes and can be utilized in accordance with the present disclosure. In some embodiments, a compound has an isotopic purity of about 5%-100% (e.g., about 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% or more, or about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 50%-100%, 80%-100%, 90-100%, 95%-100%, 96%-100%, 97%-100%, 98%-100%, 99%-100%, 95-99%, 95%-99.5%, 95%-99.9%, etc). For example, in some embodiments, about 5%-100% (e.g., about 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% or more, or about 5%-100%, 10%-100%, 20%-100%, 30%-100%, 50%-100%, 80%-100%, 90-100%, 95%-100%, 96%-100%, 97%-100%, 98%-100%, 99%-100%, 95-99%, 95%-99.5%, 95%-99.9%, etc) of all molecules of a compound wherein R^8 is an alkylheterocycle, and further wherein an alkyl moiety of any alkylheterocycle is C_{1-6}alkyl, have C_{1-6}alkyl being deuterated (e.g. $-CD_2-$).

Compositions

[0450] The present disclosure also provides a composition (e.g., a pharmaceutical composition) comprising a compound provided herein (e.g.. a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof. In some embodiments, a provided composition comprises a compound provided herein, or a pharmaceutically acceptable salt thereof. For example, the present

disclosure provides a pharmaceutical composition comprising a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, together with a pharmaceutically acceptable carrier. In some embodiments, a provided pharmaceutical composition comprises a compound provided herein or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

[0451] In some embodiments, the pharmaceutical composition is formulated for oral administration. In some embodiments, the oral pharmaceutical formulation is selected from a tablet and a capsule.

[0452] In some embodiments, the pharmaceutical composition is formulated for parenteral administration. In some embodiments, the pharmaceutical composition is formulated for intravenous administration. In some embodiments, the pharmaceutical composition is formulated for subcutaneous administration.

[0453] While it may be possible for certain compounds provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, to be administered as the raw chemical, compounds may additionally or alternatively be provided in a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more compounds disclosed herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or one or more pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration selected. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art. The pharmaceutical compositions disclosed herein may be

manufactured in any suitable manner known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0454] A pharmaceutical formulation provided herein can be suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal, and topical (including dermal, buccal, sublingual, and intraocular) administration. The most suitable route may depend on, for example, the condition and disorder of the subject to which the pharmaceutical formulation will be administered. A pharmaceutical formulation can be provided in a unit dosage form. A pharmaceutical formulation can be prepared by any suitable method. A method of preparing a pharmaceutical formulation may comprise bringing a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") in contact with one or more pharmaceutically acceptable carriers (e.g., accessory ingredients). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0455] Pharmaceutical formulations of compounds provided herein (e.g., compounds of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC' in any available form (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s) etc.)) may be provided as discrete units. For example, a formulation suitable for oral administration may be provided as capsules, cachets, and/or tablets containing a predetermined amount of the compound in any suitable form (e.g., the active ingredient); as a solution or suspension in a solvent (e.g., aqueous or non-aqueous solvent); as an emulsion (e.g., an oil-in-water liquid emulsion or water-in-oil liquid emulsion); or as a powder or granules. The active ingredient may additionally or alternatively be provided as a bolus, electuary, or paste.

[0456] Pharmaceutical preparations suitable for oral administration include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by, for example, compression or molding, optionally with one or more accessory

ingredients, such as one or more pharmaceutically acceptable excipients. Compressed tablets may be prepared by, for example, compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by, for example, molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with, for example, one or more fillers such as lactose, one or more binders such as one or more starches, and/or one or more lubricants such as talc or magnesium stearate and, optionally, one or more stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. Stabilizers and other elements may also be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain a gum, gelling agent, polymer, solvent, or combination thereof. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0457] A pharmaceutical composition comprising a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.), may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules, vials, or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing, and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, prior (e.g., immediately prior) to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0458] A pharmaceutical composition comprising a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1,

BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.), may be formulated as a solution for injection, which solution may be an aqueous or non-aqueous (oily) sterile solution and may comprise one or more antioxidants, thickening agents, suspending agents, buffers, solutes, and/or bacteriostats. The addition of one or more such additives may render the formulation isotonic with the blood of the intended recipient (e.g., subject or patient). Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0459] In addition to the formulations described elsewhere herein, the compounds provided herein (e.g., compounds of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC' in any suitable form (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.)), may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0460] A pharmaceutical composition comprising a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC') or a form thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.) that is suitable for buccal or sublingual administration may take the form of tablets, lozenges, pastilles, or gels. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or

tragacanth. A pharmaceutical composition comprising a compound provided herein or a form thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.) that is suitable for rectal administration may be formulated as a suppository or retention enema and may comprise a medium such as, for example, cocoa butter, polyethylene glycol, or other glycerides.

[0461] Certain compounds provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC') or a form thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.) may be formulated for non-systemic administration, such as topical administration. This includes the application of a compound disclosed herein, or a form thereof, externally to the epidermis or the buccal cavity and the instillation of such a compound, or a form thereof, into the ear, eye, and nose, such that the compound, or a form thereof, does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal, and intramuscular administration.

[0462] Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments, or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

[0463] For administration by inhalation, compounds (e.g., compounds of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC') or forms thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.) may be conveniently delivered from an insufflator, nebulizer pressurized packs, or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds provided herein may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[0464] Preferred unit dosage formulations are those containing an effective dose, as described herein, or an appropriate fraction thereof, of the active ingredient (e.g., a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof).

[0465] It should be understood that in addition to the ingredients particularly described elsewhere herein, the formulations described herein may include other useful agents having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0466] Compounds (e.g., compounds of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC') or forms thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.) may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of one or more compounds which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

[0467] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

Methods

[0468] The present disclosure also provides a method of modulating KRAS (e.g., KRAS having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) comprising contacting KRAS with a compound provided herein (e.g., a compound of any

one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof. For example, the present disclosure may provide a method of altering a cell phenotype, cell proliferation, KRAS activity, biochemical output produced by active or inactive KRAS, expression of KRAS, and/or binding of KRAS with a natural binding partner. Any such feature may be monitored and may be altered upon contacting KRAS with a compound provided herein, or a form thereof. A method of modulating KRAS (e.g., KRAS having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) may be a mode of treatment of a disease, disorder, or condition (e.g., a cancer), a biological assay, a cellular assay, a biochemical assay, etc. In some embodiments, a method of modulating KRAS (e.g., KRAS having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) comprises contacting a KRAS protein with a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, where the KRAS protein is in the active (GTP-bound) conformation. In some embodiments, a method of modulating KRAS (e.g., KRAS having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) comprises contacting a KRAS protein with a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, where the KRAS protein is in the inactive (GDP-bound) conformation. In some embodiments, contacting a KRAS protein with a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, comprises incubating the KRAS protein with the compound or form thereof. In some embodiments, contacting a KRAS protein with a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, comprises contacting a cell containing the KRAS protein with the compound or form thereof. In some embodiments, the cell is in a subject. In some embodiments, the subject is a human. In some embodiments, the subject is a human having a disease, disorder, or condition such as a cancer, such as a cancer characterized by a KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS.

[0469] The present disclosure also provides methods of treating a disease, disorder, or condition in a subject in need thereof using a compound provided herein, (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB,

IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof. For example, the present disclosure provides a method comprising providing (e.g., administering) to a subject (e.g., patient) in need thereof an effective amount of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof. The present disclosure also provides methods of treating a disease, disorder, or condition in a subject in need thereof using a pharmaceutical composition comprising a compound provided herein, (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof. For example, the present disclosure provides a method comprising providing (e.g., administering) to a subject (e.g., patient) in need thereof a pharmaceutical composition comprising an effective amount of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof. In some embodiments, the subject is known to have (e.g., has previously been diagnosed with) a disease, disorder, or condition such as a cancer. The disease, disorder, or condition may be a KRAS-mediated disease, such as a cancer characterized by a KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS. In some embodiments, the compound administered to the subject in need thereof according to the methods described herein is a compound described in an embodiment, example, figure, or table herein, or a stereoisomer(s) or pharmaceutically acceptable salt thereof.

[0470] The present disclosure also provides a compound as provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1,

BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient, for use as a medicament, such as a medicament for the treatment of a disease, disorder, or condition (e.g., a cancer). The present disclosure also provides a compound as provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient, for use in the manufacture of a medicament for the treatment of a disease, disorder, or condition (e.g., a cancer) in a subject in need thereof.

[0471] The present disclosure also provides the use of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient, for the treatment of a disease, disorder, or condition (e.g., a cancer, as described herein, such as a cancer characterized by a KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) in a subject in need thereof.

[0472] The present disclosure also provides the use of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient, in

the manufacture of a medicament for treating a disease, disorder, or condition (e.g., a cancer, as described herein, such as a cancer characterized by a KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) in a subject in need thereof.

[0473] The present disclosure also provides a method of inhibiting KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) (e.g., in a subject in need thereof) comprising contacting KRAS with a compound as provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient. In some embodiments, a method of inhibiting KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) comprises contacting a KRAS protein with a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, where the KRAS protein is in the active (GTP-bound) conformation. In some embodiments, a method of inhibiting KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) comprises contacting a KRAS protein with a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, where the KRAS protein is in the inactive (GDP-bound) conformation. In some embodiments, contacting a KRAS protein with a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, comprises incubating the KRAS protein with the compound or form thereof. In some embodiments, contacting a KRAS protein with a compound provided herein, or a salt, ester, tautomer, zwitterionic form, or stereoisomer(s) thereof, comprises contacting a cell containing the KRAS protein with the compound or form thereof. In some embodiments, the cell is in a subject. In some embodiments, the subject is a human. In some embodiments, the subject is a human having a disease, disorder, or condition such as a cancer, such as a cancer characterized by a KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS.

[0474] The present disclosure also provides a compound as provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1,

BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient, for use in inhibiting KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) (e.g., in a subject in need thereof). The present disclosure also provides a compound as provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient, for use in the manufacture of a medicament for inhibiting KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) in a subject in need thereof.

[0475] The present disclosure also provides the use of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient, for inhibiting KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) in a subject in need thereof.

[0476] The present disclosure also provides the use of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, or a pharmaceutical

composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient, in the manufacture of a medicament for inhibiting KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) in a subject in need thereof.

[0477] The present disclosure also provides a method comprising administering a therapeutically effective amount of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof to a subject (e.g., patient) (e.g., a subject in need thereof), thereby ameliorating, reducing, eliminating, ceasing, delaying the progression of, or improving one or more symptoms of the subject, such as one or more symptoms of a disease, disorder, or condition (e.g., a cancer). In some embodiments, the subject has a cancer characterized by a mutant KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS).

[0478] In some embodiments, administering a therapeutically effective amount of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, slows or prevents growth of a tumor. In some embodiments, administering a therapeutically effective amount of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, , IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, results in shrinkage of a tumor (e.g., tumor regression). In some embodiments, administering a therapeutically effective amount of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ,

IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, results in at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% regression of a tumor, such as for a period of one or more weeks (e.g., at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more weeks), a period of one or more months (e.g., at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more months), or a period of one or more years (e.g., at least about 1, 2, 3, or more years). In some embodiments, administering a therapeutically effective amount of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, stabilizes a tumor. In some embodiments, administering a therapeutically effective amount of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a salt, ester, tautomer, prodrug, zwitterionic form, or stereoisomer(s) thereof, stabilizes a tumor for a period of one or more weeks (e.g., at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more weeks), a period of one or more months (e.g., at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more months), or a period of one or more years (e.g., at least about 1, 2, 3, or more years). In some embodiments, the subject has a cancer characterized by a mutant KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS).

[0479] In some embodiments of any of the methods, uses, and medicaments provided herein, the disease, disorder, or condition is a cancer. In some embodiments of any of the methods, uses, and medicaments provided herein, the cancer is pancreatic cancer (e.g., pancreatic ductal adenocarcinoma), lung cancer (e.g., non-small cell lung cancer), colorectal cancer (CRC), endometrial cancer, uterine carcinosarcoma, Ewing sarcoma, osteosarcoma, Rhabdomyosarcoma, adrenocortical carcinoma, neuroblastoma, Wilm tumor, retinoblastoma, skin cancer, breast cancer, prostate cancer, head and neck cancer, ovarian cancer, neurofibromatosis type 1 (NF1). In some embodiments, the cancer is pancreatic cancer (e.g., pancreatic

ductal adenocarcinoma), lung cancer (e.g., non-small cell lung cancer adenocarcinoma), or colorectal cancer (CRC). In some embodiments, the cancer is pancreatic cancer (e.g., pancreatic ductal adenocarcinoma). In some embodiments, the cancer is lung cancer (e.g., non-small cell lung cancer adenocarcinoma). In some embodiments, the cancer is colorectal cancer (CRC). In some embodiments, the cancer is or comprises a solid tumor. In some embodiments, the disease, disorder, or condition is neurofibromatosis type 1 (NF1).

[0480] In some embodiments of any of the methods, uses, and medicaments provided herein, the disease, disorder, or condition is related to KRAS, such as a disorder associated with a mutation of KRAS or dysregulation of KRAS. In some embodiments, the disease, disorder, or condition is related to the *KRAS* gene, such as a disease, disorder, or condition associated with a mutation of the *KRAS* gene or dysregulation of the *KRAS* gene. Mutation or dysregulation of KRAS or *KRAS* may include mutation or dysregulation of human K-Ras4a and/or human K-Ras4b. In some embodiments, the disease, disorder, or condition is related to the KRAS (e.g., human K-Ras4a or K-Ras4b) signaling pathway activity, such as a disease, disorder, or condition related to aberrant KRAS signaling pathway activity. In some embodiments, the disease, disorder, or condition is related to mutation or dysregulation of human K-Ras4b. In some embodiments, the disease, disorder, or condition is related to aberrant K-Ras4b signaling pathway activity. In some embodiments, the disease, disorder, or condition is related to mutation or dysregulation of human K-Ras4a. In some embodiments, the disease, disorder, or condition is related to aberrant K-Ras4a signaling pathway activity.

Administration and Combination Therapy

[0481] The compounds provided herein (e.g., compounds of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC') and forms thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.), or compositions (e.g., pharmaceutical compositions) comprising the same, can be administered in various modes (e.g., orally, topically, or by injection). The amount of active ingredient (e.g., a compound provided herein in any suitable form thereof) administered to a subject (e.g., patient) will be the responsibility of an attendant medical provider. The specific dose level for a given subject (e.g., patient) will depend on a variety of factors including, for example, the activity of the active ingredient administered; the physical attributes of the subject (e.g., age, weight, height, body

mass index, general health, co-morbidities, sex, etc.); other characteristics of the subject (e.g., diet, level of exercise, national origin, ethnicity, etc.); time of administration; route of administration; rate of excretion; drug combination; the disease, disorder, or condition being treated; and the severity of the disease, disorder, or condition being treated.

[0482] In some embodiments, a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.) is administered in combination with an additional agent, such as an additional therapeutic agent. For example, if a subject experiences a side effect such as hypertension upon receiving a compound provided herein, or a form thereof, it may be appropriate to administer an additional agent that is effective in managing the side effect, such as an anti-hypertensive agent. In another example, the therapeutic effectiveness of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof, may be enhanced by administration of an adjuvant, which adjuvant may itself have only minimal therapeutic benefit, but in combination with another therapeutic agent may provide an enhanced overall therapeutic benefit to a subject. In a further example, the therapeutic benefit of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof, may be enhanced by administration of the compound, or a form thereof, and an additional agent (which may comprise an additional therapeutic regimen) that also provides a therapeutic benefit. For example, a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof,

may be administered in combination with an additional agent that may be effective in the treatment of a disease, disorder, or condition such as a cancer. Generally, the combination of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof, and one or more additional agents (e.g., therapeutic agents) may enhance the overall benefit experienced by the subject upon either component individually. In some embodiments, the effect may be additive. In some embodiments, the effect may be synergistic.

[0483] In some embodiments, a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.) is administered in combination with an anti-cancer agent (e.g., chemotherapeutic agent). An anti-cancer agent may be, for example, an alkylating agent, an antimitotic, a checkpoint inhibitor, an anti-metabolite, a plant alkaloid, a terpenoid, a cytotoxic agent, an antibiotic, a topoisomerase inhibitor, an aromatase inhibitor, an angiogenesis inhibitor, an anti-steroid, an anti-androgen, an mTOR inhibitor, monoclonal antibodies, or a tyrosine kinase inhibitor. An alkylating agent may be, for example, armustine, chlorambucil (LEUKERAN), cisplatin (PLATIN), carboplatin (PARAPLATIN), oxaliplatin (ELOXATIN), streptozocin (ZANOSAR), busulfan (MYLERAN), dacarbazine, ifosfamide, lomustine (CCNU), melphalan (ALKERAN), procarbazine (MATULAN), temozolomide (TEMODAR), thiotepa, or cyclophosphamide (ENDOXAN). An anti-metabolite may be, for example, cladribine (LEUSTATIN), mercaptopurine (PURINETHOL), thioguanine, pentostatin (NIPENT), cytosine arabinoside (cytarabine, ARA-C), gemcitabine (GEMZAR), fluorouracil (5-FU, CARAC), capecitabine (XELODA), leucovorin (FUSILEY), methotrexate (RHEUMATREX), or raltitrexed. An antimitotic may be, for example, a taxane such as docetaxel (TAXITERE) or paclitaxel (ABRAXANE, TAXOL), or a vinca alkaloid such as vincristine (ONCOVIN), vinblastine, vindesine, or vinorelbine (NAVELBINE). A checkpoint inhibitor may be an anti-PD-1 or anti-PD-L1 antibody such as pembrolizumab (KEYTRUDA), nivolumab (OPDIVO), MEDI4736, or MPDL3280A; anti-CTLA-4 antibody ipilimumab (YERVOY); or an agent that targets LAG3 (lymphocyte activation gene 3 protein), KIR (killer cell immunoglobulin-like receptor), 4-1BB (tumor necrosis factor receptor superfamily member

9), TIM3 (T-cell immunoglobulin and mucin-domain containing-3), or 0X40 (tumor necrosis factor receptor superfamily member 4). A topoisomerase inhibitor may be, for example, camptothecin (CTP), irinotecan (CAMPTOSAR), topotecan (HYCAMTIN), teniposide (VUMON), or etoposide (EPOSIN). A cytotoxic antibiotic may be, for example, actinomycin D (dactinomycin, COSMEGEN), bleomycin (BLENOXANE) doxorubicin (ADRIAMYCIN), daunorubicin (CERUBIDINE), epirubicin (ELLENCE), fludarabine (FLUDARA), idarubicin, mitomycin (MITOSOL), mitoxantrone (NOYANTRONE), or plicamycin. An aromatase inhibitor may be, for example, aminoglutethimide, anastrozole (ARIMIDEX), letrozole (FEMARA), vorozole (RIVIZOR), or exemestane (AROMASIN). An angiogenesis inhibitor may be, for example, genistein, sunitinib (SUTENT), or bevacizumab (AYASTIN). An anti-steroid or anti-androgen may be, for example, aminoglutethimide (CYTADREN), bicalutamide (CASODEX), cyproterone, flutamide (EULEXIN), or nilutamide (NILANDRON). A tyrosine kinase inhibitor may be, for example, imatinib (GLEEVEC), erlotinib (TARCEVA), afatinib (GILOTRIF), lapatinib (TYKERB), sorafenib (NEXAVAR), or axitinib (INLYTA). An mTOR inhibitor may be, for example, everolimus, temsirolimus (TORISEL), or sirolimus. Monoclonal antibody may be, for example, trastuzumab (HERCEPTIN) or rituximab (RITUXAN). Additional examples of agents that may be useful in combination with a compound provided herein, or an alternative form thereof, include, but are not limited to, amsacrine; Bacillus Calmette-Guerin (B-C-G) vaccine; buserelin (ETILAMIDE); chloroquine (ARALEN); clodronate, pamidronate, and other bisphosphonates; colchicine; demethoxyviridin; dichloroacetate; estramustine; filgrastim (NEUPOGEN); fludrocortisone (FLORINEF); goserelin (ZOLADEX); interferon; leucovorin; leuprolide (LUPRON); levamisole; lonidamine; mesna; metformin; mitotane (o,r'-DDD, LYSODREN); nocodazole; octreotide (SANDOSTATIN); perifosine; porfimer (particularly in combination with photo- and radiotherapy); suramin; tamoxifen; titanocene dichloride; tretinoin; anabolic steroids such as fluoxymesterone (HALOTESTIN); estrogens such as estradiol, diethylstilbestrol (DES), and dienestrol; progestins such as medroxyprogesterone acetate (MPA) and megestrol; and testosterone.

[0484] Two or more therapeutic agents, one of which is a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof, may be administered in any order or may be administered simultaneously. If administered simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple

forms (such as, for example, as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not administered simultaneously, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

[0485] Accordingly, in another aspect, the present disclosure provides a method for treating a disease, disorder, or condition (e.g., a cancer) in a subject (e.g., a human or animal subject) in need of such treatment comprising administering to the subject an amount of a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.), in combination with at least one additional agent for the treatment of the disease, disorder, or condition. In a related aspect, the present disclosure provides a composition (e.g., pharmaceutical composition) comprising a compound provided herein (e.g., a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC'), or a form thereof (e.g., salt, ester, tautomer, prodrug, zwitterionic form, stereoisomer(s), etc.), and at least one additional agent for use in the treatment of a disease, disorder, or condition (e.g., a cancer).

[0486] In some embodiments, a method provided herein is used to treat a disease, disorder, or condition (e.g., a cancer) comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV', IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC' or a pharmaceutically acceptable salt thereof, wherein the disease, disorder, or condition is a cancer that has developed a resistance to one or more chemotherapeutic drugs and/or ionizing radiation. In some embodiments, a method provided herein is used to treat a disease, disorder, or condition (e.g., a cancer) comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of Formulas A, A', A'-a, B, B-a, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, BM1, II, II', II'', II''-a, II-a, IIR', IIU', IIV',

IIZ, IIAA', IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, IIJJ, IIR1', IIU1', IIV1', IIZ1, IIAA1', IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, IIJJ1, III, IV, IV-a, IVB, IVC, V', VA', VB', and VC' or a pharmaceutically acceptable salt thereof, in combination with an additional agent, wherein the disease, disorder, or condition is a cancer that has developed a resistance to one or more chemotherapeutic drugs and/or ionizing radiation.

[0487] The compounds, compositions, and methods disclosed herein are useful for the treatment of a disease, disorder, or condition, such as a cancer. In certain embodiments, the disease is one of dysregulated cellular proliferation, including cancer. The cancer may be hormone-dependent or hormone-resistant, such as in the case of breast cancers. In certain embodiments, the cancer is or comprises a solid tumor. In other embodiments, the cancer is a lymphoma or leukemia. In certain embodiments, the cancer is a drug resistant phenotype of a cancer disclosed herein or otherwise known. Tumor invasion, tumor growth, tumor metastasis, and angiogenesis may also be treated using the compositions and methods disclosed herein. In some embodiments, the compounds, compositions, and methods provided herein are also useful in the treatment of precancerous neoplasias.

[0488] Cancers that may be treated by the methods disclosed herein include, but are not limited to, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer, breast cancer, ovarian cancer, endometrial cancer, lung cancer, and prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, colon, rectum, liver and biliary passages; pancreas, bone, connective tissue, skin, cervix, uterus, corpus endometrium, testis, bladder, kidney and other urinary tissues, including renal cell carcinoma (RCC); cancers of the eye, brain, spinal cord, and other components of the central and peripheral nervous systems, as well as associated structures such as the meninges; and thyroid and other endocrine glands. The term "cancer" also encompasses cancers that do not necessarily form solid tumors, including Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma, and hematopoietic malignancies including leukemias (Chronic Lymphocytic Leukemia (CLL), Acute Lymphocytic Leukemia (ALL), Chronic Myelogenous Leukemia (CML), Acute Myelogenous Leukemia (AML),) and lymphomas including lymphocytic, granulocytic and monocytic lymphomas. Additional types of cancers which may be treated using the compounds and methods provided herein include, but are not limited to, adenocarcinoma, angiosarcoma, astrocytoma, acoustic neuroma, anaplastic astrocytoma, basal cell carcinoma, blastoglioma, chondrosarcoma, choriocarcinoma, chordoma, craniopharyngioma, cutaneous melanoma, cystadenocarcinoma, endotheliosarcoma, embryonal carcinoma, ependymoma, Ewing's tumor, epithelial carcinoma, fibrosarcoma, gastric cancer, genitourinary tract cancers, glioblastoma multiforme, head and neck cancer, hemangioblastoma, hepatocellular carcinoma,

hepatoma, Kaposi's sarcoma, large cell carcinoma, leiomyosarcoma, leukemias, liposarcoma, lymphatic system cancer, lymphomas, lymphangiosarcoma, lymphangioendotheliosarcoma, medullary thyroid carcinoma, medulloblastoma, meningioma mesothelioma, myelomas, myxosarcoma neuroblastoma, neurofibrosarcoma, oligodendroglioma, osteogenic sarcoma, epithelial ovarian cancer, papillary carcinoma, papillary adenocarcinomas, paraganglioma, parathyroid tumors, pheochromocytoma, pinealoma, plasmacytomas, retinoblastoma, rhabdomyosarcoma, sebaceous gland carcinoma, seminoma, skin cancers, melanoma, small cell lung carcinoma, non-small cell lung carcinoma, squamous cell carcinoma, sweat gland carcinoma, synovioma, thyroid cancer, uveal melanoma, and Wilm's tumor. Additional diseases and disorders that may be treated by the methods disclosed herein include, but are not limited to, diseases or disorders related to KRAS, such as diseases or disorders associated with a mutation of KRAS (e.g., KRAS protein having a Q61H, G12C, G12D, G12V, G12S, G12A, G12R, or G13D mutation, or wild-type KRAS, including wild-type amplified KRAS) or dysregulation of KRAS, and diseases or disorders related to the *KRAS* gene, such as diseases or disorders associated with a mutation of the *KRAS* gene or dysregulation of the *KRAS* gene.

[0489] In some embodiments, the compounds, compositions, and methods provided herein are useful in the prevention and/or reduction of tumor invasion, growth, and/or metastasis.

[0490] The compounds, compositions, and methods provided herein may be useful in the treatment of humans as well as in the veterinary treatment of non-human animals including companion animals, exotic animals, and farm animals (e.g., as described herein), including mammals, rodents, and the like. For example, the compounds, compositions, and methods provided herein may be useful in the treatment of horses, dogs, or cats.

EXAMPLES

[0491] Selected abbreviations used in the preceding sections and the Examples are summarized in Table A-1.

Table A-1. Abbreviations.

Abbreviation	Term
MeCN	acetonitrile
cm	centimeter
°C	degrees Celsius
°K	degrees Kelvin
BINAP	[1,1'-Binaphthalene]-2,2'-diyl)bis(diphenylphosphane)
DCM	dichloromethane
DIEA	N,N-diisopropylethylamine (Hünig's base)
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
eq	equivalents
ESI	electrospray ion-mass spectrometry
EtOH	ethanol
EtOAc	ethyl acetate
g	gram
Hz	hertz
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uronium
HPLC	high performance liquid chromatography
HTRF	homogenous time-resolved fluorescence
h	hour
kDa	kilodalton
LC	liquid chromatography
LCMS	liquid chromatography-mass spectrometry
L	liter
MS	mass spectra
MHz	megahertz
MeOH	methanol
MTBE	methyl tert-butyl ether

Abbreviation	Term
µg	microgram
µL	microliter
µM	micromolar
µm	micron
µs	microsecond
mg	milligram
mL	milliliter
mm	millimeter
mM	millimolar
mmol	millimole
min	minute
M	molar
nL	nanoliter
nm	nanometer
NCS	N-chlorosuccinimide
NMP	N-methyl-2-pyrrolidone
PE:EA	Petroleum ether:ethyl acetate
ppm	parts per million
PTLC	preparative thin layer chromatography
^{1}HNMR	proton nuclear magnetic resonance
RBD	receptor binding domain
RP	reverse phase
rpm	revolutions per minute
SPR	surface plasmon resonance
THF	tetrahydrofuran
TMS	tetramethylsilane
TLC	thin layer chromatography
$SOCl_2$	thionyl chloride
TEA	triethylamine
TFA	trifluoroacetic acid
TCEP	tris(2-carboxyethyl)phosphine
UV	ultraviolet

Abbreviation	Term
UV/Vis	ultraviolet/visible

Materials and methods

[0492] Preparative thin layer chromatography (PTLC) separations described herein were typically performed on 20 x 20 cm plates (500-μm thick silica gel).

[0493] Chromatographic purifications were typically performed using Biotage Isolera One automated system running Biotage Isolera One 2.0.6 software (Biotage LLC, Charlotte, NC). Flow rates were the default values specified for the column in use. Reverse phase chromatography was performed using elution gradients of water and acetonitrile on KP-C18-HS Flash+ columns (Biotage LLC) of various sizes. Typical loading was between 1:50 and 1:1000 crude sample: RP SiO_2 by weight. Normal phase chromatography was performed using elution gradients of various solvents (*e.g.*, hexane, ethyl acetate, methylene chloride, methanol, acetone, chloroform, MTBE, etc.). The columns were SNAP Cartridges containing KP-SIL or SNAP Ultra (25 pm spherical particles) of various sizes (Biotage LLC). Typical loading was between 1:10 to 1:150 crude sample: SiO_2 by weight. Alternatively, silica gel chromatography was performed on a Biotage Horizon flash chromatography system.

[0494] ^{1}HNMR analyses of intermediates and exemplified compounds were typically performed on a Bruker Ascend TM 400 spectrometer (operating at 400 MHz), Bruker Ascend 700 MHz Advance Neo Spectrometer (Bruker-Biospin) or Bruker Advance ultrashield 300/54 (operating at 300 MHz) at 298 °K following standard operating procedure suggested by manufacturer. Reference frequency was set using TMS as an internal standard. Chemical shift values (δ) are reported in parts per million (ppm) with splitting patterns abbreviated to: s (singlet), br. s (broad singlet), d (doublet), dd (double doublet), t (triplet), and m (multiplet). The coupling constant (*J*) is given in Hz. Typical deuterated solvents were utilized as indicated in the individual examples.

[0495] LCMS analysis were typically performed using one of the following conditions:

[0496] (1) LCMS spectra were taken on an Agilent Technologies 6120B Quadrupole spectrometer. The mobile phase for the LC was acetonitrile (A) with 0.1% formic acid, and water (B) with 0.1% formic acid, and the eluent gradient was from 5-95% A in 6.0 min, 5%-40% A in 6.0 min, 80-100% A in 6.0 min using a poroshell 120 EC-C18 50 mm x 3.0 mm x 2.7 μm capillary column; Flow Rate: 0.7 mL/min. Mass spectra (MS) were measured by electrospray ion-mass spectroscopy (ESI). All temperatures are in degrees Celsius (°C) unless otherwise noted.

[0497] (2) LCMS spectra were taken on an Agilent Technologies 1290-6420 Triple Quadrupole spectrometer: The mobile phase for the LC was acetonitrile (A) with 0.05% formic acid, and water (B) with 0.05% formic acid, and the eluent gradient was from 5-95% A in 5.0 min, using a ZORBAX SB-C18 50 mm x 2.1 mm x 1.8 µm capillary column; Flow Rate: 0.3 mL/min. Mass spectra (MS) were measured by electrospray ion-mass spectroscopy (ESI). All temperatures are in degrees Celsius unless otherwise noted.

[0498] (3) LC-MS analysis was performed using an Agilent 6120b single quadrupole mass spectrometer with an Agilent 1260 infinity II chromatography separations module and Agilent 1260 infinity II photodiode array detector controlled by Agilent Chemstation software. The HPLC column used was an Agilent ZORBAX Eclipse XDB-C18 4.6 mm x 150 mm x 3.5 µm RapidResol column with a mobile phase of water (0.1 % formic acid) / MeCN (0.1% formic acid) and a gradient of 5-95% MeCN over 10 minutes at a flow rate of 1 mL/min. Accurate mass data was obtained using a Thermo Fisher extractive plus EMR orbitrap LCMS system. Exact mass values were calculated by ChemCalc.

[0499] (4) LCMS spectra were taken on an alliance Waters 2695 coupled to a dual absorbance detector waters 2487 and a waters micro mass ZQ-2000 single quadrupole spectrometer. The mobile phase for the LC was acetonitrile (A) and water (B) with 0.01% formic acid, and the eluent gradient was from 5-100% A in 10.0 minute using a Kromasil 100-5-C18 150 mm x 4.6 mm x 5 µm column. Mass spectra (MS) were measured by electrospray ion-mass spectroscopy (ESI). All temperatures are in degrees Celsius unless otherwise noted.

[0500] Typically, analytical HPLC mass spectrometry conditions were as follows:

[0501] LC1: Agilent Technologies 1260 Infinity coupled, Column: poroshell 120 EC-C18 150 mm x 4.6 mm x 4 µm; Temperature: 40 °C; Eluent: 5:95 v/v acetonitrile/water + 0.02% trifluoroacetic acid in 20 min; Flow Rate: 1.2 mL/min; Detection: VWD, 190-600 nm.

[0502] LC2: C18-Reverse phase preparative HPLC was performed using a Waters purification system with 2489 UV/Vis detector, 2545 Gradient module, and Fraction collector III controlled by Waters Chromescope v1.6. The preparative HPLC column used was a Waters XBridge® Prep C18 5 µm OBD™ 19 x 250 mm column with a mobile phase of water / MeCN or water (0.1% TFA) / MeCN (0.1% TFA).

[0503] Preparative HPLC were carried out with one of the following two conditions:

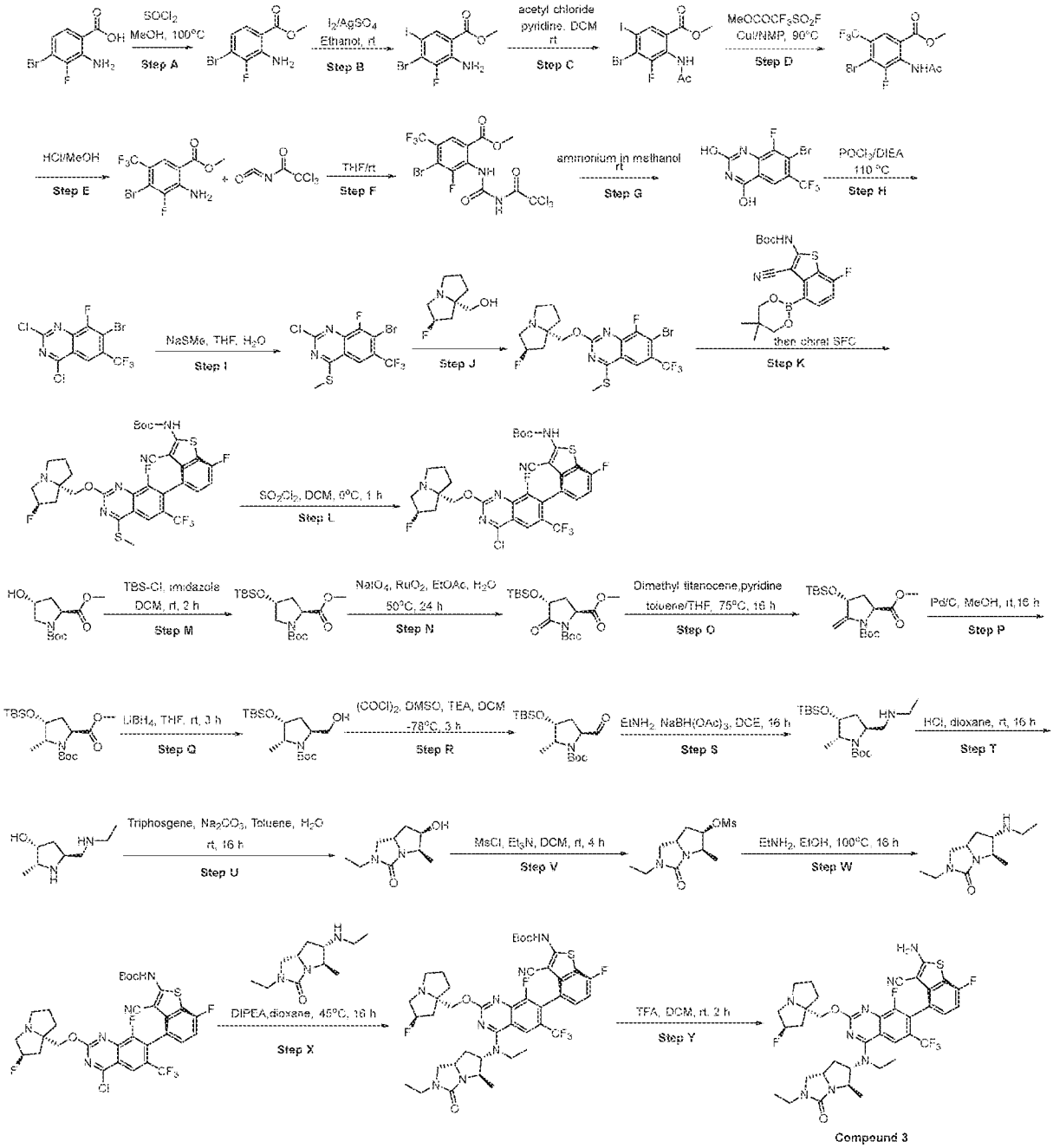
[0504] Condition 1: GILSON Preparative HPLC System; Column: Ultimate XB-C18, 21.2mm x 250mm, 5µm; Mobile phase: Water with 0.1% trifluoroacetic acid; MeCN with 0.1% trifluoroacetic acid; Method: 15 minutes gradient elution; Initial organic: 10% to 30%; Final organic: 60% to 80%; UV1: 240; UV2: 230; Flow: 15 mL/min.

[0505] Condition 2: C18-Reverse phase preparative HPLC was performed using a Waters purification system with 2489 UV/Vis detector, 2545 Gradient module, and Fraction collector III controlled by Waters Chromescope v1.6. The preparative HPLC column used was a Waters XBridge® Prep C18 5 µm OBD™ 19 x 250mm column with a mobile phase of water / MeCN or water (0.1% TFA) / MeCN (0.1% TFA).

[0506] Compound names were generated with ChemDraw Professional.

[0507] The compounds provided herein, including in various forms such as salts, esters, tautomers, prodrugs, zwitterionic forms, stereoisomers, etc., may be prepared according to various methods including those set forth in the following examples.

[0508] **Synthetic Example 1:** Preparation of 2-amino-4-((S)-4-(ethyl((5R,6S,7aS)-2-ethyl-5-methyl-3-oxohexahydro-1H-pyrrolo[1,2-c]imidazol-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (**Compound 3**)



[0509] **Step A:** Preparation of methyl 2-amino-4-bromo-3-fluorobenzoate: To stirring solution of 2-amino-4-bromo-3-fluorobenzoic acid (5.0 g, 21.4 mmol) in MeOH (30 mL) was added dropwise thionyl chloride (15.6 ml, 21 mmol) at 0 °C under argon. The resulting mixture was heated to 100 °C for 16 hours. The solvent was evaporated, and the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with a saturated aqueous $NaHCO_3$ solution then dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting crude material was purified by silica gel column chromatography using EtOAc in hexanes (0% to 20%) as eluent to give methyl 2-amino-4-bromo-3-fluorobenzoate (5.0 g, 94%) as a

solid. LCMS ESI (+) m/z 249 (M+H). ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.8, 1.8 Hz, 1H), 6.78 (dd, J = 8.8, 6.3 Hz, 1H), 5.93 (s, 1H), 3.90 (s, 1H).

[0510] Step B: Preparation of methyl 2-amino-4-bromo-3-fluoro-5-iodobenzoate: To a mixture of iodine (7.16 g, 28 mmol) and silver sulfate (5.3 g, 17 mmol) in EtOH (200 mL), methyl 2-amino-4-bromo-3-fluorobenzoate (5.0 g, 20 mmol) was added and the resulting mixture was stirred at ambient temperature for 45 minutes. The solid was filtered off and washed with DCM, and the filtrate was concentrated under vacuum. The residue was dissolved in DCM and washed with 10% sodium thiosulphate solution, brine and the resulting organic solution was dried over Na_2SO_4, filtered and concentrated under vacuum to give methyl 2-amino-4-bromo-3-fluoro-5-iodobenzoate: the title compound (6.66 g, 88% yield) as a yellow solid. LCMS ESI (+) m/z 373 (M+H). ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 1.9 Hz, 1H), 5.94 (s, 2H), 3.91 (s, 3H).

[0511] Step C: Preparation of methyl 2-acetamido-4-bromo-3-fluoro-5-iodobenzoate: The methyl 2-amino-4-bromo-3-fluoro-5-iodobenzoate (3.50 g, 9.4 mmol) and pyridine (2.3 ml, 28 mmol) were dissolved in DCM at 0 °C. Acetyl chloride (0.79 ml, 11 mmol) was added and the reaction was warmed to ambient temperature and stirred at this temperature for 16 hours. The reaction mixture was concentrated under vacuum and the residue obtained was purified by silica gel column chromatography using ethyl acetate in hexanes (0% to 30%) as eluent to give methyl 2-acetamido-4-bromo-3-fluoro-5-iodobenzoate (2.7 g, 69%) as solid. LCMS ESI (+) m/z 417 (M+H). ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.25 (s, 1H), 3.95 (s, 3H), 2.26 (s, 3H).

[0512] Step D: Preparation of methyl 2-acetamido-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate: To a stirred solution of methyl 4-bromo-2-acetamido-3-fluoro-5-iodobenzoate (1.0 g, 2.4 mmol) and methyl fluorosulfonyldifluoroacetate (0.92 g, 0.72 mmol) in NMP (22.0 mL) at ambient temperature, CuI (0.14 g, 0.73 mmol) was added and the resulting mixture was stirred at 80 °C for 16 hours. Once cooled to ambient temperature, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, concentrated and the crude material was purified by silica gel column chromatography using ethyl acetate in hexanes (0% to 20%) as eluent to give methyl 2-acetamido-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate (0.64 g, 74%) as solid. LCMS ESI (+) m/z 358 (M+H). ^{1}HNMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.10 (s, 1H), 3.93 (s, 3H), 2.28 (s, 3H).

[0513] Step E: Preparation of 2-amino-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate: A mixture of methyl 2-acetamido-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate (1.20 g, 3.35 mmol) in 3 M HCl in MeOH was heated at 60 ^{0}C for 2 hours. Once cooled to ambient temperature, the solvent was evaporated, and the crude product was partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was

separated, dried over sodium sulfate, filtered, and evaporated to provide 2-amino-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate (1.00 g, 94%) as an oil. LCMS ESI (+) m/z 316.9 (M+H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.28 (s, 2H), 3.94 (s, 3H).

[0514] Step F: Preparation of methyl 4-bromo-3-fluoro-2-(3-(2,2,2-trichloroacetyl)ureido)-5-(trifluoromethyl)benzoate: To a mixture of methyl 2-amino-4-bromo-3-fluoro-5-(trifluoromethyl)benzoate (0.80 g, 2.53 mmol) in THF (4.2 mL) was added trichloroethanecarbonyl isocyanate (0.45 mL, 3.79 mmol) at ambient temperature. After 15 minutes, the reaction mixture was evaporated, followed by the addition of MTBE and the solid formed was collected and washed with MTBE to provide methyl 4-bromo-3-fluoro-2-(3-(2,2,2-trichloroacetyl)ureido)-5-(trifluoromethyl)benzoate (0.71 g, 56 %). LCMS ESI (+) m/z 529.99 (M+Na). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.91 (s, 1H), 8.65 (s, 1H), 8.23 (s, 1H), 4.03 (s, 3H).

[0515] Step G: Preparation of 7-bromo-8-fluoro-6-(trifluoromethyl)quinazoline-2,4-diol: To a solution of methyl 4-bromo-3-fluoro-2-(3-(2,2,2-trichloroacetyl)ureido)-5-(trifluoromethyl)benzoate (0.71 g, 1.40 mmol) in methanol (7.0 mL) was added 7 M solution of ammonia in methanol (0.46 mL, 3.23 mmol) at ambient temperature and stirred at ambient temperature for 1 hour. The mixture was concentrated under reduced pressure to provide a solid which was co-evaporated with ether to provide 7-bromo-8-fluoro-6-(trifluoromethyl)quinazoline-2,4-diol (0.60 g, 100%) as solid LCMS ESI (+) m/z 260.0 (M+H). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.28 (s, 1H), 7.99 (s, 1H).

[0516] Step H: Preparation of 7-bromo-2,4-dichloro-8-fluoro-6-(trifluoromethyl)quinazoline: To a stirring solution of phosphorus oxychloride (0.97 mL, 10.5 mmol) and Hunig's base (0.40 mL, 2.29 mmol) was added 7-bromo-8-fluoro-6-(trifluoromethyl)quinazoline-2,4-diol (0.15 g, 0.46 mmol) at 0 °C. After addition, the resulting mixture was stirred at 110 °C for 1 hour. Once cooled down to ambient temperature, the mixture was evaporated and co-evaporated with chloroform to give 7-bromo-2,4-dichloro-8-fluoro-6-(trifluoromethyl)quinazoline which used as such for the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H).

[0517] Step I: Preparation of 7-bromo-2-chloro-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazoline: To a solution of 7-bromo-2,4-dichloro-8-fluoro-6-(trifluoromethyl)quinazoline (1.00 eq, 100 g, 0.27 mol) in THF (1500 mL) was added Sodium thiomethoxide (2.20 eq, 41.6 g, 0.59 mol, 20% in Water) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with DCM (2 L x 2). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was trituration with petroleum (500 mL) and the precipitated solids were collected by filtration to afford 7-bromo-2-chloro-8-fluoro-4-(methylthio)-6-

(trifluoromethyl)quinazoline (90 g, 0.24 mol, 88.89% yield) as a light yellow solid. LCMS ESI (+) m/z 374.8, 376.8 (M+H).

[0518] Step J: Preparation of (3-cyano-7-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate: To a solution of 7-bromo-2-chloro-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazoline (1.00 eq, 85 g, 0.23 mol) in 1,4-Dioxane (850 mL) was added DIEA (5.00 eq, 148 g, 1.15 mol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (1.30 eq, 47.5 g, 0.299 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 90°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum, diluted with water and extracted with ethyl acetate (1 L x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 1% to 4% to afford 7-bromo-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)-6-(trifluoromethyl)quinazoline (85.2 g, 0.17 mol, 73.9% yield) as a yellow solid. LCMS ESI (+) m/z 497.9, 499.9 (M+H).

[0519] Step K: Preparation of tert-butyl (3-cyano-7-fluoro-4-((S)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate: To a solution of 7-bromo-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)-6-(trifluoromethyl)quinazoline (1.00 eq, 54 g, 0.11mol)) in 1,4-Dioxane (2160 mL) was added tert-butyl (3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.50 eq, 68.7 g, 0.17 mol), Cs_2CO_3 (3.00 eq, 107 g, 0.33 mol) and $DPEPhosPdCl_2$ (0.20 eq, 15.7 g, 0.02 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 90°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with ethyl acetate (600 mL x 4). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate in petroleum from 0% to 100% to give product. The racemate (30 g) was separated by chiral SFC (Daicel IC 2 cm x 25 cm, 5 μm, CO2:EtOH = 80:20 (0.1% DEA in EtOH)) to afford tert-butyl (3-cyano-7-fluoro-4-((S)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate (11 g, 15.5 mmol, 14.3% yield) as the first peak and yellow solid. LCMS ESI (+) m/z 710.0 (M+H).

[0520] Step L: Preparation of tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-

2-yl]carbamate: To a solution of tert-butyl N-[3-cyano-7-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzothiophen-2-yl]carbamate (1.00 eq, 5.00 g, 7.05 mmol) in DCM (200 mL) was added dropwise Sulfuryl chloride (5.00 eq, 4.75 g, 35.20 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was adjusted pH=8 with saturated sodium bicarbonate aqueous solution and extracted with DCM (200 mL x 3). The combined organic phase was washed with water and saturated brine solution, dried over sodium sulfate, filtered and concentrated under vacuum to afford the crude tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (4.5 g, 6.44 mmol, 91.83% yield) as a yellow solid, which was used in next step directly without further purification. LCMS ESI (+) m/z 698.1 (M+H).

[0521] Step M: Preparation of 1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate: To a solution of 1-(tert-butyl) 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (1.00 eq, 50 g, 204 mmol) and imidazole (2.00 eq, 27.725 g, 408 mmol) in DCM (600 mL) under nitrogen atmosphere, was added a solution of TBSCl (1.50 eq, 4.586 g, 306 mmol) at 0°C under nitrogen atmosphere. The resulting solution was stirred for 2 hours at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched by adding water (500 mL), extracted with DCM (500 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 2% to 10% to afford 1-(tert-butyl) 2-methyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (80 g, 200 mmol, 98.24% yield). LCMS ESI (+) m/z 259.9 (M-100+H).

[0522] Step N: Preparation of 1-tert-butyl 2-methyl (2S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-5-oxo-pyrrolidine-1,2-dicarboxylate: To a solution of $NaIO_4$ (2.00 eq, 35713 mg, 167 mmol) in water (200 mL) and Ethyl acetate (400 mL) was added 1-tert-butyl 2-methyl (2S,4R)-4-[tert-butyl(dimethyl)silyl]oxypyrrolidine-1,2-dicarboxylate (1.00 eq, 30.00 g, 83.4 mmol) at rt under nitrogen atmosphere. The resulting solution was stirred at 25°C for 30 min. To the above mixture was added RuO_2 (0.0400 eq, 504 mg, 3.34 mmol). The resulting solution was stirred at 50°C for 24 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was then quenched by adding water (200 mL) and extracted with ethyl acetate (200 mL x 2). The combined organic phase was washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and concentrated under

vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate in petroleum from 0% to 2.5% to afford 1-tert-butyl 2-methyl (2S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-5-oxo-pyrrolidine-1,2-dicarboxylate (24.00 g, 57.8 mmol, 69.30% yield) as a light yellow oil. LCMS ESI (+) m/z 274.0 (M-100+H).

[0523] Step O: Preparation of 1-tert-butyl 2-methyl (2S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-5-methylene-pyrrolidine-1,2-dicarboxylate: To a mixture of titanocene dichloride (5.00 eq, 79.98 g, 321 mmol) in ether (1000 mL) was added MeLi (1.10 eq, 283 mL, 70.7 mmol) (2.5 M in ether) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched by adding water (500 mL) and extracted with ether (200 mL x 2). The combined organic phase was washed with brine (200 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was dissolved with toluene (500 mL). To the above mixture was added 1-tert-butyl 2-methyl (2S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-5-oxo-pyrrolidine-1,2-dicarboxylate (1.00 eq, 24.00 g, 64.3 mmol) and Pyridine (4.00 eq, 20330 mg, 257 mmol) in THF (80 mL) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 75°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched by adding water (300 mL) at 0°C, extracted with ethyl acetate (300 mL x 2). The combined organic phase washed with brine (300 mL), dried over anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate in petroleum from 0% to 2.5% to afford 1-tert-butyl 2-methyl (2S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-5-methylene-pyrrolidine-1,2-dicarboxylate (16.20 g, 39.2 mmol, 61.07% yield). LCMS ESI (+) m/z 272.2 (M-100+H).

[0524] Step P: Preparation of 1-tert-butyl 2-methyl (2S,4R,5R)-4-[tert-butyl(dimethyl)silyl]oxy-5-methyl-pyrrolidine-1,2-dicarboxylate : To a solution of 1-tert-butyl 2-methyl (2S,4R)-4-[tert-butyl(dimethyl)silyl]oxy-5-methylene-pyrrolidine-1,2-dicarboxylate (1.00 eq, 10.00 g, 26.9 mmol) in methanol (50 mL) was added Pd/C (0.5 eq, 14.32 g, 135 mmol, 10% Pd) under nitrogen atmosphere. The resulting mixture was recharged with nitrogen gas three times and then recharged with hydrogen gas three times. The resulting mixture was stirred at 25°C for 16 hours under hydrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate in petroleum from 0% to 2.5% to afford 1-tert-butyl 2-methyl (2S,4R,5R)-4-[tert-butyl(dimethyl)silyl]oxy-5-methyl-pyrrolidine-1,2-dicarboxylate (5.00 g, 13.4 mmol, 49.73% yield) as a colorless oil. LCMS (ESI, m/z): 274.1 (M-100+H).

[0525] Step Q: Preparation of tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-(hydroxymethyl)-2-methyl-pyrrolidine-1-carboxylate: To a solution of 1-tert-butyl 2-methyl (2S,4R,5R)-4-[tert-butyl(dimethyl)silyl]oxy-5-methyl-pyrrolidine-1,2-dicarboxylate (1.00 eq, 11.00 g, 29.4 mmol) in THF (60 mL) was added $LiBH_4$ (3.00 eq, 1.92 g, 88.3 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 3 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with aqueous NH_4Cl (150 mL) and extracted with EtOAc (50 mL x 2). The combined organic phase was dried over anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 0% to 5% to afford tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-(hydroxymethyl)-2-methyl-pyrrolidine-1-carboxylate (9.10 g, 26.3 mmol, 89.43% yield) as a white solid. LCMS ESI (+) m/z 290.1 (M-56+H).

[0526] Step R: Preparation of tert-butyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate: To a solution of DMSO (5.00 eq, 10.29 g, 132 mmol) in DCM (150 mL) was added $(COCl)_2$ (2.00 eq, 6.69 g, 52.7 mmol) at -78°C under nitrogen atmosphere. The resulting mixture was stirred at -78°C for 0.5 h under nitrogen atmosphere. To the above mixture was added tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-(hydroxymethyl)-2-methyl-pyrrolidine-1-carboxylate (1.00 eq, 9.10 g, 26.3 mmol) in (DCM 15 mL) with dropwise at -78°C under nitrogen atmosphere.. The resulting mixture was stirred at -78°C for 0.5 h under nitrogen atmosphere. Then Et_3N (6.00 eq, 15.96 g, 158 mmol) was added to the above mixture. The resulting mixture was stirred at -78°C for 3 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with aqueous NH_4Cl (100 mL) and extracted with DCM (50 mL x 2). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 0% to 5% to afford tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-formyl-2-methyl-pyrrolidine-1-carboxylate (8.00 g, 23.3 mmol, 88.43% yield) as a white solid. LCMS ESI (+) m/z 244.1 (M-100+H).

[0527] Step S: Preparation of tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-(ethylaminomethyl)-2-methyl-pyrrolidine-1-carboxylate: To a solution of tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-formyl-2-methyl-pyrrolidine-1-carboxylate (1.00 eq, 5.00 g, 14.6 mmol) and ethyl amine (2.00 eq, 15 mL, 29.1 mmol) (2 M in THF) in DCE (100 mL) was added $NaBH(OAc)_3$ (2.00 eq, 6171 mg, 29.1 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred for 16 hours at 25°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with $NaHCO_3$ (aqu.) (50 mL) and extracted with DCM (50 mL). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue

was purified by silica gel column chromatography eluting with EA in petroleum from 10% to 50% to afford tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-(ethylaminomethyl)-2-methyl-pyrrolidine-1-carboxylate (4.00 g, 9.66 mmol, 66.38% yield) as a colorless oil. LCMS ESI (+) m/z 373.2 (M+H).

[0528] Step T: Preparation of (2R,3R,5S)-5-(ethylaminomethyl)-2-methyl-pyrrolidin-3-ol: A solution of tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-(ethylaminomethyl)-2-methyl-pyrrolidine-1-carboxylate (1.00 eq, 3.95 g, 10.6 mmol) in HCl (18.9 eq, 50 mL, 200 mmol) (4 M in dioxane) was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure to afford (2R,3R,5S)-5-(ethylaminomethyl)-2-methyl-pyrrolidin-3-ol (3.30 g, 20.9 mmol) as a white solid, which was used in next step directly without further purification. LCMS ESI (+) m/z 159.1 (M+H).

[0529] Step U: Preparation of (5R,6R,7aS)-2-ethyl-6-hydroxy-5-methyl-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-3-one: To a mixture of (2R,3R,5S)-5-(ethylaminomethyl)-2-methyl-pyrrolidin-3-ol (1.00 eq, 3.30 g, 20.9 mmol) and Na_2CO_3 (10.0 eq, 22.11 g, 209 mmol) in Toluene (20 mL) and Water (100 mL) was added triphosgene (1.50 eq, 9.28 g, 31.3 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was partitioned. The aqueous layer was concentrated. The solid was triturated with DCM (200 mL) and filtered. The filtrate was concentrated under vacuum to afford (5R,6R,7aS)-2-ethyl-6-hydroxy-5-methyl-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-3-one (1.45 g, 7.87 mmol, 37.74% yield) as a white solid, which was used in next step directly without further purification. LCMS ESI (+) m/z 185.1 (M+H).

[0530] Step V: Preparation of [(5R,6R,7aS)-2-ethyl-5-methyl-3-oxo-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-6-yl] methanesulfonate: To a solution of (5R,6R,7aS)-2-ethyl-6-hydroxy-5-methyl-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-3-one (1.00 eq, 1.40 g, 7.60 mmol) in DCM (30 mL) was added Et_3N (2.00 eq, 1.53 g, 15.2 mmol). Then MsCl (1.50 eq, 1.31 g, 11.4 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 4 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 2). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum to afford [(5R,6R,7aS)-2-ethyl-5-methyl-3-oxo-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-6-yl] methanesulfonate (2.00 g,7.62 mmol) as a yellow oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 263.1 (M+H).

[0531] Step W: Preparation of (5R,6S,7aS)-2-ethyl-6-(ethylamino)-5-methyl-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-3-one: A solution of [(5R,6R,7aS)-2-ethyl-5-methyl-3-oxo-5,6,7,7a-tetrahydro-1H-

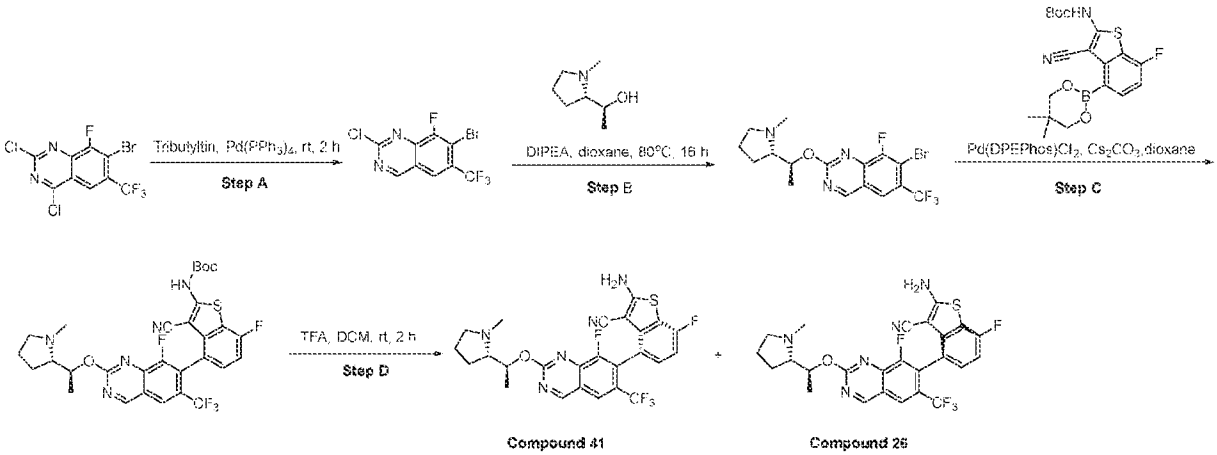
pyrrolo[1,2-c]imidazol-6-yl] methanesulfonate (1.00 eq, 2.00 g, 7.62 mmol) in Ethan amine (131 eq, 40 mL, 1000 mmol) (25% in EtOH) was stirred at 100°C for 16 hours. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 0% to 10% to afford (5R,6S,7aS)-2-ethyl-6-(ethylamino)-5-methyl-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-3-one (1.00 g, 4.73 mmol, 62.07% yield) as colorless oil. LCMS ESI (+) m/z 211.1 (M+H).

[0532] Step X: Preparation of tert-butyl (3-cyano-4-((S)-4-(ethyl((5R,6S,7aS)-2-ethyl-5-methyl-3-oxohexahydro-1H-pyrrolo[1,2-c]imidazol-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of (5R,6S,7aS)-2-ethyl-6-(ethylamino)-5-methyl-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-3-one (1.00 eq, 605 mg, 2.87 mmol) in 1,4-Dioxane (20 mL) was added tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 2.00 g, 2.87 mmol) and DIPEA (3.00 eq, 1.5 mL, 8.60 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 45°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with $NaHCO_3$(aqu.) (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 0% to 5% to afford tert-butyl (3-cyano-4-((S)-4-(ethyl((5R,6S,7aS)-2-ethyl-5-methyl-3-oxohexahydro-1H-pyrrolo[1,2-c]imidazol-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.05 g, 1.13 mmol, 39.47% yield) as a yellow solid. LCMS ESI (+) m/z 873.3 (M+H).

[0533] Step Y: Preparation of 2-amino-4-((S)-4-(ethyl((5R,6S,7aS)-2-ethyl-5-methyl-3-oxohexahydro-1H-pyrrolo[1,2-c]imidazol-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl (3-cyano-4-((S)-4-(ethyl((5R,6S,7aS)-2-ethyl-5-methyl-3-oxohexahydro-1H-pyrrolo[1,2-c]imidazol-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 1.05 g, 1.20 mmol) in DCM (10 mL) was added TFA (20.0 eq, 1.9 mL, 24.1 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The resulting mixture was concentrated under vacuum and the residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution,

extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 0% to 5% to afford 2-amino-4-((S)-4-(ethyl((5R,6S,7aS)-2-ethyl-5-methyl-3-oxohexahydro-1H-pyrrolo[1,2-c]imidazol-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (726 mg, 0.891 mmol, 74.07% yield) as a light yellow solid. LCMS ESI (+) m/z 773.3 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 7.27-7.18 (m, 1H), 7.06-6.97 (m, 1H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 4.85-4.77 (m, 1H), 4.33-4.17 (m, 2H), 4.17-4.06 (m, 1H), 4.05-3.94 (m, 1H), 3.90-3.77 (m, 1H), 3.70-3.58 (m, 2H), 3.47-3.40 (m, 1H), 3.40-3.32 (m, 1H), 3.29-3.16 (m, 4H), 3.07-2.96 (m, 1H), 2.39-1.83 (m, 9H), 1.37 (t, J = 7.0 Hz, 3H), 1.31 (d, J = 6.0 Hz, 3H), 1.14 (q, J = 6.8 Hz, 3H).

[0534] Synthetic Example 2: Preparation of 2-amino-7-fluoro-4-((R)-8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophene-3-carbonitrile (**Compound 41**) and 2-amino-7-fluoro-4-((S)-8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophene-3-carbonitrile (**Compound 26**)



[0535] Step A: Preparation of 7-bromo-2-chloro-8-fluoro-6-(trifluoromethyl)quinazoline: To a solution of 7-bromo-2,4-dichloro-8-fluoro-6-(trifluoromethyl) quinazoline (1.00 eq, 500 mg, 1.37 mmol) in Toluene (2 mL) was added bis(tributyltin) (1.00 eq, 0.69 mL, 1.37 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.0500 eq, 79 mg, 0.0687 mmol) at 25°C under N_2. After addition, the reaction mixture was stirred at 25°C for 1 h. The mixture was diluted with water and extracted with EtOAc (4x10 mL). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by prep-TLC (PE/EA=5/1) to give 7-bromo-2-chloro-8-fluoro-6-(trifluoromethyl) quinazoline (370 mg, 0.999 mmol, 72.74% yield) as a light-yellow solid. LCMS ESI (+) m/z 328.8 (M+H).

[0536] Step B: Preparation of 7-bromo-8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazoline: To a solution of 7-bromo-2-chloro-8-fluoro-6-(trifluoromethyl) quinazoline (1.00 eq, 100 mg, 0.304 mmol) in dioxane (2 mL) was added DIPEA (5.00 eq, 0.27 mL, 1.52 mmol) and (1S)-1-[(2S)-1-methylpyrrolidin-2-yl] ethanol (2.00 eq, 78 mg, 0.607 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The solvent was removed under vacuum, diluted with water, and extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by prep-TLC (DCM: MeOH 20:1) to afford 7-bromo-8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazoline (120 mg, 0.273 mmol, 89.90% yield) as a yellow solid. LCMS ESI (+) m/z 421.9 (M+H).

[0537] Step C: Preparation of tert-butyl (3-cyano-7-fluoro-4-(8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate: To a solution of 7-bromo-8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazoline (1.00 eq, 110 mg, 0.261 mmol) in 1,4-Dioxane (4 mL) was added tert-butyl (3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.80 eq, 190 mg, 0.469 mmol), Cs_2CO_3 (3.60 eq, 306 mg, 0.938 mmol), $Pd(DPEPhos)Cl_2$ (0.240 eq, 45 mg, 0.0625 mmol) and 4A molecular sieves (110 mg) at rt under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by prep-TLC (DCM: MeOH 12:1) to afford tert-butyl (3-cyano-7-fluoro-4-(8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate (130 mg, 0.103 mmol, 39.38% yield) as a brown solid. LCMS ESI (+) m/z 634.0 (M+H).

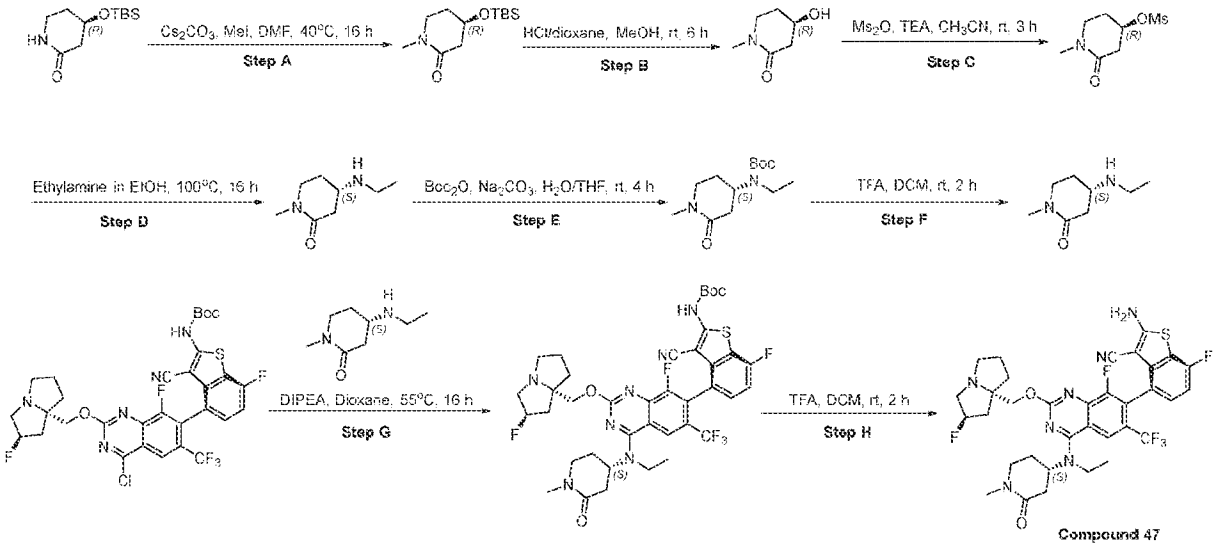
[0538] Step D: Preparation of 2-amino-7-fluoro-4-((S)-8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl (3-cyano-7-fluoro-4-(8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate (1.00 eq, 100 mg, 0.158 mmol) in DCM (2 mL) was added TFA (41.1 eq, 0.50 mL, 6.49 mmol). The resulting mixture was stirred at 25°C for 4 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was adjusted pH=8 with saturation sodium bicarbonate aqueous solution, extracted with ethyl acetate (20 mL x 4). The combined organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by prep-TLC (DCM: MeOH=15:1) to afford 2-amino-7-fluoro-4-((R)-

8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophene-3-carbonitrile (**compound 41**, 10.5 mg, 0.0194 mmol, 12.27% yield) as a white solid and 2-amino-7-fluoro-4-((S)-8-fluoro-2-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophene-3-carbonitrile (**compound 26**, 25.1 mg, 0.0429 mmol, 27.19% yield) as a yellow solid.

[0539] Compound 41: LCMS ESI (+) m/z 534.0 (M+H).^{1}H NMR (400 MHz, CD_3OD) δ 9.60 (s, 1H), 8.40 (s, 1H), 7.26-7.20 (m, 1H), 7.02 (t, 1H), 5.50-5.41 (m, 1H), 3.18-3.11 (m, 1H), 3.01-2.92 (m, 1H), 2.64 (s, 3H), 2.55-2.47 (m, 1H), 2.14-2.05 (m, 1H), 1.90-1.78 (m, 3H), 1.45 (d, 3H).

[0540] Compound 26: LCMS ESI (+) m/z 534.0 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ 9.59 (s, 1H), 8.40 (s, 1H), 7.27-7.21 (m, 1H), 7.02 (t, 1H), 5.46-5.39 (m, 1H), 3.14-3.08 (m, 1H), 2.94-2.86 (m, 1H), 2.61 (s, 3H), 2.51-2.42 (m, 1H), 2.11-2.02 (m, 1H), 1.88-1.74 (m, 3H), 1.44 (d, 3H).

[0541] Synthetic Example 3: Preparation of 2-amino-4-[4-[ethyl-[(4S)-1-methyl-2-oxo-4-piperidyl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 47**)



[0542] Step A: Preparation of (4R)-4-[tert-butyl(dimethyl)silyl]oxy-1-methyl-piperidin-2-one: To a solution of (4R)-4-[tert-butyl(dimethyl)silyl]oxypiperidin-2-one (1.00 eq, 5.00 g, 21.8 mmol) in DMF (50mL) was added Cs_2CO_3 (4.00 eq, 28.41 g, 87.2 mmol) and MeI (8.00 eq, 24.75 g, 174 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at 40°C for 16 hours. The reaction was monitored by LCMS. The resulting mixture was poured into water (100 mL) and extracted with EtOAc (50 mL x 2). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 0% to 2% to afford (4R)-4-[tert-butyl(dimethyl)silyl]oxy-1-methyl-piperidin-2-one (2.40 g, 9.86 mmol, 45.23% yield) as colorless oil. LCMS ESI (+) m/z 244 (M+H).

[0543] Step B: Preparation of (4R)-4-hydroxy-1-methyl-piperidin-2-one: To a solution of (4R)-4-[tert-butyl(dimethyl)silyl]oxy-1-methyl-piperidin-2-one (1.00 eq, 2.20 g, 9.04 mmol) in Methanol (5 mL) was added HCl/1,4-dioxane (20 mL) and stirred at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 6 hours. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford crude (4R)-4-hydroxy-1-methyl-piperidin-2-one (1.90 g) as brown oil, which was used in the next step directly without further purification. LCMS ESI (+) m/z 130 (M+H).

[0544] Step C: Preparation of (R)-1-methyl-2-oxopiperidin-4-yl methanesulfonate: To a solution of (4R)-4-hydroxy-1-methyl-piperidin-2-one (1.00 eq, 1.20 g, 9.29 mmol) in Acetonitrile (10 mL) was added TEA (5.00 eq, 6.5 mL, 46.5 mmol), then Methanesulfonic anhydride (1.30 eq, 2104 mg, 12.1 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 3 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 0% to 2% to afford (R)-1-methyl-2-

oxopiperidin-4-yl methanesulfonate (832 mg, 4.01 mmol, 43.21% yield) as yellow oil. LCMS ESI (+) m/z 208 (M+H).

[0545] Step D: Preparation of (4S)-4-(ethylamino)-1-methyl-piperidin-2-one: A solution of [(4R)-1-methyl-2-oxo-4-piperidyl] methanesulfonate (1 eq, 800 mg, 3.86 mmol) in Ethylamine/Ethanol (20 mL) was stirred at 110°C for 16 h. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford crude (4S)-4-(ethylamino)-1-methyl-piperidin-2-one (725 mg, 3.71 mmol, 96.18% yield) as brown oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 157 (M+H).

[0546] Step E: Preparation of tert-butyl (S)-ethyl(1-methyl-2-oxopiperidin-4-yl)carbamate: To a solution of (4S)-4-(ethylamino)-1-methyl-piperidin-2-one (1.00 eq, 725 mg, 4.64 mmol) in THF (15 mL) and Water (10 mL) was added Na_2CO_3 (5.00 eq, 2460 mg, 23.2 mmol). Then Boc_2O (1.00 eq, 1013 mg, 4.64 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 4 hours. The reaction was monitored by LCMS. The resulting mixture was filtered, and the filtrate was extracted with EtOAc (20 mL*3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 0% to 1% to afford tert-butyl (S)-ethyl(1-methyl-2-oxopiperidin-4-yl)carbamate (370 mg, 1.44 mmol, 31.10% yield) as colorless oil. LCMS ESI (+) m/z 257 (M+H).

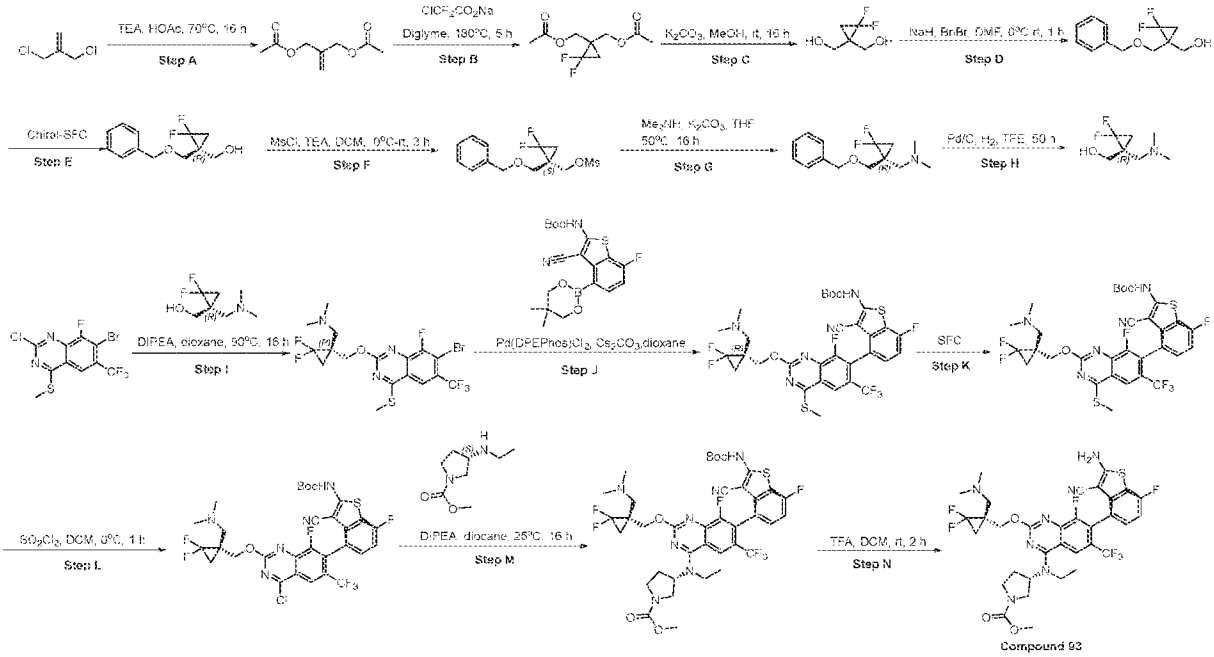
[0547] Step F: Preparation of (S)-4-(ethylamino)-1-methylpiperidin-2-one: To a solution of tert-butyl (S)-ethyl(1-methyl-2-oxopiperidin-4-yl)carbamate (1.00 eq, 370 mg, 1.44 mmol) in DCM (6 mL) was added TFA (20.0 eq, 2.2 mL, 28.9 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford crude (S)-4-(ethylamino)-1-methylpiperidin-2-one (445 mg) as a yellow oil, which was used in the next step directly without further purification. LCMS ESI (+) m/z 157 (M+H).

[0548] Step G: Preparation of tert-butyl (3-cyano-4-((S)-4-(ethyl((S)-1-methyl-2-oxopiperidin-4-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl (4-((S)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 260 mg, 0.372 mmol) in 1,4-Dioxane (5 mL) was added DIPEA (10.0 eq, 0.66 mL, 3.72 mmol) and (S)-4-(ethylamino)-1-methylpiperidin-2-one (2.00 eq, 201 mg, 0.745 mmol) at rt under nitrogen atmosphere. The

resulting mixture was stirred at 55°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (10 mL x 2). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by Prep-TLC (DCM/MeOH=10/1) to afford tert-butyl (3-cyano-4-((S)-4-(ethyl((S)-1-methyl-2-oxopiperidin-4-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (190 mg, 0.232 mmol, 62.38% yield) as a yellow solid. LCMS ESI (+) m/z 818 (M+H).

[0549] Step H: Preparation of 2-amino-4-[4-[ethyl-[(4S)-1-methyl-2-oxo-4-piperidyl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile: To a solution of tert-butyl N-[3-cyano-4-[4-[ethyl-[(4S)-1-methyl-2-oxo-4-piperidyl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 194 mg, 0.237 mmol) in DCM (3 mL) was added TFA (60.0 eq, 1.1 mL, 14.2 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 2 hours. The reaction was monitored by LCMS. The resulting mixture was concentrated, and the residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=10/1) to afford 2-amino-4-[4-[ethyl-[(4S)-1-methyl-2-oxo-4-piperidyl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (81 mg, 0.110 mmol, 46.21% yield) as a light yellow solid. LCMS ESI (+) m/z 718.2 (M+H). 1H NMR (400 MHz, CD_3OD) δ 8.20 (d, *J*=6.0 Hz, 1H), 7.23-7.20 (m, 1H), 7.01 (t, *J*=8.8 Hz, 1H), 5.36 (s, 0.5 H), 5.23 (s, 0.5 H), 4.86-4.76 (m, 1H), 4.31-4.20 (m, 2H), 3.87-3.82 (m, 2H), 3.48-3.31 (m, 2H), 3.25-3.20 (m, 3H), 3.03-2.77 (m, 6H), 2.52-2.47 (m, 1H), 2.32-2.11 (m, 4H), 2.01-1.86 (m, 3H), 1.47 (t, *J*=7.2 Hz, 3H).

[0550] Synthetic Example 4: Preparation of methyl (S)-3-(((S)-7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate (**Compound 93**)



[0551] Step A: Preparation of 2-methylenepropane-1,3-diyl diacetate: To a solution of 3-chloro-2-(chloromethyl) prop-1-ene (1.00 eq, 100 g, 800 mmol) in TEA (3.00 eq, 335 mL, 2400 mmol) was added HOAc (2.50 eq, 120 g, 2000 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 70°C for 16 hours under nitrogen atmosphere. The reaction was monitored by TLC. The resulting mixture was cooled to room temperature and quenched with water (1 L), extracted with ethyl acetate (1 L x 3), The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 0% to 10% to afford 2-methylenepropane-1,3-diyl diacetate (90 g, 523 mmol, 65.34% yield) as a yellow oil.

[0552] Step B: Preparation of (2,2-difluorocyclopropane-1,1-diyl) bis(methylene) diacetate: To a solution of 2-methylenepropane-1,3-diyl diacetate (1.00 eq, 90 g, 523 mmol) in Diglyme (900 mL), was added $ClCF_2CO_2Na$ (5.00 eq, 397.26 g, 2614 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 180°C for 5 hours. The reaction was monitored by TLC. The resulting mixture was cooled to room temperature, quenched with water (5 L) and extracted with petroleum (2 L x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum to afford crude product (2,2-difluorocyclopropane-1,1-diyl) bis(methylene) diacetate (200 g), which was used in the next step directly without further purification.

[0553] Step C: Preparation of (2,2-difluorocyclopropane-1,1-diyl) dimethanol: To a solution of (2,2-difluorocyclopropane-1,1-diyl) bis(methylene) diacetate (1.00 eq, 200 g, 900 mmol) in Methanol (1250

mL), was added K_2CO_3 (2.00 eq, 248 g, 1800 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by TLC. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 10% to 50% to afford (2,2-difluorocyclopropane-1,1-diyl)dimethanol (37 g, 268 mmol, 29.8% yield) as a yellow oil.

[0554] Step D: Preparation of (1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol: To a solution of NaH (1.1 eq, 11.8 g, 295 mmol, 60% in oil) in DMF (460 mL) was added (2,2-difluorocyclopropane-1,1-diyl) dimethanol (1.00 eq, 37 g, 268 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1 h under nitrogen atmosphere. To the above mixture was added BnBr (1.00 eq, 45.8 g, 268 mmol) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 1 h under nitrogen atmosphere. The reaction was monitored by TLC. The resulting mixture was quenched with NH_4Cl (400 mL) and extracted with ethyl acetate (600 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate in petroleum from 0% to 10% to afford (1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol (20 g, 87 mmol, 32.78% yield) as a yellow solid.

[0555] Step E: Preparation of (R)-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol and (S)-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol: The racemate was separated by Chiral-SFC with the following condition (Column B, 95% CO_2 and 5%(IPA+HEX=1:1)). This resulted in (R)-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol (Peak1, 3.6 g, ee >98%) and (S)-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol (BBHB-031 Peak2, 3.9 g, ee >95%) as a yellow solid.

[0556] Step F: Preparation of (S)-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methyl methanesulfonate: To a solution of (R)-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol (1.00 eq, 3600 mg, 15.8 mmol)) in DCM (36 mL) was added TEA (4.00 eq, 6.5 g, 63.1 mmol). Then Methane sufonyl chloride (2.00 eq, 3614 mg, 31.5 mmol) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 3 hours under nitrogen atmosphere. The reaction was monitored by TLC. The resulting mixture was quenched with NH_4Cl (36 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum to afford crude product (S)-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methyl methanesulfonate (5 g), which was used in next step directly without further purification.

[0557] Step G: Preparation of (R)-1-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)-N,N-dimethylmethanamine: To a solution of (S)-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methyl methanesulfonate (1.00 eq, 5000 mg, 16.3 mmol) in Me_2NH (5.00 eq, 41 mL, 81.6 mmol, 2M in THF) was added K_2CO_3 (2.00 eq, 4.8 g, 32.6 mmol) at rt. The resulting mixture was stirred at 50°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (150 mL), extracted with ethyl acetate (60 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum to afford crude product (R)-1-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)-N,N-dimethylmethanamine (4 g, 15.7 mmol, 77.94% yield), which was used in next step directly without further purification. LCMS ESI (+) m/z 256.1 (M+H).

[0558] Step H: Preparation of (R)-(1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methanol: To a solution of (R)-1-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)-N,N-dimethylmethanamine (1.00 eq, 4 g, 15.7 mmol) in TFE (40 mL) was added Pd/C (2 g, 10% Pd) under nitrogen atmosphere. The resulting mixture was recharged with nitrogen gas three times and then recharged with hydrogen gas three times. The resulting mixture was stirred at 25°C for 50 hours under hydrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was filtered and filter cake was washed with MeOH (50 mL). The combined filtrate was treated with 4M HCl in dioxane and then concentrated under vacuum to afford crude product (R)-(1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methanol (3 g, 15.3 mmol, 97.92% yield) as a yellow solid. LCMS ESI (+) m/z 166.1 (M+H).

[0559] Step I: Preparation of (R)-1-(1-(((7-bromo-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)-N,N-dimethylmethanamine: To a solution of 7-bromo-2-chloro-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin (1.00 eq, 1.5 g, 4.01 mmol) in 1,4-Dioxane (15 mL), was added (R)-(1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methanol (2.50 eq, 1655 mg, 10.02 mmol) and DIPEA (5.00 eq, 2587 mg, 20.05 mmol). The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with water (15 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 10% to 30% to afford (R)-1-(1-(((7-bromo-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)-N,N-dimethylmethanamine (1.3 g, 2.35 mmol, 88.28% yield). LCMS ESI (+) m/z 506.1 (M+H).

[0560] Step J: Preparation of tert-butyl (3-cyano-4-(2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)-7-

fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of (R)-1-(1-(((7-bromo-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)-N,N-dimethylmethanamine (1.00 eq, 1.3 g, 2.58 mmol) 1,4-Dioxane (52 mL) was added tert-butyl (3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.50 eq, 1044 mg, 3.87 mmol), $Pd(DPEPhos)Cl_2$ (0.400 eq, 739 mg, 1.032 mmol) and Cs_2CO_3 (3.00 eq, 2528 mg, 7.74 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (150 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 10% to 50% to afford tert-butyl (3-cyano-4-(2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.2 g, 1.61 mmol, 49.31% yield) as a yellow solid. LCMS ESI (+) m/z 716.2 (M+H).

[0561] Step K: Preparation of tert-butyl (3-cyano-4-((S)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: The racemate of tert-butyl (3-cyano-4-(2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate was separated by Chiral-SFC (Column IG-3-95%(Hex with 0.1%DEA) and 5%EtOH) to afford tert-butyl (3-cyano-4-((S)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (Peak2, 300 mg, ee >95%). LCMS ESI (+) m/z 716.2 (M+H).

[0562] Step L: Preparation of tert-butyl (4-((S)-4-chloro-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl (3-cyano-4-((S)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 60 mg, 0.0838 mmol) in DCM (0.6 mL) was added SO_2Cl_2 (5.00 eq, 57 mg, 0.419 mmol) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum and the residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered

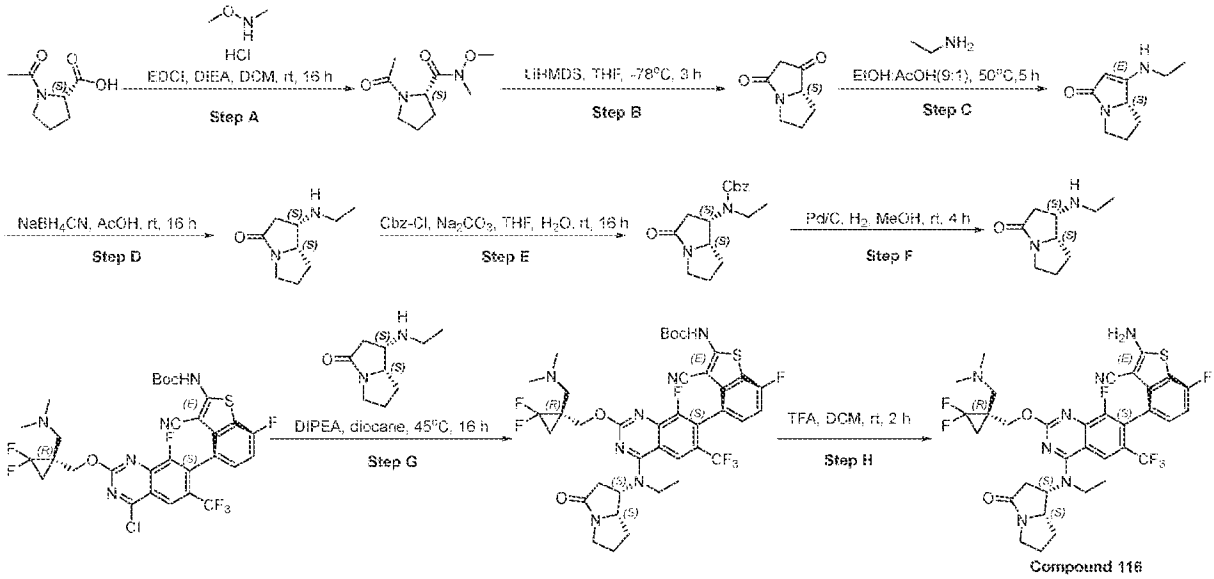
and concentrated under vacuum to crude product tert-butyl (4-((S)-4-chloro-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (60 mg, 0.0818 mmol, 97.59% yield) as a yellow solid, which was used in next step directly without further purification. LCMS ESI (+) m/z 704.1 (M+H).

[0563] Step M: Preparation of methyl (S)-3-(((S)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate: To a solution of tert-butyl (4-((R)-4-chloro-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 60 mg, 0.0852 mmol) in 1,4-Dioxane (0.5 mL) was added methyl (S)-3-(ethylamino)pyrrolidine-1-carboxylate (2.00 eq, 29 mg, 0.170 mmol) and DIEA (3.00 eq, 26 mg, 0.256 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with water (2 mL) and extracted with ethyl acetate (2 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by prep-TLC with ethyl acetate/petroleum ether (1/ 1) to afford methyl (S)-3-(((S)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate (15 mg, 0.0163 mmol, 19.16% yield) as a white solid. LCMS ESI (+) m/z 840.3 (M+H).

[0564] Step N: Preparation of methyl (S)-3-(((S)-7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate: To a solution of methyl (S)-3-(((S)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate (1.00 eq, 15 mg, 0.0179 mmol) in DCM (0.40 mL) was added TFA (0.20 mL) at rt under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 3 hours. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum and the residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC with MeOH /DCM (1/10) to afford methyl (S)-3-(((S)-7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoro-6-(trifluoromethyl)quinazolin-4-

yl)(ethyl)amino)pyrrolidine-1-carboxylate (12 mg,0.0156 mmol, 87.55 % yield) as an off-white solid. LCMS ESI (+) m/z 740.1 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.25-7.18 (m, 1H), 7.04-6.96 (m, 1H), 5.01 (d, *J*=6.3 Hz, 1H), 4.61-4.53 (m, 2H), 3.95-3.72 (m, 4H), 3.72 (s, 3H), 3.67-3.56 (m, 1H), 3.47-3.40 (m, 1H), 2.87 (d, *J*=12.9 Hz, 1H), 2.55-2.44 (m, 2H), 2.39-2.34 (m, 1H), 2.30 (s, 6H), 1.71-1.63 (m, 1H), 1.45 (t, *J*=7.0 Hz, 3H), 1.41-1.37 (m, 1H).

[0565] Synthetic Example 5: Preparation of 2-amino-4-((S)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl) methoxy)-4-(ethyl((1S,7aS)-3-oxohexahydro-1H-pyrrolizin-1-yl)amino)-8-fluoro-6-(trifluoromethyl) quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (**Compound 116**)



[0566] Step A: Preparation of (S)-1-acetyl-N-methoxy-N-methylpyrrolidine-2-carboxamide: To a solution of acetyl-L-proline (1.00 eq, 50 g, 318 mmol) in DCM (500 mL) was added N,O-dimethylhydroxylamine hydrogen chloride (2 eq, 62 g, 636 mmol), DIEA (3 eq, 123 g, 954 mmol), HoBt (3 eq, 129 g, 954 mmol) and EDCI (3 eq, 183 g, 954 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with water (600 mL) and extracted with ethyl acetate (600 mL x 3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 10% to 50% to afford (S)-1-acetyl-N-methoxy-N-methylpyrrolidine-2-carboxamide (18 g, 90 mmol, 26.8% yield). LCMS ESI (+) m/z 201.1 (M+H).

[0567] Step B: Preparation of (S)-tetrahydro-1H-pyrrolizine-1,3(2H)-dione: To a solution of (S)-1-acetyl-N-methoxy-N-methylpyrrolidine-2-carboxamide (1.00 eq, 18 g, 90 mmol) in THF (180 mL), was added

LiHMDS (2.00 eq, 90 mL, 180 mmol, 2M in THF) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred at -78°C for 3 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with MeOH (200 mL). The resulting mixture was concentrated under vacuum to afford crude (S)-tetrahydro-1H-pyrrolizine-1,3(2H)-dione (24 g), which was used in next step directly without further purification. LCMS ESI (+) m/z 140.1 (M+H).

[0568] Step C: Preparation of (S)-1-(ethylamino)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one: A solution of (S)-tetrahydro-1H-pyrrolizine-1,3(2H)-dione (1.00 eq, 24 g, 173 mmol) in $EtNH_2$ (240 mL, 30% in EtOH) and HOAc (27 mL) was stirred at 50°C for 5 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford crude (S)-1-(ethylamino)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (25 g), which was used in next step directly without further purification. LCMS ESI (+) m/z 167.1 (M+H).

[0569] Step D: Preparation of (1S,7aS)-1-(ethylamino)hexahydro-3H-pyrrolizin-3-one: To a solution of (S)-1-(ethylamino)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (1.00 eq, 25 g, 150 mmol) in Acetic acid (250 mL) was added $NaBH_3CN$ (2.00 eq, 18.97 g, 300 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated. The residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with ethyl acetate (300 mL x 3). The aqueous layer was concentrated under vacuum to afford a crude product (1S,7aS)-1-(ethylamino) hexahydro-3H-pyrrolizin-3-one (28 g, 166 mmol, 24.32% yield), which was used in next step directly without further purification. LCMS ESI (+) m/z 169.1 (M+H).

[0570] Step E: Preparation of benzyl ethyl((1S,7aS)-3-oxohexahydro-1H-pyrrolizin-1-yl)carbamate: To a solution of (1S,7aS)-1-(ethylamino) hexahydro-3H-pyrrolizin-3-one (1.00 eq, 28 g, 166 mmol) in THF (40 mL) and water (40 mL) was added Na_2CO_3 (3.00 eq, 53 g, 498 mmol). Then Cbz-Cl (2.00 eq, 57 g, 332 mmol) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was extracted with ethyl acetate (60 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 10% to 50% to afford benzyl ethyl((1S,7aS)-3-oxohexahydro-1H-pyrrolizin-1-yl)carbamate (1200 mg, 3.97 mmol, 14.51% yield) as a white solid. LCMS ESI (+) m/z 303.2 (M+H).

[0571] Step F: Preparation of (1S,7aS)-1-(ethylamino)hexahydro-3H-pyrrolizin-3-one: To a solution of benzyl ethyl((1S,7aS)-3-oxohexahydro-1H-pyrrolizin-1-yl)carbamate (1.00 eq, 1200 mg, 3.97 mmol) in

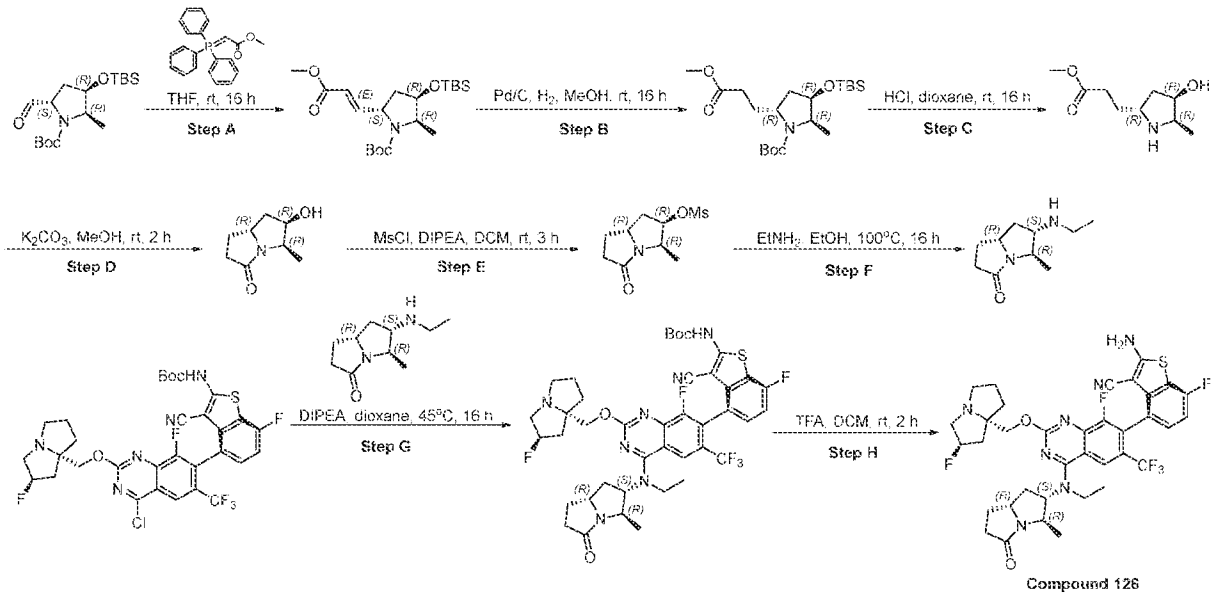
Methanol (15 mL) was added Pd/C (300 mg) under nitrogen atmosphere. The resulting mixture was recharged with nitrogen gas three times and then recharged with hydrogen gas three times. The reaction mixture was stirred at 25°C for 3 hours under hydrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was filtered. The filter cake was washed with MeOH (50 mL). The filtrate was concentrated under vacuum to afford (1S,7aS)-1-(ethylamino)hexahydro-3H-pyrrolizin-3-one (700 mg), which was used in next step directly without further purification. LCMS ESI (+) m/z 169.1 (M+H).

[0572] Step G: Preparation of tert-butyl (3-cyano-4-((S)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-4-(ethyl((1S,7aS)-3-oxohexahydro-1H-pyrrolizin-1-yl)amino)-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl (4-((R)-4-chloro-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl) methoxy)-8-fluoro-6-(trifluoromethyl) quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl) carbamate (1.00 eq, 35 mg, 0.0497 mmol) in 1,4-Dioxane (0.5 mL) was added (1S,7aS)-1-(ethylamino)hexahydro-3H-pyrrolizin-3-one (2.00 eq, 17 mg, 0.0994 mmol) and DIEA (3.00 eq, 15 mg, 0.149 mmol). The reaction mixture was stirred at 45°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with water (2 mL) and extracted with ethyl acetate (2 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by prep-TLC with DCM/MeOH (10/1) to afford tert-butyl (3-cyano-4-((S)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-4-(ethyl((1S,7aS)-3-oxohexahydro-1H-pyrrolizin-1-yl)amino)-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (25 mg, 0.0296 mmol, 59.48% yield). LCMS ESI (+) m/z 836.3 (M+H).

[0573] Step H: Preparation of 2-amino-4-((S)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl) methoxy)-4-(ethyl((1S,7aS)-3-oxohexahydro-1H-pyrrolizin-1-yl)amino)-8-fluoro-6-(trifluoromethyl) quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl (3-cyano-4-((S)-2-(((R)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-4-(ethyl((1S,7aS)-3-oxohexahydro-1H-pyrrolizin-1-yl)amino)-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 20 mg, 0.0239 mmol) in DCM (0.6 mL) was added TFA (0.20 mL) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The resulting mixture was concentrated under vacuum and the residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by prep-TLC with MeOH /DCM (1/10) to afford 2-amino-4-((S)-2-(((R)-

1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-4-(ethyl((1S,7aS)-3-oxohexahydro-1H-pyrrolizin-1-yl)amino)-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (13 mg, 0.0168 mmol, 70.11% yield) as a white solid. LCMS ESI (+) m/z 736.1 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 7.25-7.19 (m, 1H), 7.05-6.95 (m, 1H), 4.55-4.45 (m, 4H), 3.94-3.87 (m, 2H), 3.62-3.54 (m, 2H), 3.12 (t, *J*=9.4 Hz, 1H), 2.92-2.79 (m, 2H), 2.60 (d, 1H), 2.31 (s, 6H), 2.23-2.17 (m, 2H), 2.12-2.06 (m, 1H), 1.69-1.59 (m, 2H), 1.55 (t, *J* = 7.0 Hz, 3H), 1.45-1.41 (m, 1H).

[0574] Synthetic Example 6: Preparation of 2-amino-4-((S)-4-(ethyl((2S,3R,7aR)-3-methyl-5-oxohexahydro-1H-pyrrolizin-2-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile **(Compound 126)**



[0575] Step A: Preparation of tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-[(E)-3-methoxy-3-oxo-prop-1-enyl]-2-methyl-pyrrolidine-1-carboxylate: To a solution of tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-formyl-2-methyl-pyrrolidine-1-carboxylate (1.00 eq, 1250 mg, 3.64 mmol) in THF (20 mL) was added Methyl(triphenylphosphoranylidene)acetate (1.20 eq, 1460 mg, 4.37 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with ethyl acetate (50 mL), washed with water (20 mL) and brine (20 mL). The organic phase was concentrated under a vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 0% to 10% to afford tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-[(E)-3-methoxy-3-oxo-prop-

1-enyl]-2-methyl-pyrrolidine-1-carboxylate (1000 mg, 2.38 mmol, 65.34% yield) as a colorless oil. LCMS ESI (+) m/z 300.1 (M-100+H).

[0576] Step B: Preparation of tert-butyl (2R,3R,5R)-3-[tert-butyl(dimethyl)silyl]oxy-5-(3-methoxy-3-oxo-propyl)-2-methyl-pyrrolidine-1-carboxylate: To a solution of tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-[(E)-3-methoxy-3-oxo-prop-1-enyl]-2-methyl-pyrrolidine-1-carboxylate (1.00 eq, 1.00 g, 2.50 mmol) in methanol (20 mL) was added Pd/C (0.200 eq, 266 mg, 0.501 mmol, 10%Pd) under nitrogen atmosphere. The resulting mixture was recharged with nitrogen gas three times and then recharged with hydrogen gas three times. The resulting mixture was stirred at room temperature for 16 h under hydrogen atmosphere. The reaction was monitored by LCMS. The solids were filtered out and the solvent was evaporated under vacuum to afford tert-butyl (2R,3R,5R)-3-[tert-butyl(dimethyl)silyl]oxy-5-(3-methoxy-3-oxo-propyl)-2-methyl-pyrrolidine-1-carboxylate (960 mg, 2.39 mmol, 95.52% yield) as a colorless oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 424.2 (M+Na).

[0577] Step C: Preparation of methyl 3-[(2R,4R,5R)-4-hydroxy-5-methyl-pyrrolidin-2-yl]propanoate: A solution of tert-butyl (2R,3R,5R)-3-[tert-butyl(dimethyl)silyl]oxy-5-(3-methoxy-3-oxo-propyl)-2-methyl-pyrrolidine-1-carboxylate (1.00 eq, 960 mg, 2.39 mmol) in HCl (16.7 eq, 10 mL, 40.0 mmol, 4M in dioxane) was stirred at 25°C for 16 hours. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford crude methyl 3-[(2R,4R,5R)-4-hydroxy-5-methyl-pyrrolidin-2-yl]propanoate (660 mg, 3.52 mmol, 147.46% yield) as a white solid, which was used in next step directly without further purification. LCMS ESI (+) m/z 188.1 (M+H).

[0578] Step D: Preparation of (5R,6R,7aR)-6-hydroxy-5-methylhexahydro-3H-pyrrolizin-3-one : To a solution of methyl 3-[(2R,4R,5R)-4-hydroxy-5-methyl-pyrrolidin-2-yl]propanoate (1.00 eq, 660 mg, 3.52 mmol) in methanol (10 mL) was added K_2CO_3 (4.00 eq, 1946 mg, 14.1 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with DCM (10 mL) and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 0% to 10% to afford (5R,6R,7aR)-6-hydroxy-5-methylhexahydro-3H-pyrrolizin-3-one (305 mg, 1.97 mmol, 55.76% yield) as a white solid. LCMS (ESI, m/z): 156.1 (M+H).

[0579] Step E: Preparation of (2R,3R,7aR)-3-methyl-5-oxohexahydro-1H-pyrrolizin-2-yl methanesulfonate: To a solution of (5R,6R,7aR)-6-hydroxy-5-methylhexahydro-3H-pyrrolizin-3-one (1.00 eq, 200 mg, 1.29 mmol) in DCM (5 mL) was added TEA (2.00 eq, 0.36 mL, 2.58 mmol). Then MsCl (1.50 eq, 221 mg, 1.93 mmol) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The

resulting mixture was stirred at 25℃ for 3 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with water (5 mL), extracted with DCM (5 mL x 2). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum to afford crude (2R,3R,7aR)-3-methyl-5-oxohexahydro-1H-pyrrolizin-2-yl methanesulfonate (310 mg, 1.33 mmol, 103.11% yield) as a yellow oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 234.1 (M+H).

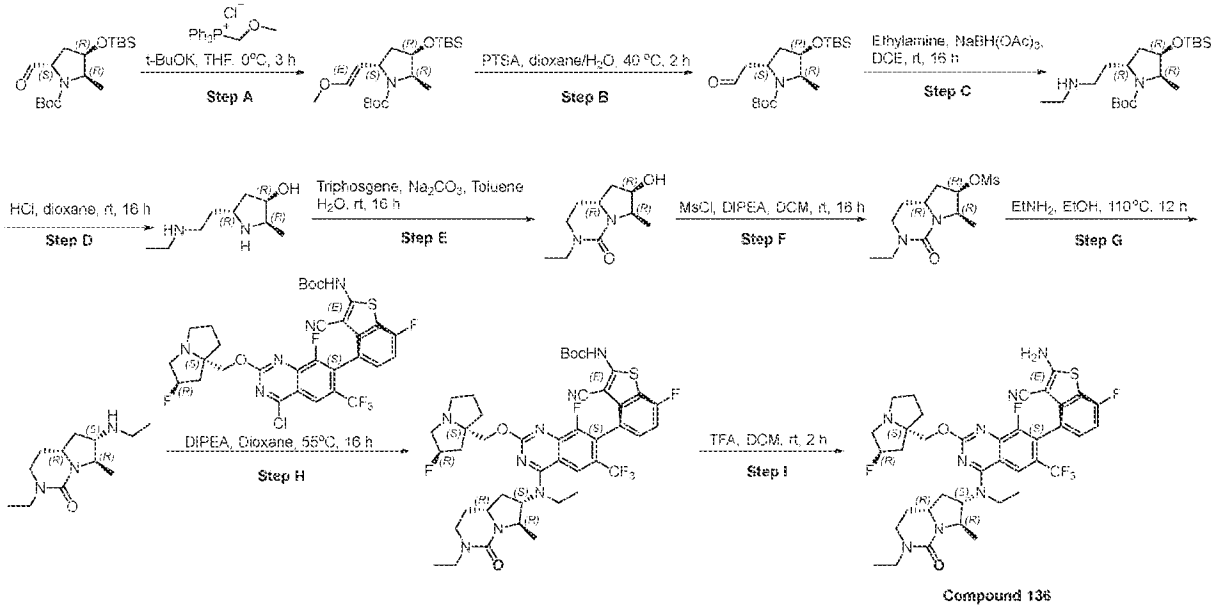
[0580] Step F: Preparation of (5R,6S,7aR)-6-(ethylamino)-5-methylhexahydro-3H-pyrrolizin-3-one: A solution of [(2R,3R,8R)-3-methyl-5-oxo-1,2,3.6,7,8-hexahydropyrrolizin-2-yl] methanesulfonate (1.00 eq, 340 mg, 1.46 mmol) in ethyl amine (206 eq, 10 mL, 300 mmol) (30% in EtOH) was stirred at 100℃ for 16 hours. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by perp-TLC (DCM/MeOH=10/1) to afford (5R,6S,7aR)-6-(ethylamino)-5-methylhexahydro-3H-pyrrolizin-3-one (110 mg, 0.513 mmol, 35.20% yield) as a colorless oil. LCMS ESI (+) m/z 183.1 (M+H).

[0581] Step G: Preparation of tert-butyl (3-cyano-4-((S)-4-(ethyl((2S,3R,7aR)-3-methyl-5-oxohexahydro-1H-pyrrolizin-2-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl (4-((S)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 70 mg, 0.100 mmol) in 1,4-Dioxane (1 mL) was added (5R,6S,7aR)-6-(ethylamino)-5-methylhexahydro-3H-pyrrolizin-3-one (2.00 eq, 37 mg, 0.201 mmol) and DIPEA (4.00 eq, 0.071 mL, 0.401 mmol) at 25℃ under nitrogen atmosphere. The resulting mixture was stirred at 45℃ for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL) and concentrated under vacuum. The residue was purified by Prep-TLC (DCM/MeOH=12/1) to afford tert-butyl (3-cyano-4-((S)-4-(ethyl((2S,3R,7aR)-3-methyl-5-oxohexahydro-1H-pyrrolizin-2-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (39 mg, 0.0448 mmol, 44.71% yield) as a yellow solid. LCMS ESI (+) m/z 844.2 (M+H).

[0582] Step H: Preparation of 2-amino-4-((S)-4-(ethyl((2S,3R,7aR)-3-methyl-5-oxohexahydro-1H-pyrrolizin-2-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl (3-cyano-4-((S)-4-(ethyl((2S,3R,7aR)-3-methyl-5-oxohexahydro-1H-pyrrolizin-2-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-

fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 39 mg, 0.0462 mmol) in DCM (4 mL) was added TFA (20.0 eq, 0.071 mL, 0.924 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum and the residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by Prep-TLC (DCM/MeOH=8/1) to afford 2-amino-4-((S)-4-(ethyl((2S,3R,7aR)-3-methyl-5-oxohexahydro-1H-pyrrolizin-2-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (29 mg, 0.0370 mmol, 80.11% yield) as a light yellow solid. LCMS ESI (+) m/z 744.3 (M+H). 1H NMR (400 MHz, CD_3OD) 8.22 (s, 1H), 7.26-7.20 (m, 1H), 7.06-6.97 (m, 1H), 5.44 (s, 0.5H), 5.30 (s, 0.5H), 4.62-4.51 (m, 1H), 4.49-4.38 (m, 1H), 4.37-4.14 (m, 3H), 4.00-3.88 (m, 1H), 3.84-3.71 (m, 1H), 3.57-3.35 (m, 3H), 3.13 (s, 1H), 2.84-2.71 (m, 1H), 2.54-2.17 (m, 7H), 2.13-1.88 (m, 4H), 1.53 (t, J = 7.0 Hz, 3H), 1.36 (d, J = 6.4 Hz, 3H).

[0583] Synthetic Example 7: Preparation of 2-amino-4-((S)-4-(ethyl((4aR,6S,7R)-2-ethyl-7-methyl-1-oxooctahydropyrrolo[1,2-c]pyrimidin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: **(Compound 136)**



[0584] Step A: Preparation of tert-butyl (2R,3R,5S)-3-((tert-butyldimethylsilyl)oxy)-5-((E)-2-methoxyvinyl)-2-methylpyrrolidine-1-carboxylate: To a solution of (Methoxymethyl)triphenylphosphonium chloride (1.00 eq, 7.48 g, 21.8 mmol) in THF (50mL) was added t-BuOK (1.00 eq, 2.45 g, 21.8 mmol) at 0°C under nitrogen atmosphere. The resulting solution was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then a solution of tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-formyl-2-methyl-pyrrolidine-1-carboxylate (1.00 eq, 7.50 g, 21.8 mmol) in DCM (50 mL) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 2 hours. The reaction was monitored by LCMS. The resulting mixture was quenched with NH_4Cl.aq (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 0% to 10% to afford tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-[(E)-2-methoxyvinyl]-2-methyl-pyrrolidine-1-carboxylate (5.10 g, 13.7 mmol, 62.87% yield) as a colorless oil. LCMS ESI (+) m/z 372.5 (M+H).

[0585] Step B: Preparation of tert-butyl (2R,3R,5S)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-5-(2-oxoethyl)pyrrolidine-1-carboxylate: To a solution oftert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-5-[(E)-2-methoxyvinyl]-2-methyl-pyrrolidine-1-carboxylate (1.00 eq, 5.12 g, 13.8 mmol) in 1,4-Dioxane (4 mL) and water (4 mL) was added PTSA (0.500 eq, 0.54 g, 6.89 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred 40°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with $NaHCO_3$.aq (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate in petroleum from 2% to 10% to afford tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-2-methyl-5-(2-oxoethyl)pyrrolidine-1-carboxylate (3.00 g, 8.39 mmol, 60.89% yield) as a yellow solid. LCMS ESI (+) m/z 358.2 (M+H).

[0586] Step C: Preparation of tert-butyl (2R,3R,5R)-3-((tert-butyldimethylsilyl)oxy)-5-(2-(ethylamino)ethyl)-2-methylpyrrolidine-1-carboxylate: To a solution of tert-butyl (2R,3R,5S)-3-[tert-butyl(dimethyl)silyl]oxy-2-methyl-5-(2-oxoethyl)pyrrolidine-1-carboxylate (1.00 eq, 1.00 g, 2.80 mmol) in DCE (10mL) was added ethylamine (5.00 eq, 7 mL, 14.0 mmol, 2M in THF) at 0°C under nitrogen atmosphere. The resulting solution was stirred at room temperature for 1 h under nitrogen atmosphere. Then $NaBH(OAc)_3$ (2.00 eq, 1.19 g, 5.59 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 12 hours. The reaction was

monitored by LCMS. The resulting mixture was then quenched with water (20 mL), extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 0% to 5% to afford tert-butyl (2R,3R,5R)-3-[tert-butyl(dimethyl)silyl]oxy-5-[2-(ethylamino)ethyl]-2-methyl-pyrrolidine-1-carboxylate (600 mg, 1.24 mmol, 44.44% yield) as a white solid. LCMS ESI (+) m/z 387.3 (M+H).

[0587] Step D: Preparation of (2R,3R,5R)-5-(2-(ethylamino)ethyl)-2-methylpyrrolidin-3-ol: A mixture of tert-butyl (2R,3R,5R)-3-[tert-butyl(dimethyl) silyl]oxy-5-[2-(ethylamino)ethyl]-2-methyl-pyrrolidine-1-carboxylate (1.00 eq, 600 mg, 1.55 mmol) in HCl (10 mL, 40 mmol, 4M in dioxane) was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The solvent was removed under vacuum to afford crude (2R,3R,5R)-5-[2-(ethylamino)ethyl]-2-methyl-pyrrolidin-3-ol (220 mg, 1.22 mmol, 78.82% yield) as yellowish solid, which was used in next step directly without further purification. LCMS ESI (+) m/z 173.1 (M+H).

[0588] Step E: Preparation of (4aR,6R,7R)-2-ethyl-6-hydroxy-7-methylhexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one: To the solution of (2R,3R,5R)-5-[2-(ethylamino) ethyl]-2-methyl-pyrrolidin-3-ol (1.00 eq, 220 mg, 1.28 mmol) in toluene (10 mL) and water (20 mL) was added Na_2CO_3 (6.00 eq, 811.96 mg, 7.66 mmol) and triphosgene (0.70 eq, 266 mg, 0.89 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (20 mL), extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to afford (4aR,6R,7R)-2-ethyl-6-hydroxy-7-methyl-3,4,4a,5,6,7-hexahydropyrrolo[1,2-c] pyrimidin-1-one (260 mg, 1.11 mmol, 87.28% yield) as a colourless oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 199.1 (M+H).

[0589] Step F: Preparation of (4aR,6R,7R)-2-ethyl-7-methyl-1-oxooctahydropyrrolo[1,2-c]pyrimidin-6-yl methanesulfonate: To a solution of (4aR,6R,7R)-2-ethyl-6-hydroxy-7-methyl-3,4,4a,5,6,7-hexahydropyrrolo[1,2-c]pyrimidin-1-one (1.00 eq, 260 mg, 1.31 mmol) in DCM (10 mL) was added DIPEA (5.00 eq, 0.91 mL, 6.56 mmol). Then MsCl (1.50 eq, 429 mg, 1.97 mmol) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with water (20 mL) and extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (40 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from

0% to 5% to afford [(4aR,6R,7R)-2-ethyl-7-methyl-1-oxo-3,4,4a,5,6,7-hexahydropyrrolo[1,2-c]pyrimidin-6-yl] methanesulfonate (220 mg, 0.72 mmol, 55.24% yield) as a colorless oil. LCMS ESI (+) m/z 277.0 (M+H).

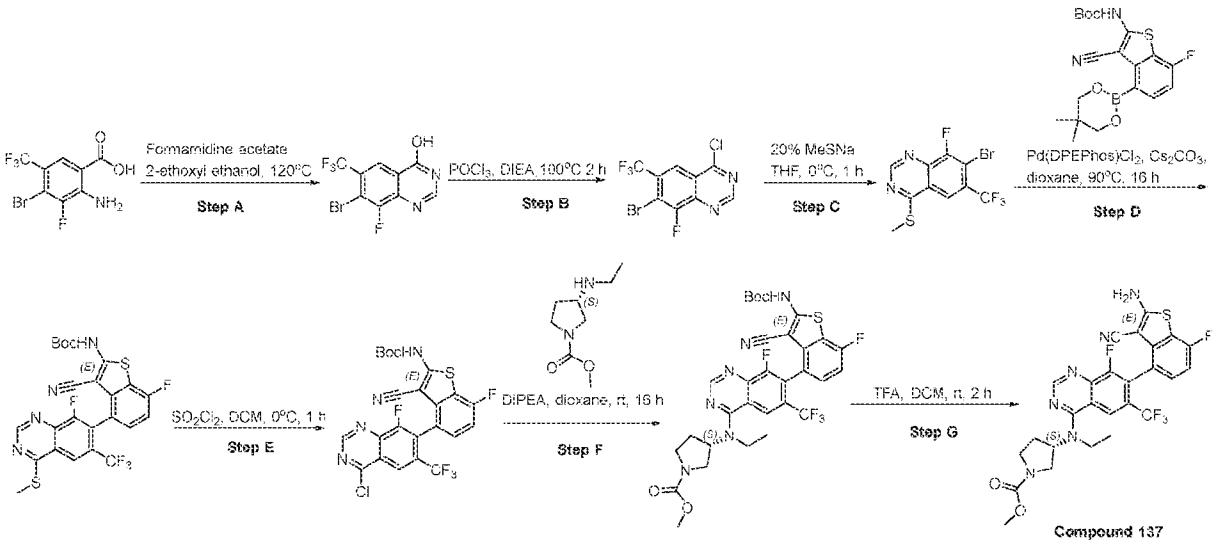
[0590] Step G: Preparation of (4aR,6S,7R)-2-ethyl-6-(ethylamino)-7-methylhexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one: A solution of [(4aR,6R,7R)-2-ethyl-7-methyl-1-oxo-3,4,4a,5,6,7-hexahydropyrrolo[1,2-c]pyrimidin-6-yl] methanesulfonate (1.00 eq. 267 mg, 0.965 mmol) in ethylamine (30.0 eq. 217 mg, 4.81 mmol) in ethanol (10 mL) was stirred at 110°C for 12 hours. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=5:1) to afford (4aR,6S,7R)-2-ethyl-6-(ethylamino)-7-methyl-3,4,4a,5,6,7-hexahydropyrrolo[1,2-c]pyrimidin-1-one (160 mg, 0.64 mmol, 66.23% yield) as a light yellow oil. LCMS ESI (+) m/z 226.1 (M+H).

[0591] Step H: Preparation of tert-butyl (3-cyano-4-((S)-4-(ethyl((4aR,6S,7R)-2-ethyl-7-methyl-1-oxooctahydropyrrolo[1,2-c]pyrimidin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 80 mg, 0.115 mmol) in dioxane (2 mL) was added (4aR,6S,7R)-2-ethyl-6-(ethylamino)-7-methyl-3,4,4a,5,6,7-hexahydropyrrolo[1,2-c]pyrimidin-1-one (3.00 eq, 77 mg, 0.344 mmol) and DIPEA (5.00 eq, 0.47 mL, 2.66 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 55°C for 16 hours. The reaction was monitored by LCMS. The resulting mixture was quenched with water (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH =15:1) to afford tert-butyl N-[4-[4-[[(4aR,6S,7R)-2-ethyl-7-methyl-1-oxo-3,4,4a,5,6,7-hexahydropyrrolo[1,2-c]pyrimidin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (50 mg, 0.0496 mmol, 43.28% yield) as a light yellow solid. LCMS ESI (+) m/z 887.3 (M+H).

[0592] Step I: Preparation of 2-amino-4-((S)-4-(ethyl((4aR,6S,7R)-2-ethyl-7-methyl-1-oxooctahydropyrrolo[1,2-c]pyrimidin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl N-[4-[4-[[(4aR,6S,7R)-2-ethyl-7-methyl-1-oxo-3,4,4a,5,6,7-hexahydropyrrolo[1,2-c]pyrimidin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-

hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 50 mg, 0.0564 mmol) in DCM (6 mL) was added TFA (345 eq, 1.5 mL, 19.5 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was adjusted pH=8 with Na_2CO_3.aq (10 mL) and extracted with DCM (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC (DCM: MeOH=10:1) to afford 4-[4-[[(4aR,6S,7R)-2-ethyl-7-methyl-1-oxo-3,4,4a,5,6,7-hexahydropyrrolo[1,2-c]pyrimidin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-2-amino-7-fluoro-benzothiophene-3-carbonitrile (22 mg, 0.0255 mmol, 45.2% yield) as a yellowish solid. LCMS ESI (+) m/z 787.2 (M+H). ^{1}HNMR (400 MHz, CD_3OD): 8.22 (s, 1H), 7.18-7.26 (m, 1H), 6.98-7.05 (m, 1H), 5.41 (s, 0.5 H), 5.27 (s, 0.5H), 4.38-4.58 (m, 2H), 4.21-4.32(m, 2H), 3.74-4.02 (m, 3H), 3.54-3.65 (m, 1H), 3.33-3.50 (m, 3H), 3.14-3.29 (m, 3H), 3.03-3.13 (m, 1H), 1.87-2.41 (m, 9H), 1.65-1.80 (m, 1H), 1.34-1.52 (m, 6 H), 1.07-1.15 (m, 3H).

[0593] Synthetic Example 8: Preparation of methyl (3S)-3-((7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate **(Compound 137)**



[0594] Step A: Preparation of 7-bromo-8-fluoro-6-(trifluoromethyl)quinazolin-4-ol: To a solution of 2-amino-4-bromo-3-fluoro-5-(trifluoromethyl)benzoic acid (1.00 eq, 9.00 g, 29.8 mmol) in 2-ethoxyl ethanol (90 mL) was added Formamidine acetate (4.00 eq, 12.41 g, 119 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred 120°C for 16 hours under nitrogen atmosphere. The reaction was

monitored by LCMS. The resulting mixture was diluted with water and extracted with ethyl acetate (100 mL x 4). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with MeOH in DCM from 0% to 2% to afford 7-bromo-8-fluoro-6-(trifluoromethyl)quinazolin-4-ol (5.65 g, 7.89 mmol, 26.49% yield) as a yellow solid. LCMS ESI (+) m/z 312.8 (M+H).

[0595] Step B: Preparation of 7-bromo-4-chloro-8-fluoro-6-(trifluoromethyl)quinazoline: To a solution of 7-bromo-8-fluoro-6-(trifluoromethyl)quinazolin-4-ol (1.00 eq, 5.65 g, 18.16 mmol) in $POCl_3$ (10.0 eq, 27 g, 182 mmol) was added DIPEA (4.00 eq, 9.4 g, 72.7 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at 100°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum, then diluted with ice water and extracted with methyl ether (50 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuo to afford 7-bromo-4-chloro-8-fluoro-6-(trifluoromethyl)quinazoline (5.29 g,13.1 mmol, 75.96% yield) as a brown solid, which was used in the next step directly without further purification. LCMS ESI (+) m/z 330.8 (M+H).

[0596] Step C: Preparation of 7-bromo-8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazoline: To a solution of 7-bromo-4-chloro-8-fluoro-6-(trifluoromethyl)quinazoline (1.00 eq, 5.04 g, 15.3 mmol) in THF (60 mL) was added Sodium thiomethoxide (1.05 eq, 5.63 g, 16.1 mmol) 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with NH_4Cl at 0°C, extracted with ethyl acetate (10 mL x 4). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum The residue was purified by silica gel column chromatography eluting with EA in petroleum from 0% to 3% to afford 7-bromo-8-fluoro-4-methylsulfanyl-6-(trifluoromethyl)quinazoline (3.93 g, 10.6 mmol, 69.03% yield) as a yellow solid. LCMS ESI (+) m/z 340.8 (M+H).

[0597] Step D: Preparation of tert-butyl (3-cyano-7-fluoro-4-(8-fluoro-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate: To a solution of 7-bromo-8-fluoro-4-methylsulfanyl-6-(trifluoromethyl)quinazoline (1.00 eq, 1.00 g, 2.93 mmol) in 1,4-Dioxane (40 mL) was added tert-butyl N-[3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzothiophen-2-yl]carbamate (1.50 eq, 1.78 g, 4.40 mmol), $Pd(DPEPhos)Cl_2$ (0.400 eq, 0.84 g, 1.17 mmol), Cs_2CO_3 (3.00 eq, 2.87 g, 8.79 mmol) and molecular sieves (1.00 g) at rt under nitrogen atmosphere. The resulting mixture was stirred 90°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with water, extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was

purified by silica gel column chromatography eluting with EA in petroleum from 0% to 20% to afford tert-butyl N-[3-cyano-7-fluoro-4-[8-fluoro-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzothiophen-2-yl]carbamate (514 mg, 0.838 mmol, 28.58% yield) as a yellow solid. LCMS ESI (+) m/z 552.8 (M+H).

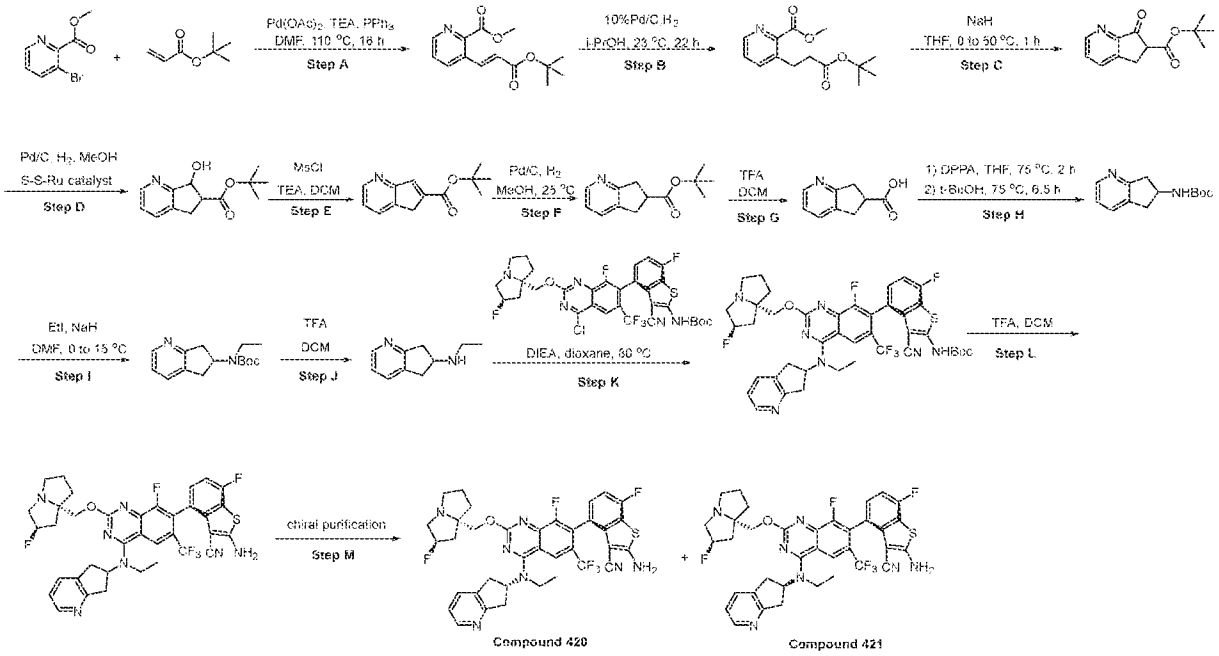
[0598] Step E: Preparation of tert-butyl (4-(4-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl N-[3-cyano-7-fluoro-4-[8-fluoro-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzothiophen-2-yl]carbamate (1.00 eq, 50 mg, 0.0905 mmol) in DCM (2 mL) was added SO_2Cl_2 (7.00 eq, 85 mg, 0.633 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred 0°C for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mmixture was quenched with saturated sodium bicarbonate aqueous solution, extracted with DCM (10 mL *3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum to afford tert-butyl N-[4-[4-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (52 mg, 0.0795 mmol, 87.83% yield) as a yellow solid, which was used in the next step directly without further purification. LCMS ESI (+) m/z 540.8 (M+H).

[0599] Step F: Preparation of methyl (3S)-3-((7-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate: To a solution of tert-butyl N-[4-[4-chloro-8-fluoro-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 52 mg, 0.0954 mmol) in 1,4-Dioxane (2 mL) was added DIPEA (5.00 eq, 0.085 mL, 0.477 mmol) and (methyl (3S)-3-(ethylamino)pyrrolidine-1-carboxylate (1.50 eq, 25 mg, 0.143 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=20/1) to afford methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (46 mg, 0.0659 mmol, 69.11% yield) as a yellow solid. LCMS ESI (+) m/z 677.1 (M+H).

[0600] Step G: Preparation of methyl (3S)-3-((7-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate: To a solution of methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (1.00 eq, 46 mg, 0.0677 mmol) in

DCM (2 mL) was added TFA (133 eq, 0.60 mL, 7.79 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum and the residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by Prep-TLC (DCM: MeOH=15:1) to afford methyl (3S)-3-[[7-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (16 mg, 0.0283 mmol, 41.83% yield) as an off-white solid. LCMS ESI (+) m/z 577.0 (M+H). ^{1}HNMR (400 MHz, CD_3OD) δ 8.74 (s, 1H), 8.33 (s, 1H), 7.28-7.25 (m, 1H), 7.07-7.02 (m, 1H), 5.13-5.05 (m, 1H), 3.98-3.83 (m, 3H,) 3.81-3.70 (m, 4H), 3.60-3.54 (m, 1H), 3.50-3.43 (m,1H), 2.50-2.34 (m, 2H), 1.47-1.42 (m, 3H).

[0601] Synthetic Example 9: 2-amino-4-[4-[[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 420**) and 2-amino-4-[4-[[(6R)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 421**) .



[0602] **Step A:** Preparation of 3-[(E)-3-tert-butoxy-3-oxo-prop-1-enyl]pyridine-2-carboxylate: A solution of methyl 3-bromopyridine-2-carboxylate (1.00 eq, 10.00 g, 46.3 mmol) in DMF (15mL) was added tert-butyl prop-2-enoate (1.20 eq, 7.12 g, 55.5 mmol), TEA (2.00 eq, 13 mL, 92.6 mmol), $Pd(OAc)_2$ (0.100 eq, 11.04 g, 4.63 mmol), triphenylphosphin (0.200 eq, 243 mg, 0.926 mmol) under Ar, and the mixture was stirred for 16 hrs at 110 °C. The reaction was determined complete by TLC. The mixture was extracted with EtOAc (200 mL x 3), and the combined organics were concentrated to dryness under vacuum. The mixture was purified on silica gel chromatography, eluting with 25% EtOAc in petroleum ether methyl to give 3-[(E)-3-tert-butoxy-3-oxo-prop-1-enyl]pyridine-2-carboxylate (2.8 g, 10.6 mmol, 22.9 % yield) as a yellow oil. LCMS: (ES+): m/z 264.2[M]$^+$.

[0603] **Step B:** Preparation of methyl 3-(3-tert-butoxy-3-oxo-propyl)pyridine-2-carboxylate: Methyl 3-[(E)-3-tert-butoxy-3-oxo-prop-1-enyl]pyridine-2-carboxylate (1.00 eq, 2.60 g, 8.89 mmol) was dissolved in methanol (120mL) and Pd/C (0.550 eq, 520 mg, 4.89 mmol) was added. The mixture was degassed with H_2 and repeated three times. The mixture was stirred for 1h at 25 °C. The reaction was monitored by LC-MS and TLC (DCM:MeOH=20:1, Rf=0.3). The reaction mixture was filtered on Celite, and the filtrate was concentrated under vacuum to give methyl 3-(3-tert-butoxy-3-oxo-propyl)pyridine-2-carboxylate (2.35 g,8.86 mmol, 99.66 % yield) as a yellow oil. LCMS: (ES+): m/z 266.1[M]$^+$.

[0604] **Step C:** Preparation of tert-butyl 7-oxo-5,6-dihydrocyclopenta[b]pyridine-6-carboxylate: Methyl 3-(3-tert-butoxy-3-oxo-propyl)pyridine-2-carboxylate (1.00 eq, 2.00 g, 7.54 mmol) was dissolved in THF (3mL) and to this was added NaH (2.50 eq, 754 mg, 18.8 mmol) at 0 °C. The mixture was stirred for 2h at 50 °C. The reaction was determined complete by TLC (DCM:MeOH=5:1, Rf=0.5). Water was added and the solution was acidified with hydrochloric acid (1M) to pH 1. The mixture was extracted with DCM (50 mL x 3) and the combined organics were concentrated to dry under vacuum, to give crude product tert-butyl 7-oxo-5,6-dihydrocyclopenta[b]pyridine-6-carboxylate (1.41 g,6.04 mmol, 80.18 % yield) as yellow solid. LCMS: (ES+): m/z 234.1[M]$^+$.

[0605] **Step D:** Preparation of tert-butyl 7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate: Tert-butyl 7-oxo-5,6-dihydrocyclopenta[b]pyridine-6-carboxylate (1.00 eq, 1.40 g, 5.40 mmol) was dissolved in methanol (120mL) and Pd/C (0.731 eq, 420 mg, 3.95 mmol) was added. The mixture was degassed with H_2 and repeated three times. The mixture was stirred for 4 h at 25 °C. The mixture was filtered on Celite, and the filtrate was concentrated to dryness under vacuum. The crude was purified by prep-TLC(DCM:MeOH=20:1, Rf=0.5), to give product tert-butyl 7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate (570 mg, 2.42 mmol, 44.85 % yield) as a yellow solid. LCMS: (ES+): m/z 236.2[M]$^+$.

[0606] Step E: Preparation of give tert-butyl 5H-cyclopenta[b]pyridine-6-carboxylate: A solution of tert-butyl 7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate (1.00 eq, 540 mg, 2.30 mmol) in DCM (10 mL) was added TEA (3.00 eq, 0.96 mL, 6.89 mmol), and to this was added methanesulfonyl chloride (1.20 eq, 0.21 mL, 2.75 mmol) at 0 °C. The mixture was stirred for 1h at 0 °C. The reaction was determined complete by TLC. The mixture was extracted with DCM (20 mL x 3) and the combined organics were concentrated to dryness under vacuum. The mixture was purified by Prep-TLC (DCM/MeOH=20/1, Rf=0.4) to give tert-butyl 5H-cyclopenta[b]pyridine-6-carboxylate (400 mg,1.84 mmol, 80.21 % yield) as a yellow solid. LCMS: (ES+): m/z 218.2[M]$^+$.

[0607] Step F: Preparation of tert-butyl 6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate: Tert-butyl 5H-cyclopenta[b]pyridine-6-carboxylate (1.00 eq, 400 mg, 1.66 mmol) was dissolved in methanol (40 mL) and Pd/C (0.731 eq, 129 mg, 1.21 mmol) was added. The mixture was degassed with H_2 and repeated three times. The mixture was stirred for 4 h at 25 °C. The mixture was then filtered on Celite, and the filtrate was concentrated to dryness under vacuum. The crude was purified by prep-TLC (DCM:MeOH=20:1, Rf=0.5), to give product tert-butyl 6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate (305 mg,1.39 mmol, 83.95 % yield) as a yellow oil. LCMS: (ES+): m/z 220.3[M]$^+$.

[0608] Step G: Preparation of 6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid: To a solution of tert-butyl 6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate (1.00 eq, 270 mg, 1.23 mmol) in DCM (5mL) was added TFA (15.8 eq, 1.5 mL, 19.5 mmol) and the mixture was stirred at 30 °C for 2 h. LC-MS showed it was completed. The reaction mixture was concentrated to give crude 6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (400 mg,2.45 mmol, 199.08 % yield) as a yellow oil. LCMS: (ES+): m/z 164.1[M]$^+$.

[0609] Step H: Preparation of tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate: A solution of 6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (1.00 eq, 380 mg, 2.33 mmol), N,N-Diisopropylethylamine (3.00 eq, 1.2 mL, 6.99 mmol) and DPPA (1.20 eq, 769 mg, 2.79 mmol) in tert-butanol (5mL) was heated at 90 °C for 8 h. The reaction was determined complete by TLC. The organics were removed under vacuum and the residue was purified by Prep-TLC (DCM/MeOH = 20/1, Rf = 0.5) to give tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (135 mg,0.576 mmol, 24.74 % yield) as a light yellow solid. LCMS: (ES+): m/z 235.2[M]$^+$.

[0610] Step I: Preparation of tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-N-ethyl-carbamate: To a solution of tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (1.00 eq, 0.062 mL, 0.512 mmol) in DMF (5mL) was added sodium (4.00 eq, 49 mg, 2.05 mmol). Then iodoethane

(1.50 eq, 0.062 mL, 0.768 mmol) was added and stirred at 20 °C for 2h. TLC showed it was completed. Water was added to quench the reaction, and the product was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by Pre-TLC (5% CH_3OH in DCM) to afford tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-N-ethyl-carbamate (108 mg,0.412 mmol, 80.38 % yield) as a yellow oil. LCMS: (ES+): m/z 263.2[M]$^+$.

[0611] Step J: Preparation of tert-butyl N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine: Tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-N-ethyl-carbamate (1.00 eq, 108 mg, 0.412 mmol) was dissolved in DCM (3mL) and TFA (31.5 eq, 1.0 mL, 13.0 mmol) was added at rt. The mixture was stirred for 2h at rt. The reaction was determined complete by TLC (DCM:MeOH=10:1, Rf=0.2). The reaction was concentrated to dryness in vacuo to afford crude tert-butyl N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine (70 mg,0.431 mmol, 104.81 % yield) as a yellow solid. LCMS: (ES+): m/z 163.1[M]$^+$.

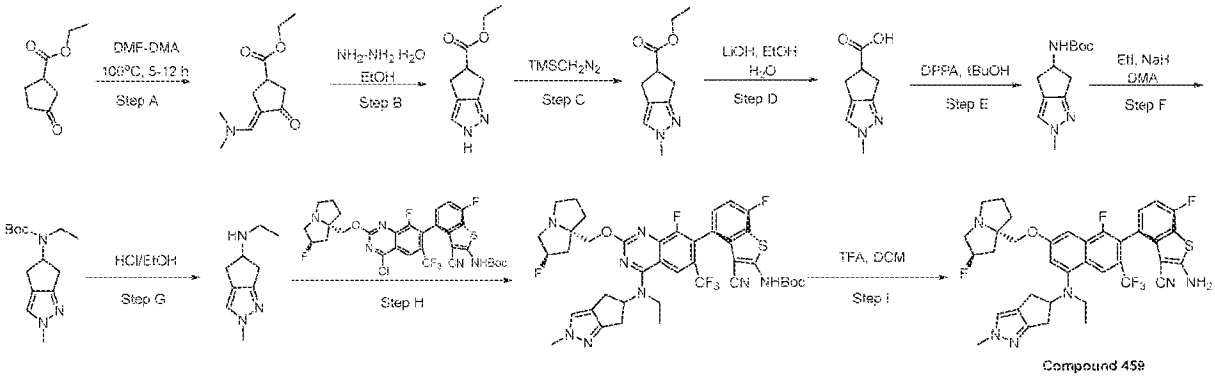
[0612] Step K: Preparation of tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate: A mixture of N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine (2.00 eq, 70 mg, 0.432 mmol) tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 150 mg, 0.216 mmol) and DIEA (5.00 eq, 0.18 mL, 1.08 mmol) in 1,4-Dioxane (2 mL) was stirred at 80 °C for 3h under Ar. The reaction was monitored by LC-MS. Then the mixture was partitioned between EA/water. The organic phase was dried over Na_2SO_4, filtered, concentrated and purified by prep-TLC(8%MeOH/DCM, Rf=0.5) to give tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoro methyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (80 mg, 0.097 mmol, 45 % yield) as light yellow solid. LCMS: (ES+): m/z 824.2[M]$^+$.

[0613] Step L: Preparation of 2-amino-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene -3-carbonitrile: To a solution of tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 80 mg, 0.097 mmol) in DCM (3mL) was added TFA (306 eq, 1.0 mL, 13.0 mmol). The mixture was stirred for 2h at rt. The reaction was determined complete by LCMS. The mixture was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to

afford 2-amino-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene -3-carbonitrile (50 mg, 0.069 mmol, 71.1 % yield) as a yellow solid. LCMS m/z[M+1]$^+$: 724.1. ^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, *J* = 5.7 Hz, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.28 (s, 1H), 7.87 – 7.81 (m, 1H), 7.23 (dd, *J* = 8.3, 5.0 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.46 (d, *J* = 51.9 Hz, 1H), 5.15 (t, *J* = 7.5 Hz, 1H), 4.43 (t, *J* = 11.9 Hz, 1H), 4.29 (dd, *J* = 12.6, 7.0 Hz, 1H), 4.04 – 3.97 (m, 2H), 3.87 – 3.63 (m, 7H), 3.41 – 3.34 (m, 1H), 2.50 – 2.34 (m, 2H), 2.27 – 2.12 (m, 3H), 1.94 – 1.84 (m, 1H), 1.63 (t, *J* = 7.0 Hz, 3H).

[0614] Step M: Preparation of 2-amino-4-[4-[[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 420**) and 2-amino-4-[4-[[(6R)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 421**): 2-amino-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (1.00 eq, 50 mg, 0.0691 mmol) was separated by chiral-SFC to give 2-amino-4-[4-[[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 420,** 22 mg, 0.0297 mmol, 43.03 % yield), LCMS m/z[M+1]$^+$: 724.1, 1H NMR (400 MHz, CD_3OD) δ 8.35 (d, J = 4.6 Hz, 1H), 8.23 (s, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.30 – 7.19 (m, 2H), 7.04 – 6.98 (m, 1H), 5.21 (d, J = 55.2 Hz, 1H), 5.10 – 5.04 (m, 1H), 3.95 – 3.88 (m, 2H), 3.86 – 3.73 (m, 3H), 3.70 – 3.64 (m, 1H), 3.52 – 3.40 (m, 3H), 3.10 (dd, J = 11.8, 3.9 Hz, 2H), 2.95 – 2.88 (m, 1H), 2.10 – 1.98 (m, 2H), 1.91 – 1.79 (m, 2H), 1.75 – 1.66 (m, 2H), 1.55 (t, J = 7.0 Hz, 3H), and 2-amino-4-[4-[[(6R)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 421,** 9.7 mg,0.0134 mmol, 19.36 % yield), LCMS m/z[M+1]$^+$ 724.1, 1H NMR (400 MHz, CD_3OD) δ 8.35 (d, J = 4.9 Hz, 1H), 8.24 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.29 – 7.19 (m, 2H), 7.04 – 6.98 (m, 1H), 5.19 (d, J = 52.6 Hz, 2H), 3.94 – 3.60 (m, 7H), 3.51 – 3.44 (m, 2H), 3.16 – 3.10 (m, 2H), 2.97 – 2.88 (m, 1H), 2.12 – 2.02 (m, 2H), 1.92 – 1.74 (m, 4H), 1.54 (t, J = 7.0 Hz, 3H).

[0615] Synthetic Example 10: 2-amino-4-[4-[ethyl-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 459**)



[0616] Step A: Preparation of ethyl (3Z)-3-(dimethylaminomethylene)-4-oxo-cyclopentanecarboxylate: A mixture of ethyl 3-oxocyclopentanecarboxylate (1.00 eq, 9000 mg, 57.6 mmol) and N,N-dimethylformamide dimethyl acetal (100 eq, 772 mL, 5763 mmol) was heated to 100 °C and stirred for 5h. TLC showed it was completed. The solvent was removed under vacuum. The residue was taken up with EA, washed with brine, and concentrated. The residue was purified by prep-TLC with DCM/CH_3OH=20/1 to afford desired product of ethyl (3Z)-3-(dimethylaminomethylene)-4-oxo-cyclopentanecarboxylate (4.70 g, 22.2 mmol, 38.61 % yield) as a light brown semi-solid. LCMS m/z [M+1]212.1.

[0617] Step B: Preparation of ethyl 2,4,5,6-tetrahydrocyclopenta[c]pyrazole-5-carboxylate: To a solution of ethyl (3Z)-3-(dimethylaminomethylene)-4-oxo-cyclopentanecarboxylate (1.00 eq, 4.70 g, 22.2 mmol) in ethanol (60mL) was added hydrazine hydrate (3.00 eq, 2.1 mL, 66.7 mmol) at 25 °C and stirred overnight. TLC showed it was completed. The solvent was removed under vacuum. The residue was purified by flash column chromatography eluting 1-5 %MeOH in DCM. The desired fractions were concentrated to dryness in vacuo to afford desired product of ethyl 2,4,5,6-tetrahydrocyclopenta[c]pyrazole-5-carboxylate (1.70 g, 9.43 mmol, 42.40 % yield) as a light brown semi-solid. LCMS m/z [M+1]181.2.

[0618] Step C: Preparation of ethyl 2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazole-5-carboxylate: To a solution of ethyl 2,4,5,6-tetrahydrocyclopenta[c]pyrazole-5-carboxylate (1.00 eq, 1600 mg, 8.88 mmol) and trifluoromethanesulfonic acid, (0.100 eq, 0.079 mL, 0.888 mmol) in ethyl acetate (5 mL) was added $TMSCH_2N_2$ (1.10 eq, 1116 mg, 9.77 mmol) at rt. Then the reaction was heated to 50 °C and stirred overnight. TLC showed (Rf = 0.4, DCM / CH_3OH = 20 / 1) small scale SM left. After quenching with *aq.* $NaHCO_3$, the mixture was taken up with EA, washed with brine, and concentrated. The residue was purified by prep-TLC with DCM/CH_3OH=20/1 to afford desired product of ethyl 2-methyl-5,6-dihydro-4H-

cyclopenta[c]pyrazole-5-carboxylate (790 mg,4.07 mmol, 45.81 % yield) as a light brown oil. LCMS m/z [M+1]195.2.

[0619] Step D: Preparation of 2-Methyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazole-5-carboxylic acid: A mixture of ethyl 2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazole-5-carboxylate (1.00 eq, 790 mg, 4.07 mmol), hydroxylithium (3.00 eq, 292 mg, 12.2 mmol) in methanol (2mL) and water (1mL) was stirred at 20 °C for 3h. LCMS showed it was completed. After quenching with $KHSO_4$, the solvent was removed under vacuum. The residue was dissolved into DCM, and the mixture was filtered through a Celite pad, and the filtrate was concentrated to give the crude product, which was used into next reaction without further purification. LCMS m/z [M+1]167.2.

[0620] Step E: Preparation of tert-butyl N-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)carbamate: A mixture of 2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazole-5-carboxylic acid (1.00 eq, 550 mg, 3.31 mmol) , [azido(phenoxy)phosphoryl]oxybenzene (2.00 eq, 1822 mg, 6.62 mmol) and N,N-Diisopropylethylamine (2.00 eq, 1.2 mL, 6.62 mmol) in tert-butanol (5mL) was stirred at rt for 30 min. Then the mixture was heated to 80 °C overnight. LCMS showed it was completed. After the solvent was removed under vacuum, the residue was purified by prep-TLC with DCM/MeOH=30/1 to afford desired product of tert-butyl N-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)carbamate (310 mg, 1.31 mmol, 39.47 % yield) as a light brown semi-sold. LCMS m/z [M+1]238.2.

[0621] Step F: Preparation of tert-butyl N-ethyl-N-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)carbamate: To a solution of tert-butyl N-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)carbamate (1.00 eq, 260 mg, 1.10 mmol) in DMF (3 mL) was added sodium (3.00 eq, 79 mg, 3.29 mmol) at 0 °C. After stirring for 30min, then iodoethane (2.00 eq, 0.18 mL, 2.19 mmol) in DMF (1 mL) was added into the mixture and stirred for 2h. Then it was warmed to rt and stirred overnight. LCMS showed it was completed. After quenching with $AqNH_4Cl$, the mixture was taken up with EA, washed with brine, and concentrated. The residue was purified by Prep-TLC with DCM/CH_3OH=20/1 to afford desired product of tert-butyl N-ethyl-N-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)carbamate (120 mg, 0.452 mmol, 41.27 % yield). LCMS m/z [M+1] 266.2.

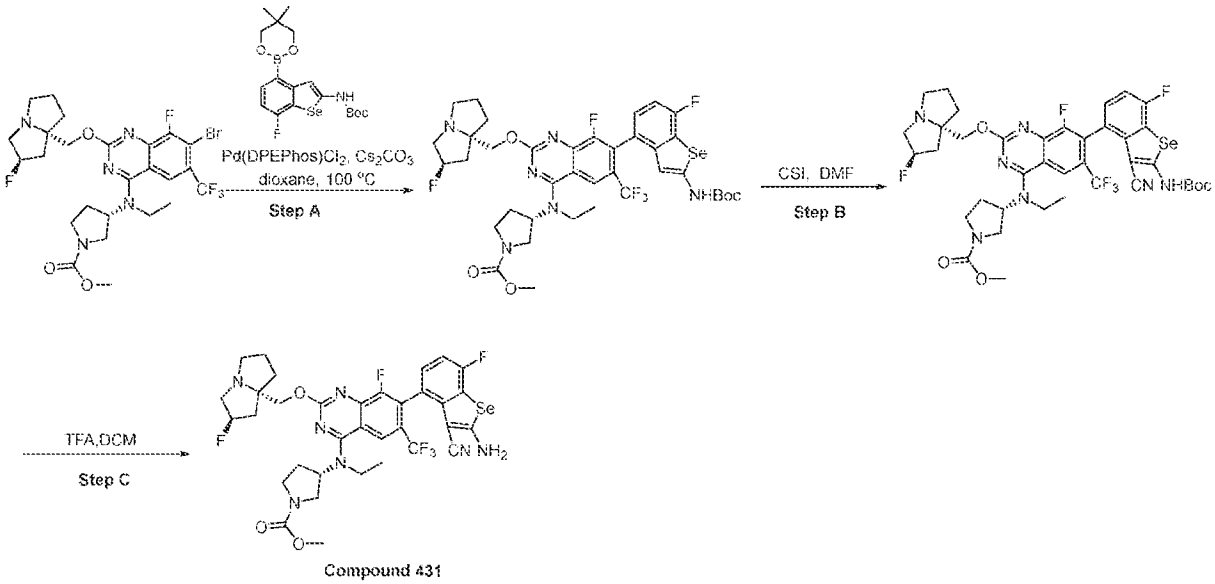
[0622] Step G: Preparation of N-ethyl-2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-amine: To a solution of tert-butyl N-ethyl-N-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)carbamate (1.00 eq, 170 mg, 0.641 mmol) in ethanol (5mL) was added HCl/dioxane (4M, 3 mL) and stirred for 2h. TLC showed it was completed. The solvent was removed under vacuum. The pH was adjusted to ~8 with *aq.* $NaHCO_3$, and diluted with DCM, dried with Na_2SO_4, filtrated, and concentrated to afford desired product of N-ethyl-

2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-amine (75 mg, 0.454 mmol, 70.85 % yield). LCMS m/z [M+1] 166.3.

[0623] Step H: Preparation of tert-butyl N-[3-cyano-4-[4-[ethyl-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate: A mixture of N,N-Diisopropylethylamine (5.00 eq, 0.40 mL, 2.27 mmol), N-ethyl-2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-amine (1.00 eq, 75 mg, 0.454 mmol) and tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-3-methyl-benzothiophen-2-yl]carbamate (0.200 eq, 62 mg, 0.0908 mmol) in 1,4-Dioxane (3mL) was stirred at 80 °C overnight. LCMS showed it was completed. After quenching with *aq.* NH_4Cl, the mixture was taken up with EA, washed with brine, and concentrated. The residue was purified by prep-TLC with DCM/CH_3OH=20/1 to afford desired product of tert-butyl N-[3-cyano-4-[4-[ethyl-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (45 mg, 0.0544 mmol, 11.99 % yield). LCMS m/z [M+1] 828.2.

[0624] Step I: Preparation of 2-amino-4-[4-[ethyl-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile: A mixture of trifluoroacetic acid (100 eq, 0.10 mL, 1.33 mmol) and tert-butyl N-[3-cyano-4-[4-[ethyl-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 22 mg, 0.0133 mmol) in 20 °C was stirred at 20 °C for 3h. TLC showed it was completed. Then it was taken up with DCM, washed with aq$NaHCO_3$, brine, and then concentrated. The residue was purified by prep-TLC with DCM/CH3OH=10/1 and prep-HPLC to afford desired product of 2-amino-4-[4-[ethyl-(2-methyl-5,6-dihydro-4H-cyclopenta[c]pyrazol-5-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (4.6 mg, 0.00626 mmol, 47.06 % yield) as a white solid. LCMS m/z [M+1] 727.1. ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 7.68 – 7.28 (m, 1H), 7.22 (dd, *J* = 8.5, 5.0 Hz, 1H), 7.02 (t, *J* = 8.9 Hz, 1H), 5.35 (d, *J* = 53.3 Hz, 1H), 5.22 – 4.95 (m, 1H), 4.46 – 4.36 (m, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 3.84 – 3.76 (m, 3H), 3.70 (q, *J* = 7.1 Hz, 2H), 3.46 (d, *J* = 14.0 Hz, 1H), 3.11 (d, *J* = 10.0 Hz, 2H), 3.05 (m, 1H), 2.95 – 2.93 (m, 2H), 2.81 – 2.66 (m, 1H), 2.66 – 2.38 (m, 1H), 2.39 – 2.23 (m, 4H), 2.19 (d, *J* = 9.3 Hz, 1H), 2.05 (s, 2H), 1.93 (s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H).

[0625] Synthetic Example 11: Methyl (3S)-3-[[7-(2-amino-3-cyano-7-fluoro-benzoselenophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (**Compound 431**) .



[0626] Step A: Preparation of methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-7-fluoro-benzoselenophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)q uinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate: To a mixture of methyl (3S)-3-[[7-bromo-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (1.00 eq, 180 mg, 0.289 mmol), Cs_2CO_3 (3.0 eq, 283 mg, 0.868 mmol) and Pd(DPEPhos)cl_2 (0.400 eq, 83 mg, 0.116 mmol) in 1,4-Dioxane (2 mL) was added tert-butyl-N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzoselenophen-2-yl]carbamate (3.00 eq, 370 mg, 0.868 mmol). Then it was heated to 100℃ for 4h under the protection of Ar. TLC showed it was completed. After cooling to rt. The reaction filtered and the filtered cake washed with EtOAc, the solution was taken up with EtOAc, washed with brine, concentrated. The mixture was purified by Perp - TLC (Petroleum ether : EtOAc = 0 : 1 Rf = 0.4) to afford desired product of methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-7-fluoro-benzoselenophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (140 mg,0.164 mmol, 56.57 % yield) as an brown oil. LCMS: (ES+): m/z 857.3[M]+.

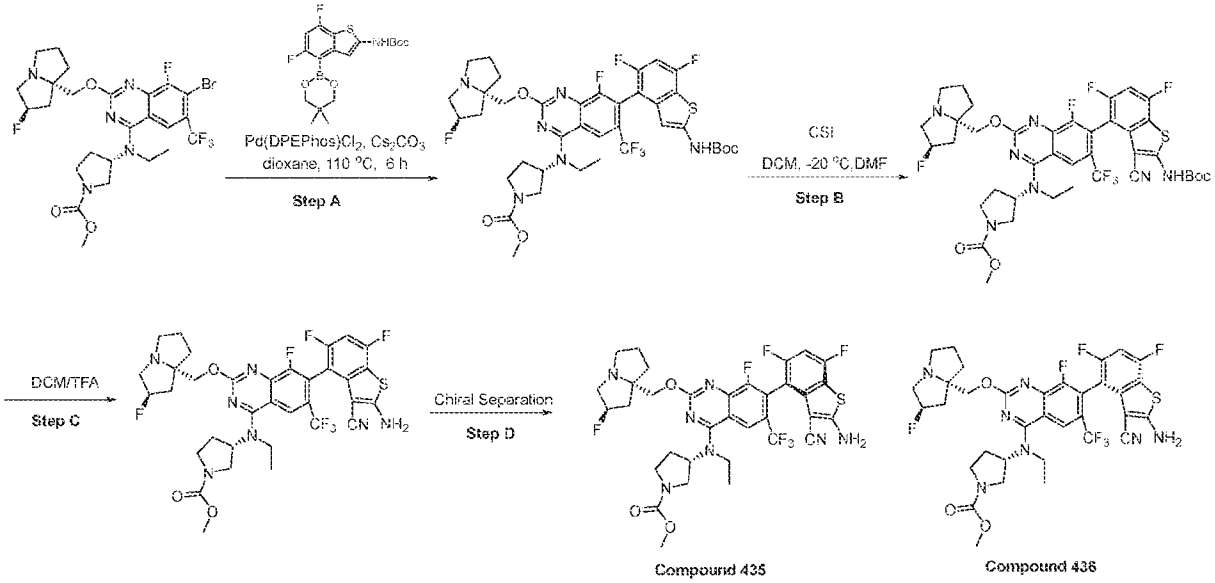
[0627] Step B: Preparation of methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzoselenophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate: A solution of chlorosulfonyl

isocyanate (5.00 eq, 0.075 mL, 0.865 mmol) in DCM (2 mL)in the flask bathed in the ice to -40°C, methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-7-fluoro-benzoselenophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (1.00 eq, 130 mg, 0.152 mmol) in DCM (2 mL) was added to the obtained solution drop wise. The reaction was monitored by LC-MS after 4hrs at -40°C, then the DMF (2 mL) was added to the obtained reaction and stirred at room temperature for 2hrs with the protection of N_2. The reaction was completed monitored by TLC (DCM : MeOH = 10 : 1, Rf = 0.4). The reaction was quenched by addition of $NaHCO_3$ solution, the residue was taken up in EtOAc (150 mL) and the organics washed with 2 x 60 mL water then 1 x 60 mL saturated brine solution. The organics were then separated and dried (Na_2SO_4) before concentration to dryness. The crude was then purified by Prep-TLC (DCM / MeOH =10 : 1, Rf = 0.4) to afford methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzoselenophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (100 mg, 0.148 mmol, 81.30% yield) was a white solid. LCMS: (ES+): m/z 882.4[M]+.

[0628] Step C: Preparation of methyl (3S)-3-[[7-(2-amino-3-cyano-7-fluoro-benzoselenophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate: To a mixture of methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzoselenophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (1.00 eq, 130 mg, 0.148 mmol) in DCM (4 mL) was added TFA (135 eq, 1.5 mL, 19.9 mmol). The mixture was stirred at 15°C for 4h. TLC showed it was completed. The mixture was concentrated to get a crude, the crude was purified by Prep-HPLC to afford methyl (3S)-3-[[7-(2-amino-3-cyano-7-fluoro-benzoselenophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (8.7 mg,0.0109 mmol, 7.37 % yield) as a white solid. LCMS: (ES+): m/z 782.1[M]+. ^{1}H NMR (400 MHz, CD_3OD): δ 8.27 (s, 1H), 7.23 - 7.19 (m, 1H), 6.98 (t, J = 8.4 Hz, 1H), 5.62 (d, J = 53.2 Hz, 1H), 5.08 - 5.00 (m, 1H), 4.69 - 4.58 (m, 2H), 4.06 - 3.79 (m, 7H), 3.64 - 3.53 (m, 1H), 3.49 - 3.42 (m, 2H), 2.71 - 2.33 (m, 8H), 2.20 - 2.14 (m, 1H), 1.50 - 1.46 (m, 3H), 1.33 - 1.29 (m, 2H).

[0629] Synthetic Example 12: methyl (3S)-3-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (**Compound 435**) and methyl (3S)-3-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-

hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (**Compound 436**).



[0630] Step A: Preparation of methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-5,7-difluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate: To a solution of methyl (3S)-3-[[7-bromo-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy]-6-(trifluoromethyl) quinazolin-4-yl]-ethyl-amino] pyrrolidine-1-carboxylate (1.00 eq, 600 mg, 0.964 mmol) in 1,4-Dioxane (12 mL) in the flask. tert-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,7-difluoro-benzothiophen-2-yl] carbamate (1.20 eq, 460 mg, 1.16 mmol), Dichloro[bis(diphenylphosphinophenyl) ether] palladium (II) (0.200 eq, 138 mg, 0.193 mmol) and Cs_2CO_3 (2.00 eq, 628 mg, 1.93 mmol) were added to the obtained solution, the mixture was heated to 110 °C for another 4hrs with the protection of argon. The reaction was completely monitored by TLC (DCM:MeOH=20:1, Rf=0.4). The reaction was filtered by celite, and the filtrate was concentrated to dryness. The residue was purified by flash column chromatography eluting 5% MeOH in DCM to give methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-5,7-difluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (205 mg,0.248 mmol, 25.72 % yield) as a yellow solid. LCMS: (ES+): m/z 827.2 $[M]^+$.

[0631] Step B: Preparation of methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-5,7-difluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate: To a solution of methyl (3S)-3-

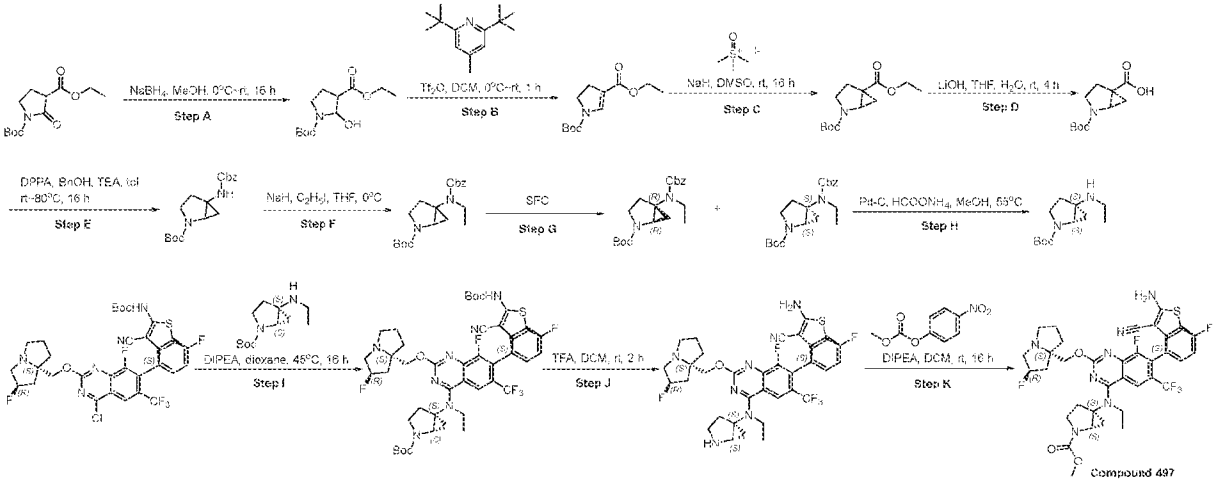
[[7-[2-(tert-butoxycarbonylamino)-5,7-difluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (1.00 eq, 316 mg, 0.382 mmol) in DCM (6mL) in the flask bathed in the ice to 20 °C, chlorosulfonyl isocyanate (5.00 eq, 0.17 mL, 1.91 mmol) in DCM (2 mL) was added to the obtained solution drop wise, the reaction was monitored by LC-MS after 4hrs at -15 °C, then the DMF (4mL) was added to the obtained reaction and stirred at room temperature for 2hrs with the protection of N_2.The reaction was completed monitored by TLC (DCM:MeOH=20:1, Rf=0.3). The reaction was quenched by the addition of $NaHCO_3$ solution, the residue was taken up in EtOAc (30 mL) and the organics washed with 2 x 30 mL water then 2 x 30 mL saturated brine solution. The organics were then separated and dried (Na_2SO_4) before concentration to dryness. The crude was purified by flash column chromatography eluting 5% MeOH in DCM. The desired fractions were concentrated to dryness in vacuo, methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-5,7-difluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (104 mg, 0.122 mmol, 31.95 % yield) was obtained as a yellow oil. LCMS: (ES+): m/z 852.2 $[M]^+$.

[0632] Step C: Preparation of methyl (3S)-3-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy]-6-(trifluoromethyl) quinazolin-4-yl]-ethyl-amino] pyrrolidine-1-carboxylate: To a solution of methyl (3S)-3-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-5,7-difluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (1.00 eq, 60 mg, 0.0704 mmol) in DCM (3mL)) was added TFA (1.0 mL) .). The mixture was stirred for 2 h at 30 °C. The organics were concentrated to dry under vacuum. The residue was purified by Prep-HPLC to give methyl (3S)-3-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy]-6-(trifluoromethyl) quinazolin-4-yl]-ethyl-amino] pyrrolidine-1-carboxylate (29 mg, 0.0352 mmol, 49.95 % yield). LCMS: (ES+): m/z 752.3 $[M]^+$.

[0633] Step D: Preparation of methyl (3S)-3-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (**Compound 435**) and methyl (3S)-3-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (**Compound 436**): Methyl (3S)-3-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-

fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (1.00 eq, 42 mg, 0.0559 mmol) was separated by chiral-SFC to give methyl (3S)-3-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (15 mg, 0.0193 mmol, 34.51 % yield), LC-MS: (ES+): m/z 752.3 $[M]^+$, ^1H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 6.92-7.03 (m, 1H), 5.30 (d, J = 53.9 Hz, 1H), 4.95-5.07 (s, 1H), 4.20-4.33 (m, 2H), 3.68-3.98 (m, 7H), 3.53-3.64 (m, 1H), 3.37-3.49 (m, 1H), 3.10-3.25 (m, 3H), 2.92-3.07 (m, 1H), 2.06-2.53 (m, 5H), 1.81-2.05 (m, 3H), 1.38-1.51 (t, J = 6.9 Hz, 3H), and methyl (3S)-3-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]pyrrolidine-1-carboxylate (12 mg,0.0154 mmol, 27.59 % yield), LC-MS: (ES+): m/z 752.3 $[M]^+$, ^1H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 6.95 (t, J = 9.6 Hz, 1H), 5.29 (d, J = 53.9 Hz, 1H), 4.98-5.06 (m, 1H), 4.19-4.33 (m, 2H), 3.69-3.95 (m, 7H), 3.52-3.64 (m, 1H), 3.38-3.50 (m, 1H), 3.13-3.26 (m, 3H), 2.93-3.06 (m, 1H), 2.08-2.52 (m, 5H), 1.84-2.05 (m, 3H), 1.38-1.48 (m, 3H).

[0634] Synthetic Example 13: methyl (1S,5S)-5-[[7-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]-2-azabicyclo[3.1.0]hexane-2-carboxylate (**Compound 497**).



[0635] Step A: Preparation of 1-tert-butyl 3-ethyl 2-hydroxypyrrolidine-1,3-dicarboxylate: To a solution of 1-tert-butyl 3-ethyl 2-oxopyrrolidine-1,3-dicarboxylate (1.00 eq, 4.00 g, 15.5 mmol) in Methanol (40 mL) was added $NaBH_4$ (1.50 eq, 882 mg, 23.3 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h. The reaction was monitored by LCMS. The reaction was concentrated. The residue was dissolved in EA (100 mL), washed with water and brine, dried over sodium

sulfate, filtered and concentrated to dryness to afford 1-tert-butyl 3-ethyl 2-hydroxypyrrolidine-1,3-dicarboxylate (3.00 g, 4.74 mmol, 75% yield), which was used directly in the next step without further purification. LCMS ESI (+) m/z 282.1 (M+Na).

[0636] **Step B:** Preparation of 1-tert-butyl 4-ethyl 2,3-dihydropyrrole-1,4-dicarboxylate: To a solution of 1-tert-butyl 3-ethyl 2-hydroxypyrrolidine-1,3-dicarboxylate (1.00 eq, 3.00 g, 11.6 mmol) in DCM (30 mL) was added 2,6-di-tert-butyl-4-methylpyridine (2.00 eq, 4.75 g, 23.1 mmol). Then Tf_2O (1.00 eq, 3.26 g, 11.6 mmol) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 1 h under nitrogen atmosphere. The resulting mixture was diluted with water and extracted with EA (4x50 mL). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford 1-tert-butyl 4-ethyl 2,3-dihydropyrrole-1,4-dicarboxylate (400 mg, 0.580 mmol, 14.33% yield) as a colorless oil. LCMS ESI (+) m/z 242.1 (M+H). ^{1}H NMR (400 MHz, CDCl3) δ 7.50 (d, 1H), 4.18-4.21 (m, 2H), 3.83-3.86 (m, 2H), 2.82-2.84 (m, 2H), 1.49 (s, 9H), 1.28 (t, 3H).

[0637] **Step C:** Preparation of 2-tert-butyl 5-ethyl 2-azabicyclo [3.1.0] hexane-2,5-dicarboxylate: To a solution of Trimethylsulfoxonium iodide (2.50 eq, 912 mg, 4.14 mmol) in DMSO (4 mL) was added NaH (2.20 eq, 88 mg, 3.65 mmol) was added dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h under nitrogen atmosphere. Then 1-tert-butyl 4-ethyl 2,3-dihydropyrrole-1,4-dicarboxylate (1.00 eq, 400 mg, 1.66 mmol) was added to above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (4x20 mL). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC to afford 2-tert-butyl 5-ethyl 2-azabicyclo [3.1.0] hexane-2,5-dicarboxylate (250 mg, 0.568 mmol, 57.84% yield) as a colorless oil. LCMS ESI (+) m/z 200.0(M+1-56). 1H NMR (400 MHz, CDCl3) δ 4.11-4.17 (m, 2H), 3.78-3.79 (m, 2H), 2.96-3.03 (m, 1H), 2.53-2.58 (m, 1H), 2.00-2.06 (m, 1H), 1.47 (s, 10H), 1.25 (t, 3H), 1.14-1.18 (m, 1H).

[0638] **Step D:** Preparation of 2-tert-butoxycarbonyl-2-azabicyclo [3.1.0] hexane-5-carboxylic acid:

[0639] To a solution of 2-tert-butyl 5-ethyl 2-azabicyclo [3.1.0] hexane-2,5-dicarboxylate (1.00 eq, 250 mg, 0.979 mmol) in THF (2 mL) and water (1 mL) was added LiOH (2.00 eq, 47 mg, 1.96 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The reaction was monitored by LCMS. The resulting mixture was acidified with 1N HCl aqueous solution, extracted with EA (4x5 mL). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated to afford 2-tert-butoxycarbonyl-2-azabicyclo [3.1.0] hexane-5-carboxylic acid (360 mg, 1.38 mmol,

161.79% yield) as a yellow oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 172.0 (M+1-56).

[0640] Step E: Preparation of tert-butyl 5-(benzyloxycarbonylamino)-2-azabicyclo [3.1.0] hexane-2-carboxylate: To a solution of 2-tert-butoxycarbonyl-2-azabicyclo [3.1.0] hexane-5-carboxylic acid (1.00 eq, 360 mg, 1.58 mmol) in Toluene (4 mL) was added TEA (1.30 eq, 208 mg, 2.06 mmol), BnOH (5.00 eq, 855 mg, 7.92 mmol) and DPPA (1.30 eq, 566 mg, 2.06 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (4x10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC to afford tert-butyl 5-(benzyloxycarbonylamino)-2-azabicyclo [3.1.0] hexane-2-carboxylate (160 mg, 0.371 mmol, 37.12% yield) as a yellow solid. LCMS ESI (+) m/z 277.0 (M+1-56).

[0641] Step F: Preparation of tert-butyl 5-[benzyloxycarbonyl(ethyl)amino]-2-azabicyclo [3.1.0] hexane-2-carboxylate: To a solution of tert-butyl 5-(benzyloxycarbonylamino)-2-azabicyclo [3.1.0] hexane-2-carboxylate (1.00 eq, 150 mg, 0.451 mmol) in THF (2 mL) was added NaH (1.50 eq, 27 mg, 0.677 mmol) 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1 h under nitrogen atmosphere. Then C_2H_5I (2.00 eq, 141 mg, 0.903 mmol) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (4x10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC to afford tert-butyl 5-[benzyloxycarbonyl(ethyl)amino]-2-azabicyclo [3.1.0] hexane-2-carboxylate (110 mg, 0.302 mmol, 67.90% yield) as a colorless oil. LCMS ESI (+) m/z 305.3 (M+1-55), 383.3 (M+Na)

[0642] Step G: Preparation of tert-butyl (1S,5S)-5-(((benzyloxy)carbonyl) (ethyl)amino)-2-azabicyclo [3.1.0] hexane-2-carboxylate:Tert-butyl 5-[benzyloxycarbonyl(ethyl)amino]-2-azabicyclo [3.1.0] hexane-2-carboxylate (1.00 eq, 110 mg, 0.302 mmol) was purified by chiral-SFC to give tert-butyl (1S,5S)-5-(((benzyloxy)carbonyl) (ethyl)amino)-2-azabicyclo [3.1.0] hexane-2-carboxylate (45 mg, 0.125 mmol) as a white solid in the second peak.

[0643] Step H: Preparation of tert-butyl (1S,5S)-5-(ethylamino)-2-azabicyclo [3.1.0] hexane-2-carboxylate: To a solution of tert-butyl (1S,5S)-5-[benzyloxycarbonyl(ethyl)amino]-2-azabicyclo [3.1.0] hexane-2-carboxylate (1.00 eq, 45 mg, 0.125 mmol) in Methanol (2 mL) was added Pd/C (10 mg) and ammonium formate (2.50 eq, 20 mg, 0.317 mmol). The resulting mixture was stirred at 55°C for 1 h. The

reaction was monitored by LCMS. The mixture was filtered and concentrated to dryness to obtain tert-butyl (1S,5S)-5-(ethylamino)-2-azabicyclo [3.1.0] hexane-2-carboxylate (33 mg, 0.131 mmol, 125% yield), which was used in the next step directly without further purification. LCMS ESI (+) m/z 227.1 (M+H).

[0644] Step I: Preparation of tert-butyl (1S,5S)-5-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy]-6-(trifluoromethyl) quinazolin-4-yl]-ethyl-amino]-2-azabicyclo [3.1.0] hexane-2-carboxylate: To a solution of tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 70 mg, 0.100 mmol) in 1,4-Dioxane (2 mL) was added tert-butyl (1S,5S)-5-(ethylamino)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.50 eq, 34 mg, 0.150 mmol) and DIEA (3.00 eq, 0.052 mL, 0.301 mmol). The resulting mixture was stirred at 45°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (4x10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC to afford tert-butyl (1S,5S)-5-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]-2-azabicyclo[3.1.0]hexane-2-carboxylate (18 mg, 0.0124 mmol, 20.22% yield) as a yellow solid. LCMS ESI (+) m/z 888.4 (M+H).

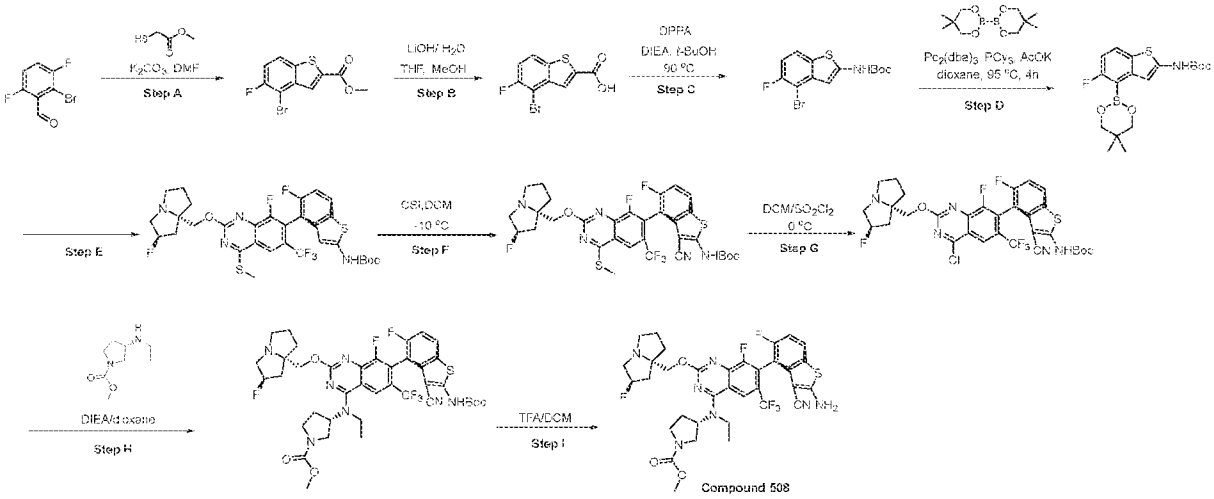
[0645] Step J: Preparation of 2-amino-4-[4-[[(1S,5S)-2-azabicyclo [3.1.0] hexan-5-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy]-6-(trifluoromethyl) quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile: To a solution of tert-butyl (1S,5S)-5-[[7-[2-(tert-butoxycarbonylamino)-3-cyano-7-fluoro-benzothiophen-4-yl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.00 eq, 18 mg, 0.0203 mmol) in DCM (2 mL) was added TFA (0.70 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The reaction was monitored by LCMS. The resulting mixture was concentrated to dryness to obtain 2-amino-4-[4-[[(1S,5S)-2-azabicyclo[3.1.0]hexan-5-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (18 mg, 0.0209 mmol, 129.49% yield) , which was used in the next step directly without further purification. LCMS ESI (+) m/z 688.3 (M+H).

[0646] Step K: Preparation of methyl (1S,5S)-5-[[7-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy]-6-(trifluoromethyl) quinazolin-4-yl]-ethyl-amino]-2-azabicyclo [3.1.0] hexane-2-carboxylate: To a solution of 2-amino-4-[4-

[[(1S,5S)-2-azabicyclo[3.1.0]hexan-5-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (1.00 eq, 18 mg, 0.0262 mmol) in DCM (2 mL) was added DIEA (5.00 eq, 0.023 mL, 0.131 mmol). Then a solution of methyl (4-nitrophenyl) carbonate (1.00 eq, 5.2 mg, 0.0262 mmol) in DCM (0.2 mL) was added to the above mixture 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (3x5 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (DCM/MeOH=15/1) to afford methyl (1S,5S)-5-[[7-(2-amino-3-cyano-7-fluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]-2-azabicyclo[3.1.0]hexane-2-carboxylate (3.5 mg, 0.00429 mmol, 23.17% yield) as a white solid. LCMS ESI (+) m/z 746.2 (M+H).

[0647] 1H NMR (400 MHz, CD3OD) δ 8.37 (s, 1H), 7.20-7.24 (m, 1H), 7.01 (t, 1H), 5.41 (s, 0.5H), 5.28 (s, 0.5H), 4.28-4.37 (m, 2H), 3.95-4.01 (m, 1H), 3.85-3.87 (m, 1H), 3.68 (s, 3H), 3.34-3.36 (m, 1H), 3.06-3.26 (m, 3H), 2.74-2.82 (m, 1H), 2.63-2.68 (m, 1H), 2.25-2.43 (m, 2H), 2.14-2.21 (m, 2H), 1.90-2.08 (m, 4H), 1.56-1.66 (m, 1H), 1.47 (t, 3H), 0.87-0.94 (m, 2H).

[0648] **Synthetic Example 14:** Methyl (S)-3-(((R)-7-(2-amino-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate (**Compound 508**)



[0649] **Step A:** Preparation of methyl 4-bromo-5-fluorobenzo[b]thiophene-2-carboxylate: A mixture of 2-bromo-3,6-difluorobenzaldehyde (1.00 eq, 25 g, 113.12 mmol) in DMF (250 mL) were added K_2CO_3 (2.50 eq, 39.08g, 282.80 mmol), methyl 2-mercaptoacetate (1.10 eq,13.2 g, 124.43 mmol) at 0 °C and stirred at -

20 °C for 2hrs under Ar. LCMS showed the starting material was consumed completely. 100 mL water was added to the reaction. The reaction mixture was filtered, and the filter cake was washed with 200 mL of water, dried in vacuum to give methyl 4-bromo-5-fluorobenzo[b]thiophene-2-carboxylate (9.76 g, 33.75 mmol, 29.84 % yield). 1H NMR (400 MHz, DMSO-d6) δ: 7.17-8.12 (m, 1H), 7.51 – 7.42 (m, 1H), 7.39 – 7.28 (m, 1H), 3.92 (s, 3H).

[0650] Step B: Preparation of 4-bromo-5-fluorobenzo[b]thiophene-2-carboxylic acid: A mixture of methyl 4-bromo-5-fluorobenzo[b]thiophene-2-carboxylate (1.00 eq, 9.76g, 33.75 mmol) was dissolved in THF/MeOH/water (1/1/1) and were added $LiOH.H_2O$ (3.00 eq, 252 mg, 1.66 mmol). The mixture stirred for 3 hrs at 30 °C. TLC showed the reaction was complete. The mixture was adjusted to pH 4 with solid $Na_2S_2O_5$. The reaction mixture was filtered, and the filter cake was dried in vacuum to give 4-bromo-5-fluorobenzo[b]thiophene-2-carboxylic acid (7.99 g, 29.04 mmol, 86.05 % yield) LCMS m/z[M+1]+ found 273.0.

[0651] Step C: Preparation of tert-butyl (4-bromo-5-fluorobenzo[b]thiophen-2-yl)carbamate: A mixture of 4-bromo-5-fluorobenzo[b]thiophene-2-carboxylic acid (1.00 eq, 7.99 g, 29.04 mmol) in tBuOH (100 mL) was added DPPA (1.20 eq, 1.46 g, 34.85 mmol), DIEA (1.10 eq, 4.12g, 31.94mmol), and was stirred for 8hrs at 95 °C under Ar. TLC show the reaction completely. The reaction was concentrated to give a residue. The residue was washed with 100 mL of 15% aqueous NaOH and was extracted with EtOAc (100 mL x 3). The filtrate was concentrated to dryness to give crude product. The crude product was chromatographed on silica gel to give tert-butyl (4-bromo-5-fluorobenzo[b]thiophen-2-yl)carbamate (5.51 g, 15.97 mmol, 55.0 % yield).

^{1}H NMR (400 MHz, CDCl3) δ7.77 – 7.63 (m, 1H), 7.01 (J = 8.0 Hz, 1H), 6.82 (s, 1H),1.55 (s, 9H).

[0652] Step D: Preparation of tert-butyl (4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate: To the solution of tert-butyl (4-bromo-5-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 5.51 g,15.97 mmol) in 1,4-dioxane (6mL) were added Pd2(dba)3 (0.02 eq, 177.51 mg,0.194mmol), PCy3 (0.04 eq, 179.14 mg,0.64 mmol), AcOK (3 eq, 4.69 g, 47.91 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (1.20 eq, 2.58 g, 11.4 mmol). The mixture was stirred for 4 hr at 95 °C. LCMS showed the starting material was consumed completely. The reaction was filtered and concentrated. The crude product was chromatographed on silica gel to give tert-butyl (4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluorobenzo[b]thiophen-2-yl)carbamate (3.79g,10.00 mmol, 62.6 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.77 – 7.60 (m, 1H), 7.73 – 7.21 (m, 1H), 7.05 – 6.87 (m, 1H), 3.84 (s, 4H), 1.53 (s, 9H), 1.07 (s, 6H).

[0653] Step E: Preparation of tert-butyl N-[5-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzothiophen-2-yl]carbamate: To a stirred solution of 7-bromo-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazoline (1.00 eq, 200 mg, 0.401 mmol) in toluene (6 mL) were added (R,R)-Baryphos (0.120 eq, 25 mg, 0.0482 mmol), Cs_2CO_3 (3.00 eq, 392 mg, 1.20 mmol), $Pd_2(dba)_3$ (0.0500 eq, 18 mg, 0.0201 mmol) and tert-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluoro-benzothiophen-2-yl]carbamate (2.00 eq, 304 mg, 0.803 mmol). The mixture was kept stirring overnight at 30 °C under argon. TLC (PE:THF = 2:1, Rf = 0.3) showed the completion of the reaction. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified by prep-TLC (PE:THF=2:1) to give the product tert-butyl N-[5-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzothiophen-2-yl]carbamate (205 mg, 0.299 mmol, 74.60% yield) as a white solid. LCMS m/z [M+1]: 685.3.

[0654] Step F: Preparation of tert-butyl N-[3-cyano-5-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzothiophen-2-yl]carbamate: To a mixture of tert-butyl N-[4-[(E)-2-fluoro-1-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]vinyl]-5-[(Z)-prop-1-enyl]-2-thienyl]carbamate (1.00 eq, 143 mg, 0.204 mmol) in DCM (2 mL) was added CSI (4.00 eq, 212 mg, 0.815 mmol) dropwise at -10 °C under Ar. LCMS showed the starting material was consumed completely. The reaction was washed with 1 x 20mL *aq.* $NaHCO_3$ aqueous solution and was taken up in DCM (2 x 20 mL). The organics were then separated and dried ($MgSO_4$) before concentration to give a crude. The crude was purified by Pre-TLC to give tert-butyl N-[3-cyano-5-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzothiophen-2-yl]carbamate (70 mg, 0.0690 mmol, 33.87 % yield). LCMS m/z[M+1]+ 710.3.

[0655] Step G: Preparation of tert-butyl (4-((R)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate: To a mixture of tert-butyl (3-cyano-5-fluoro-4-((R)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate (1.00 eq, 70 mg,0.0690 mmol) in DCM (2mL) was added SO2Cl2 (4.00 eq, 212 mg, 0.815 mmol) dropwise at -10 °C under Ar. LCMS showed the starting material was consumed completely. The reaction was washed with 1x20mL *aq.* $NaHCO_3$ and taken up in DCM (2 x20

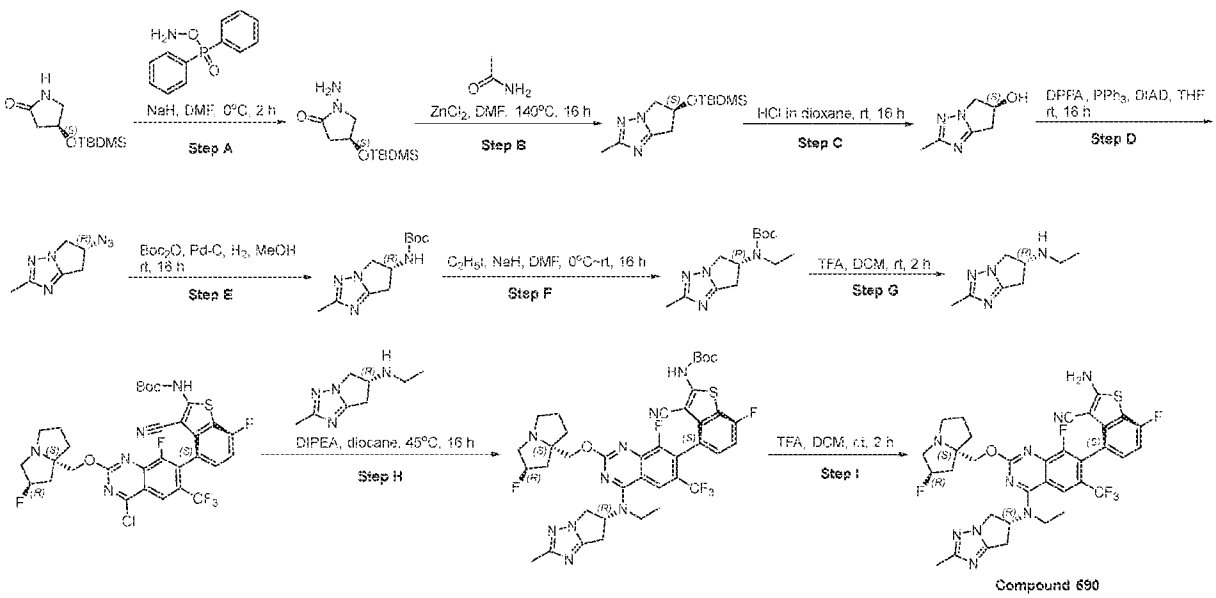
mL). The organics were then separated and dried ($MgSO_4$) before concentration to give tert-butyl (4-((R)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate (65 mg, crude). LCMS m/z[M+1]+ 698.1.

[0656] Step H: Preparation of methyl (S)-3-(((R)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate: A mixture of tert-butyl (4-((R)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-5-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 200 mg, 0.126 mmol) in dioxane/DIEA(2/1) was added methyl (S)-3-(ethylamino)pyrrolidine-1-carboxylate (3.00 eq, 52 mg, 0.379 mmol) .The reaction mixture was strried at 80 °C for 16 hrs. Lcms showed the starting material was consumed completely. The reaction was extraced with EtOAc (20 mL). The organics were then separated and dried (Na2SO4) before concentrating to dryness. The residue was purified by Pre-TLC to give methyl (S)-3-(((R)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate (15 mg, crude).

[0657] Step I: Preparation of methyl (S)-3-(((R)-7-(2-amino-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate: A mixture of methyl (S)-3-(((R)-7-(2-((tert-butoxycarbonyl)amino)-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate (1.00 eq, 15mg, crude) in DCM/TFA (3/1) was stirred at 15 °C for 2h. lcms showed the starting material was consumed completely. The reaction was washed with 5 mL saturated sodium bicarbonate aqueous solution and extraced with EtOAc (15mL).The residue was purified by Prep-HPLC to give methyl (S)-3-(((R)-7-(2-amino-3-cyano-5-fluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)pyrrolidine-1-carboxylate (0.4 mg, 0.0005 mmol, 94.90 % yield). LCMS m/z[M+1]+ 734.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.57 (m, 1H), 7.05 (t, J = 8.0 Hz, 1H), 5.38 – 52.5 (m, 3H), 4.96 (t, J = 7.2 Hz, 1H), 4.33 – 4.25 (m, 2H), 3.94 – 3.91 (m, 1H), 3.75 – 3.71 (s, 5H), 3.43 – 3.23 (m, 5H), 3.02 (m, 1H), 2.32 – 2.18 (m, 5H), 1.98 –1.91 (m, 4H), 1.38 (t, J = 7.6 Hz, 3H).

[0658] Synthetic Example 15: 2-amino-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (**Compound 590**)

[0659]



[0660] Step A: (S)-1-amino-4-((tert-butyldimethylsilyl)oxy)pyrrolidin-2-one: To a solution of (4S)-4-[tert-butyl(dimethyl)silyl]oxypyrrolidin-2-one (1.00 eq, 6.00 g, 27.9 mmol) in DMF (60 mL) was added NaH (1.50 eq, 1.00 g, 41.8 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1 h under nitrogen atmosphere. Then diphenylphosphinic acid (1.50 eq, 9.12 g, 41.8 mmol) was added to the above mixture dropwise at 0°C. The resulting mixture stirred at 0°C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with water (100 mL) and extracted with EA (50 mLx3). The combined organic layers were washed with brine (50 mLx2), dried over sodium sulfate and concentrated to afford (4S)-1-amino-4-[tert-butyl(dimethyl)silyl]oxy-pyrrolidin-2-one (2.15 g, 8.14 mmol, 29.20% yield) as a yellow solid. LCMS ESI (+) m/z 231.1 (M+H).

[0661] Step B: (S)-6-((tert-butyldimethylsilyl)oxy)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole: To a solution of (4S)-1-amino-4-[tert-butyl(dimethyl)silyl]oxy-pyrrolidin-2-one (1.00 eq, 2.15 g, 9.33 mmol) in DMF (22 mL) was added acetamide (5.00 eq, 2.76 g, 46.7 mmol) and $ZnCl_2$ (0.300 eq, 381 mg, 2.80 mmol) at room temperature. The resulting mixture was stirred at 140°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched by adding water (50 mL), extracted with EA (50 mLx3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was

purified by silica gel column chromatography to afford tert-butyl-dimethyl-[[(6S)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl]oxy]silane (346 mg, 1.09 mmol, 11.70% yield). LCMS ESI (+) m/z 254.1 (M+H).

[0662] Step C: (S)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-ol: A solution of tert-butyl-dimethyl-[[(6S)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl]oxy]silane (1.00 eq, 346 mg, 1.37 mmol) in 4N HCl in Dioxane (2.0 mL) was stirred at room temperature for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with EA (10 mLx3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered and concentrated under vacuum to afford (6S)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-ol (90 mg, 0.591 mmol, 43.25% yield) as a light yellow solid. LCMS ESI (+) m/z 140.1 (M+H).

[0663] Step D: (R)-6-azido-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole: To a solution of PPh_3 (2.00 eq, 340 mg, 1.29 mmol) in THF (2 mL) was added DIAD (2.00 eq, 0.36 mL, 1.29 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then DPPA (1.50 eq, 267 mg, 0.970 mmol) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then (6S)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-ol (1.00 eq, 90 mg, 0.647 mmol) in THF (2 mL) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (50 mL x3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=20/1) to give (6R)-6-azido-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole (73 mg, 0.162 mmol, 25.03% yield) as an off-white solid. LCMS ESI (+) m/z 165.1 (M+H).

[0664] Step E: tert-butyl (R)-(2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl)carbamate: To a solution of (6R)-6-azido-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole (1.00 eq, 73 mg, 0.445 mmol) in Methanol (2 mL) was added Boc_2O (1.50 eq, 146 mg, 0.667 mmol) and Pd/C (0.930 eq, 16 mg, 0.414 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h under H_2. The reaction was monitored by LCMS. The reaction mixture was filtered, concentrated. The residue was purified by prep-TLC (DCM/MeOH=1/1) to give tert-butyl N-[(6R)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl]carbamate (45 mg, 0.172 mmol, 38.66 % yield) as a colourless oil. LCMS ESI (+) m/z 239.0 (M+H).

[0665] Step F: tert-butyl (R)-ethyl(2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl)carbamate: To a solution of tert-butyl N-[(6R)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl]carbamate (1.00 eq, 45 mg, 0.189 mmol) in DMF (2 mL) was added NaH (1.50 eq, 6.8 mg, 0.283 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then C_2H_5I (1.20 eq, 0.041 mL, 0.227 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (10 mL *3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (PE/EA=1/1) to give tert-butyl N-ethyl-N-[(6R)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl]carbamate (37 mg, 0.102 mmol, 54.10% yield) as a colorless oil. LCMS ESI (+) m/z 267.1 (M+H).

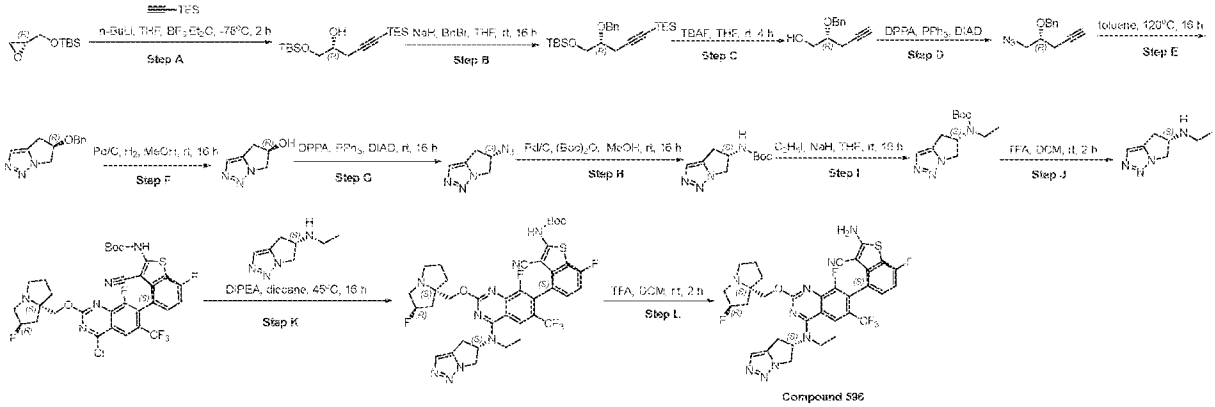
[0666] Step G: (R)-N-ethyl-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-amine: To a solution of tert-butyl N-ethyl-N-[(6R)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl]carbamate (1.00 eq, 37 mg, 0.139 mmol) in DCM (1 mL) was added TFA (0.3 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to give (6R)-N-ethyl-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-amine (45 mg, 0.224 mmol, 161.45 % yield) as a yellow oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 167.3 (M+H).

[0667] Step H: tert-butyl (3-cyano-4-((S)-4-(ethyl((R)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 120 mg, 0.172 mmol) in 1,4-Dioxane (2 mL) was added DIEA (3.00 eq, 0.092 mL, 0.516 mmol) and (6R)-N-ethyl-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-amine (1.50 eq, 43 mg, 0.258 mmol) at room temperature. The resulting mixture was stirred at 45°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (3* 10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by TLC (DCM: MeOH=20:1) to afford tert-butyl N-[3-cyano-4-[4-[ethyl-[(6R)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-

benzothiophen-2-yl]carbamate (44 mg, 0.0239 mmol, 13.91% yield) as a yellow solid. LCMS ESI (+) m/z 828.2 (M+H).

[0668] Step 1: 2-amino-4-((S)-4-(ethyl((R)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl N-[3-cyano-4-[4-[ethyl-[(6R)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 44 mg, 0.0531 mmol) in DCM (1.5 mL) was added TFA (122 eq, 0.50 mL, 6.49 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was concentrated under vacuum and the residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with EA (10 mLx3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC with (DCM/MeOH=10/1) to afford 2-amino-4-[4-[ethyl-[(6R)-2-methyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (3.0 mg, 0.00408 mmol, 7.67% yield) as an off-white solid. LCMS ESI (+) m/z 728.3(M+H). 1H NMR (400 MHz, CD3OD) δ 8.20 (s, 1H), 7.23-7.19 (m, 1H),7.01 (t, 1H), 5.35-5.31 (m, 1.5H), 5.28-5.22 (m, 1H), 5.17 (s, 0.5H), 4.66-4.62 (m, 1H), 4.46 (t, 1H), 3.93 (d, 2H), 3.72-3.69 (m, 1H), 3.63-3.61 (m, 1H), 3.59-3.54 (m, 1H), 3.37-3.33 (m, 1H), 3.23-3.16 (m, 2H), 3.01-3.29 (m, 1H), 2.39 (s, 3H), 2.20-2.16 (m, 1H), 2.07-2.02 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.77(m,1H), 1.63(t,3H).

[0669] Synthetic Example 16: 2-amino-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (**Compound 596**)



[0670] Step 1: Preparation of (R)-1-((tert-butyldimethylsilyl)oxy)-5-(triethylsilyl)pent-4-yn-2-ol: To a solution of triethyl(ethynyl)silane (1.20 eq, 8.94 g, 63.7 mmol) in THF (100 mL) was added n-BuLi (1.30 eq, 4.42 g, 69.0 mmol) at -78°C under nitrogen atmosphere. The mixture was stirred at -78°C for 10 min. Then $BF_3.Et_2O$ (1.10 eq, 8.29 g, 58.4 mmol) was added to the above mixture dropwise. The resulting mixture was stirred at -78°C for 15 min. Then tert-butyl-dimethyl-[[(2R)-oxiran-2-yl]methoxy]silane (1.00 eq, 10.00 g, 53.1 mmol) was added to the above mixture at -78°C under nitrogen atmosphere. The resulting mixture was stirred at -78°C for 2 h under nitrogen atmosphere. The resulting mixture was quenched with ammonium chloride aqueous solution. The resulting mixture was diluted with water and extracted with EA (3x100 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography to give (R)-1-((tert-butyldimethylsilyl)oxy)-5-(triethylsilyl)pent-4-yn-2-ol (5.60 g, 15.3 mmol, 28.88% yield) as a yellow oil.

[0671] Step 2: Preparation of (R)-(4-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)pent-1-yn-1-yl)triethylsilane: To a solution of NaH (2.00 eq, 0.82 g, 34.1 mmol) in THF (56mL) was added (R)-1-((tert-butyldimethylsilyl)oxy)-5-(triethylsilyl)pent-4-yn-2-ol (1.00 eq, 5.60 g, 17.0 mmol) at 0°C under nitrogen atmosphere. The mixture was stirred at 0°C for 30 min under nitrogen atmosphere. Then BnBr (2.00 eq, 5.83 g, 34.1 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The resulting mixture was quenched with water, extracted with EA (3x 50 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography to give (R)-(4-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)pent-1-yn-1-yl)triethylsilane (5.00 g, 10.7 mmol, 63.06% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ7.25-7.15 (m, 5H), 4.70-4.55 (m, 2H), 3.70-3.63 (m, 2H), 3.62-3.49 (m, 1H), 2.58-2.41 (m, 2H), 0.97-0.88 (m, 6H), 0.87-0.55 (m, 12H), 0.61-0.43 (m, 6H), 0.04-0.00 (m, 6H).

[0672] Step C: Preparation of (R)-2-(benzyloxy)pent-4-yn-1-ol: To a solution of (R)-(4-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)pent-1-yn-1-yl)triethylsilane (1.00 eq, 5.00 g, 10.7 mmol) in THF (50 mL) was added TABF (5.00 eq, 50 mL, 53.5 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at rt for 4 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (50 mL x3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography to give (R)-2-(benzyloxy)pent-4-yn-1-ol (2.00 g, 10.53 mmol, 98.4 % yield) as a yellow oil. LCMS ESI (+) m/z 191.1 (M+H).

[0673] Step D: Preparation of (R)-(((1-azidopent-4-yn-2-yl)oxy)methyl)benzene: To a solution of Triphenylphosphine (2.00 eq, 5.52 g, 21.05 mmol) in THF (50 mL) was added DIAD (2.00 eq, 4.25 g, 21.05 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then DPPA (2 eq, 5.79 g, 21.05 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then a solution of (R)-2-(benzyloxy)pent-4-yn-1-ol (1.00 eq, 2.00 g, 10.53 mmol) in THF (10 mL) added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography to give (R)-(((1-azidopent-4-yn-2-yl)oxy)methyl)benzene (1.70 g, 7.91 mmol, 75.1% yield) as an off-white solid. LCMS ESI (+) m/z 216.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.40-7.26 (m, 5H), 4.72-4.57 (m, 2H), 3.77-3.68 (m, 1H), 3.47-3.40 (m, 2H), 2.58-2.42 (m, 2H), 2.03 (t, 1H).

[0674] Step E: Preparation of (R)-5-(benzyloxy)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole: A solution of (R)-(((1-azidopent-4-yn-2-yl)oxy)methyl)benzene (1.00 eq, 1.70 g, 7.91 mmol) in toluene (20 mL) was stirred at 120°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography to give (R)-5-(benzyloxy)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (1.30 g, 6.05 mmol, 76.4% yield) as an off-white solid. LCMS ESI (+) m/z 216.0 (M+H).

[0675] Step F: Preparation of (R)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-ol: To a solution of (R)-5-(benzyloxy)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (1.00 eq, 1.3 g, 6.05 mmol) in MeOH (13 mL) was added Pd/C (400 mg) at rt. The resulting mixture was stirred at rt for 16 h under H_2. The reaction was monitored by LCMS. The resulting mixture was filtered. The filtrate was concentrated and dried in vacuum. The residue was purified by silica gel column chromatography to give (R)-5,6-dihydro-4H-

pyrrolo[1,2-c][1,2,3]triazol-5-ol (610 mg, 4.88 mmol, 80.7% yield) as a colorless oil. LCMS ESI (+) m/z 126.2 (M+H).

[0676] Step G: Preparation of (S)-5-azido-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole: To a solution of Triphenylphosphine (2.00 eq, 1.26 g, 4.80 mmol) in THF (10 mL) was added DIAD (2.00 eq, 970 mg, 4.80 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then DPPA (2 eq, 1.32 g, 4.80 mmol) at was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then a solution of (R)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-ol (1.00 eq, 300 mg, 2.40 mmol) in THF (5 mL) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography to give (S)-5-azido-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (290 mg, 1.93 mmol, 80.6% yield) as an off-white solid. LCMS ESI (+) m/z 151.2 (M+H).

[0677] Step H: Preparation of tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)carbamate: To a solution of (S)-5-azido-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazole (1.00 eq, 290 mg, 1.93 mmol) in MeOH (5 mL) was added Boc_2O (2.00 eq, 842 mg, 3.86 mmol) and Pd/C (90 mg) at rt. The resulting mixture was stirred at rt for 16 h under H_2. The reaction was monitored by LCMS. The resulting mixture was filtered, and the filtrate was concentrated. The residue was purified by prep-TLC to give tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)carbamate (300 mg, 1.34 mmol, 69.4% yield) as a colorless oil. LCMS ESI (+) m/z 225.1 (M+H).

[0678] Step I: Preparation of tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)(ethyl)carbamate: To a solution of tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)carbamate (1.00 eq, 300 mg, 1.34 mmol) in DMF (5 mL) was added NaH (2.0 eq, 64 mg, 2.68 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then Iodoethane (1.2 eq, 406 mg, 1.61 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (20 mL x3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC to give tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)(ethyl)carbamate (280 mg, 1.11 mmol, 82.8% yield) as a colorless oil. LCMS ESI (+) m/z 253.1 (M+H).

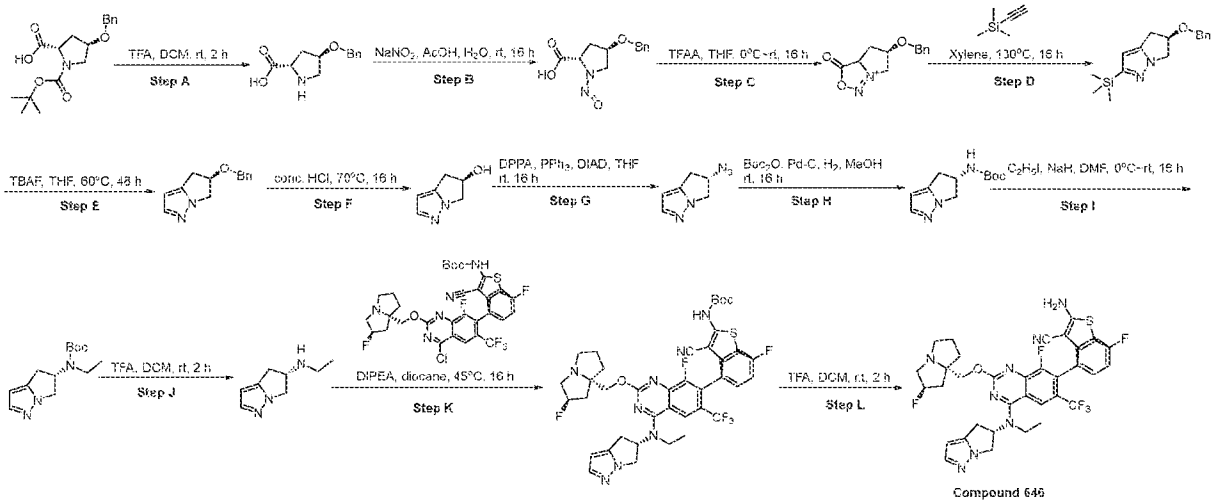
[0679] Step J: Preparation of (S)-N-ethyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-amine: To a solution of tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)(ethyl)carbamate (1.00 eq, 280 mg, 1.11 mmol) in DCM (3 mL) was added TFA (1 mL) at rt under nitrogen atmosphere. The resulting mixture was stirred at rt for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to give (S)-N-ethyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-amine (310 mg, crude) as a yellow oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 153.1 (M+H).

[0680] Step K: Preparation of tert-butyl (3-cyano-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl (4-((S)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 70 mg, 0.1 mmol) in 1,4-Dioxane (2 mL) was added DIPEA (3.00 eq, 38.8 mg, 0.3 mmol), and (S)-N-ethyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-amine (2.00 eq, 31 mg, 0.2 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at 45°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (3* 10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (DCM: MeOH=20:1) to afford tert-butyl (3-cyano-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (40 mg, 0.049 mmol, 49.2% yield) as a yellow solid. LCMS ESI (+) m/z 814.4 (M+H).

[0681] Step L: Preparation of 2-amino-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl (3-cyano-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 40 mg, 0.049 mmol) in DCM (3 mL) was added TFA (352 eq, 1.0 mL, 13.0 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at rt for 2 h. The resulting mixture was concentrated under vacuum. The residue was adjusted pH to 7~8 with $NaHCO_3$ aqueous solution, extracted with EA (10 mLx3). The combined organic phase washed with water and saturated brine solution, dried over sodium sulfate and concentrated. The residue was then purified by prep-HPLC to give 2-amino-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-5-yl)(ethyl)amino)-8-

fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (5.9 mg, 0.00807 mmol, 16.4% yield) as a white solid. MS (ESI), [M+H] + =714.2. ^{1}H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.56 (s, 1H), 7.25-7.17 (m, 1H), 7.06-6.97 m, 1H), 5.43-5.34 (m, 1H), 5.33 (s, 0.5H), 5.19 (s, 0.5H), 5.00-4.94 (m, 1H), 4.78-4.72 (m, 1H), 3.94 (q, 2H), 3.60-3.41 (m, 4H), 3.20-3.09 (m, 3H), 2.99-2.91 (m, 1H), 2.21-1.99 (m, 2H), 1.95-1.74 (m, 4H), 1.63 (t, 3H).

[0682] Synthetic Example 17: 2-amino-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (**Compound 646**)



[0683] Step A: Preparation of (2S,4R)-4-(benzyloxy)pyrrolidine-2-carboxylic acid: To a solution of (2S,4R)-4-(benzyloxy)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1.00 eq, 39.00 g, 0.12 mol) in DCM (390 mL) was added TFA (78 mL) at 0°C under nitrogen atmosphere. The resulting mixture was stirred 25°C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated to afford (2S,4R)-4-(benzyloxy)pyrrolidine-2-carboxylic acid (50 g, crude) as an yellow oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 222.1 (M+H).

[0684] Step B: Preparation of (2S,4R)-4-(benzyloxy)-1-nitrosopyrrolidine-2-carboxylic acid: To a solution of (2S,4R)-4-(benzyloxy)pyrrolidine-2-carboxylic acid (1.00 eq, 50.00 g, 0.23 mol) in H_2O (150 mL) was added a solution of $NaNO_2$ (1.5 eq, 23.4 g, 0.34 mol) in H_2O (100 mL) solution at 0°C under nitrogen atmosphere. Then acetic acid (50 mL) was added to the above mixture at 0°C. The resulting mixture was stirred at 25°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. Filter the reaction solution, rinse the filter cake with water, and vacuum dry the filter cake to

afford (2S,4R)-4-(benzyloxy)-1-nitrosopyrrolidine-2-carboxylic acid (26.7 g, 0.11 mol, 46.38% yield) as a white solid. LCMS ESI (+) m/z 251.1 (M+H).

[0685] Step C: Preparation of (5R)-5-(benzyloxy)-3-oxo-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,2,3]oxadiazol-7-ium: To a solution of (2S,4R)-4-(benzyloxy)-1-nitrosopyrrolidine-2-carboxylic acid (1.00 eq, 26.7 g, 0.11 mol) in THF (267 mL) was added TFAA (1.5 eq, 34.7 g, 0.17 mol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred 25°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with sodium bicarbonate aqueous solution at 0°C, extracted with EA (200 mLx3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluted with (PE/EA=2/1) to afford (5R)-5-(benzyloxy)-3-oxo-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,2,3]oxadiazol-7-ium (12.8 g, 54.88 mmol, 49.9% yield) as an off-white solid.

[0686] LCMS ESI (+) m/z 233.1(M+H). 1H NMR (400 MHz, CDCl3) δ 7.31-7.41 (m, 5H), 4.83-4.88 (m, 5H), 4.63-4.66 (m, 1H), 4.54-4.57 (m, 1H), 4.46-4.51 (m, 1H), 4.35-4.39 (m, 1H), 3.11-3.16 (m, 1H), 2.95-3.00 (m, 1H).

[0687] Step D: Preparation of (R)-5-(benzyloxy)-2-(trimethylsilyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole: To a solution of (5R)-5-(benzyloxy)-3-oxo-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,2,3]oxadiazol-7-ium (1.00 eq, 12.8 g, 54.88 mmol) in Xylene (128 mL) was added Trimethylsilylacetylene (3.00 eq, 16.17 g, 164.64 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred 130°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel eluted with (PE/EA=3/1) to afford (R)-5-(benzyloxy)-2-(trimethylsilyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (2.3 g, 8.03 mmol, 14.6 % yield) as a yellow oil. LCMS ESI (+) m/z 287.1 (M+H). 1H NMR (400 MHz, CDCl3) δ 7.28-7.34 (m, 5H), 6.09 (s, 1H), 4.77-4.83 (m, 1H), 4.56-4.62 (m, 2H), 4.33-4.38 (m, 1H), 4.15-4.19 (m, 1H), 3.14-3.20 (m, 1H), 2.91-2.96 (m, 1H), 0.26-0.27 (m, 9H).

[0688] Step E: Preparation of (R)-5-(benzyloxy)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole: To a solution of (R)-5-(benzyloxy)-2-(trimethylsilyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (1.00 eq, 2.3 g, 8.03 mmol) in THF (2 mL) was added TABF (10.00 eq, 80.3 mL, 80.3 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 60°C for 48 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (50 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated

under vacuum. The residue was purified by column chromatography on silica gel eluted with (PE/EA=2/1) to afford (R)-5-(benzyloxy)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (1.28 g, 5.97 mmol, 74.4 % yield) as a yellow oil. LCMS ESI (+) m/z 215.1 (M+H). 1H NMR (400 MHz, CDCl3) δ 7.50 (s, 1H), 7.28-7.49 (m, 5H), 5.96 (s, 1H), 4.77-4.80 (m, 1H), 4.56-4.60 (m, 2H), 4.30-4.32 (m, 1H), 4.14-4.17 (m, 1H), 3.16-3.22 (m, 1H) , 2.94-2.99 (m, 1H).

[0689] Step F: Preparation of (R)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-ol: To a solution of (R)-5-(benzyloxy)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (1.00 eq, 700 mg, 3.27 mmol) in conc. hydrochloric acid (5 mL) . The resulting mixture was stirred at 70°C for 16 h. The reaction was monitored by LCMS. The resulting mixture was quenched with sodium bicarbonate aqueous solution at 0°C, extracted with EA (20 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=15/1) to give (R)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-ol (300 mg, 2.42 mmol, 73.9 % yield) as an off-white solid. LCMS ESI (+) m/z 124.1 (M+H).

[0690] Step G: Preparation of (S)-5-azido-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole: To a solution of Triphenylphosphine (2.00 eq, 1.56 g, 5.96 mmol) in THF (15 mL) was added DIAD (2.00 eq, 1.2 g, 5.96 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then DPPA (1.5 eq, 1.2 g, 4.48 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then a solution of (R)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-ol (1.00 eq, 370 mg, 2.98 mmol) in THF (5 mL) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (50 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (PE/EA=1/1) to give (S)-5-azido-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (300 mg, 2.01 mmol, 67.6% yield) as an off-white solid. LCMS ESI (+) m/z 150.1 (M+H).

[0691] Step H: Preparation of tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)carbamate: To a solution of (S)-5-azido-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (1.00 eq, 300 mg, 2.01 mmol) in MeOH (10 mL) was added Boc_2O (2.00 eq, 876.36 mg, 4.02 mmol) and Pd/C (30 mg) at 25°C. The resulting mixture was stirred at 25°C for 16 h under H_2. The reaction was monitored by LCMS. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by prep-TLC (PE/EA=1/1) to give tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)carbamate (280 mg, 1.25 mmol, 62.4% yield) as a colorless oil. LCMS ESI (+) m/z 224.1 (M+H).

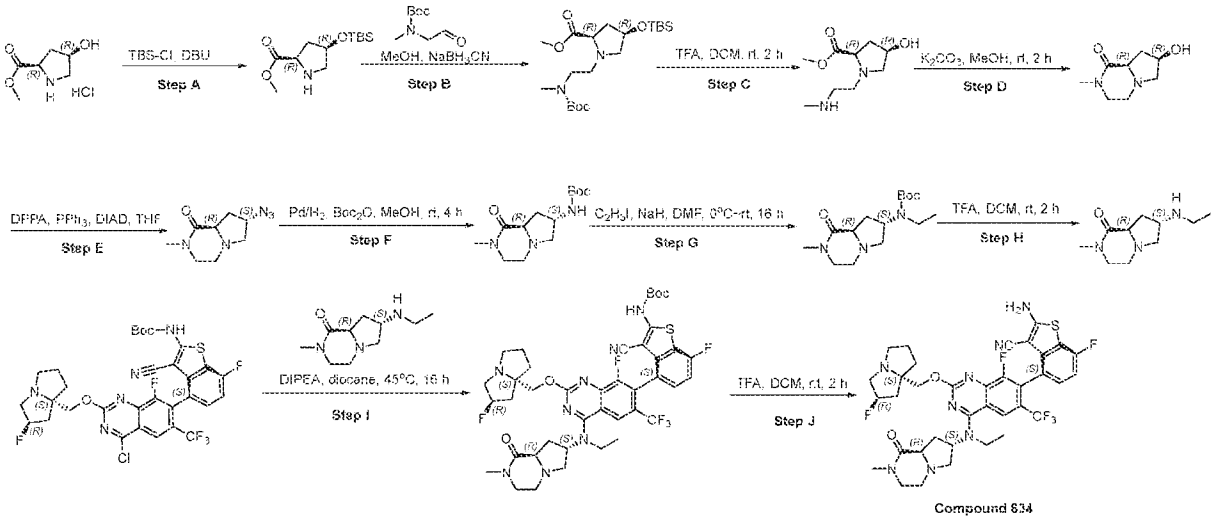
[0692] **Step I:** Preparation of tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)carbamate: To a solution of tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)carbamate (1.00 eq, 80 mg, 0.36 mmol) in DMF (5 mL) was added NaH (1.5 eq, 21.6 mg, 0.54 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then Iodoethane (1.2 eq, 67.4 mg, 0.43 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (20 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (PE/EA=1/1) to give tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)carbamate (70 mg, 0.28 mmol, 77.4% yield) as a colorless oil. LCMS ESI (+) m/z 252.1 (M+H).

[0693] **Step J:** Preparation of (S)-N-ethyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-amine: To a solution of tert-butyl (S)-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)carbamate (1.00 eq, 70 mg, 0.28 mmol) in DCM (3 mL) was added TFA (1 mL) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to give (S)-N-ethyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-amine (100 mg, crude) as a yellow oil. LCMS ESI (+) m/z 152.1 (M+H).

[0694] **Step K:** Preparation of tert-butyl (3-cyano-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl (4-((S)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 70 mg, 0.1 mmol) in 1,4-Dioxane (2 mL) was added DIPEA (3.00 eq, 38.8 mg, 0.3 mmol) and (S)-N-ethyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-amine (2.00 eq, 30.2 mg, 0.2 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 45°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was diluted with water and extracted with EA (3 x 10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by TLC (DCM: MeOH=20:1) to afford tert-butyl (3-cyano-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (50 mg, 0.062 mmol, 61.6% yield) as a yellow solid. LCMS ESI (+) m/z 813.1 (M+H).

[0695] Step L: Preparation of 2-amino-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl (3-cyano-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 50 mg, 0.062 mmol) in DCM (3 mL) was added TFA (202 eq, 1 mL, 12.52 mmol) at 25°C. The resulting mixture was stirred at 25°C for 2 h under nitrogen atmosphere. The reaction mixture was monitored by LCMS. The reaction mixture was adjusted pH=8 with sat. $NaHCO_3$, extracted with EA (10 mL x 4). The combined organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by prep-TLC (DCM: MeOH=10:1) to afford 2-amino-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (20.6 mg, 0.029 mmol, 46.7% yield) as a white solid. LCMS ESI (+) m/z 713.1 (M+H). 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.55 (d, 1H), 7.20-7.23 (m, 1H), 7.01 (t, 1H), 6.11 (s, 1H), 5.24-5.32 (m, 1.5H), 5.19 (m, 0.5H), 4.73-4.78 (m, 1H), 4.50 (t, 1H), 3.90-3.96 (m, 2H), 3.56-3.63 (m, 3H), 3.35-3.41 (m, 1H), 3.12-3.17 (m, 3H), 2.95-2.96 (m, 1H), 1.97-2.25 (m, 2H), 1.75-1.87 (m, 4H), 1.60 (t, 3H).

[0696] Synthetic Example 18: 2-amino-4-((S)-4-(ethyl((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (**Compound 634**)



[0697] Step A: Preparation of methyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate:

[0698] To a solution of methyl (2R,4R)-4-hydroxypyrrolidine-2-carboxylate (1.00 eq, 10.00 g, 55.1 mmol) in DMF (100mL) was added TEA (2.50 eq, 13.90 g, 137.7 mmol) and DBU (0.10 eq, 839 mg, 5.5 mmol) at 0°C under nitrogen atmosphere. Then TBSCl (1.20 eq, 9.97 g, 66.1 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (3x150 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography to give methyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate (4.70 g, 18.1 mmol, 32.91% yield) as a yellow oil. LCMS ESI (+) m/z 260.1 (M+H).

[0699] **Step B:** Preparation of methyl (2R,4R)-1-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate: To a solution of methyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate (1.00 eq, 4.70 g, 18.1 mmol) in MeOH (50 mL) was added tert-butyl methyl(2-oxoethyl)carbamate (2.00 eq, 6.26 g, 36.2 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at rt for 1 h under nitrogen atmosphere. Then $NaBH_3CN$ (2.00 eq, 2.28 g, 36.2 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The resulting mixture was diluted with water and extracted with EA (3x50 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography to give methyl (2R,4R)-1-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate (6.40 g, 15.4 mmol, 84.94% yield) as a yellow oil. LCMS ESI (+) m/z 417.2 (M+H).

[0700] **Step C:** Preparation of methyl (2R,4R)-4-hydroxy-1-(2-(methylamino)ethyl)pyrrolidine-2-carboxylate: To a solution of methyl (2R,4R)-1-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate (1.00 eq, 6.40 g, 15.4 mmol) in MeOH (30 mL) was added hydrochloric acid gas (30 mL, 30.0 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford methyl (2R,4R)-4-hydroxy-1-(2-(methylamino)ethyl)pyrrolidine-2-carboxylate (6.00 g crude, 29.7 mmol) as an off-white solid, which was used in the next step directly without further purification. LCMS ESI (+) m/z 203.0 (M+H).

[0701] **Step D:** Preparation of (7R,8aR)-7-hydroxy-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one:

[0702] To a solution of methyl (2R,4R)-4-hydroxy-1-(2-(methylamino)ethyl)pyrrolidine-2-carboxylate (1.00 eq, 6.00 g crude, 29.7 mmol) in MeOH (60 mL) was added K_2CO_3 (10.00 eq, 40.99 g, 297.0

mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at rt for 1 h under nitrogen atmosphere. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give (7R,8aR)-7-hydroxy-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one (1.60 g, 9.4 mmol, 31.65% yield) as an off-white solid. LCMS ESI (+) m/z 171.1 (M+H).

[0703] **Step E:** Preparation of (7S,8aR)-7-azido-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one:

[0704] To a solution of Triphenylphosphine (2.00 eq, 4.93 g, 18.8 mmol) in THF (20 mL) was added DIAD (2.00 eq, 3.80 g, 18.8 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then DPPA (2.00 eq, 5.17 g, 18.8 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then a solution of (7R,8aR)-7-hydroxy-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one (1.00 eq, 1.60 g, 9.4 mmol) in THF (10 mL) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography to give (7S,8aR)-7-azido-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one (1.82 g, 9.3 mmol, 98.94% yield) as an off-white solid. LCMS ESI (+) m/z 196.0 (M+H).

[0705] **Step F:** Preparation of tert-butyl ((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)carbamate: To a solution of (7S,8aR)-7-azido-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one (1.00 eq, 800 mg, 4.1 mmol) in MeOH (5 mL) was added Boc_2O (2.00 eq, 1.79 g, 8.2 mmol) and Pd/C (300 mg) at rt. The resulting mixture was stirred at rt for 16 h under H_2. The reaction was monitored by LCMS. The resulting mixture was filtered. The filtrate was concentrated. The residue was purified by silica gel column chromatography to give tert-butyl ((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)carbamate (700 mg, 2.6 mmol, 63.41 % yield) as a colorless oil. LCMS ESI (+) m/z 270.1 (M+H). ^1H NMR (400 MHz, CDCl3) δ 3.63-3.37 (m, 2H), 3.24-3.08 (m, 2H), 3.0-2.96 (m, 2H), 2.93 (s, 3H), 2.59 (d, 1H), 2.40-2.30 (m, 1H), 2.15 (s, 1H), 2.07-1.99 (m, 1H), 1.42 (s, 9H).

[0706] **Step G:** Preparation of tert-butyl ethyl((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)carbamate: To a solution of tert-butyl ((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)carbamate (1.00 eq, 700 mg, 2.6 mmol) in DMF (5 mL) was added NaH (2.0 eq, 125 mg, 5.2 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then Iodoethane (1.2 eq, 500 mg, 3.2 mmol) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and

extracted with EA (10 mLx3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC to give tert-butyl ethyl((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)carbamate (420 mg, 1.41 mmol, 54.23% yield) as a colorless oil. LCMS ESI (+) m/z 298.1 (M+H). ^{1}H NMR (400 MHz, CDCl3) δ 3.56-3.38 (m, 2H), 3.26-3.12 (m, 4H), 3.07-2.95 (m, 2H), 2.93 (s, 3H), 2.87-2.79 (m, 1H), 2.71-2.64 (m, 1H), 2.37-2.25 (m, 1H), 2.22-2.12 (m, 1H), 1.44 (s, 9H), 1.12 (t, 3H).

[0707] Step H: Preparation of (7S,8aR)-7-(ethylamino)-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one: To a solution of tert-butyl ethyl((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)carbamate (1.00 eq, 420 mg, 1.41 mmol) in DCM (6 mL) was added TFA (2 mL) at rt under nitrogen atmosphere. The resulting mixture was stirred at rt for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to give (7S,8aR)-7-(ethylamino)-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one (430 mg, crude) as a yellow oil, which was used in next step directly without further purification.

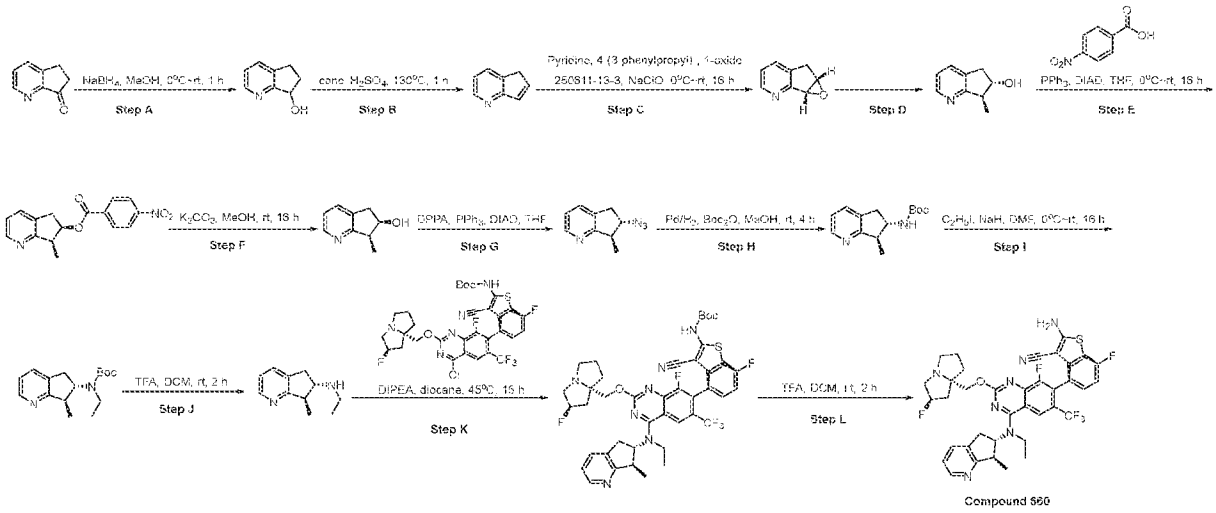
[0708] LCMS ESI (+) m/z 198.1 (M+H).

[0709] Step I: Preparation of tert-butyl (3-cyano-4-((S)-4-(ethyl((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl (4-((S)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 70 mg, 0.1 mmol) in 1,4-Dioxane (2 mL) was added DIPEA (3.00 eq, 38.8 mg, 0.3 mmol) and (7S,8aR)-7-(ethylamino)-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one (2.00 eq, 40 mg, 0.2 mmol) at rt. The resulting mixture was stirred at 45℃ for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (3x10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by TLC (DCM: MeOH=20:1) to afford tert-butyl (3-cyano-4-((S)-4-(ethyl((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (40 mg, 0.047 mmol, 46.6% yield) as a yellow solid. LCMS ESI (+) m/z 859.2 (M+H).

[0710] Step J: Preparation of 2-amino-4-((S)-4-(ethyl((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl (3-cyano-4-((S)-4-(ethyl((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)amino)-8-fluoro-2-

(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 40 mg, 0.047 mmol) in DCM (3 mL) was added TFA (352 eq, 1.0 mL, 13.0 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred at rt for 2 h. The resulting mixture was concentrated under vacuum. The residue was adjusted pH to 7~8 with NaHCO3 aqueous solution, extracted with EA (10 mLx3). The combined organic phase washed with water and saturated brine solution, dried over sodium sulfate and concentrated. The residue was purified by prep-TLC to give 2-amino-4-((S)-4-(ethyl((7S,8aR)-2-methyl-1-oxooctahydropyrrolo[1,2-a]pyrazin-7-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (12 mg, 0.01583 mmol, 33.68% yield) as a white solid. MS (ESI), m/z: [M+H] + =759.1. ^{1}H NMR (400 MHz, CD3OD) δ 8.18 (s, 1H), 7.24-7.18 (m, 1H), 7.04-6.98 (m, 1H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 4.99-4.95 (m, 1H), 4.40-4.30 (d, 1H), 4.26-4.19 (d, 1H), 4.03-3.93 (m, 1H), 3.92-3.8 (m, 2H), 3.65-3.58 (m, 1H), 3.42-3.34 (m, 2H), 3.27-3.18 (m, 3H), 3.16-3.12 (m, 2H), 3.07-2.99 (m, 2H), 2.96 (s, 3H), 2.57-2.44 (m, 2H), 2.35-2.11 (m, 3H), 2.03-1.96 (m, 2H), 1.93-1.84 (m, 1H), 1.42 (t, 3H).

[0711] Synthetic Example 19: 2-amino-4-((S)-4-(((S)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (**Compound 660**)



[0712] Step A: Preparation of 6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol: To a solution of 5,6-dihydro-7H-cyclopenta[b]pyridin-7-one (1.00 eq, 20.00 g, 150.21 mmol) in MeOH (200mL) was added $NaBH_4$ (1.00 eq, 5.68 g, 150.21 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at rt for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with saturated ammonium chloride solution at 0°C, extracted with EA (100 mL x 4). The combined organic

phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography to afford 6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (17 g, 113.19 mmol, 75.35% yield) as a white solid. LCMS ESI (+) m/z 136.3 (M+H).

[0713] **Step B:** Preparation of 5H-cyclopenta[b]pyridine and 7H-cyclopenta[b]pyridine: A solution of 6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (1.00eq, 17 g, 113.19 mmol) in concentrated sulfuric acid (6.6 eq, 73 g, 747 mmol) was stirred at 130°C for 1 h. The resulting mixture was poured into ice water, adjusted pH=10 with 6N sodium hydroxide aqueous solution, extracted with DCM (100 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate and concentrated under reduced pressure to obtain 5H-cyclopenta[b]pyridine and 7H-cyclopenta[b]pyridine (8 g, 68 mmol, 60% yield) of a mixture of the two isomers as a black oil, which was used in the next step without further purification. LCMS ESI (+) m/z 118.2 (M+H).

[0714] **Step C:** Preparation of (1aR,6aS)-6,6a-dihydro-1aH-oxireno[4,5]cyclopenta[1,2-b]pyridine and (1 aS,6aR) 2,6b-dihydro-1aH-oxireno[3,4] cyclopenta[1,2-b]pyridine: To a mixture of (R,R)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (0.412 g, 0.01eq.), 4-(3-phenylpropyl)pyridine-N-oxide (0.412 g, 0.03eq) and 5H-cyclopenta[b] pyridine and 7H-cyclopenta[b]pyridine (1.00eq, 8 g, 68 mmol) in DCM (8ml) was added NaOCl (50 ml, 2.5 eq, 2N) at 0°C under nitrogen atmosphere. The resulting mixture is then stirred at 0°C for 1 h and the temperature is let warm up to rt overnight. The resulting mixture was diluted with water and DCM. The aqueous layer is separated and extracted three times with DCM. The combined organic phase was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford 3.50 g (quantitative) of a mixture of the two desired isomers as a yellow oil. LCMS ESI (+) m/z 134.1 (M+H). 1H NMR (400 MHz, CDCl3) δ 8.37 (d, 1H), 7.54 (d, 1H), 7.16 (q, 1H), 4.34 (d, 1H), 4.16 (t, 1H), 3.25 (d, 1H), 2.99 (dd, 1H).

[0715] **Step D:** Preparation of (6S,7S)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-ol:

[0716] Methyllithium (2.6 ml) was added to a suspension of CuCN (209.5 mg, 2.3 mmol) in THF (5.3 ml) at -78°C and gradually raised to -10°C under nitrogen atmosphere. After stirring for 5 min at the temperature, the mixture was cooled to -78°C. To the above mixture was added $BF_3.Et_2O$ (0.29 ml, 2.3 mmol) and a solution of (1aR,6aS)-6,6a-dihydro-1aH-oxireno[4,5]cyclopenta[1,2-b]pyridine and (1 aS,6aR) 2,6b-dihydro-1aH-oxireno[3,4] cyclopenta[1,2-b]pyridine (193 mg, 1.06 mmol) in THF (1 mL). After being stirred for another 2 h at this temperature, the resulting mixture was raised to room temperature, quenched with saturated aqueous NH_4Cl, and extracted with ether. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by column

chromatography to afford (6S,7S)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-ol (204 mg, 74%) as yellow crystals. LCMS ESI (+) m/z 150.2 (M+H). 1H NMR (400 MHz, CDCl3) δ 8.38 (s, 1H), 7.48 (d, 1H), 7.07 (q, 1H), 4.24 (q, 1H), 3.25 (dd, 1H), 3.12-3.09 (m, 1H), 2.86 (dd, 1H), 1.38 (d, 3H).

[0717] Step E: Preparation of (6R,7S)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl 4-nitrobenzoate: To a solution of (6S,7S)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-ol (1.00 eq, 300 mg, 2.01 mmol) in THF (5mL) was added 4-nitrobenzoic acid (1.50 eq, 504 mg, 3.02 mmol) and PPh_3 (2.00 eq, 1058 mg, 4.02 mmol) at 0°C under nitrogen atmosphere. Then DIAD (2.00 eq, 1.1 mL, 4.02 mmol) was added to the above mixture 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by prep-TLC to afford [(6R,7S)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl] 4-nitrobenzoate (150 mg, 0.327 mmol, 16.25% yield) as a yellow solid. LCMS ESI (+) m/z 299.0 (M+H).

[0718] Step F: Preparation of (6R,7S)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-ol: To a solution of (6R,7S)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl 4-nitrobenzoate (1.00 eq, 250 mg, 0.838 mmol) Methanol (5 mL) was added K_2CO_3 (3.00 eq, 347 mg, 2.51 mmol). The resulting mixture was stirred at 25°C for 5 h. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum and the residue was purified by prep-TLC to afford (6R,7S)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-ol (100 mg, 0.603 mmol, 71.98% yield) as a yellow solid. LCMS ESI (+) m/z 150.1 (M+H).

[0719] Step G: Preparation of (6S,7R)-6-azido-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine: To a solution of (6R,7S)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-ol (1.00 eq, 100 mg, 0.670 mmol) in THF (1 mL) was added DPPA (2.00 eq, 369 mg, 1.34 mmol), PPh_3 (2.00 eq, 353 mg, 1.34 mmol) at room temperature. Then DIAD (2.00 eq, 0.37 mL, 1.34 mmol) was added to the above mixture dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by prep-TLC to afford (6S,7R)-6-azido-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (50 mg, 0.287 mmol, 42.82% yield) as a yellow solid. LCMS ESI (+) m/z 175.1 (M+H).

[0720] Step H: Preparation of tert-butyl ((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate: To a solution of (6S,7R)-6-azido-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (1.00 eq, 60 mg, 0.344 mmol) in methanol (5 mL) was added Pd/C (1.00 eq, 37 mg, 0.344 mmol) and Boc_2O (2.00 eq, 150 mg, 0.689 mmol) at room temperature. The resulting mixture was stirred at room temperature for

16 h under hydrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was filtered and concentrated under vacuum. The residue was purified by prep-TLC to afford tert-butyl ((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (70 mg, 0.276 mmol, 80.21% yield) as a yellow solid. LCMS ESI (+) m/z 249.0 (M+H).

[0721] Step I: Preparation of tert-butyl ethyl((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate: To a solution of tert-butyl ((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (1.00 eq, 70 mg, 0.282 mmol) in DMF (2 mL) was added NaH (3.00 eq, 20 mg, 0.846 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1 h under nitrogen atmosphere. Then MeI (1.50 eq, 0.034 mL, 0.423 mmol) was added to the above mixture dropwise. The resulting mixture stirred at room temperature for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with water (10 mL) and extracted with EA (10 mL*3). The combined organic layers were washed with brine (5 mLx2), dried over sodium sulfate and concentrated. The residue was purified by prep-TLC to afford tert-butyl ethyl((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (40 mg, 0.127 mmol, 45.18% yield) as a white solid. LCMS ESI (+) m/z 277.3 (M+H).

[0722] Step J: Preparation of (6S,7R)-N-ethyl-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine:

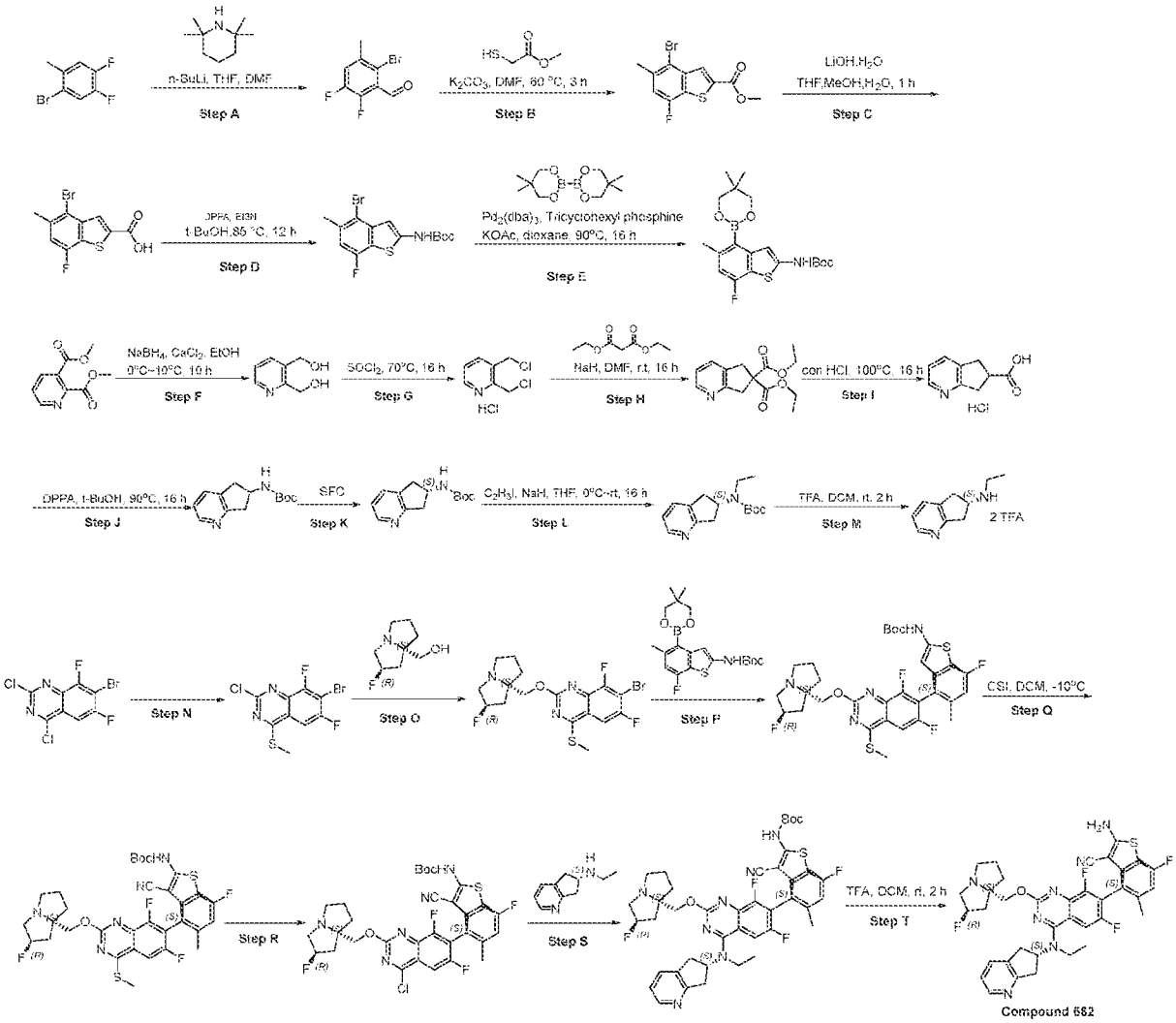
[0723] To a solution of tert-butyl ethyl((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (1.00 eq, 50 mg, 0.181 mmol) in DCM (3 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under vacuum to give crude (6S,7R)-N-ethyl-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine (40 mg, 0.163 mmol, 90.32% yield), which was used in next step directly without further purification. LCMS ESI (+) m/z 177.2 (M+H).

[0724] Step K: Preparation of tert-butyl (3-cyano-4-((S)-4-(ethyl((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate: To a solution of tert-butyl (4-((S)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 50 mg, 0.0716 mmol) in 1,4-Dioxane (2 mL) was added DIEA (5.00 eq, 0.064 mL, 0.358 mmol) and (6S,7R)-N-ethyl-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine (1.10 eq, 14 mg, 0.0788 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 45°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (10 mL x 3). The combined organic phase was washed with brine, dried over

sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=20/1) to afford tert-butyl (3-cyano-4-((S)-4-(ethyl((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (50 mg, 0.0376 mmol, 52.49% yield) as a yellow solid. LCMS ESI (+) m/z 838.1 (M+H).

[0725] Step L: Preparation of 2-amino-4-((S)-4-(ethyl((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile: To a solution of tert-butyl (3-cyano-4-((S)-4-(ethyl((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 50 mg, 0.0597 mmol) in DCM (3 mL) was added TFA (1.00 eq, 1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under vacuum and the residue was adjusted pH=8 with saturated sodium bicarbonate aqueous solution, extracted with EA (10 mL x 3). The combined organic phase was washed with water and brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC to give 2-amino-4-((S)-4-(ethyl((6S,7R)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (22 mg, 0.0283 mmol, 47.48% yield) as an off-white solid. LCMS ESI (+) m/z 738.2 (M+H). 1H NMR (400 MHz, CD3OD) δ 8.38 (d, 1H), 8.25 (s, 1H), 7.74 (d, 1H), 7.27 (dd, 1H), 7.22 (dd, 1H), 7.00 (t, 1H), 5.30 (s, 0.5H), 5.16 (s, 0.5H), 4.60-4.51 (m, 1H), 4.10-4.02 (m, 2H), 3.90-3.76 (m, 3H), 3.70-3.63 (m, 2H), 3.47-3.36 (m, 1H), 3.22-3.12 (m, 2H), 3.01-2.93 (m, 1H), 2.21-2.04 (m, 2H), 1.93-1.80 (m, 2H), 1.75-1.64 (m, 2H), 1.59 (t, 3H), 1.48 (d, 3H).

[0726] Synthetic Example 20: 2-amino-4-[4-[ethyl-[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]amino]-6,8-difluoro-2-[[rac-(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophene-3-carbonitrile (**Compound 662**)



[0727] Step A: Preparation of 2-bromo-5,6-difluoro-3-methylbenzaldehyde: To a solution of 2,2,6,6-tetramethylpiperidine (1.20 eq, 20.061 g, 142 mmol) in THF (240 mL) was added n-BuLi (1.10 eq, 130 mmol) at -78°C under nitrogen atmosphere. The resulting mixture was stirred at -78°C for 1 h under nitrogen atmosphere. Then 1-bromo-4,5-difluoro-2-methylbenzene (1.00 eq, 24.50 g, 118 mmol) was added to the above mixture with dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred at -78°C for 2 h under nitrogen atmosphere. DMF (1.50 eq, 12.9 g, 178 mmol) was added to the above mixture at -78°C under nitrogen atmosphere. The resulting mixture was stirred at -78°C for 0.5 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with NH_4Cl (100 mL) and extracted with EA (100 mL*x*3). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated. The residue was purified by silica gel column with ethyl to afford 2-bromo-5,6-difluoro-3-methyl-benzaldehyde (19.00 g, 64.7 mmol, 54.65 % yield) as a white solid. 1H NMR (400 MHz, CDCl3) δ 10.25 (s, 1H), 7.29-7.23 (m, 1H), 2.37 (s, 3H).

[0728] **Step B:** Preparation of Methyl 4-bromo-7-fluoro-5-methylbenzo[b]thiophene-2-carboxylate: To a solution of 2-bromo-5,6-difluoro-3-methyl-benzaldehyde (1.00 eq, 19.00 g, 81.20 mmol) and K_2CO_3 (2.00 eq, 22.41 g, 162.4 mmol) in DMF (200 mL) was added methyl 2-mercaptoacetate (1.11 eq, 9.55 g, 91.13 mmol). The resulting mixture was stirred at 60°C for 3 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was poured into ice water (600 mL) and extracted with EA (200 mLx3). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and concentrated. The residue was purified by silica gel column with ethyl to afford methyl 4-bromo-7-fluoro-5-methyl-benzothiophene-2-carboxylate (20.00 g, 52.8 mmol, 57.70% yield) as a white solid. 1H NMR (400 MHz, CDCl3) δ 8.17 (s, 1H), 7.07 (d, 1H), 3.96 (s, 3H), 2.52 (s, 3H).

[0729] **Step C:** Preparation of 4-bromo-7-fluoro-5-methylbenzo[b]thiophene-2-carboxylic acid: To a solution of methyl 4-bromo-7-fluoro-5-methyl-benzothiophene-2-carboxylate (1.00 eq, 5.00 g, 16.5 mmol) in THF (20 mL), Methanol (20 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (3.45 eq, 2.388 g, 56.9 mmol). The resulting mixture was stirred at 25°C for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was acidified to pH=3 with 4 M HCl. The resulting mixture was extracted with EA (60 mLx3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and concentrated. The residue was purified by silica gel column with ethyl to afford 4-bromo-7-fluoro-5-methylbenzo[b]thiophene-2-carboxylic acid (4.10 g, 14.24 mmol, 68.79% yield) as a white solid. LCMS ESI (+) m/z 288.9 (M+H). 1H NMR (400 MHz, $DMSOd_6$) δ 10.13 (s, 1H), 7.84 (d, 1H), 7.44 (t, 1H), 2.44 (d, 3H).

[0730] **Step D:** Preparation of Tert-butyl (4-bromo-7-fluoro-5-methylbenzo[b]thiophen-2-yl) carbamate:

[0731] To a solution of 4-bromo-7-fluoro-5-methyl-benzothiophene-2-carboxylic acid (1.00 eq, 4.10 g, 14.23 mmol) and DPPA (1.30 eq, 5.09 mg, 18.50 mmol) in t-BuOH (55 mL) was added TEA (2.00 eq, 2.88 g, 28.46 mmol). The resulting mixture was stirred at 85°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with EA (200 mL), washed with brine (40 mL), dried over sodium sulfate and concentrated. The residue was purified by silica gel column with ethyl to afford tert-butyl (4-bromo-7-fluoro-5-methylbenzo[b]thiophen-2-yl) carbamate (3.50 g, 9.74 mmol, 67.1 % yield) as a white solid. LCMS ESI (+) m/z 360.0 (M+H). 1H NMR (400 MHz, DMSO d6) δ 11.12 (s, 1H), 7.18-7.03 (m, 1H), 6.84 (d, J = 3.5 Hz, 1H), 2.45-2.33 (m, 3H), 1.52 (s, 9H).

[0732] **Step E:** Preparation of tert-butyl (4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-5-methylbenzo[b]thiophen-2-yl) carbamate: To a solution of tert-butyl (4-bromo-7-fluoro-5-methylbenzo[b]thiophen-2-yl) carbamate (1.00 eq, 3.50 g, 9.74 mmol) and 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane) (1.20 eq, 2.64 g, 11.7 mmol) in 1,4-dioxane (150 mL) was added KOAc (3.00 eq,

1.7 mL, 29.25 mmol) , $Pd_2(dba)_3$ (0.02 eq, 160 mg, 0.195 mmol) and Tricyclohexyl phosphine (0.04 eq, 110 mg, 0.39 mmol) . The resulting mixture was stirred at 90°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated, and the residue was dissolved in EA (100 mL). Filtrated and the filtrate was concentrated. The residue was purified by silica gel column with ethyl to afford tert-butyl (4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-5-methylbenzo[b]thiophen-2-yl) carbamate (2.50 g, 5.72 mmol, 53.71% yield) as a white solid. LCMS ESI (+) m/z 338.0 (M+H-56). 1H NMR (400 MHz, DMSO d6) δ 10.81 (s, 1H), 7.09 (d, *J* = 3.9 Hz, 1H), 6.83 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 4H), 2.46 (s, 3H), 1.49 (s, 9H), 1.04 (s, 6H).

[0733] Step F: Preparation of pyridine-2,3-diyldimethanol: To a solution of dimethyl pyridine-2,3-dicarboxylate (1.00 eq, 100 g, 512.69 mmol) in EtOH (1.5 L) was added $NaBH_4$ (3.00 eq, 58.15 g, 1.54 mol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 10 minutes under nitrogen atmosphere. Then $CaCl_2$ (0.88 eq, 50.00 g, 451.17 mmol) was added to the above mixture at 10°C under nitrogen atmosphere. The resulting mixture was stirred at 25°C for 16 h under nitrogen atmosphere. The resulting solution was quenched with water (100 mL). The resulting mixture was filtered. The filter cake was washed with EtOH. The filtration was concentrated under reduced pressure to give pyridine-2,3-diyldimethanol (79.00 g, 451.33 mmol, 88.03% yield) as an off-white solid. LCMS ESI (+) m/z 140.1 (M+H).

[0734] Step G: Preparation of 2,3-bis(chloromethyl)pyridine hydrochloride: A solution of pyridine-2,3-diyldimethanol (1.00 eq, 79.00 g, 451.33 mmol) in thionyl chloride (2.30 eq, 130.00 g, 1.09 mol) was stirred at 25°C for 1 h. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was trituration with MTBE, filtered to give 2,3-bis(chloromethyl)pyridine hydrochloride (90.00 g, 426.60 mmol, 94.52% yield) as an off-white solid. LCMS ESI (+) m/z 176.1 (M+H). ^{1}H NMR (400 MHz, DMSO d6) δ 8.61 (dd, 1H), 8.06 (dd, 1H), 7.55 (dd, 1H), 4.97 (d, 4H).

[0735] Step H: Preparation of diethyl 5,7-dihydro-6H-cyclopenta[b]pyridine-6,6-dicarboxylate: To a solution of diethyl malonate (1.20 eq, 81.99 g, 511.92 mmol) in DMF (900 mL) was added NaH (2.50 eq, 42.8 g, 1.07 mol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h. Then 2,3-bis(chloromethyl)pyridine hydrochloride (1.00 eq, 90.00 g, 426.60 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 100°C for 16 h. The reaction was monitored by LCMS. The resulting mixture was diluted with water (3000 mL) and extracted with EA (1000 mLx3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography to give diethyl 5,7-dihydro-

6H-cyclopenta[b]pyridine-6,6-dicarboxylate (66.00 g, 250.84 mmol, 58.80% yield) as an off-white solid. LCMS ESI (+) m/z 264.1 (M+H).

[0736] Step I: Preparation of 6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid hydrochloride: A solution of diethyl 5,7-dihydro-6H-cyclopenta[b]pyridine-6,6-dicarboxylate (1.00 eq, 66.00 g, 250.84 mmol) in conc. HCl (330 mL) and H_2O (330 mL) was stirred at 100°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford 6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid hydrochloride (40.00 g crude, 201.01 mmol, 80.13% yield) as an off-white solid, which was used in the next step directly without further purification. LCMS ESI (+) m/z 164.1 (M+H). ^{1}H NMR (400 MHz, DMSO) δ 8.65 (d, 1H), 8.40 (d, 1H), 7.81 (dd, 1H), 3.52-3.19 (m, 4H).

[0737] Step J: Preparation of tert-butyl (6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate: To a solution of 6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid hydrochloride (1.00 eq, 40.00 g, 245.13 mmol) in t-butanol (400 mL) was added DPPA (1.50 eq, 101.11 g, 367.69 mmol) and DIEA (3.00 eq, 74.41 g, 735.38 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 90°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (400 mL*3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude was purified by silica gel column chromatography to give tert-butyl (6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (18.00 g, 30.73 mmol, 38% yield) as an off-white solid. LCMS ESI (+) m/z 235.1 (M+H).

[0738] Step K: Preparation of tert-butyl (S)-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate: The racemate was separated by chiral-SFC (Chromatographic columns: IG; Mobile Phase: EtOH-CO_2; Gradient: 30% EtOH+70% CO_2) to give tert-butyl (S)-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (8.00 g, 44% yield) as an off-white solid in the first peak. ^{1}H NMR (400 MHz, DMSO) δ 8.28 (d, 1H), 7.56 (d, 1H), 7.22 (d, 1H), 7.12 (dd, 1H), 4.30-4.17 (m, 1H), 3.20-3.10 (m, 2H), 2.87-2.75 (m, 2H), 1.40 (s, 9H).

[0739] Step L: Preparation of tert-butyl (S)-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)(ethyl)carbamate: To a solution of tert-butyl (S)-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (1.00 eq, 3.00 g, 12.80 mmol) in DMF (30 mL) was added NaH (2.00 eq, 614.6 mg, 25.60 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 0.5 h under nitrogen atmosphere. Then C_2H_5I (1.00 eq, 1.99 g, 12.80 mmol) was added to the above mixture at 0°C under nitrogen atmosphere. The resulting solution was stirred at 25°C for 16 h. The reaction was monitored by LCMS. The resulting mixture was diluted with water (120 mL) and extracted with EA (30 mLx3). The combined organic phase was washed

with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography to give tert-butyl (S)-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)(ethyl)carbamate (2.70 g, 9.26 mmol, 72% yield) as a yellow oil. LCMS ESI (+) m/z 263.1 (M+H).

[0740] Step M: Preparation of (S)-N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine: To a solution of tert-butyl (S)-(6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)(ethyl)carbamate (1.00 eq, 2.70 g, 10.30 mmol) in DCM (15 mL) was added TFA (7.11 eq, 5.0 mL, 73.1 mmol) at 0°C under nitrogen atmosphere. The resulting solution was stirred at 25°C for 2 h. The reaction was monitored by LCMS. The resulting mixture was concentrated to give (S)-N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine (5.00 g, 9.25 mmol, 89% yield) as a yellow oil, which was used in next step directly without further purification. LCMS ESI (+) m/z 163.1 (M+H).

[0741] Step N: Preparation of 7-bromo-2-chloro-6,8-difluoro-4-methylsulfanyl-quinazoline: To a solution of 7-bromo-2,4-dichloro-6,8-difluoro-quinazoline (1.00 eq, 5.00 g, 15.9 mmol) in THF (50 mL) was added MeSNa (1.20 eq, 6.69 g, 19.1 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred 0°C for 1 hour under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with sat. NH_4Cl aqueous solution at 0°C, extracted with EA (100 mLx4). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was trituration with PE and filtered to afford 7-bromo-2-chloro-6,8-difluoro-4-methylsulfanyl-quinazoline (4.90 g,12.5 mmol, 78.43 % yield) as an off-white solid. LCMS ESI (+) m/z 326.8 (M+H).

[0742] Step O: Preparation of 7-bromo-6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazoline: To a solution of 7-bromo-2-chloro-6,8-difluoro-4-methylsulfanyl-quinazoline (1.00 eq, 1.00 g, 3.07 mmol) in 1,4-Dioxane (10 mL) was added DIEA (5.00 eq, 1.98 g, 15.4 mmol) and [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methanol (1.50 eq, 734 mg, 4.61 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 105°C for 16 hours under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (20 mLx4). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was trituration with PE: EA=2:1 to afford 7-bromo-6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy] quinazoline (740 mg, 1.35 mmol, 44.07% yield) as a yellow solid. LCMS ESI (+) m/z 450.0 (M+H).

[0743] Step P: Preparation of tert-butyl N-[4-[6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophen-2-yl]

carbamate: To a solution of 7-bromo-6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazoline (1.00 eq, 740 mg, 1.65 mmol) in toluene (10 mL) was added tert-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-5-methyl-benzothiophen-2-yl]carbamate (2.00 eq, 1298 mg, 3.30 mmol), (R,R)-BaryPhos (0.120 eq, 104 mg, 0.198 mmol), Cs_2CO_3 (3.00 eq, 1613 mg, 4.95 mmol), $Pd_2(dba)_3$ (0.0500 eq, 76 mg, 0.0825 mmol) and 4A molecular sieves (500 mg) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 85°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with water, extracted with EA (20 mLx3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with EA in petroleum from 0% to 50% to afford tert-butyl N-[4-[6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophen-2-yl] carbamate (860 mg, 0.928 mmol, 56.22 % yield) as a yellow solid. LCMS ESI (+) m/z 649.1 (M+H).

[0744] Step Q: Preparation of tert-butyl N-[3-cyano-4-[6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophen-2-yl] carbamate: To a solution of tert-butyl N-[4-[6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophen-2-yl] carbamate (1.00 eq, 500 mg, 0.771 mmol) in DCM (10 mL) was added chlorosulfonyl isocyanate (8.00 eq, 0.54 mL, 6.17 mmol) at -20°C under nitrogen atmosphere. The resulting mixture was stirred at -20°C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with sodium bicarbonate aqueous solution at -20°C, extracted with EA (20 mLx3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=20/1) to afford tert-butyl N-[3-cyano-4-[6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophen-2-yl] carbamate (350 mg, 0.312 mmol, 40.44 % yield) as a yellow solid. LCMS ESI (+) m/z 674.0 (M+H).

[0745] Step R: Preparation of tert-butyl N-[4-[4-chloro-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazolin-7-yl]-3-cyano-7-fluoro-5-methyl-benzothiophen-2-yl] carbamate: To a solution of tert-butyl N-[3-cyano-4-[6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophen-2-yl] carbamate (1.00 eq, 50 mg, 0.0742 mmol) in DCM (2mL) was added SO_2Cl_2 (4.00 eq, 40 mg, 0.297 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1 h under nitrogen

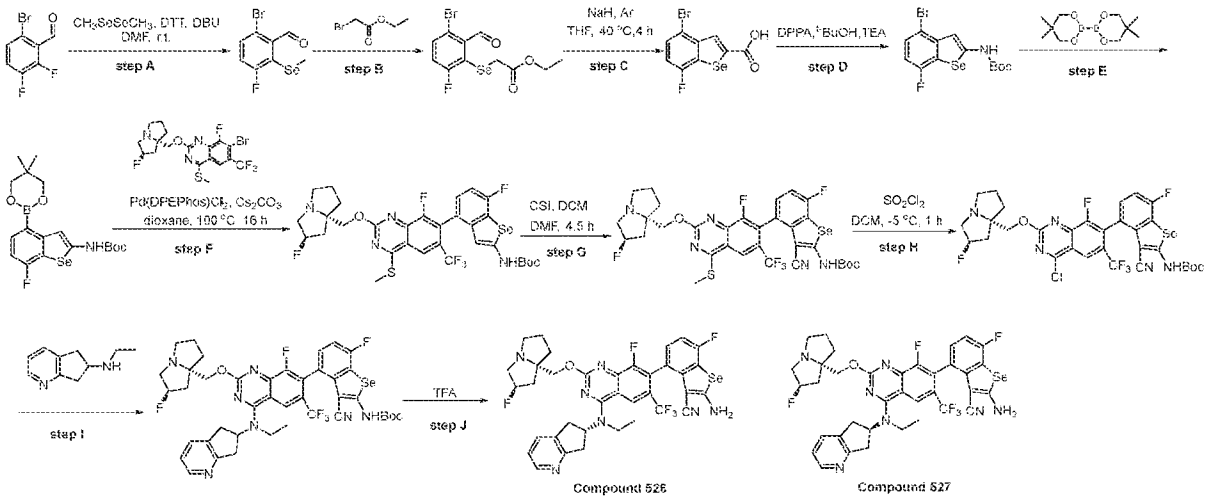
atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched with saturated sodium bicarbonate aqueous solution, extracted with DCM (10 mL x3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum to afford tert-butyl N-[4-[4-chloro-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-3-cyano-7-fluoro-5-methyl-benzothiophen-2-yl]carbamate (50 mg,0.0355 mmol, 47.83 % yield) as a yellow solid, which was used in the next step directly without further purification. LCMS ESI (+) m/z 662.0 (M+H).

[0746] Step S: Preparation of tert-butyl N-[3-cyano-4-[4-[ethyl-[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl] amino]-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophen-2-yl] carbamate: To a solution of tert-butyl N-[4-[4-chloro-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahy dropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-3-cyano-7-fluoro-5-methyl-benzothiophen-2-yl]carbamate (1.00 eq, 50 mg, 0.0755 mmol) in 1,4-Dioxane (2 mL) was added DIEA (5.00 eq, 49 mg, 0.378 mmol) and (6S)-N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine (1.50 eq, 18 mg, 0.113 mmol) at 25°C under nitrogen atmosphere. The resulting mixture was stirred at 45°C for 16 h under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water and extracted with EA (10 mL x3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (DCM/MeOH=20/1) to afford tert-butyl N-[3-cyano-4-[4-[ethyl-[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]amino]-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophen-2-yl]carbamate (27 mg, 0.0154 mmol, 20.42% yield) as a yellow solid. LCMS ESI (+) m/z 788.2 (M+H).

[0747] Step T: Preparation of 2-amino-4-[4-[ethyl-[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl] amino]-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl] methoxy] quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophene-3-carbonitrile:To a solution of tert-butyl N-[3-cyano-4-[4-[ethyl-[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]amino]-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophen-2-yl]carbamate (1.00 eq, 27 mg, 0.0343 mmol) in DCM (2 mL) was added TFA (274 eq, 0.70 mL, 9.39 mmol) at 25°C. The resulting mixture was stirred at 25°C for 2 h. The reaction was monitored by LCMS. The reaction solution was adjusted pH to 8 with saturation sodium bicarbonate aqueous solution, extracted with EA (10 mLx3) The combined organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by prep-TLC (DCM/MeOH=15/1) to give 2-amino-4-[4-[ethyl-[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]amino]-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-

hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-7-fluoro-5-methyl-benzothiophene-3-carbonitrile (4.0 mg, 0.00533 mmol, 15.55% yield) as an off-white solid. LCMS ESI (+) m/z 688.3 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (d, 1H), 7.73 (d, 1H), 7.61-7.64 (m, 1H), 7.25-7.28 (m, 1H), 6.97 (d, 1H), 5.35 (s, 0.5H), 5.21 (s, 0.5H), 5.04-5.08 (m, 1H), 3.81-3.94 (m, 4H), 3.68-3.74 (m, 1H), 3.57-3.63 (m, 1H), 3.41-3.48 (m, 2H), 3.24-3.26 (m, 3H), 2.99-3.05 (m, 1H), 2.20-2.29 (m, 1H), 2.16 (s, 3H), 1.89-2.03 (m, 3H), 1.71-1.82 (m, 2H), 1.48 (t, 3H).

[0748] Synthetic Example 21: 2-amino-4-[4-[[(6R)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzoselenophene-3-carbonitrile (**Compound 526**) and 2-amino-4-[4-[[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydro pyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzoselenophene-3-carbonitrile (**Compound 527**)



[0749] Step A: Preparation of 6-bromo-3-fluoro-2 -methylselanyl-benzaldehyde: To a solution of DL-Dithiothreitol (1.00 eq, 17.45 g, 113 mmol) in DMF (250 mL) was added dmethyldiselenide (0.400 eq, 8.51 g, 45.2 mmol) at 0 °C under Ar. After stirring for 0.5h at 0 °C, 6-bromo-2,3-difluoro-benzaldehyde (1.00 eq, 25.00 g, 113 mmol) in DMF was added to the solution slowly. Then the solution was stirred at 0 °C for 0.5 h. After that DBU (2.50 eq, 43.05 g, 283 mmol) was added to the solution slowly and stirred for 3 h at 0 °C. The mixture was poured into ice-water and diluted with EtOAc (600 mL) and the organics washed with 2 x 300 mL water, 300 mL brine. The organics were separated and dried ($MgSO_4$) before concentration to dryness. The crude was purified by column chromatography silica gel eluted with (Petroleum ether / EtOAc = 30:1 ~ 10:1) to afford 6-bromo-3-fluoro-2 -methylselanyl-benzaldehyde (19.20 g, 64.9 mmol,

57.34 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.35 (s, 1H), 7.51 – 7.48 (m, 1H), 7.09 – 7.04 (m, 1H), 2.43 – 2.39 (m, 3H).

[0750] Step B: Preparation of ethyl 2-(3-bromo-6-fluoro-2-formyl-phenyl)selanylacetate: A solution of 6-bromo-3-fluoro-2-methylselanyl-benzaldehyde (1.00 eq, 19.20 g, 64.9 mmol) in ethyl bromoacetate (20.8 eq, 150 mL, 1347 mmol) was stirred at 100 °C for 16 h. TLC showed no SM remained, the mixture concentrated to dryness to afford a crude, and the crude was purified by column chromatography on silica gel eluted with (Petroleum ether / EtOAc =30 : 1 – 10 : 1) to give ethyl 2-(3-bromo-6-fluoro-2-formyl-phenyl)selanylacetate (16.10 g, 43.7 mmol, 67.44 % yield) as a yellow solid, it was a mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.74 (s, 1H), 7.75 – 7.71 (m, 1H), 7.27 – 7.23 (m, 1H), 4.17 (d, J = 7.2, 2H), 2.53 (s, 2H), 2.36 (s, 3H), 1.26 – 1.23 (m, 3H).

[0751] Step C: Preparation of 4-bromo-7-fluoro-benzoselenophene-2-carboxylic acid: To a solution of ethyl ethyl 2-(3-bromo-6-fluoro-2-formyl-phenyl)selanylacetate (1.00 eq, 8.10 g, 22.0 mmol) in THF (80 mL) were added NaH (2.00 eq, 1.76 g, 44.0 mmol). The resulting mixture was stirred at 40 °C for 12 h. The reaction was monitored by TLC. When the sm was consumed. The mixture was added to ice-water, the solution was adjusted to pH = 4, EA (400 mL) was added to the mixture. The organic layer was washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The crude was (Petroleum ether / EtOAc = 10:1) was added to the mixture, the solution microwave for 5min. The solution filtered and the filtered cake was washed with petroleum ether to give 4-bromo-7-fluoro-benzoselenophene-2-carboxylic acid (4.50 g, 14.0 mmol, 63.50 % yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.38 (d, J = 3.6 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.15 – 7.11 (m, 1H).

[0752] Step D: Preparation of tert-butyl N-(4-bromo-7-fluoro-benzoselenophen-2-yl)carbamate: To a solution of 4-bromo-7-fluoro-benzoselenophene-2-carboxylic acid (1.00 eq, 8.00 g, 24.8 mmol) and N,N-Diisopropylethylamine (1.20 eq, 5.2 mL, 29.8 mmol) in tert-butanol (80 mL) was added [azido(phenoxy)phosphoryl]oxybenzene (1.20 eq, 8.20 g, 29.8 mmol). The reaction was stirred at 90 °C for 16h. LC-MS showed no starting material remaining. The reaction was concentrated to dryness, and the residue was taken up in EtOAc (200 ml). The organics phase was washed with 100 ml water, 100 ml brine. The organics were separated and dried ($MgSO_4$) before concentration to dryness. The crude was purified by flash column chromatography (Petroleum ether: EtOAc = 10:1) to give a crude product. Petroleum ether /EtOAc = 10/1 was added to the crude and slurry for 30 min, the suspension was filtered and the filter cake washed with Petroleum ether to afford tert-butyl N-(4-bromo-7-fluoro-benzoselenophen-2-yl)carbamate (6.50 g,16.5 mmol, 66.55 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.41 (m, 1H),

6.96 (d, J = 3.6 Hz, 1H), 6.78 (t, J = 8.8 Hz, 1H), 1.55 (s, 9H). LCMS m/z[M-1]$^-$ cacld:391.93/393.93; found: 391.9/393.9, t(R)= 4.39 min.

[0753] Step E: Preparation of tert-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzoselenophen-2-yl]carbamate: A solution of tert-butyl N-(4-bromo-7-fluoro-benzoselenophen-2-yl)carbamate (1.00 eq, 3.90 g, 9.92 mmol) in 1,4-dioxane (50mL) in the flask, 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (2.00 eq, 4.48 g, 19.8 mmol), $Pd_2(dba)_3$ (0.0200 eq, 0.18 g, 0.198 mmol), tricyclohexyl phosphine (0.040 eq, 0.11 g, 0.397 mmol) and AcOK (3.00 eq, 2.92 g, 29.8 mmol) were added to the obtained solution. The mixture was heated to 95 °C for another 16 hrs with the protection of argon. LC-MS showed no SM remained. The reaction filtered and the filtered cake washed with EtOAc. Then the solution was concentrated to dryness. The crude was purified by column chromatography silica gel eluted with (Petroleum ether / EtOAc = 10 : 1 to 0 : 1) to give a crude. The crude was washed with petroleum ether to give tert-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzoselenophen-2-yl]carbamate (2.40 g, 5.63 mmol, 56.77 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 – 7.69 (m, 1H), 7.63 (d, J = 4.0 Hz, 1H), 6.92 (t, J = 8.8 Hz, 1H), 3.80 (s, 4H), 1.49 (s, 9H), 0.98 (s, 6H). LCMS m/z[M-1]$^-$ cacld:425.15; found: 358.0.

[0754] Step F: Preparation of tert-butyl N-[7-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzoselenophen-2-yl]carbamate: To a solution of 7-bromo-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]meth oxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazoline (1.00 eq, 500 mg, 1.00 mmol) in 1,4-Dioxane (8 mL) were added Pd(DPEPhos)Cl_2 (0.30 eq, 215 mg, 0.301 mmol) , tert-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-benzoselenophen-2-yl]carbamate (1.50 eq, 641 mg, 1.51 mmol) and Cs_2CO_3 (2.00 eq, 654 mg, 2.01 mmol), the mixture was bubbled with Ar for 1~2 min and then sealed. The mixture was stirred 4 h at 100 °C. The mixture was concentrated to dryness and the residue was purified by silica gel column (EA: PE=1:1) to give the product tert-butyl N-[7-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzoselenophen-2-yl]carbamate (450 mg, 0.615 mmol, 61.30% yield). LCMS: (ES+): m/z 733.2; $[M]^+$.

[0755] Step G: Preparation of tert-butyl N-[3-cyano-5-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzoselenophen-2-yl]carbamate: To a solution of tert-butyl N-[7-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahy dropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzoselenophen-2-yl]carbamate (1.00 eq, 100 mg, 0.137 mmol) in DCM (1 mL) was added

chlorosulfonyl isocyanate (5.00 eq, 97 mg, 0.685 mmol) in DCM (0.5 mL) at -20 °C. The reaction was stirred 4 h at -20 °C, then DMF (1.5 mL) was added to the mixture and stirred 0.5 h at -20 °C. The reaction was quenched with *aq.* $NaHCO_3$ and extracted with EtOAc. The organics were removed and the residue was purified by Prep-TLC to give tert-butyl N-[3-cyano-5-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzoselenophen-2-yl]carbamate (50 mg, 0.0661 mmol, 48.35 % yield). LCMS: (ES+): m/z 758.2 $[M]^+$.

[0756] Step H: Preparation of tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzoselenophen-2-yl]carbamate: To a solution of tert-butyl N-[3-cyano-7-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzoselenophen-2-yl]carbamate (1.00 eq, 25 mg, 0.0330 mmol) in DCM (2 mL) at 0 °C was added SO_2Cl_2 (5.00 eq, 0.012 mL, 0.165 mmol) under N_2. The mixture was stirred at 0 °C for 1 h and monitored by TLC (PE:EtOAc=1:1). When the SM was consumed, the mixture was partitioned between DCM/*aq.*$NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, concentrated to give crude tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzoselenophen-2-yl]carbamate (25 mg, 0.0336 mmol, 101.56 % yield) as light yellow solid, which was used into next reaction without further purification.

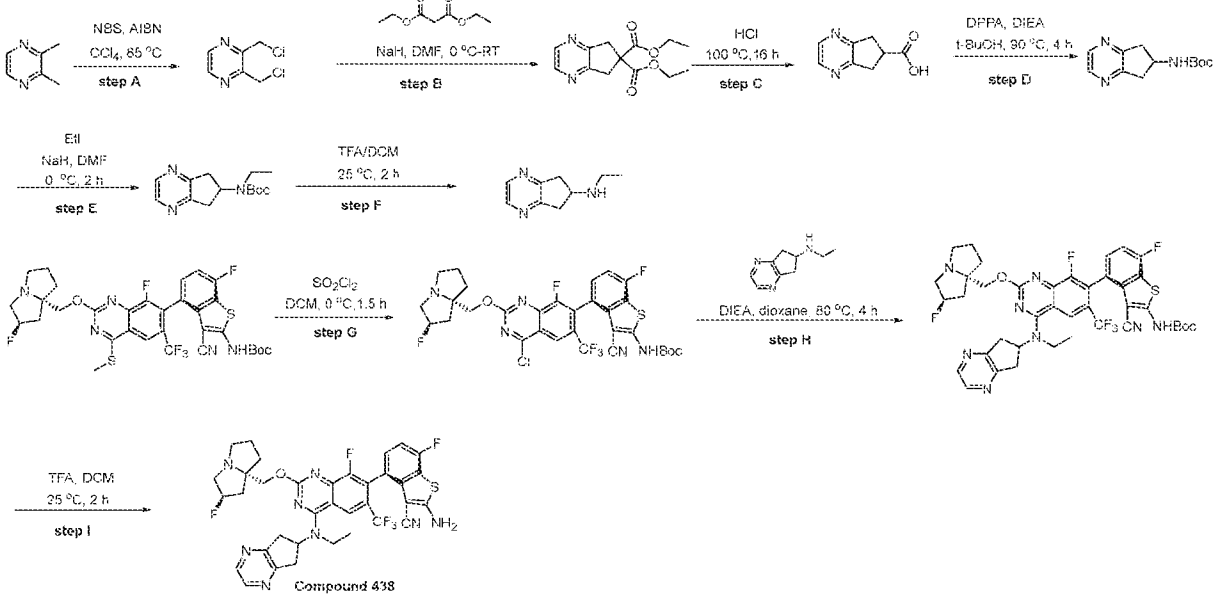
[0757] Step I: Preparation of tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzoselenophen-2-yl]carbamate: A mixture of tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzoselenophen-2-yl]carbamate (1.00 eq, 25 mg, 0.0336 mmol) N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-amine (3.00 eq, 16 mg, 0.101 mmol) DIEA (5.00 eq, 17 mg, 0.168 mmol) in 1,4-dioxane (2mL) was stirred at 70°C for 4 h. The reaction was monitored by LC-MS. When the sm consumed. The mixure was concentrated and purified by prep-TLC(eluent with 8% MeOH in DCM) to give tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzoselenophen-2-yl]carbamate (10 mg, 0.0115 mmol, 34.22 % yield) as light yellow solid. LCMS: (ES+): m/z 871.7[M+H]+, tR =3.866 min.

[0758] Step J: Preparation of to 2-amino-4-[4-[[(6R)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzoselenophene-3-carbonitrile (**Compound 526**) and 2-

amino-4-[4-[[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydro pyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzoselenophene-3-carbonitrile (**Compound 527**): To a solution of tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzoselenophen-2-yl]carbamate (1.00 eq, 30 mg, 0.0345 mmol) in DCM (2 mL) was added TFA (377 eq, 1.0 mL, 13.0 mmol) at 20 °C The resulting mixture was stirred at 20 °C for 2 h. The reaction was monitored by LC-MS. When the starting material was consumed. The mixture was concentrated and purified by prep-HPLC to 2-amino-4-[4-[[(6R)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzoselenophene-3-carbonitrile (1.5 mg,0.00192 mmol, 5.57 % yield) as the first peak LCMS: (ES+): m/z 772.1 [M+H]+, ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.27 (s, 1H), 7.99 (s, 1H), 7.52 (s, 1H), 7.26 – 7.18 (m, 1H), 6.97 (t, J = 8.5 Hz, 1H), 5.47 (d, J = 50.8 Hz, 2H), 5.11 (s, 1H), 4.04 – 3.94 (m, 2H), 3.91 – 3.73 (m, 4H), 3.62 (s, 2H), 3.59 – 3.53 (m, 1H), 3.37 (s, 1H), 2.45 (d, J = 28.6 Hz, 2H), 2.20 (dd, J = 13.2, 5.9 Hz, 3H), 2.03 (s, 3H), 1.61 (t, J = 6.3 Hz, 3H).

[0759] and 2-amino-4-[4-[[(6S)-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydro pyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzoselenophene-3-carbonitrile (2.3 mg, 0.00290 mmol, 8.42 % yield) as the second peak LCMS: (ES+): m/z 772.1 [M+H]+, ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.27 (s, 1H), 7.99 (d, J = 6.3 Hz, 1H), 7.52 (s, 1H), 7.25 – 7.18 (m, 1H), 6.97 (t, J = 8.5 Hz, 1H), 5.48 (d, J = 48.5 Hz, 1H), 5.11 (s, 1H), 3.98 (d, J = 6.7 Hz, 2H), 3.78 (d, J = 12.6 Hz, 4H), 3.66 – 3.58 (m, 2H), 3.59 – 3.54 (m, 1H), 3.38 (s, 1H), 2.52 – 2.40 (m, 2H), 2.31 – 2.13 (m, 3H), 2.03 (s, 3H), 1.61 (t, J = 6.3 Hz, 3H).

[0760] Synthetic Example 22: 2-amino-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 438**)



[0761] **Step A**: Preparation of 2,3-bis(chloromethyl): To a solution of 2,3-dimethylpyrazine (1.00 eq, 10.00 g, 92.5 mmol) in CCl_4 (100 mL) was added NCS (2.20 eq, 27.06 g, 203 mmol) and AIBN (0.20 eq, 3.04 g, 18.5 mmol). The mixture was refluxed overnight under N_2. The precipitated solid was removed by filtration and washed with CCl_4. The filtrate was concentrated to dryness under vacuum. The crude was purified by silica gel column chromatography (EtOAc: PE=1:30) to give the 2,3-bis(chloromethyl)pyrazine (7.00 g, 39.5 mmol, 42.76 % yield). LC-MS: (ES+): m/z 177.0 $[M]^+$.

[0762] **Step B**: Preparation of diethyl 5,7-dihydro-6H-cyclopenta [b]pyrazine-6,6-dicarboxylate: To a suspension of NaH (2.20 eq, 2.98 g, 74.5 mmol) in DMF (50 mL) was added Diethyl malonate (1.0 eq, 5.42 g, 33.9 mmol) in DMF at 0 °C. The resulting mixture was stirred at 25 °C for 0.5 h, then 2,3-bis(chloromethyl)pyrazine (1.00 eq, 6 g, 33.9 mmol) in DMF (10 mL) was added to the mixture at 0 °C. The reaction was warmed to 25 °C and stirred for 3 h. When the SM consumed, the mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organics were concentrated and purified by silica gel column (eluting with ethyl acetate/petroleum ether =1/5) to give diethyl 5,7-dihydro-6H-cyclopenta [b]pyrazine-6,6-dicarboxylate (3.7 g, 14.0 mmol, 41.34% yield). LC-MS: (ES+): m/z 265.1 $[M]^+$.

[0763] **Step C**: Preparation of 6,7-dihydro-5H-cyclopenta [b]pyrazine-6-carboxylic acid: Diethyl 5,7-dihydro-6H-cyclopenta[b]pyrazine-6,6-dicarboxylate (1.00 eq, 3.7 g, 14.01 mmol) in cont. HCl (10 mL) was stirred for 16 hrs at 100 °C. The mixture was concentrated to dryness under vacuum, then adjusted pH to 8~9 with saturated $NaHCO_3$ solution and extracted with EtOAc, The organic layer was concentrated and

purified by silica gel column (eluting with 10% MeOH/DCM) to get 6,7-dihydro-5H-cyclopenta [b]pyrazine-6-carboxylic acid (1.7 g, 10.36 mmol, 73.99 % yield). LC-MS: (ES+): m/z 165.1 [M]+.

[0764] Step D: Preparation of tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl)carbamate: To a solution of 6,7-dihydro-5H-cyclopenta[b]pyrazine-6-carboxylic acid (1.00 eq, 1.40 g, 8.53 mmol) in tert-butanol (20 mL) were added DPPA (1.05 eq, 2.46 g, 8.95 mmol) and DIEA (5.00 eq, 5.50 g, 42.6 mmol). The mixture was stirred 90 °C for 4 h. The mixture was concentrated to dryness under vacuum and purified by silica gel column, eluting with 50% EtOAc in petroleum ether to get tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl)carbamate (900 mg, 3.83 mmol, 44.85 % yield). LC-MS: (ES+): m/z 236.2 $[M]^+$.

[0765] Step E: Preparation of tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl)-N-ethyl-carbamate: To a suspension of NaH (2.00 eq, 0.408 g 10.2 mmol) in DMF (10 mL) was added tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl)carbamate (1.00 eq, 1.20 g, 5.10 mmol) at -5 °C under Ar. The mixture was stirred at -5 °C for 0.5 h. To the above mixture was added iodoethane (1.50 eq, 1.193g, 7.65 mmol). The mixture was stirred at -5 °C for 1.5 h. The mixture was quenched with water and extracted with EtOAc. The organic layers were concentrated to dryness under vacuum and purified by silica gel column, eluting with 40% EtOAc in petroleum ether to get tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl)-N-ethyl-carbamate (1.00 g, 3.80 mmol, 74.46 % yield). LC-MS: (ES+): m/z 264.2 $[M]^+$.

[0766] Step F: Preparation of N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyrazin-6-amine: To a solution of tert-butyl N-(6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl)-N-ethyl-carbamate (1.00 eq, 500 mg, 1.90 mmol) in DCM (5 mL) was added TFA (2.5 mL). The mixture was stirred for 2 hrs at 25 °C. LC-MS showed the starting material was consumed completely. The mixture was concentrated to dryness under vacuum. The residue was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layers were concentrated and purified by silica gel column eluting with 10% MeOH in DCM to give N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyrazin-6-amine (200 mg, 1.22 mmol, 64.54% yield). LC-MS: (ES+): m/z 164.2 $[M]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.30 (s, 2H), 3.81 - 3.69 (m, 1H), 3.37 - 3.32 (m, 2H), 2.96 - 2.91 (m, 2H), 2.78 - 2.72 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H).

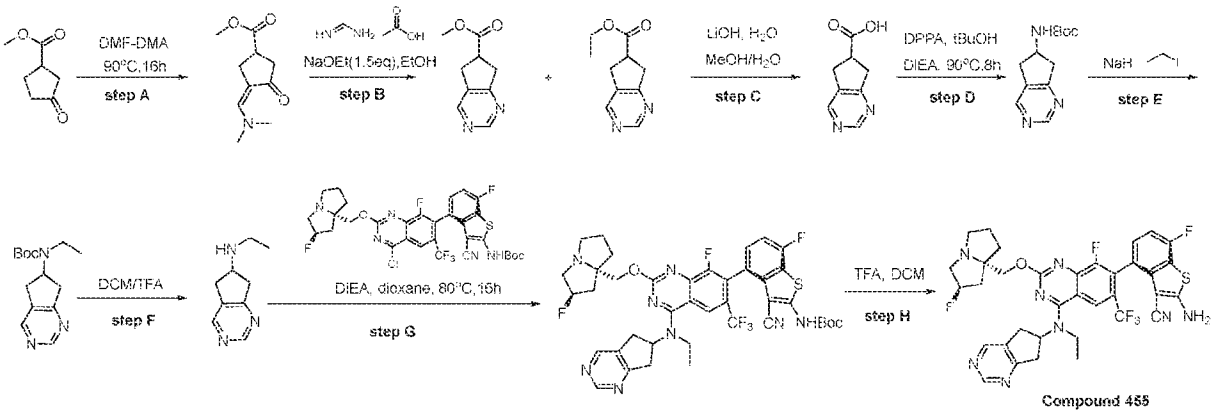
[0767] Step G: Preparation of tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate: To a solution of tert-butyl N-[3-cyano-7-fluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzothiophen-2-yl]carbamate (1.00 eq, 80 mg, 0.113 mmol) in DCM (2 mL) was added SO_2Cl_2 (5.00 eq, 76 mg, 0.564 mmol) at 0 °C. The mixture was stirred for 1.5 h at 0 °C. The mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layers were dried with Na_2SO_4 and

concentrated to give tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (80 mg crude, 0.115 mmol, 101.67 % yield). LCMS: (ES+): m/z 698.3.

[0768] Step H: Preparation of tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazo lin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate: To a solution of N-ethyl-6,7-dihydro-5H-cyclopenta[b]pyrazin-6-amine (2.00 eq, 25 mg, 0.155 mmol) in 1,4-Dioxane (1 mL) were added tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzo thiophen-2-yl]carbamate (1.00 eq, 54 mg, 0.0774 mmol) and DIEA (5.00 eq, 39 mg, 0.387 mmol), the mixture was stirred for 4 h at 75 °C. The mixture was concentrated and purified by prep-TLC eluting with 10% MeOH in DCM to give tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazo lin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (25 mg, 0.0303 mmol, 39.18% yield). LC-MS: (ES+): m/z 825.4 $[M]^+$.

[0769] Step I: Preparation of 2-amino-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile: To a solution of tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quina zolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 40 mg, 0.0485 mmol) in DCM (2 mL) was added TFA (1.0 mL). The mixture was stirred for 2 hrs at 25 °C. TLC (DCM:MeOH = 8:1) showed the starting material was consumed completely. The mixture was concentrated to dryness under vacuum and purified by prep-HPLC to give product 2-amino-4-[4-[6,7-dihydro-5H-cyclopenta[b]pyrazin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (13 mg, 0.0172 mmol, 35.57% yield) as light yellow solid. LC-MS: (ES+): m/z 725.4 $[M]^+$. ^{1}H NMR (400 MHz, CD_3OD): δ 8.42 (s, 2H), 8.28 (s, 1H), 7.28 - 7.21 (m, 1H), 7.03 (t, J = 8.7 Hz, 1H), 5.48 (d, J = 51.2 Hz, 1H), 5.08 - 5.00 (m, 1H), 4.21 - 4.18 (m, 1H), 4.07 - 3.95 (m, 3H), 3.90 - 3.54 (m, 7H), 3.40 - 3.33 (m, 1H), 2.48 - 2.41 (m, 2H), 2.29 - 2.15 (m, 2H), 2.04 - 1.85 (m, 2H), 1.64 (t, J = 7.2 Hz, 3H).

[0770] Synthetic Example 23: 2-amino-4-[4-[6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 455**)



[0771] **Step A**: Preparation of methyl (3Z)-3-(dimethylaminomethylene)-4-oxo-cyclopentanecarboxylate: A mixture of methyl 3-oxocyclopentanecarboxylate (1.00 eq, 10.00 g, 70.3 mmol) in N, N-dimethylformamide dimethyl acetal (1.30 eq, 12 mL, 91.5 mmol) was stirred at 90 °C for 16h. TLC showed no SM remained. The reaction was concentrated to dryness. The crude was purified by silica gel chromatography to afford methyl (3Z)-3-(dimethylaminomethylene)-4-oxo-cyclopentanecarboxylate (10.00 g,50.7 mmol, 72.07 % yield).

[0772] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 3.71 – 3.69 (m, 3H), 3.20 – 3.05 (m, 7H), 2.60– 1.99 (m, 4H).

[0773] **Step B**: Preparation of ethyl 6,7-dihydro-5H-cyclopenta[d]pyrimidine-6-carboxylate: NaH (1.50 eq, 3.29 g, 60.8 mmol) was added into Ethanol (80 mL) at 0 °C. After stirring for 1h at 0 °C then the methyl (3Z)-3-(dimethylaminomethylene)-4-oxo-cyclopentanecarboxylate (1.00 eq, 8.00 g, 40.6 mmol) and acetic acid;methanimidamide (3.00 eq, 12.67 g, 122 mmol) was added subsequently and stirred at 90 °C for 16h. TLC showed no SM remained. The reaction was concentrated to dryness and taken up in EtOAc (150 mL). The organics were washed with 2 x 150 mL water, 1 x 150 mL brine. The organics were separated and dried ($MgSO_4$) before concentration to dryness. The crude was purified by silica gel chromatography (PE: EA=1:1, Rf= 0.3) to afford ethyl 6,7-dihydro-5H-cyclopenta[d]pyrimidine-6-carboxylate (4.40 g,22.9 mmol, 56.43 % yield). LCMS m/z $[M+1]^+$ cacld. 193.09; found 193.2.

[0774] **Step C**: Preparation of 6,7-dihydro-5H-cyclopenta[d]pyrimidine-6-carboxylic acid: To a mixture of ethyl 6,7-dihydro-5H-cyclopenta[d]pyrimidine-6-carboxylate (1.00 eq, 3.20 g, 16.6 mmol) in Methanol (20 mL) /Water (20 mL) was added LiOH (1.50 eq, 599 mg, 25.0 mmol) at 0 °C. The reaction was stirred at 25 °C for 2h. TLC showed no SM remained. The reaction was adjusted pH=2 and concentrated to dryness to afford crude 6,7-dihydro-5H-cyclopenta[d]pyrimidine-6-carboxylic acid (2.30 g,14.0 mmol, 84.16 % yield). LCMS m/z $[M+1]^+$ cacld. 165.06; found 165.1.

[0775] **Step D**: Preparation of tert-butyl N-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl)carbamate: To a solution of 6,7-dihydro-5H-cyclopenta[d]pyrimidine-6-carboxylic acid (1.00 eq, 2500 mg, 15.2 mmol), N,N-Diisopropylethylamine (5.00 eq, 13 mL, 76.1 mmol) in tert-butanol (20 mL) was added DPPA (1.30 eq, 5444 mg, 19.8 mmol). The mixture was stirred at 90 °C for 8 hours. TLC showed no SM remained. The reaction was concentrated to dryness and the residue was taken up in EA (100 mL) and the organics washed with 2 x 100 mL saturated $NaHCO_3$ solution then 1 x 100 mL saturated brine solution. The organics were then separated and dried (Na_2SO_4) before concentration to dryness. The crude product was purified by column chromatography on silica gel (PE: EA=0:1, Rf=0.5 to give the product tert-butyl N-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl)carbamate (700 mg, 2.98 mmol, 19.54 % yield) . LCMS m/z [M+1] cacld. 236.13; found 236.1.

[0776] **Step E**: Preparation of tert-butyl N-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl)-N-ethyl-carbamate: To a mixture of tert-butyl N-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl)carbamate (1.00 eq, 600 mg, 2.55 mmol) in DMF (15 mL) was added NaH (3.00 eq, 184 mg, 7.65 mmol) at 0 °C. The reaction was stirred at 0 °C for 30min, then iodoethane (1.50 eq, 0.31 mL, 3.83 mmol) was added. The reaction was stirred at 0 °C for 1h. TLC showed no SM remained. The reaction was taken up in EtOAc (30 mL) and the organics washed with 1 x 30 mL water, 1 x 30 mL brine. The organics were separated and dried ($MgSO_4$) before concentration to dryness. The crude was purified by silica gel chromatography (PE: EA=0:1 Rf=0.3) to afford tert-butyl N-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl)-N-ethyl-carbamate (400 mg,1.52 mmol, 59.57 % yield). LCMS m/z $[M+1]^+$ cacld. 264.16; found 264.2.

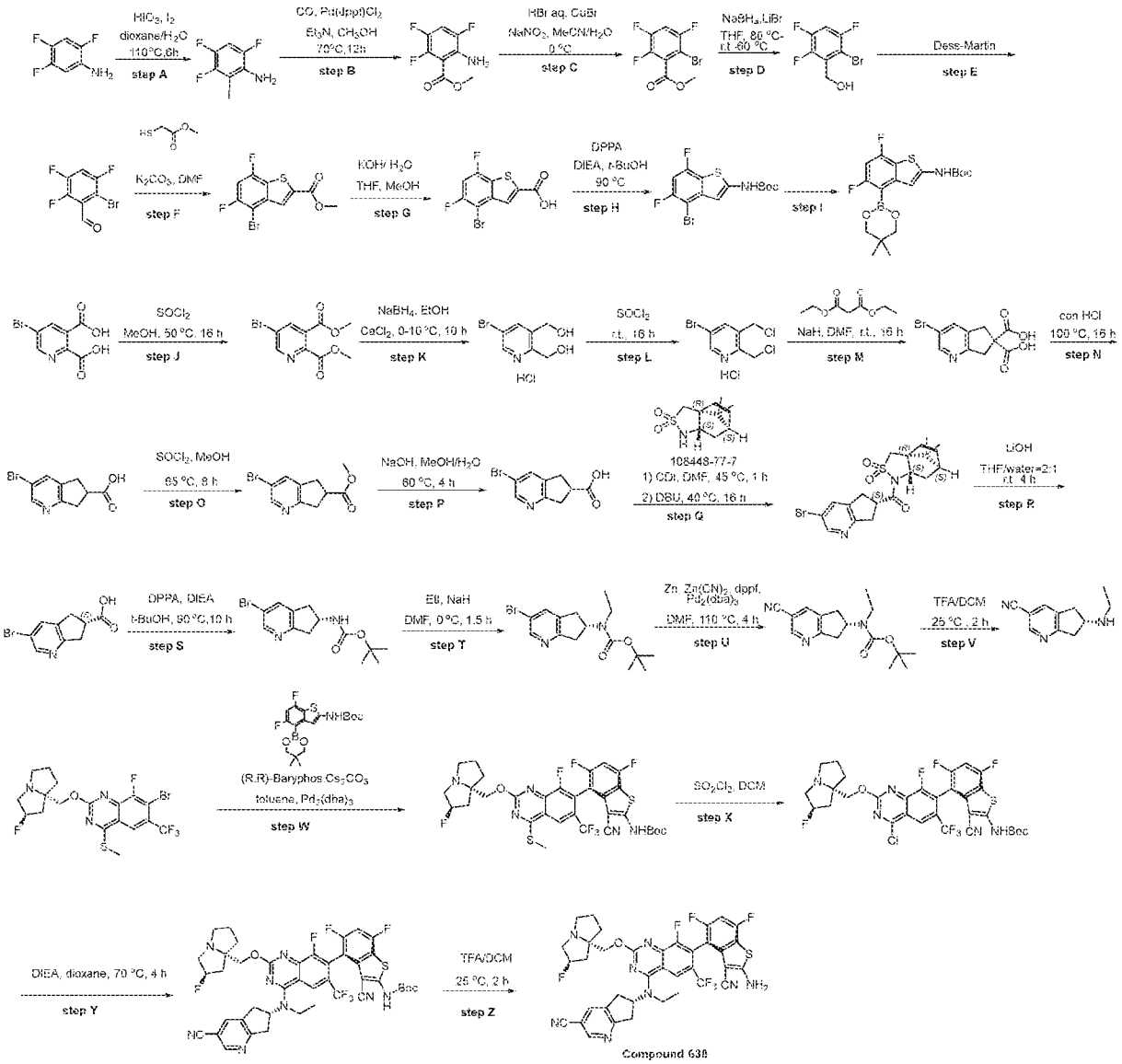
[0777] **Step F**: Preparation of N-ethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-amine: To a mixture of tert-butyl N-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl)-N-ethyl-carbamate (1.00 eq, 100 mg, 0.380 mmol) in DCM (3 mL) was added TFA (34.2 eq, 1.0 mL, 13.0 mmol) at 0 °C. The reaction was stirred at 25 °C for 1h. TLC showed no SM remained. The reaction was concentrated to dryness to afford crude N-ethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-amine (80 mg, 0.490 mmol, 129.07 % yield). LCMS m/z $[M+1]^+$ cacld. 164.11; found 164.2.

[0778] **Step G**: Preparation of tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate: To a solution of N-ethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-amine (1.50 eq, 25 mg, 0.150 mmol) in 1,4-dioxane (5 mL) was added DIEA (5.00 eq, 51 mg, 0.501 mmol) at 0 °C. After stirring at r.t for 30min, then tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 70 mg, 0.100

mmol) was added. The reaction was stirred at 80 °C for 16h. TLC showed no SM remained. The reaction was taken up in EtOAc (20 mL) and the organics washed with 2 x 20 mL water, 1 x 20 mL brine. The organics were separated and dried ($MgSO_4$) before concentration to dryness. The crude was purified by Perp-TLC(DCM:MeOH=18:1 Rf=0.2) to afford tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (50 mg,0.0606 mmol, 60.45 % yield). LCMS m/z $[M+1]^+$ cacld. 825.27; found 825.4.

[0779] Step H: Preparation of 2-amino-4-[4-[6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile: To a solution of tert-butyl N-[3-cyano-4-[4-[6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 50 mg, 0.0606 mmol) in DCM (3 mL) was added TFA (214 eq, 1.0 mL, 13.0 mmol) at 0 °C. The reaction was stirred at 25 °C for 1h. TLC showed no starting material remained. The reaction was concentrated to dryness. The crude was then purified by Perp-HPLC to afford 2-amino-4-[4-[6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-yl(ethyl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (7.4 mg, 0.0102 mmol, 16.87 % yield). ^1H NMR (400 MHz, CD_3OD) δ 9.00 (s, 1H), 8.61 (s, 1H), 8.30 (s, 1H), 7.22 – 7.19 (m, 1H), 7.01 (t, J = 8.9 Hz, 1H), 5.89 – 5.85 (m, 1H), 5.35 (d, J = 52.8 Hz, 1H), 4.79 – 4.59 (m, 1H), 4.12 – 3.79 (m, 4H), 3.38 – 3.36 (m, 3H), 3.32 – 3.12 (m, 2H), 2.76 – 1.87 (m, 8H), 1.58 – 1.55 (m, 3H). LCMS m/z $[M+1]^+$ cacld. 725.22; found 725.3.

[0780] Synthetic Example 24: (6S)-6-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2 -fluoro-1,2,3,5,6,7-hexahydro pyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]-6,7-dihydro-5H-cyclopenta[b] pyridine-3-carbonitrile (**Compound 638**)



[0781] **Step A**: Preparation of 3,4,6-trifluoro-2-iodo-aniline: a solution of 2,4,5-trifluoroaniline (1.00 eq, 4.00 g, 27.2 mmol) in 1,4-Dioxane (80 mL) in the flask, Iodine (0.500 eq, 3.45 g, 13.6 mmol) was added to the obtained solution, then iodic acid (1.05 eq, 5.02 g, 28.6 mmol) in Water (20mL) was added to the obtained solution for several batches, then the mixture was stirred at 110 °C for 5hrs with the protection of N_2. The reaction was completed monitored by TLC (PE:EA=10:1, Rf=0.6. PE:EA=3:1, Rf=0.95). The reaction was quenched by the addition of $Na_2S_2O_3$ solution, and the residue was concentrated to dryness and the residue was taken up in EtOAc (100 mL). The organics were washed with 2 x 100 mL water, then 2 x 100 mL saturated brine solution. The organics were separated and dried over Na_2SO_4 before concentrating to dryness. Then the crude was purified by flash column chromatography eluting with 10%

EA in hexane. The desired fractions were concentrated to dryness in vacuo to give 3,4,6-trifluoro-2-iodo-aniline (2.01 g, 6.33 mmol, 23.29 % yield) as a yellow oil. LCMS m/z $[M+1]^+$ cacld. 273.92; found 273.9.

[0782] Step B: Preparation of methyl 2-amino-3,5,6-trifluoro-benzoate: A solution of 3,4,6-trifluoro-2-iodo-aniline (1.00 eq, 23.00 g, 84.3 mmol) in Methanol (200 mL) in the flask, [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.100 eq, 6.16 g, 8.43 mmol) and Triethylamine (5.00 eq, 73 mL, 421 mmol) were added to the obtained solution, the mixture was heated to 70 °C for another 12hrs with the pressure of carbon monoxide (10.0 eq, 24.45 g, 843 mmol) . The reaction was completed monitored by TLC (PE:EA=10:1, Rf=0.4). The reaction was filtered by celite and the filtrate was concentrated to dryness and the residue was taken up in EtOAc (200 ml). The crude was then purified by flash column chromatography eluting 15% EA in PE. The desired fractions were concentrated to dryness in vacuo, methyl 2-amino-3,5,6-trifluoro-benzoate (19.30 g, 68.7 mmol, 81.52 % yield) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.01 (m, 1H), 5.50 (br, 2H), 3.94 (s, 3H).

[0783] Step C: Preparation of methyl 2-bromo-3,5,6-trifluoro-benzoate: A solution of methyl 2-amino-3,5,6-trifluoro-benzoate (1.00 eq, 10.00 g, 48.7 mmol) in Acetonitrile (100 mL) and Water (10 mL) in the flask bathed in the ice, CuBr (2.00 eq, 13.99 g, 97.5 mmol) and Hydrobromic acid (2.00 eq, 5.3 mL, 97.5 mmol) were added to the obtained solution, then $NaNO_2$ (2.00 eq, 6.73 g, 97.5 mmol) was added to the obtained mixture slowly, then the mixture was stirred at 0 °C for 2hrs with the protection of N_2. The reaction was completed monitored by TLC (PE:EA=1:1, Rf=0.9). The reaction was quenched by $NaHCO_3$ solution, the residue was taken up in EtOAc(200 mL). The organics were washed with 2 x 200 mL water then 2 x 200 mL brine solution. The organics were then separated and dried (Na_2SO_4) before concentration to dryness. Then the crude was purified by flash column chromatography eluting with 5%EA in hexane. The desired fractions were concentrated to dryness in vacuo, methyl 2-bromo-3,5,6-trifluoro-benzoate (6.10 g,22.7 mmol, 46.51 % yield) was obtained as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.08 (m, 1H), 4.00 (s, 3H).

[0784] Step D: Preparation of (2-bromo-3,5,6-trifluoro-phenyl)methanol: A solution of methyl 2-bromo-3,5,6-trifluoro-benzoate (1.00 eq, 5.00 g, 18.6 mmol) in THF (25 mL) in the flask bathed in the ice, $LiBH_4$ (1.80 eq, 0.73 g, 33.5 mmol) was added to the obtained solution, then the reaction was stirred at 25 °C for another 4hrs and then the ice bath was removed before the reaction was stirred at room temperature. The reaction was completed monitored by TLC (PE:EA=10:1, Rf=0.6). The reaction was quenched by water and the reaction was concentrated to dryness and the residue was taken up in EtOAc(30 mL) and the organics washed with 2 x 30 mL water then 2 x 30 mL brine solution. The organics were then separated and dried ($MgSO_4$) before concentration to dryness. The crude was then purified by flash column

chromatography eluting with 15% MeOH in DCM. The desired fractions were concentrated to dryness in vacuo, (2-bromo-3,5,6-trifluoro-phenyl)methanol (3.60 g,14.9 mmol, 80.37 % yield) was obtained as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 – 6.89 (m, 1H), 3.99 (s, 2H), 3.94 (s, 1H).

[0785] Step E: Preparation of 2-bromo-3,5,6-trifluoro-benzaldehyde: A solution of (2-bromo-3,5,6-trifluoro-phenyl)methanol (1.00 eq, 300 mg, 1.24 mmol) in DCM (10 mL) in the flask bathed in the ice, Dess-Martin Periodinane (1.30 eq, 686 mg, 1.62 mmol) was added to the obtained solution, then the reaction was stirred at 25 °C for another 2hrs. The reaction was completed monitored by TLC (PE:EA=10:1, Rf=0.7). The reaction was quenched by $NaHCO_3$ water solution, and the reaction was concentrated to dryness and the residue was taken up in EtOAc (30 mL) and the organics washed with 2 x 30 ml water then 2 x 30 mL saturated brine solution. The organics were then separated and dried ($MgSO_4$) before concentrating to dryness. The crude was then purified by flash column chromatography eluting 15% EA in PE. The desired fractions were concentrated to dryness in vacuo, 2-bromo-3,5,6-trifluoro-benzaldehyde (278 mg,1.16 mmol, 93.45 % yield) was obtained as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22(s, 1H), 7.24 – 7.20 (m, 1H).

[0786] Step F: Preparation of methyl 4-bromo-5,7-difluoro-benzothiophene-2-carboxylate: A solution of 2-bromo-3,5,6-trifluoro-benzaldehyde (1.00 eq, 12.00 g, 50.2 mmol) in DMF (300 mL) in the flask bathed in the ice to -10 °C , K_2CO_3 (3.00 eq, 20.79 g, 151 mmol) was added to the obtained solution, then methyl 2-sulfanylacetate (1.05 eq, 5.60 g, 52.7 mmol) in DMF (300 mL) was added to the obtained solution drop wise within 1hr, the reaction was stirred at -10 °C for another 2hrs. The reaction was completed monitored by TLC (PE:EA=10:1, Rf=0.7). The reaction was quenched by water and the reaction was and the residue was taken up in EtOAc (300 mL) and the organics washed with 2 x 200 mL water then 2 x 200 mL saturated brine solution. The organics were then separated and dried (Na_2SO_4) before concentration to dryness. The crude was then purified by flash column chromatography eluting 15% EA in PE. The desired fractions were concentrated to dryness in vacuo, methyl 4-bromo-5,7-difluoro-benzothiophene-2-carboxylate (11.30 g,36.8 mmol, 73.28 % yield) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.06 (t, J = 12.0 Hz, 1H), 73.98 (s, 3H).

[0787] Step G: Preparation of 4-bromo-5,7-difluorobenzo[b]thiophene-2-carboxylic acid: A solution of methyl 4-bromo-5,7-difluoro-benzothiophene-2-carboxylate (1.00 eq, 1.00 g, 3.26 mmol) in Methanol (10 mL),THF (10mL) and Water (5 mL) in the flask, KOH (5.00 eq, 912 mg, 16.3 mmol) was added to the obtained solution drop wise, then the reaction was stirred at room temperature for 2hrs with the protection of N_2.The reaction was completed monitored by TLC (PE:EA=1:1, Rf=0.1). The reaction was quenched by addition of NH_4Cl solution, the residue was taken up in EtOAc (30 mL) and the organics washed with 2

x 30 mL water then 2 x 30 mL saturated brine solution. The organics were then separated and dried (Na_2SO_4) before concentration to dryness. The desired fractions were concentrated to dryness in vacuo, 4-bromo-5,7-difluoro-benzothiophene-2-carboxylic acid (0.90 g,3.07 mmol, 94.31 % yield) was obtained as a yellow solid for next step directly. LCMS m/z $[M+1]^+$ cacld. 292.90; found 291.0 [M-1]

[0788] Step H: Preparation of tert-butyl (4-bromo-5,7-difluorobenzo[b]thiophen-2-yl)carbamate: A solution of 4-bromo-5,7-difluoro-benzothiophene-2-carboxylic acid (1.00 eq, 10.00 g, 34.1 mmol) in tert-butanol (100 mL) in the flask, [azido(phenoxy)phosphoryl]oxybenzene (1.10 eq, 10329 mg, 37.5 mmol) and DIEA (3.00 eq, 10358 mg, 102 mmol) were added to the obtained solution, the reaction mixture was heated to 95 °C for another 5hrs with the protection of N_2. The reaction was completed monitored by TLC (PE:EA=3:1, Rf=0.5). The reaction was concentrated to dryness and the residue was taken up in EtOAc (1 mL). The crude was then purified by flash column chromatography eluting 30% EtOAc in hexane. The desired fractions were concentrated to dryness in vacuo, tert-butyl N-(4-bromo-5,7-difluoro-benzothiophen-2-yl)carbamate (9.90 g,27.2 mmol, 79.67% yield) was obtained as a yellow oil. LCMS m/z $[M+1]^+$ cacld. 363.91; found 362.0[M-1].

[0789] Step I: Preparation of tert-butyl (4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,7-difluorobenzo[b]thiophen-2-yl)carbamate: A solution of tert-butyl N-(4-bromo-5,7-difluoro-benzothiophen-2-yl)carbamate (1.00 eq, 8.00 g, 22.0 mmol) in 1,4-Dioxane (200 mL) in the flask, 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (1.20 eq, 5.95 g, 26.4 mmol) , $Pd_2(dba)_3$ (0.0200 eq, 0.40 g, 0.439 mmol), Tricyclohexyl phosphine (0.04 eq, 0.25 g, 0.879 mmol) and AcOK (3.00 eq, 6.47 g, 65.9 mmol) were added to the obtained solution, the mixture was heated to 95 °C for another 4 hrs with the protection of argon. The reaction was completed monitored by TLC (PE:EA=5:1, Rf=0.4). The reaction was filtered by celite and the filtrate was concentrated to dryness and the residue was taken up in EtOAc (100 mL). The crude was then purified by flash column chromatography eluting 25% EA in hexane. The desired fractions were concentrated to dryness in vacuo, the crude target tert-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,7-difluoro-benzothiophen-2-yl]carbamate (5.30 g,13.3 mmol, 60.74 % yield) was obtained as a yellow solid. LCMS m/z $[M+1]^+$ cacld. 398.13; found 328.1 [M- dimethylpentane+1].

[0790] Step J: Preparation of dimethyl 5-bromopyridine-2,3-dicarboxylate: To a solution of 5-bromopyridine-2,3-dicarboxylic acid (1.00 eq, 100 g, 406 mmol) in Methanol (1000 mL) was added $SOCl_2$ (5.00 eq, 144 mL, 2032 mmol). The mixture was stirred at 50 °C for 16 h. The reaction was monitored by LC-MS. When the SM consumed. The mixture was concentrated and partitioned between EtOAc / sat $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, concentrated. The crude was slurried in

10%EA/PE for 16 h, filtered to give dimethyl 5-bromopyridine-2,3-dicarboxylate (107 g, 390 mmol, 96.05 % yield) as white solid. LC-MS: (ES+): m/z 276.0 $[M+H]^+$.

[0791] **Step K**: Preparation of [5-bromo-2-(hydroxymethyl)-3-pyridyl]methanol: To a solution of dimethyl 5-bromopyridine-2,3-dicarboxylate (1.00 eq, 102 g, 370 mmol) in Ethanol (70 mL) was added $NaBH_4$ (3.00 eq, 43 g, 1115.2 mmol) at 0 °C under Ar. To the above solution was added $CaCl_2$ (0.880 eq, 36.4 g, 327.4 mmol) in Ethanol (40 mL) dropwised. The resulting suspension was stirred at 25 °C for 16 h. The mixture was quenched with water, filtered. The filtrate was concentrated, and diluted with Ethanol (70 mL). The mixture was filtered. The filtrate was acidified with 4N HCl/dioxane. The resulting suspension was filtered. The filter cake was dried under vacuum to give [5-bromo-2-(hydroxymethyl)-3-pyridyl]methanol (50 g, 197.7 mmol, 53.42 % yield) as HCl salt (white solid) LC-MS: (ES+): m/z 220.0 $[M+H]^+$.

[0792] **Step L**: Preparation of 5-bromo-2,3-bis(chloromethyl)pyridine: $SOCl_2$ (3.34 eq, 32 mL, 449 mmol) was cooled to 0 °C under Ar and then treated with [5-bromo-2-(hydroxymethyl)-3-pyridyl]methanol (1.00 eq, 32 g, 126 mmol). The mixture was warmed to 25 °C and stirred for 16 h. LC-MS showed BBH-091-Bs-2 was consumed. The mixture was diluted with MTBE (300 mL). The resulting suspension was filtered. The filter cake was collected and then dried under vacuum to give 5-bromo-2,3-bis(chloromethyl)pyridine (25.9 g, 89.7 mmol, 71.15 % yield) as white solid.

[0793] LC-MS ESI (+) m/z 255.2 $[M+H]^+$, t(R)= 3.84 min.

[0794] **Step M**: Preparation of diethyl 3-bromo-5,7-dihydrocyclopenta[b]pyridine-6,6-dicarboxylate: To a suspension of NaH (3.20 eq, 8.3 g, 208 mmol) in DMF (200 mL) was added diethyl malonate (1.20 eq, 12 mL, 77.9 mmol) in DMF (200 mL) at 0°C under Ar. The resulting mixture was stirred at 25 °C for 30 min before treated with 5-bromo-2,3-bis(chloromethyl)pyridine (1.00 eq, 18.8 g, 64.9 mmol) in DMF at 0 °C. The reaction was then warmed to 25 °C and stirred for 16 h. The reaction was monitored by LC-MS. When the sm was consumed, the mixture was quenched with water and concentrated to dryness to give crude diethyl 3-bromo-5,7-dihydrocyclopenta[b]pyridine-6,6-dicarboxylate (25 g,73.1 mmol, 112.58 % yield) as brown solid.

[0795] LC-MS ESI (+) m/z 343.2 $[M+H]^+$.

[0796] **Step N**: Preparation of 3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid: To a solution of crude 3-bromo-5,7-dihydrocyclopenta[b]pyridine-6,6-dicarboxylic acid (1.00 eq, 34.7 g, 121.3 mmol) in HCl (1.00 eq, 49 g, 121.3 mmol) was stirred at 100°C for 16 h. The reaction was monitored by LC-MS, then the BBH-091-Bs-4 was consumed volatiles were removed by concentration under reduced pressure. NaOH (2 N) was added (pH~10), washed with EtOAc (300 mL). Then HCl (4 N) was added

(pH~5) to water phase, The product is filtered off and recrystallized from water, The filtrate was concentrated to dryness to give crude 3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (6.7 g, 27.6 mmol, 22.54 % yield) as brown solid. LCMS: (ES+): m/z 243.2 $[M+H]^+$.

[0797] **Step O**: Preparation of methyl 3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate: To a solution of 3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (1.00 eq, 6.7 g, 27.6 mmol) in Methanol (50 mL) was added $SOCl_2$ (5.00 eq, 1.6 g, 138 mmol) and stirred at 65 °C for 10 h. LC-MS showed the completion of the reaction. The mixture was cooled to room temperature. Then sat $NaHCO_3$ (30 mL) was added to quench the reaction, and the product was extracted with EtOAc (20 mL x 3). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, PE/EtOAc = 3/1) to give the product methyl 3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate (5.2 g, 20.3 mmol, 73.55 % yield) as a yellow oil. LC-MS ESI (+) m/z 257.2 $[M+H]^+$.

[0798] **Step P**: Preparation of 3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid: To a solution of methyl 3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylate (1.00 eq, 5.2 g, 20.3 mmol) in methanol (20 mL) and water (10 mL) was added NaOH (1.50 eq, 1.2 g, 30.5 mmol). The resulting mixture was stirred at 60 °C for 4 h. The mixture was concentrated and diluted with water (20 mL). The aqueous phase was acidified with HCl (1 N) to pH~6, The resulting suspension was filtered, the filter cake was dried under vacuum to give 3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (3.9 g, 16.2 mmol, 79.80 % yield) as a white solid. LC-MS: (ES+): m/z 243.2 $[M+H]^+$.

[0799] **Step Q**: Preparation of [(6S)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-[(1R,5S,7S)-10,10-dimethyl-3,3-dioxo-3λ6-thia-4-azatricyclo[5.2.1.01,5]decan-4-yl]methanone: To a solution of crude 3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (1.00 eq, 3.4 g, 14.0 mmol) in DMF (34 mL) was added CDI (1.10 eq, 2.5 g, 15.4 mmol). The mixture was stirred at 45 °C for 1 h, then treated with (1R)-(+)-2,10-CAMPHORSULTAM (1.00 eq, 3.0 g, 14.0 mmol) and DBU (1.00 eq, 2.1 g, 14.0 mmol). The mixture was then stirred at 40 °C for 18 h. Then water (50 mL) was added to quench the reaction. The mixture was extracted with EtOAc (40 mL x 3), dried over anhydrous Na_2SO_4, filtered, the filtrate was concentrated and purified by column chromatography (silica gel, PE/EtOAc = 3/1) to afford [(6S)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-[(1R,5S,7S)-10,10-dimethyl-3,3-dioxo-3λ6-thia-4-azatricyclo[5.2.1.01,5]decan-4-yl]methanone (1.9 g, 4.3 mmol, 30.71 % yield) as a white solid. LC-MS: (ES+): m/z 440.2 $[M+H]^+$.

[0800] **Step R**: Preparation of (6S)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid: To a solution of [(6S)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-[(1R,5S,7S)-10,10-dimethyl-3,3-

dioxo-3λ6-thia-4-azatricyclo[5.2.1.01,5]decan-4-yl]methanone (1.00 eq, 1.9 g, 4.3 mmol) in THF (20 mL), Water (10 mL) was added LiOH (3.00 eq, 310 mg, 12.9 mmol). The resulting mixture was stirred at 20 °C for 4 h. The mixture was diluted with water (40 mL), extracted with EtOAc (30 mL x 3). The aqueous phase was acidified with HCl (1N) to PH~6, The suspension was filtered, the filter cake was dried under vacuum to give (6S)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (705 mg, 2.9 mmol, 67.72 % yield) as white solid.LCMS: (ES+): m/z 243.0 $[M+H]^+$.

[0801] Step S: Preparation of tert-butyl (S)-(3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate: A mixture of (6S)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (1.00 eq, 651 mg, 2.69 mmol), DIEA (3.00 eq, 817 mg, 8.07 mmol), DPPA (1.20 eq, 888 mg, 3.23 mmol) in tert-butanol (6.5 mL) was stirred at 90 °C for 10 h under Ar. The mixture was concentrated and purified by Prep-TLC (PE: EtOAc = 1:1) to give tert-butyl (S)-(3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (365 mg, 1.17 mmol, 44.15 % yield) as light yellow solid. LC-MS ESI (+) m/z 314.2 $[M+H]^+$.

[0802] Step T: Preparation of tert-butyl (S)-(3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate: To a solution of tert-butyl (S)-(3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (1.00 eq, 363 mg, 1.15 mmol) in DMF (5 mL) at 0 °C under Ar was added NaH (4.00 eq, 184 mg, 4.60 mmol). The mixture was stirred at 0 °C for 30 min before treated with EtI (4.00 eq, 594 mg, 4.60 mmol). The mixture was then stirred at 0 °C for 1.5 h. The reaction was quenched with water, partitioned between EtOAc (30 mL)/water (10 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated and purified by prep-TLC (PE:EA = 3:1) to give tert-butyl N-ethyl-N-[(6S)-3-bromo-6,7-dihydro-5H-cyclopenta [b]pyridin-6-yl]carbamate (319 mg, 0.93 mmol, 80.86 % yield) as light yellow oil. LCMS: (ES+): m/z 342.1 $[M+H]^+$.

[0803] Step U: Preparation of tert-butyl (S)-(3-cyano-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)(ethyl)carbamate: To a solution of tert-butyl N-ethyl-N-[(6S)-3-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]carbamate (1.00 eq, 105 mg, 0.308 mmol) in DMF (3 mL) were added DPPF (0.500 eq, 85 mg, 0.154 mmol), $Pd_2(dba)_3$ (0.500 eq, 141 mg, 0.154 mmol), Zn (4.00 eq, 81 mg, 1.232 mmol) and $Zn(CN)_2$ (6.00 eq, 217 mg, 1.848 mmol). The mixture was bubbled with Ar for 1~2 min and sealed. The reaction was allowed to slowly warm to 110 °C for 4 h. The mixture was poured into water (15 mL), and the product was extracted with EtOAc (10 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and purified by prep-TLC (PE/EtOAc = 1/1) to give tert-butyl (S)-(3-cyano-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)(ethyl)carbamate (74 mg, 0.258 mmol, 83.6 % yield) as a light solid. LC-MS ESI (+) m/z 288.2 $[M+H]^+$.

[0804] **Step V**: Preparation of (S)-6-(ethylamino)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile: To a solution of tert-butyl (S)-(3-cyano-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)(ethyl)carbamate (1.00 eq, 74 mg, 0.258 mmol) in DCM (3 mL) was added TFA (178 eq, 1.5 mL, 45.92 mmol) and stirred at 25 °C for 2 h. TLC showed no BBH-091-Dz-1 was remained. The reaction was concentrated to give crude (S)-6-(ethylamino)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (86 mg, 0.459 mmol, 178 % yield) as a yellow solid. LC-MS ESI (+) m/z 188.2 $[M+H]^+$, t(R)=0.48 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36-9.10 (m, 1H), 8.74 (s, 1H), 7.98 (s, 1H), 4.34 – 4.05 (m, 1H), 3.67 (d, J = 4.8 Hz, 2H), 3.53 (d, J = 4.8 Hz, 2H), 3.32 – 3.10 (m, 2H), 1.43 (t, J = 6.8 Hz, 3H).

[0805] **Step W**: Preparation of tert-butyl ((R)-3-cyano-5,7-difluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate: To a mixture of 7-bromo-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)-6-(trifluoromethyl)quinazoline (1.00 eq, 1.0 g, 2.01 mmol), tert-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,7-difluoro-benzothiophen-2-yl]carbamate (2.00 eq, 1.594 g, 4.01 mmol) in toluene (15 mL) were added cesium carbonate (2.00 eq, 2.18 g, 6.69 mmol), (R,R)-BaryPhos (0.400 eq, 702 mg, 1.34 mmol) and $Pd_2(dba)_3$ (0.200 eq, 1.308 g, 4.01 mmol). The mixture was stirred at 50 °C for 16 hrs under Ar. TLC showed no SM remained. The mixture was extracted with EtOAc (50 mL) and water, then washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by Prep-TLC(PE:EA=1:1 Rf=0.3) to give tert-butyl ((R)-3-cyano-5,7-difluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(methylthio)-6-(trifluoromethyl)quinazolin-7-yl)benzo[b]thiophen-2-yl)carbamate (0.8 g, 1.14 mmol, 56.73 % yield). LC-MS 703.3. >99% diastereoselectivity (d.e.) of the product was determined in the Chiral HPLC condition: Chiralpak AD-H, 4.6x250 mm, 5 μm; column temp: 35 °C; mobile phase: A, 0.1% TEA in IPA and B, n-hexane; flow rate: 0.8 mL/min; 25 minutes run time.

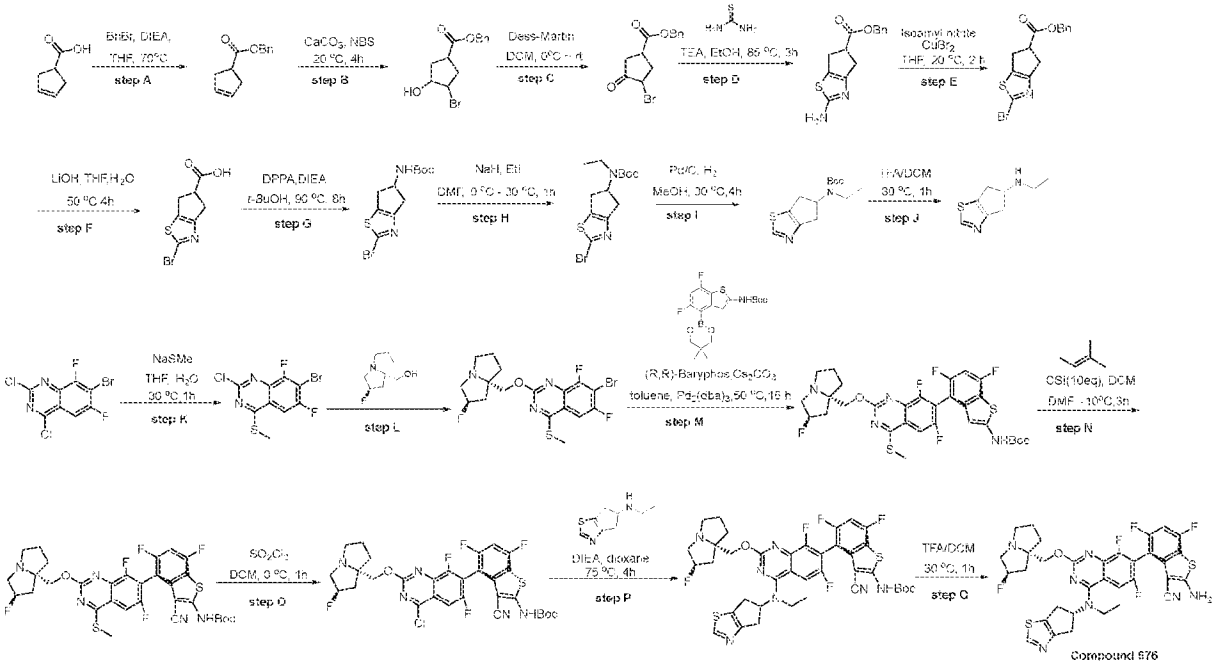
[0806] **Step X**: Preparation of tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-5,7-difluoro-benzothiophen-2-yl]carbamate: To a solution of tert-butyl N-[3-cyano-5,7-difluoro-4-[8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-methylsulfanyl-6-(trifluoromethyl)quinazolin-7-yl]benzothiophen-2-yl]carbamate (1.00 eq, 31 mg, 0.0426 mmol) in DCM (3 mL) was added sulfuryl chloride (4.00 eq, 23 mg, 0.170 mmol) at 0 °C. The mixture was then stirred for 2.5 h at 0 °C. LC-MS showed no starting material remaining. Then saturated aqueous $NaHCO_3$ (4 mL) was added to quench the reaction. The product was extracted with DCM. The combined organics were rinsed with brine, dried over anhydrous Na_2SO_4, filtered. The filtrate was concentrated to give the crude tert-butyl

N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-5,7-difluoro-benzothiophen-2-yl]carbamate (33 mg, 0.0461 mmol, 108.18% yield) as yellow solid. LCMS ESI (+) m/z 716.2 $[M+H]^+$.

[0807] Step Y: Preparation of tert-butyl N-[3-cyano-4-[4-[[(6S)-3-cyano-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexa hydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carba mate: To a solution of crude tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-5,7-difluoro-benzothiophen-2-yl]carbamate (1.00 eq, 33 mg, 0.0461 mmol), N,N-Diisopropylethylamine (5.00 eq, 0.040 mL, 0.230 mmol) and (S)-6-(ethylamino)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (2.67 eq, 23 mg, 0.123 mmol) in 1,4-Dioxane (2 mL) was stirred at 70 °C for 4 h. LC-MS showed no tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-5,7-difluoro-benzothiophen-2-yl]carbamate was remained. The mixture was concentrated and purified by Pre-TLC (DCM/MeOH=15/1) to give the crude tert-butyl N-[3-cyano-4-[4-[[(6S)-3-cyano-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexa hydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carba mate (13 mg, 0.0150 mmol, 32.54 % yield) as a yellow oil. LCMS ESI (+) m/z 867.3 $[M+H]^+$.

[0808] Step Z: Preparation of (6S)-6-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2 -fluoro-1,2,3,5,6,7-hexahydro pyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]-6,7-dihydro-5H-cyclopenta[b] pyridine-3-carbonitrile: To a solution of crude tert-butyl N-[3-cyano-4-[4-[[(6S)-3-cyano-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl]-ethyl-amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexa hydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carba mate (1.00 eq, 13 mg, 0.015 mmol) in DCM (2 mL) was added TFA (866 eq, 1.0 mL, 13.0 mmol) and stirred at 25 °C for 2 h. LC-MS showed it was completed. The reaction mixture was filtered by diatomite, concentrated and purified by Pre-HPLC to give (6S)-6-[[7-(2-amino-3-cyano-5,7-difluoro-benzothiophen-4-yl)-8-fluoro-2-[[(2R,8S)-2 -fluoro-1,2,3,5,6,7-hexahydro pyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-4-yl]-ethyl-amino]-6,7-dihydro-5H-cyclopenta[b] pyridine-3-carbonitrile (4.84 mg, 0.0058 mmol, 38.45 % yield) as a white solid. LCMS ESI (+) m/z 767.2 $[M+H]^+$ ^1H NMR (400 MHz, CD_3OD) δ 8.78 (s, 1H), 8.30 (s, 1H), 8.07 (s, 1H), 6.98 (t, J = 9.6 Hz, 1H), 5.50 (d, J = 52.0 Hz, 1H), 5.20 - 5.06 (m, 1H), 4.37 - 4.12 (m, 2H), 4.01 - 3.89 (m, 2H), 3.89 - 3.71 (m, 4H), 3.65 - 3.47 (m, 3H), 2.56 - 2.39 (m, 2H), 2.32 - 2.16 (m, 2H), 2.11 - 1.86 (m, 3H), 1.59 (t, J = 6.8 Hz, 3H).

[0809] Synthetic Example 25: 2-amino-4-[4-[[(5R)-5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl]-ethyl-amino]-6,8-difluoro-2-[[(2R,8S) -2- fluoro-1,2,3, 5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothiophene-3-carbonitrile (**Compound 676**)



[0810] Step A: Preparation of benzyl cyclopent-3-ene-1-carboxylate: To a solution of cyclopent-3-ene-1-carboxylic acid (1.00 eq, 30.00 g, 268 mmol) in THF (300 mL) were added DIEA (4.00 eq, 177 mL, 1070 mmol) and benzyl bromide (2.00 eq, 64 mL, 535 mmol). After stirring at 70 °C for 4 h, the reaction was finished based by TLC (PE: EtOAc= 10:1, Rf=0.6). The mixture extracted with EtOAc (100 mL x 2). The combined organics were concentrated to dryness under vacuum. The residue was purified quickly on silica gel chromatography (eluting with 2% EtOAc in Petroleum ether) to give benzyl cyclopent-3-ene-1-carboxylate (48.45 g, 240 mmol, 89.54 % yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 5.66 (s, 2H), 5.14 (s, 2H), 3.18 (dd, J = 12.5, 5.2 Hz, 1H), 2.73 – 2.63 (m, 4H).

[0811] Step B: Preparation of benzyl 3-bromo-4-hydroxy-cyclopentanecarboxylate: A solution of benzyl cyclopent-3-ene-1-carboxylate (1.00 eq, 47.00 g, 232 mmol) in acetonitrile (450 mL) was treated with $CaCO_3$ (2.00 eq, 46.52 g, 465 mmol) in water (150 mL). The mixture was cooled to 0 °C and a solution of 2-bromocyclopentane-1,3-dione (2.00 eq, 82.26 g, 465 mmol) in acetonitrile (450 mL) was added slowly. The mixture was stirred at room temperature for 4 hours, filtered and concentrated under vacuum. Water was then added, and the product was extracted 3 times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting orange solid was taken up in dichloromethane. The solid is filtered, rinsed with dichloromethane

and the filtrate was concentrated under vacuum to afford benzyl 3-bromo-4-hydroxy-cyclopentanecarboxylate (52.00 g, 174 mmol, 74.80 % yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 5H), 5.15 (s, 2H), 4.37 (s, 1H), 4.25 – 4.21 (m, 1H), 3.27 – 3.20 (m, 1H), 2.86 (d, J = 6.2 Hz, 1H), 2.72 – 2.56 (m, 2H), 2.46 – 2.38 (m, 1H), 1.97 (d, J = 14.5 Hz, 1H).

[0812] Step C: Preparation of benzyl 3-bromo-4-oxo-cyclopentanecarboxylate: A solution of benzyl 3-bromo-4-hydroxy-cyclopentanecarboxylate (1.00 eq, 46.00 g, 154 mmol) in DCM (1200 mL) was cooled to 0 °C and treated with a solution of Dess-Martin Periodinane (2.00 eq, 130.43 g, 308 mmol) in DCM (1200 mL). The mixture was stirred at room temperature for 48 hours. The reaction was complete detected by LC-MS (DCM:MeOH=15:1, Rf=0.3). The reaction was concentrated to dryness and the residue was taken up in EtOAc (30 mL). The organics was washed with sat. $NaHCO_3$ (2 x 20 mL), 20 mL saturated brine. The organics were separated and dried over Na_2SO_4, concentrated to dryness. The crude was purified by column chromatography on silica gel (eluting with 25 % EtOAc in petroleum ether) to give the product benzyl 3-bromo-4-oxo-cyclopentanecarboxylate (35.00 g, 118 mmol, 76.60 % yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 5H), 5.18 (s, 2H), 4.35 (t, J = 4.6 Hz, 1H), 3.55 – 3.46 (m, 1H), 2.75 – 2.67 (m, 1H), 2.58 – 2.49 (m, 3H).

[0813] Step D: Preparation of benzyl 2-amino-5,6-dihydro-4H-cyclopenta[d]thiazole-5-carboxylate: A solution of benzyl 3-bromo-4-oxo-cyclopentanecarboxylate (1.00 eq, 5.00 g, 16.8 mmol) in Ethanol (60 mL) were added thiourea (1.30 eq, 1665 mg, 21.9 mmol) and TEA (2.00 eq, 3405 mg, 33.7 mmol).The mixture was stirred for 2 h at 85 °C. The reaction was complete detected by LC-MS. The reaction was concentrated to dryness and the residue was taken up in EtOAc (30 mL). The organics were washed with 5 x 30 mL water, then 80 mL brine. The organics were separated and dried over Na_2SO_4 before concentrating to dryness. The mixture was purified quickly on silica gel chromatography eluting with DCM:MeOH=10:1(Rf=0.2), to give product benzyl 2-amino-5,6-dihydro-4H-cyclopenta[d]thiazole-5-carboxylate (3.2 g, 11.7 mmol, 69.2 % yield) as a yellow solid. LC-MS: 275.1.

[0814] Step E: Preparation of benzyl 2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazole-5-carboxylate: To a mixture of benzyl 2-amino-5,6-dihydro-4H-cyclopenta[d]thiazole-5-carboxylate (1.00 eq, 1.40 g, 5.10 mmol) and $CuBr_2$ (1.10 eq, 1254 mg, 5.61 mmol) in CH_3CN (30 mL) was added tert-butyl nitrite (1.50 eq, 789 mg, 7.65 mmol) at 20 °C. Then the mixture was stirred at 20 °C for 1 h. The reaction was complete detected by LC-MS. After cooling to rt, the mixture was quenched with *aq.* ammonium chloride and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified on silica gel chromatography, eluting with 50% EtOAc in Petroleum ether (Rf=0.3), to give benzyl 2-

bromo-5,6-dihydro-4H-cyclopenta[d]thiazole-5-carboxylate (704 mg,2.08 mmol, 40.79 % yield) as a yellow solid. LC-MS: 338.0.

[0815] Step F: Preparation of 2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazole-5-carboxylic acid: Benzyl 2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazole-5-carboxylate (1.00 eq, 1.20 g, 3.55 mmol) was dissolved in THF (15 mL), followed by the addition of LiOH (1.20 eq, 102 mg, 4.26 mmol) solution in water (7 mL) .The mixture was stirred for 4 h at 50 °C. The reaction was complete detected by TLC. Water was added and the solution was acidified with hydrochloric acid (1 M) to pH=3. The mixture was extracted with EtOAc （10 mL x 3） . The combined organics were concentrated to dryness under vacuum to afford crude 2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazole-5-carboxylic acid (838.2 mg, 3.38 mmol, 98.25 % yield) as a purple oil. LC-MS: 204.1.

[0816] Step G: Preparation of tert-butyl N-(2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl)carbamate: To a solution of 2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazole-5-carboxylic acid (1.00 eq, 0.90 g, 3.63 mmol) in tert-butanol (20 mL) were added DPPA (1.20 eq, 1197 mg, 4.35 mmol) and N,N-Diisopropylethylamine (3.00 eq, 1.9 mL, 10.9 mmol) . The mixture was stirred for 8 h at 90 °C. The reaction was complete detected by TLC. The organics were removed under vacuum and the residue was purified by Prep-TLC (DCM/MeOH = 20/1, Rf-0.5) to give tert-butyl N-(2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl)carbamate (530 mg,1.66 mmol, 45.77 % yield) as yellow oil. LC-MS: 318.0.

[0817] Step H: Preparation of tert-butyl N-(2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl)-N-ethyl-carbamate: To a solution of tert-butyl N-(2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl)carbamate (1.00 eq, 550 mg, 1.72 mmol) in DMF (6 mL) was added NaH (4.00 eq, 0.38 mL, 6.89 mmol) at 0 °C . After stirring for 30 min at 0 °C. Iodoethane (1.50 eq, 0.21 mL, 2.58 mmol) was added. The mixture was stirred for 1 h at r.t. The reaction was complete detected by TLC (PE:EtOAc=4:1, Rf=0.4). The mixture extracted with EtOAc (20 mL x3), the combined organics were concentrated under vacuum. The mixture was purified on silica gel chromatography, eluting with 25% EtOAc in Petroleum ether to give the product tert-butyl N-(2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl)-N-ethyl-carbamate (310 mg,0.893 mmol, 51.81 % yield) as yellow oil. LC-MS: 349.1

[0818] Step I: Preparation of tert-butyl N-(5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl)-N-ethyl-carbamate: To a solution of tert-butyl N-(2-bromo-5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl)-N-ethyl-carbamate (1.00 eq, 300 mg, 0.777 mmol) was dissolved in methanol (20 mL). was added Pd/C (1.77 eq, 146 mg, 1.37 mmol). The mixture was degassed with H_2 and repeated three times. The mixture was stirred for 2 h at 35 °C and then reacted completely by LC-MS. After filtered on Celite, the filtrated was concentrated to dry under vacuum. The crude was purified by prep-TLC (DCM:MeOH=20:1, Rf=0.5), to give product tert-

butyl N-(5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl)-N-ethyl-carbamate (165 mg,0.615 mmol, 79.08 % yield) as yellow oil. LC-MS: 269.1.

[0819] Step J: Preparation of N-ethyl-5,6-dihydro-4H-cyclopenta [d]thiazol-5-amine: to a solution of tert-butyl N-(5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl)-N-ethyl-carbamate (1.00 eq, 160 mg, 0.596 mmol) in DCM (5 mL) was added TFA (43.5 eq, 2.0 mL, 26.0 mmol). The mixture was stirred for 2 h at 20 °C. The reaction was complete detected by TLC (DCM:MeOH=10:1, Rf=0.5). The reaction was concentrated to dryness in vacuo to afford crude N-ethyl-5,6-dihydro-4H-cyclopenta [d]thiazol-5-amine (100 mg, 0.594 mmol, 99.69 % yield) as yellow oil. LC-MS:169.1.

[0820] Step K: Preparation of 7-bromo-2-chloro-6,8-difluoro-4-methylsulfanyl-quinazoline: To a mixture of 7-bromo-2,4-dichloro-6,8-difluoro-quinazoline (1.00 eq, 3.40 g, 10.8 mmol) in THF (30 mL) was added NaSMe (1.05 eq, 3.99 g, 11.4 mmol) dropwise at 0 °C under Ar for 2 h. The mixture was extracted with EtOAc (50 mL x 3) , washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was trituration with PE, filtered to give 7-bromo-2-chloro-6,8-difluoro-4-methylsulfanyl-quinazoline (3.26 g, 10.0 mmol, 92.45 % yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 7.9, 2.1 Hz, 1H), 2.76 (s, 3H)

[0821] Step L: Preparation of 7-bromo-6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazoline: To a mixture of 7-bromo-2-chloro-6,8-difluoro-4-methylsulfanyl-quinazoline (1.00 eq, 3.00 g, 7.37 mmol), [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (3.00 eq, 3521 mg, 22.1 mmol) in 1,4-Dioxane (30 mL) was added DIEA (5.00 eq, 4764 mg, 36.9 mmol). The resulting mixture was stirred at 100 °C for 16 h under Ar. LC-MS showed the starting material was consumed completely. The reaction was concentrated to give a crude produce. The crude was purified by flash column chromatography (eluting with 30% EtOAc in petroleum ether). The desired fractions were concentrated to dryness in vacuo to give 7-bromo-6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazoline (2.00 g, 4.02 mmol, 54.47 % yield) as a yellow solid. LC-MS: 448.0.

[0822] Step M: Preparation of tert-butyl N-[4-[6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexa hydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carbamate: To a mixture of 7-bromo-6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydro pyrrolizin-8-yl]methoxy]quinazoline (1.00 eq, 1.50 g, 3.35 mmol), tert-butyl N-[4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,7-difluoro-benzothiophen-2-yl]carbamate (2.00 eq, 2.66 g, 6.69 mmol) in toluene (30mL) were added cesium carbonate (2.00 eq, 2.18 g, 6.69 mmol), (R,R)-BaryPhos (0.400 eq, 702 mg, 1.34 mmol) and $Pd_2(dba)_3$ (0.200 eq, 613 mg, 0.669 mmol). The mixture was stirred at

45 °C for 16 hrs under Ar. TLC showed no SM remained. The mixture was extracted with EtOAc (20 mL), washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by Prep-TLC(PE:EA=1:1 Rf=0.3) to give tert-butyl N-[4-[6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexa hydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carbamate (2.00 g, 3.06 mmol, 91.58 % yield) as a yellow solid. LC-MS 653.2.

[0823] Step N: Preparation of tert-butyl N-[3-cyano-4-[6,8-difluoro-4-methyl sulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carbamate: To a solution of tert-butyl N-[4-[6,8-difluoro-4-methylsulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carbamate (1.00 eq, 700 mg, 1.07 mmol) in anhydrous DCM (5 mL) was added chlorosulfonyl isocyanate (6.00 eq, 0.56 mL, 6.43 mmol) in anhydrous DCM (0.1 mL) at -10 °C under Ar. The reaction was stirred at -10 °C for 2.5 h. Then 2-methyl-2-butene (6.00 eq, 0.68 mL, 6.43 mmol) in anhydrous DCM (0.1 mL) and DMF (5 mL) was added to the mixture subsequently. The mixture was stirred at -10 °C for 1 h. The mixture was dissolved in 50 mL of ethyl acetate, and quenched with saturated $NaHCO_3$ solution (20 mL), washed with brine (30 mL×2). The organic phase was dried over anhydrous Na_2SO_4. The crude was purified by flash column chromatography eluting 30% EtOAc in petroleum ether. The desired fractions were concentrated to dryness in vacuo to give tert-butyl N-[3-cyano-4-[6,8-difluoro-4-methyl sulfanyl-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carbamate (580 mg, 0.856 mmol, 79.80 % yield). LCMS: 678.2.

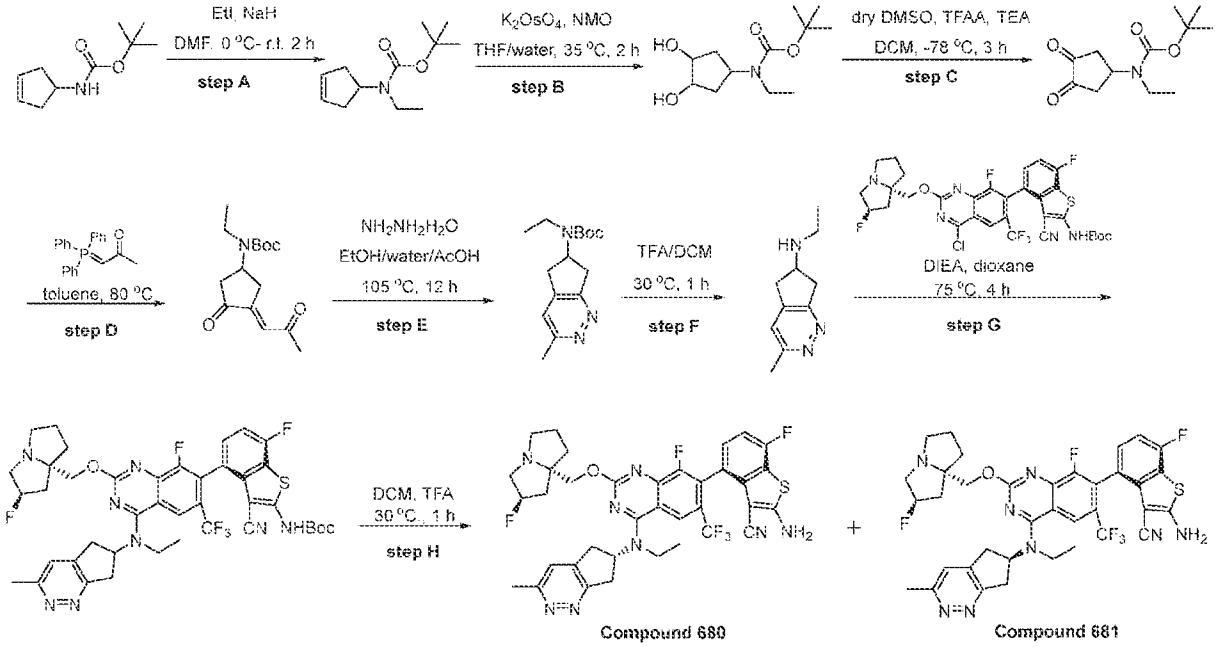
[0824] Step O: Preparation of tert-butyl N-[4-[4-chloro-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-3-cyano-5,7-difluoro-benzothiophen-2-yl]carbamate: To a solution of tert-butyl N-[3-cyano-4-[6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydro pyrrolizin-8-yl]methoxy]-4-methylsulfanyl-quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carbamate (1.00 eq, 100 mg, 0.148 mmol) in DCM (2 mL) was added SO_2Cl_2 (4.00 eq, 80 mg, 0.590 mmol) in DCM at 0 °C under Ar. After stirring at 0 °C for 1 h, the reaction was complete detected by TLC (PE:EtOAc=1:1, Rf = 05). It was quenched with *aq.*$NaHCO_3$ at 0 °C, taken up with DCM. The organic phase was dried over Na_2SO_4, concentrated to give tert-butyl N-[4-[4-chloro-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-3-cyano-5,7-difluoro-benzothiophen-2-yl]carbamate (95 mg,0.143 mmol, 96.66 % yield) as light yellow solid. LCMS:666.1.

[0825] Step P: Preparation of tert-butyl N-[3-cyano-4-[4-[5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl(ethyl)amino]-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothio phen-2-yl]carbamate: A mixture of N-ethyl-5,6-

dihydro-4H-cyclopenta[d]thiazol-5-amine (2.00 eq, 25 mg, 0.150 mmol) tert-butyl N-[4-[4-chloro-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quina zolin-7-yl]-3-cyano-5,7-difluoro-benzothiophen-2-yl]carbamate (1.00 eq, 50 mg, 0.0751 mmol) DIEA (5.00 eq, 0.067 mL, 0.375 mmol) in 1,4-dioxane (2 mL) was stirred at 75 °C for 4 h under Ar. The reaction was monitored by LC-MS. When the starting material consumed, the mixture was partitioned between EA/water. The organic phase was dried over Na_2SO_4, filtered, concentrated and purified by prep-TLC(10%MeOH/DCM, Rf=0.5) to give tert-butyl N-[3-cyano-4-[4-[5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl(ethyl)amino]-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothio phen-2-yl]carbamate (34 mg,0.0426 mmol, 56.77 % yield) as light yellow solid. LC-MS: 798.2.

[0826] Step Q: Preparation of 2-amino-4-[4-[[(5R)-5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl]-ethyl-amino]-6,8-difluoro-2-[[(2R,8S) -2- fluoro-1,2,3, 5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothiophene-3-carbonitrile: A solution of tert-butyl N-[3-cyano-4-[4-[5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl(ethyl)amino]-6,8-difluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothiophen-2-yl]carbamate (1.00 eq, 34 mg, 0.0426 mmol) in DCM (2 mL) was added TFA (305 eq, 1.0 mL, 13.0 mmol). The mixture was stirred for 2 h at r.t. The reaction was complete detected by LC-MS. The solvent was removed under vacuum. The residue was purified by Prep-HPLC to afford 2-amino-4-[4-[[(5R)-5,6-dihydro-4H-cyclopenta[d]thiazol-5-yl]-ethyl-amino]-6,8-difluoro-2-[[(2R,8S) -2- fluoro-1,2,3, 5,6,7-hexahydropyrrolizin-8-yl]methoxy]quinazolin-7-yl]-5,7-difluoro-benzothiophene-3-carbonitrile (12 mg,0.0162 mmol, 38.01 % yield) as a yellow solid. LCMS m/z[M+1]$^+$ cacld. 698.17; found 698.1. ^{1}H NMR (400 MHz, CD_3OD) δ 8.98 (s, 1H), 7.68 (d, J = 10.2 Hz, 1H), 7.01 (t, J = 9.7 Hz, 1H), 5.52 (d, J = 51.8 Hz, 1H), 5.37 – 5.30 (m, 1H), 4.18 – 4.11 (m, 1H), 4.04 – 3.80 (m, 6H), 3.62 – 3.36 (m, 5H), 2.56 – 2.42 (m, 2H), 2.31 – 2.19 (m, 2H), 2.09 – 1.96 (m, 2H), 1.61 – 1.51 (m, 3H).

[0827] Synthetic Example 26: 2-amino-4-[4-[ethyl-[(6S)-3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 680**) and 2-amino-4-[4-[ethyl-[(6R)-3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3, 5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 681**)



[0828] **Step A**: Preparation of tert-butyl N-cyclopent-3-en-1-yl-N-ethyl-carbamate: To a solution of tert-butyl N-cyclopent-3-en-1-ylcarbamate (1.00 eq, 5.00 g, 27.3 mmol) in DMF (40 mL) was added sodium hydride (4.00 eq, 4.37 g, 109 mmol) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min before treated with EtI (4.00 eq, 23 mL, 109 mmol). The mixture was warmed to 25 °C and stirred for 2 h before poured into *aq.* NH_4Cl. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude product tert-butyl N-cyclopent-3-en-1-yl-N-ethyl-carbamate (7.20 g,34.1 mmol, 124.88 % yield) as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 – 5.53 (m, 2H), 4.65 (s, 1H), 3.15 (q, J = 6.7 Hz, 2H), 2.58 (dd, J = 14 .8, 9.1 Hz, 2H), 2.35 (dd, J = 14.9, 5.8 Hz, 2H), 1.46 (s, 9H), 1.12 (t, J = 7.0 Hz, 3H).

[0829] **Step B**: Preparation of tert-butyl N-(3,4-dihydroxycyclopentyl)-N-ethyl-carbamate: To a solution of tert-butyl N-cyclopent-3-en-1-yl-N-ethyl-carbamate (1.00 eq, 7.20 g, 34.1 mmol) in THF (70 mL) and water (18 mL) were added K_2OsO4H_2O (0.1000 eq, 1.26 g, 3.41 mmol) and NMO (3.00 eq, 12.01 g, 102 mmol). The resulting mixture was stirred at 20 °C for 2 h. The mixture was diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to give tert-butyl N-(3,4-dihydroxycyclopentyl)-N-ethyl-carbamate (4.40 g,17.9 mmol, 52.64 % yield) as brown oil.

[0830] **Step C**: Preparation of tert-butyl N-(3,4-dioxocyclopentyl)-N-ethyl-carbamate: To a solution of TFAA (3.00 eq, 6.9 mL, 53.8 mmol) in DCM (40mL) at -78 °C under Ar. was added DMSO (3.00 eq, 3.8 mL, 53.8 mmol). The resulting mixture was stirred at -78 °C for 10 min before treated with tert-butyl N-(3,4-dihydroxycyclopentyl)-N-ethyl-carbamate (1.00 eq, 4.40 g, 17.9 mmol) in DCM (20mL). The mixture

was stirred at -78 °C for 2 h before treated with TEA (5.00 eq, 12 mL, 89.7 mmol). The mixture was quenched with *sat.* NH_4Cl, extracted with DCM. The organic phase was concentrated and purified by silica gel column chromatography (eluent with MeOH/DCM = 0 to 10 %) to give tert-butyl N-(3,4-dioxocyclopentyl)-N-ethyl-carbamate (2.10 g, 8.70 mmol, 48.52 % yield) LC-MS: (ES+): m/z 186.1 $[M+H-56]^+$.

[0831] **Step D**: Preparation of tert-butyl N-[(3E)-3-acetonylidene-4-oxo-cyclopentyl]-N-ethyl-carbamate: To a suspension of tert-butyl N-(3,4-dioxocyclopentyl)-N-ethyl-carbamate (1.00 eq, 500 mg, 2.07 mmol) in Toluene (10 mL) was added 1-(triphenyl-λ5-phosphanylidene) propan-2-one (1.50 eq, 990 mg, 3.11 mmol). The mixture was stirred at 80 °C for 16 h. The reaction was monitored by LC-MS and concentrated to dryness. The crude product was purified by prep-TLC (Petroleum ether/ EtOAc =2/1) to give tert-butyl N-[(3E)-3-acetonylidene-4-oxo-cyclopentyl]-N-ethyl-carbamate (182 mg, 0.647 mmol, 31.22 % yield) as white solid. LC-MS: (ES+): m/z 226.2 $[M+H-56]^+$.

[0832] **Step E**: Preparation of tert-butyl N-ethyl-N-(3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl) carbamate: To a suspension of tert-butyl N-[(3E)-3-acetonylidene-4-oxo-cyclopentyl]-N-ethyl-carbamate (1.00 eq, 182 mg, 0.648 mmol) in ethanol (16 mL) were added Water (4 mL), AcOH (4 mL) and $N_2H_4H_2O$ (182 mg). The mixture was stirred at 105 °C for 10 h. The reaction was monitored by LC-MS. The reaction was taken up in EtOAc (50 mL) and the organics washed with water (2 x 30 mL) and *aq.* $NaHCO_3$ (30 mL). The organics were separated and dried (Na_2SO_4) before concentrated to dryness. The crude was purified by prep- TLC to give the product tert-butyl N-ethyl-N-(3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl) carbamate (81 mg, 0.292 mmol, 44 % yield). LC-MS: (ES+): m/z 278.3 [M+H] +.

[0833] **Step F**: Preparation of N-ethyl-3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-amine: To a solution of tert-butyl N-ethyl-N-(3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl) carbamate (1.00 eq, 81 mg, 0.292 mmol) in DCM (2 mL) was added TFA (1 mL). The mixture was stirring at 30 °C for 2 h. TLC (DCM/MeOH= 15:1, Rf=0.5) showed the starting material was consumed completely. The mixture was concentrated to dryness and purified by Prep-TLC to get N-ethyl-3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-amine (45 mg, 0.254 mmol, 87 % yield). LC-MS: (ESI): m/z 178.1 [M+1] +. ^1H NMR (400 MHz, CD_3OD) δ 7.49 (s, 1H), 3.97 - 3.87 (m, 1H), 3.56 – 3.36 (m, 2H), 3.21 - 3.10 (m, 1H), 3.06 – 2.90 (m, 3H), 2.63 (s, 3H), 1.27 - 1.20 (m, 3H).

[0834] **Step G**: Preparation of tert-butyl N-[3-cyano-4-[4-[ethyl-(3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate: A mixture of N-

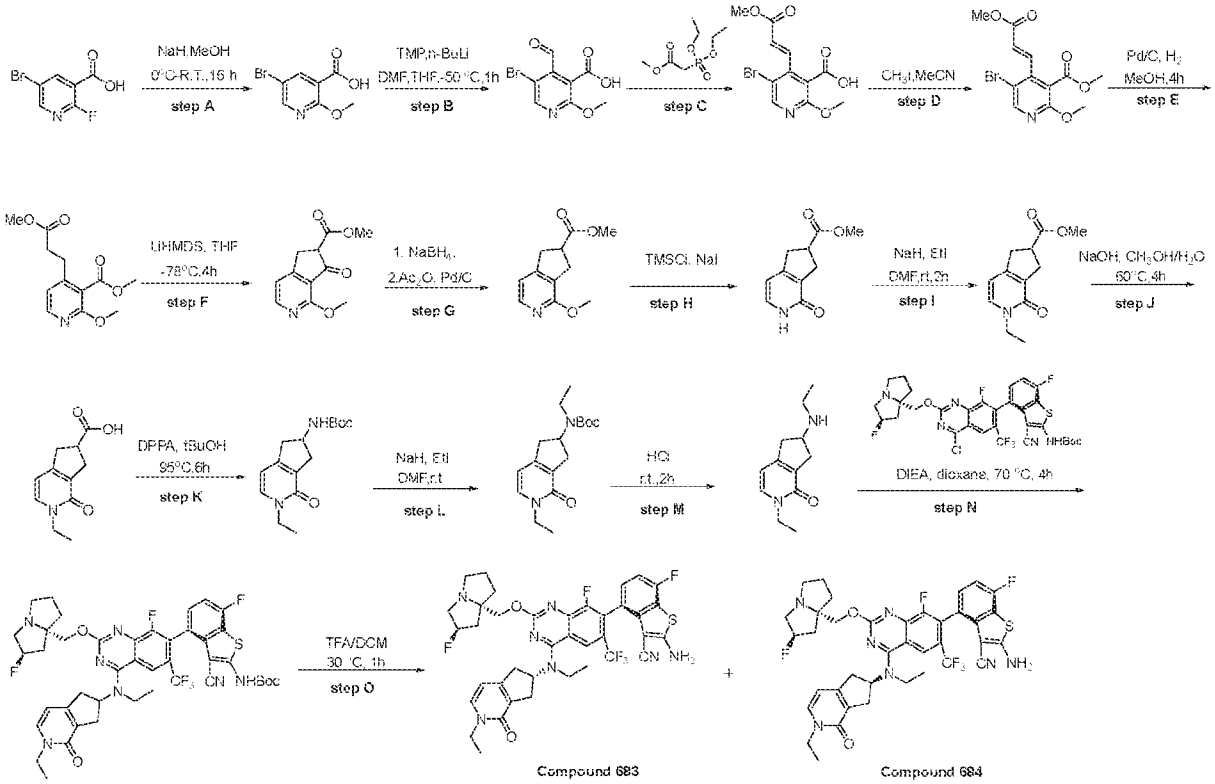
ethyl-3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-amine (3.00 eq, 45 mg, 0.254 mmol) tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 60 mg, 0.084 mmol), DIEA (4.00 eq, 44 mg, 0.339 mmol) in 1,4-Dioxane (3 mL) was stirred at 75 °C for 4 h under Ar. The reaction was monitored by LC-MS. When the SM consumed, the mixture was concentrated and purified by prep-TLC(10%MeOH/DCM, Rf=0.5) to give crude product tert-butyl N-[3-cyano-4-[4-[ethyl-(3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (32 mg,0.038 mmol, 45.46% yield) as light yellow solid. LC-MS: (ESI): m/z 839.2 [M+1] +.

[0835] Step H: Preparation of 2-amino-4-[4-[ethyl-[(6S)-3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 680**) and 2-amino-4-[4-[ethyl-[(6R)-3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3, 5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 681**): To a solution of tert-butyl N-[3-cyano-4-[4-[ethyl-(3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoro methyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 32 mg, 0.0358 mmol) in DCM (2 mL) was added TFA (1.0 mL). The mixture was stirred for 2 h at r.t. The reaction was complete detected by LC- MS. The mixture was concentrated to dryness under vacuum. The residue was purified by prep-HPLC to afford 2-amino-4-[4-[ethyl-[(6S)-3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 680**, 1.4 mg, 0.00176 mmol, 4.62 % yield) as the first peak: LC-MS: (ESI): m/z 739.3 [M+1] +, ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.71 (s, 1H), 7.26 - 7.20 (m, 1H), 7.03 (dd, J = 9.5, 8.4 Hz, 1H), 5.47 (d, J= 51.3 Hz, 1H), 5.05 - 5.00 (m, 1H), 4.20 - 4.15 (m, 1H), 4.34 - 4.29 (m, 1H), 4.01 - 3.96 (m, 2H), 3.82 - 3.60 (m, 7H), 2.75 (s, 3H), 2.47 - 2.42 (m, 1H), 2.28 - 2.17 (m, 3H), 2.10 - 2.01 (m, 2H), 1.89 - 1.84 (m, 1H), 1.67 - 1.61 (m, 3H) and 2-amino-4-[4-[ethyl-[(6R)-3-methyl-6,7-dihydro-5H-cyclopenta[c]pyridazin-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3, 5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 681,** 0.75 mg, 0.00097 mmol, 2.54 % yield) as the second peak: LC-MS: (ESI): m/z 739.3 [M+1] +, ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.61 (s, 1H), 7.26 - 7.19 (m, 1H), 7.02 (d, J = 9.6, 8.8 Hz, 1H),

5.48 (d, J = 51.9 Hz, 1H), 5.03 - 4.98 (m, 1H), 4.19 - 4.14 (m, 1H), 4.05 - 4.00 (m, 1H), 3.99 - 3.95 (m, 1H), 3.84 - 3.62 (m, 8H), 2.72 (s, 3H), 2.42 - 2.40 (m, 1H), 2.24 - 2.16 (m, 3H), 2.10 - 2.01 (m, 2H), 1.90 - 1.84 (m, 1H), 1.68 - 1.60 (m, 3H).

[0836] Synthetic Example 27: 2-amino-4-((S)-4-(ethyl((S)-2-ethyl-1-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[c]pyridin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile(**Compound 683**) and 2-amino-4-((S)-4-(ethyl((R)-2-ethyl-1-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[c]pyridin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile

[0837] (Compound 684)



[0838] Step A: Preparation of 5-bromo-2-methoxy-pyridine-3-carboxylic acid: A solution of 5-bromo-2-fluoro-pyridine-3-carboxylic acid (1.00 eq, 22.80 g, 104 mmol) in methanol (20 mL) at 0 °C was treated with NaH (3.00 eq, 7.46 g, 311 mmol) and vigorously stirred at 0 °C for 16h. During this time, nitrogen was sparged through the solution. The reaction mixture was poured-into 10% citric acid solution inducing precipitation of a white solid. The solid was filtered and rinsed exhaustively with water. Finally, the white solid 5-bromo-2-methoxy-pyridine-3-carboxylic acid (17.00 g, 73.3 mmol, 70.70 % yield) was dried

overnight under high vacuum in the presence of solid NaOH and used without further purification LCMS: (ES^+): m/z 229.9 $[M-1]^+$.

[0839] Step B: Preparation of 5-bromo-4-formyl-2-methoxy-pyridine-3-carboxylic acid: A solution of 2,2,6,6-tetramethylpiperidine (4.00 eq, 29.22 g, 207 mmol) in THF (120 mL) at -50 C was treated with n-butyllithium (4.00 eq, 13.25 g, 207 mmol) and stirred for 5 min. 5-bromo-2-methoxy-pyridine-3-carboxylic acid (1.00 eq, 12.00 g, 51.7 mmol) was added via cannula over 30min as a solution in THF (120 mL) . The resulting mixture stirred for 30 mm at -50 °C. Then DMF (3.00 eq, 12 mL, 155 mmol) was added into the mixture dropwise. After stirring 15 minutes the reaction mixture was quenched by the addition of 40 mL of 10% citiric acid solution (aqueous) and the reaction warmed to room temperature. After stirring for 30 min, excess THF removed by concentration under reduced pressure. The residue-was poured into 120 mL of 3% citric acid (aqueous) and extracted with 3 x 50 mL EtOAc. The combined organics were dried with $MgSO_4$, filtered, and concentrated to dryness. 5-bromo-4-formyl-2-methoxy-pyridine-3-carboxylic acid (7.40 g, 28.5 mmol, 55.02 % yield) was directly used into the next reaction without further purification. LCMS: (ES^+): m/z 259.9.

[0840] Step C: Preparation of (E)-5-bromo-2-methoxy-4-(3-methoxy-3-oxoprop-1-en-1-yl)nicotinic acid: A solution of 5-bromo-4-formyl-2-methoxy-pyridine-3-carboxylic acid (1.00 eq, 8.80 g, 33.8 mmol), chiorolithium (1.00 eq, 1.43 g, 33.8 mmol) and methyl 2-dimethoxyphosphorylacetate (2.00 eq, 12.33 g, 67.7 mmol) in acetonitrile (88 mL) at 25 °C was treated with DBU (3.00 eq, 15 mL, 102 mmol) and stirred at 25 °C for 2 h. Initially, the solution is heterogeneous with the pyridine being insoluble. Upon the addition of the DBU the solution becomes homogeneous and darkens in colour. After 1 h, the reaction appears to be mostly complete. During addition and a precipitate has formed. Volatiles were removed by concentration under reduced pressure. The crude mixture was used in the next step without further purification. LCMS: (ES^+): m/z 315.9 $[M-1]^+$.

[0841] Step D: Preparation of methyl 5-bromo-2-methoxy-4-[(E)-3-methoxy-3-oxo- prop-1-enyl]pyridine-3-carboxylate: The product residue was solubilized with DMF (88 mL) and treated with CH_3I (7.00 eq, 12 mL, 195 mmol). After 2 h, the reaction mixture was poured into 300 mL of water and extracted with 4 x 40 mL Et_2O. The combined organics were rinsed with 20 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using 5-20% EtOAc/hexane to afford methyl 5-bromo-2-methoxy-4-[(E)-3-methoxy-3-oxo- prop-1-enyl]pyridine-3-carboxylate (6.40 g,19.4 mmol, 69.64 % yield). LCMS: (ES^+): m/z 331.1 $[M+1]^+$.

[0842] Step E: Preparation of methyl 2-methoxy-6-(3-methoxy-3-oxo- propyl)benzoate: A solution of methyl 3-bromo-6-methoxy-2-[(E)-3-methoxy-3-oxo-prop-1-enyl] benzoate (1.00 eq, 5800 mg, 17.6

mmol) in methanol (58 mL) was added Pd/C (1.00 eq, 1875 mg, 17.6 mmol). The mixture was stirred at r.t. for 16h under H_2 atmosphere. The reaction was concentrated to dryness. The crude was purified by flash column chromatography eluting 20%EtOAc in PE. The desired fractions were concentrated to dryness in vacuo to give methyl 2-methoxy-6-(3-methoxy-3-oxo- propyl)benzoate (3200 mg, 12.7 mmol, 71.99 %yield). LCMS: (ES^+): m/z 254.1 $[M+1]^+$.

[0843] **Step F**: Preparation of methyl 1-methoxy-7-oxo-5,6-dihydro cyclopenta[c]pyridine-6-carboxylate: A solution of methyl 2-methoxy-4-(3-methoxy-3-oxo-propyl)pyridine-3-carboxylate (1.00 eq, 2800 mg, 11.1 mmol) at -78 °C was treated with 1N LiHMDS in THF (2.00 eq, 3029 mg, 22.1 mmol) by dropwise addition over 30 minutes. Once the addition was completed, LC-MS indicated a small amount of starting material remained so an additional 1 mL of LiHMDS was added and the reaction allowed to stir for another 15 minutes. The reaction mixture was quenched by the addition of 30 mL of saturated aqueous NH_4Cl. THF was removed by concentration under reduced pressure. The reaction mixture diluted with 60 mL of EtOAc and an additional 30 mL of water. A thick precipitate formed that could be eliminated by the addition of 10% citric acid solution. The reaction mixture was extracted with 3 x 30 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The crude was purified by flash column chromatography eluting 20%EtOAc in Isohexane. The desired fractions were concentrated to dryness in vacuo.to give methyl 1-methoxy-7-oxo-5,6-dihydro cyclopenta[c]pyridine-6-carboxylate (1800 mg, 8.14 mmol, 73.60 % yield). LCMS: (ES^+): m/z 222.1 $[M+1]^+$.

[0844] **Step G**: Preparation of methyl 1-methoxy-6,7-dihydro-5H-cyclopenta[c]pyridine-6-carboxylate: A solution of methyl 1-methoxy-7-oxo-5,6-dihydrocyclopenta[c]pyridine-6- carboxylate (1.00 eq, 7500 mg, 33.9 mmol) in methanol (75 mL) was treated with $NaBH_4$ (1.00 eq, 1283 mg, 33.9 mmol) for 2 h. The reaction mixture was quenched by the addition of 30 mL of saturated aqueous NH_4Cl. The reaction mixture was diluted with 60 mL of EtOAc and 30 mL of water. The reaction mixture was extracted with 3 x 30 mL EtOAc. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness.

[0845] A solution of int in methanol (75 mL) was treated with acetic anhydride (1.00 eq, 3.2 mL, 33.9 mmol) and Pd/C (1.00 eq, 3608 mg, 33.9 mmol) and stirred at r.t. for 16 h under H_2. The crude was purified by flash column chromatography eluting 50%EtOAc in PE. The desired fractions were concentrated to dryness in vacuo to give methyl 1-methoxy-6,7-dihydro-5H-cyclopenta[c]pyridine-6-carboxylate (5200 mg, 25.1 mmol, 74.01 % yield). LCMS: (ES^+): m/z 208.2 $[M+1]^+$.

[0846] **Step H**: Preparation of methyl 1-hydroxy-6,7- dihydro-5H-cyclopenta[c]pyridine-6-carboxylate: A solution of methyl 1-methoxy-6,7-dihydro-5H-cyclopenta[c]pyridine-6-carboxylate (1.00 eq, 5400 mg,

26.1 mmol) in acetonitrile (50mL) was added TMSCl (4.00 eq, 13 mL, 104 mmol) and sodium iodide (4.00 eq, 15623 mg, 104 mmol). The mixture was stirred at r.t. for 16h. The reaction was concentrated to dryness and the residue was taken up in EtOAc (20 mL) and the organics washed with 2 x10 mL water then 1 x10 mL saturated brine solution. The organics were separated and dried ($MgSO_4$) before concentration to dryness. The crude was purified by flash column chromatography eluting 10%MeOH in DCM to give methyl 1-hydroxy-6,7- dihydro-5H-cyclopenta[c]pyridine-6-carboxylate (4570 mg,23.7 mmol, 90.78 % yield). LCMS: (ES^+): m/z194.1 $[M+1]^+$.

[0847] **Step I**: Preparation of methyl 2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c] pyridine-6-carboxylate: To a solution of methyl 1-oxo-2,5,6,7-tetrahydrocyclopenta[c]pyridine-6-carboxylate (1.00 eq, 1500 mg, 7.76 mmol) in DMF (15 mL) was added NaH (1.50 eq, 280 mg, 11.6 mmol) and EtI (1.50 eq, 0.94 mL, 11.6 mmol). After the reaction was stirred at rt for 2h, it was concentrated to dryness and the residue was taken up in EtOAc (10 mL) and the organics washed with 2 x 10 mL water then 1 x 10 mL saturated brine solution. The organics were separated and dried ($MgSO_4$) before concentration to dryness. The crude was purified by flash column chromatography eluting 5%MeOH in DCM to give methyl 2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c] pyridine-6-carboxylate (900 mg, 4.07 mmol, 52.39 % yield). LCMS: (ES^+): m/z 222.1 $[M+1]^+$.

[0848] **Step J**: Preparation of 2-ethyl-1-oxo-6,7-dihydro-5H- cyclopenta[c]pyridine-6-carboxylic acid: A solution of methyl 2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c]pyridine-6- carboxylate (1.00 eq, 860 mg, 3.89 mmol) in methanol (10 mL) and water (6 mL) was added NaOH (4.00 eq, 622 mg, 15.5 mmol). After the reaction was stirred at 60 °C for 4h, it was taken up in 2N HCl and EtOAc (20 mL) and the organics washed with 2 x10 mL water then 1 x10 mL saturated brine solution. The organics were concentrated to dryness in vacuo to give 2-ethyl-1-oxo-6,7-dihydro-5H- cyclopenta[c]pyridine-6-carboxylic acid (720 mg,3.47 mmol, 89.39 % yield). LCMS: (ES^+): m/z 206.1 $[M-1]^+$.

[0849] **Step K**: Preparation of tert-butyl N-(2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-6-yl)carbamate: A mixture of 2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c]pyridine-6-carboxylic acid (1.00 eq, 700 mg, 3.38 mmol), DIEA (3.00 eq, 1025 mg, 10.1 mmol), DPPA (1.10 eq, 1022 mg, 3.72 mmol) in tert-butanol (1 mL) under N_2 was stirred at 90 °C for 6 h. The mixture was concentrated and purified by Prep-TLC(PE:EA=4:1) to give tert-butyl N-(2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-6-yl)carbamate (400 mg, 1.44 mmol, 42.54 % yield). LCMS: (ES^+): m/z 278.1 $[M+1]^+$.

[0850] **Step L**: Preparation of tert-butyl N-ethyl-N-(2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-6-yl) carbamate: A solution of tert-butyl N-(2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c] pyridin-6-yl)

carbamate (1.00 eq, 350 mg, 1.26 mmol) in DMF (4 mL) was added NaH (2.00eq, 60 mg, 2.51 mmol) and EtI (1.00 eq, 0.10 mL, 1.26 mmol). The reaction was stirred at r.t. for 2h, The reaction was taken up in EtOAc (10 mL), washed with 2 x10 mL water 10 mL brine. The organics were separated and dried ($MgSO_4$) before concentration to dryness. The crude was purified by flash column chromatography eluting 10%EtOAc in isohexane. The desired fractions were concentrated to dryness in vacuo to give tert-butyl N-ethyl-N-(2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-6-yl) carbamate (179 mg, 0.584 mmol, 46.43 % yield). LCMS: (ES^+): m/z 307.1 $[M+1]^+$.

[0851] Step M: Preparation of 2-ethyl-6-(ethylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-one: A solution of tert-butyl N-ethyl-N-(2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c] pyridine-6-yl)carbamate (1.00 eq, 180 mg, 0.587 mmol) in 1,4-dioxane/HCl(g) (1.00 eq, 0.050 mL, 0.587 mmol) was stirred at r.t. for 2h, The reaction was concentrated to dryness to give 2-ethyl-6-(ethylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-one (94 mg, 0.456 mmol, 77.57 % yield). LCMS: (ES^+): m/z 207.1 $[M-1]^+$.

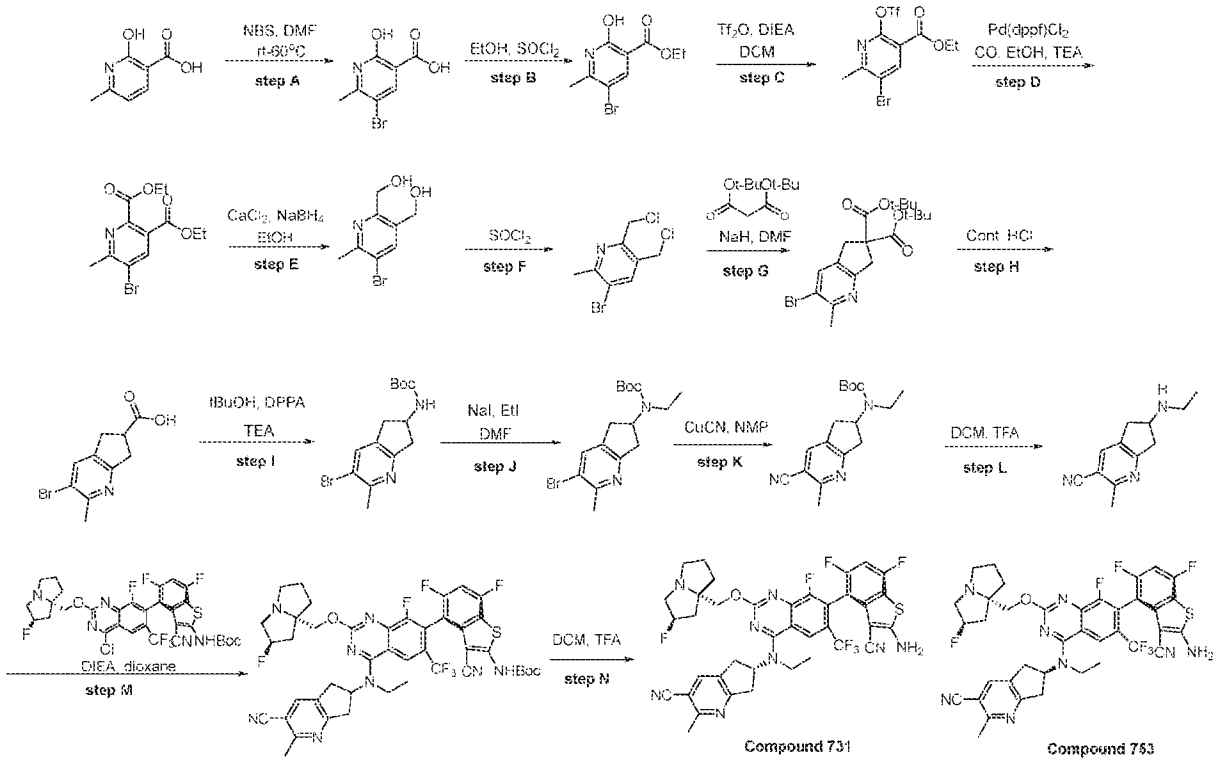
[0852] Step N: Preparation of tert-butyl N-[3-cyano-4-[4-[ethyl-(2-ethyl-1-oxo-6,7- dihydro-5H-cyclopenta[c]pyridin-6-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate: A mixture of 2-ethyl-6-(ethylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-one (5.00 eq, 59 mg, 0.287 mmol) tert-butyl N-[4-[4-chloro-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahy dropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-3-cyano-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 40 mg, 0.0573 mmol), DIEA (2.00 eq, 0.020 mL, 0.115 mmol) in 1,4-dioxane (3 mL) was stirred at 80 °C for 2 h. The reaction was monitored by LC-MS. When the starting material is consumed. The mixture was concentrated and purified by prep-TLC(eluent with 8% MeOH in DCM) to give tert-butyl N-[3-cyano-4-[4-[ethyl-(2-ethyl-1-oxo-6,7- dihydro-5H-cyclopenta[c]pyridin-6-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (20 mg, 0.0230 mmol, 40.22 % yield) as light yellow solid. LCMS: (ES^+): m/z 868.3 $[M+1]^+$.

[0853] Step O: Preparation of 2-amino-4-((S)-4-(ethyl((S)-2-ethyl-1-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[c]pyridin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile(**Compound 683**) and 2-amino-4-((S)-4-(ethyl((R)-2-ethyl-1-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[c]pyridin-6-yl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile

[0854] (**Compound 684**): A solution of tert-butyl N-[3-cyano-4-[4-[ethyl-(2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c] pyridin-6-yl)amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-

yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophen-2-yl]carbamate (1.00 eq, 20 mg, 0.0230 mmol) in DCM (2 mL) was added TFA (324 eq, 0.58 mL, 7.47 mmol). The mixture was stirred for 2h at r.t. The reaction was completed by LC-MS. The mixture was concentrated to dry under vacuum and the residue was purified by Prep-HPLC to afford 2-amino-4-[4-[ethyl -[(6S)-2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 683,** 3.4 mg, 0.00419 mmol, 18.20 % yield) as the first peak: ^{1}H NMR (400 MHz, CD_3OD, ppm): δ 8.37-8.34 (m, 1H), 8.29 (s, 1H), 7.91 (s, 1H), 7.27-7.21 (m, 1H), 7.08-6.97 (m, 1H), 5.59-5.38 (m, 1H), 5.24-5.11 (m, 1H), 4.41-4.13 (m, 2H), 4.04-3.68 (m, 6H), 3.65-3.37 (m, 5H), 2.85-2.71 (m, 2H), 2.55-2.39 (m, 2H), 2.32-1.79 (m, 4H),1.66-1.54 (m, 3H),1.38-1.27 (m, 3H). LCMS: (ES$^+$): m/z 768.2 $[M+1]^+$ and 2-amino-4-[4-[ethyl- [(6R)-2-ethyl-1-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-6-yl]amino]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(trifluoromethyl)quinazolin-7-yl]-7-fluoro-benzothiophene-3-carbonitrile (**Compound 684,** 2.1 mg, 0.00265 mmol, 11.49 % yield) as the second peak: LCMS: (ES$^+$): m/z 768.2; ^{1}H NMR (400 MHz, CD_3OD, ppm): δ 8.37-8.34 (m, 1H), 8.29 (s, 1H), 7.91 (s, 1H), 7.27-7.21 (m, 1H), 7.08-6.97 (m, 1H), 5.59-5.38 (m, 1H), 5.24-5.11 (m, 1H), 4.41-4.13 (m, 2H), 4.04-3.68 (m, 6H), 3.65-3.37 (m, 5H), 2.85-2.71 (m, 2H), 2.55-2.39 (m, 2H), 2.32-1.79 (m, 4H), 1.66-1.54 (m, 3H), 1.38-1.27 (m, 3H).

[0855] Synthetic Example 28: (S)-6-(((R)-7-(2-amino-3-cyano-5,7-difluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (**Compound 731**) and (6R)-(R)-6-(((R)-7-(2-amino-3-cyano-5,7-difluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (**Compound 753**)



[0856] **Step A**: Preparation of 5-bromo-2-hydroxy-6-methyl-pyridine-3-carboxylic acid: 2-hydroxy-6-methylnicotinic acid (1.00 eq, 92976 mg, 522 mmol) was dissolved in DMF (500 mL), to which was added NBS (1.00 eq, 92976 mg, 522 mmol) portion wise. After the addition was completed, the reaction was carried out at 0 °C for 5 hours. After the reaction was completed, the reaction solution was cooled to -5°C and poured into water (500 mL) slowly. The precipitated solid was collected by filtration, washed with water (100 mL×3), and spin-dried to obtain 5-bromo-2-hydroxy-6-methyl-pyridine-3-carboxylic acid (106.0 g, 87.45 % yield). ^{1}H NMR (400MHz, CD_3OD) δ ppm 8.28 (s,1 H), 2.41 (s, 3 H).

[0857] **Step B**: Preparation of ethyl 5-bromo-2-hydroxy-6-methyl-pyridine-3-carboxylate: Bromo-2-hydroxy-6-methyl-pyridine-3-carboxylic acid (1.00 eq, 5200 mg, 22.4 mmol) and DMF (3 drops) were dissolved in DCM (10 mL) placed in an ice-water bath under nitrogen protection, oxalyl chloride (1.30 eq, 2.6 mL, 29.1 mmol) was added dropwise to the above solution, warmed to room temperature and stirred for 2 hours. Ethanol (10.0 eq, 13 mL, 224 mmol) was added dropwise to the reaction solution, and the reaction was carried out at room temperature for 1 hour. Saturated aqueous sodium bicarbonate solution (30 mL) was added to the reaction liquid, the precipitated solid was collected by filtration, and spin-dried to obtain ethyl 5-bromo-2-hydroxy-6-methyl-pyridine-3-carboxylate (5.10 g, 19.6 mmol, 87.50 % yield). ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.26 (s, 1 H), 4.41 (q, J = 7.24 Hz, 2 H), 2.59 (s, 3H), 1.43-1.39 (t, J =7.16 Hz, 3H).

[0858] Step C: Preparation of ethyl 5-bromo-6-methyl-2-(trifluoromethylsulfonyloxy)pyridine-3-carboxylate: Ethyl 5-bromo-2-hydroxy-6-methyl-pyridine-3-carboxylate (1.00 eq, 0.10 g, 0.384 mmol), N,N-Diisopropylethylamine (3.00 eq, 0.20 mL, 1.15 mmol) were dissolved in 2 mL dichloromethane and placed in an ice-water bath under nitrogen protection adjusted to 0 ℃ , and then trifluoromethanesulfonic anhydride (1.50 eq, 0.097 mL, 0.577 mmol) was added dropwise. The mixture was stirred at room temperature overnight. After completion of the reaction, water was added, extracted with dichloromethane. The combined organics were washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane /ethyl acetate = 5/1 vol/vol) to afford ethyl 5-bromo-6-methyl-2-(trifluoromethylsulfonyloxy)pyridine-3-carboxylate (60 mg, 0.153 mmol, 39.80 % yield) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.53 (s, 1H), 4.45 (q, J = 14.2 Hz, 2 H), 2.68 (s, 3H), 1.44-1.40 (t, J =7.3 Hz, 3H).

[0859] Step D: Preparation of diethyl 5-bromo-6-methyl-pyridine-2,3-dicarboxylate: The suspension of Ethyl 5-bromo-6-methyl-2-(trifluoromethylsulfonyloxy)pyridine-3-carboxylate (1.00 eq, 5000 mg, 12.8 mmol), triethylamine (2.00 eq, 3.6 mL, 25.5 mmol) and $Pd(dppf)Cl_2$ in ethanol (30 mL) was stirred under carbon monooxide at 30 ℃ overnight. Then the reaction mixture was poured into water, extracted with ethyl acetate (20 mL×3).The organic extracts were washed with water (20 mL) and brine (20 mL×2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.The residue was purified by column chromatography (petroleum ether: ethyl acetate (2:1 to 1:1) as eluent to give diethyl 5-bromo-6-methyl-pyridine-2,3-dicarboxylate (3.50 g,11.1 mmol, 86.83 % yield). ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.32 (s, 1H), 4.47-4.35 (m, 4H), 2.74 (s, 3H), 1.42-1.35 (m, 6H).

[0860] Step E: Preparation of [5-bromo-2-(hydroxymethyl)-6-methyl-3-pyridyl]methanol: To a solution of diethyl 5-bromo-6-methyl-pyridine-2,3-dicarboxylate (1.00 eq, 3500 mg, 11.1 mmol) in ethanol (50 mL) was added $NaBH_4$ (5.00 eq, 2094 mg, 55.4 mmol) at 0 ℃ under Ar. To the above solution was added $CaCl_2$ (1.00 eq, 1229 mg, 11.1 mmol) in ethanol (100 mL) slowly. The resulting suspension was stirred at r.t. for 16 h. The mixture was quenched with water and then filtered. The filtrate was concentrated and the diluted with Ethanol (50 mL). The mixture was filtered. The filtrate was acidified with 4M HCl/dioxane and adjusted to pH=7. The resulting suspension was filtered. The filter cake was dried under vacuum to give [5-bromo-2-(hydroxymethyl)-6-methyl-3-pyridyl]methanol (2.30 g,9.91 mmol, 89.52 % yield) as HCl salt (white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.62(s, 1H), 4.89 (m, 2H), 4.47 (m, 2H), 2.80 (s, 3H).

[0861] Step F: Preparation of 5-bromo-2,3-bis(chloromethyl)-6-methyl-pyridine: Sulfurous dichloride (8.30 eq, 6.0 mL, 82.2 mmol) was cooled to 0 oC under Ar, then treated with [5-bromo-2-(hydroxymethyl)-6-methyl-3-pyridyl]methanol (1.00 eq, 2.30 g, 9.91 mmol). The mixture was warmed to

r.t. and stirred at r.t. for 1h. LC-MS showed SM was consumed completely. The mixture was diluted with MTBE (10 mL). The resulting suspension was filtered. The filter cake was collected and dried under vacuum to give 5-bromo-2,3-bis(chloromethyl)-6-methyl-pyridine (1.60 g, 5.95 mmol, 60.03 % yield) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 8.19 (s, 1H), 4.90 (s, 2H), 4.84 (s, 2H), 2.58 (s, 3H).

[0862] Step G: Preparation of ditert-butyl 3-bromo-2-methyl-5,7-dihydrocyclopenta[b]pyridine-6,6-dicarboxylate: To a solution of sodium hydride (3.50 eq, 165 mg, 6.88 mmol) in DMF (10 mL) at 0 ℃ under Ar was added ditert-butyl propanedioate (1.20 eq, 0.49 mL, 2.36 mmol) in DMF. The resulting mixture was stirred at r.t. for 30 min before treated with 5-bromo-2,3-bis(chloromethyl)-6-methyl-pyridine hydrochloride (1.00 eq, 0.60 g, 1.96 mmol) in DMF at -25 ℃ . The reaction was then warmed to r.t. and stirred at r.t. for 5 h. The reaction was monitored by LC-MS. When the sm was consumed completely, the mixture was quenched with water, extracted with dichloromethane. The organic was washed with water (20 mL), brine (20 mL×2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether: ethyl acetate (5:1 to 2:1) to give ditert-butyl 3-bromo-2-methyl-5,7-dihydrocyclopenta[b]pyridine-6,6-dicarboxylate (320 mg,0.776 mmol, 39.51 % yield) as oil. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.62(s, 1H), 3.53(s, 2H), 3.44 (s, 2H), 2.62 (s, 3H),1.45 (s, 18H).

[0863] Step H: Preparation of 3-bromo-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid: Ditert-butyl 3-bromo-2-methyl-5,7-dihydrocyclopenta[b]pyridine-6,6-dicarboxylate (1.00 eq, 1800 mg, 4.37 mmol) in HCl (20 mL) was stirred at 100 ℃ for 16 h before concentrated to dryness. The residue was adjused to pH=10 with 1N NaOH and extracted with EA twice. The aqueous phase was acidified with con HCl to pH=3. The suspension was filtered. The filter cake was dried under vacuum to give 3-bromo-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (550 mg, 2.15 mmol, 49.19 % yield) as white solid. ^{1}H NMR (400MHz, D_2O) δ ppm 8.41 (s, 1H), 3.66-3.46 (m, 1H), 3.48-.346 (m, 2H), 3.43-3.26 (m, 2H), 2.71 (m, 3H).

[0864] Step I: Preparation of give tert-butyl N-(3-bromo-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate: A mixture of 3-bromo-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-6-carboxylic acid (1.00 eq, 630 mg, 2.46 mmol), TEA (0.5 mL), DPPA (1.20 eq, 812 mg, 2.95 mmol) in tert-butanol (3mL) under N_2 was stirred at 90 ℃ for 10 h. The mixture was concentrated and purified by Prep-TLC(PE:EA=1:1) to give tert-butyl N-(3-bromo-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)carbamate (170 mg, 0.520 mmol, 21.12 % yield) as light yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.63(s, 1H), 3.33-3.26 (m, 2H), 2.85-2.78 (m, 2H), 2.62 (s, 3H), 1.44 (s, 9H).

[0865] Step J: Preparation of tert-butyl N-(3-bromo-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-N-ethyl-carbamate: To a solution of tert-butyl N-(3-bromo-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl) carbamate (1.00 eq, 170 mg, 0.520 mmol) in DMF (4mL) at 0 °C under N_2 was added NaH (4.00 eq, 83 mg, 2.08 mmol) . The mixture was stirred at 0 °C for 45 min before treated with EtI (4.00 eq, 0.36 mL, 2.08 mmol). The mixture was then stirred at 0 °C for 1.5 h. The reaction was quenched with water, partitioned between EtOAc/water. The organic phase was dried over Na_2SO_4, filtered, concentrated and purified by prep-TLC (PE:EA=3:1) to give tert-butyl N-(3-bromo-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-N-ethyl-carbamate (138 mg, 0.388 mmol, 74.77 % yield) as light yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.60 (s, 1H), 3.23-3.02 (m, 6H), 2.63 (s, 3H), 1.40 (s, 9H), 1.15-1.11(m, 3H).

[0866] Step K: Preparation of tert-butyl N-(3-cyano-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-N-ethyl-carbamate: To a solution of tert-butyl N-(3-bromo-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-N-ethyl-carbamate (1.00 eq, 138 mg, 0.350 mmol) in DMF (3 mL) were added DPPF (0.500 eq, 97 mg, 0.175 mmol), $Pd_2(dba)_3$(0.500 eq, 160 mg, 0.175 mmol), Zn (2.00 eq, 153 mg, 0.699 mmol) and $Zn(CN)_2$ (6.00 eq, 246 mg, 2.10 mmol). The mixture was bubbled with Ar for 1~2 min and sealed. The reaction slowly warmed to 110 °C for 3 h. The mixture was poured into water, and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and purified by Prep-TLC (PE/EtOAc = 1/1) to give tert-butyl N-(3-cyano-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-N-ethyl-carbamate (83 mg,0.275 mmol, 78.78 % yield) as a light-yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.63 (s, 1H), 3.28-3.13 (m, 6H), 2.72 (s. 3H), 1.38(s, 9H), 1.16-1.12 (m, 3H).

[0867] Step L: Preparation of 6-(ethylamino)-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile: To a solution of tert-butyl-N-(3-cyano-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)-N-ethyl-carbamate (1.00 eq, 83 mg, 0.275 mmol) in DCM (2 mL) was added trifluoroacetic acid (178 eq, 3.8 mL, 48.9 mmol) and stirred at 25 °C for 2 h. TLC showed no SM remained. The reaction was concentrated to give crude 6-(ethylamino)-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (62 mg, 0.308 mmol, 111.86 % yield) as a yellow oil. ^{1}H NMR (400MHz, CD_3OD) δ ppm 7.98(s, 1H), 4.22-4.15 (m, 1H), 3.57-3.48 (m, 2H), 3.24-3.13 (m, 4H), 2.71(s, 3H), 1.36-1.32 (m, 3H).

[0868] Step M: Preparation of tert-butyl (3-cyano-4-((7R)-4-((3-cyano-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-5,7-difluorobenzo[b]thiophen-2-yl)carbamate: To a solution of crude tert-butyl (4-((R)-4-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-

7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-3-cyano-5,7-difluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 41 mg, 0.0587 mmol) , N,N-Diisopropylethylamine (5.00 eq, 0.051 mL, 0.294 mmol) and 6-(ethylamino)-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (2.36 eq, 28 mg, 0.139 mmol) in 1,4-Dioxane (2 mL) was stirred at 70 °C for 4 h. LC-MS showed no SM remained. Then water was added to quench the reaction, and the product was extracted with EtOAc. The combined organics were rinsed with brine, dried over anhydrous Na_2SO_4, filtered, the filtrate was concentrated and purified by Pre-TLC (DCM/MeOH=15/1) to give the crude tert-butyl (3-cyano-4-((7R)-4-((3-cyano-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-6-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-5,7-difluorobenzo[b]thiophen-2-yl)carbamate (45 mg, 0.0521 mmol, 88.79 % yield) as a yellow oil. LC-MS: (ES+): m/z 882.6 $[M]^+$.

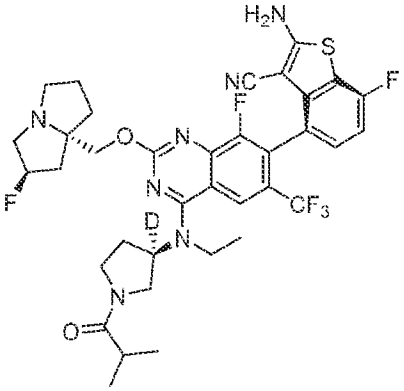
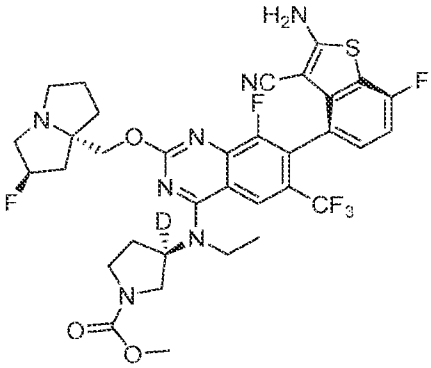
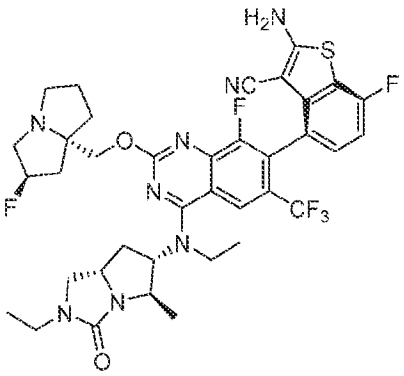
[0869] Step N: Preparation of (S)-6-(((R)-7-(2-amino-3-cyano-5,7-difluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (**Compound 731**) and (6R)-(R)-6-(((R)-7-(2-amino-3-cyano-5,7-difluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (**Compound 753**): To a solution of tert-butyl (3-cyano-4-((7R)-4-((3-cyano-2-methyl-6,7-dihydro-5H-cyclopenta[b] pyridin-6-yl)(ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-(trifluoromethyl)quinazolin-7-yl)-5,7-difluorobenzo[b]thiophen-2-yl)carbamate (1.00 eq, 46 mg, 0.0533 mmol)in DCM (2 mL) was added TFA (1.0 mL). The mixture was stirred for 2 hrs at 25 °C. TLC (DCM:MeOH =10:1) showed the starting material was consumed completely. The mixture was concentrated to dryness under vacuum and purified by prep-HPLC to give product (S)-6-(((R)-7-(2-amino-3-cyano-5,7-difluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy) -6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (**Compound 731,** 2.73 mg, 0.00498 mmol, 9.35 % yield) as the first peak: LC-MS: (ES+): m/z 781.2$[M]^+$, ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 7.99 (s, 1H), 7.00-6.95 (m, 1H), 5.49 (d, J = 52.0 Hz, 1H), 5.16 – 5.12 (m, 2H), 4.34 – 4.17 (m, 2H), 4.03 – 3.55 (m, 9H), 2.77 – 2.70 (m, 3H), 2.60 – 2.46 (m, 2H), 2.27 – 2.23 (m, 2H), 2.03 – 1.71 (m, 2H), 1.59 – 1.56 (m, 3H) and (R)-6-(((R)-7-(2-amino-3-cyano-5,7-difluorobenzo[b]thiophen-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy) -6-(trifluoromethyl)quinazolin-4-yl)(ethyl)amino)-2-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (**Compound 753,** 1.63 mg,0.00498 mmol, 9.35 % yield) as the second peak: LC-MS: (ES+): m/z 781.2$[M]^+$, ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 7.99 (s, 1H), 7.00-6.95

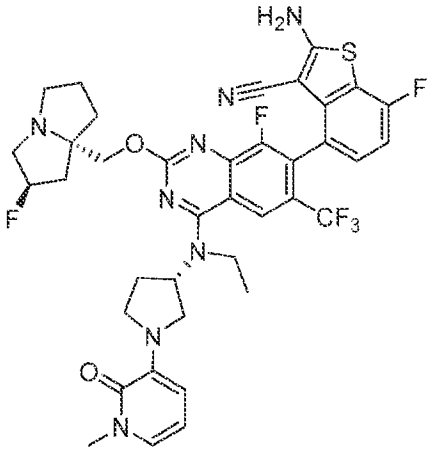
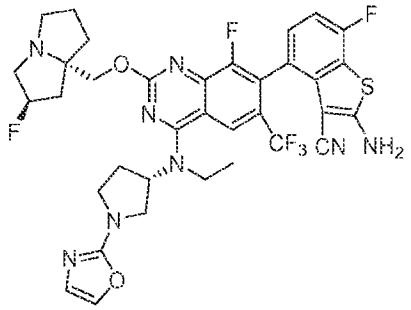
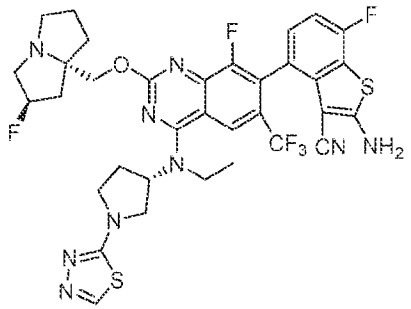
(m, 1H), 5.49 (d, J = 52.0 Hz, 1H), 5.16 – 5.12 (m, 2H), 4.34 – 4.17 (m, 2H), 4.03 – 3.55 (m, 9H), 2.77 – 2.70 (m, 3H), 2.60 – 2.46 (m, 2H), 2.27 – 2.23 (m, 2H), 2.03 – 1.71 (m, 2H),1.59 – 1.56 (m, 3H).

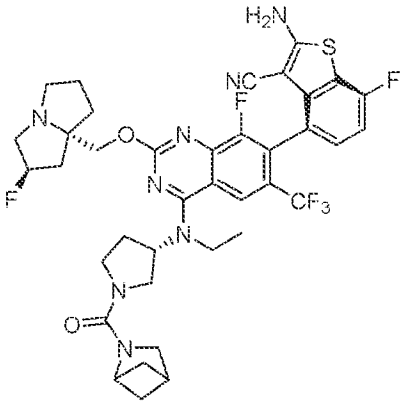
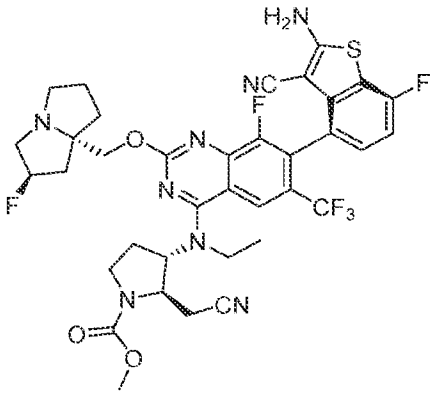
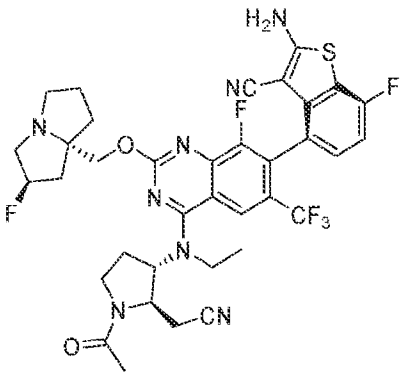
[0870] A compound of present disclosure, such as a compound of a formula included in Table 3 ,Table 3a, Table 3b, or Table 3c may be synthesized according to one of the general routes outlined in Synthetic Examples 1-28 or by various other methods generally known in the art.

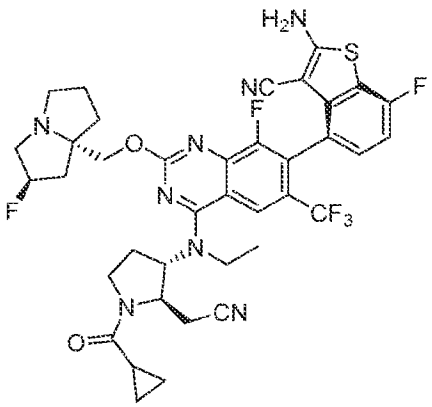
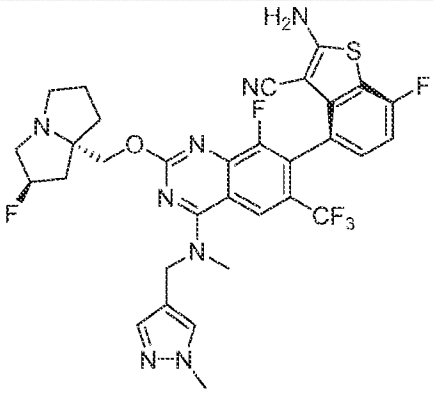
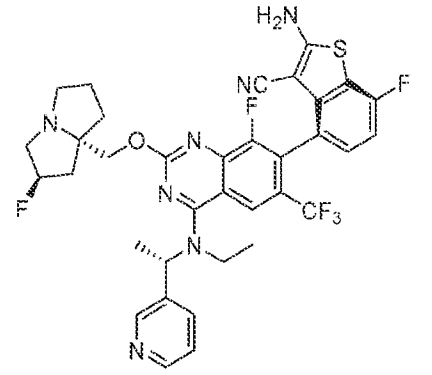
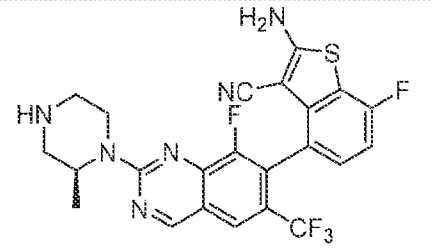
[0871] Table 3 includes selected compounds of the present disclosure.

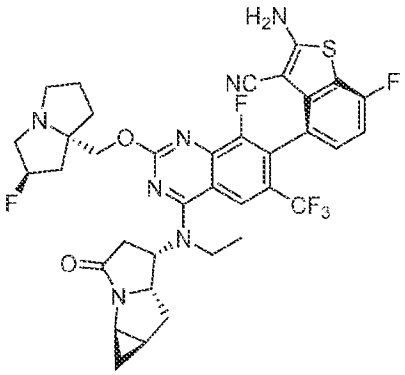
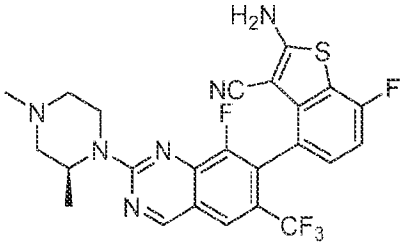
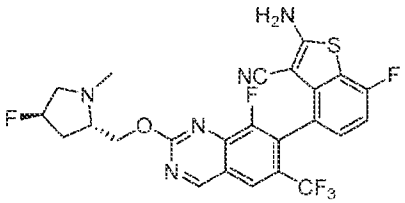
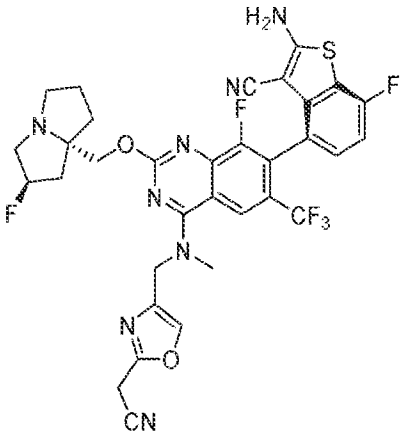
Table 3. Selected compounds of the present disclosure.

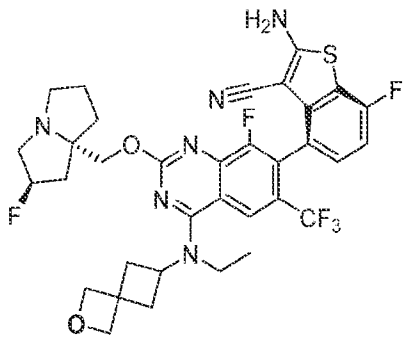
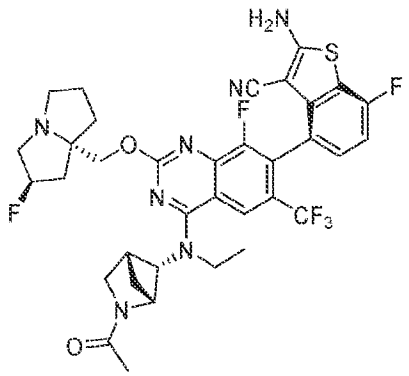
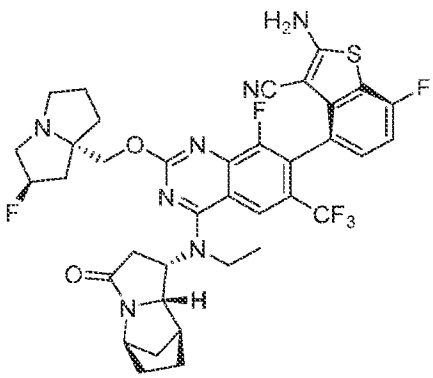
Cmpd. No.	Structure	Analytical Data
1		LCMS m/z [M+1]: 747.27 ^{1}HNMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 7.23-7.20 (m, 1H),7.03-6.98 (m, 1H), 5.35 (s, 0.5H), 5.22 (s, 0.5H), 4.32-4.22 (m, 2H), 4.15-4.10 (m, 0.5H), 3.98-3.86(m, 0.5H), 3.86-3.75 (m, 4H), 3.74-3.71 (m, 0.5H), 3.51-3.42 (m, 0.5H), 3.30-3.17 (m, 3H), 2.99-2.98 (m, 1H), 2.82-1.75 (m, 1H), 2.41-1.85 (m, 8H), 1.45-1.28 (m, 3H), 1.13-1.11 (m, 6H).
2		LCMS m/z [M+1]: 735.2 ^{1}HNMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.23-7.20 (m, 1H), 7.04-6.99 (m, 1H), 5.40 (s, 0.5H), 5.27 (s, 0.5H), 4.40-4.18 (m, 2H), 3.96-3.77 (m, 3H), 3.71 (s, 3H), 3.62-3.52 (m, 1H), 3.50-3.35 (m, 2H), 3.30-3.21 (m, 3H),3.13-3.00 (m, 1H), 2.54-1.86 (m, 8H), 1.45 (t, J = 6.8 Hz, 3H).
3		LCMS m/z [M+1]: 773.3 ^{1}HNMR (400 MHz, CD_3OD)) δ 8.24 (s, 1H), 7.26 – 7.19 (m, 1H), 7.06 – 6.97 (m, 1H), 5.37 (s, 0.5H), 5.24 (s, 0.5H), 4.86 – 4.78 (m, 1H), 4.26 (dd, J = 33.9, 10.5 Hz, 2H), 4.16 – 4.06 (m, 1H), 4.05 – 3.92 (m, 1H), 3.92 – 3.78 (m, 1H), 3.73 – 3.56 (m, 2H), 3.50 – 3.32 (m, 2H), 3.29 – 3.17 (m, 4H), 3.07 – 2.97 (m, 1H), 2.40 – 2.20 (m, 3H), 2.19 – 2.05 (m, 2H),

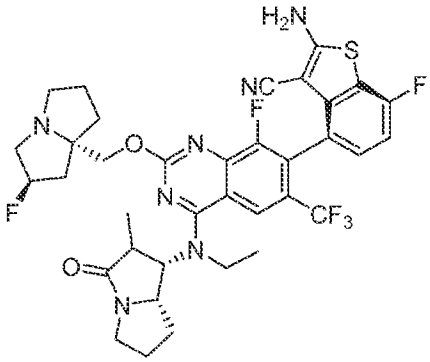
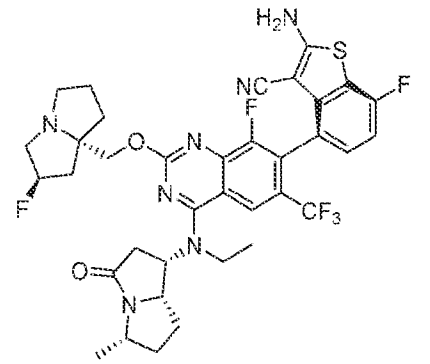
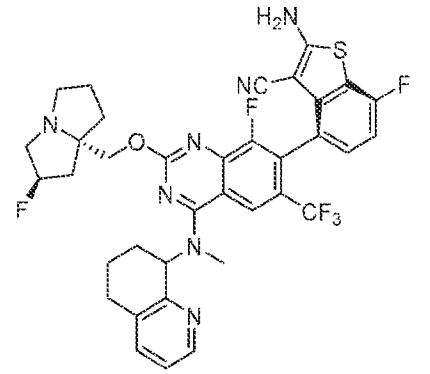
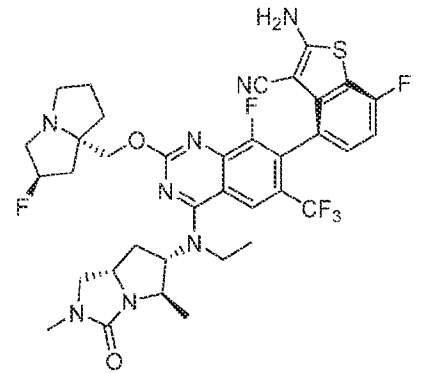
Cmpd. No.	Structure	Analytical Data
		2.04 – 1.94 (m, 2H), 1.94 – 1.83 (m, 1H), 1.38 (t, J = 6.9 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H), 1.19 – 1.09 (m, 3H).
4		LCMS m/z [M+1]: 782.8 1H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 8.28 – 8.23 (m, 1H), 7.14 (d, J = 5.9 Hz, 1H), 7.01 (t, J = 9.0 Hz, 1H), 6.68 (d, J = 6.9 Hz, 1H), 6.29 (t, J = 7.0 Hz, 1H), 5.31 (d, J = 53.7 Hz, 2H), 5.18 – 5.09 (m, 1H),, 4.56 (s, 1H), 3.53 – 3.42 (m, 1H), 4.41 – 4.34 (m, 1H),4.30 – 4.25 (m, 3H), 3.79 – 3.71 (m, 1H), 3.56 (s, 3H), 3.53 – 3.42 (m, 1H), 3.29 – 3.12 (m, 3H), 3.08 – 3.00 (m, 1H), 2.49 – 2.21 (m, 4H), 2.14 – 2.07 (m, 1H), 2.05 – 1.96 (m, 1H), 1.92 – 1.85 (m, 1H), 1.46 (t, J = 5.9 Hz, 3H), 1.36 – 1.26 (m, 1H).
5		LCMS m/z [M+1]: 743 1H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 7.40-7.45 (m, 1H), 7.21-7.25 (m, 1H), 7.01 (t, J= 8.9 Hz, 1H), 6.81-6.88 (m, 1H), 5.36 (d, J= 53.6 Hz, 1H), 5.06-5.16 (m, 1H), 4.29-4.40 (m, 2H), 3.76-4.01 (m, 5H), 3.37-3.62 (m, 4H), 3.09-3.20 (m, 1H), 2.18-2.67 (m, 4H), 1.93-2.13 (m, 4H), 1.43-1.51 (m, 3H).
6		LCMS m/z [M+1]: 760.0 1H NMR (400 MHz, CD_3OD) δ 8.86 (s, 1H), 8.30 (s, 1H), 7.21--7.25 (m, 1H),7.02 (d, J = 9.2 Hz, 1H), 5.53 (d, J = 52.2 Hz, 1H), 5.13 -5.21(m, 1H), 4.57-4.72 (m, 2H), 3.65-4.08 (m, 9H), 3.41-3.47 (m, 1H), 2.03-2.75 (m, 8H), 1.54 (t, J = 5.2 Hz, 3H).

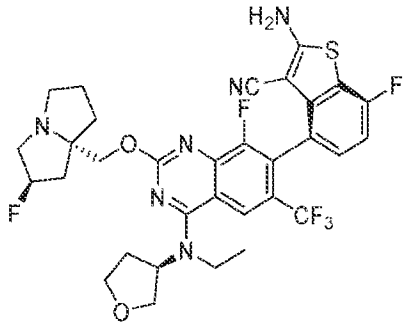
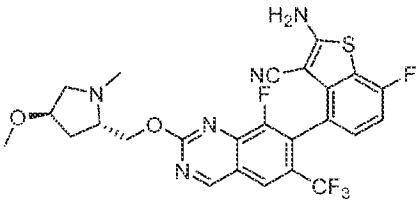
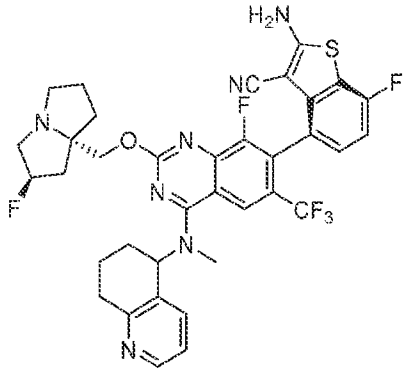
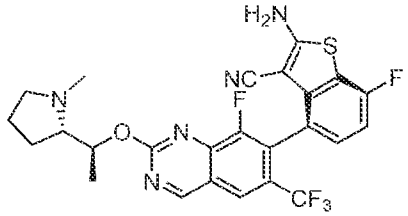
Cmpd. No.	Structure	Analytical Data
7		LCMS m/z [M+1]: 785.2 1HNMR (400 MHz, CD_3OD) δ 8.25 (s, 1 H), 7.23-7.20 (m, 1H), 7.03-7.99 (m, 1H), 5.36 (s, 0.5 H), 5.23 (s, 0.5H), 5.06-4.97 (m, 1H), 4.31-4.23 (m, 3H), 3.98-3.80 (m, 3H), 3.79-3.64 (m, 2H), 3.61-3.51 (m, 1H), 3.48-3.44 (m, 1H), 3.27-3.14 (m, 3H), 3.06-2.96 (m, 1H), 2.89-2.80 (m, 1H), 2.54-2.41 (m, 1H), 2.39-2.17 (m, 3H), 2.16-2.08 (m, 1H), 2.06-1.79 (m, 5H), 1.47 (t, 3H), 1.39-1.26 (m, 3H).
8		LCMS m/z [M+1]: 773.3 1H NMR (400 MHz, CD_3OD) δ = 8.28 (s, 1H), 7.22 (dd, J=8.3, 5.0 Hz, 1H), 7.01 (dd, J=9.4, 8.4 Hz, 1H), 5.40 (s, 0.5H), 5.26 (s, 0.5H), 5.10 (s, 1H), 4.41 (s, 1H), 4.29 (q, J=10.7 Hz, 2H), 4.09 – 3.90 (m, 2H), 3.88 – 3.71 (m, 4H), 3.47 (dd, J=43.3, 4.8 Hz, 2H), 3.24 (d, J=14.4, 2H), 3.05 (ddd, J=29.1, 16.3, 11.1 Hz, 2H), 2.70 – 2.57 (m, 1H), 2.46 – 1.85 (m, 8H), 1.47 (dd, J=15.0, 8.1 Hz, 3H).
9		LCMS m/z [M+1]: 757.2 1H NMR (400 MHz, CD_3OD) δ = 8.27 (d, J=14.0 Hz, 1H), 7.22 (dd, J=8.3, 5.1 Hz, 1H), 7.01 (dd, J=9.4, 8.5 Hz, 1H), 5.39 (s, 0.5H), 5.25 (s, 0.5H), 5.09 (dd, J=16.2, 7.4 Hz, 1H), 4.57 (td, J=6.4, 2.7, 1H), 4.28 – 4.20 (m, 2H), 4.09 – 3.96 (m, 2H), 3.86 – 3.65 (m, 2H), 3.46 – 3.33 (m, 1H), 3.25 (dd, J=17.0, 6.2 Hz, 2H), 3.03 (ddd, J=19.8, 11.9, 3.2 Hz, 2H), 2.76 – 2.63 (m, 1H), 2.36 (dddd, J=23.5, 17.4, 10.1, 6.8 Hz, 3H), 2.21 – 1.87 (m, 8H), 1.55 – 1.45 (m, 3H).

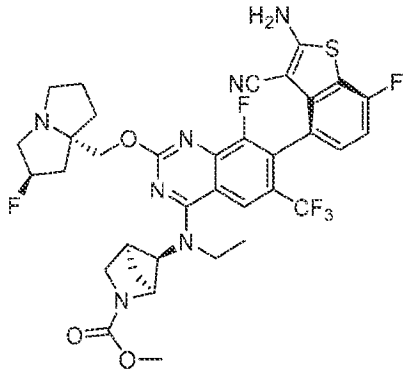
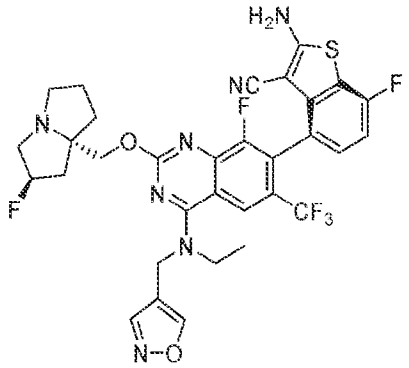
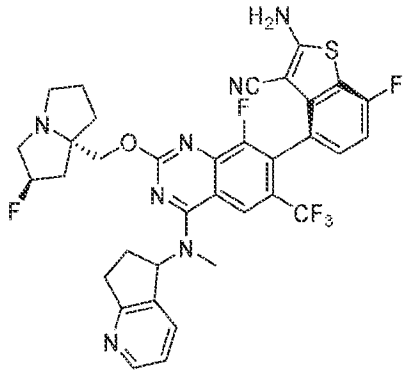
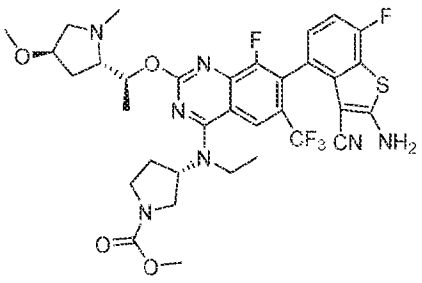
Cmpd. No.	Structure	Analytical Data
10		LCMS m/z [M+1]: 783.3 1H NMR (400 MHz, CD_3OD) δ = 8.28 (d, J=10.6 Hz, 1H), 7.22 (dd, J=8.3, 5.0 Hz, 1H), 7.05 – 6.96 (m, 1H), 5.24 (dd, J=51.3, 31.6 Hz, 2H), 4.59 – 4.46 (m, 1H), 4.33 – 4.16 (m, 3H), 4.02 (dd, J=15.5, 7.1 Hz, 1H), 3.82 (ddd, J=12.3, 9.4, 4.4 Hz, 2H), 3.40 – 3.31 (m, 1H), 3.26 – 3.22 (m, 2H), 3.07 – 2.91 (m, 2H), 2.79 – 2.66 (m, 1H), 2.52 – 2.41 (m, 1H), 2.40 – 1.84 (m, 8H), 1.53 – 1.42 (m, 3H), 0.99 – 0.84 (m, 4H).
11		LCMS m/z [M+1]: 687.2 1HNMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.74 (s, 1H),7.19-7.18 (m, 1H), 7.02-6.97(m, 1H), 5.36 (s, 0.5H), 5.22 (s, 0.5H), 4.90-4.88 (m, 2H), 4.40-4.25 (m, 2H), 3.88 (s, 3H), 3.52 (s, 3H), 3.31-3.13 (m,3H), 3.01-2.98 (m, 1H), 2.35-2.15(m, 3H), 2.15-1.85 (m, 3H).
12		LCMS m/z [M+1]: 712.2 1HNMR (400 MHz, CD_3OD) δ 8.73 (s, 1H), 8.59 (s, 1H), 8.32 (s, 1H), 8.14 (s, 1H), 7.62 (s, 1H), 7.26 – 7.18 (m, 1H), 7.07 – 6.98 (m, 1H), 6.01 (d, J = 7.0 Hz, 1H), 5.61 (s, 0.5H), 5.48 (s, 0.5H), 4.56 – 4.44 (m, 2H), 4.04 – 3.77 (m, 5H), 3.48 – 3.42 (m, 1H), 2.67 – 2.47 (m, 2H), 2.46 – 2.22 (m, 3H), 2.08 (s, 1H), 1.96 (d, J = 6.9 Hz, 3H), 1.43 (t, J = 6.9 Hz, 3H).
13		LCMS m/z [M+1]: 519.2 1H NMR (400 MHz, CD_3OD) δ 9.27 (d, 1H), 8.08 (s, 1H), 7.17-7.21 (m, 1H), 6.99 (t, 1H), 5.17-5.19 (m, 1H), 4.83 (d, 1H), 3.34-3.35 (m, 1H), 2.96 (d,

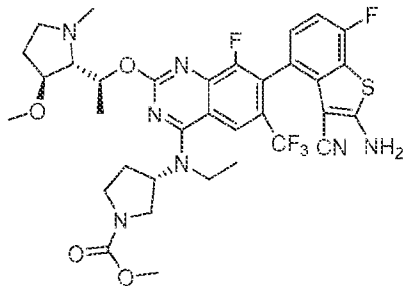
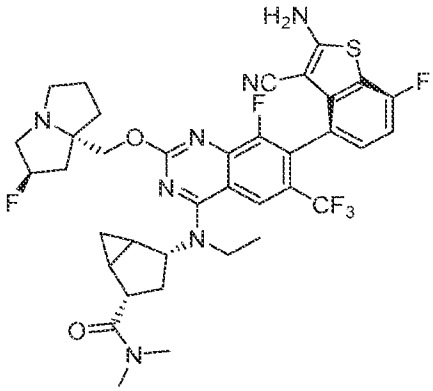
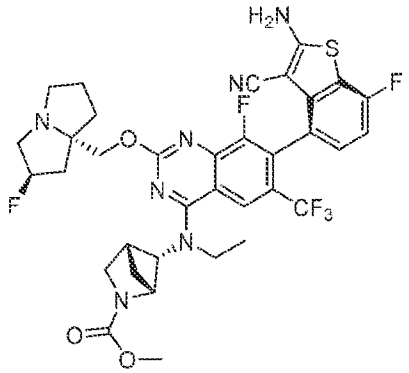
Cmpd. No.	Structure	Analytical Data
		1H), 2.86 (d, 1H), 2.27-2.32 (m, 4H), 2.06-2.12 (m, 1H), 1.35-1.37 (m, 3H).
13-1		LCMS m/z [M+1]: 742.2 1H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 7.23-7.19 (m, 1H), 7.01 (t, 1H), 5.43 (s, 0.5H), 5.29 (s, 0.5H), 4.47-4.41 (m,1H), 4.30-4.20 (m, 3H), 3.86-3.84 (m, 2H), 3.73-3.70 (m, 1H), 3.55-3.47 (m, 2H), 3.08 (s, 1H), 2.91-2.84 (m, 1H) , 2.48-2.39 (m, 1H), 2.35-2.24 (m,2H), 2.21-2.11 (m, 2H), 2.07-1.83 (m, 5H), 1.74-1.70 (m, 1H), 1.54 (t, 3H),0.91-0.88 (m, 1H), 0.80-0.74 (m, 1H).
13-2		LCMS m/z [M+1]: 519.2 1H NMR (400 MHz, CD_3OD) δ 9.27 (d, 1H), 8.08 (s, 1H), 7.17-7.21 (m, 1H), 6.99 (t, 1H), 5.17-5.19 (m, 1H), 4.83 (d, 1H), 3.34-3.35 (m, 1H), 2.96 (d, 1H), 2.86 (d, 1H), 2.27-2.32 (m, 4H), 2.06-2.12 (m, 1H), 1.35-1.37 (m, 3H).
14		LCMS m/z [M+1]: 538.2 1H NMR (400 MHz, CD_3OD) δ 9.60 (d, 1H), 8.41 (s, 1H), 7.22-7.25 (m, 1H), 7.02 (t, 1H), 5.26 (s, 0.5H), 5.12 (s, 0.5H), 4.58-4.70 (m, 2H), 3.46-3.57 (m, 1H), 3.21-3.25 (m, 1H), 2.63-2.74 (m, 1H), 2.58 (s, 3H), 2.27-2.36 (m, 1H), 2.00-2.12 (m, 1H).
15		LCMS m/z [M+1]: 713.3 1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.07 (d, 1H), 7.18-7.22 (m, 1H), 7.00 (t, 1H), 5.36 (s, 0.5H), 5.23 (s, 0.5H), 4.92-4.98 (m, 2H), 4.31 (d, 1H), 4.23 (d, 1H), 3.54 (s, 2H), 3.20-3.29 (m, 6H), 2.98-3.02 (m, 1H), 2.21-2.37(m, 2H), 2.11-2.16 (m, 1H), 1.94-2.03 (m, 2H), 1.84-1.91 (m, 1H).

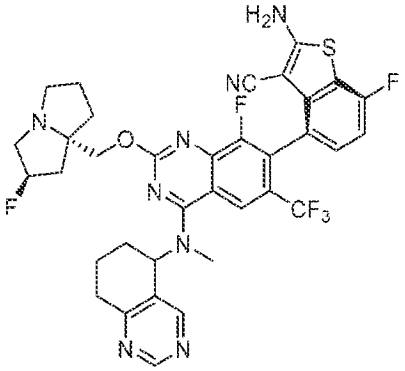
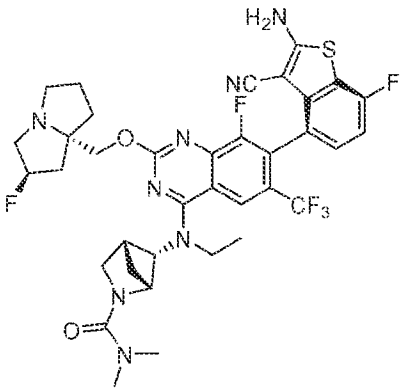
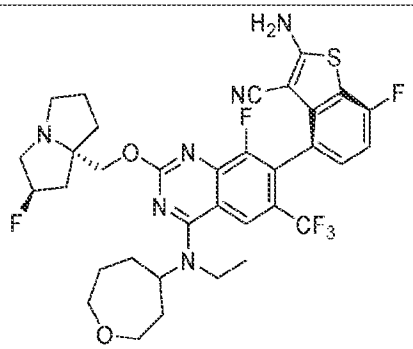
Cmpd. No.	Structure	Analytical Data
16		LCMS m/z [M+1]: 703.2 1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.18-7.21 (m, 1H), 6.98-7.03 (m, 1H), 5.34 (s, 0.5H), 5.19-5.25 (m, 1.5H), 4.80 (s, 1.5H), 4.68 (d, 1.5H), 4.32-4.44 (m, 1H), 4.27 (d, 1H), 4.16 (d, 1H), 3.65-3.83 (m, 3H), 3.16-3.31 (m, 3H), 2.93-3.00 (m, 1H), 2.76-2.81 (m, 1H), 2.33-2.45 (m, 2H), 2.05-2.27 (m, 4H), 1.82-1.99 (m, 4H), 1.25 (t, 3H).
17		LCMS m/z [M+1]: 730.1 1HNMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 7.24-7.19 (m, 1H), 7.03-695 (m, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 5.00 (d, 0.5H), 4.79 (d, 0.5H), 4.39-4.29 (m, 2H), 4.23-4.17 (m, 1H), 4.03-3.88 (m, 1H), 3.78-3.64 (m, 1H), 3.50-3.45 (m, 0.5H), 3.28-3.18 (m, 3H), 3.15-3.11 (m, 0.5H), 3.10-3.02 (m, 1H), 2.98-2.89 (m, 1H), 2.44-2.12 (m, 4H), 2.07-1.98 (m, 2H), 1.96-1.80 (m, 4H), 1.30-1.19 (m, 5H).
18		LCMS m/z [M+1]: 756.3 1H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 7.23-7.20 (m, 1H), 7.01 (t, 1H), 5.40 (s, 0.5H), 5.26 (s, 0.5H), 4.67-4.60 (m,1H) , 4.44 (s, 1H), 4.33-4.26 (m, 2H), 4.02-3.90 (m, 3H), 3.47-3.38 (m, 2H), 3.29-3.20 (m, 3H), 3.09-3.03 (m, 1H) , 2.66-2.65 (m, 1H), 2.49-2.41 (m,1H), 2.33-2.16 (m, 2H), 2.14-1.81 (m, 5H), 1.80-1.67 (m, 2H), 1.53-1.49 (m, 3H),1.29-1.28 (m, 2H).

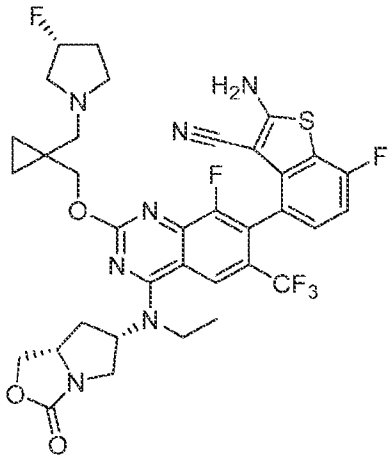
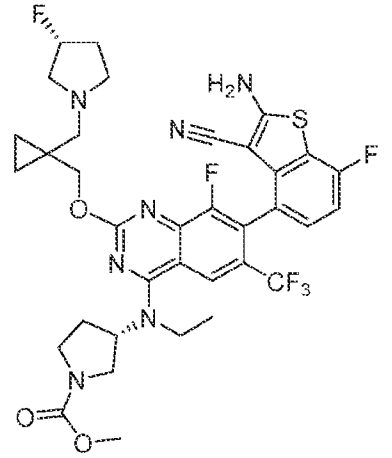
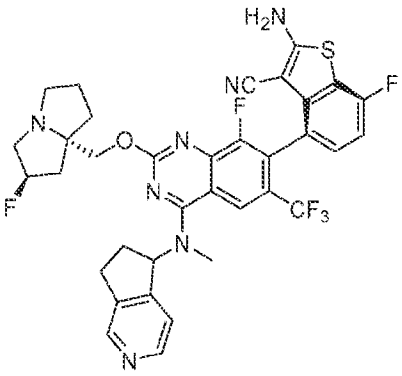
Cmpd. No.	Structure	Analytical Data
19		LCMS m/z [M+1]: 744.2. 1H NMR (400 MHz, CD_3OD) δ8.23 (s, 1H), 7.24-7.21 (m, 1H), 7.01 (t, J=8.8 Hz, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 4.45-4.41 (m, 1H), 4.24-4.21 (m, 3H), 4.02-3.82 (m, 3H), 3.57-3.55 (m, 1H), 3.36-3.03 (m, 5H), 2.36-1.90 (m, 10H), 1.54 (t, J=7.2 Hz, 3H), 1.26 (d, J=7.2 Hz, 3H)
20		LCMS m/z [M+1]: 744.1 ^{1}HNMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 7.20-7.23 (m, 1H), 7.01 (t, 1H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 4.48-4.58 (m, 2H), 4.21-4.29 (m, 2H), 3.83-3.97 (m, 3H), 3.58-3.64 (m, 1H), 3.16-3.26 (m, 3H), 2.99-3.05 (m, 1H), 2.78-2.84 (m, 1H), 2.40-2.45 (m, 1H), 2.08-2.35 (m, 4H), 1.89-2.00 (m, 3H), 1.60-1.75 (m, 2H), 1.52 (t, 3H), 1.29 (d, 3H).
21		LCMS m/z [M+1]: 724.1 1H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 5.9 Hz, 1H), 8.44 – 8.31 (m, J = 14.7, 4.0 Hz, 1H), 7.66 (t, J = 6.9 Hz, 1H), 7.33 – 7.17 (m, 2H), 7.04 – 6.95 (m, 1H), 6.15 (s, 0.5H), 5.82 (s, 0.5H), 5.35 (s, 0.5H), 5.22 (s, 0.5H), 4.30 – 4.05 (m, 2H), 3.31 (d, J = 1.6 Hz, 3H), 3.28 – 3.21 (m, 3H), 3.09 – 2.97 (m, J = 13.4, 9.0 Hz, 2H), 2.91 (d, J = 15.6 Hz, 1H), 2.53 – 2.08 (m, 6H), 2.03 – 1.81 (m, 4H).
22		LCMS m/z [M+1]: 759.3 1H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 7.26 – 7.21 (m, 1H), 7.05 – 6.98 (m, 1H), 5.38 (s, 0.5H), 5.25 (s, 0.5H), 4.80 – 4.72 (m, 1H), 4.30 (d, J = 10.5 Hz, 1H), 4.22 (d, J = 10.5 Hz, 1H), 4.18 – 4.10 (m, 1H), 4.03 – 3.95 (m, 1H), 3.91 – 3.80 (m, 1H), 3.71 – 3.56 (m, 2H), 3.49 – 3.43 (m, 1H), 3.35 (d, J = 14.1 Hz, 1H), 3.28 – 3.22 (m, 2H), 3.07 – 2.99 (m, 1H),

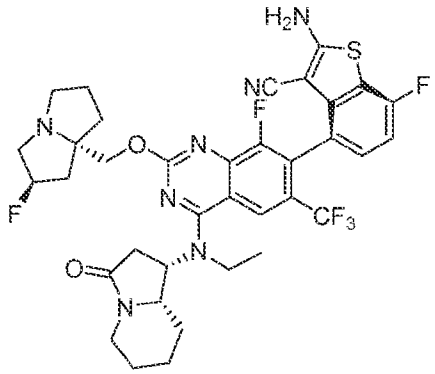
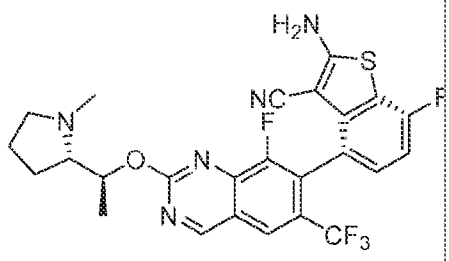
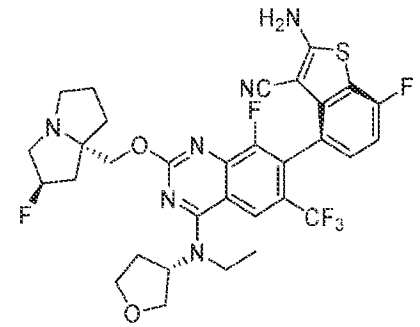
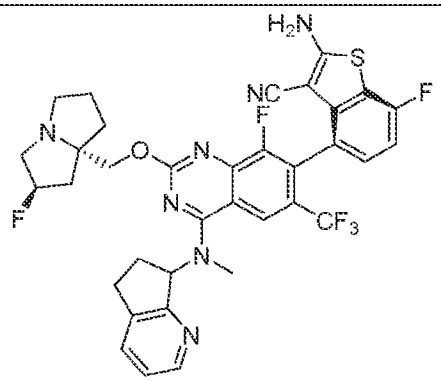
Cmpd. No.	Structure	Analytical Data
		2.85 (s, 3H), 2.40 – 2.14 (m, 5H), 2.05 – 1.96 (m, 2H), 1.95 – 1.85 (m, 1H), 1.40 (t, J = 7.0 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H).
23		LCMS m/z [M+1]: 677.1 1H NMR (400 MHz, CD_3OD) δ = 8.23 (s, 1H), 7.22 (dd, J=8.3, 5.0 Hz, 1H), 7.01 (dd, J=9.4, 8.4 Hz, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 5.16 – 5.08 (m, 1H), 4.32 (q, J=10.7 Hz, 2H), 4.24 – 4.16 (m, 1H), 4.05 – 3.88 (m, 3H), 3.86 – 3.73 (m, 2H), 3.36 (d, J=2.7 Hz, 1H), 3.26 (d, J=6.7 Hz, 2H), 3.11 – 3.00 (m, 1H), 2.58 – 2.49 (m, 1H), 2.29 (dddd, J=39.0, 25.5, 16.5, 6.5 Hz, 4H), 2.05 – 1.88 (m, 3H), 1.40 (t, J=7.0 Hz, 3H).
24		LCMS m/z [M+1]: 550.0 1H NMR (400 MHz, CD_3OD) δ 9.59 (s, 1H), 8.41 (s, 1H), 7.26-7.21 (m, 1H), 7.02 (t, 1H), 4.68-4.55 (m, 2H), 4.03-3.95 (m, 1H), 3.45-3.39 (m, 1H), 3.29 (d, 3H), 3.13-3.06 (m, 1H), 2.55 (d, 3H), 2.46-2.40 (m, 1H), 2.17-2.10 (m, 1H), 2.05-1.98 (m, 1H).
25		LCMS m/z [M+1]: 724.2 1HNMR (400 MHz, CD_3OD) δ 8.48 – 8.34 (m, 2H), 7.75 – 7.67 (m, 1H), 7.32 – 7.18 (m, 2H), 7.06 – 6.97 (m, 1H), 6.26 (s, 1H), 5.35 (s, 0.5H), 5.22 (s, 0.5H), 4.33 – 4.12 (m, 2H), 3.32 (s, 3H), 3.29 – 3.19 (m, 3H), 3.15 – 2.94 (m, 3H), 2.42 – 1.78 (m, 10H).
26		LCMS m/z [M+1]: 534.0 1H NMR (400 MHz, CD_3OD) δ 9.60 (s, 1H), 8.40 (s, 1H), 7.26-7.20 (m, 1H), 7.02 (t, 1H), 5.50-5.41 (m, 1H), 3.18-3.11 (m, 1H), 3.01-2.92 (m, 1H), 2.64 (s, 3H), 2.55-2.47 (m, 1H), 2.14-2.05 (m, 1H), 1.90-1.78 (m, 3H), 1.45 (d, 3H).

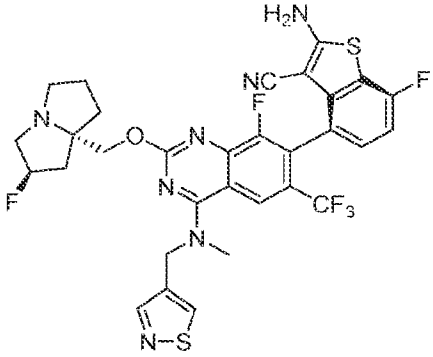
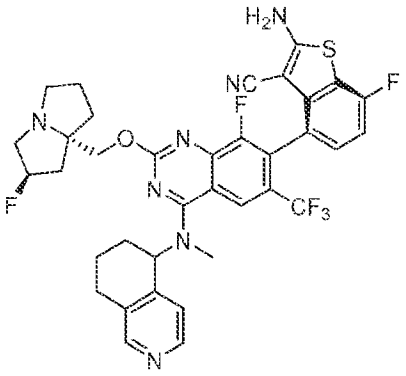
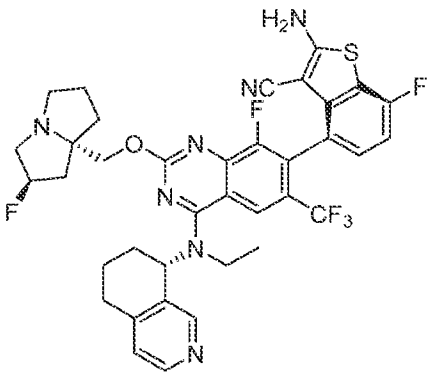
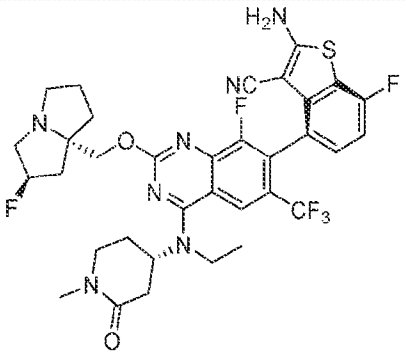
Cmpd. No.	Structure	Analytical Data
27		LCMS m/z [M+1]: 746.1 1H NMR (400 MHz, CD_3OD) δ 8.06 (d, 1H), 7.23-7.7 (m, 1H), 7.00 (t, 1H), 5.39 (s, 0.5H), 5.25 (s, 0.5H), 4.72 (d, 1H), 4.41-4.33 (m, 1H), 4.31-4.23 (m, 1H), 4.02 (d, 1H), 3.82 (s, 2H), 3.48 (s, 2H), 3.29-3.15 (m, 6H), 3.05 (s, 1H), 2.46-2.06 (m, 4H), 2.05-1.96 (m, 2H), 1.94-1.80 (m, 2H), 1.47 (d, 1H), 1.16 (t, 3H).
28		LCMS m/z [M+1]: 688.2 1H-NMR (400 MHz, CD_3OD): 8.84 (s, 1 H), 8.60 (s, 1 H), 8.22 (s, 1 H), 7.16-7.24 (m, 1 H), 6.96-7.04 (s, 1 H), 5.45 (s, 0.5 H), 5.32 (s, 0.5 H), 4.90-4.93 (m, 2 H), 4.30-4.49 (m, 2 H), 3.83-3.95 (m, 2 H), 3.42-3.57 (m, 3 H), 3.11-3.21 (m, 1 H), 2.30-2.46 (m, 2 H), 2.18-2.26 (m, 1 H), 2.04-2.16 (m, 2 H), 1.92-2.02 (m, 1 H), 1.50-1.64 (m, 3 H).
29		LCMS m/z [M+1]: 710.21 1HNMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.44 (s, 1H),7.84-7.82 (m, 1H), 7.31-7.24(m, 1H),7.24-7.21(m, 1H), 6.99(m, 1H), 6.52-6.47(m, 1H), 5.34 (s, 0.5H), 5.21 (s, 0.5H), 4.48-4.14 (m, 2H), 3.31 (m, 3H), 3.18-3.16 (m, 4H), 2.97 (m, 1H), 2.75 (m,1H), 2.23-2.18(m, 5H), 1.98-1.83 (m, 3H).
30		LCMS m/z [M+1]: 734.1 1H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.26 – 7.20 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.46 – 5.37 (m, 1H), 5.08 – 5.01 (m, 1H), 4.21 – 4.15 (m, 1H), 4.05 – 3.72 (m, 9H), 3.62 – 3.55 (m, 1H), 3.49 – 3.40 (m, 5H), 3.23 – 3.12 (m, 3H), 2.62 – 2.38 (m, 3H), 2.34 – 2.31 (m, 1H), 2.05 – 1.97 (m, 1H), 1.58 – 1.44 (m, 6H).

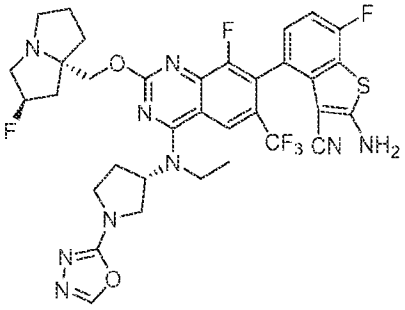
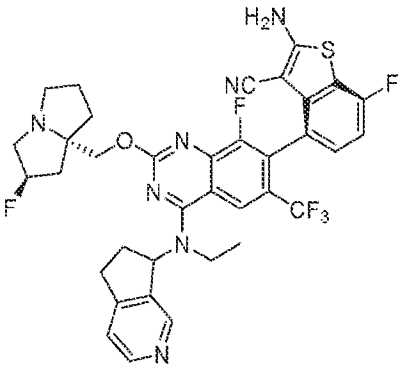
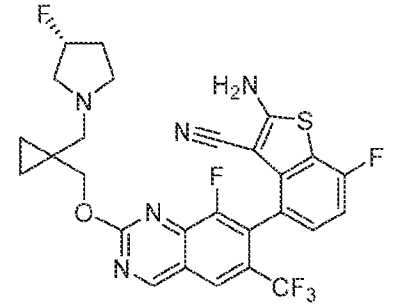
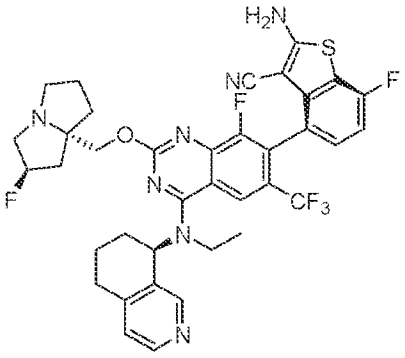
Cmpd. No.	Structure	Analytical Data
31		LCMS m/z [M+1]: 734.1 1H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.23 (dd, J = 8.4, 5.0 Hz, 1H), 7.11 – 6.90 (m, 1H), 5.46 (d, J = 20.8 Hz, 1H), 5.02 (s, 1H), 4.05 (s, 1H), 3.91 (dt, J = 7.3, 3.3 Hz, 2H), 3.92 – 3.67 (m, 7H), 3.58 (s, 1H), 3.45 (dd, J = 16.7, 8.2 Hz, 1H), 3.43 – 3.35 (m, 3H), 3.26 – 3.00 (m, 3H), 2.48 (s, 1H), 2.34 (d, J = 15.1 Hz, 2H), 2.17 (s, 1H), 1.93 – 1.77 (m, 1H), 1.75 – 1.48 (m, 3H), 1.55 – 1.30 (m, 3H).
32		LCMS m/z [M+1]: 758.2 1H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.24-7.18 (m, 1H), 7.00 (t, 1H), 5.37 (s, 0.5H), 5.31-5.22 (m, 1.5H), 4.32 (d, 1H), 4.22 (d, 1H), 4.05-3.96 (m, 1H), 3.91-3.82 (m, 1H), 3.52-3.48 (m, 1H), 3.29-3.26 (m, 3H), 3.21 (s, 3H), 3.08-2.92 (m, 4H), 2.35-2.21 (m, 2H), 2.19-2.08 (m, 2H), 2.04-1.86 (m, 4H), 1.76-1.70 (m, 1H), 1.66-1.52 (m, 4H), 0.92-0.82 (m, 1H), 0.74-0.67 (m, 1H).
33		LCMS m/z [M+1]: 746.1 1H NMR (400 MHz, CD_3OD) δ 8.07 (d, 1H), 7.24-7.17 (m, 1H), 7.00 (t, 1H), 5.39 (s, 0.5H), 5.25 (s, 0.5H), 4.66-4.60 (m,1H) , 4.37-4.33 (m, 1H), 4.28-4.25 (m, 1H), 4.12 (d, 1H), 3.97-3.73 (m, 2H), 3.59-3.45 (m, 3H), 3.24-3.19 (m, 3H), 3.15-3.13 (m, 1H), 3.07-2.91 (m.2H), 2.40-2.24 (m, 2H), 2.19-2.13 (m, 1H), 2.08-1.76 (m,5H), 1.43-1.39 (m, 1H), 1.33-1.25 (m, 3H).

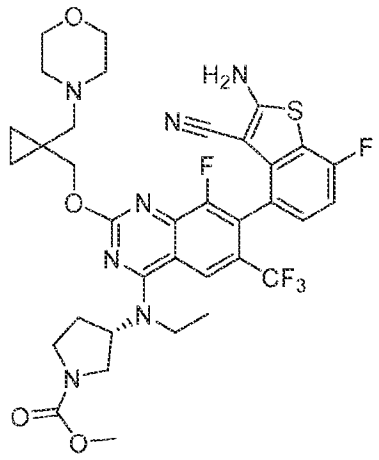
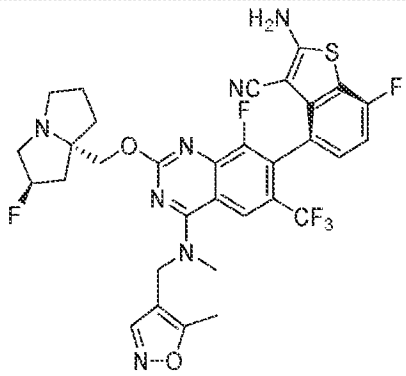
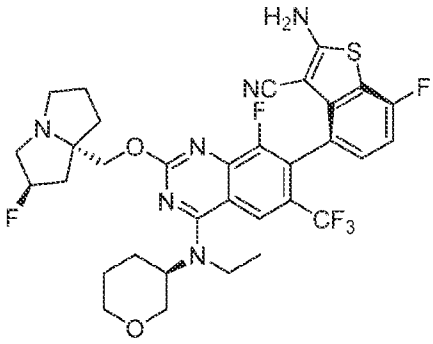
Cmpd. No.	Structure	Analytical Data
34		LCMS m/z [M+1]: 725.1 1H NMR (400 MHz, CD_3OD) δ 8.94 (s, 1H), 8.59 (s, 1H), 8.42 (s, 1H), 7.24-7.21 (m,1H), 7.01 (t, 1H), 6.25-6.19 (m,1H), 5.33(s, 0.5H), 5.20 (S, 0.5H), 4.18 (s,2H), 3.39 (s,3H), 3.25-3.15 (m,3H), 3.07-2.97 (m, 3H), 2.38-2.32 (m, 1H), 2.28-2.19 (m, 4H), 2.14-2.05 (m, 2H), 2.00-1.93 (m, 2H), 1.87-1.80 (m, 1H).
35		LCMS m/z [M+1]: 759.2 1H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 7.23-7.19 (m, 1H), 7.00 (t, 1H), 5.38 (s, 0.5H), 5.25 (s, 0.5H), 4.49 (d,1H), 4.35-4.32 (m, 1H), 4.26-4.23 (m, 1H), 4.07 (s, 1H), 3.90-3.85 (m, 2H), 3.24-3.21 (m, 3H), 3.10-3.01 (m, 3H) , 2.77 (s, 6H), 2.39-2.23(m,2H), 2.20-2.14 (m, 1H), 2.03-1.97 (m, 2H), 1.93-1.86 (m, 1H), 1.73 (d, 1H), 1.33-1.30 (m, 2H), 1.22 (t, 3H).
36		LCMS m/z [M+1]: 705.2 1H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.22 (t, 1H), 7.01 (t, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 4.52-4.56 (m, 1H), 4.29-4.33 (m, 1H), 4.28-4.30 (m, 1H), 3.67-3.86 (m, 6H), 3.35-3.49 (m, 1H), 3.12-3.30 (m, 2H), 3.05 (s, 1H), 1.84-2.37 (m, 12H), 1.42 (t, 3H).

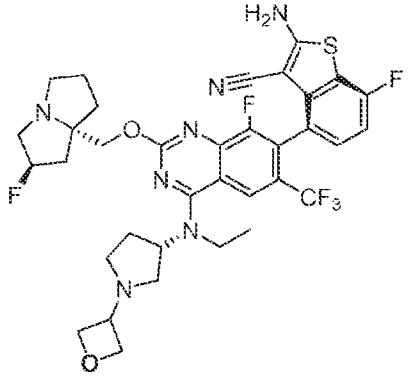
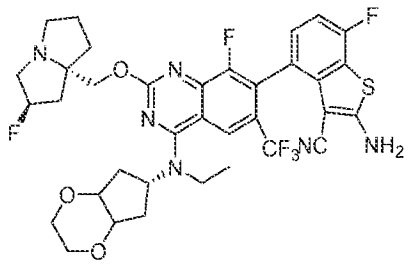
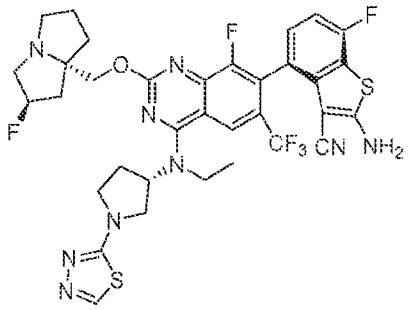
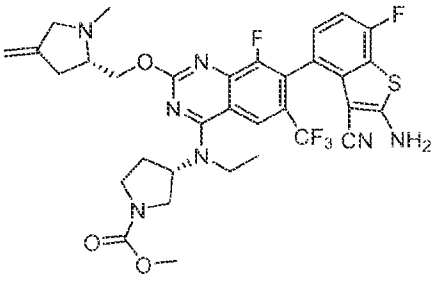
Cmpd. No.	Structure	Analytical Data
37		LCMS m/z [M+1]: 746.1 1H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 7.19-7.23 (m, 1H), 7.00 (t, 1H), 5.21 (s, 0.5H), 5.04-5.07 (m, 1.5H), 4.61 (t, 1H), 4.28-4.44 (m, 3H), 4.15-4.24 (m, 1H), 3.80-3.91 (m, 1.5H), 3.59-3.75 (m, 1.5H), 2.92-3.06 (m, 2H), 2.71-2.89 (m, 2H), 2.51-2.69 (m, 2H), 2.31-2.47 (m, 2H), 1.89-2.24 (m, 3H), 1.43-1.49 (m, 3H), 0.68-0.81 (m, 2H), 0.46-0.60 (m, 2H).
38		LCMS m/z [M+1]: 748.1 1H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 7.19-7.23 (m, 1H), 7.00 (t, 1H), 5.19 (s, 0.5H), 4.96-5.06 (m, 1.5H), 4.33-4.45 (m, 2H), 3.77-3.93 (m, 3H), 3.72 (s, 3H), 3.58-3.63 (m, 1H), 3.38-3.46 (m, 1H), 2.84-2.98 (m, 2H), 2.69-2.81 (m, 1H), 2.44-2.67 (m, 4H), 2.30-2.39 (m, 1H), 1.88-2.19 (m, 3H), 1.41-1.45 (m, 3H), 0.62-0.72 (m, 2H), 0.46-0.56 (m, 2H)
39		LCMS m/z [M+1]: 710.1 1H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.40 (s, 2H), 7.44 (d, 1H), 7.25-7.20 (m, 1H), 7.01 (t, 1H), 6.50 (t, 1H), 5.37 (s, 0.5H), 5.24 (s, 0.5H), 4.33-4.27 (m, 0.5H), 4.22 (s, 1H), 4.19-4.13 (m, 0.5H), 3.27-3.19 (m, 3H), 3.18-2.98 (m, 3H), 2.79-2.72 (m, 1H), 2.46-2.31 (m, 2H), 2.28-2.10 (m, 3H), 2.03-1.96 (m, 2H), 1.91-1.84 (m, 1H), 1.30-1.27 (m, 2H).

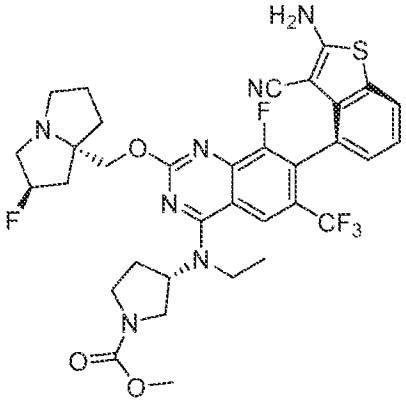
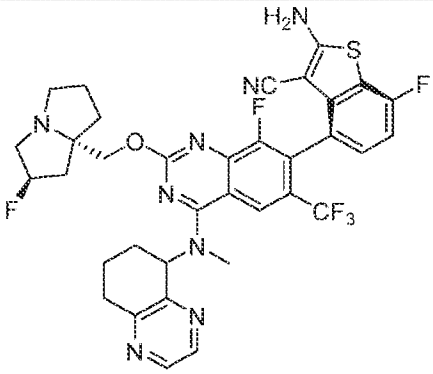
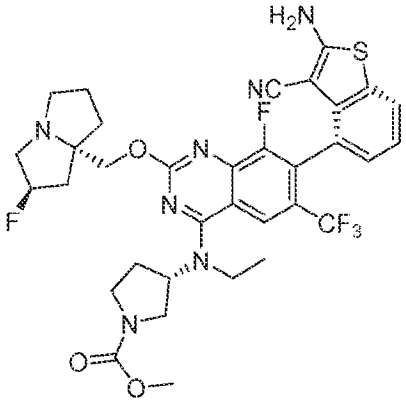
Cmpd. No.	Structure	Analytical Data
40		LCMS m/z [M+1]: 744.1 1H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 7.24-7.18 (m, 1H), 7.01 (t, 1H), 5.46-5.42 (m, 0.5H), 5.32-5.28 (m, 0.5H), 4.24-4.04 (m, 4H), 4.00-3.88 (m, 2H), 3.85-3.76 (m, 1H), 3.56-3.32 (m, 3H), 3.15-3.05 (m, 2H), 2.86-2.75 (m, 2H), 2.48-2.33 (m, 1H), 2.29-1.87 (m, 8H), 1.75 (d, 1 H), 1.59 (t, 3 H), 1.54-1.43 (m, 2H).
41		LCMS m/z [M+1]: 534.0 1H NMR (400 MHz, CD_3OD) δ 9.59 (s, 1H), 8.40 (s, 1H), 7.27-7.21 (m, 1H), 7.02 (t, 1H), 5.46-5.39 (m, 1H), 3.14-3.08 (m, 1H), 2.94-2.86 (m, 1H), 2.61 (s, 3H), 2.51-2.42 (m, 1H), 2.11-2.02 (m, 1H), 1.88-1.74 (m, 3H), 1.44 (d, 3H).
42		LCMS m/z [M+1]: 677.3 1H NMR (400 MHz, CD_3OD) δ = 8.23 (s, 1H), 7.21 (dd, J=8.3, 5.0 Hz, 1H), 7.04 – 6.96 (m, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 5.19 – 5.07 (m, 1H), 4.32 (dd, J=48.1, 10.7 Hz, 2H), 4.19 (td, J=8.6, 4.0 Hz, 1H), 4.03 (dd, J=9.9, 4.1 Hz, 1H), 3.98 – 3.74 (m, 4H), 3.41 – 3.32 (m, 1H), 3.29 – 3.19 (m, 2H), 3.05 (dd, J=9.6, 3.9 Hz, 1H), 2.50 (dd, J=8.2, 4.4 Hz, 1H), 2.40 – 2.14 (m, 4H), 1.99 (ddd, J=40.7, 20.3, 4.3 Hz, 3H), 1.40 (t, J=7.0 Hz, 3H).
43		LCMS m/z [M+1]: 710.3 1HNMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.44 (s, 1H),7.82-7.80 (m, 1H), 7.34-7.23(m, 1H),7.24-7.21(m, 1H), 6.99(m, 1H), 6.39-6.37(m, 0.5H), 6.23-6.18(m, 0.5H), 5.35 (s, 0.5H), 5.21 (s, 0.5H), 4.30-4.15 (m, 2H), 3.31 (m, 3H), 3.18-3.16 (m, 4H), 2.97 (m, 1H), 2.75 (m,1H), 2.23-2.18(m, 5H), 1.98-1.83 (m, 3H).

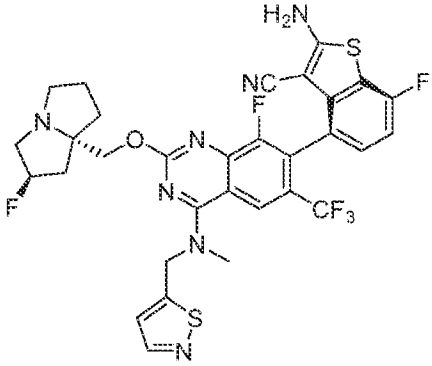
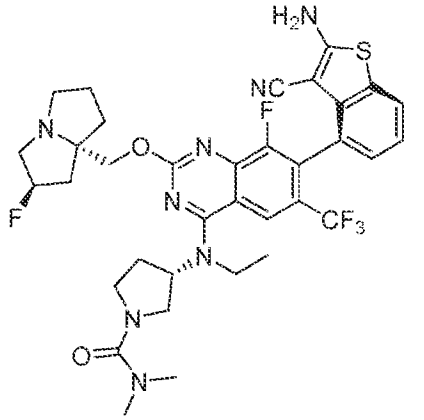
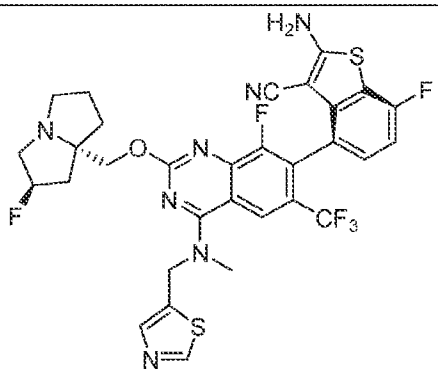
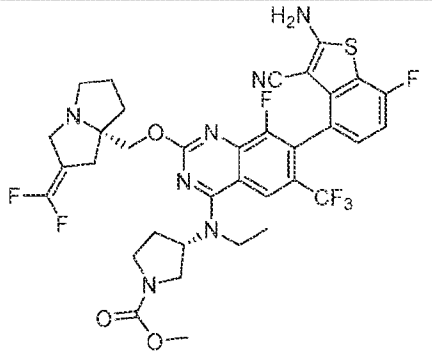
Cmpd. No.	Structure	Analytical Data
44		LCMS m/z [M+1]: 690.0 1H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.65 (s, 1H), 8.33 (s, 1H), 7.20 (t, J = 3.2 Hz, 1H), 7.00 (t, J = 9.6 Hz, 1H), 5.37 (s, 0.5H), 5.24-5.11 (m, 2.5H), 4.29 (d, J = 10.4 Hz, 1H), 4.33 (d, J = 10.8 Hz, 1H), 3.59 (s, 3H), 3.28-3.19 (m, 3H), 3.06-2.98 (m, 1H), 2.37-2.10 (m, 3H), 2.04-1.81 (m, 3H).
45		LCMS m/z [M+1]: 724.2 1H NMR (400 MHz, CD_3OD) δ 8.63 (s, 1H), 8.55 – 8.45 (m, 2H), 7.75 – 7.68 (m, 1H), 7.27 – 7.21 (m, 1H), 7.05 (t, J = 9.2 Hz, 1H), 6.33 (s, 1H), 5.60 (s, 0.5H), 5.47 (s, 0.5H), 4.70 – 4.62 (m, 1H), 4.60 – 4.52 (m, 1H), 4.05 – 3.93 (m, 1H), 3.92 – 3.83 (m, 2H), 3.51 – 3.37 (m, 4H), 3.10 – 3.00 (m, 2H), 2.68 – 2.58 (m, 1H), 2.58 – 2.52 (m, 1H), 2.47 – 2.35 (m, 2H), 2.34 – 2.20 (m, 4H), 2.13 – 2.02 (m, 2H).
46		LCMS m/z [M+1]: 738.2 1HNMR (400 MHz, CD_3OD) δ 8.39 (s, 1H), 8.31 – 8.24 (m, 2H), 7.29 – 7.17 (m, 2H), 7.05 – 6.95 (m, 1H), 5.55 (s, 1H), 5.32 (s, 0.5H), 5.18 (s, 0.5H), 4.07 (d, J = 10.3 Hz, 1H), 3.99 – 3.63 (m, 3H), 3.23 – 3.16 (m, 2H), 3.14 – 3.10 (m, 1H), 3.06 – 2.89 (m, 3H), 2.54 – 2.39 (m, 1H), 2.37 – 2.27 (m, 1H), 2.27 – 2.09 (m, 3H), 2.01 – 1.87 (m, 4H), 1.86 – 1.76 (m, 1H), 1.58 – 1.42 (m, 3H).
47		LCMS m/z [M+1]: 718.1 1H NMR (400 MHz, CD_3OD) δ8.21 (s, 1H), 7.23-7.20 (m, 1H), 7.01 (t, J=8.8 Hz, 1H), 5.39 (s, 0.5 H), 5.26 (s, 0.5 H), 5.04-5.00 (m, 1H), 4.34-4.25 (m, 2H), 3.85 (s, 2H), 3.48-3.31 (m, 3H), 3.06-2.79 (m, 6H), 2.51-1.91 (m, 10H), 1.47 (t, J=7.2 Hz, 3H).

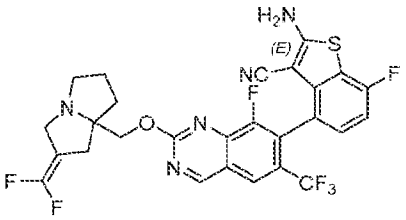
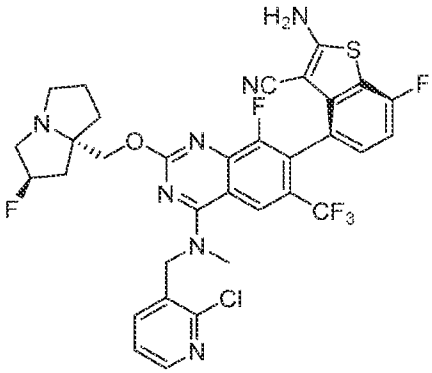
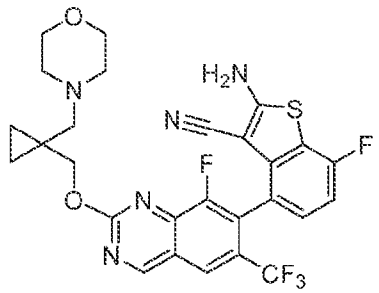
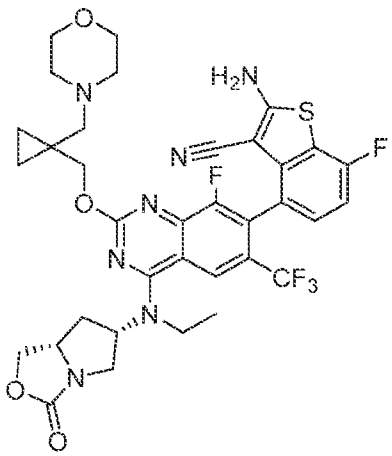
Cmpd. No.	Structure	Analytical Data
48		LCMS m/z [M+1]: 744.1 1HNMR(400 MHz, CD_3OD): δ 8.51 (s, 1H), 8.41 (s, 1H), 7.21-7.25 (m, 1H), 7.02 (d, J = 9.2 Hz, 1H), 5.48 (d, J = 51.6 Hz, 1H), 5.11-5.19 (m, 1H), 4.57-4.70 (m, 2H), 3.76-4.12 (m, 8H), 3.63-3.69 (m, 1H), 3.41-3.52 (m, 1H), 2.50-2.71 (m, 4H), 2.25-2.35 (m, 3H), 2.05-2.20 (m, 1H), 1.45-1.54 (m, 3H).
49		LCMS m/z [M+1]: 724.1 1H NMR (400 MHz, CD_3OD) δ 8.45-8.37 (m, 2H), 8.33 (s, 1H), 7.44 (d, 1H), 7.25-7.19 (m, 1H), 7.05-6.99 (m, 1H), 6.13-5.98 (m, 1H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 4.11 (d, 1H), 3.98 (d, 1H), 3.93-3.82 (m, 1H), 3.70-3.61 (m, 1H), 3.22-3.15 (m, 2H), 3.13-3.02 (m, 2H), 2.78-2.67 (m, 1H), 2.65-2.54 (m, 1H), 2.32-1.79 (m, 8H), 1.42 (t, 3H).
50		LCMS m/z [M+1]: 578.0 1H NMR (400 MHz, CD_3OD) δ 9.59 (s, 1H), 8.40 (s, 1H), 7.27-7.19 (m, 1H), 7.02 (t, 1H), 5.32-5.28 (m, 0.5H), 5.18-5.14 (m, 0.5H), 4.61-4.43 (m, 2H), 3.26-2.76 (m, 6H), 2.27-2.04 (m, 2H), 0.83 (s, 2H), 0.67 (s, 2H).
51		LCMS m/z [M+1]: 738.2 1HNMR (400 MHz, CD_3OD) δ 8.56 – 8.31 (m, 3H), 7.60 (s, 1H), 7.29 – 7.18 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.71 – 5.57 (m, 1.5H), 5.47 (s, 0.5H), 4.57 (d, J = 12.1 Hz, 1H), 4.28 – 4.04 (m, 2H), 4.01 – 3.73 (m, 4H), 3.45 – 3.39 (m, 1H), 3.11 (d, J = 11.2 Hz, 2H), 2.64 – 2.47 (m, 3H), 2.42 (s, 1H), 2.35 – 2.21 (m, 4H), 2.03-1.97 (m, 2H), 1.57 (s, 3H).

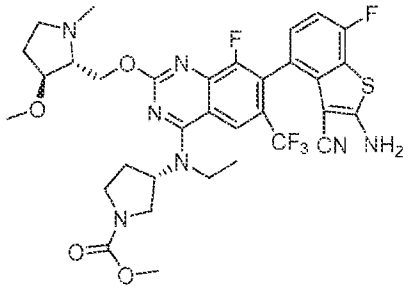
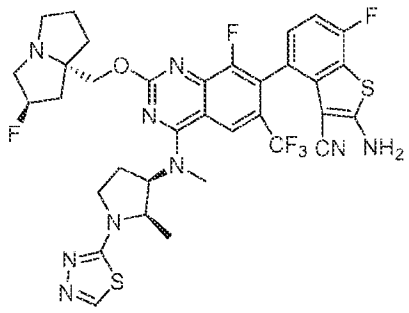
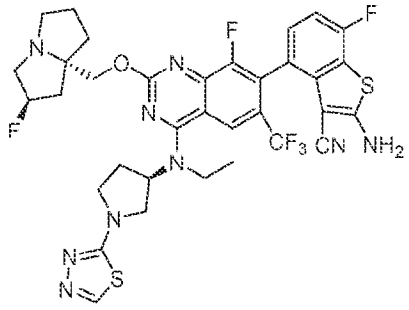
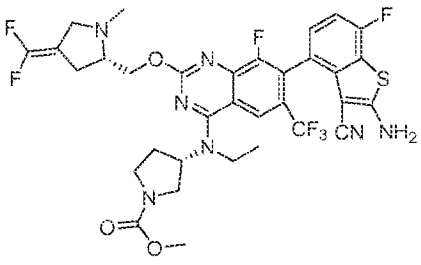
Cmpd. No.	Structure	Analytical Data
52		LCMS m/z [M+1]: 746.1 1H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 7.24-7.21 (m, 1H), 7.04-8.99 (m, 1H), 5.03-4.97 (m, 1H), 4.48-4.34 (m, 2H), 3.97-3.85 (m, 3H), 3.75-3.70(s, 3H), 3.66-3.60 (m, 4H), 3.49-3.42 (m, 1H), 2.62-2.24 (m, 8H), 1.49-1.42 (m, 3H), 1.38 -1.33(m, 2H), 0.73-0.66 (m, 2H), 0.53-0.45 (m, 2H).
53		LCMS m/z [M+1]: 688.0 1H-NMR (400 MHz, CD_3OD): 8.47 (s, 1 H), 8.32 (s, 1 H), 7.17-7.23 (m, 1 H), 6.96-7.03 (m, 1 H), 5.37 (s, 1 H), 5.24 (s, 0.5 H), 4.88-4.95 (m, 2 H), 4.21-4.38 (m, 2 H), 3.51 (s, 3 H), 3.31-3.37 (m, 1 H), 33.20-3.28 (m, 2 H), 2.98-3.02 (m, 1 H), 2.52 (s, 3 H), 2.21-2.37 (m, 2 H), 2.11-2.19 (m, 1 H), 1.95-2.05 (m, 2 H), 1.83-1.93 (m, 1 H).
54		LCMS m/z [M+1]: 691.2 1HNMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 7.21-7.20 (m, 1H), 7.03-7.00(m, 1H), 5.52-5.23 (m, 2H), 4.87 (m, 1H), 4.25-4.14 (m, 2H), 4.05 (m, 1H), 3.88-3.82 (m, 3H), 3.45 (m, 1H), 3.31-3.29 (m,3H), 2.99 (m, 1H), 2.12-1.85 (m, 10H), 1.28 (s, 3H).

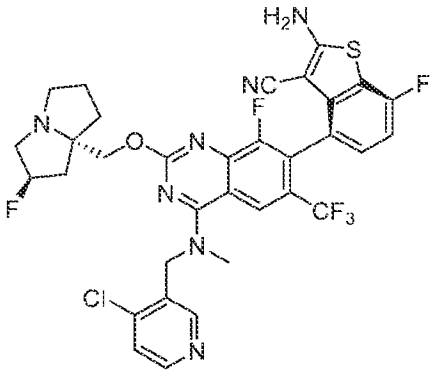
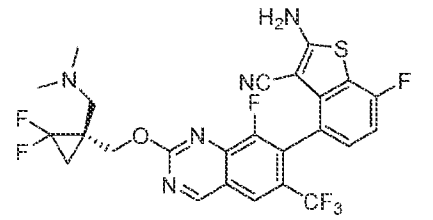
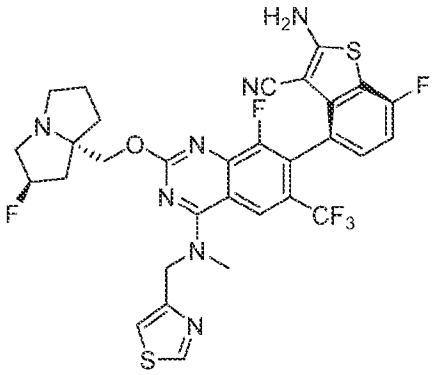
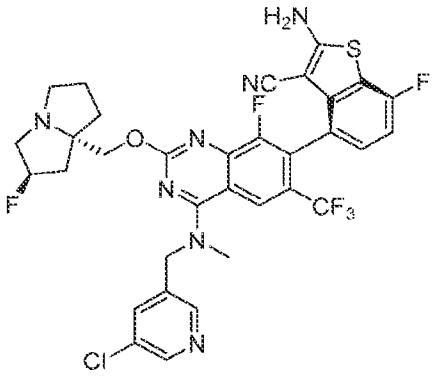
Cmpd. No.	Structure	Analytical Data
55		LCMS m/z [M+1]: 732.1 1H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.28 – 7.18 (m, J = 8.3, 5.0 Hz, 1H), 7.07 – 7.01 (m, 1H), 5.59 (s, 0.5H), 5.46 (s, 0.5H), 5.05 – 4.92 (m, 2H), 4.82 – 4.70 (m, 2H), 4.62 (s, 1H), 4.05 – 3.74 (m, 8H), 3.51 – 3.37 (m, 2H), 3.32 – 3.28 (m, J = 3.3, 1.6 Hz, 3H), 2.81 – 2.41 (m, 6H), 2.38 – 2.24 (m, J = 11.8, 7.0 Hz, 2H), 1.55 (t, J = 7.0 Hz, 3H).
56		LCMS m/z [M+1]: 733.1 1H NMR (400 MHz, CD_3OD): δ 8.25 (d, J = 11.6 Hz, 1H), 7.24 – 7.21 (m, 1H), 7.05 – 7.01 (m, 1H), 5.56 (d, J = 52.0 Hz, 1H), 5.11 – 5.03 (m, 1H), 4.77 – 4.60 (m, 2H), 4.09 – 3.42 (m, 12H), 2.77-2.11 (m, 10H), 1.45 (t, J = 7.0 Hz, 3H).
57		LCMS m/z [M+1]: 760.1 1HNMR(400 MHz, CD_3OD): δ 8.65 (s, 1H), 8.27 (s, 1H), 7.21-7.24 (m, 1H), 7.02 (t, J = 8.9 Hz, 1H), 5.37 (d, J = 52.8 Hz, 1H), 5.11-5.16 (m, 1H), 4.37-4.57 (m, 2H), 3.86-4.04 (m, 5H), 3.41-3.69 (m, 4H), 3.10-3.21 (m, 1H), 2.28-2.73 (m, 4H), 1.85-2.15 (m, 4H), 1.52 (t, J = 6.8 Hz, 3H).
58		LCMS m/z [M+1]: 702.1 1H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.23 (dd, J = 8.4, 5.0 Hz, 1H), 7.09 – 6.95 (m, 1H), 5.26 (s, 2H), 5.06 (dd, J = 15.7, 7.9 Hz, 1H), 4.92 (dd, J = 25.6, 12.3 Hz, 2H), 4.77 – 4.62 (m, 1H), 4.31 (s, 1H), 4.08 (s, 1H), 3.85 (ddd, J = 30.0, 16.7, 11.7 Hz, 4H), 3.75 (d, J = 8.8 Hz, 1H), 3.67 (d, J = 45.6 Hz, 3H), 3.55 (d, J = 9.7 Hz, 1H), 3.50 – 3.39 (m, 1H), 3.09 (t, J = 8.1 Hz, 3H), 2.83 (d, J = 11.9 Hz, 1H), 2.42 (d, J = 24.9 Hz, 2H), 1.44 (dt, J = 33.6, 8.2 Hz, 3H).

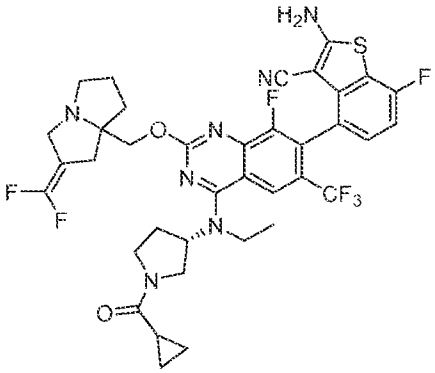
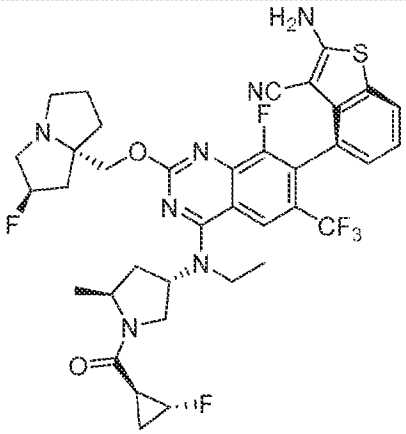
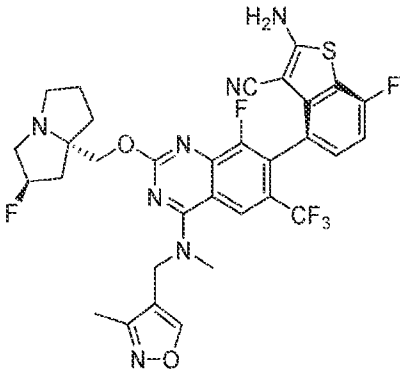
Cmpd. No.	Structure	Analytical Data
59		LCMS m/z [M+1]: 716.3 1HNMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.70 – 7.65 (m, 1H), 7.27 – 7.16 (m, 2H), 5.37 (s, 0.5H), 5.24 (s, 0.5H), 5.08 – 4.95 (m, 1H), 4.33 – 4.20 (m, 2H), 3.97 – 3.81 (m, 3H), 3.80 – 3.74 (m, 1H), 3.72 (s, 3H), 3.64 – 3.53 (m, 1H), 3.50 – 3.39 (m, 1H), 3.28 – 3.11 (m, 3H), 3.07 – 2.97 (m, 1H), 2.53 – 2.40 (m, 1H), 2.40 – 2.19 (m, 3H), 2.18 – 2.08 (m, 1H), 2.05 – 1.95 (m, 2H), 1.92 – 1.83 (m, 1H), 1.45 (t, J = 6.9 Hz, 3H).
60		LCMS m/z [M+1]: 725.1 1H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.42-8.43 (m, 2H), 7.19-7.22 (m, 1H), 7.00 (t, 1H), 5.90 (d, 1H), 5.33 (s, 0.5H), 5.20 (s, 0.5H), 4.07-4.20 (m, 1H), 3.91 (s, 1H), 3.40-3.48 (m, 2H), 3.04-3.24 (m, 6H), 2.95-3.01 (m, 1H), 2.32-2.44 (m, 2H), 2.18-2.28 (m, 2H), 2.01-2.16 (m, 3H), 1.83-1.97 (m, 3H).
61		LCMS m/z [M+1]: 716.3 1HNMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.71 – 7.62 (m, 1H), 7.27 – 7.14 (m, 2H), 5.37 (s, 0.5H), 5.24 (s, 0.5H), 5.08 – 4.96 (m, 1H), 4.32 – 4.21 (m, 2H), 3.96 – 3.67 (m, 7H), 3.66 – 3.53 (m, 1H), 3.52 – 3.38 (m, 1H), 3.28 – 3.17 (m, 3H), 3.09 – 2.96 (m, 1H), 2.54 – 2.08 (m, 5H), 2.05 – 1.82 (m, 3H), 1.44 (t, J = 6.9 Hz, 3H).

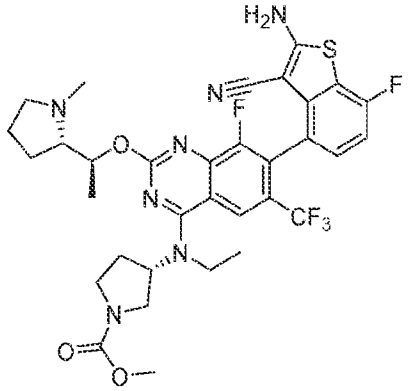
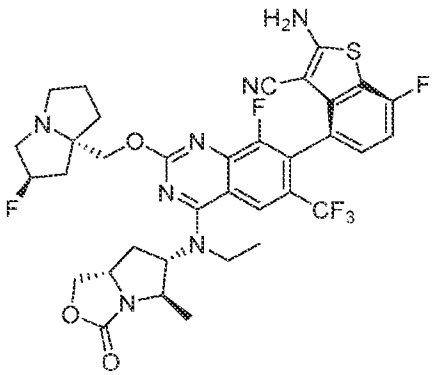
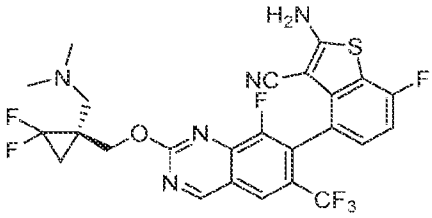
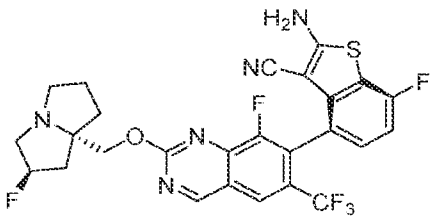
Cmpd. No.	Structure	Analytical Data
62		LCMS m/z [M+1]: 690.0 1H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.36 (s, 1H), 7.47 (s, 1H), 7.22-7.19 (m, 1H), 7.00 (t, J=8.8 Hz, 1H), 5.38-5.22 (m, 3H), 4.34 (dd, J=43.5, 10.6 Hz, 2H), 3.60 (s, 3H), 3.28-3.21 (m, 3H), 3.04-3.01 (m, 1H), 2.37-2.13 (m, 3H), 2.00-1.88 (m, 3H).
63		LCMS m/z [M+1]: 729.3 1HNMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 7.70 – 7.63 (m, 1H), 7.27 – 7.12 (m, 2H), 5.36 (s, 0.5H), 5.23 (s, 0.5H), 5.05 – 4.93 (m, 1H), 4.35 – 4.19 (m, 2H), 3.95 – 3.73 (m, 3H), 3.70 – 3.45 (m, 3H), 3.26 – 3.13 (m, 3H), 3.08 – 2.94 (m, 1H), 2.89 (s, 6H), 2.47 – 2.05 (m, 5H), 2.06 – 1.79 (m, 3H), 1.45 (t, J = 6.9 Hz, 3H).
64		LCMS m/z [M+1]: 690.0 1H-NMR (400 MHz, CD_3OD): 9.00 (s, 1 H), 8.37 (s, 1 H), 8.03 (s, 1 H), 7.16-7.25 (m, 1 H), 6.97-7.05 (m, 1 H), 5.39-5.44 (m, 1 H), 5.18-5.31 (m, 2.5 H), 4.30-4.48 (m, 2 H), 3.57 (s, 3 H), 3.34-3.53 (m, 3 H), 3.03-3.13 (m, 1 H), 2.25-2.45 (m, 2 H), 2.15-2.23 (m, 1 H), 1.99-2.10 (m, 2 H), 1.85-1.98 (m, 1 H).
65		LCMS m/z [M+1]: 764.1 1H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.20-7.23 (m, 1H), 7.01 (t, 1H), 5.00-5.04 (m, 1H), 4.35-4.39 (m, 1H), 4.28-4.31 (m, 1H), 3.74-3.94 (m, 5H), 3.71 (s, 3H), 3.47-3.59 (m, 3H), 3.19 (s, 1H), 2.75-2.83 (m, 2H), 2.36-2.56 (m, 3H), 2.00-2.16 (m, 1H), 1.89-1.96 (m, 3H), 1.42-1.45 (m, 3H).

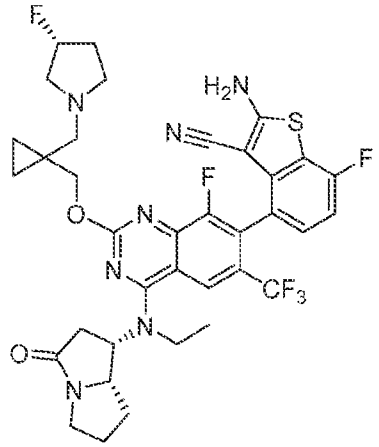
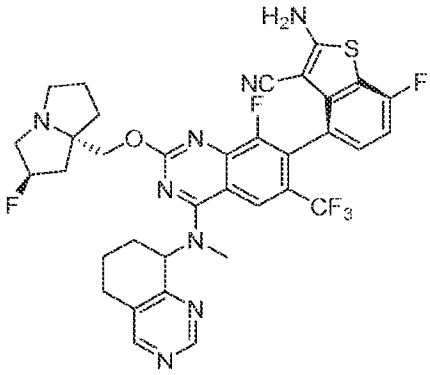
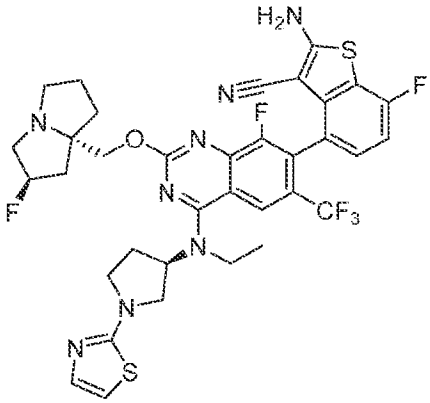
Cmpd. No.	Structure	Analytical Data
66		LCMS m/z [M+1]: 594.0 1H NMR (400 MHz, CD_3OD) δ 9.60 (s, 1H), 8.41 (s, 1H), 7.22 (s, 1H), 7.06-6.95 (m, 1H), 4.52-4.46 (m, 1H), 4.41-4.37 (m, 1H), 3.90-3.75 (m, 1H), 3.49-3.41 (m, 1H), 2.89-2.66 (m, 3H), 2.59-2.52 (m, 1H), 2.20-2.11 (m, 1H), 2.02-1.90 (s, 3H).
67		LCMS m/z [M+1]: 718.1 1H NMR (400 MHz, CD_3OD) δ 8.41 – 8.32 (m, 1H), 8.26 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 12.5 Hz, 1H), 7.20 (d, J = 13.3 Hz, 1H), 7.01 (d, J = 17.9 Hz, 1H), 5.33 (d, J = 15.0.5 Hz, 1H), 5.19 (s, 0.5H), 5.18 – 5.03 (m, 2H), 4.18 – 4.04 (m, 2H), 3.66 (s, 3H), 3.28 – 3.15 (m, 3H), 3.04 – 2.94 (m, 1H), 2.25 (d, J = 36.0 Hz, 2H), 2.08 – 1.90 (m, 3H), 1.88 – 1.75 (m, 1H).
68		LCMS m/z [M+1]: 576.2 1H NMR (400 MHz, CD_3OD) δ 9.58 (d, 1H), 8.39 (s, 1H), 7.28-7.20(m, 1H), 7.06-7.00 (m, 1H), 4.58 (d, 1H), 4.49 (d, 1H), 3.64 (t, 4H), 2.62-2.44 (s, 6H), 0.72-0.78 (m, 2H), 0.57-0.50 (m, 2H).
69		LCMS m/z [M+1]: 744.1 1H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 7.24-7.20 (m, 1H), 7.04-7.00 (m, 1H), 4.98-4.92 (m, 1H), 4.65-4.60 (m, 1H), 4.40-4.38 (m, 2H), 4.33-4.19(m, 2H), 3.96-3.84 (m, 2H), 3.82-3.69 (m, 5H), 3.66-3.59 (m, 1H), 3.16-2.82 (m, 5H), 2.72-2.63 (m, 1H), 2.54-2.46(m, 1H), 2.42-2.33 (m, 1H), 1.54-1.46 (m, 3H), 0.93-0.86 (m, 1H), 0.82-0.77 (m, 1H), 0.69-0.56 (m, 2H).

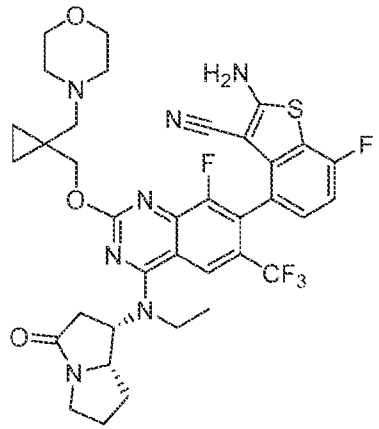
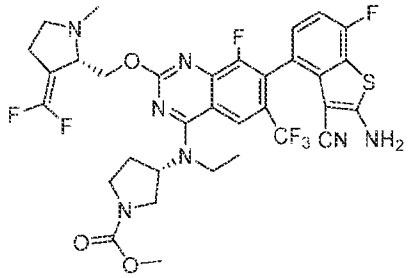
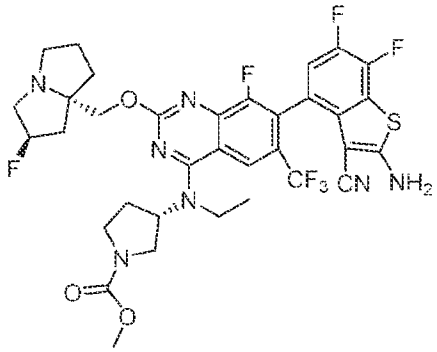
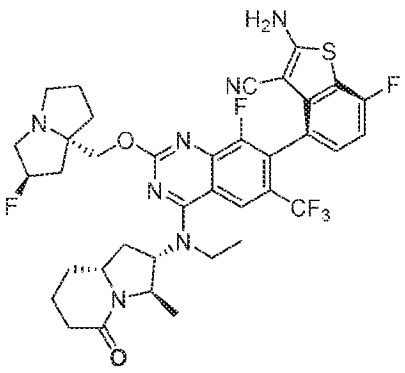
Cmpd. No.	Structure	Analytical Data
70		LCMS m/z [M+1]: 720.1 1H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.23 (dd, J = 8.3, 5.0 Hz, 1H), 7.06 – 6.99 (m, 1H), 5.06 (dd, J = 16.3, 8.1 Hz, 1H), 4.97 – 4.85 (m, 3H), 4.70 (td, J = 13.0, 6.4 Hz, 1H), 4.15 (s, 1H), 3.98 – 3.78 (m, 5H), 3.73 (s, 3H), 3.63 – 3.51 (m, 1H), 3.47 – 3.40 (m, 4H), 3.11 (s, 3H), 2.48 – 2.17 (m, 4H), 1.47 (t, J = 6.9 Hz, 3H).
70-1		LCMS m/z [M+1]: 760.2 1H NMR (400 MHz, CD_3OD) δ 8.67 (s, 1H), 8.44 (s, 1H), 7.25 – 7.23 (m, 1H), 7.05 – 7.01 (d, J = 16.0 Hz, 1H), 5.62 – 5.49 (d, J = 52.0 Hz, 1H), 5.01 – 4.96 (m, 2H), 4.75 – 4.60 (m, 2H), 3.92 – 3.81 (m, 3H), 3.71 (s, 2H), 3.58 – 3.38 (m, 2H), 3.31 – 3.30 (m, 4H), 2.88 – 2.82 (m, 1H), 2.67 – 2.57(m, 3H), 2.34 – 2.15 (m, 3H), 1.25 – 1.18 (m, 2H).
71		LCMS m/z [M+1]: 760.2 1H NMR (400 MHz, CD_3OD) δ 8.67 (s, 1H), 8.30 (s, 1H), 7.25 – 7.22 (m, 1H), 7.05 – 7.01 (d, J = 16.0 Hz, 1H), 5.60 – 5.47 (d, J = 52 Hz, 1H), 5.14 – 5.10 (m, 2H), 4.70 – 4.57 (m, 2H), 4.25 – 3.81 (m, 3H), 3.81 – 3.60 (s, 2H), 3.52 – 3.43 (m, 2H), 2.77 – 2.22 (m, 10H), 1.57 – 1.54 (m, 2H), 1.38 – 1.35(m, 1H).
72		LCMS m/z [M+1]: 738.0 1H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.29 – 7.15 (m, 1H), 7.10 – 6.96 (m, 1H), 5.06 (dd, J = 15.8, 7.7 Hz, 1H), 4.92 (d, J = 15.3 Hz, 1H), 4.79 – 4.70 (m, 1H), 4.43 (d, J = 14.5 Hz, 1H), 4.12 (s, 1H), 4.04 (d, J = 13.6 Hz, 1H), 3.98 – 3.78 (m, 3H), 3.75 (d, J = 11.5 Hz, 1H), 3.66 (d, J = 52.6 Hz, 3H), 3.55 (d, J = 8.2 Hz, 1H), 3.49 – 3.39 (m, 1H), 3.15 (d, J = 5.1 Hz, 3H), 3.08 (s, 1H), 2.85 (s, 1H), 2.39 (s, 2H), 1.45 (tt, J = 32.6, 16.3 Hz, 3H).

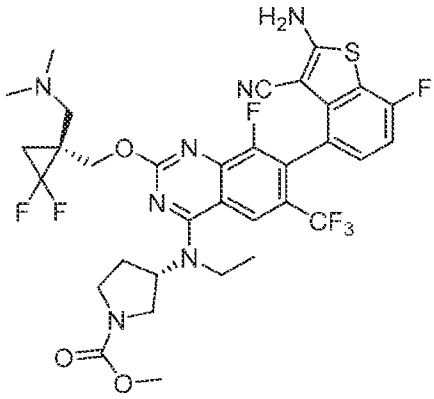
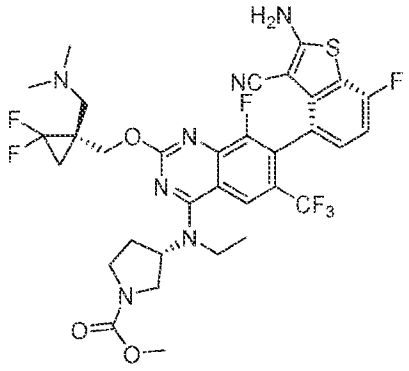
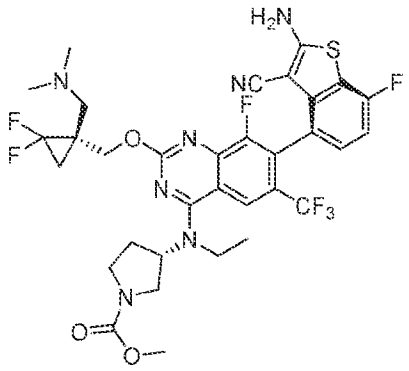
Cmpd. No.	Structure	Analytical Data
73		LCMS m/z [M+1]: 718.2 1H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.47 (d, 1H), 8.25 (s, 1H), 7.60 (d, 1H), 7.18-7.22 (m, 1H), 7.00 (t, 1H), 5.34 (s, 0.5H), 5.20 (d, 1.5H), 4.20 (d, 1H), 4.13 (d, 1H), 3.64 (s, 2H), 3.17-3.29 (m, 5H), 2.96-3.03 (m, 1H), 2.20-2.32 (m, 1H), 2.13-2.20 (m, 1H), 2.02-2.10 (m, 1H), 1.90-2.02 (m, 2H), 1.79-1.88 (m, 1H).
74		LCMS m/z [M+1]: 569.9 1H NMR (400 MHz, CD_3OD) δ 9.61 (s, 1H), 8.42 (s, 1H), 7.27-7.21 (m, 1H), 7.02 (t, 1H), 4.70 (s, 2H), 3.00-2.92 (m, 1H), 2.61-2.54 (m, 1H), 2.35 (s, 6H), 1.78-1.72 (m, 1H), 1.50-1.43 (m, 1H).
75		LCMS m/z [M+1]: 690.0 1H NMR (400 MHz, CD_3OD) δ 9.08 (d, J = 2.0 Hz, 1H), 8.45 (s, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.21 - 7.14 (m, 1H), 6.94 - 7.05(m, 1H), 5.36 (s, 0.5H), 5.22 (s, 0.5H), 5.20 - 5.19 (m, 2H), 4.30 - 4.19 (m, 2H), 3.56 (s, 3H), 3.25-3.20 (m, 3H), 3.02 - 2.98 (m, 1H), 2.36 - 2.20(m, 2H), 2.16 - 2.04 (m, 1H), 2.04 - 1.94 (m, 2H), 1.91 - 1.85 (m, 1H).
76		LCMS m/z [M+1]: 718.0 1H NMR (400 MHz, CD_3OD) δ 8.58 (d, J = 1.7 Hz, 1H), 8.53 (d, J = 2.3 Hz, 1H), 8.36 (s, 1H), 8.01 (m, 1H), 7.21 (m, 1H), 7.01 (m, 1H), 5.34 (s, 0.5H), 5.21 (s, 0.5H), 5.19 – 4.99 (m, 2H), 4.16 (m, 2H), 3.64 (s, 3H), 3.25 - 3.15(m, 3H), 3.03 – 2.94 (m, 1H), 2.31-2.15 (m, 2H), 2.14-2.04 (m, 1H), 2.03 – 1.90 (m, 2H), 1.89-1.79 (m, 1H).

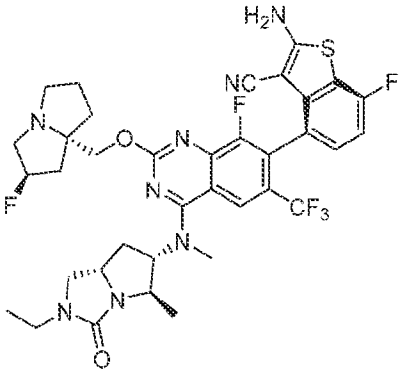
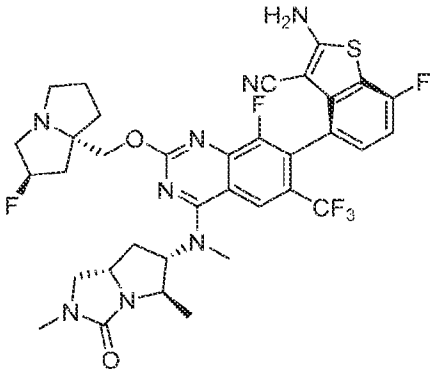
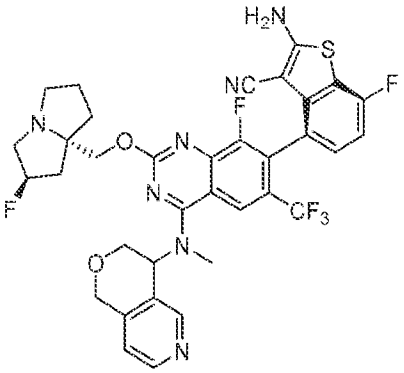
Cmpd. No.	Structure	Analytical Data
77		LCMS m/z [M+1]: 774.1 1H NMR (400 MHz, CD_3OD) δ 8.25-8.26 (m , 1H), 7.20-7.23 (m, 1H), 7.01 (t, 1H), 5.03-5.11 (m, 1H), 4.37-4.40 (m, 1H), 4.27-4.33 (m, 1H), 3.76-4.10 (m, 6H), 3.57-3.61 (m, 1H), 3.47-3.52 (m, 1H), 3.12-3.22 (m, 2H), 2.80-2.84 (m, 1H), 2.38-2.58 (m, 3H), 2.13-2.18 (m, 1H),1.94-2.01 (m, 3H), 1.82-1.87 (m, 1H),1.44-1.52 (m, 3H), 0.81-0.94 (m, 4H).
78		LCMS m/z [M+1]: 758.1 1HNMR (400 MHz, CD_3OD) δ 8.28 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.29 – 7.16 (m, 2H), 5.51 (s, , 0.5H), 5.39 (s, 0.5H), 5.34 – 5.18 (m, 1H), 4.98 – 4.92 (m, 0.5H), 4.79 – 4.64 (m, 0.5H), 4.64 – 4.23 (m, 3H), 4.03 – 3.80 (m, 3H), 3.78 – 3.68 (m, 1H), 3.68 – 3.54 (m, 2H), 3.29 – 3.17 (m, 2H), 2.89 – 2.60 (m, 1H), 2.59 – 1.95 (m, 8H), 1.58 – 1.40 (m, 5H), 1.33 – 1.24 (m, 3H).
79		LCMS m/z [M+1]: 688.19 1H NMR (400 MHz, CD3OD) δ 8.70 (s, 1H), 8.29 (s, 1H), 7.20 (dd, J = 8.1, 5.0 Hz, 1H), 7.04 – 6.96 (m, 1H), 5.34 (s, 1H), 5.21 (s, 1H), 4.91 (d, J = 4.4 Hz, 1H), 4.24 (dd, J = 28.6, 10.5 Hz, 2H), 3.58 – 3.47 (m, 3H), 3.25 – 3.11 (m, 3H), 3.04 – 2.95 (m, 1H), 2.39 – 2.27 (m, 3H), 2.25 – 2.08 (m, 3H), 2.04 – 1.93 (m, 2H), 1.87 (d, J = 13.7 Hz, 1H).

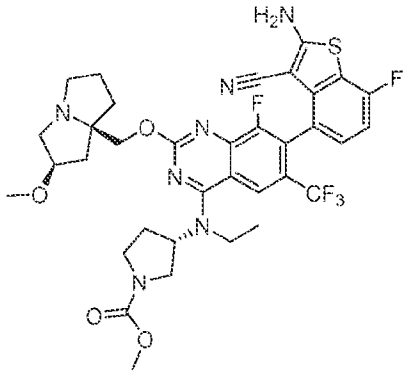
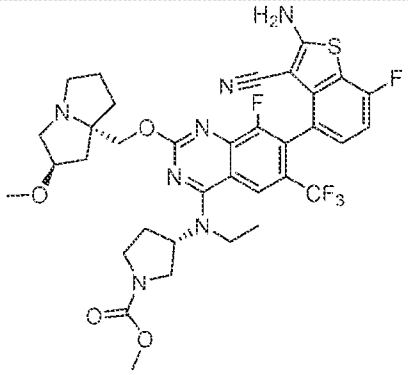
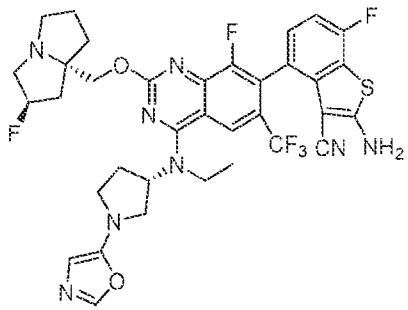
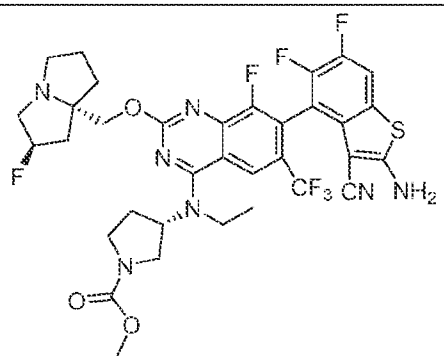
Cmpd. No.	Structure	Analytical Data
80		LCMS m/z [M+1]: 704.1 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.25-7.19 (m, 1H), 7.02 (t, 1H), 5.41-5.32 (m, 1H), 5.04-4.97 (m, 1H), 3.95-3.86 (m, 2H), 3.82-3.70 (m, 5H), 3.68-3.62 (m, 1H), 3.61-3.53 (m, 2H), 3.47-3.41 (m, 1H), 3.26-3.22 (m, 1H), 3.12 (s, 3H), 2.53-2.34 (m, 3H), 2.23-2.16 (m, 1H), 2.12-2.04 (m, 1H), 1.97-1.89 (m, 1H), 1.58-1.41 (m, 6H).
81		LCMS m/z [M+1]: 746.3 1HNMR (400 MHz, CD3OD) δ 8.19 (s, 1H), 7.27 – 7.18 (m, 1H), 7.07 – 6.97 (m, 1H), 5.40 (s, 0.5H), 5.27 (s, 0.5H), 4.61 (t, J = 8.5 Hz, 1H), 4.48 – 4.17 (m, 6H), 4.00 – 3.85 (m, 1H), 3.79 – 3.67 (m, 1H), 3.59 – 3.36 (m, 1H), 3.28 – 3.19 (m, 2H), 3.06 (d, J = 5.4 Hz, 1H), 2.76 – 2.64 (m, 1H), 2.51 – 2.16 (m, 4H), 2.09 – 1.83 (m, 3H), 1.54 (t, J = 7.0 Hz, 3H), 1.40 (d, J = 6.2 Hz, 3H).
82		LCMS m/z [M+1]: 570.1 1H NMR (400 MHz, CD3OD) δ 9.60 (s, 1H), 8.41 (s, 1H), 7.27-7.21 (m, 1H), 7.02 (t, 1H), 4.70 (s, 2H), 2.96-2.87 (m, 1H), 2.57-2.49 (m, 1H), 2.31 (s, 6H), 1.78-1.70 (m, 1H), 1.48-1.42 (m, 1H).
83		LCMS m/z [M+1]: 564.1 1H NMR (400 MHz, CD3OD) δ 9.68 (s, 1H), 8.47 (s, 1H), 7.26-7.21 (m, 1H), 7.03 (t, 1H), 5.65-5.61 (m, 0.5H), 5.52-5.48 (m, 0.5H), 4.80-4.68 (dq, 2H), 3.98-3.80 (m, 3H), 3.46-3.39 (m, 1H), 2.77-2.64 (m, 1H), 2.62-2.56 (m, 1H), 2.48-2.40 (m, 1H), 2.36-2.26 (m, 2H), 2.22-2.15 (m, 1H).

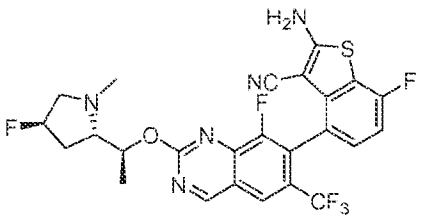
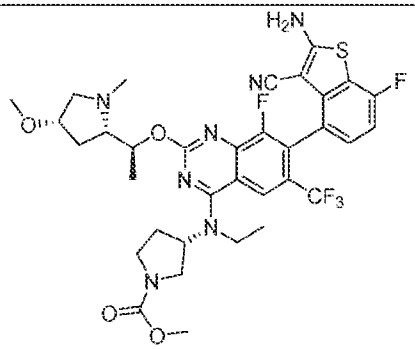
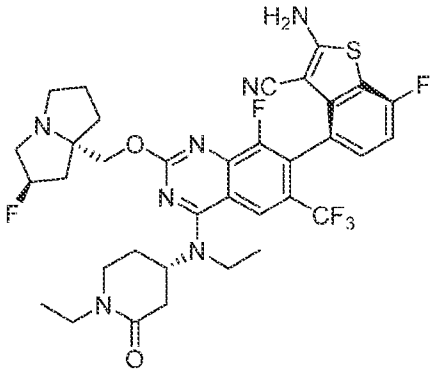
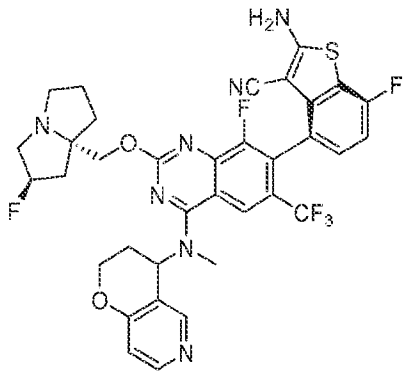
Cmpd. No.	Structure	Analytical Data
84		LCMS m/z [M+1]: 744.3 1H NMR (400 MHz, CD3OD) δ 8.18 (d, 1H), 7.20-7.21 (m, 1H), 7.01 (t, 1H), 5.29 (s, 0.5H), 5.16 (s, 0.5H), 4.51-4.60 (m, 1H), 4.42-4.47 (m, 1H), 4.37 (d, 1H), 4.27 (t, 1H), 3.84-3.95 (m, 3H), 3.48-3.60 (m, 2H), 3.05-3.21 (m, 3H), 2.83-2.93 (m, 2H), 1.96-2.36 (m, 6H), 1.58-1.66 (m, 1H), 1.53 (t, 3H), 1.29 (t, 1H), 0.68 (d, 4H).
85		LCMS m/z [M+1]: 725.3 1H NMR (400 MHz, CD3OD) δ 8.90 (d, 1H), 8.60 (d, 1H), 8.49 (s, 1H), 7.17-7.24 (m, 1H), 7.00 (t, 1H), 5.35 (s, 0.5H), 5.22 (s, 0.5H), 4.23 (d, 1H), 4.09 (d, 1H), 3.96 (s, 1H), 3.38-3.58 (m, 3H), 3.14-3.26 (m, 3H), 2.92-3.06 (m, 3H), 2.13-2.46 (m, 5H), 1.92-2.11 (m, 4H), 1.79-1.88 (m, 1H).
86		LCMS m/z [M+1]: 759.2 1H NMR (400 MHz, CD3OD) δ 8.304 (s, 1H), 7.29 (d, J = 40 Hz, 1H), 7.24 (t, J =5 Hz, 1H), 7.01 – 7.05 (m, 1H), 6.91 – 6.92 (m, 1H), 5.52 (d, J =51 Hz 1H), 5.18 (m, 1H), 4.61 – 4.72 (m, 4H), 3.84 – 4.03 (m, 6H), 3.69 – 3.71 (m, 1H), 3.42 – 3.48 (m, 1H), 2.27 – 2.77 (m, 8H), 1.52 – 1.56 (m, 3H).

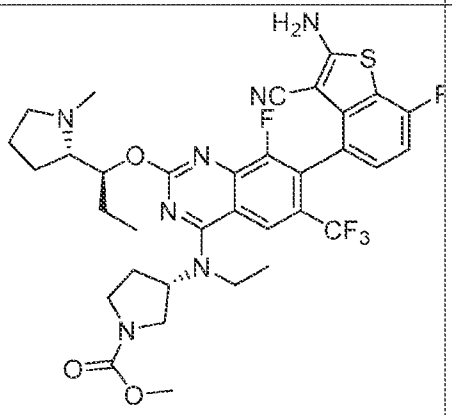
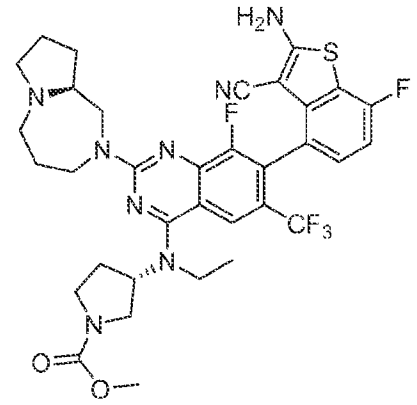
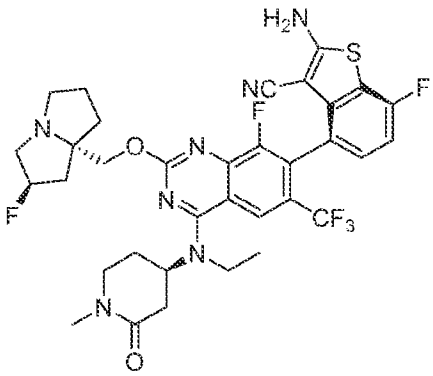
Cmpd. No.	Structure	Analytical Data
87		LCMS m/z [M+1]: 742.3 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.25-7.22 (m, 1H), 7.05-7.01 (m, 1H), 4.58-4.29 (m, 4H), 4.13-3.68 (m, 7H), 3.58-3.39 (m, 3H), 3.37-3.34(m, 1H), 3.14-3.10 (m, 2H), 2.94-2.87 (m, 1H), 2.25-2.11 (m, 4H), 1.66-1.54 (m, 4H), 1.33-1.29 (m, 1H), 0.97-0.88 (m, 4H).
88		LCMS m/z [M+1]: 680.3 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 7.25 – 7.21 (m, 1H), 7.03 (t, J = 8.7 Hz, 1H), 5.09 – 4.94 (m, 2H), 4.78 – 4.75 (m, 1H), 3.91 – 3.43 (m, 12H), 3.13 – 3.12 (m, 3H), 2.90 – 2.81 (m, 2H), 2.48 – 2.39 (m, 2H) , 1.49 – 1.46 (m, 3H).
89		LCMS m/z [M+1]: 752.2 1H NMR (400 MHz, CD3OD) δ 8.28 (m, 1H), 7.22-7.26 (m, 1H), 5.50-5.63(m, 1H), 5.02-5.06 (m, 1H), 4.59-4.68(m, 2H), 3.43-3.90(m, 14H), 2.13–2.66(m,9H), 1.46-1.50(m, 3H).
90		LCMS m/z [M+1]: 758.2 1H NMR (400MHz, CD3OD) δ 8.21 (s, 1H), 7.27 - 7.14 (m, 1H), 7.09 - 6.94 (m, 1H), 5.40 - 5.35 (m, 0.54H), 5.27 - 5.21 (m, 0.53H), 4.73 - 4.60 (m, 1H), 4.49 - 4.36 (m, 1H), 4.27 - 4.09 (m, 2H), 4.01 - 3.86 (m, 1H), 3.84 - 3.68 (m, 2H), 3.29 - 3.21 (m, 3H), 3.09 - 2.98 (m, 1H), 2.46 - 1.80 (m, 14H), 1.53 - 1.48 (m, 3H), 1.42 - 1.36 (m, 3H).

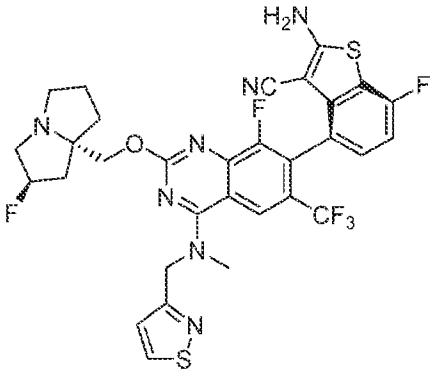
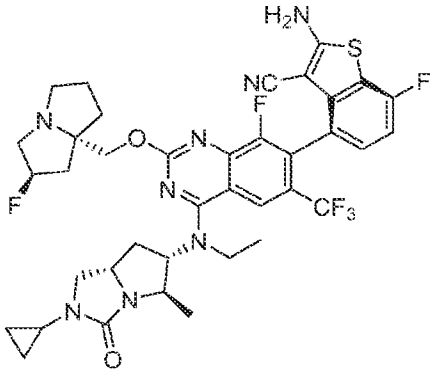
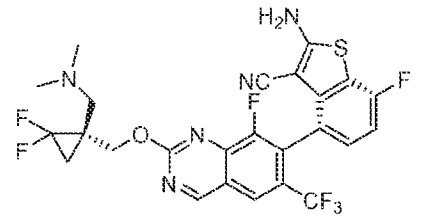
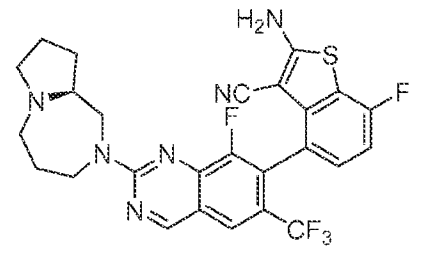
Cmpd. No.	Structure	Analytical Data
91		LCMS m/z [M+1]: 740.1 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.25 – 7.19 (m, J = 8.3, 5.1 Hz, 1H), 7.05 – 6.97 (m, 1H), 5.07 – 4.95 (m, J = 15.5, 7.8 Hz, 1H), 4.64 – 4.52 (m, J = 29.4, 11.4 Hz, 2H), 3.96 – 3.75 (m, 4H), 3.72 (s, 3H), 3.65 – 3.57 (m, J = 10.8, 8.0 Hz, 1H), 3.46 (d, J = 13.4 Hz, 1H), 2.85 (d, J = 12.3 Hz, 1H), 2.52 – 2.31 (m, 3H), 2.27 (s, 6H), 1.72 – 1.63 (m, J = 7.8, 6.5, 2.9 Hz, 1H), 1.47 – 1.42 (m, J = 6.9, 3.5 Hz, 3H), 1.40 – 1.34 (m, J = 8.0, 4.6 Hz, 1H).
92		LCMS m/z [M+1]: 740.1 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.27 – 7.17 (m, J = 8.3, 5.1 Hz, 1H), 7.01 (t, J = 9.4, 8.4 Hz, 1H), 5.08 – 4.96 (m, 1H), 4.63 – 4.54 (m, 2H), 3.94 – 3.74 (m, 4H), 3.71 (s, 3H), 3.64 – 3.57 (m, 1H), 3.49 – 3.41 (m, J = 13.1, 5.4 Hz, 1H), 2.89 (s, 1H), 2.59 – 2.45 (m, 2H), 2.41 (d, J = 19.2 Hz, 1H), 2.33 (s, 6H), 1.74 – 1.66 (m, J = 13.1, 8.0, 4.8 Hz, 1H), 1.44 (t, J = 6.9 Hz, 3H), 1.40 – 1.36 (m, 1H).
93		LCMS m/z [M+1]: 740.1 1H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.25 – 7.18 (m, J = 8.4, 5.0 Hz, 1H), 7.04 – 6.96 (m, J = 9.4, 8.5 Hz, 1H), 5.01 (d, J = 6.3 Hz, 1H), 4.61 – 4.53 (m, 2H), 3.95 – 3.72 (m, 4H), 3.72 (s, 3H), 3.67 – 3.56 (m, J = 16.8, 8.8 Hz, 1H), 3.47 – 3.40 (m, 1H), 2.87 (d, J = 12.9 Hz, 1H), 2.55 – 2.44 (m, 2H), 2.39 – 2.34 (m, J = 7.2, 4.6 Hz, 1H), 2.30 (s, 6H), 1.71 – 1.63 (m, J = 13.0, 8.1, 4.9 Hz, 1H), 1.45 (t, J = 7.0 Hz, 3H), 1.41 – 1.37 (m, J = 8.8, 4.0 Hz, 1H).

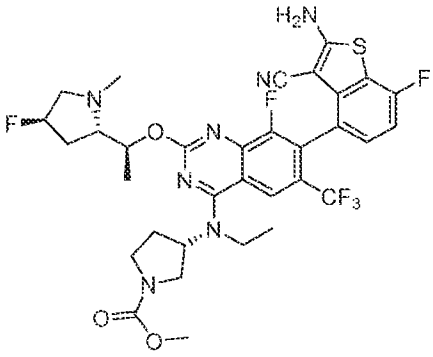
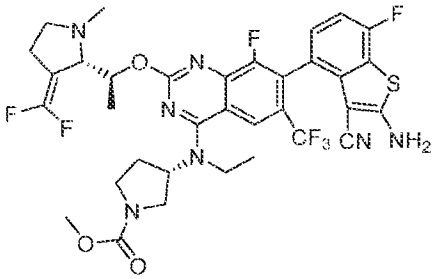
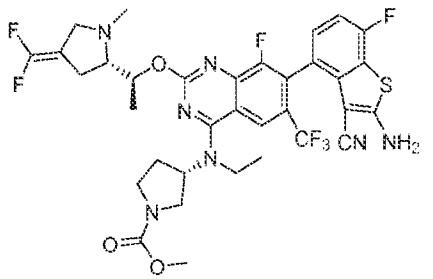
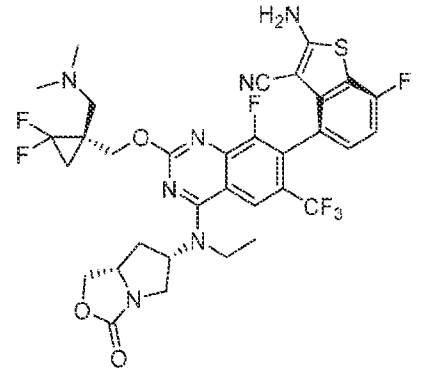
Cmpd. No.	Structure	Analytical Data
94		LCMS m/z [M+1]: 759.1 1H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 7.23-7.20 (m, 1H), 7.03-6.99 (m, 1H), 5.37 (s, 0.5H), 5.29 (s, 0.5H), 5.27-5.23 (m, 1H), 4.34-4.31(m, 1H), 4.24-4.21 (m, 1H), 4.08-4.03 (m, 2H), 3.68-3.64 (m, 1H), 3.48-3.44 (m, 1H), 3.36(s, 3H), 3.31-3.21 (m, 5H), 3.03-2.99 (m, 1H), 2.46-2.40 (m, 1H), 2.36-2.28 (m, 1H), 2.24-2.14(m, 2H), 2.02-1.95 (m, 2H), 1.92-1.87 (m, 2H), 1.41-1.40 (m, 3H), 1.17-1.14 (m, 3H).
95		LCMS m/z [M+1]: 745.2 1H NMR (400 MHz, CD3OD) δ 8.32 (s, 1H), 7.24-7.18 (m, 1H), 7.00 (t, 1H), 5.40-5.36 (m, 0.5H), 5.28-5.20 (m, 1.5H), 4.36-4.22 (dq, 2H), 4.09-4.00 (m, 2H), 3.64-3.58 (m, 1H), 3.47-3.43 (m, 1H), 3.40-3.31 (m, 4H), 3.28-3.22 (m, 2H), 3.07-3.00 (m, 1H), 2.85 (s, 3H), 2.44-2.38 (m, 1H), 2.35-2.27 (m, 1H), 2.26-2.21 (m, 1H), 2.19-2.13 (m, 1H), 2.06-1.88 (m, 4H), 1.39 (d, 3 H).
96		LCMS m/z [M+1]: 726.2 1H NMR (400 MHz, CD3OD) δ 8.77 (s, 1H), 8.57 (s, 1H), 8.46 (s, 1H), 7.55 (s, 1H), 7.22-7.25 (m, 1H), 7.03 (t, 1H), 6.33 (s, 1H), 5.62 (s, 0.5H), 5.49 (s, 0.5H), 5.04-5.08 (m, 1H), 4.89 (s, 1H), 4.72-4.76 (m, 1H), 4.58-4.65 (m, 1H), 4.43-4.47 (m, 1H), 4.31-4.35 (m, 1H), 3.97-4.07 (m, 1H), 3.84-3.94 (m, 2H), 3.42-3.49 (m, 4H), 2.57-2.73 (m, 2H), 2.30-2.43 (m, 3H), 2.07-2.11 (m, 1H).

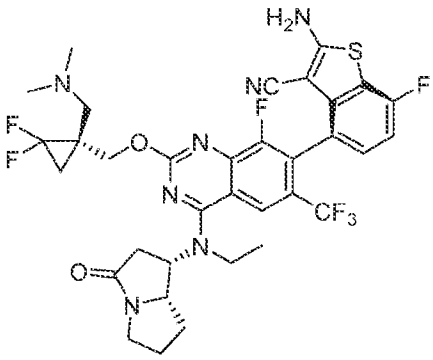
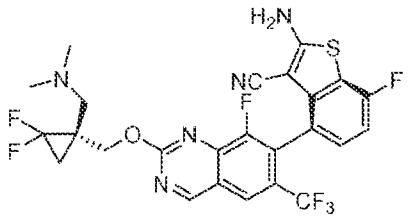
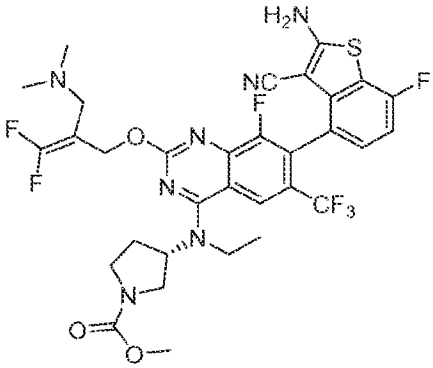
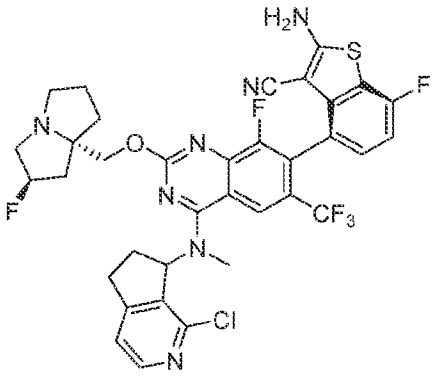
Cmpd. No.	Structure	Analytical Data
97		LCMS m/z [M+1]: 746.1 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.26 – 7.20 (m , 1H), 7.03 (t, J = 9.6 Hz, 1H), 5.10 – 4.95 (m , 2H), 4.83 – 4.59 (m , 2H), 4.24 – 4.16 (m, 1H), 3.96 – 3.78 (m, 5H), 3.72 (s, 3H), 3.69 – 3.56 (m, 2H), 3.50 – 3.39 (m, 2H), 3.37 – 3.35 (m, 3H), 2.54 – 2.36 (m, 4H), 2.29 – 2.17 (m, 3H), 2.11 – 2.04 (m, 1H), 1.49 (t, J = 6.8 Hz, 3H)
98		LCMS m/z [M+1]: 746.1 1H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.24 (dd, J = 8.0, 4.0 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 5.17 – 4.97 (m, 1H), 4.71 – 4.51 (m, 2H), 4.32 – 4.22 (m, 1H), 4.02 – 3.35 (m, 16H), 2.54 – 2.00 (m, 8H), 1.48 (t, J = 8.0 Hz, 3H).
99		LCMS m/z [M+1]: 743.1 1HNMR (400 MHz, CD3OD): δ 8.31 (s, 1H), 7.21-7.25 (m, 1H), 7.0 (t, J = 8.9 Hz, 1H), 6.59-6.68 (m, 1H), 6.27-6.32 (m, 1H), 5.72-5.78 (m, 1H), 5.43 (d, J = 54.8 Hz, 1H), 4.27-4.75 (m, 3H), 3.39-4.20 (m, 7H), 3.05-3.17 (m, 4H), 2.06-2.46 (m, 8H).
100		LCMS m/z [M+1]: 752.2 1H NMR (400 MHz, CD3OD) δ 8.15 (s, 1H), 7.03-7.07 (m, 1H), 5.54 (d, J = 50.2 Hz, 1H), 4.98-5.04 (m, 1H), 3.86-3.94(m, 6H), 3.75-3.84(m, 2H), 3.68-3.75(m, 4H), 3.36-3.62(m, 4H), 2.17-2.81 (m, 8H), 1.42 (t, J = 6.9 Hz, 3H).

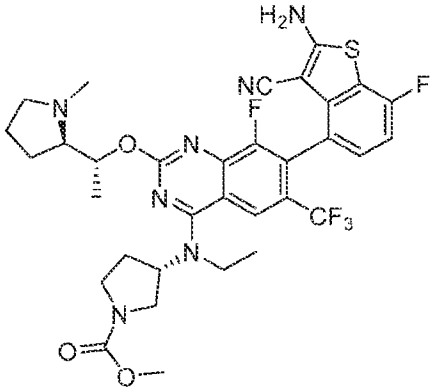
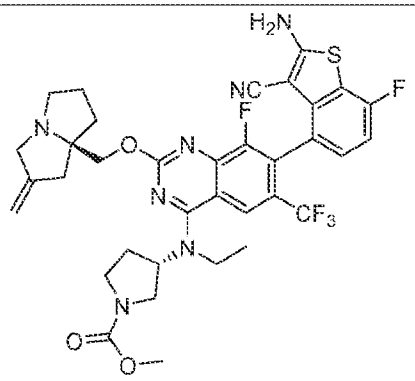
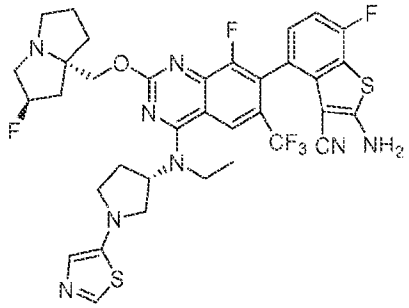
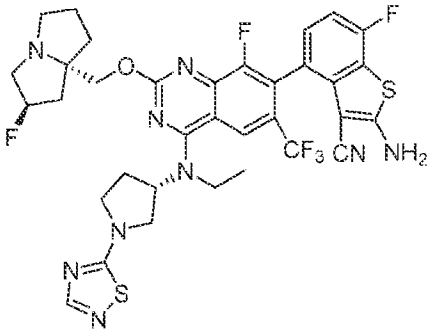
Cmpd. No.	Structure	Analytical Data
101		LCMS m/z [M+1]: 552.2 1H NMR (400 MHz, CD3OD) δ 9.59 (s, 1H), 8.39 (s, 1H), 7.25-7.22 (m, 1H), 7.02 (t,1H), 5.50-5.44 (m, 1H), 5.22 (s,0.5H), 5.08 (s, 0.5H), 3.51-3.38 (m, 1H), 3.23-3.17 (m,1H), 2.77-2.67 (m,1H), 2.65-2.56 (m,3H), 2.31-2.18 (m, 1H), 2.04-1.89 (m, 1H), 1.43-1.41 (m, 3H).
102		LCMS m/z [M+1]: 734.3 1H NMR (400 MHz, CD3OD) δ8.24 (s, 1H), 7.23-7.20 (m, 1H), 7.01 (t, J=8.8 Hz, 1H), 5.40 (s, 1H), 5.04-5.02 (m, 1H), 3.98-3.75 (m, 4H), 3.72 (s, 3H), 3.53-3.44 (m, 2H), 3.31 (s, 6H), 3.05-2.97 (m, 1H), 2.69-2.54 (m, 3H), 2.42-2.35 (m, 3H), 1.86 (m, 1H).
103		LCMS m/z [M+1]: 732.3 1HNMR (400 MHz, CD3OD) δ 8.20 (d, J = 6.9 Hz, 1H), 7.26 – 7.16 (m, 1H), 7.06 – 6.95 (m, 1H), 5.36 (s, 0.5H), 5.23 (s, 0.5H), 4.82 – 4.71 (m, 1H), 4.34 – 4.17 (m, 2H), 3.95 – 3.74 (m, 2H), 3.58 – 3.37 (m, 4H), 3.27 – 3.17 (m, 3H), 3.07 – 2.89 (m, 9.8 Hz, 2H), 2.87 – 2.72 (m, 1H), 2.56 – 2.39 (m, 1H), 2.40 – 2.06 (m, 4H), 2.06 – 1.78 (m, 3H), 1.48 (t, J = 6.9 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).
104		LCMS m/z [M+1]: 726.1 1H NMR (400 MHz, CD3OD) δ 8.43 (d, J = 5.5 Hz, 1H), 8.30 (d, J = 9.1 Hz, 1H), 8.25 (d, J = 6.3 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 5.8 Hz, 1H), 6.31 (s, 1H), 5.39 (d, 1H), 5.29 (d, J = 21.5 Hz, 1H), 5.12 (d, 1H), 4.60 (s, 1H), 4.44 (s, 1H), 4.31 (s, 1H), 3.65 – 3.56 (m, J = 16.0, 9.0 Hz, 1H), 3.37 (d, J = 1.8 Hz, 3H), 3.22 – 3.17 (m, 1H), 3.11 – 3.06 (m, 1H), 2.41 – 2.33 (m, J = 23.8

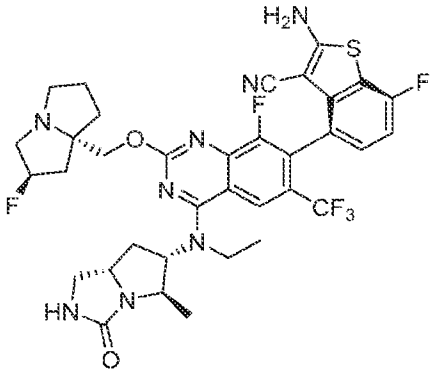
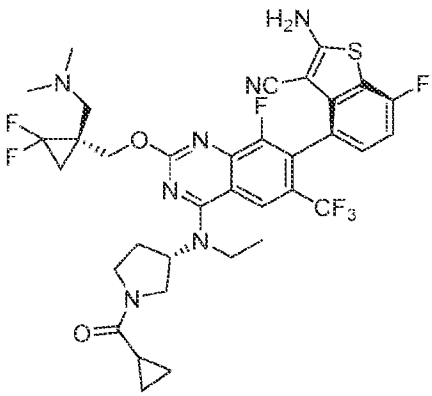
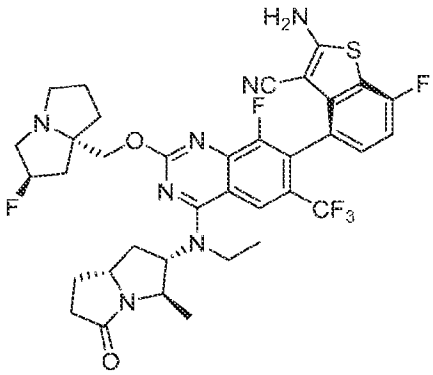
Cmpd. No.	Structure	Analytical Data
		Hz, 2H), 2.22 – 2.17 (m, J = 8.0 Hz, 2H), 2.07 – 2.02 (m, 2H), 1.99 – 1.92 (m, 2H).
105		LCMS m/z [M+1]: 718.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.25-7.18 (m, 1H), 7.02 (t, 1H), 5.40-5.32 (m, 1H), 5.07-4.98 (m, 1H), 3.96-3.79 (m, 3H), 3.72 (s, 3H), 3.59-3.52 (m, 1H), 3.49-3.39 (m, 2H), 3.04-2.72 (m, 5H), 2.47-2.35 (m, 2H), 2.28-2.16 (m, 2H), 2.05-1.98 (m, 2H), 1.91-1.78 (m, 2H), 1.62-1.57 (m, 1H), 1.49-1.42 (m, 3H), 1.07-0.97 (m, 3H).
106		LCMS m/z [M+1]: 715.1 1H NMR (400 MHz, CD3OD) δ 8.03 (s, 1H), 7.18 (t, 1H), 6.99 (t, 1H), 5.34 (t, 0.5H), 4.85-4.75 (m, 1H), 4.53-4.37 (m, 1H), 4.22-3.97 (m, 2H), 3.94-3.78 (m, 2H), 3.75-3.63 (m, 4H), 3.60-3.34 (m, 4H), 3.22-3.07 (m, 2H), 2.48-2.40 (m, 1H), 2.37-2.29 (m, 1H), 2.24-2.07 (m, 2H), 2.06-1.94 (m, 2H), 1.93-1.76 (m, 2H), 1.70-1.53 (m, 2H), 1.34 (t, 3H).
107		LCMS m/z [M+1]: 718.1 1H-NMR (400 MHz, CD3OD): 8.23 (s, 1 H), 7.19-7.24 (m, 1 H), 6.98-7.05 (m, 1 H), 5.48 (s, 0.5 H), 5.35 (s, 0.5 H), 4.78-4.85 (m, 1 H), 4.45-4.53 (m, 1 H), 4.35-4.44 (m, 1 H), 3.3.78-3.96 (m, 2 H), 3.46-3.74 (m, 4 H), 3.17-3.27 (m, 1 H), 2.88-3.02 (m, 4 H), 2.73-2.86 (m, 1 H), 2.36-2.57 (m, 3 H), 2.11-2.29 (m, 4 H), 1.95-2.04 (m, 1 H), 1.46-1.55 (m, 3 H).

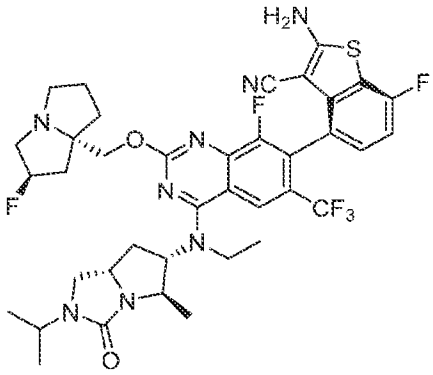
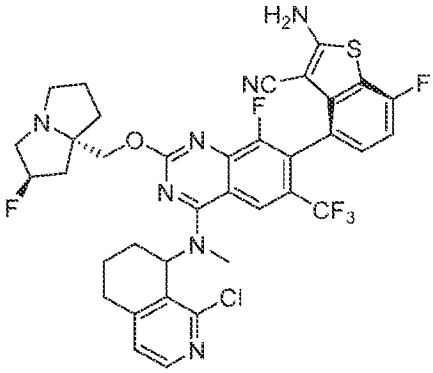
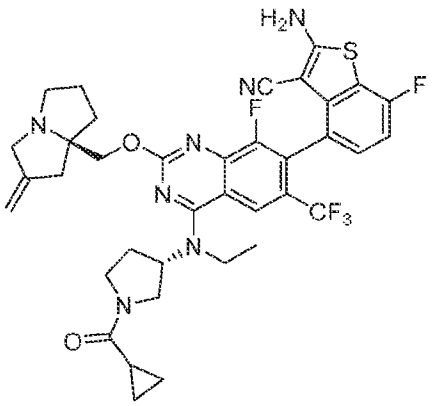
Cmpd. No.	Structure	Analytical Data
108		LCMS m/z [M+1]: 690.0 1H NMR (400 MHz, CD3OD) δ 8.98 (d, J = 4.7 Hz, 1H), 8.38 (s, 1H), 7.44 (d, J = 4.7 Hz, 1H), 7.21-7.19 (m, 1H), 7.03-6.98 (m, 1H), 5.37 (s, 1H), 5.23 (s, 1H), 5.22-5.21 (m, 2H), 4.25-4.14 (m, 2H), 3.64 (s, 3H), 3.27-3.21 (m, 3H), 3.08 – 2.98 (m, 1H), 2.37 – 2.24 (m, 1H), 2.24 – 2.17 (m, 1H), 2.18 – 2.05 (m, 1H), 2.06 – 1.93 (m, 2H), 1.92 – 1.78 (m, 1H).
109		LCMS m/z [M+1]: 785.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.28 – 7.20 (m, J = 8.3, 5.0 Hz, 1H), 7.01 (t, J = 9.4, 8.5 Hz, 1H), 5.40 (s, 0.5H), 5.27 (s, 0.5H), 4.82 – 4.77 (m, 1H), 4.36 (d, J = 10.8 Hz, 1H), 4.28 (d, J = 10.8 Hz, 1H), 4.14 – 4.07 (m, J = 13.2, 6.6 Hz, 1H), 3.99 – 3.93 (m, 1H), 3.90 – 3.80 (m, 1H), 3.70 – 3.59 (m, 2H), 3.41 – 3.37 (m, 1H), 3.33 (s, 1H), 3.30 (s, 2H), 3.10 – 3.04 (m, 1H), 2.60 – 2.54 (m, J = 6.8, 4.0 Hz, 1H), 2.44 – 2.09 (m, 5H), 2.06 – 1.89 (m, 3H), 1.39 (t, J = 6.9 Hz, 3H), 1.30 (d, J = 6.5 Hz, 3H), 0.78 – 0.67 (m, 4H).
110		LCMS m/z [M+1]: 569.9 1H NMR (400 MHz, CD3OD) δ 9.60 (d, J = 1.2 Hz, 1H), 8.41 (s, 1H), 7.29 – 7.19 (m, J = 8.3, 4.9 Hz, 1H), 7.06 – 6.97 (m, J = 9.4, 8.4 Hz, 1H), 4.70 (s, 2H), 2.93 – 2.84 (m, J = 13.0, 3.8 Hz, 1H), 2.52 – 2.38 (m, J = 6.5, 3.2 Hz, 1H), 2.28 (s, 6H), 1.76 – 1.67 (m, 1H), 1.46 – 1.38 (m, 1H).
111		LCMS m/z [M+1]: 545.0 1H NMR (400 MHz, CD3OD) δ 9.27 (s, 1H), 8.09 (s, 1H), 7.19 (t, 1H), 6.99 (t, 1H), 4.43-3.94 (m, 3H), 3.57-3.42 (m, 1H), 3.22-3.07 (m, 2H), 2.95-2.75 (m, 1H), 2.60-2.34 (m, 2H), 2.23-1.80 (m, 5H), 1.72-1.58 (m, 1H).

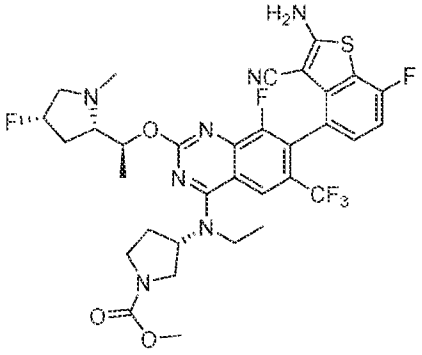
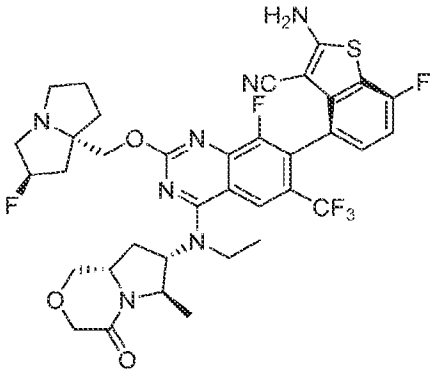
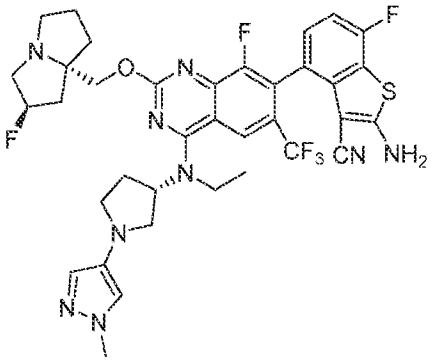
Cmpd. No.	Structure	Analytical Data
112		LCMS m/z [M+1]: 722.3 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 0.5H), 7.23-7.20 (m, 1H), 7.03-6.98 (m, 1H), 5.36-5.31 (m,1H), 5.22 (s, 0.5H), 5.08 (s,0.5H), 5.01 (t, 1H), 3.95-3.86 (m, 2H), 3.75-3.71 (m, 3H), 3.58-3.38 (m, 4H), 2.80-2.70 (m, 1H), 2.61 (s, 3H), 2.48-2.37 (m, 2H), 2.30-2.16 (m, 2H), 2.03-1.87 (m, 2H),1.46-1.41 (m, 3H), 1.38-1.35 (m, 3H).
113		LCMS m/z [M+1]: 752.1 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.20-7.25 (m, 1H), 7.03 (t, J = 9.08 Hz, 1H), 5.45-5.60 (m, 1H), 4.95-5.10 (m, 1H), 4.65-4.74 (m, 1H), 3.70-4.02 (m, 8H), 3.37-3.59 (m, 3H), 3.08-3.15 (m, 3H), 2.75-2.96 (m, 2H), 2.33-2.55 (m, 2H), 1.55-1.62 (m, 3H), 1.46 (t, J = 6.84 Hz, 3H).
114		LCMS m/z [M+1]: 752.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.26 – 7.19 (m, 1H), 7.03 (t, J = 8.8 Hz, 1H), 5.53 (s, 1H), 5.03 (s, 1H), 4.38 (d, J = 14.4 Hz, 1H), 4.13 – 4.02 (m, 2H), 3.98 – 3.82 (m, 3H), 3.79 – 3.68 (m, 4H), 3.62 – 3.52 (m, 1H), 3.48 – 3.41 (m, 1H), 3.18 – 3.03 (m, 4H), 2.79 – 2.66 (m, 1H), 2.56 – 2.32 (m, 2H), 1.54 (d, J = 6.0 Hz, 3H), 1.46 (t, J = 6.8 Hz, 3H).
115		LCMS m/z [M+1]: 738.1 1H NMR (400 MHz, CD3OD) δ 8.18(s, 1H), 7.19-7.24 (m, 1H), 7.01(t, 1H), 4.91-4.99 (m, 1H), 4.61 (t, 2H), 4.46 (d, 1H), 4.36-4.42 (m, 1H), 4.18-4.25 (m, 1H), 3.81-3.92 (m, 2H), 3.69-3.71 (m, 1H), 3.59-3.66 (m, 1H), 2.78 (s, 2H), 2.45-2.54 (m, 1H), 2.29-2.38 (m, 6H), 1.74-1.82 (m, 1H), 1.33-1.53 (m, 5H).

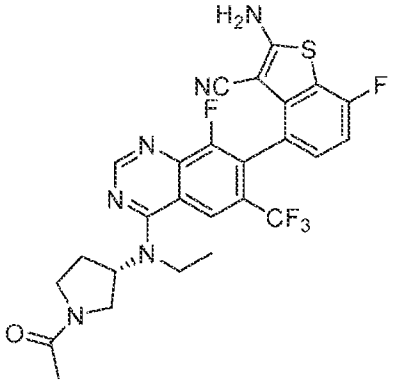
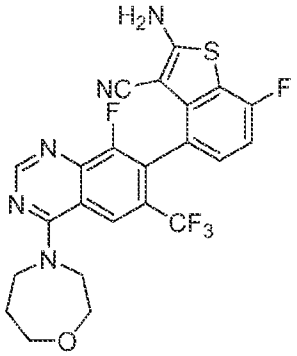
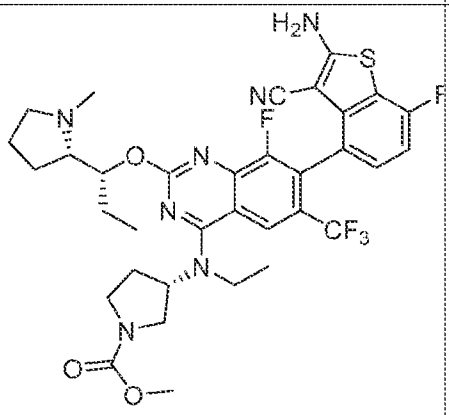
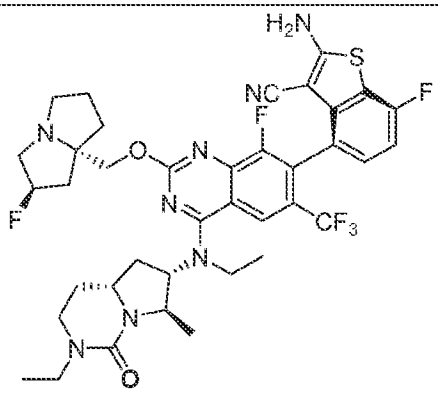
Cmpd. No.	Structure	Analytical Data
116		LCMS m/z [M+1]: 736.1 1H NMR (400 MHz, CD3OD) δ 8.19 (s, 1H), 7.25 – 7.19 (m, J = 5.2 Hz, 1H), 7.05 – 6.95 (m, J = 9.4, 8.5 Hz, 1H), 4.55 – 4.45 (m, J = 14.1, 8.5 Hz, 4H), 3.94 – 3.87 (m, J = 7.1 Hz, 2H), 3.62 – 3.54 (m, 2H), 3.12 (t, J = 9.4 Hz, 1H), 2.92 – 2.79 (m, 2H), 2.60 (d, 1H), 2.31 (s, 6H), 2.23 – 2.17 (m, 2H), 2.12 – 2.06 (m, 1H), 1.69 – 1.59 (m, 2H), 1.55 (t, J = 7.0 Hz, 3H), 1.45 – 1.41 (m, 1H).
117		LCMS m/z [M+1]: 569.9 1H NMR (400 MHz, CD3OD) δ 9.60 (d, J = 1.2 Hz, 1H), 8.42 (s, 1H), 7.28 – 7.21 (m, J = 8.8, 4.5 Hz, 1H), 7.08 – 6.99 (m, J = 9.4, 8.4 Hz, 1H), 4.70 (s, 2H), 2.88 (d, J = 12.7, 3.4 Hz, 1H), 2.50 (d, J = 15.2 Hz, 1H), 2.30 (s, 6H), 1.77 – 1.69 (m, J = 13.1, 8.1, 5.0 Hz, 1H), 1.47 – 1.41 (m, 1H).
118		LCMS m/z [M+1]: 726.3 1HNMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.27 – 7.19 (m, 1H), 7.06 – 6.98 (m, 1H), 5.09 (s, 3H), 3.98 – 3.81 (m, 3H), 3.72 (s, 4H), 3.64 (s, 1H), 3.59 – 3.54 (m, 2H), 3.50 – 3.43 (m, 1H), 2.72 – 2.31 (m, 8H), 1.49 – 1.42 (m, 3H).
119		LCMS m/z [M+1]: 744.0 1H NMR (400 MHz, CD3OD) δ 8.34-8.31 (m, 1H), 8.30 (t, 1H), 7.42 (d, 1H), 7.25-7.20 (m, 1H), 7.03-6.98 (m, 1H), 6.49 (s, 0.5H), 6.35 (s, 0.5H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 4.36-4.28 (m, 1H), 4.25-4.20 (m, 1H), 3.65-3.61 (m, 1H), 3.38-3.33 (m, 1H), 3.24-3.19 (m, 4H), 3.17-3.11 (m, 1H), 3.06-3.01 (m, 1H), 2.95-3.89 (m, 1H), 2.40-2.30 (m, 1H), 2.31-2.20 (m, 2H), 2.18-2.14 (m, 1H), 2.04-1.87 (m, 4H).

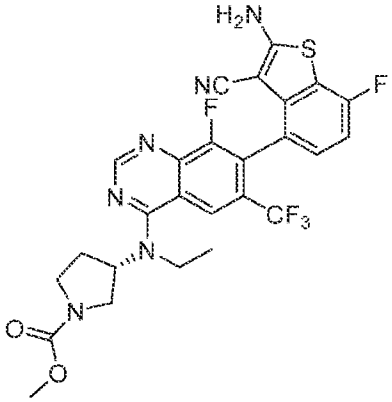
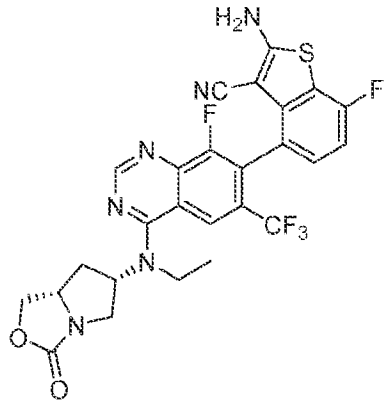
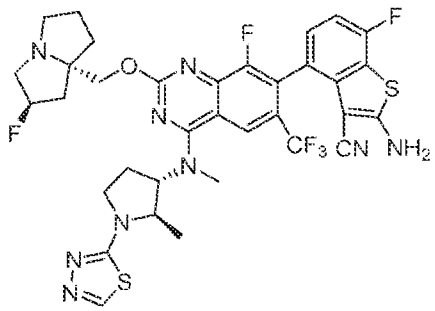
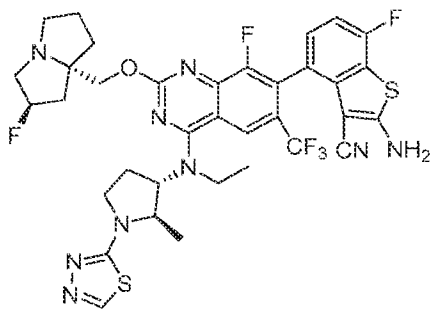
Cmpd. No.	Structure	Analytical Data
120		LCMS m/z [M+1]: 704.3 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.23-7.19 (m, 1H), 7.00 (t, 1H), 5.35-5.29 (m, 1H), 5.03-4.96 (m, 1H), 3.93-3.81 (m, 3H), 3.79-3.68 (m, 4H), 3.64-3.59 (m, 1H), 3.49-3.31 (m, 2H), 3.16-3.11 (m, 1H), 2.85 (s, 1H), 2.64-2.43 (m, 5H), 2.38-2.32 (m, 1H), 2.11-2.04 (m, 1H), 1.85-1.77 (m, 2H), 1.47-1.41 (m, 3H), 1.40-1.36 (m, 3H).
121		LCMS m/z [M+1]: 728.1 1H NMR (400 MHz, CD3OD) δ = 8.25 (s, 1H), 7.22 (dd, J=8.3, 5.1, 1H), 7.06 – 6.97 (m, 1H), 5.12 – 4.99 (m, 3H), 4.42 (d, J=9.5, 2H), 4.01 – 3.35 (m, 12H), 2.88 (d, J=16.0, 2H), 2.60 (d, J=15.8, 1H), 2.41 (d, J=35.7, 2H), 2.25 – 2.18 (m, 1H), 2.11 – 1.92 (m, 3H), 1.45 (td, J=6.8, 2.1, 3H).
122		LCMS m/z [M+1]: 759.2 1HNMR(400 MHz, CD3OD): δ 8.39 (s, 1H), 8.29 (s, 1H), 7.21-7.25 (m, 1H), 6.97-7.05 (m, 2H), 5.57 (d, J = 52.4 Hz, 1H), 5.17-5.22 (m, 1H), 4.56-4.69 (m, 2H), 3.63-4.04 (m, 8H), 3.36-3.47 (m, 2H), 2.50-2.71 (m, 4H), 2.03-2.31 (m, 4H), 1.52 (t, J = 6.8 Hz, 3H).
123		LCMS m/z [M+1]: 760.2 1HNMR(400 MHz, CD3OD): δ 8.31 (s, 1H), 8.00 (s, 1H), 7.21-7.25 (m, 1H), 7.02 (d, J = 9.2 Hz, 1H), 5.53 (d, J = 52.4 Hz, 1H), 5.14-5.22 (m, 1H), 4.56-4.66 (m, 2H), 3.83-4.02 (m, 8H), 3.40-3.68 (m, 2H), 2.50-2.73 (m, 4H), 2.10-2.26 (m, 3H), 2.05-2.19 (m, 1H), 1.54 (d, J = 5.8 Hz, 3H).

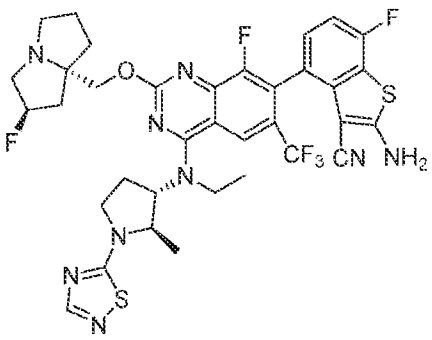
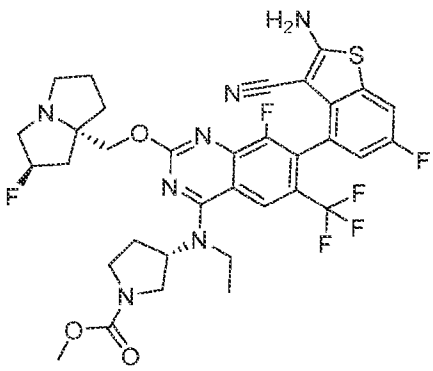
Cmpd. No.	Structure	Analytical Data
124		LCMS m/z [M+1]: 745.1 1H NMR (400 MHz, CD3OD) δ 6.90 (s, 1H), 5.95 – 5.86 (m, J = 8.3, 5.1 Hz, 1H), 5.71 – 5.65 (m, J = 8.6 Hz, 1H), 4.08 (s, 0.5H), 3.94 (s, 0.5H), 3.35 – 3.24 (m, 1H), 3.00 (d, J = 10.5 Hz, 1H), 2.93 – 2.85 (m, J = 13.1, 8.3 Hz, 2H), 2.81 – 2.73 (m, 1H), 2.64 – 2.51 (m, J = 13.9, 6.8 Hz, 1H), 2.38 – 2.30 (m, 2H), 2.13 – 2.07 (m, J = 9.4, 2.2 Hz, 1H), 1.91 (t, J = 9.6 Hz, 3H), 1.75 – 1.68 (m, J = 15.0, 9.6 Hz, 1H), 1.14 – 0.83 (m, 5H), 0.74 – 0.57 (m, 3H), 0.13 (t, J = 6.9 Hz, 3H), 0.01 (d, J = 6.3 Hz, 3H).
125		LCMS m/z [M+1]: 750.1 1H NMR (400 MHz, CD3OD) δ 8.26 (d, 1H), 7.19-7.25 (m, 1H), 7.01 (t, 1H), 4.96-5.17 (m, 1.5H), 4.58 (s, 2H), 4.25-4.30 (m, 0.5H), 4.05-4.11 (m, 0.5H), 3.96-4.02 (m, 0.5H), 3.80-3.94 (m, 3H), 3.73-3.79 (m, 0.5H), 3.63-3.68 (m, 0.5H), 3.34-3.50 (m, 1H), 2.88 (t, 1H), 2.41-2.66 (m, 3H), 2.27-2.40 (m, 6H), 1.80-1.89 (m, 1H), 1.64-1.72 (m, 1H), 1.43-1.50 (m, 3H), 0.81-0.94 (m, 4H).
126		LCMS m/z [M+1]: 744.3 1HNMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.26 – 7.20 (m, 1H), 7.06 – 6.97 (m, 1H), 5.44 (s, 0.5H), 5.30 (s, 0.5H), 4.62 – 4.51 (m, 1H), 4.49 – 4.38 (m, 1H), 4.37 – 4.14 (m, 3H), 4.00 – 3.88 (m, 1H), 3.84 – 3.71 (m, 1H), 3.57 – 3.35 (m, 3H), 3.13 (s, 1H), 2.84 – 2.71 (m, 1H), 2.54 – 2.17 (m, 7H), 2.13 – 1.88 (m, 4H), 1.53 (t, J = 7.0 Hz, 3H), 1.36 (d, J = 6.4 Hz, 3H).

Cmpd. No.	Structure	Analytical Data
127		LCMS m/z [M+1]: 787.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.26-7.22 (m, 1H), 7.06 – 6.99 (m, 1H), 5.39 (s, 0.5H), 5.25 (s, 0.5H), 4.38 – 4.29 (m, 1H), 4.29-4.20 (m, 1H), 4.20 – 4.05 (m, 2H), 4.04 – 3.94 (m, 1H), 3.87 - 3.78(m, 1H), 3.68 – 3.53 (m, 2H), 3.43-3.40 (m, 1H), 3.30-3.18 (m, 4H), 3.10 – 2.98 (m, 1H), 2.40 – 2.13 (m, 4H), 2.10 – 1.85 (m, 4H), 1.41 – 1.26 (m, 7H), 1.24 – 1.13 (m, 5H).
128		LCMS m/z [M+1]: 758.1 1H NMR (400 MHz, CD3OD) δ 8.36 (s, 1H), 8.20 (d, J = 5.1 Hz, 1H), 7.29 (d, J = 5.0 Hz, 1H), 7.22-7.20 (m, 1H), 7.05 – 6.96 (m, 1H), 6.05 (s, 1H), 5.39 (s, 0.5H), 5.25 (s, 0.5H), 4.29-4.24 (m, 2H), 3.31-3.27 (m, 5H), 3.14 – 3.00 (m, 2H), 2.95-2.91 (m, 1H), 2.66-2.55 (m, 1H), 2.46 – 2.06 (m, 6H), 2.06 – 1.96 (m, 2H), 1.94-1.81 (m, 2H).
129		LCMS m/z [M+1]: 738.3 1H NMR (400 MHz, CD3OD) δ = 8.27 (d, J=3.9, 1H), 7.23 (dd, J=8.5, 5.2, 1H), 7.02 (t, J=8.8, 1H), 5.09 (s, 2H), 4.84 – 4.80 (m, 1H), 4.43 (dt, J=11.3, 7.9, 2H), 4.25 (d, J=8.8, 0.5H), 4.10 (s, 0.5H), 4.04 – 3.88 (m, 3H), 3.78 (dd, J=18.3, 8.7, 1H), 3.62 – 3.36 (m, 3H), 2.99 – 2.82 (m, 2H), 2.56 (ddd, J=22.6, 13.1, 4.5, 2H), 2.47 – 2.30 (m, 1H), 2.22 (dd, J=14.6, 6.4, 1H), 2.02 (dd, J=20.8, 15.1, 3H), 1.89 – 1.81 (m, 1H), 1.59 (d, J=7.4, 1H), 1.52 – 1.44 (m, 3H), 0.92 – 0.86 (m, 4H).

Cmpd. No.	Structure	Analytical Data
130		LCMS m/z [M+1]: 722.3 1H NMR (400 MHz, CD3OD) δ = 8.23 (s, 1H), 7.25 – 7.19 (m, 1H), 7.04 – 6.97 (m, 1H), 5.42 (d, J=6.5, 1H), 5.22 (d, J=4.8, 0.5H), 5.09 – 4.99 (m, 1.5H), 3.89 (ddd, J=17.7, 15.1, 9.4, 3H), 3.72 (s, 4H), 3.65 – 3.39 (m, 3H), 3.28 – 3.22 (m, 1H), 2.91 (s, 1H), 2.57 (d, J=3.0, 3H), 2.44 (dd, J=18.3, 8.9, 2H), 2.25 – 2.12 (m, 1H), 2.03 (d, J=5.3, 1H), 1.45 (t, J=7.1, 3H), 1.40 (d, J=6.2, 3H).
131		LCMS m/z [M+1]: 760.24 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.24 (m, 1H), 7.04 (m, 1H), 5.34 (s, 0.5H), 5.21 (s, 0.5H), 4.75 (m, 1H), 4.23 (m, 1H), 4.21 (m, 1H), 4.16 (m, 1H), 4.12 (m, 2H), 4.09 (m, 1H), 3.92 (m, 1H), 3.79 (m, 1H), 3.56-3.47 (m, 2H), 3.21-3.12 (m, 3H), 2.98-2.97 (m, 1H), 2.53-2.45 (m, 1H), 2.29-2.27 (m, 2H), 2.18-2.11 (m, 2H), 1.96-1.92 (m, 3H), 1.56-1.53 (m, 3H), 1.45-1.44 (m, 3H).
132		LCMS m/z [M+1]: 756.2 1HNMR(400 MHz, CD3OD): δ 8.28(s, 1H), 7.28 (s, 1H), 7.21-7.25 (m, 2H), 7.02 (t, J =16.0 Hz, 1H), 5.49 (d, J = 52.4 Hz, 1H), 5.10-5.16 (m, 1H), 4.59-4.75 (m, 2H), 3.83-4.06 (m, 5H), 3.82 (s, 3H), 3.59-3.67 (m, 2H), 3.38-3.47 (m, 1H), 3.04-3.13 (m, 1H), 2.45-2.69 (m, 4H), 2.16-2.31 (m, 3H), 2.02-2.11 (m, 1H), 1.49 (t, J = 6.9 Hz, 3H).

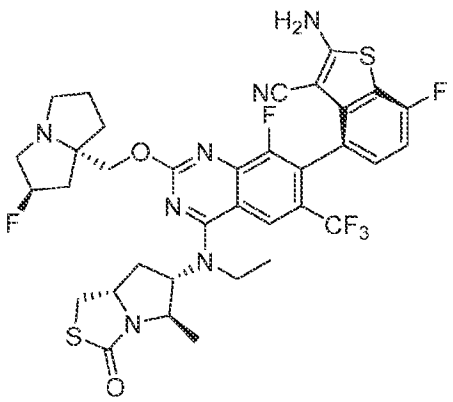
Cmpd. No.	Structure	Analytical Data
133		LCMS m/z [M+1]: 561.0 1H NMR (400 MHz, CD3OD) δ 8.75-8.70 (m, 1H), 8.34-8.30 (m, 1H), 7.27-7.22 (m, 1H), 7.03 (t, 1H), 5.14-5.05 (m, 1H), 4.08-3.99 (m, 1H), 3.90-3.83 (m, 2H), 3.72-3.53 (m, 2H), 3.48-3.36 (m, 1H), 2.52-2.38 (m, 2H), 2.12-2.05 (m, 3H), 1.49-1.41 (m, 3H).
134		LCMS m/z [M+1]: 506.0 1H NMR (400 MHz, CD3OD) δ 8.61 (s, 1H), 8.33 (S, 1H), 7.26-7.21 (m, 1H), 7.02 (t, 1H), 4.26-4.16 (m, 4H), 4.01 (t, 2H), 3.86-3.79 (m, 2H), 2.23-2.17 (m, 2H).
135		LCMS m/z [M+1]: 718.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.26-7.19 (m, 1H), 7.05-6.98 (m, 1H), 5.49-5.43 (m, 1H), 5.08-5.01 (m, 1H), 3.96-3.80 (m, 3H), 3.80-3.67 (m, 4H), 3.58-3.51 (m, 1H), 3.50-3.35 (m, 2H), 2.99-2.68 (m, 4H), 2.49-2.34 (m, 2H), 2.21-2.11 (m, 2H), 2.08-1.81 (m, 4H), 1.78-1.71 (m, 1H), 1.45 (t, 3H), 1.09-1.00 (m, 3H).
136		LCMS m/z [M+1]: 787.2 1H-NMR (400 MHz, CD_3OD): 8.22 (s, 1 H), 7.18-7.26 (m, 1 H), 6.98-7.05 (m, 1 H), 5.41 (s, 0.5 H), 5.27 (s, 0.5 H), 4.38-4.58 (m, 2 H), 4.21-4.32(m, 2 H), 3.74-4.02 (m, 3 H), 3.54-3.65 (m, 1 H), 3.33-3.50 (m, 3 H), 3.14-3.29(m, 3 H), 3.03-3.13 (m, 1 H), 1.87-2.41 (m, 9 H), 1.65-1.80 (m, 1 H), 1.34-1.52 (m, 6 H), 1.07-1.15 (m, 3 H).

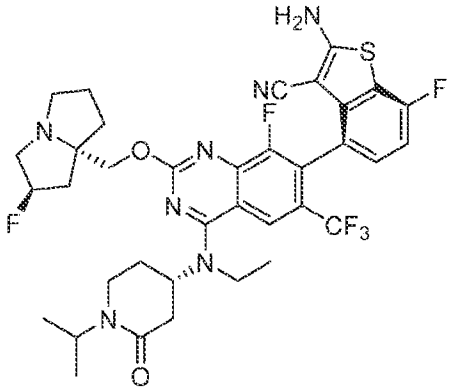
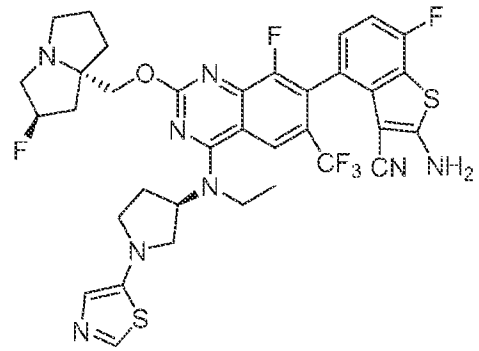
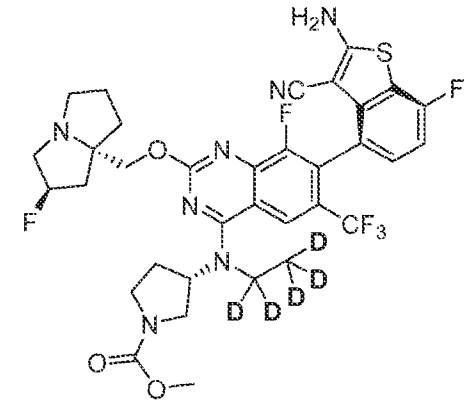
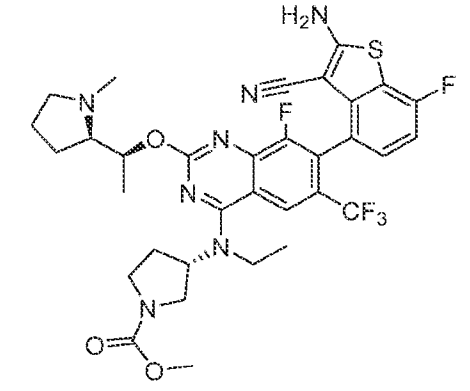
Cmpd. No.	Structure	Analytical Data
137		LCMS m/z [M+1]: 577.0 1H NMR (400 MHz, CD3OD) δ 8.74 (s, 1H), 8.33 (s, 1H), 7.28-7.25 (m, 1H), 7.07-7.02 (m,1H), 5.13-5.05 (m, 1H), 3.98-3.83 (m,3H), 3.81-3.70 (m, 4H), 3.60-3.54 (m,1H), 3.50-3.43 (m,1H), 2.50-2.34 (m,2H), 1.47-1.42 (m, 3H).
138		LCMS m/z [M+1]: 575.0 1H NMR (400 MHz, CD3OD) δ 8.60 (d, 1H), 8.23 (s, 1H), 7.26-7.22 (m, 1H), 7.04-7.00 (m,1H), 4.78-4.72 (m, 1H), 4.66-4.61 (m,1H), 4.39-4.34 (m, 1H), 4.28-4.21 (m,1H), 3.95-3.83 (m,3H), 23.63-3.54 (m,1H), 2.45-2.36 (m,2H), 1.58-1.53 (m, 3H).
139		LCMS m/z [M+1]: 760.2 1HNMR(400 MHz, CD3OD): δ 8.67 (s, 1H), 8.38 (s, 1H), 7.21-7.24 (m, 1H), 7.02 (t, J = 9.2 Hz, 1H), 5.56 (d, J = 52.4 Hz, 1H), 5.15-5.20 (m, 1H), 4.59-4.77 (m, 2H), 4.33-4.38 (m, 1H), 3.75-4.03 (m, 5H), 3.51 (s, 3H), 3.42-3.48 (m, 1H), 2.53-2.78 (m, 4H), 2.29-2.44 (m, 3H), 2.10-2.18 (m, 1H), 1.52 (t, J = 6.4 Hz, 3H).
140		LCMS m/z [M+1]: 774.2 1H NMR (400 MHz, CD3OD) δ 8.66 (s, 1H), 8.23 (s, 1H), 7.23 (dd, J = 8.4, 5.2 Hz, 1H), 7.06-6.98 (m, 1H), 5.29 (d, J = 54.4 Hz, 1H), 4.71-4.63 (m, 1H), 4.61-4.46 (m, 2H), 4.3-4.15 (m, 2H), 4.03-3.70 (m, 4H), 3.34-3.20 (m, 2H), 3.09-2.99 (m, 1H), 2.84-2.73 (m, 1H), 2.64-2.52 (m, 1H), 2.28-2.14 (m, 2H), 2.07-1.83 (m, 4H), 1.55-1.45 (m, 6H).

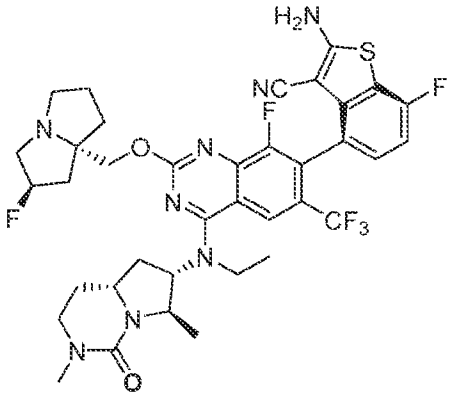
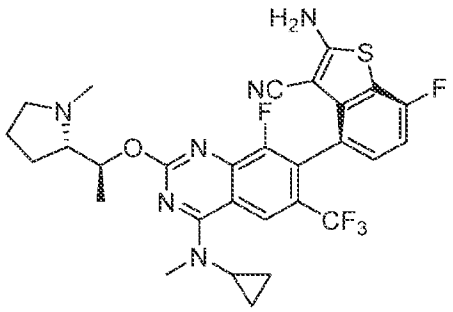
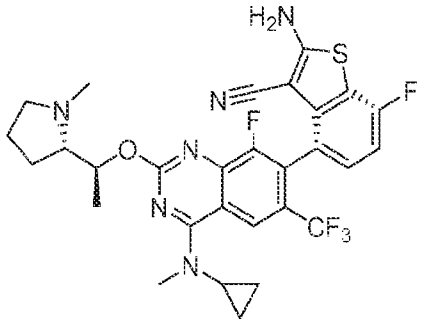
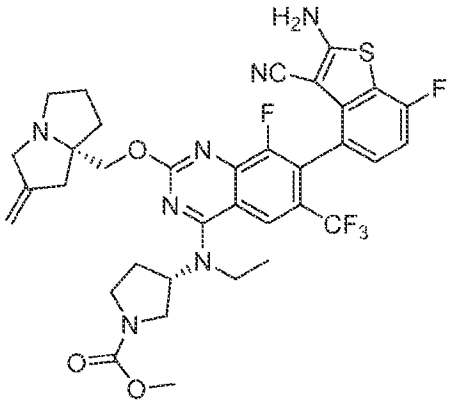
Cmpd. No.	Structure	Analytical Data
141		LCMS m/z [M+1]: 774.2 1H NMR (400 MHz, CD3OD) δ 8.22 (d, J = 4.8 Hz, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.22 (dd, J = 8.4, 5.2 Hz, 1H), 7.01 (t, J = 8.8 Hz, 1H), 5.26 (d, J = 54.8 Hz, 1H), 4.80-4.39 (m, 3H), 4.26-4.09 (m, 2H), 4.06-3.63 (m, 4H), 3.28-3.12 (m, 2H), 3.06-2.92 (m, 1H), 2.90-2.73 (m, 1H), 2.61-2.49 (m, 1H), 2.29-2.07 (m, 2H), 2.04-1.75 (m, 4H), 1.57-1.35 (m, 6H).
142		LCMS m/z [M+1]: 734.2 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 7.56 (dd, J = 8.3, 2.4 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 5.56 (d, J = 51.9 Hz, 1H), 5.05 (dt, J = 15.8, 7.9 Hz, 2H), 4.76 – 4.56 (m, 2H), 3.97 – 3.85 (m, 4H), 3.73 (s, 3H), 3.68 – 3.55 (m, 2H), 3.54 – 3.41 (m, 3H), 2.60 (dd, J = 13.2, 8.6 Hz, 1H), 2.52 – 2.31 (m, 4H), 2.17 (s, 1H), 1.49 (d, J = 2.1 Hz, 3H), 0.59 – 0.45 (m, 1H), 0.40 (d, J = 2.8 Hz, 1H).

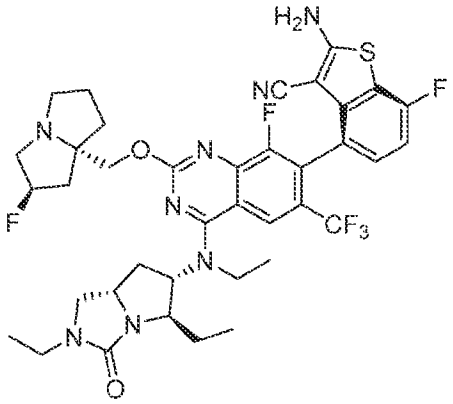
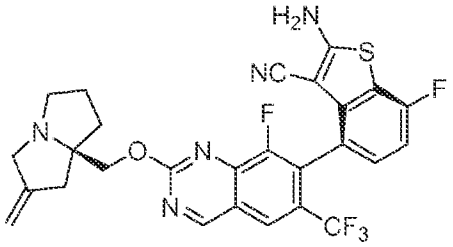
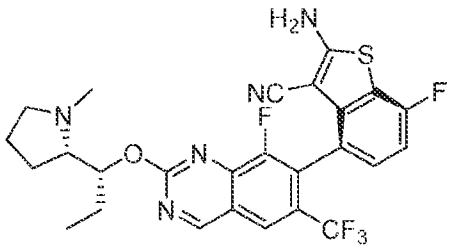
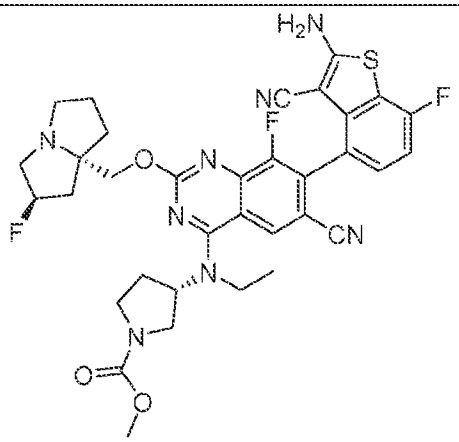
[0872] Table 3a includes selected compounds of the present disclosure.

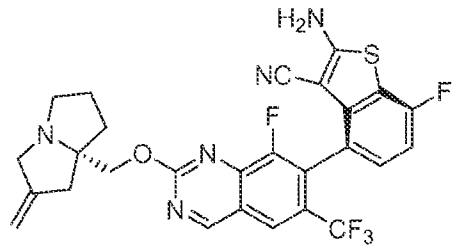
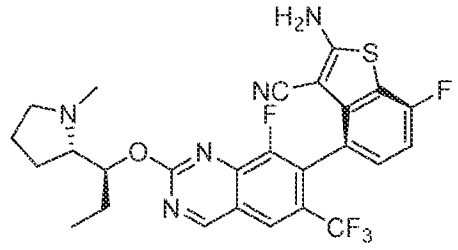
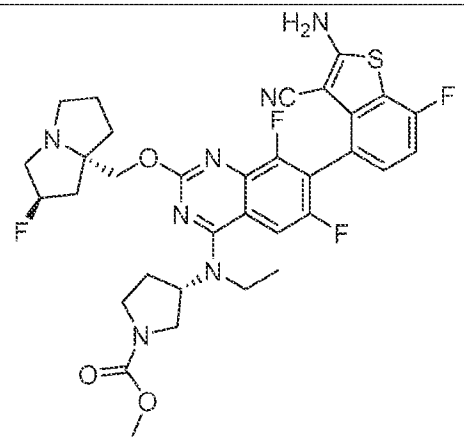
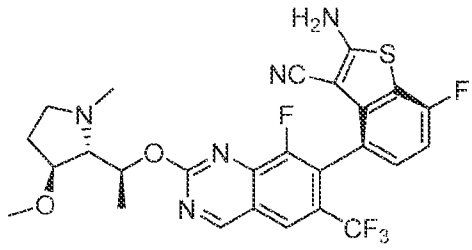
Table 3a. Selected compounds of the present disclosure.

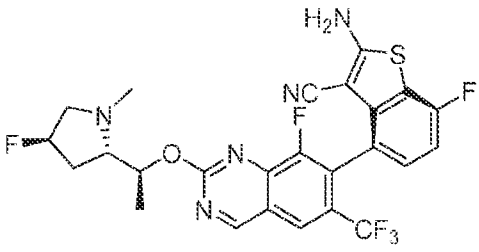
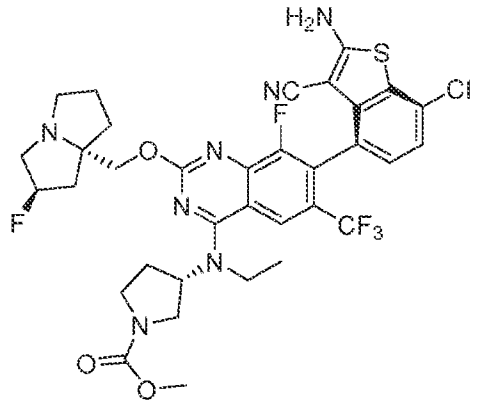
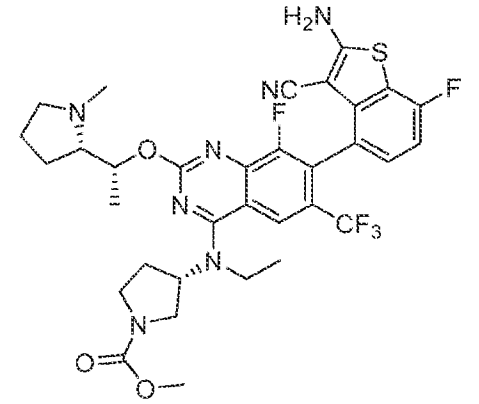
Cmpd. No.	Structure	Analytical Data
143		LCMS m/z [M+1]: 762.1 1H NMR (400 MHz, CD3OD) δ 8.20 (s, 1H), 7.25-7.21 (m, 1H), 7.08 – 6.97 (m, 1H), 5.44 (s, 0.5H), 5.31 (s, 0.5H), 4.60 – 4.40 (m, 3H), 4.37 – 4.19 (m, 2H), 3.98-3.91 (m, 1H), 3.81-3.76 (m, 1H), 3.65 – 3.35 (m, 5H), 3.13-3.09 (m, 1H), 2.72 – 2.62 (m, 1H), 2.50-2.19 (m, 4H), 2.05-1.97 (m, 3H), 1.58-1.54 (m, 3H), 1.42-1.40 (m, 3H).

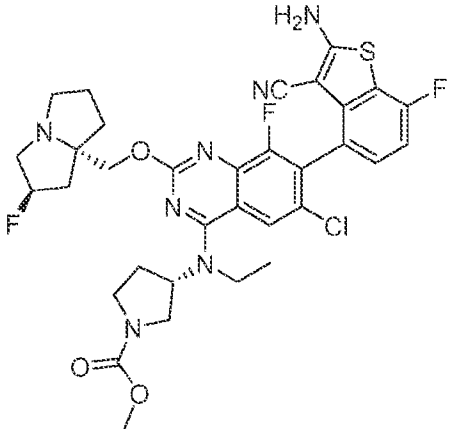
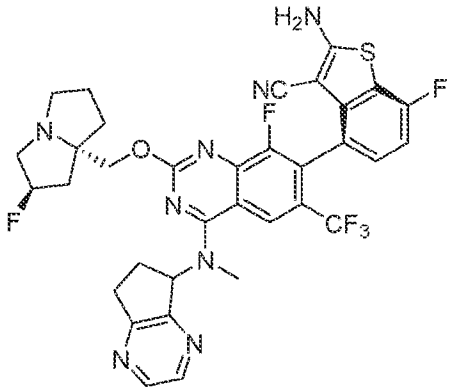
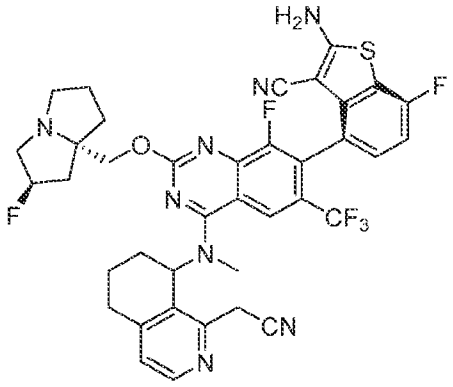
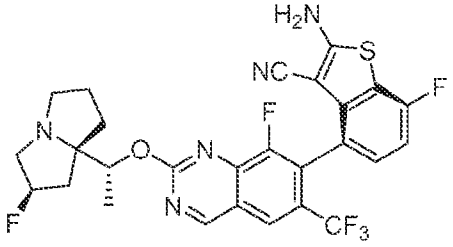
Cmpd. No.	Structure	Analytical Data
144		LCMS m/z [M+1]: 746.2 1H NMR (400 MHz, CD3OD) δ 8.19 (d, 1H), 7.20-7.23 (m, 1H), 7.01 (t, 1H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 4.77-4.82 (m, 2H), 4.31 (d, 1H), 4.24 (d, 1H), 3.78-3.89 (m, 2H), 3.47-3.54 (m, 1H), 3.31-3.39 (m, 2H), 2.95-3.08 (m, 2H), 2.76-2.86 (m, 1H), 2.05-2.53 (m, 6H), 1.81-2.04 (m, 4H), 1.46-1.50 (m, 3H), 1.17-1.19 (m, 6H).
145		LCMS m/z [M+1]: 759.2 1H NMR (400 MHz, CD3OD) δ 8.24-8.42 (m, 2H), 7.19-7.29 (m, 1H), 6.94-7.08 (m, 2H), 5.52 (d, J = 51.8 Hz, 1H), 5.10-5.22 (m, 1H), 4.48-4.71 (m, 2H), 3.58-4.08 (m, 8H), 3.34-3.49 (m, 2H), 2.45-2.85 (s, 4H), 2.15-2.35 (m, 3H), 1.85-2.01 (m, 1H), 1.46-1.57 (m, 3H).
146		LCMS m/z [M+1]: 739.1 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.24-7.18 (m, 1H), 7.00 (t, 1H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 5.04-4.97 (m, 1H), 4.25 (q, 2H), 3.91 (t, 1H), 3.79-3.66 (m, 4H), 3.60-3.54 (m, 1H), 3.46-3.39 (m, 1H), 3.26-3.16 (m, 3H), 3.04-2.97 (m, 1H), 2.49-2.42 (m, 3H), 2.37-2.20 (m, 1H), 2.15-2.09 (m, 1H), 2.01-1.85 (m, 3H).
147		LCMS m/z [M+1]: 704.3 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.25-7.19 (m, 1H), 7.01 (t, 1H), 5.64-5.57 (m, 1H), 5.08-5.01 (m, 1H), 3.93-3.84 (m, 2H), 3.77-3.69 (m, 3H), 3.63 (s, 1H), 3.58-3.53 (m, 1H), 3.48-3.40 (m, 2H), 2.88-2.75 (m, 3H), 2.49-2.31 (m, 3H), 2.26-2.14 (m, 3H), 2.07-1.95 (m, 3H), 1.49-1.38 (m, 6H).

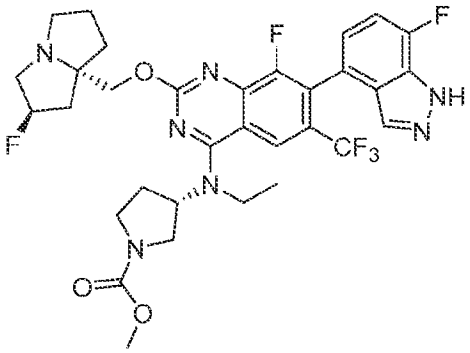
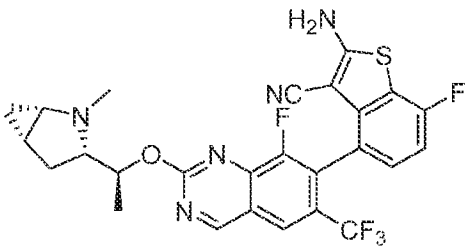
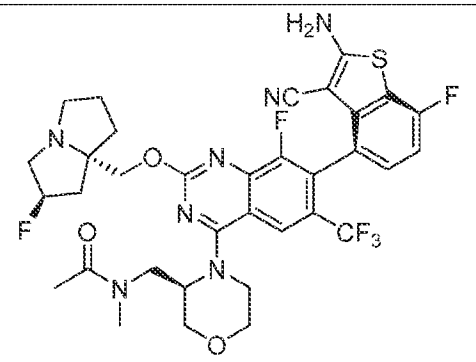
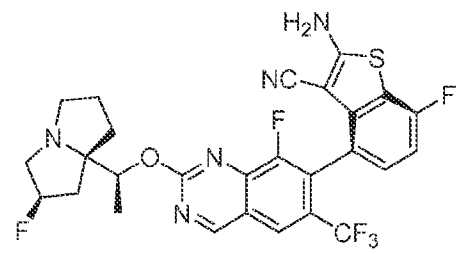
Cmpd. No.	Structure	Analytical Data
148		LCMS m/z [M+1]: 773.2 1H-NMR (400 MHz, CD_3OD): 8.20 (s, 1 H), 7.18-7.25 (m, 1 H), 6.97-7.04 (m, 1 H), 5.40 (s, 0.5 H), 5.27 (s, 0.5 H), 4.53-4.62 (m, 1 H), 4.33-4.44 (m, 2 H), 3.89-4.01 (m, 1 H), 3.66-3.86 (m, 2 H), 3.32-3.48 (m, 2 H), 3.20-3.29(m, 3 H), 3.00-3.11 (m, 1 H), 2.92 (s, 3 H), 2.31-2.46 (m, 2 H), 2.12-2.30 (m, 3 H), 1.95-2.11 (m, 3 H), 1.75-1.94 (m, 2 H), 1.41-1.56 (m, 3 H), 1.35-1.40 (m, 3 H).
149		LCMS m/z [M+1]: 603.2 1H NMR (400 MHz, CD3OD) δ 8.85 (s, 1H), 7.23-7.20 (m, 1H), 7.03-6.98 (m, 1H), 5.38-5.34 (m,1H), 3.56-3.55 (m, 1H), 3.48-3.43 (m,3H), 3.36-3.32 (m,1H), 2.79 (s, 3H), 2.20-2.16 (m,1H), 2.07-1.79 (m,5H), 1.44-1.43 (m, 3H), 1.08-1.05 (m, 2H), 0.83-0.82 (m, 2H).
150		LCMS m/z [M+1]: 603.0 1H NMR (400 MHz, CD3OD) δ 8.85 (s, 1H), 7.24-7.20 (m, 1H), 7.03-6.98 (m, 1H), 5.39-5.32 (m,1H), 3.57-3.54 (m, 1H), 3.47-3.44 (m,3H), 3.38-3.34 (m,1H), 2.81 (s, 3H), 2.20 (s,1H), 2.03-1.82 (m,5H), 1.45-1.43 (m, 3H), 1.08-1.04 (m, 2H), 0.83-0.80 (m, 2H).
151		LCMS m/z [M+1]: 728.1 1H NMR (400 MHz, CD3OD) δ = 8.23 (s, 1H), 7.22 (dd, J=8.1, 5.2, 1H), 7.01 (t, J=8.9, 1H), 5.09 – 4.97 (m, 3H), 4.30 (d, J=4.1, 2H), 3.95 – 3.79 (m, 3H), 3.75 (s, 1H), 3.72 (s, 3H), 3.56 (dd, J=10.8, 7.9, 1H), 3.44 (s, 1H), 3.36 (d, J=14.4, 1H), 3.22 – 3.15 (m, 1H), 2.77 (t, J=13.7, 2H), 2.45 (dd, J=37.4, 22.6, 3H), 2.19 – 1.82 (m, 5H), 1.48 – 1.39 (m, 3H).

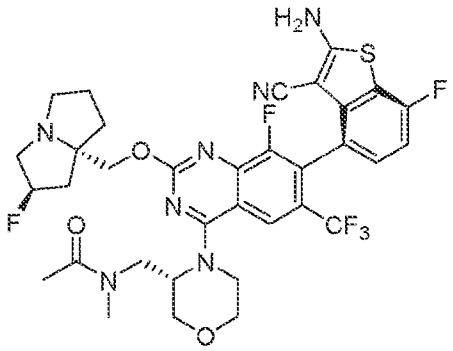
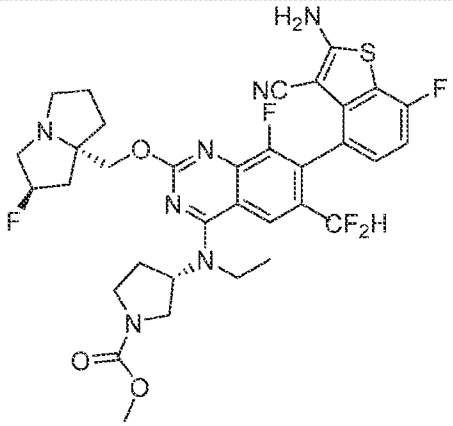
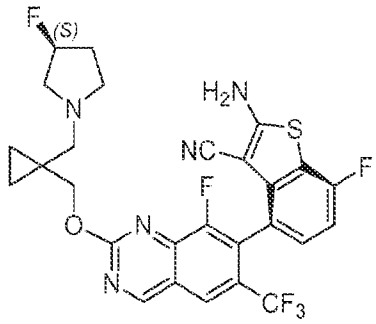
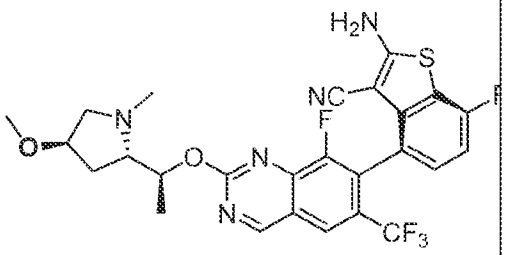
Cmpd. No.	Structure	Analytical Data
152		LCMS m/z [M+1]: 787.3 1H NMR (400 MHz, CD3OD) δ = 8.23 (s, 1H), 7.23 (dd, J=8.3, 5.1, 1H), 7.01 (t, J=8.9, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 4.94 (dd, J=6.3, 4.0, 1H), 4.31 (dd, J=40.1, 10.7, 2H), 3.91 (dt, J=14.4, 6.0, 3H), 3.67 – 3.32 (m, 5H), 3.29 – 3.20 (m, 2H), 3.05 (dd, J=9.5, 3.9, 1H), 2.47 – 1.81 (m, 9H), 1.69 – 1.59 (m, 1H), 1.51 (dd, J=14.6, 7.0, 1H), 1.36 (t, J=6.9, 3H), 1.16 (t, J=7.2, 3H), 0.92 (t, J=7.3, 3H).
153		LCMS m/z [M+1]: 558.0 1H NMR (400 MHz, CD3OD) δ 9.69 (s, 1H), 8.48 (s, 1H), 7.27-7.21 (m, 1H), 7.04 (t, 1H), 5.36-5.26 (m, 2H), 4.81 (s, 2H), 4.37 (d, 1H), 3.96 (d, 1H), 3.83-3.75 (m, 1H), 3.28-3.25 (m, 1H), 3.15-3.09 (m, 1H), 3.83 (d, 1H), 2.48-2.40 (m, 1H), 2.31-2.13 (m, 3H).
154		LCMS m/z [M+1]: 548.0 1H NMR (400 MHz, CD3OD) δ 9.58 (s, 1H), 8.39 (s, 1H), 7.26-7.18 (m, 1H), 7.02 (t, 1H), 5.82-5.76 (m, 1H), 3.12-3.04 (m, 1H), 2.79-2.67 (m, 1H), 2.53 (s, 3H), 2.43-2.33 (m, 1H), 2.21-1.96 (m, 3H), 1.88-1.82 (m, 2H), 1.79-1.72 (m, 1H), 1.02 (t, 3H).
155		LCMS m/z [M+1]: 691.1 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.30-7.34 (m, 1H), 7.07 (t, 1H),5.37 (s, 0.5H), 5.23 (m, 0.5H), 5.00-5.04 (m, 1H), 4.23-4.30 (m, 2H), 3.73-3.93 (m, 3H), 3.71 (s, 3H), 3.57 (t, 1H), 3.45-3.47 (m, 1H), 3.41-3.42 (m, 1H), 3.12-3.24 (m, 3H), 2.98-3.02 (m, 1H), 2.20-2.42 (m, 4H), 2.08-2.16 (m, 1H), 1.94-2.04 (m, 2H), 1.82-1.93 (m, 1H), 1.37-1.42 (m, 3H).

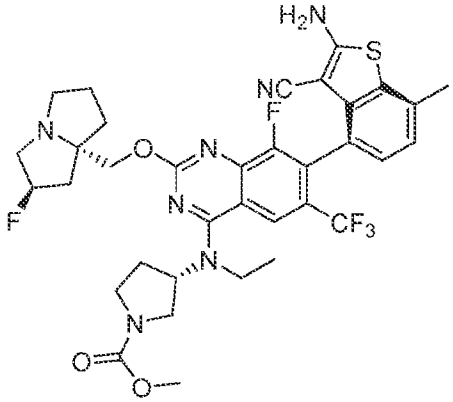
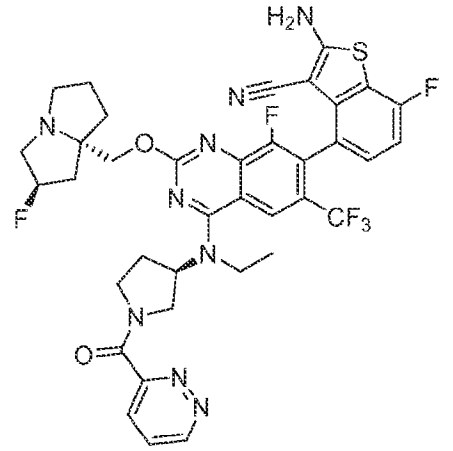
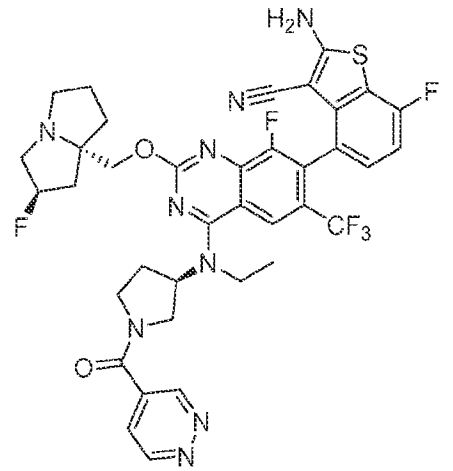
Cmpd. No.	Structure	Analytical Data
156		LCMS m/z [M+1]: 558.0 1H NMR (400 MHz, CD3OD) δ 9.59 (s, 1H), 8.40 (s, 1H), 7.27-7.20 (m, 1H), 7.02 (t, 1H), 4.99 (s, 2H), 4.48-4.35 (dq, 2H), 3.77 (d, 1H), 3.35 (d, 1H), 3.21-3.14 (m, 1H), 2.86-2.79 (d, 1H), 2.78-2.71 (m, 1H), 2.55-2.48 (d, 1H), 2.20-2.13 (m, 1H), 2.02-1.85 (m, 3H).
157		LCMS m/z [M+1]: 548.0 1H NMR (400 MHz, CD3OD) δ 9.61 (s, 1H), 8.40 (s, 1H), 7.27-7.21 (m, 1H), 7.02 (t, 1H), 5.51-5.44 (m, 1H), 3.19-3.07 (m, 2H), 2.64 (s, 3H), 2.57-2.49 (m, 1H), 2.09-1.99 (m, 2H), 1.90-1.77 (m, 4H), 1.01 (t, 3H).
158		LCMS m/z [M+1]: 684.1 1H NMR (400 MHz, CD3OD) δ 7.60 (d, 1H), 7.33-7.23 (m, 1H), 7.09-6.99 (m, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 4.98-4.90 (m, 1H), 4.35-4.19 (m, 2H), 3.95-3.67 (m, 7H), 3.54-3.39 (m, 2H), 3.28-3.16 (m, 3H), 3.10-2.99 (m, 1H), 2.42-2.12 (m, 5H), 2.05-1.86 (m, 3H), 1.36-1.29 (m, 3H).
159		LCMS m/z [M+1]: 564.0 1H NMR (400 MHz, CD3OD) δ 9.60 (s, 1H), 8.40 (s, 1H), 7.25-7.22 (m, 1H), 7.02 (t, 1H), 5.49-5.45 (m, 1H), 3.92-3.91 (m,1H), 3.30-3.29 (m, 4H), 3.12-3.09 (m, 1H), 2.98-2.93 (m,1H), 2.67 (s, 3H), 2.02-1.97 (m, 1H), 1.93-1.85 (m, 1H), 1.50 (d, 3H).

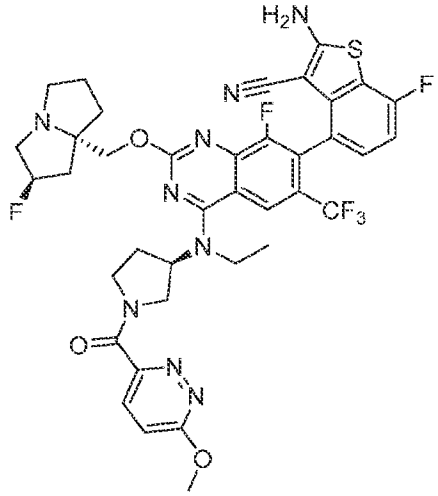
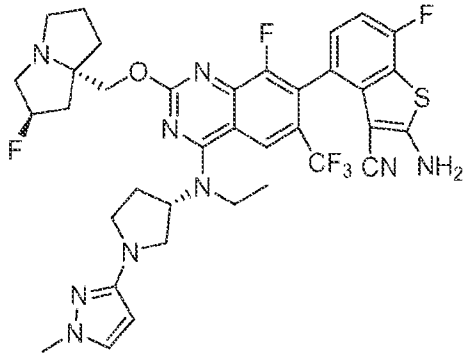
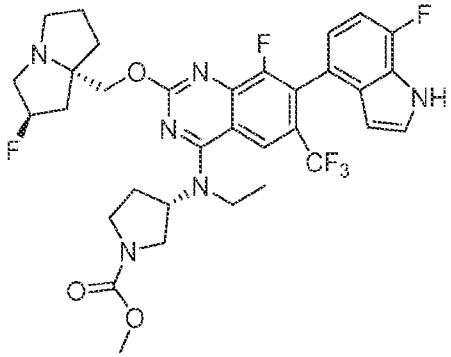
Cmpd. No.	Structure	Analytical Data
160		LCMS m/z [M+1]: 552.0 1H NMR (400 MHz, CD3OD) δ 9.60 (d, 1H), 8.40 (s, 1H), 7.25-07.22 (m, 1H), 7.02 (t,1H), 5.49-5.44 (m, 1H), 5.24 (s,0.5H), 5.10 (s, 0.5H), 3.54-3.42 (m, 1H), 3.27-3.24 (m,1H), 2.84-2.73 (m,1H), 2.66 (s,3H), 2.33-2.24 (m, 1H), 2.05-1.92 (m, 1H), 1.43 (d,3H).
161		LCMS m/z [M+1]: 749.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.28 – 7.18 (m, J = 22.4, 8.1 Hz, 2H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 5.01 (s, 1H), 4.36 – 4.24 (m, J = 21.2, 10.6 Hz, 2H), 3.95 – 3.80 (m, J = 10.0, 9.0, 5.7 Hz, 3H), 3.76 (dd, J = 10.9, 2.6 Hz, 1H), 3.72 (s, 3H), 3.62 – 3.54 (m, J = 10.9, 8.0 Hz, 1H), 3.50 – 3.35 (m, J = 27.1, 18.3 Hz, 2H), 3.30 (s, 2H), 3.06 (d, J = 5.1 Hz, 1H), 2.46 – 2.33 (m, 2H), 2.28 – 2.22 (m, 1H), 2.17 – 2.13 (m, 1H), 2.07 – 1.83 (m, 4H), 1.45 (t, J = 6.9 Hz, 3H).
162		LCMS m/z [M+1]: 704.1 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.21-7.23 (m, 1H), 7.01 (t, 1H), 5.59-5.62 (m, 1H), 5.03-5.07 (m, 1H), 3.81-3.94 (m, 3H), 3.72-3.77 (m, 4H), 3.53-3.58 (m, 1H), 3.43-3.47 (m, 1H), 2.72-2.79 (m, 3H), 2.33-2.48 (m, 3H), 2.16-2.18 (m, 2H), 1.91-2.03 (m, 3H), 1.57-1.61 (m, 1H), 1.43-1.46 (m, 6H).

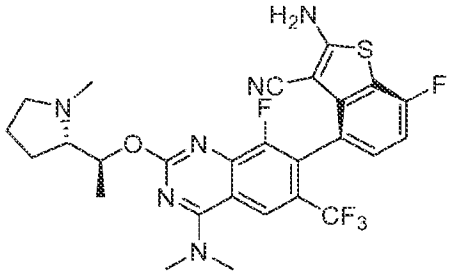
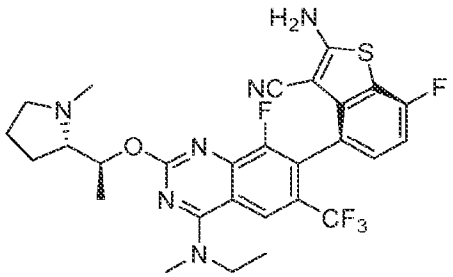
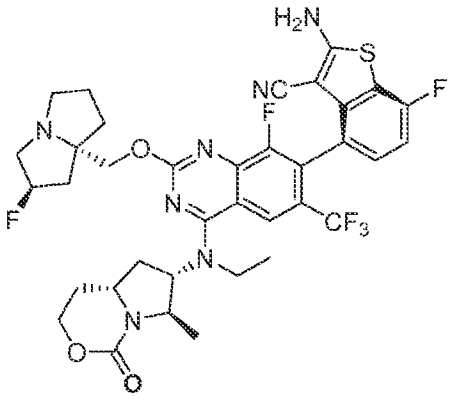
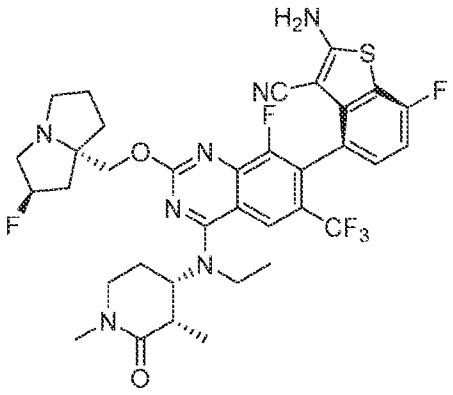
Cmpd. No.	Structure	Analytical Data
163		LCMS m/z [M+1]: 700.1 1H NMR (400 MHz, CD3OD) δ 7.94 (s, 1H), 7.23-7.17 (m, 1H), 7.03 (t, 1H), 5.44-5.39 (m, 0.5H), 5.31-5.26 (m, 0.5H), 4.99-4.92 (m, 1H), 4.38-4.26 (m, 2H), 3.94-3.78 (m, 3H), 3.77-3.66 (m, 4H), 3.57-3.50 (m, 1H), 3.49-3.31 (m, 4H), 3.13-3.07 (m, 1H), 2.46-2.25 (m, 4H), 2.20-2.14 (m, 1H), 2.09-2.00 (m, 2H), 1.96-1.88 (m, 1H), 1.40-1.32 (m, 3H).
164		LCMS m/z [M+1]: 711.1 1H NMR (400 MHz, CD3OD) δ 8.56-8.38 (m, 3H), 7.25-7.18 (m, 1H), 7.05-6.97 (m, 1H), 6.30-6.22 (m, 0.5H), 6.17-6.12 (m, 0.5H), 5.42-5.37 (m, 0.5H), 5.29-5.24 (m, 0.5H), 4.34-4.26 m, 0.5H), 4.21-4.16 (m, 0.5H), 4.12-4.02 (m, 1H), 3.42-3.32 (m, 4H), 3.26-3.11 (m, 3H), 3.10-3.03 (m, 1H), 2.90-2.81 (m, 1H), 2.59-2.09 (m, 5H), 2.07-1.97 (m, 2H), 1.94-1.85 (m, 1H).
165		LCMS m/z [M+1]: 763.1 1H NMR (400 MHz, CD3OD) δ 7.93 – 7.84 (m, 1H), 7.66 (d, J = 61.6 Hz, 1H), 7.23 – 7.11 (m, 1H), 7.06 – 6.96 (m, 1H), 6.94-6.87 (m, 1H), 5.55-5.33 (m, 1H), 4.72-4.44 (m, 3H), 3.79-3.45 (m, 3H), 3.22-3.11 (m, 4H), 2.92-2.75 (m, 2H), 2.74 – 1.83 (m, 12H).
166		LCMS m/z [M+1]: 578.0 1H-NMR (400 MHz, CD_3OD): 9.60 (s, 1 H), 8.40 (s, 1 H), 7.19-7.26 (m, 1 H), 6.99-7.06 (m, 1 H), 5.48 (s, 0.5 H), 5.32-5.38 (m, 1.5 H), 3.38-3.54 (m, 1 H), 2.95-3.16 (m, 2 H), 2.58-

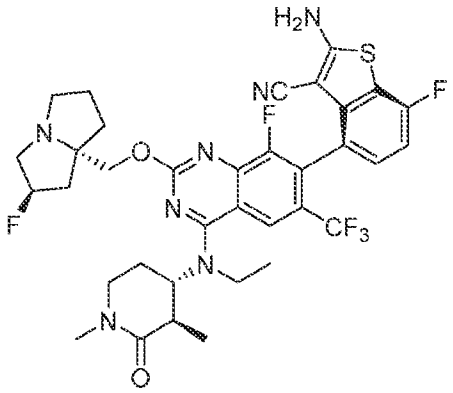
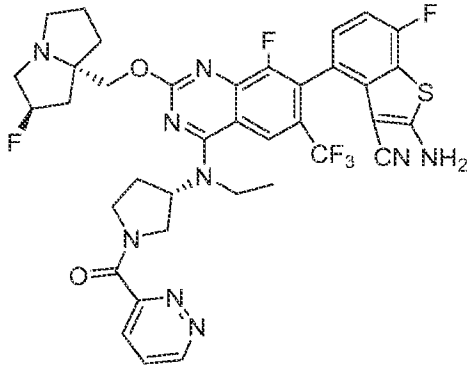
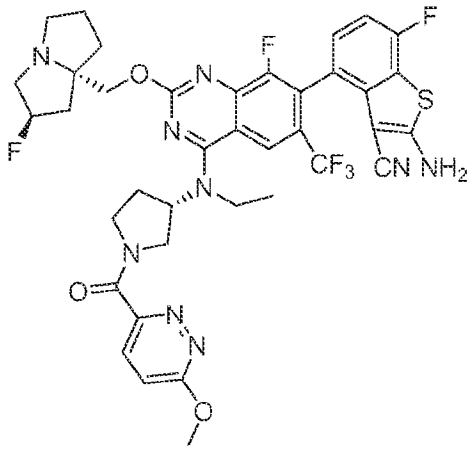
Cmpd. No.	Structure	Analytical Data
		2.77 (m, 1 H), 1.76-2.33 (m, 6 H), 1.46-1.52 (m, 3 H).
167		LCMS m/z [M+1]: 678.3 1H NMR (400 MHz, CD3OD) δ 8.35 (s, 1H), 7.72 (d, J = 3.1 Hz, 1H), 7.26 (dd, J = 10.8, 7.8 Hz, 1H), 7.09 (dd, J = 7.8, 3.8 Hz, 1H), 5.56 (d, J = 51.9 Hz, 1H), 5.06 (dd, J = 15.9, 8.1 Hz, 1H), 4.65 (dd, J = 13.5, 10.1 Hz, 2H), 3.91 (dd, J = 17.2, 10.7 Hz, 5H), 3.73 (s, 4H), 3.69 – 3.41 (m, 4H), 2.77 – 2.54 (m, 2H), 2.52 – 2.27 (m, 5H), 2.15 (s, 1H), 1.50 (dd, J = 7.0, 5.7 Hz, 3H).
168		LCMS m/z [M+1]: 546.0 1H NMR (400 MHz, CD3OD) δ 9.58 (d, 1H), 8.38 (s, 1H), 7.21-7.25 (m, 1H), 7.02 (t, 1H), 5.15-5.22 (m, 1H), 3.44-3.54 (m, 1H), 2.71 (d, 3H), 2.42-2.53 (m, 2H), 1.58-1.62 (m, 2H), 1.33-1.35 (m, 3H), 0.71-0.78 (m, 1H), 0.43-0.47 (m, 1H).
169		LCMS m/z [M+1]: 734.1 1H NMR (400 MHz, CD3OD) δ 8.13 (s, 1H), 7.24-7.16 (m, 1H), 7.00 (t, 1H), 5.47 (s, 0.5H), 5.40-5.31 (m, 1.5H), 4.54-4.30 (m, 3H), 4.03-4.80 (m, 4H), 3.65-3.40 (m, 4H), 3.23-3.04 (m, 3H), 2.89 (s, 3H), 2.51-2.34 (m, 2H), 2.26-2.11 (m, 3H), 2.02-1.97 (m, 1H), 1.85-1.64 (m, 3H).
170		LCMS m/z [M+1]: 578.0 1H-NMR (400 MHz, CD_3OD): 9.57 (s, 1 H), 8.38 (s, 1 H), 7.19-7.27 (m, 1 H), 6.98-7.06 (m, 1 H), 5.29-5.37 (m, 1.5 H), 5.18 (s, 0.5 H), 3.14-3.25 (m, 3 H), 2.96-3.03 (m, 1 H), 1.95-2.32 (m, 6 H), 1.37-1.45 (m, 3 H).

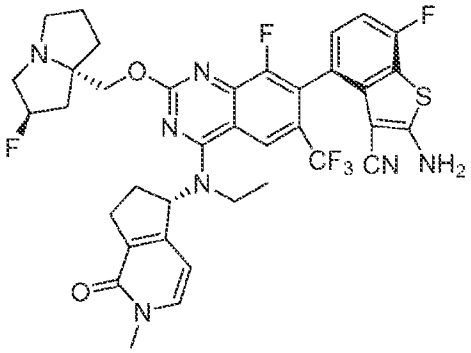
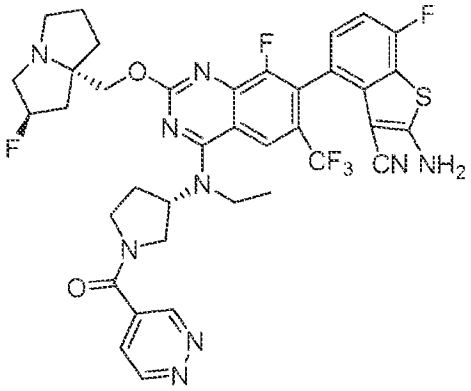
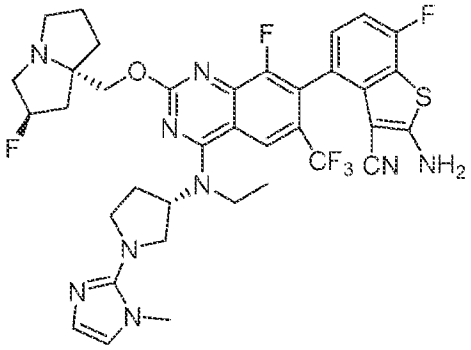
Cmpd. No.	Structure	Analytical Data
171		LCMS m/z [M+1]: 734.1 1H NMR (400 MHz, CD3OD) δ8.13-8.09 (m, 1H), 7.21-7.16 (m, 1H), 7.04-6.98 (m, 1H), 5.46-5.42 (m, 0.5H), 5.34-5.28 (m, 1.5H), 4.47-4.34 (m, 3H), 7.09-3.80 (m, 5H), 3.59-3.39 (m, 4H), 3.17-3.05 (m, 2H), 2.95-2.90 (m, 3H), 2.46-2.30 (m, 2H), 2.23-2.17 (m, 1H), 2.12-2.05 (m, 2H), 1.99-1.92 (m, 1H), 1.80-1.73 (m, 3H).
172		LCMS m/z [M+1]: 716.1 1H NMR (400 MHz, CD3OD) δ 8.14 (s, 1H), 7.21-7.24 (m, 1H), 7.03 (t, 1H), 6.40-6.67 (m, 1H), 5.43 (s, 0.5H), 5.30 (s, 0.5H), 5.00-5.04 (m, 1H), 4.31-4.40 (m, 2H), 3.80-3.94 (m, 3H), 3.71-3.77 (m, 4H), 3.54-3.59 (m, 1H), 3.30-3.47 (m, 4H), 3.12 (s, 1H), 2.29-2.46 (m, 4H), 2.16-2.22 (m, 1H), 2.03-2.09 (m, 2H), 1.93-1.96 (m, 1H), 1.41-1.44 (m, 3H).
173		LCMS m/z [M+1]: 578.0 1H NMR (400 MHz, CD3OD) δ 9.57 (s, 1H), 8.39 (s, 1H), 7.27-7.20 (m, 1H), 7.02 (t, 1H), 5.23-5.19 (m, 0.5H), 5.09-5.05 (m, 0.5H), 4.57-4.45 (dq, 2H), 3.07-2.83 (m, 3H), 2.80-2.74 (m, 1H), 2.63-2.50 (m, 2H), 2.21-2.12 (m, 1H), 2.02-1.93 (m, 1H), 0.76 (t, 2H), 0.58 (t, 2H).
174		LCMS m/z [M+1]: 564.0 1H NMR (400 MHz, CD3OD) δ 9.60 (s, 1H), 8.40 (s, 1H), 7.27-7.21 (m, 1H), 7.02 (t, 1H), 5.49-5.43 (m, 1H), 3.98-3.92 (m, 1H), 3.40-3.35 (m, 1H), 3.32 (s, 3H), 3.20-3.14 (m, 1H), 2.63 (s, 3H), 2.59-2.53 (m, 1H), 2.14-2.07 (m, 1H), 1.99-1.92 (m, 1H), 1.43 (d, 3H).

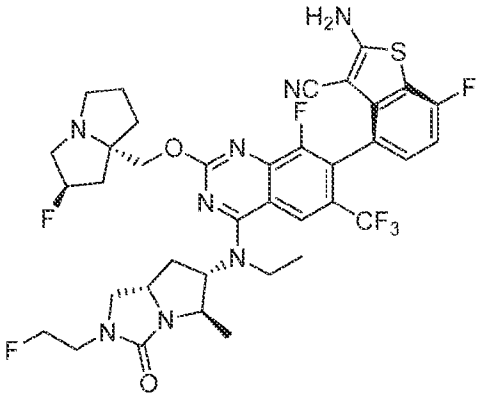
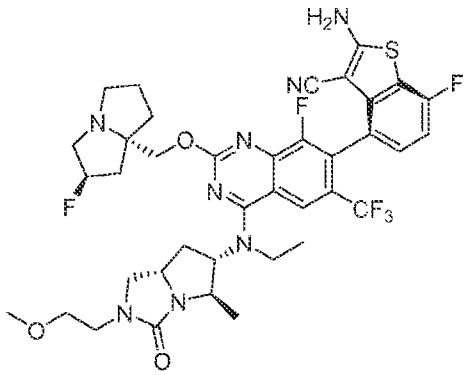
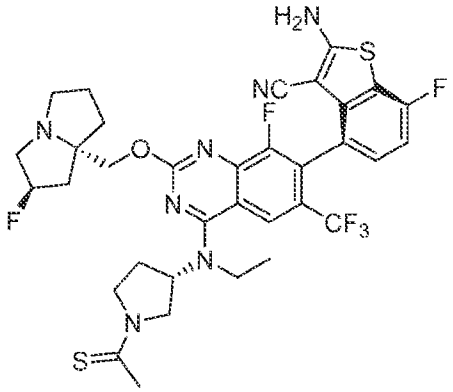
Cmpd. No.	Structure	Analytical Data
175		LCMS m/z [M+1]: 730.2 1HNMR (400 MHz, CD3OD) δ 8.45 (s, 1H), 8.26 (s, 1H), 7.10 (dd, J = 19.2, 7.7 Hz, 2H), 5.54 (s, 0.5H), 5.41 (s, 0.5H), 5.11 – 4.96 (m, 1H), 4.65 – 4.42 (m, 2H), 4.03 – 3.40 (m, 13H), 2.63 – 2.28 (m, 8H), 2.23 (s, 2H), 2.03 (s, 1H), 1.47 (t, J = 6.9 Hz, 3H).
176		LCMS m/z [M+1]: 782.3 1H NMR (400 MHz, CD3OD) δ 9.28 (dd, J1 = 1.6Hz, J2 = 5.2Hz, 1H), 8.29 (d, J = 25.6Hz, 1H), 8.06-8.03 (m, 1H), 7.92-7.85 (m, 1H), 7.23-7.04 (m, 1H), 7.03-7.02 (m, 1H), 7.5.56 (d, J = 56.0Hz, 1H), 5.10-4.94 (m, 1H), 4.78-4.73 (m, 1H), 4.69-4.64 (m, 2H), 4.39-4.18 (m, 2H), 4.14-3.98 (m, 2H), 3.97-3.87 (m, 4H), 3.84-3.68 (m, 1H), 3.50-3.42 (m, 1H), 2.79-2.60 (m, 2H), 2.53-2.26 (m, 2H), 2.19-2.07 (m, 1H), 1.53 (q, J = 6.8Hz, 3H).
177		LCMS m/z [M+1]: 782.3 1H NMR (400 MHz, CD3OD) δ 9.39-9.33 (m, 2H), 8.29 (d, J = 32.0Hz, 1H), 7.91-7.85 (m, 1H), 7.26-7.20 (m, 1H), 7.06-7.00 (m, 1H), 5.54 (d, J = 52.0Hz, 1H), 5.19-4.96 (m, 1H), 4.72-4.57 (m, 2H), 4.24-4.08 (m, 1H), 4.03-3.98 (m, 2H), 3.96-3.81 (m, 4H), 3.79-3.68 (m, 2H), 3.51-3.46 (m, 1H), 2.71-2.50 (m, 3H), 2.47-2.29 (m, 4H), 2.17-2.09 (m, 1H), 1.52-1.46 (m, 3H).

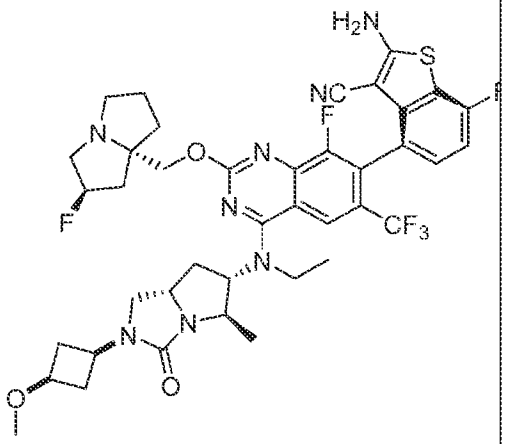
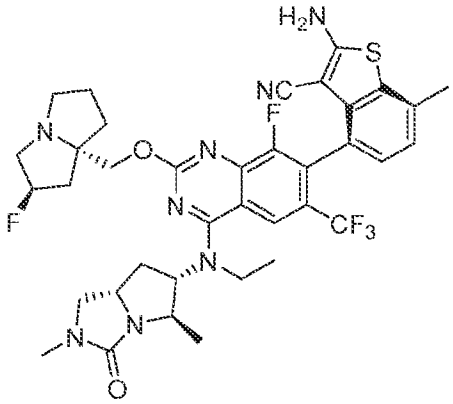
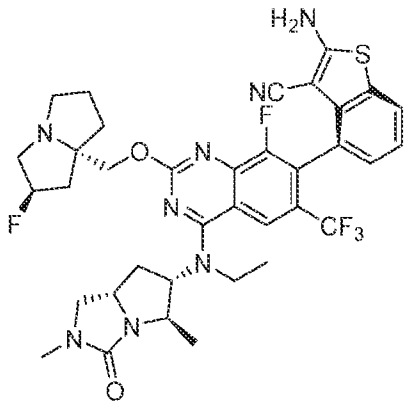
Cmpd. No.	Structure	Analytical Data
178		LCMS m/z [M+1]: 812.3 1H NMR (400 MHz, CD3OD) δ .8.29 (d, J = 24.0Hz, 1H), 7.93 (dd, J1 = 4.0Hz, J2 = 8.0Hz, 1H), 7.30 (t, J = 8.0Hz, 1H), 7.26-7.20 (m, 1H), 7.05-7.00 (m, 1H), 5.64-5.50 (m, 1H), 5.09-4.96 (m, 1H), 4.76-4.64 (m, 2H), 4.38-4.25 (m, 1H), 4.23-4.04 (m, 5H), 4.03-3.68 (m, 6H), 3.50-3.42 (m, 1H), 2.78-2.63 (m, 1H), 2.60-2.53 (m, 2H), 2.48-2.24 (m, 4H), 2.19-2.05 (m, 1H), 1.56-1.53 (m, 3H).
179		LCMS m/z [M+1]: 756.26 1H NMR (400 MHz, CD3OD): δ 8.29 (s, 1H), 7.51 - 7.49 (m, 1H), 7.25-7.21 (m, 1H), 7.02 (t, J = 9.3 Hz, 1H), 5.71-5.65 (m, 1H), 5.52 (d, J = 52.2 Hz, 1H), 5.18 - 5.07 (m, 1H), 4.57 – 4.77 (m, 2H), 4.68 - 4.60 (m, 1H), 4.47 - 4.18 (m, 2H), 4.04 - 3.80 (m, 5H), 3.77 (s, 3H), 3.74 - 3.60 (m, 3H), 3.74 - 3.60 (m, 3H), 3.48 - 3.40 (m, 1H), 2.64 - 2.46 (m, 4H), 2.30 - 2.20 (m, 3H), 2.17 - 2.05 (m, 1H), 1.51 (t, J = 6.8 Hz, 3H).
180		LCMS m/z [M+1]: 677.4 1H NMR (400 MHz, CD3OD) δ 8.33 (s, 1H), 7.28-7.32 (m, 1H), 6.89-6.99 (m, 2H), 6.04 (s, 1H), 5.55 (d, J = 52.9 Hz, 1H), 5.05-5.09 (m, 1H), 4.60-4.75 (m, 2H), 3.76-4.05 (m, 7H), 3.73 (s, 3H), 3.40-3.63 (m, 3H), 2.05-2.73 (m, 8H), 1.50 (t, J = 6.08 Hz, 3H).

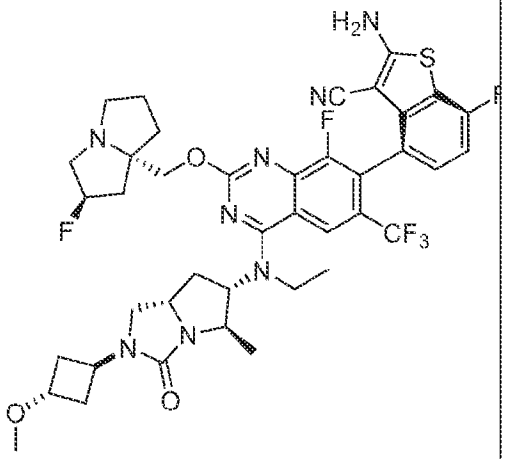
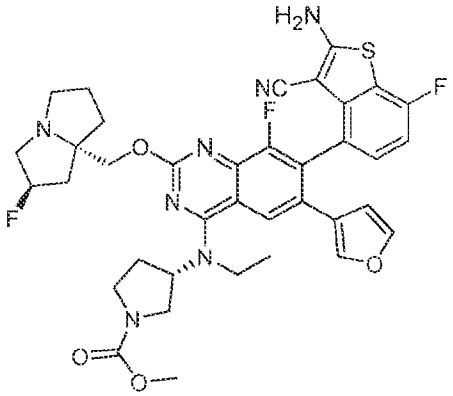
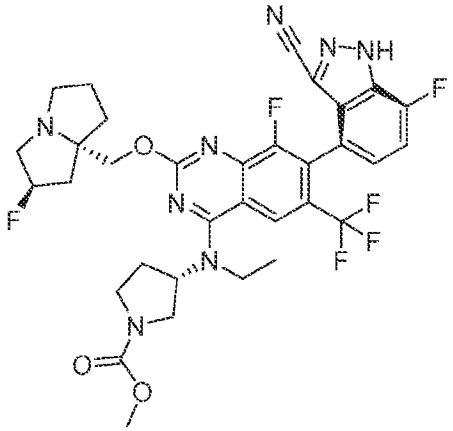
Cmpd. No.	Structure	Analytical Data
181		LCMS m/z [M+1]: 577.2 1H NMR (400 MHz, CD3OD) δ 8.85 (s, 1H), 7.24-7.20 (m, 1H), 7.03-6.98 (m, 1H), 5.39-5.32 (m,1H), 3.57-3.54 (m, 1H), 3.47-3.44 (m,3H), 3.38-3.34 (m,1H), 2.81 (s, 3H), 2.20 (s,1H), 2.03-1.82 (m,5H), 1.45-1.43 (m, 3H), 1.08-1.04 (m, 2H), 0.83-0.80 (m, 2H).
182		LCMS m/z [M+1]: 591.2 1H NMR (400 MHz, CD3OD) δ 8.85 (s, 1H), 7.24-7.20 (m, 1H), 7.03-6.98 (m, 1H), 5.39-5.32 (m,1H), 3.57-3.54 (m, 1H), 3.47-3.44 (m,3H), 3.38-3.34 (m,1H), 2.81 (s, 3H), 2.20 (s,1H), 2.03-1.82 (m,5H), 1.45-1.43 (m, 3H), 1.08-1.04 (m, 2H), 0.83-0.80 (m, 2H).
183		LCMS m/z [M+1]: 760.2 1HNMR (400 MHz, CD3OD) δ8.22 (s, 1H), 7.23 (q, 1H), 7.07 – 6.97 (m, 1H), 5.51 (s, 0.5H), 5.38 (s, 0.5H), 4.74 – 4.66 (m, 1H), 4.47 – 4.24 (m, 4H), 4.03 – 3.88 (m, 2H), 3.87 – 3.45 (m, 4H), 3.24 – 3.16 (m, 2H), 2.63 – 1.79 (m, 10H), 1.58 (q, 3H), 1.42 (d, J = 6.4 Hz, 3H).
184		LCMS m/z [M+1]: 732.3 1HNMR (400 MHz, CD3OD) δ 8.17 (s, 1H), 7.33 – 7.17 (m, 1H), 7.08 – 6.96 (m, 1H), 5.35 (s, 0.5H), 5.22 (s, 0.5H), 4.39 (s, 1H), 4.30 (d, J = 10.3 Hz, 1H), 4.18 (d, J = 10.3 Hz, 1H), 4.08 – 3.93 (m, 1H), 3.73 – 3.42 (m, 4H), 3.22 – 3.16 (m, 2H), 3.04 – 2.91 (m, 4H), 2.75-2.61 (m, 2H), 2.33 – 2.24 (m, 2H), 2.24 – 2.18 (m, 1H), 2.16 – 2.08 (m, 1H), 2.01 – 1.93 (m, 2H), 1.88

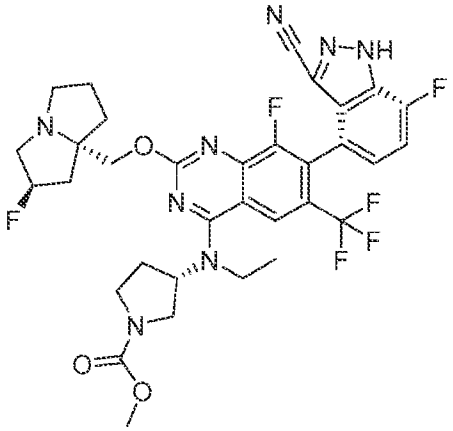
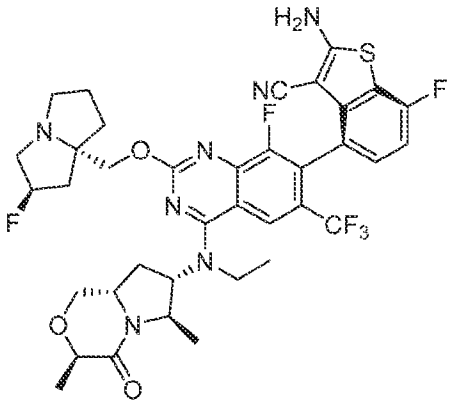
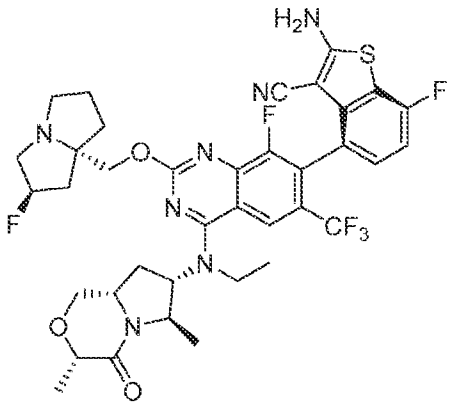
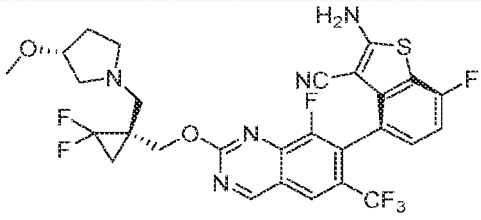
Cmpd. No.	Structure	Analytical Data
		(t, J = 11.2 Hz, 1H), 1.44 (t, J = 6.9 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H).
185		LCMS m/z [M+1]: 732.3 1HNMR (400 MHz, CD3OD) δ 8.12 (s, 1H), 7.23 (dd, J = 8.4, 5.2 Hz, 1H), 7.07 – 6.93 (m, 1H), 5.36 (s, 0.5H), 5.22 (s, 0.5H), 4.52 – 4.41 (m, 1H), 4.29 – 4.20 (m, 2H), 4.11 – 3.99 (m, 1H), 3.66 – 3.43 (m, 4H), 3.22 – 3.16 (m, 2H), 3.03 – 2.92 (m, 5H), 2.64 – 2.54 (m, 1H), 2.42 – 2.33 (m, 1H), 2.28 – 2.20 (m, 1H), 2.17 – 2.09 (m, 1H), 2.02 – 1.83 (m, 4H), 1.41 (t, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H).
186		LCMS m/z [M+1]: 782.4 1H NMR (400 MHz, CD3OD) δ 9.25-9.36 (m, 1H), 8.29 (d, J = 31.3 Hz, 1H), 8.00-8.14 (m, 1H), 7.83-7.95 (m, 1H), 7.17-7.30 (m, 1H), 6.97-7.08 (m, 1H), 5.48-5.69 (m, 1H), 4.93-5.15 (m, 1H), 4.57-4.77 (m, 1H), 3.68-4.43 (m, 9H), 3.37-3.54 (m, 1H), 2.08-2.83 (m, 8H), 1.96-2.05 (m, 1H), 1.47-1.60 (m, 3H).
187		LCMS m/z [M+1]: 812.3 1H NMR (400 MHz, CD3OD) δ 8.24-8.35 (m, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.17-7.35 (m, 2H), 6.96-7.08 (m, 1H), 5.45-5.71 (m, 1H), 4.92-5.13 (m, 1H), 4.52-4.81 (m, 2H), 3.63-4.40 (m, 12H), 3.40-3.53 (m, 1H), 2.12-2.76 (m, 8H), 1.47-1.60 (m, 3H).

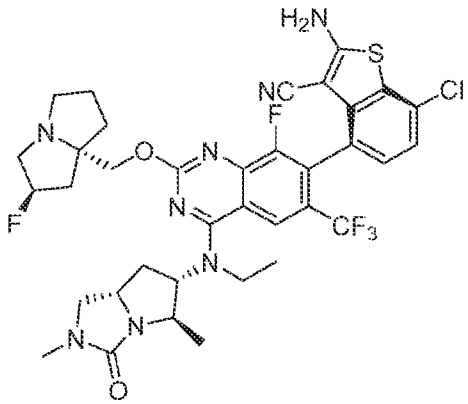
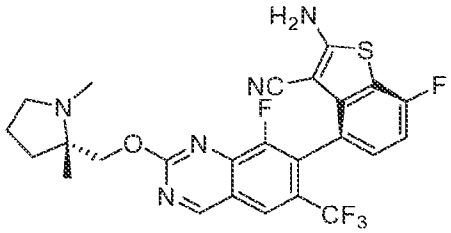
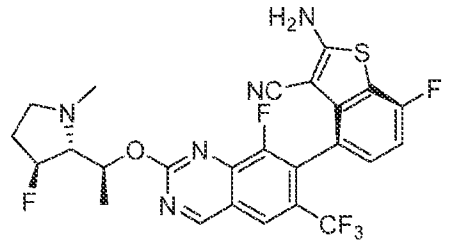
Cmpd. No.	Structure	Analytical Data
188		LCMS m/z [M+1]: 754.2 1H NMR (400 MHz, CD3OD) δ 8.33 (s, 1H), 7.55 (d, J = 6.8 Hz, 1H), 7.23 (dd, J = 8.3, 5.0 Hz, 1H), 7.10 – 6.96 (m, 1H), 6.33 (d, J = 6.8 Hz, 1H), 5.79 (s, 1H), 5.55 (d, J = 53.2 Hz, 1H), 4.41 (d, J = 11.9 Hz, 1H), 4.21 (s, 1H), 4.04 – 3.97 (m, 1H), 3.93 - 3.75 (m, 3H), 3.59 (s, 3H), 3.49 - 3.33 (m, 2H), 3.14 – 3.03 (m, 1H), 2.95 - 2.81 (m, 1H), 2.78 - 2.66 (m, 1H), 2.65 – 2.42 (m, 3H), 2.32 (t, J = 8.2 Hz, 3H), 2.08 (s, 1H), 1.52 (t, J = 6.6 Hz, 3H).
189		LCMS m/z [M+1]: 782.3 1H NMR (400 MHz, CD3OD): δ 9.44-9.33 (m, 2H), 8.30 (d, J = 30.8 Hz, 1H), 7.91- 7.87 (m, 1H), 7.34 - 7.20 (m, 1H), 7.04 -7.00 (m, 1H), 5.54 (d, J = 52.2 Hz, 1H), 5.25 - 4.98 (m, 1H), 4.79 - 4.51 (m, 2H), 4.25 - 3.57 (m, 9H), 3.51 - 3.45 (m, 1H), 2.74 - 2.32 (m, 7H), 2. 01 - 2.13 (m, 1H), 1.57 - 1.41 (m, 3H).
190		LCMS m/z [M+1]: 756.3 1H NMR (400 MHz, CD3OD): δ 8.31 (s, 1H), 7.25 - 7.21 (m, 1H), 7.05 - 6.97 (m, 3H), 5.54 (d, J = 52.4 Hz, 1H), 5.29 - 5.23 (m, 1H), 4.76 - 4.61 (m, 2H), 4.13 - 3.76 (m, 12H), 3.51 - 3.40 (m, 1H), 2.68 - 2.56 (m, 4H), 2.42 - 2.31 (m, 3H), 2. 21 - 2.01 (m, 1H), 1.55 - 1.45 (m, 3H).

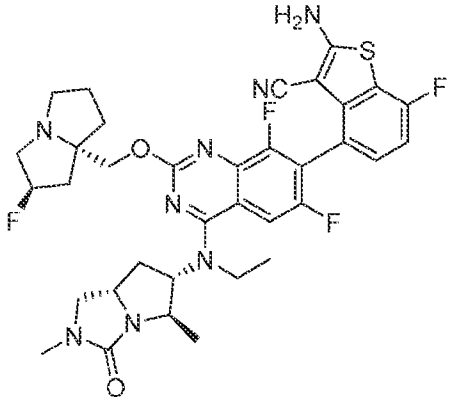
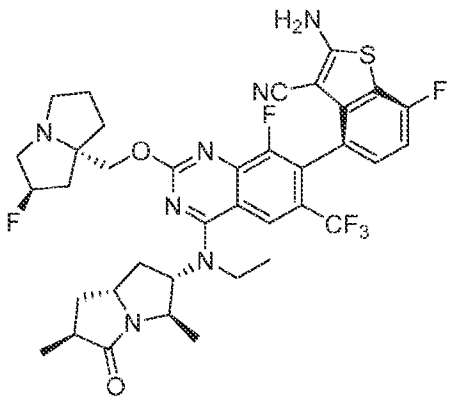
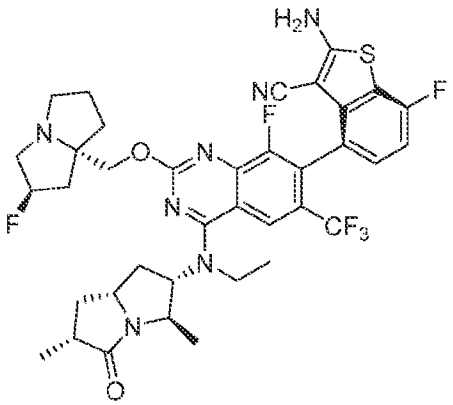
Cmpd. No.	Structure	Analytical Data
191		LCMS m/z [M+1]: 791.2 1H NMR (400 MHz, CD3OD): δ 8.24 (s, 1H), 7.25-7.22 (m, 1H), 7.04-6.99 (m, 1H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 4.66-4.63 (m, 1H), 4.54-4.51 (m, 1H), 4.32-4.10 (m, 3H), 4.06-4.00 (m, 1H), 3.90 – 3.79 (m, 1H), 3.78-3.70 (m, 1H), 3.69 – 3.43 (m, 4H), 3.30 – 3.12 (m, 4H), 3.04-2.97 (m, 1H), 2.39-1.87 (m, 8H), 1.41-1.27 (m, 6H).
192		LCMS m/z [M+1]: 803.2 1H-NMR (400 MHz, CD3OD): 8.24 (s, 1 H), 7.20-7.25 (m, 1 H), 6.98-7.04(m, 1 H), 5.42 (s, 0.5 H), 5.29 (s, 0.5 H), 4.77-4.86 (m, 2 H), 4.26-4.42 (m, 2 H), 4.09-4.17 (m, 1 H), 3.82-4.02 (m, 2 H), 3.60-3.75 (m, 2 H), 3.39-3.58 (m, 6 H), 3.33-3.37 (m, 4 H), 3.07-3.14 (m, 1 H), 1.92-2.40 (m, 8 H), 1.34-1.43 (m, 3 H), 1.29-1.33 (m, 3 H).
193		LCMS m/z [M+1]: 734.1 1H NMR (400 MHz, CD3OD) δ = 8.26 (s, 1H), 7.25 – 7.18 (m, 1H), 7.02 (t, J=9, 1H), 5.44 (s, 0.5H), 5.31 (s, 0.5H), 5.12 – 4.97 (m, 1H), 4.46-4.29 (m, 3H), 4.26-4.09 (m, 1H), 4.02 – 3.86 (m, 3H), 3.80 – 3.71 (m, 1H), 3.50-3.35 (m, 3H), 3.13(s, 1H), 2.78-2.66 (m, 1H), 2.63 – 2.40 (m, 5H), 2.39-2.20 (m, 3H), 2.15-1.88 (m, 4H), 1.50 (t, J=6.8, 3H).

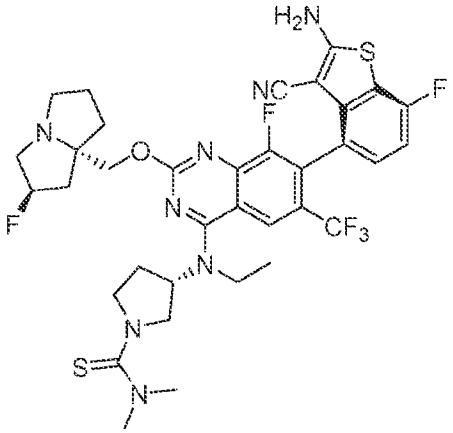
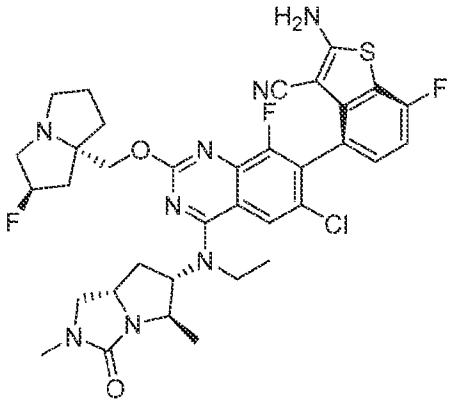
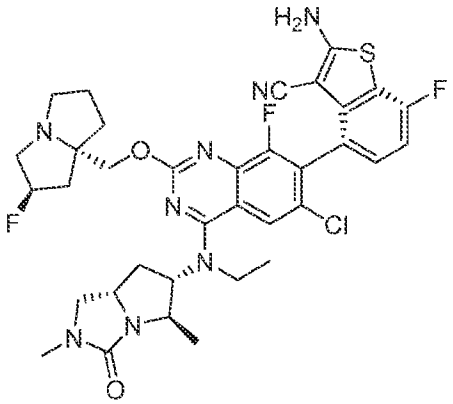
Cmpd. No.	Structure	Analytical Data
194		LCMS m/z [M+1]: 829.2 1H NMR (400 MHz, CD3OD) δ 8.23 (d, J = 10.4 Hz, 1H), 7.29 – 7.19 (m, J = 12.0, 6.1 Hz, 1H), 7.01 (t, J = 8.9 Hz, 1H), 5.40 (s, 0.5H), 5.26 (s, 0.5H), 4.59 (s, 1H), 4.37 – 4.22 (m, J = 34.5, 10.8 Hz, 2H), 4.15 – 3.99 (m, 3H), 3.87 – 3.77 (m, J = 13.8, 7.0 Hz, 1H), 3.72 – 3.59 (m, 3H), 3.54 – 3.49 (m, J = 9.4, 2.1 Hz, 1H), 3.49 – 3.35 (m, 1H), 3.30 – 3.26 (m, 2H), 3.26 (s, 3H), 3.09 – 3.03 (m, 1H), 2.56 – 2.47 (m, 2H), 2.38 – 2.28 (m, 2H), 2.20 – 2.02 (m, 6H), 2.00 – 1.84 (m, 2H), 1.40 – 1.28 (m, 6H).
195		LCMS m/z [M+1]: 755.3 1HNMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.10 (d, J = 7.7 Hz, 2H), 5.41 (s, 0.5H), 5.28 (s, 0.5H), 4.77 – 4.64 (m, 1H), 4.44 – 4.22 (m, 2H), 4.16 (m, 1H), 4.04 – 3.94 (m, 1H), 3.92 – 3.77 (m, 1H), 3.72 – 3.54 (m, 2H), 3.52 – 3.32 (m, 4H), 3.16 – 3.02 (m, 1H), 2.85 (s, 3H), 2.46 (d, J = 13.0 Hz, 3H), 2.43 – 2.14 (m, 5H), 2.13 – 1.84 (m, 3H), 1.41 (t, J = 6.9 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H).
196		LCMS m/z [M+1]: 741.3 1HNMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.68 (dd, J = 7.5, 1.4 Hz, 1H), 7.27 – 7.16 (m, 2H), 5.43 (s, 0.5H), 5.29 (s, 0.5H), 4.78 – 4.67 (m, 1H), 4.43 – 4.25 (m, 2H), 4.16 (p, J = 6.6 Hz, 1H), 4.07 – 3.94 (m, 1H), 3.94 – 3.78 (m, 1H), 3.74 – 3.54 (m, 2H), 3.54 – 3.34 (m, 4H), 3.16 – 3.04 (m, 1H), 2.85 (s, 3H), 2.50 – 2.15 (m, 5H), 2.15 – 2.01 (m, 2H), 1.99 – 1.87 (m, 1H), 1.42 (t, J = 6.9 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H).

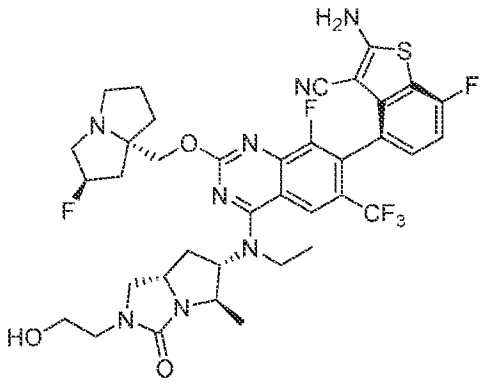
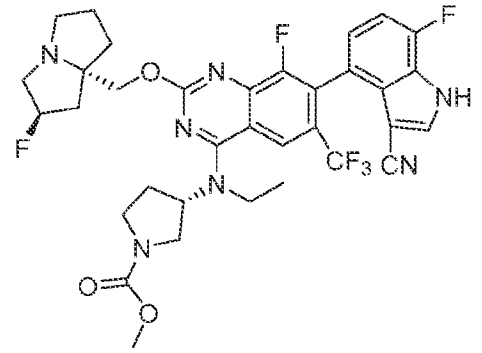
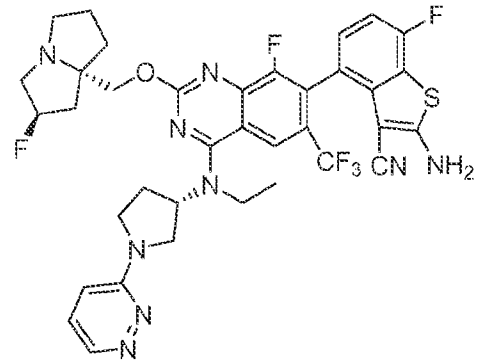
Cmpd. No.	Structure	Analytical Data
197		LCMS m/z [M+1]: 829.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.25-7.22 (m, 1H), 7.02 (t, J = 9.0 Hz, 1H), 5.41 (s, 0.5H), 5.28 (s, 0.5H), 4.82-4.76 (m, 1H), 4.65-4.57 (m, 1H), 4.37-4.27 (m, 2H), 4.19-4.12 (m, 1H), 4.06-3.97 (m, 2H), 3.90 – 3.81 (m, 1H), 3.72 (t, J = 8.8 Hz, 1H), 3.68-3.61 (m, 1H), 3.57-3.54 (m, 1H), 3.48-3.42 (m, 1H), 3.35 (s, 1H), 3.27 (s, 4H), 3.12-3.06 (m, 1H), 2.51-2.42 (m, 2H), 2.37 – 2.10 (m, 7H), 2.09-2.00 (m, 2H), 1.97 – 1.87 (m, 1H), 1.41 – 1.31 (m, 6H).
198		LCMS m/z [M+1]: 732.4 1H NMR (400 MHz, CD3OD) δ 7.95 (s, 1H), 7.34 (d, J = 1.4 Hz, 1H), 7.18 – 7.15 (m, 1H), 7.06 (s, 1H), 7.00 (t, J = 8.8 Hz, 1H), 6.18 (s, 1H), 5.49 (d, J = 53.0 Hz, 1H), 5.09 – 5.01 (m, 1H), 4.64 – 4.50 (m, 2H), 3.91 – 3.37 (m, 13H), 2.67 – 2.03 (m, 8H), 1.43 (t, J = 6.8 Hz, 1H).
202		LCMS m/z [M+1]: 703.5 1H NMR (400 MHz, CD3OD) δ 8.20 (s, 1H), 7.69 – 7.57 (m, 1H), 7.51 (s, 1H), 5.56 (s, 1H), 5.35 (s, 1H), 5.21 – 4.99 (m, 3H), 3.88 (dd, J = 42.7, 9.9 Hz, 5H), 3.71 (s, 4H), 3.63 – 3.36 (m, 4H), 2.91 (s, 2H), 2.63 – 2.23 (m, 5H), 2.01 (t, J = 46.3 Hz, 3H), 1.45 (d, J = 24.5 Hz, 3H).

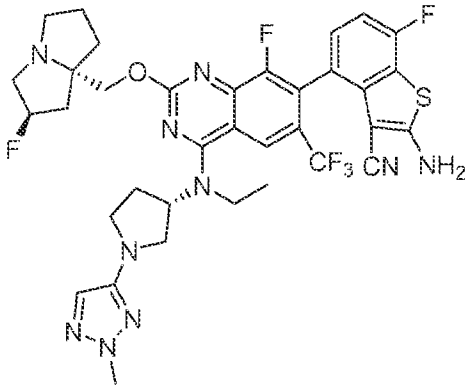
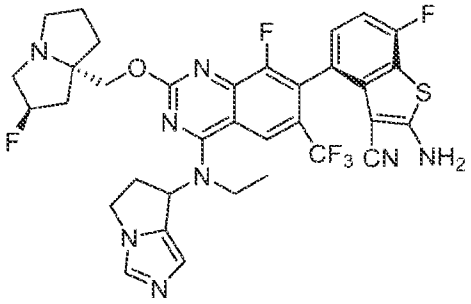
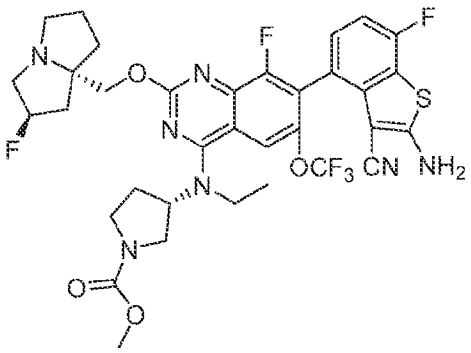
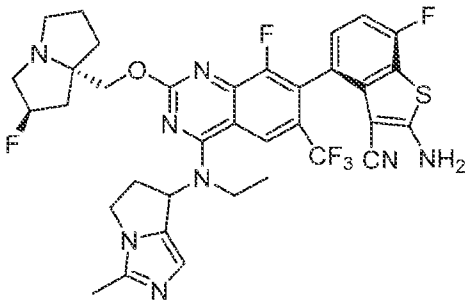
Cmpd. No.	Structure	Analytical Data
203		LCMS m/z [M+1]: 703.5 1H NMR (400 MHz, CD3OD) δ 8.37 (s, 1H), 7.50 – 7.40 (m, 1H), 7.36 (d, J = 3.3 Hz, 1H), 5.57 (d, J = 51.7 Hz, 1H), 5.14 – 4.98 (m, 1H), 4.65 (d, J = 17.5 Hz, 2H), 3.89 (d, J = 12.6 Hz, 5H), 3.76 (d, J = 19.0 Hz, 4H), 3.58 (dd, J = 35.0, 28.0 Hz, 4H), 2.69 (dd, J = 38.6, 14.1 Hz, 2H), 2.38 (dd, J = 19.7, 7.7 Hz, 5H), 2.16 (s, 1H), 1.49 (t, J = 6.8 Hz, 3H).
205		LCMS m/z [M+1]: 774.3 1HNMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.29 – 7.18 (m, 1H), 7.04 – 6.94 (m, 1H), 5.34 (s, 0.5H), 5.21 (s, 0.5H), 4.77 – 4.69 (m, 1H), 4.49 – 4.37 (m, 1H), 4.35 – 4.01 (m, 5H), 4.00 – 3.88 (m, 1H), 3.83 – 3.68 (m, 1H), 3.63 – 3.52 (m, 1H), 3.24 – 3.15 (m, 3H), 3.04 – 2.91 (m, 1H), 2.53 – 2.40 (m, 1H), 2.30 – 2.09 (m, 4H), 2.00 – 1.82 (m, 3H), 1.53 (t, J = 7.0 Hz, 3H), 1.42 (dd, J = 6.6, 1.9 Hz, 6H).
206		LCMS m/z [M+1]: 774.3 1HNMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.29 – 7.17 (m, 1H), 7.10 – 6.95 (m, 1H), 5.35 (s, 0.5H), 5.21 (s, 0.5H), 4.80 – 4.71 (m, 1H), 4.57 – 4.47 (m, 1H), 4.40 – 4.14 (m, 3H), 4.09 – 3.98 (m, 2H), 3.96 – 3.84 (m, 1H), 3.82 – 3.63 (m, 2H), 3.25 – 3.15 (m, 3H), 3.03 – 2.92 (m, 1H), 2.35 – 2.09 (m, 5H), 2.03 – 1.81 (m, 3H), 1.48 (d, J = 7.0 Hz, 3H), 1.46 – 1.40 (m, 6H).
207		LCMS m/z [M+1]: 626.0 1H NMR (400 MHz, CD3OD) δ 9.67 (s, 1H), 8.46 (s, 1H), 7.32 – 7.19 (m, J = 8.1, 5.2 Hz, 1H), 7.04 (t, J = 8.9 Hz, 1H), 4.89 (s, 1H), 4.74

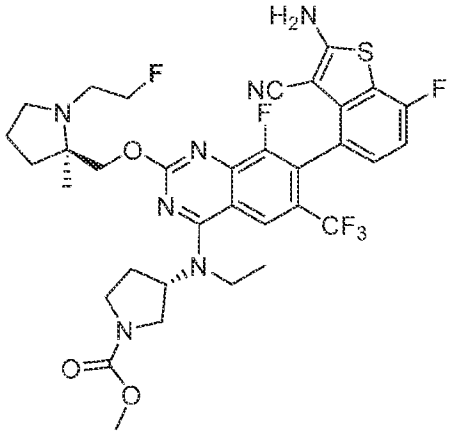
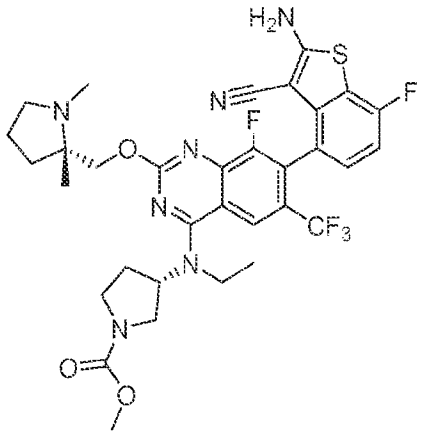
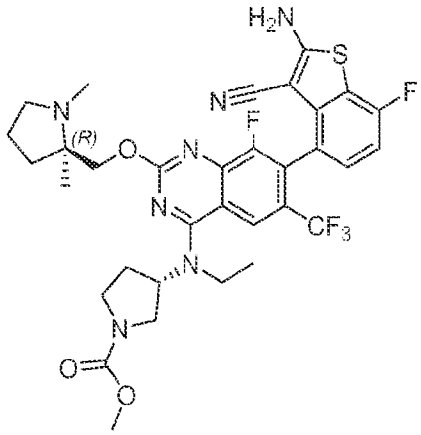
Cmpd. No.	Structure	Analytical Data
		(s, 1H), 4.27 – 3.81 (m, 4H), 3.39 (s, 6H), 2.19 (s, 2H), 2.03 (s, 1H), 1.86 (s, 1H).
208		LCMS m/z [M+1]: 775.1 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.27 – 7.17 (m, 2H), 5.40 (s, 0.5H), 5.27 (s, 0.5H), 4.79 – 4.69 (m, J = 17.5, 6.8 Hz, 1H), 4.37 – 4.23 (m, J = 30.5, 10.9 Hz, 2H), 4.18 – 4.11 (m, 1H), 3.99 (s, 1H), 3.91 – 3.81 (m, J = 14.7, 7.1 Hz, 1H), 3.71 – 3.57 (m, 2H), 3.49 – 3.35 (m, J = 9.5, 2.2 Hz, 2H), 3.10 (d, J = 25.3 Hz, 3H), 2.85 (s, 3H), 2.39 – 2.17 (m, 5H), 1.98 (d, J = 43.9 Hz, 3H), 1.41 (t, J = 6.9 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H).
209		LCMS m/z [M+1]: 534.0 1H NMR (400 MHz, CD3OD) δ = 9.65 (s, 1H), 8.45 (s, 1H), 7.24 (dd, J=8.3, 4.9, 1H), 7.06 – 7.01 (m, 1H), 4.68 (q, J=12.0, 2H), 3.40 (s, 1H), 3.18 (d, J=8.0, 1H), 2.77 (s, 3H), 2.26 (dd, J=12.9, 6.0, 1H), 2.18 (d, J=7.5, 1H), 1.59 (d, J=6.8, 2H), 1.44 (s, 3H).
210		LCMS m/z [M+1]: 552.0 1H NMR (400 MHz, CD3OD) δ 9.58 (s, 1H), 8.39 (s, 1H), 7.21-7.24 (m, 1H), 7.02 (t, 1H), 5.72-5.74 (m, 1H), 5.45-5.46 (m, 0.5H), 5.32-5.35 (m, 0.5H),3.03 (s, 1H), 2.61 (s, 1H), 2.49 (s, 3H), 2.13-2.20 (m, 1H), 2.02-2.07 (m, 2H), 1.53-1.54 (m, 3H).

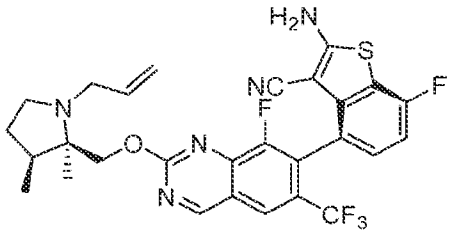
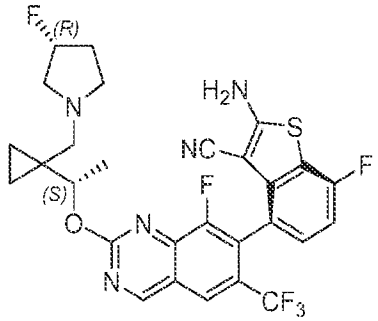
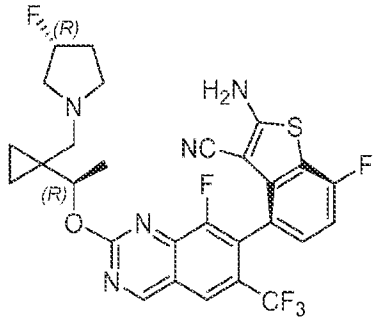
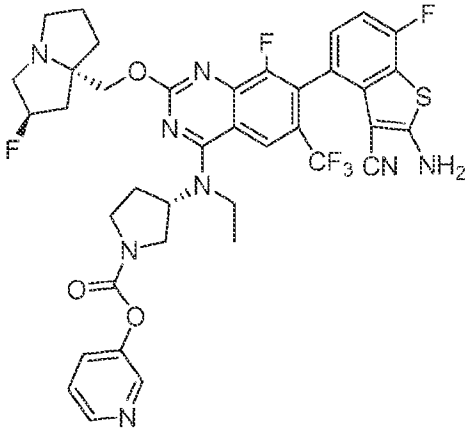
Cmpd. No.	Structure	Analytical Data
211		LCMS m/z [M+1]: 709.1 1H NMR (400 MHz, CD3OD) δ 7.60 (t, 1H), 7.34-7.25 (m, 1H), 7.04 (t, 1H), 5.41 (s, 0.5H), 5.28 (s, 0.5H), 4.77-4.67 (m, 1H), 4.42-4.20 (m, 2H), 4.08-3.89 (m, 3H), 3.62-3.33 (m, 6H), 3.15-3.05 (m, 1H), 2.85 (s, 3H), 2.46-2.01 (m, 7H), 1.92 (s, 1H), 1.32-1.28 (m, 3H), 1.25-1.17 (m, 3H).
212		LCMS m/z [M+1]: 758.1 1H NMR (400 MHz, CD3OD) δ 8.23-8.30 (m, 1H), 7.24-7.20 (m, 1H), 7.01 (t, 1H), 5.36 (s, 0.5H), 5.23 (s, 0.5H), 4.81-4.77 (m, 1H), 4.31-4.25 (m, 1.5H), 4.22-4.16 (m, 1.5H), 4.08-4.02 (m, 1H), 3.94-3.88 (m, 1H), 3.79-3.73 (m, 1H), 3.25-3.18 (m, 3H), 3.03-2.98 (m, 1H), 2.89-2.82 (m, 1H), 2.64-2.58 (m, 1H), 2.41-2.36 (m, 1H), 2.35-2.30 (m, 1H), 2.27-2.20 (m, 2H), 2.17-2.12 (m, 2H), 2.01-1.96 (m, 2H), 1.91-1.86 (m, 1H), 1.44 (t, 3H), 1.36-1.33 (m, 3H), 1.20 (d, 3H).
213		LCMS m/z [M+1]: 758.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.25-7.19 (m, 1H), 7.01 (t, 1H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 4.79-4.76 (m, 1H), 4.33-4.19 (m, 3H), 4.08-4.01 (m, 1H), 3.94-3.86 (m, 1H), 3.80-3.73 (m, 1H), 3.26-3.20 (m, 3H), 3.05-2.99 (m, 1H), 2.89-2.82 (m, 1H), 2.64-2.57 (m, 1H), 2.42-2.12 (m, 6H), 2.03-1.96 (m, 2H), 1.92-1.86 (m, 1H), 1.44 (t, 3H), 1.35-1.33 (m, 3H), 1.20 (d, 3H).

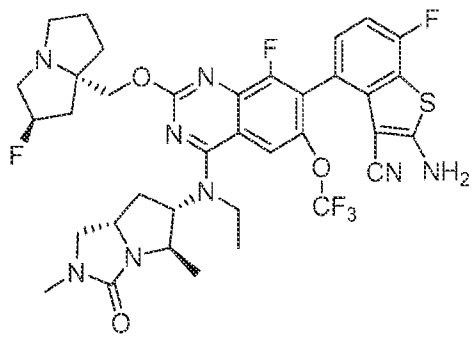
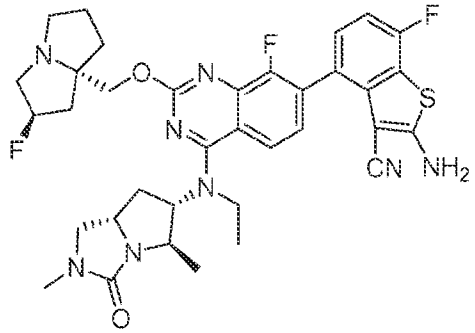
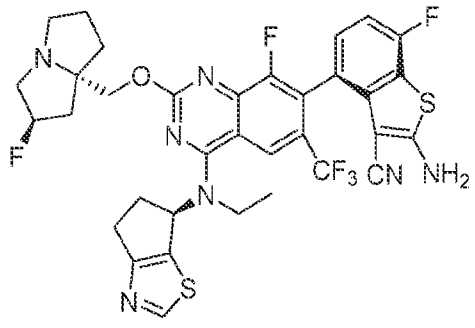
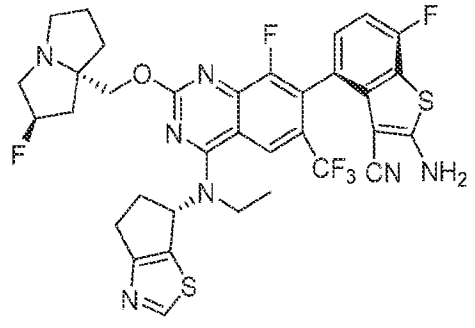
Cmpd. No.	Structure	Analytical Data
214		LCMS m/z [M+1]: 763.3 1H NMR (400 MHz, CD3OD) δ 8.33-8.22 (s, 1H), 7.30-7.18 (m, 1H), 7.09-6.95 (m, 1H), 5.52-5.45 (m, 0.5H), 5.38-5.34 (m, 0.5H), 5.07-4.96 (m, 1H), 4.63-4.24 (m, 2H), 4.05-3.75 (m, 6H), 3.71-3.49 (m, 3H), 3.23-3.17 (m, 1H), 3.14-3.04 (s, 6H), 2.54-2.48 (m, 1H), 2.41-2.33 (m, 2H), 2.31-2.23 (m, 1H), 2.18-2.10 (m, 2H), 2.09-1.87 (m, 2H), 1.52-1.44 (m, 3H).
215		LCMS m/z [M+1]:725.1 1H NMR (400 MHz, CD3OD) δ 7.95 (s, 1H), 7.25-7.20 (m, 1H), 7.04 (t, 1H), 5.50-5.45 (m, 0.5H), 5.36-5.32 (m, 0.5H), 4.73-4.63 (m, 1H), 4.49-4.32 (dq, 2H), 4.16-4.07 (m, 1H), 4.04-3.86 (m, 2H), 3.63-3.41 (m, 5H), 3.11-2.91 (m, 3H),2.85 (s, 2H), 2.42-1.95 (m, 8H), 1.37-1.31 (m, 3H), 1.30-1.28 (m, 3H).
216		LCMS m/z [M+1]: 725.1 1H NMR (400 MHz, CD3OD) δ 7.93 (s, 1H), 7.26-7.19 (m, 1H), 7.04 (t, 1H), 5.52-5.47 (m, 0.5H), 5.39-5.34 (m, 0.5H), 4.70-4.62 (m, 1H), 4.54-4.40 (m, 2H), 4.10-3.91 (m, 3H), 3.62-3.40 (m, 5H), 3.09-2.96 (m, 3H), 2.85 (s, 2H), 2.59-2.36 (m, 3H), 2.32-2.11 (m, 4H), 2.06-2.00 (m, 1H), 1.33-1.27 (m, 6H).

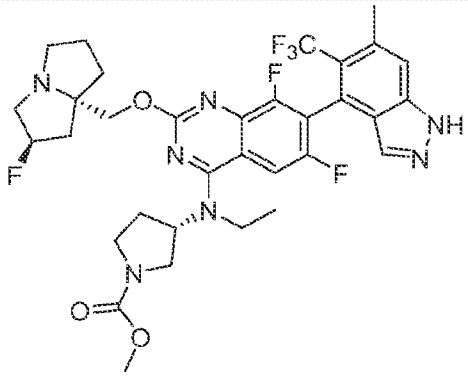
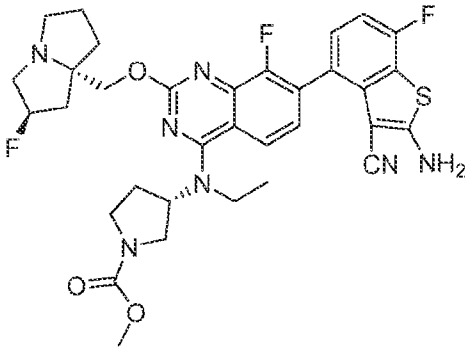
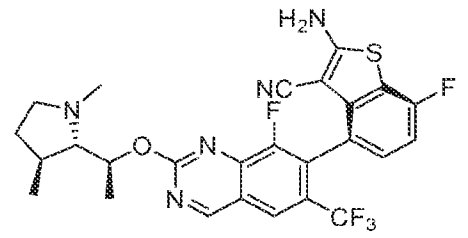
Cmpd. No.	Structure	Analytical Data
217		LCMS m/z [M+1]: 789.3 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.21-7.24 (m, 1H), 7.01 (t, 1H), 5.40 (s, 0.5H), 5.26 (s, 0.5H), 4.25-4.37 (m, 2H), 3.97-4.14 (m, 3H), 3.84-3.89 (m, 2H), 3.64-3.75 (m, 4H), 3.46-3.55 (m, 2H), 3.35-3.38 (m, 2H), 3.04-3.12 (m, 2H), 2.26-2.38 (m, 3H), 2.13-2.21 (m, 2H), 1.99-2.07 (m, 2H), 1.89-1.94 (m, 1H), 1.28-1.40 (m, 6H).
218		LCMS m/z [M+1]: 702.3 1H NMR (400 MHz, CD3OD) δ 8.33 (s, 1H), 8.06 (s, 1H), 7.18-7.23 (m, 2H), 5.56 (d, J = 51.8 Hz, 1H), 5.02-5.11 (m, 1H), 4.58-4.72 (m, 2H), 3.76-4.05 (m, 7H), 3.73 (s, 3H), 3.40-3.63 (m, 3H), 2.05-2.76 (m, 8H), 1.49 (t, J = 6.92 Hz, 3H).
219		LCMS m/z [M+1]: 755.3 1H NMR (400 MHz, CD3OD) 8.55 (d, J = 4.0 Hz, 1H), 8.33 (s, 1H), 7.84 (dd, J = 9.6, 4.4 Hz, 1H), 7.68 (dd, J = 9.6, 5.6 Hz, 1H), 7.24 (dd, J = 8.4, 5.2 Hz, 1H), 7.06 – 7.01 (m, 1H), 5.52 (d, J = 52.0 Hz, 1H), 5.37 – 5.21 (m, 1H), 4.78 – 4.48 (m, 2H), 4.30 – 4.15 (m, 1H), 4.13 – 3.79 (m, 8H), 3.78 – 3.65 (m, 1H), 3.54 – 3.38 (m, 1H), 2.78 – 2.48 (m, 4H), 2.46 – 2.24 (m, 2H), 2.21 – 2.01 (m, 1H), 1.52 (td, J = 6.8, 2.8 Hz, 3H).

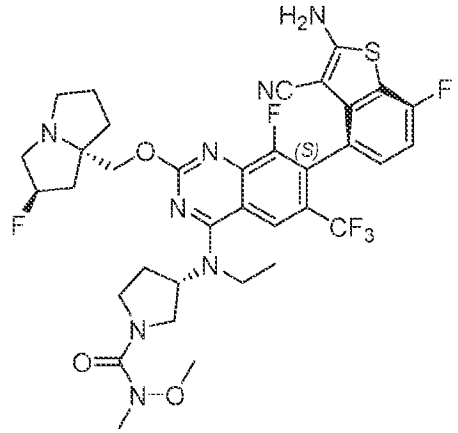
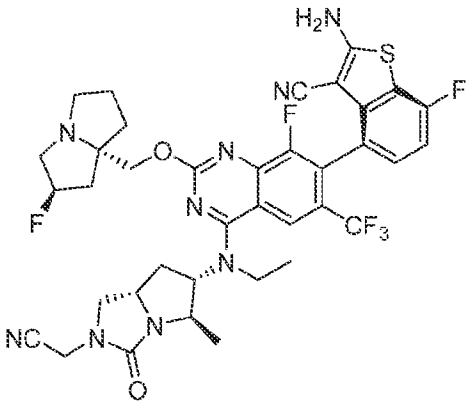
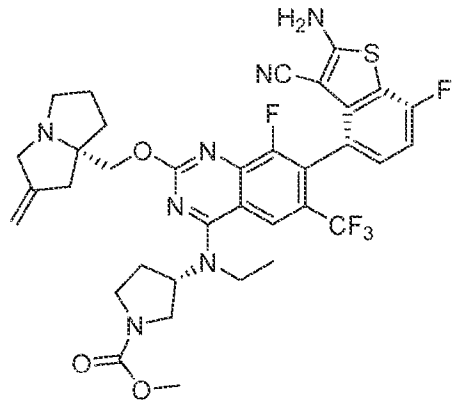
Cmpd. No.	Structure	Analytical Data
220		LCMS m/z [M+1]: 757.3 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.18-7.28 (m, 1H), 6.98-7.12 (m, 2H), 5.46 (d, J = 52 Hz 1H), 5.10-5.25 (m, 1H), 4.54-4.74 (m, 2H), 3.81-4.07 (m, 8H), 3.67 -3.77 (m, 2H), 3.38-3.64 (m, 2H), 3.23-3.28 (m, 1H), 2.47-2.71 (m, 4H), 2.07-2.36 (m, 4H), 1.40-1.56 (m, 3H).
221		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD3OD): δ 8.87 - 8.81 (m, 1H),8 .31 (s, 1H), 7.46 (m, 1H),7.27 - 7.19 (m, 1H), 7.05 - 7.01 (m, 1H), 5.93 - 5.83 (m, 1H), 5.64-5.45 (m, 1H), 4.73 - 4.44 (m, 3H), 4.05 - 3.81 (m, 5H), 3.50 - 3.40 (m, 2H), 3.15 - 2.93 (m, 1H), 2.66 - 2.25 (m, 6H), 2.12 - 1.98 (m, 1H), 1.60 - 1.23 (m, 5H).
223		LCMS m/z [M+1]: 750.2 1H NMR (400 MHz, CD3OD) δ 7.88 (s, 1H), 7.28 – 7.23 (m, 1H), 7.06 (t, J = 9.2 Hz, 1H), 5.56 (d, J = 52.0 Hz, 1H), 5.06 – 4.96 (m, 1H), 4.75 – 4.57 (m, 2H), 4.08 – 3.75 (m, 7H), 3.72 (s, 3H), 3.63 – 3.39 (m, 3H), 2.77 – 2.51 (m, 2H), 2.50 – 2.28(m, 5H), 2.22– 2.06 (m, 1H), 1.43 (t, J = 6.8 Hz, 3H).
224		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) 8.32 (s, 1H), 7.39 (s, 1H), 7.24 - 7.21 (m, 1H), 7.05 - 7.01 (m, 1H), 6.02-5.99 (m, 1H), 5.53 (d, *J* = 52.1 Hz, 1H), 4.77 - 4,74 (m, 1H), 4.77-4,74 m, 1H), 4.63 - 4.58 (m, 2H), 4.38 - 4.32 (m, 1H), 3.99 - 3.88 (m, 5H), 3.47 - 3.42 (m, 1H), 3.00 - 2.94 (m, 1H), 2.61 - 2.59 (m, 1H), 2.55 - 2.51 (m,

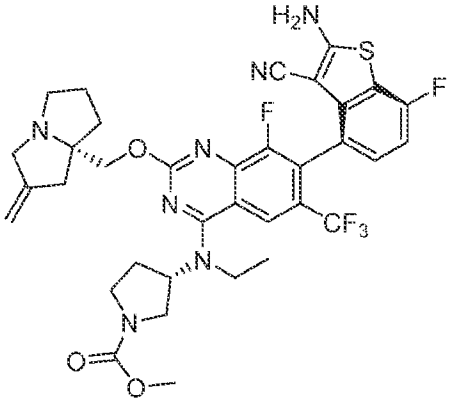
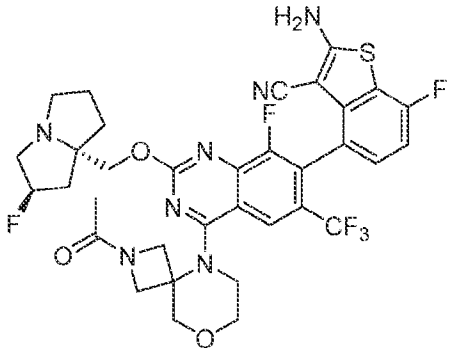
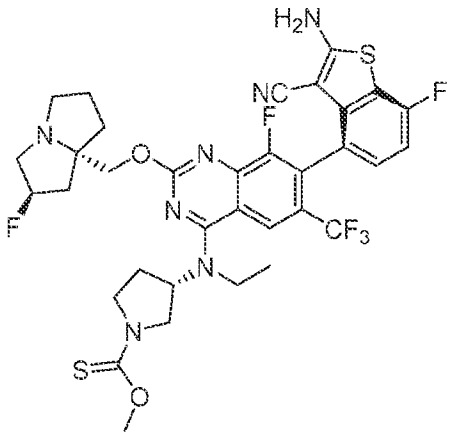
Cmpd. No.	Structure	Analytical Data
		1H), 2.47 - 2.43 (m, 1H), 2.36 - 2.03 (m, 2H), 2.06 - 2.03 (m, 1H), 1.52 - 1.47 (m, 3H), 1.38 - 1.29 (m.2 H).
225		LCMS m/z [M+1]: 714.2 1H NMR (400 MHz, DMSO-d6) δ 8.09 (s, 1H), 7.63 – 7.74 (m, 1H), 7.11 – 7.25 (m, 1H), 5.30 – 5.45 (m, 1H), 4.34-4.63 (m, 2H), 4.04-4.26 (m, 2H), 3.65-3.99 (m, 2H), 3.36-3.64 (m, 5H), 3.28 – 3.30 (m, 1H), 2.74 – 3.20 (m, 2H), 2.06 – 2.29 (m, 4H), 1.93 – 2.05 (m, 2H), 1.76 – 1.90 (m, 2H), 1.60 – 1.72 (m, 2H), 1.39 – 1.54 (m, 2H).
227		LCMS m/z [M+1]: 704.1 1H NMR (400 MHz, CD3OD) δ = 8.29 (s, 1H), 7.24 (dd, J=8.3, 5.1, 1H), 7.08 – 7.00 (m, 1H), 5.09 (s, 1H), 4.70 (t, J=20.8, 2H), 3.90 (dd, J=14.2, 7.2, 3H), 3.73 (s, 6H), 3.48 (s, 1H), 3.31 (s, 2H), 2.97 (s, 3H), 2.54 – 2.30 (m, 3H), 2.13 (dd, J=23.6, 17.5, 3H), 1.50 (s, 3H), 1.29 (s, 3H).
228		LCMS m/z [M+1]: 704.3 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.20-7.24 (m, 1H), 7.01 (t, 1H), 4.98-5.04 (m, 1H), 4.42-4.51 (m, 2H), 3.81-3.95 (m, 3H), 3.71-3.78 (m, 4H), 3.57-3.62 (m, 1H), 3.43-3.47 (m, 1H), 3.03-3.12 (m, 2H), 2.64 (s, 3H), 2.45-2.52 (m, 1H), 2.33-2.39 (m, 1H), 2.12-2.20 (m, 1H), 1.87-2.03 (m, 3H), 1.42-1.48 (m, 3H), 1.32 (s, 3H).

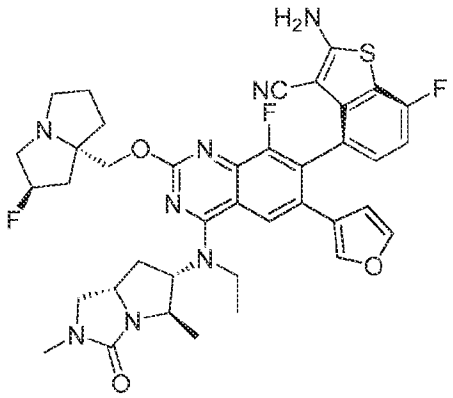
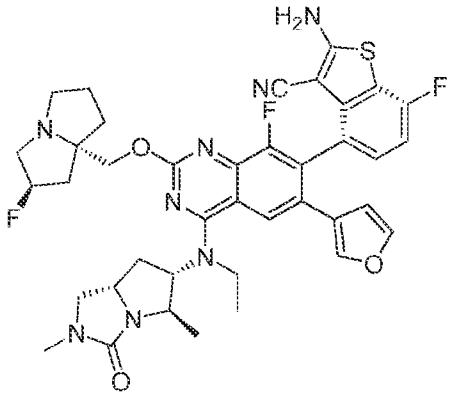
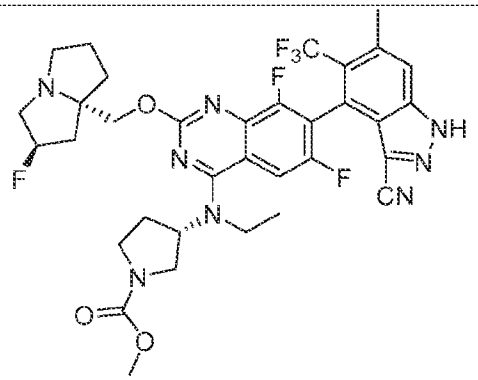
Cmpd. No.	Structure	Analytical Data
230		LCMS m/z [M+1]: 574.0 1H NMR (400 MHz, CD3OD) δ 9.61 (s, 1H), 8.42 (s, 1H), 7.26-7.19 (m, 1H), 7.03 (t, 1H), 5.93-5.83 (m, 1H), 5.31-5.23 (m, 1H), 5.18-5.09 (m, 1H), 4.64-4.58 (m, 1H), 4.51-4.46 (m, 1H), 3.60-3.54 (m, 1H), 3.06-3.00 (m, 1H), 2.03-2.01 (m, 1H), 1.73-1.70 (m, 2H), 1.46-1.43 (m, 2H), 1.13 (d, 3H), 0.97 (t, 3H).
231		LCMS m/z [M+1]: 592.0 1H NMR (400 MHz, CD3OD) δ 9.58 (s, 1H), 8.39 (s, 1H), 7.27-7.23 (m, 1H), 7.07 – 7.00 (m, 1H), 5.68-5.66 (m, 1H), 5.22 (s, 0.5H), 5.08 (s, 0.5H), 3.07-2.97 (m, 2H), 2.77-2.68 (m, 2H), 2.22-1.97 (m, 4H), 1.48 (d, J = 6.4 Hz, 3H), 1.03-0.96 (m, 2H), 0.88-0.82 (m, 2H).
232		LCMS m/z [M+1]: 592.0 1H NMR (400 MHz, CD3OD) δ 9.58 (s, 1H), 8.39 (s, 1H), 7.27-7.23 (m, 1H), 7.07 – 7.00 (m, 1H), 5.65 -5.58(m, 1H), 5.23 (s, 0.5H), 5.09 (s, 0.5H), 2.99-2.86 (m, 2H), 2.81-2.70 (m, 2H), 2.21-1.94 (m, 4H), 1.49 (d, J = 6.3 Hz, 3H), 1.02-0.93 (m, 2H), 0.89-0.84 (m, 2H).
233		LCMS m/z [M+1]: 797.3 1H NMR (400 MHz, CD3OD): δ 8.66 - 8.46 (m, 2H), 8.32 (s, 1H), 8.00 - 7.81 (m, 1H), 7.70 - 7.57 (m, 1H), 7.28 - 7.20 (m, 1H), 7.08 - 6.94 (m, 1H), 5.54 (d, J = 51.7 Hz, 1H), 5.23 - 5.06 (m, 1H), 4.61 - 4.76 (m, 2H), 4.21 - 3.53 (m, 9H), 3.50 - 3.39 (m, 1H), 2.78 - 2.26 (m, 7H), 2.23 - 2.06 (m, 1H), 1.61 - 1.43 (m, 3H).

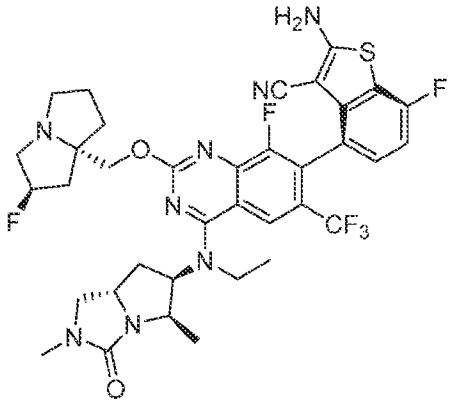
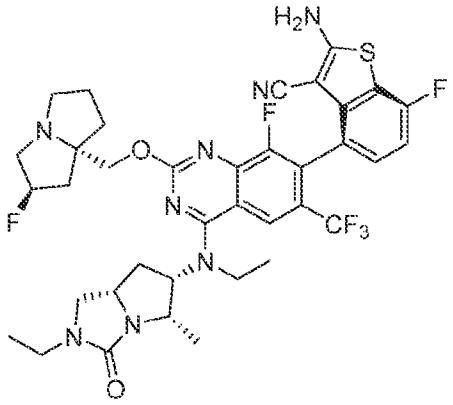
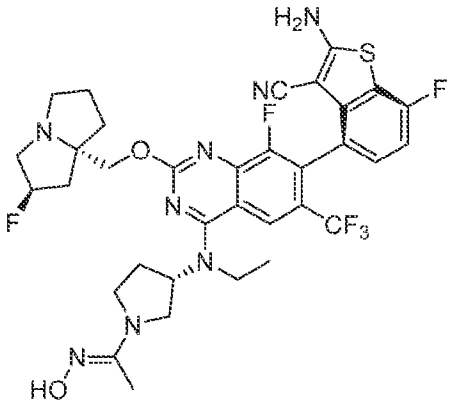
Cmpd. No.	Structure	Analytical Data
234		LCMS m/z [M+1]: 775.3 1H NMR (400 MHz, CD3OD) δ 7.86 (s, 1H), 7.28 – 7.25 (m, 1H), 7.05 (t, J = 9.0 Hz, 1H), 5.55 (d, J = 51.8 Hz, 1H), 4.69 – 4.54 (m, 3H), 4.22 – 4.19 (m, 1H), 3.98 – 3.86 (m, 5H), 3.65 – 3.61 (m, 2H), 3.47 – 3.45 (m, 2H), 2.86 (s, 3H), 2.70 – 2.01 (m, 8H), 1.46 – 1.42 (m, 3H), 1.28 – 1.27 (m, 3H).
235		LCMS m/z [M+1]: 691.4 1H NMR (400 MHz, CD3OD) δ 7.96 – 7.93 (m, 1H), 7.42 – 7.38 (m, 1H), 7.30 – 7.27 (m, 1H), 7.04 (t, J = 9.0 Hz, 1H), 5.53 (d, J = 51.8 Hz, 1H), 4.78 – 4.56 (m, 3H), 4.17 – 3.81 (m, 6H), 3.65 – 3.45 (m, 4H), 2.86 (s, 3H), 2.76 – 2.08 (m, 8H), 1.45 – 1.41 (m, 3H), 1.27 – 1.23 (m, 3H).
236		LCMS m/z [M+1]: 730.2 1H NMR (400 MHz, CD3OD) δ 9.07 (s, 1H), 8.33 (s, 1H), 7.26 – 7.21 (m, 2H), 7.06 – 7.00 (m, 2H), 6.22 – 6.18 (m, 1H), 5.57 (d, J = 52.1 Hz, 3H), 4.64 – 4.58 (m, 2H), 3.93 – 3.88 (m, 2H), 3.80 – 3.73 (m, 2H), 3.49 – 3.46 (m, 1H), 3.24 – 3.18 (m, 2H), 3.04 – 2.99 (m, 1H), 2.86 – 2.81 (m, 1H), 2.63 – 2.56 (m, 2H), 2.43 – 2.31 (m, 4H), 2.12 (s, 2H), 1.30 (t, J = 5.5 Hz, 3H).
237		LCMS m/z [M+1]: 730.2 1H NMR (400 MHz, CD3OD) δ 9.07 (s, 1H), 8.32 (s, 1H), 7.24 (dd, J = 8.3, 5.0 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.17 (d, J = 7.5 Hz, 1H), 5.57 (d, J = 52.0 Hz, 1H), 4.68 (d, J = 12.3 Hz, 1H), 4.46 (d, J = 12.4 Hz, 1H), 3.95 – 3.72 (m, 5H), 3.49 – 3.42 (m, 1H), 3.26 – 3.16 (m, 2H), 3.05 –

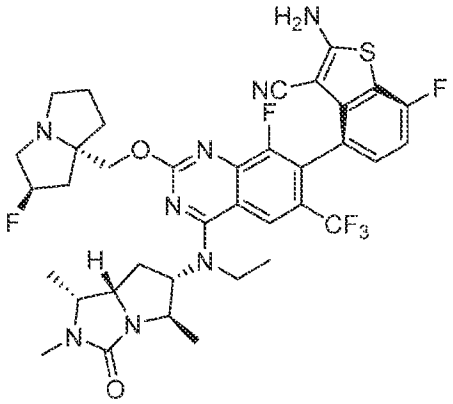
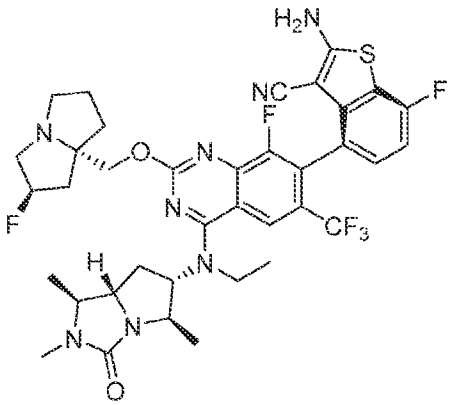
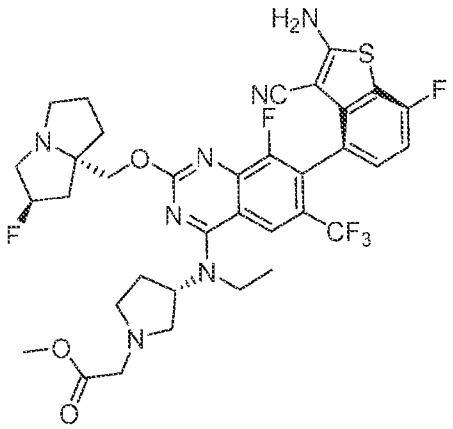
Cmpd. No.	Structure	Analytical Data
		2.98 (m, 1H), 2.87 – 2.80 (m, 1H), 2.67 – 2.55 (m, 2H), 2.47 – 2.27 (m, 4H), 2.16 – 2.07 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H).
239		LCMS m/z [M+1]: 692.3 1H NMR (400 MHz, CD3OD) δ 7.76 (d, J = 9.9 Hz, 1H), 7.71 (s, 1H), 7.61 (s, 1H), 5.63 (s, 0.5 H), 5.50 (s, 0.5 H), 5.02 (s, 2H), 4.63 (t, J = 12.0 Hz, 2H), 4.04 – 3.78 (m, 7H), 3.72 (s, 3H), 3.58-3.43 (m, 3H), 2.71 (s, 3H), 2.64 – 2.53 (m, 2H), 2.43 – 2.32 (m, 4H), 2.15 (s, 1H), 1.40 (t, J = 6.8 Hz, 3H).
240		LCMS m/z [M+1]: 666.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (d, *J* = 8.8 Hz, 1H), 7.39 (t, *J* = 7.9Hz, 1H), 7.30 - 7.26(m, 1H), 7.04 (t, *J* = 8.8 Hz, 1H), 5.54 (d, *J* = 52.4 Hz, 1H), 5.12 - 5.02 (m, 1H), 4.78 - 4.72(m, 1H), 4.59 (t, *J* = 16.9 Hz, 1H), 3.99 - 3.83 (m, 6H), 3.78 - 3.72 (m, 4H), 3.58 - 3.44 (m, 3H), 2.72 - 2.52 (m, 2H), 2.50 - 2.27 (m, 5H), 2.24 - 2.01(m, 1H), 1.29 - 1.41 (m, 3H).
241		LCMS m/z [M+1]: 548.1 1H NMR (400 MHz, CD3OD) δ 9.60 (s, 1H), 8.40 (s, 1H), 7.26-7.21 (m, 1H), 7.02 (t, 1H), 5.54-5.48 (m, 1H), 3.12-3.05 (m, 1H), 2.663 (s, 3H), 2.63-2.47 (m, 2H), 2.32-2.24 (m, 1H), 2.07-2.00 (m, 1H), 1.57-1.50 (m, 1H), 1.49 (d, 3H), 1.14 (d, 3H).

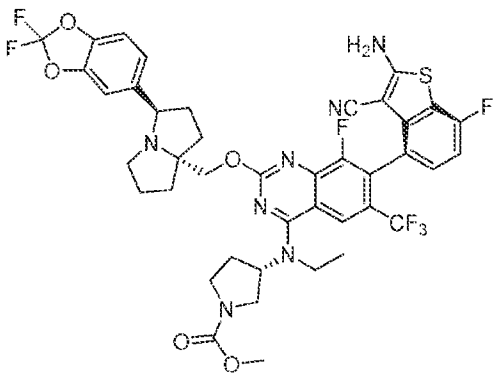
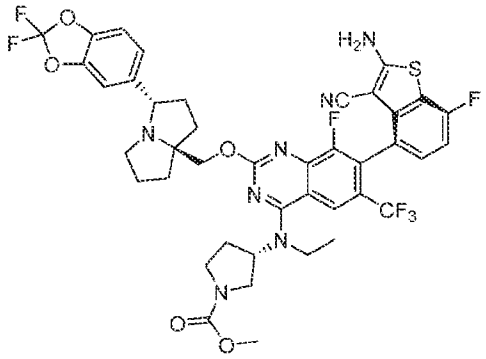
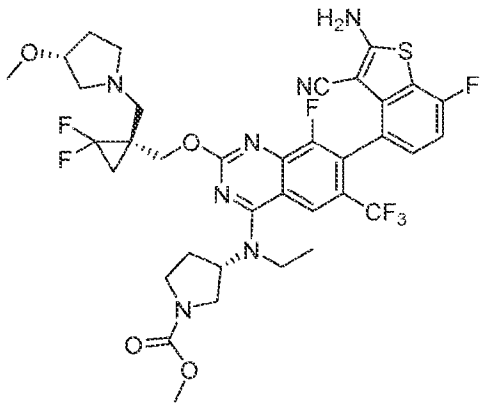
Cmpd. No.	Structure	Analytical Data
242		LCMS m/z [M+1]: 763.2 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.23-7.20 (m, 1H), 7.03-6.99 (s, 1H), 5.42 (s, 0.52H), 5.29 (s, 0.52H), 5.01 (s, 1H), 4.38-4.30 (m, 2H), 3.88-3.72 (m, 5H), 3.70 (s, 3H), 3.61-3.39 (m, 4H), 3.12-3.10 (m, 1H), 3.01 (s, 3H), 2.47-1.93 (m, 8H), 1.49-1.45 (m, 3H).
243		LCMS m/z [M+1]: 784.2 1H NMR (400 MHz, CD3OD) δ 8.50 (s, 1H), 8.24 (s, 1H), 7.27-7.20 (m, 1H), 7.02 (t, 1H), 5.51-5.45 (m, 0.5H), 5.37-5.33 (m, 0.5H), 4.67-4.58 (m, 1H), 4.51-4.40 (m, 2H), 4.35 (d, 1H), 4.30-4.24 (m, 1H), 4.16-4.07 (m, 1H), 3.95-3.50 (m, 7H), 3.27-3.17 (m, 2H), 2.57-2.23 (m, 5H), 2.21-2.09 (m, 2H), 2.04-1.95 (m, 1H), 1.49-1.42 (m, 3H), 1.38-1.29 (m, 3H).
244		LCMS m/z [M+1]: 728.3 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.24-7.19 (m, 1H), 7.01 (t, 1H), 5.08-4.97 (m, 3H), 4.32 (s, 2H), 3.94-3.86 (m, 2H), 3.83-3.75 (m, 2H), 3.71 (s, 3H), 3.58-3.53 (m, 1H), 3.48-3.43 (m, 1H), 3.41-3.37 (m, 1H), 3.23-3.20 (m, 1H), 3.83-3.74 (m, 2H), 2.54-2.48 (m, 1H), 2.45-2.33 (m, 2H), 2.19-2.13 (m, 1H), 2.04-1.84 (m, 4H), 1.43 (t, 3H).

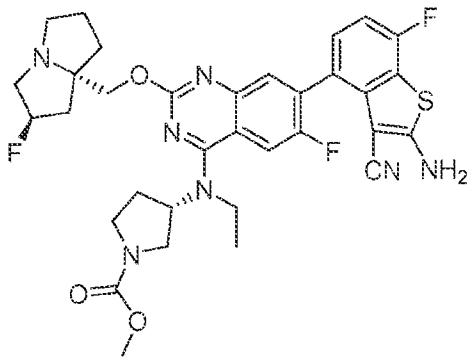
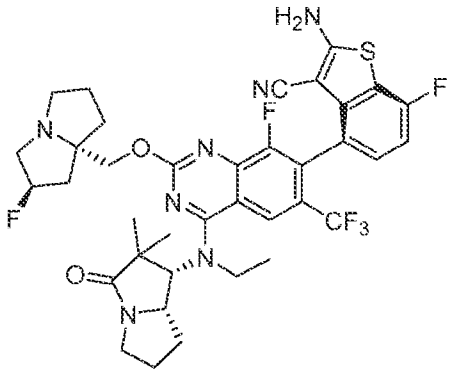
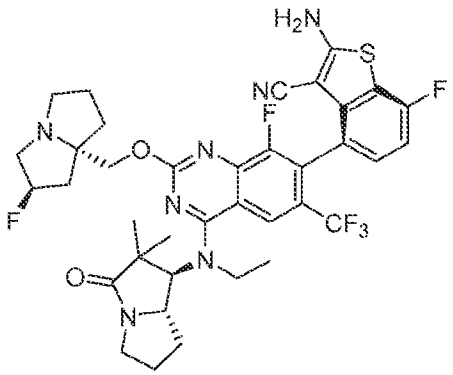
Cmpd. No.	Structure	Analytical Data
245		LCMS m/z [M+1]: 728.3 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.24-7.19 (m, 1H), 7.01 (t, 1H), 5.02 (s, 3H), 4.38-4.27 (m, 2H), 3.93-3.82 (m, 3H), 3.79-3.68 (m, 4H), 3.59-3.53 (m, 1H), 3.47-3.38 (m, 2H), 3.25-3.21 (m, 1H), 3.85-3.75 (m, 2H), 2.55-2.49 (m, 1H), 2.46-2.32 (m, 2H), 2.19-2.13 (m, 1H), 2.04-1.84 (m, 4H), 1.44 (t, 3H).
246		LCMS m/z [M+1]: 732.1 1H NMR (400 MHz, CD3OD) δ8.15 (s, 1H), 7.26-7.14 (m, 1H), 7.05-6.96 (m, 1H), 5.45-5.38 (m, 0.5H), 5.31-5.26 (m, 0.5H), 4.55-4.45 (m, 1H), 4.40-4.12 (m, 7H), 4.08-3.94 (m, 2H), 3.63-3.54 (m, 2H), 3.44-3.32 (m, 3H), 3.14-3.05 (m, 1H), 2.36-2.14 (m, 3H), 2.11-1.98 (m, 3H), 1.95-1.92 (s, 3H).
247		LCMS m/z [M+1]: 750.3 1H NMR (400 MHz, CD3OD) δ8.28-8.18 (m, 1H), 7.26-7.17 (m, 1H), 7.07-6.95 (m, 1H), 5.42-5.36 (m, 0.5H), 5.28-5.21 (m, 0.5H), 5.04-4.93 (m, 1H), 4.30-4.25 (m, 2H), 4.17-4.06 (m, 1H), 4.02-3.98 (m, 3H), 3.94-3.75 (m, 3H), 3.72-3.34 (m, 2H), 3.29-3.20 (m, 3H), 3.10-2.98 (m, 1H), 2.69-2.48 (m, 1H), 2.47-2.21 (m, 3H), 2.19-2.12 (m, 1H), 2.05-1.98 (m, 2H), 1.95-1.84 (m, 1H), 1.51-1.43 (m, 3H).

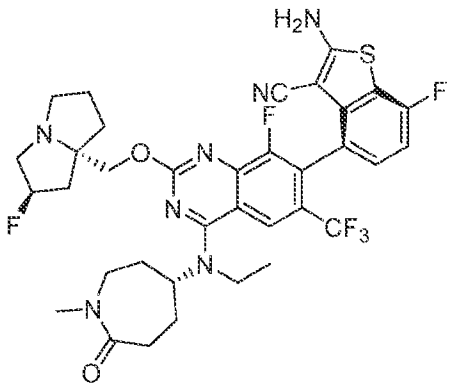
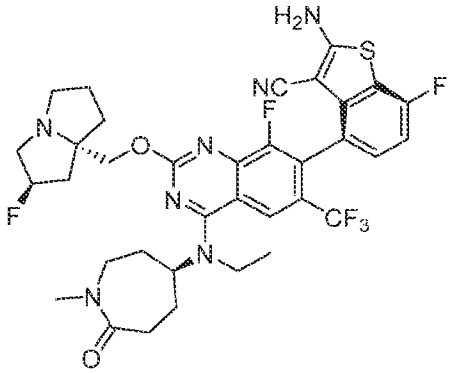
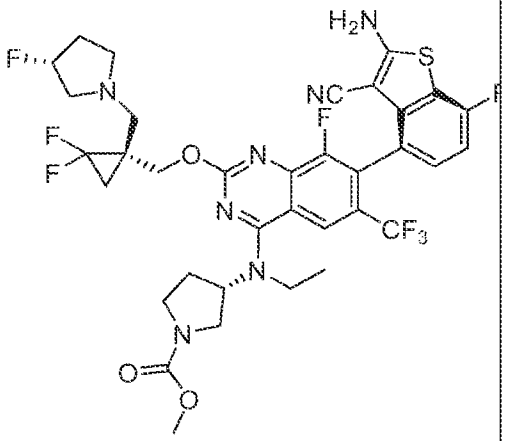
Cmpd. No.	Structure	Analytical Data
248		LCMS m/z [M+1]: 757.3 1H NMR (400 MHz, CD3OD) δ 7.90 (s, 1H), 7.33 (s, 1H), 7.20 – 7.16 (m, 1H), 7.06 (s, 1H), 6.99 (t, J = 8.8 Hz, 1H), 6.19 (s, 1H), 5.36 (d, J = 52.7 Hz, 1H), 4.80 – 4.73 (m, 1H), 4.38 – 4.26 (m, 2H), 4.15 – 3.91 (m, 3H), 3.62 – 3.37 (m, 6H), 3.13 – 3.07 (m, 1H), 2.84 (s, 3H), 2.43 – 1.92 (m, 8H), 1.37 (t, J = 6.9 Hz, 3H), 1.27 (d, J = 6.5 Hz, 3H).
249		LCMS m/z [M+1]: 757.3 1H NMR (400 MHz, CD3OD) δ 7.87 (s, 1H), 7.33 (s, 1H), 7.22 – 7.18 (m, 1H), 7.05 (s, 1H), 7.00 (t, J = 8.8 Hz, 1H), 6.19 (s, 1H), 5.35 (d, J = 52.8 Hz, 1H), 4.80 – 4.77 (m, 1H), 4.36 – 4.28 (m, 2H), 4.05 – 3.96 (m, 3H), 3.62 – 3.36 (m, 5H), 3.28 – 3.08 (m, 2H), 2.83 (s, 3H), 2.47 – 1.92 (m, 8H), 1.34 (t, J = 6.9 Hz, 3H), 1.20 (d, J = 6.5 Hz, 3H).
251		LCMS m/z [M+1]: 717.3 1H NMR (400 MHz, CD3OD): δ 7.89 (s, 1H), 7.80 - 7.75 (m, 1H), 5.57 (d, J = 51.2 Hz, 1H), 5.04 - 5.00 (m, 1H), 4.72 - 4.58 (m, 2H), 4.05 - 3.80 (m, 6H), 3.79 - 3.62 (m, 4H), 3.55 - 3.43 (m, 3H), 2.71 - 2.53 (m, 5H), 2.41 - 2.35 (m, 5H), 2.22 - 2.05 (m, 1H) 1.40 - 1.28 (m, 3H).

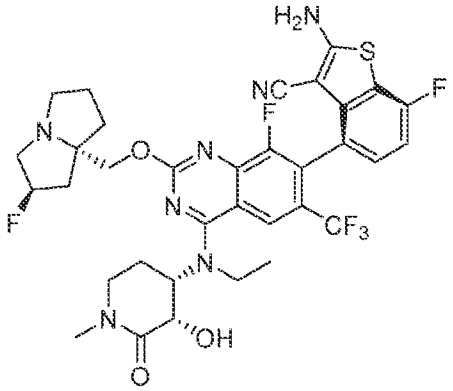
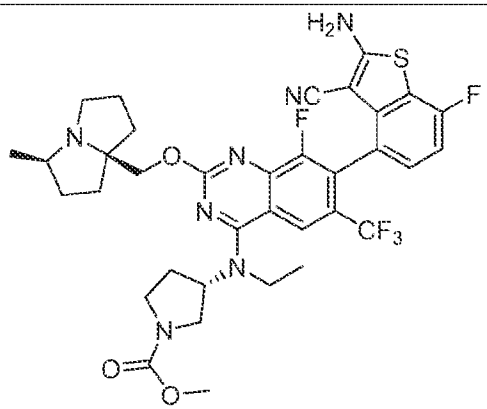
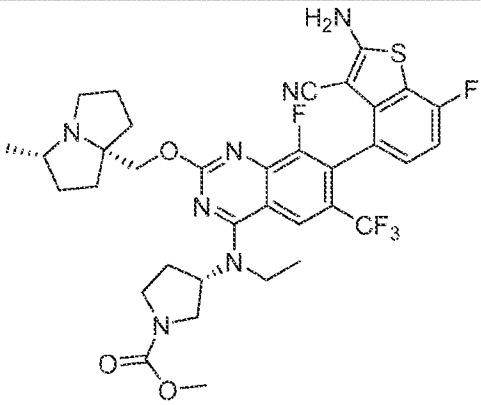
Cmpd. No.	Structure	Analytical Data
252		LCMS m/z [M+1]: 759.3 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.22 (dd, J = 8.3, 5.0 Hz, 1H), 7.02 (t, J = 8.9 Hz, 1H), 5.47 (s, 0.5H), 5.34 (s, 0.5H), 4.77 – 4.68 (m, 2H), 4.44-4.28 (m, 3H), 4.02-3.88 (m, 2H), 3.74-3.48 (m, 2H), 3.47-3.39 (m, 2H), 3.23-3.06 (m, 2H), 2.84 (s, 3H), 2.76-2.63 (m, 1H), 2.58-2.41 (m, 1H), 2.37-2.24 (m, 2H), 2.17-1.95 (m, 4H), 1.44 (t, J = 6.8 Hz, 3H), 1.08 (d, J = 6.3 Hz, 3H).
253		LCMS m/z [M+1]: 773.2 1H NMR (400 MHz, CD3OD) δ 8.34 (s, 1H), 7.25-7.21 (m, 1H), 7.04-7.00 (m, 1H), 5.52 (s, 0.5H), 5.38 (s, 0.5H), 5.17-5.13 (m, 1H), 4.56 (s, 1H), 4.45-4.40 (m, 2H), 4.06 (s, 3H), 3.91-3.87 (m, 1H), 3.72-3.68 (m, 1H), 3.63 (s, 2H), 3.48-3.42 (m, 2H), 3.21-3.16 (m, 2H), 2.54-2.48 (m, 2H), 2.44 (s, 1H), 2.31-2.54 (m, 2H), 2.21-2.19 (m, 2H), 2.03 (s, 1H), 1.49 (t, 3H), 1.21 (d, 3H), 1.14 (t, 3H).
254		LCMS m/z [M+1]: 733.2 1H-NMR (400 MHz, CD_3OD): 8.28 (s, 1 H), 7.25 (s, 1 H), 7.05 (s, 1 H), 5.38 (m, 2 H), 5.07 (s, 1 H), 4.21-4.40 (m, 2 H), 3.83-3.93 (m, 2 H), 3.54-3.77 (m, 2 H), 3.39-3.54 (m, 1 H), 3.02-3.24 (m, 1 H), 2.79 (s, 3 H), 2.36-2.58 (m, 2 H), 1.92-2.33 (m, 8 H), 1.50 (s, 3 H).

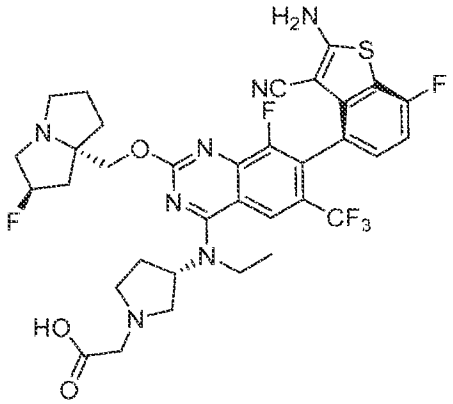
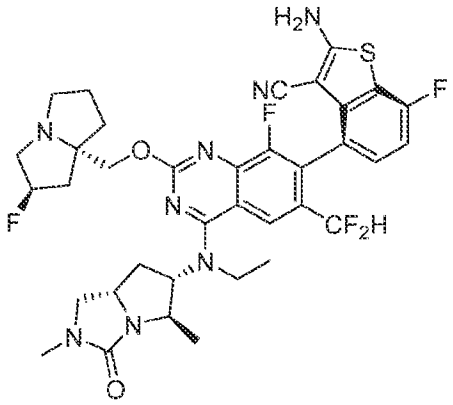
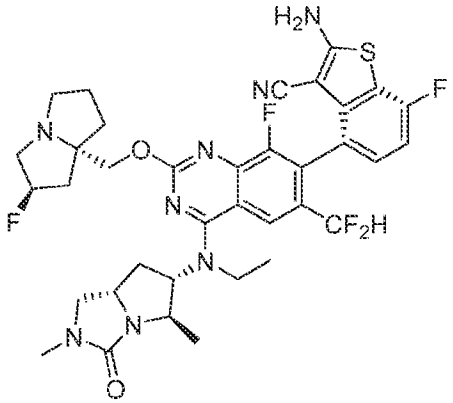
Cmpd. No.	Structure	Analytical Data
255		LCMS m/z [M+1]: 773.3 1HNMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.28 – 7.19 (m, 1H), 7.05 – 6.95 (m, 1H), 5.37 (s, 0.5H), 5.24 (s, 0.5H), 4.80 – 4.72 (m, 1H), 4.34 – 4.17 (m, 2H), 4.18 – 4.08 (m, 1H), 3.92 – 3.76 (m, 1H), 3.76 – 3.55 (m, 3H), 3.27 – 3.18 (m, 3H), 3.07 – 2.95 (m, 1H), 2.83 (s, 3H), 2.39 – 2.08 (m, 5H), 2.05 – 1.96 (m, 2H), 1.95 – 1.83 (m, 1H), 1.37 (p, J = 14.7, 7.7 Hz, 3H), 1.34 – 1.29 (m, 6H).
256		LCMS m/z [M+1]: 773.3 1HNMR (400 MHz, CD3OD) δ 8.17 (s, 1H), 7.29 – 7.14 (m, 1H), 7.01 (t, J = 8.9 Hz, 1H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 4.42 – 4.19 (m, 3H), 4.11 – 3.87 (m, 3H), 3.85 – 3.68 (m, 1H), 3.51 – 3.36 (m, 1H), 3.22 (s, 3H), 3.10 – 2.95 (m, 1H), 2.72 (s, 3H), 2.61 – 2.48 (m, 1H), 2.42 – 2.26 (m, 1H), 2.25 – 2.09 (m, 3H), 2.05 – 1.95 (m, 2H), 1.95 – 1.86 (m, 1H), 1.54 (d, J = 6.7 Hz, 3H), 1.46 (t, J = 6.9 Hz, 3H), 1.32 (d, J = 6.2 Hz, 3H).
257		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.24-7.18 (m, 1H), 7.00 (t, 1H), 5.42-5.37 (m, 0.5H), 5.29-5.24 (m, 0.5H), 5.15-5.07 (m, 1H), 4.38 (d, 1H), 4.28 (d, 1H), 4.05-3.94 (m, 2H), 3.72 (s, 3H), 3.55-3.32 (m, 4H), 3.27-3.23 (m, 1H), 3.17-3.03 (m, 3H), 2.93 (t, 1H), 2.72-2.64 (m, 1H), 2.43-2.15 (m, 5H), 2.07-1.90 (m, 3H), 1.40 (t, 3H).

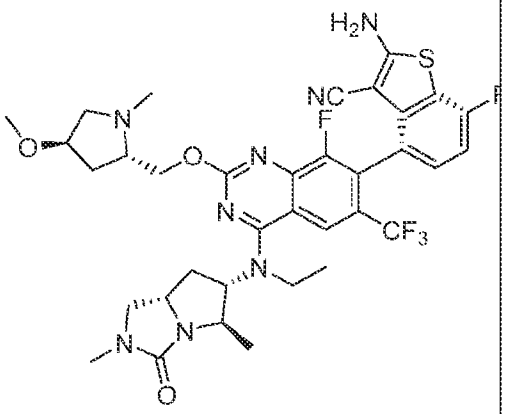
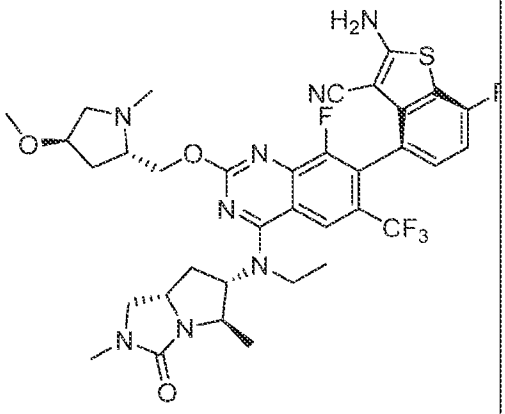
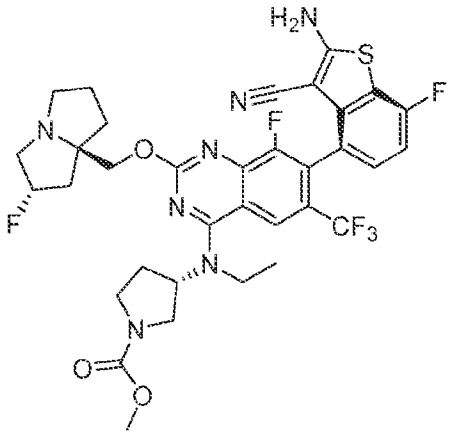
Cmpd. No.	Structure	Analytical Data
258		LCMS m/z [M+1]: 872.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.42 (s, 1H), 7.36-7.30 (M, 1H), 7.27-7.17 (m, 2H), 7.02 (t, 1H), 5.08-5.01 (m, 1H), 4.64-4.56 (m, 1H), 4.50-4.43 (m, 1H), 3.98-3.83 (m, 3H), 3.80-3.73 (m, 1H), 3.70 (s, 3H), 3.63-3.56 (m, 1H), 3.48-3.42 (m, 1H), 2.67 (s, 2H), 2.55-2.43 (m, 2H), 2.40-2.30 (m, 2H), 2.27-2.16 (m, 2H), 2.11-2.05 (m, 1H), 2.04-1.78 (m, 4H), 1.48 (t, 3H).
259		LCMS m/z [M+1]: 872.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.40 (s, 1H), 7.33 (d, 1H), 7.28-7.17 (m, 2H), 7.01 (t, 1H), 5.06-4.99 (m, 1H), 4.62-4.55 (m, 1H), 4.53-4.46 (m, 1H), 4.00-3.84 (m, 3H), 3.82-3.75 (m, 1H), 3.70 (s, 3H), 3.64-3.57 (m, 1H), 3.49-3.42 (m, 1H), 2.70 (s, 2H), 2.58-2.44 (m, 2H), 2.41-2.26 (m, 3H), 2.24-2.17 (m, 1H), 2.15-2.08 (m, 1H), 2.07-1.81 (m, 4H), 1.49 (t, 3H).
260		LCMS m/z [M+1]: 796.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.24 – 7.14 (m, 1H), 7.01 (t, J = 8.9 Hz, 1H), 5.02 (s, 1H), 4.70 – 4.52 (m, J = 23.8, 10.4 Hz, 2H), 3.98 – 3.77 (m, 5H), 3.72 (s, 3H), 3.64 – 3.54 (m, 1H), 3.46 (d, J = 12.9 Hz, 2H), 3.24 (s, 3H), 2.97 (s, 1H), 2.87 – 2.60 (m, J = 50.5, 36.2 Hz, 5H), 2.42 (d, J = 41.6 Hz, 2H), 2.09 – 1.98 (m, J = 13.8, 6.7 Hz, 1H), 2.09 – 2.01 (m, J = 13.8, 6.7 Hz, 1H),1.50 – 1.40 (m, J = 11.7, 6.8 Hz, 3H).

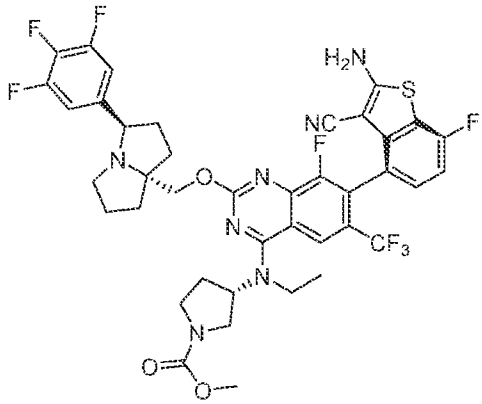
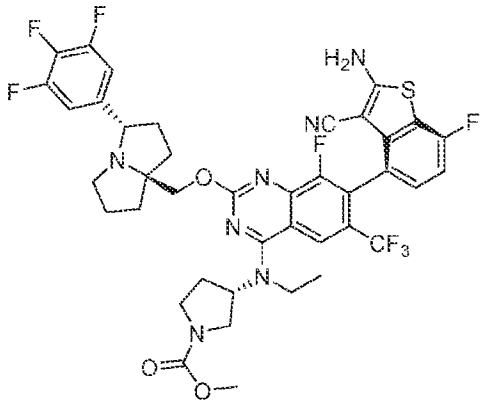
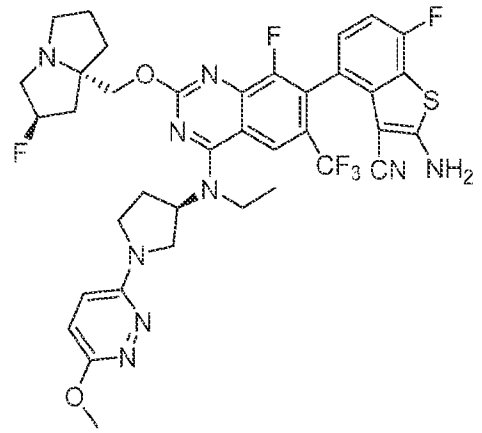
Cmpd. No.	Structure	Analytical Data
261		LCMS m/z [M+1]: 666.3 1H NMR (400 MHz, CD3OD) δ 7.87 (d, J = 12 Hz, 1H), 7.65 (d, J = 6.8 Hz, 1H), 7.28 (m, 1H), 7.04 (t, J = 8.9 Hz, 1H), 5.59 (d, J = 51.4 Hz, 1H), 5.15 (s, 1H), 4.63 – 4.78 (m, 2H), 3.85 – 4.04 (m, 6H), 3.69 – 3.82 (m, 4H), 3.60 (t, J = 22.7 Hz, 1H), 3.42 – 3.53 (m, 2H), 2.55 – 2.79 (m, 2H), 2.29 – 2.54 (m, 5H), 2.13 – 2.247 (m, 1H), 1.45 (t, J = 6.7 Hz, 3H).
262		LCMS m/z [M+1]: 758.3 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.26 -7.22 (m, 1H), 7.02 (t, J = 9.0 Hz, 1H), 5.41 (s, 0.5H), 5.27 (s, 0.5H), 4.72 (d, J = 5.6 Hz, 1H), 4.38 – 4.26 (m, 2H), 4.22 (d, J = 10.4 Hz, 1H), 4.06 - 4.01 (m, 2H), 3.65 - 3.58 (m, 1H), 3.48 - 3.39 (m, 1H), 3.23 - 3.12 (m, 3H), 3.11 – 3.01 (m, 1H), 2.45 – 2.07 (m, 6H), 2.06 - 1.99 (m, 2H), 1.96 - 1.88 (m, 1H), 1.70 – 1.58 (m, 1H), 1.43 (t, J = 7.0 Hz, 3H), 1.31 (s, 3H), 1.24 (s, 3H).
263		LCMS m/z [M+1]: 758.3 1H NMR (400 MHz, CD3OD) δ 8.31 (s, 1H), 7.24 - 7.21 (m, 1H), 7.02 (t, J = 9.0 Hz, 1H), 5.42 (s, 0.5H), 5.28 (s, 0.5H), 4.38 – 4.25 (m, 3H), 4.21 – 4.10 (m, 1H), 4.02 - 3.93 (m, 1H), 3.65 - 3.58 (m, 1H), 3.50 – 3.33 (m, 2H), 3.28 – 3.12 (m, 3H), 3.11 - 3.05 (m, 1H), 243 - 2.15 (m, 6H), 2.07 - 2.00 (m, 2H), 1.96 - 1.87 (m, 1H), 1.76 – 1.65 (m, 1H), 1.38 (t, J = 7.0 Hz, 3H), 1.29 (s, 3H), 1.16 (s, 3H).

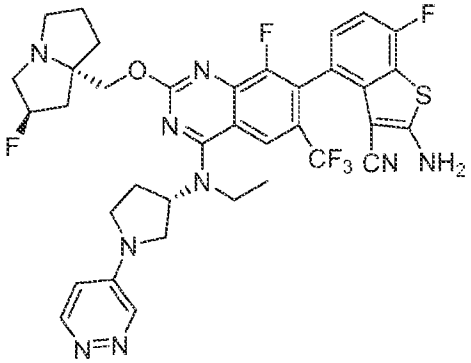
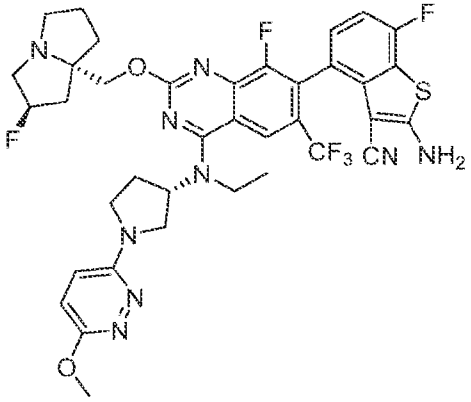
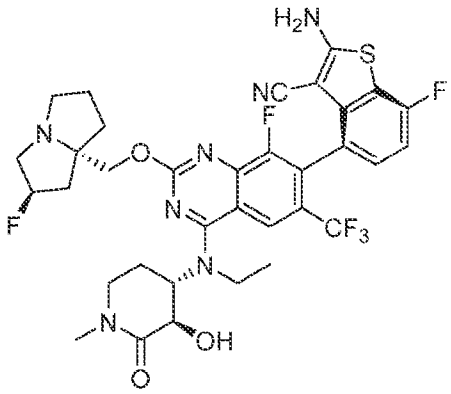
Cmpd. No.	Structure	Analytical Data
264		LCMS m/z [M+1]: 732.3 1H NMR (400 MHz, CD3OD) δ 8.36 (s, 1H), 7.22 - 7.19 (m, 1H), 7.01 (t, J = 9.0 Hz, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 4.35 (d, J = 10.8 Hz, 1H), 4.25 (d, J = 10.8 Hz, 1H), 4.00 - 3.85 (m, 3H), 3.69 – 3.60 (m, 4H), 3.43 - 3.32 (m, 1H), 3.29 - 3.22 (m, 2H), 3.19 - 3.12 (m, 1H), 3.09 - 3.03 (m, 1H), 2.53 – 1.99 (m, 9H), 1.99 - 1.88 (m, 3H), 1.14 (t, J = 7.2 Hz, 3H).
265		LCMS m/z [M+1]: 758.3 1H NMR (400 MHz, CD3OD) δ 8.36 (s, 1H), 7.23 - 7.20 (m, 1H), 7.01 (t, J = 9.0 Hz, 1H), 5.41 (s, 1H), 5.27 (s, 1H), 4.41 – 4.19 (m, 2H), 3.97 – 3.82 (m, 3H), 3.70 – 3.58 (m, 4H), 3.50 – 3.32 (m, 3H), 3.21 - 3.14 (m, 1H), 3.12 – 3.03 (m, 1H), 2.55 – 2.23 (m, 6H), 2.19 – 2.12 (m, 1H), 2.10 – 1.99 (m, 2H), 1.99 – 1.83 (m, 3H), 1.15 (t, J = 7.2 Hz, 3H).
267		LCMS m/z [M+1]: 784.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.25 – 7.18 (m, J = 8.2, 5.0 Hz, 1H), 7.01 (t, J = 8.9 Hz, 1H), 5.18 (s, 0.5H), 5.03 (d, J = 6.0 Hz, 1.5H), 4.65 (d, J = 12.5 Hz, 2H), 3.94 – 3.82 (m, 3H), 3.76 (s, 1H), 3.72 (s, 3H), 3.60 (d, J = 8.4 Hz, 1H), 3.48 – 3.41 (m, 1H), 2.97 – 2.74 (m, 4H), 2.69 (d, J = 12.8 Hz, 1H), 2.46 (d, J = 7.7 Hz, 2H), 2.36 (s, 1H), 2.19 – 2.05 (m, J = 20.4, 13.9, 7.5 Hz, 1H), 2.00 – 1.88 (m, 1H), 1.66 – 1.59 (m, J = 11.8, 6.6 Hz, 1H), 1.45 (t, J = 6.9 Hz, 3H), 0.96 – 0.88 (m, J = 11.8, 7.2 Hz, 1H).

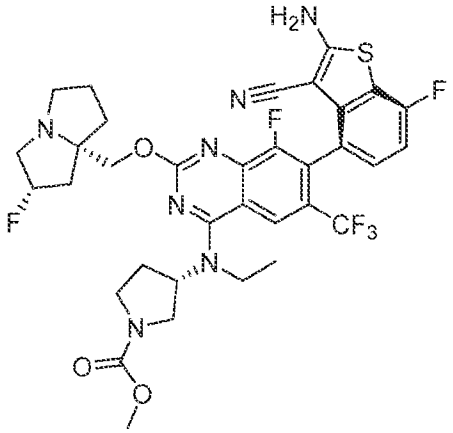
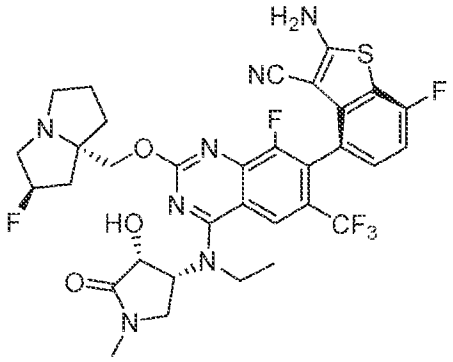
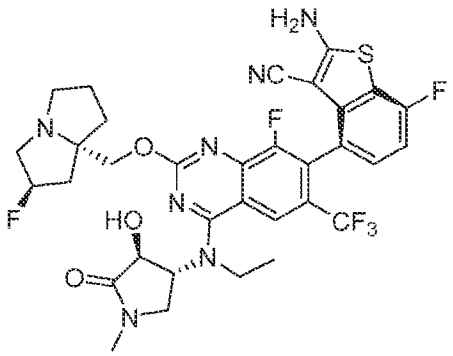
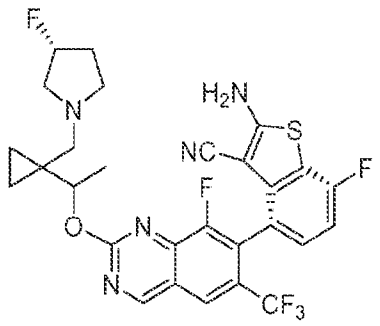
Cmpd. No.	Structure	Analytical Data
268		LCMS m/z [M+1]: 734.1 1H NMR (400 MHz, CD3OD) δ 8.33 (s, 1H), 7.23-7.26 (m, 1H), 7.03 (t, 1H), 5.41 (s, 0.5H), 5.28 (s, 0.5H), 4.60 (s, 1H), 4.17-4.23 (m, 3H), 3.86-4.06 (m, 3H), 3.61-3.63 (m, 1H), 3.32-3.49 (m, 3H), 3.11-3.14 (m, 2H), 3.01 (s, 3H), 2.25-2.35 (m, 3H), 2.15-2.17 (m, 1H), 1.92-2.03 (m, 4H), 1.59-1.66 (m, 3H).
269		LCMS m/z [M+1]: 730.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.25 – 7.21 (m, 1H), 7.03 (t, J = 9.0 Hz, 1H), 5.07 – 4.97 (m, 1H), 4.72 – 4.52 (m, 2H), 4.00 – 3.81 (m, 3H), 3.81 – 3.75 (m, 1H), 3.72 (s, 3H), 3.65 – 3.57 (m, 1H), 3.52 – 3.37 (m, 4H), 2.58 – 2.32 (m, 3H), 2.30 – 2.02 (m, 6H), 1.99 – 1.85 (m, 1H), 1.53 – 1.39 (m,, 6H).
270		LCMS m/z [M+1]: 730.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.24 – 7.21 (m, 1H), 7.03 (t, J = 8.8 Hz, 1H), 5.06 – 4.95 (m, 1H), 4.73 – 4.53 (m, 2H), 4.01 – 3.82 (m, 3H), 3.82 – 3.75 (m, 1H), 3.72 (s, 3H), 3.67 – 3.56 (m, 1H), 3.55 - 3.38 (m, 4H), 2.57 – 2.30 (m, 3H), 2.30 – 2.01 (m, 6H), 2.01 - 1.85 (m, 1H), 1.53 – 1.37 (m, 6H).

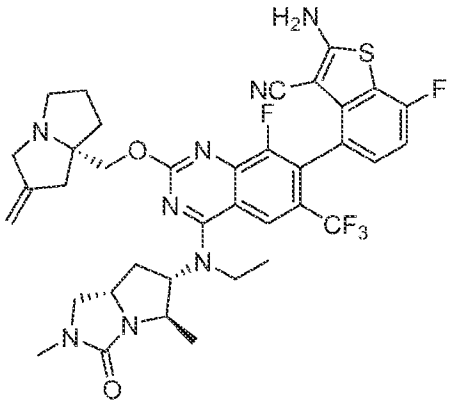
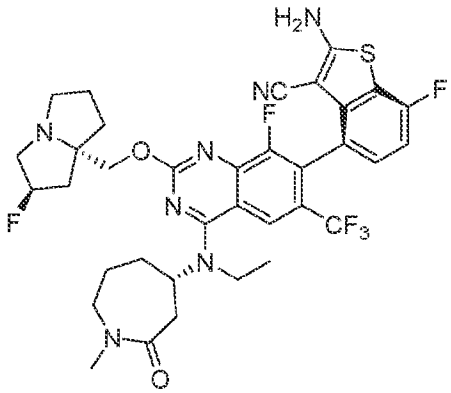
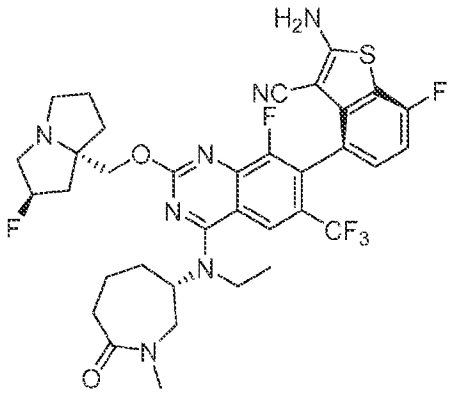
Cmpd. No.	Structure	Analytical Data
271		LCMS m/z [M+1]: 734.1 1H NMR (400 MHz, CD3OD) δ 8.48 (s, 1H), 8.20 (s, 1H), 7.26-7.17 (m, 1H), 7.02 (t, 1H), 5.54-5.49 (m, 0.5H), 5.41-5.36 (m, 0.5H), 4.91-4.85 (m, 1H), 4.75-4.67 (m, 1H), 4.51 (d, 1H), 4.25-4.16 (m, 1H), 4.08-3.99 (d, 1H), 3.98-3.50 (m, 8H), 3.43-3.35 (m, 1H), 3.27-3.20 (m, 1H), 2.70-2.43 (m, 4H), 2.36-2.18 (m, 3H), 2.13-2.04 (m, 1H), 1.60 (t, 3H).
272		LCMS m/z [M+1]: 741.2 1H NMR (400 MHz, CD3OD) δ 8.14 (s, 1H), 7.26-7.21 (m, 1H), 7.03 (t, 1H), 6.67 (s, 0.3H), 6.54 (s, 0.4H), 6.40 (s, 0.3H), 5.39 (s, 0.5H), 5.25 (s, 0.5H), 4.79-4.74 (m, 1H), 4.69 (t, 1H), 4.45-4.38 (m, 1H), 4.34-4.27 (m, 1H), 4.26-4.21 (m, 1H), 4.14-4.08 (m, 1H), 3.99-3.94 (m, 1H), 3.90-3.84 (m, 1H), 3.65-3.56 (m, 2H), 3.47-3.42 (m, 1H), 3.24-3.21 (m, 1H), 3.06-3.01 (m, 1H), 2.85 (s, 3H), 2.39-2.23 (m, 3H), 2.20-2.15 (m, 2H), 2.05-1.97 (m, 2H), 1.93-1.87 (m, 1H), 1.39-1.35 (m, 3H), 1.30 (d, 3H).
273		LCMS m/z [M+1]: 741.2 1H NMR (400 MHz, CD3OD) δ 8.12 (s, 1H), 7.25-7.20 (m, 1H), 7.03 (t, 1H), 6.67 (s, 0.3H), 6.53 (s, 0.4H), 6.39 (s, 0.3H), 5.42 (s, 0.5H), 5.28 (s, 0.5H), 4.79-4.73 (m, 1H), 4.40-4.29 (m, 2H), 4.10-4.03 (m, 1H), 4.00-3.91 (m, 2H), 3.63-3.53 (m, 2H), 3.48-3.65 (m, 3H), 3.10-3.00 (m, 3H), 2.85 (s, 3H), 2.43-2.33 (m, 2H), 2.24-2.15 (m, 2H), 2.10-1.88 (m, 4H), 1.31-1.27 (m, 3H), 1.23 (d, 3H).

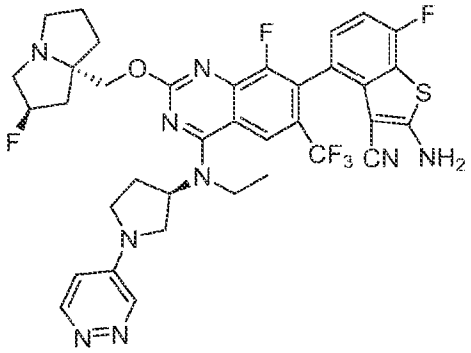
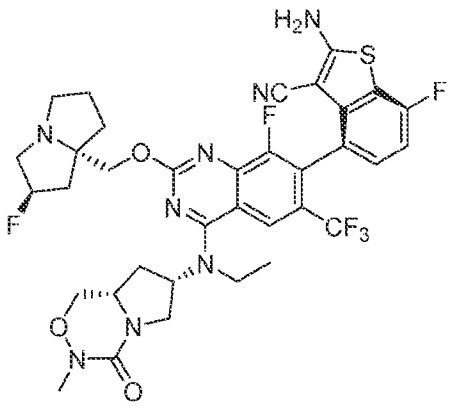
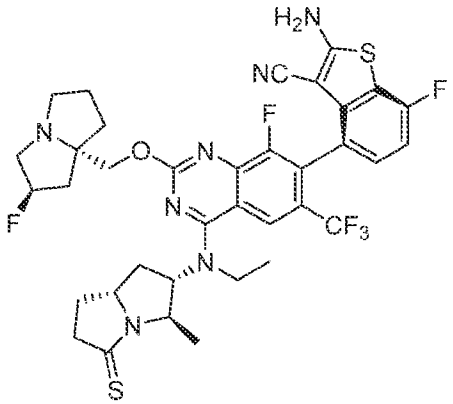
Cmpd. No.	Structure	Analytical Data
274		LCMS m/z [M+1]: 745.2 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.23 (dd, J = 8.4, 5.1 Hz, 1H), 7.02 (t, J = 8.9 Hz, 1H), 4.82-4.74 (m, 1H), 4.50 (d, J = 5.1 Hz, 2H), 4.12 – 3.85 (m, 4H), 3.68-3.50 (m, 2H), 3.50 – 3.40 (m, 2H), 3.25 (s, 3H), 3.15-3.00 (m, 1H), 2.85 (s, 3H), 2.56 (s, 3H), 2.50 – 2.33 (m, 2H), 2.24 – 2.08 (m, 2H), 2.05 – 1.94 (m, 1H), 1.41-1.33 (m, 3H), 1.24 (d, J = 6.5 Hz, 3H).
275		LCMS m/z [M+1]: 745.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.24 (dd, J = 8.3, 5.1 Hz, 1H), 7.08 – 6.94 (m, 1H), 4.81-4.73 (m, 1H), 4.48 (d, J = 4.8 Hz, 2H), 4.15-4.12 (m, 1H), 4.04 – 3.93 (m, 2H), 3.90-3.80 (m, 1H), 3.72-3.55 (m, 2H), 3.51 – 3.38 (m, 2H), 3.32 (s, 3H), 3.10 – 2.99 (m, 1H), 2.86 (s, 3H), 2.54 (s, 3H), 2.43 (dd, J = 10.5, 5.0 Hz, 1H), 2.39-2.26 (m, 1H), 2.24 – 2.05 (m, 2H), 2.04 – 1.90 (m, 1H), 1.40 (t, J = 6.9 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H).
276		LCMS m/z [M+1]: 734.2 1H NMR (400 MHz, CD3OD) δ 8.42 (s, 1H), 8.26 (s, 1H), 7.20-7.24 (m, 1H), 7.02 (t, 1H), 5.56 (s, 0.5H), 5.43 (s, 0.5H), 4.97-5.05 (m, 1H), 4.52-4.59 (m, 2H), 3.81-3.94 (m, 4H), 3.71-3.78 (m, 6H), 3.56-3.66 (m, 1H), 3.41-3.48 (m, 1H), 3.33-3.38 (m, 1H), 2.44-2.66 (m, 3H), 2.25-2.38 (m, 4H), 2.03-2.18 (m, 1H), 1.47 (t, 3H).

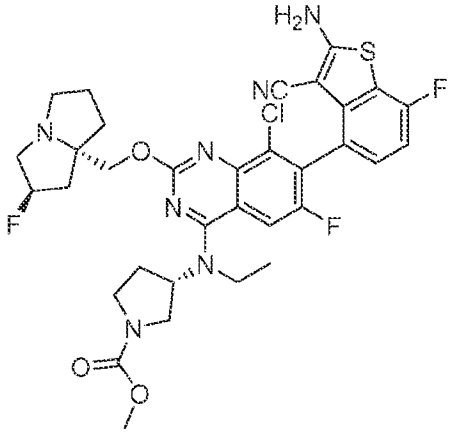
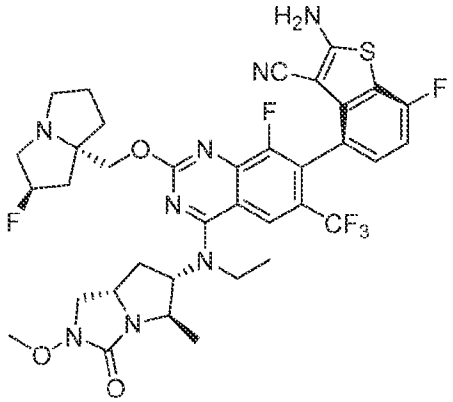
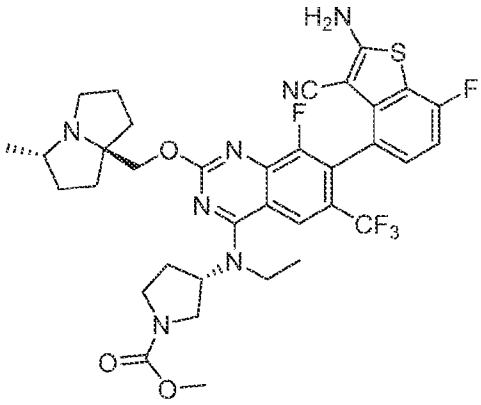
Cmpd. No.	Structure	Analytical Data
277		LCMS m/z [M+1]: 846.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.31-7.21 (m, 3H), 7.01 (t, 1H), 5.02 (t, 1H), 4.53-4.40 (m,2H), 4.39-4.36 (m, 1H), 3.98-3.84 (m, 3H), 3.79-3.73 (m,1H), 3.60 (d,3H), 3.63-3.57 (m,1H), 3.47-3.43 (m,1H), 2.59-2.44 (m, 3H), 2.40-2.30 (m, 2H), 2.27-2.25 (m, 1H),2.14-2.05 (m,2H), 2.02-1.99 (m,1H),1.82-1.78 (m,3H), 1.47 (t,3H).
278		LCMS m/z [M+1]: 846.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.29-7.20 (m, 3H), 7.01 (t, 1H), 5.01 (t, 1H), 4.54-4.36 (m,2H), 4.38-4.36 (m, 1H), 3.95-3.84 (m, 3H), 3.79-3.74 (m,1H), 3.70 (s,3H), 3.64-3.59 (m,1H), 3.47-3.43 (m,1H), 2.57-2.47 (m, 3H), 2.39-2.27 (m, 2H), 2.25-2.22 (m, 1H),2.18-2.13 (m,1H), 2.11-2.07 (m,1H),2.02-1.97 (m,1H), 1.85-1.78 (m,3H), 1.47 (t,3H).
279		LCMS m/z [M+1]: 784.3 1H NMR (400 MHz, CD3OD) δ 8.33 (s, 1H), 7.75 (dd, J = 10.0, 4.4 Hz, 1H), 7.56 (d, J = 10.0 Hz, 1H), 7.32 – 7.20 (m, 1H), 7.04 (t, J = 8.8 Hz, 1H), 5.54 (d, J = 52.0 Hz, 1H), 5.36 – 5.19 (m, 1H), 4.78 – 4.57 (m, 2H), 4.30 – 4.15 (m, 1H), 4.12 – 4.01 (m, 2H), 3.99 (s, 3H), 3.97 – 3.71 (m, 6H), 3.50 – 3.39 (m, 1H), 2.74 – 2.53 (m, 4H), 2.42 – 2.24 (m, 3H), 2.19 – 1.96 (m, 1H), 1.52 (t, J = 6.8 Hz, 3H).

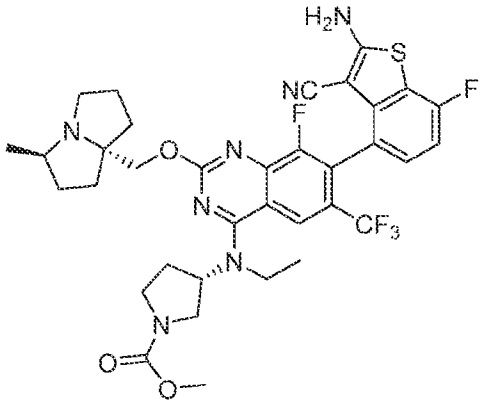
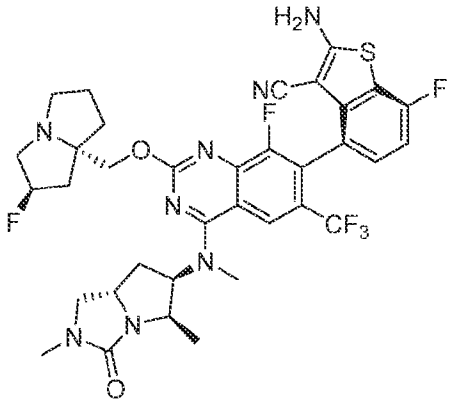
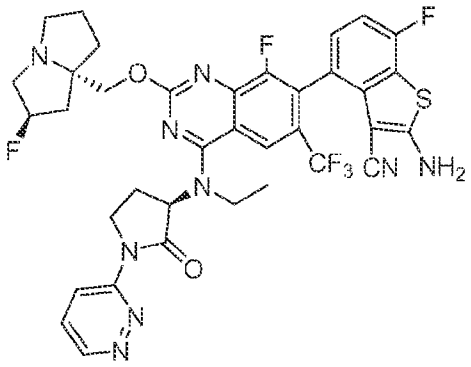
Cmpd. No.	Structure	Analytical Data
280		LCMS m/z [M+1]: 755.3 1H NMR (400 MHz, CD3OD) 8.69 (m, 2H), 8.33 (s, 1H), 7.25-7.22 (m, 2H), 7.05-7.01 (m, 1H), 5.57 (m, 1H), 5.29 (m, 1H), 4.83-4.71 (m, 2H), 4.66-3.83 (m, 9H), 3.47–3.03 (m, 1H), 2.67–2.60 (m, 4H), 2.58-2.53 (m, 3H), 2.37-2.31 (m, 1H), 1.53-1.51 (m, 3H).
281		LCMS m/z [M+1]: 784.2 ^{1}H NMR (400 MHz, CD_3OD) 6 8.33 (s, 1H), 7.77-7.73 (m, 1H), 7.56 (d, J = 10.3 Hz, 1H), 7.25- 7.22 (m, 1H), 7.04 (t, J = 8.8 Hz, 1H), 5.52 (d, J = 52.0 Hz, 1H), 5.31 - 5.25 (m, 1H), 4.75 - 4.61 (m, 2H), 4.25 - 4.17 (m, 1H), 4.03 - 3.73 (m, 11H), 3.46 (s, 1H), 2.69 - 2.50 (m, 4H), 2.44 - 2.30 (m, 3H), 2.15 - 1.13 (m, 1H), 1.54 - 1.49 (m, 3H).
282		LCMS m/z [M+1]: 734.2 1H NMR (400 MHz, CD3OD) δ 8.54 (s, 1H), 7.20-7.23 (m, 1H), 7.00 (t, 1H), 5.41 (s, 0.5H), 5.27 (s, 0.5H), 4.64-4.66 (m, 1H), 4.54-4.59 (m, 1H), 4.37-4.40 (m, 1H), 4.28-4.30 (m, 1H), 3.86-3.90 (m, 2H), 3.42-3.47 (m, 4H), 3.08-3.12 (m, 2H), 2.96 (s, 3H), 2.51-2.54 (m, 1H), 2.27-2.42 (m, 2H), 2.16-2.20 (m, 2H), 2.00-2.10 (m, 2H), 1.90-1.99 (m, 1H),1.45 (t, 3H).

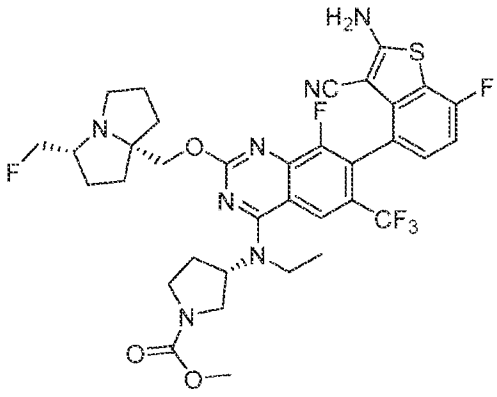
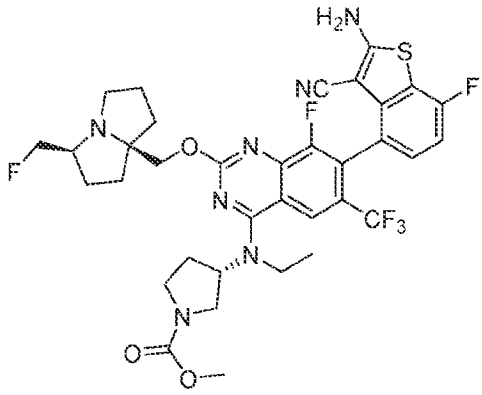
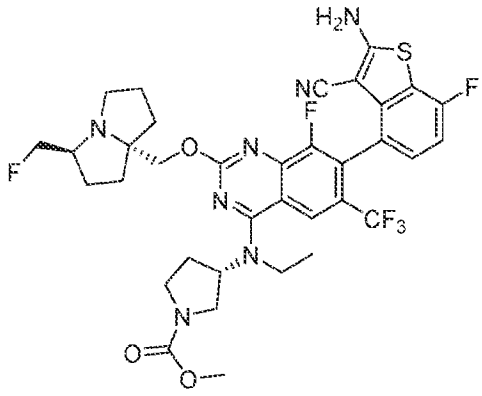
Cmpd. No.	Structure	Analytical Data
283		LCMS m/z [M+1]: 734.1 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.20-7.23 (m, 1H), 7.01 (t, 1H), 5.38 (s, 0.5H), 5.25 (s, 0.5H), 5.04-5.11 (m, 1H), 4.30-4.43 (m, 2H), 3.82-3.96 (m, 3H), 3.71-3.76 (m, 4H), 3.50-3.58 (m, 1H), 3.39-3.47 (m, 2H), 3.06-3.12 (m, 1H), 2.83-2.97 (m, 1H), 2.71-2.76 (m, 1H), 2.34-2.53 (m, 3H), 2.08-2.15 (m, 1H), 1.81-2.04 (m, 4H), 1.44 (t, 3H).
284		LCMS m/z [M+1]: 720.1 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.25-7.16 (m, 1H), 7.03-6.97 (m, 1H), 5.43 (s, 0.5H), 5.30 (s, 0.5H), 4.99-4.90 (m, 1H), 4.56 (d, 1H), 4.35-4.23 (m, 2H), 3.97-3.82 (m, 2H), 3.79-3.71 (m, 1H), 3.66-3.56 (m, 1H), 3.47-3.35 (m, 2H), 3.22-2.95 (m, 3H), 2.94 (s, 3H), 2.28-2.18 (m, 2H), 2.09-1.92 (m, 4H), 1.49 (t, 3H).
285		LCMS m/z [M+1]: 720.1 1H NMR (400 MHz, CD3OD) δ 8.35 (s, 1H), 7.26-7.17 (m, 1H), 7.07-6.97 (t, 1H), 5.66 (s, 0.5H), 5.51 (s, 0.5H), 4.98-4.95 (m, 1H), 4.55-4.36 (m, 3H), 4.09-3.86 (m, 5H), 3.83-3.72 (m, 2H), 3.48-3.41 (m, 1H), 3.29-3.23 (m, 1H), 2.96 (s, 3H), 2.75-2.51 (m, 2H), 2.40-2.28 (m, 3H), 2.14 (s, 1H), 1.62 (t, 3H).
286		LCMS m/z [M+1]: 592.2 H NMR (400 MHz, CD3OD) δ 9.56 (s, 1H), 8.38 (s, 1H), 7.30 – 7.16 (m, 1H), 7.05-7.01 (m, 1H), 5.72-5.71 (m, 1H), 5.17 (s, 0.5H), 5.03 (s, 0.5H), 2.95-2.80 (m, 2H), 2.76-2.55 (m, 2H), 2.45 – 1.78 (m, 4H), 1.46 (d, J = 6.3 Hz, 3H), 0.85-0.67 (m, 2H), 0.50 – 0.35 (m, 2H).

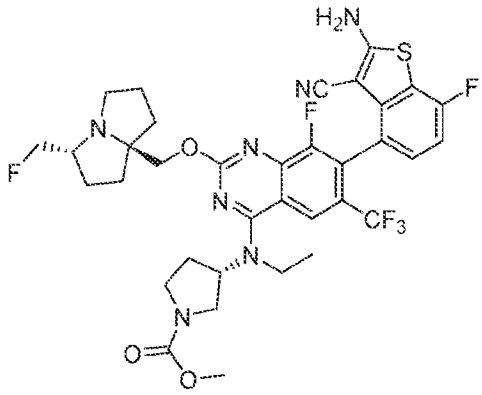
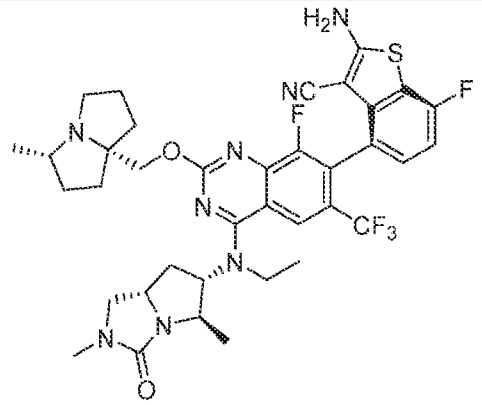
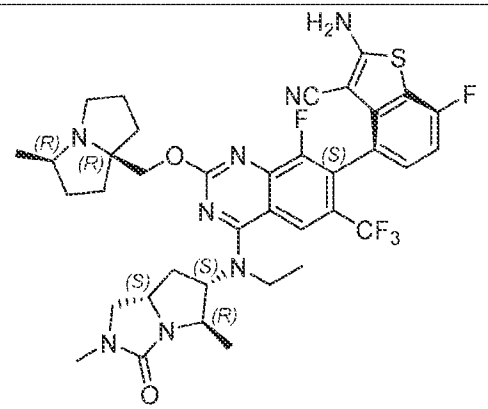
Cmpd. No.	Structure	Analytical Data
287		LCMS m/z [M+1]: 753.2 1H NMR (400 MHz, CD3OD) δ 8.26-8.21 (m, 1H), 7.26-7.21 (m, 1H), 7.02 (t, 1H), 5.17 (s, 2H), 4.68-4.63 (m, 1H), 4.55-4.46 (m, 2H), 4.23-4.13 (m, 2H), 4.02-3.87 (m, 3H), 3.70-3.66 (m, 1H), 3.63-3.56 (m, 2H), 3.49-3.41 (m, 2H), 2.85 (s, 3H), 2.35-2.24 (m, 3H), 2.18 (t, 1H), 2.11-1.96 (m, 4H), 1.48-1.39 (m, 3H), 1.32-1.30 (m, 3H).
288		LCMS m/z [M+1]: 732.2 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.26-7.20 (m, 1H), 7.02 (t, 1H), 5.51-5.47 (m, 0.5H), 5.40-5.31 (m, 1.5H), 4.60-4.55 (m, 1H), 4.31 (d, 1H), 3.98-3.90 (m, 1H), 3.86-3.73 (m, 2H), 3.60-3.46 (m, 3H), 3.41-3.35 (m, 1H), 3.23-3.17 (m, 1H), 3.03 (s, 3H), 2.66 (d, 1H), 2.46-2.35 (m, 2H), 2.27-2.02 (m, 7H), 1.80-1.71 (m, 1H), 1.63-1.58 (m, 1H), 1.51 (t, 3H).
289		LCMS m/z [M+1]: 732.1 1H NMR (400 MHz, CD3OD) δ 8.42 (s, 1H), 7.26-7.18 (m, 1H), 7.02 (t, 1H), 5.41-5.37 (m, 0.5H), 5.28-5.23 (m, 0.5H), 4.38-4.20 (m, 3H), 4.09-3.86 (m, 3H), 3.72 (s, 3H), 3.29-3.21 (m, 3H), 3.15-3.02 (m, 2H), 2.53-2.11 (m, 6H), 2.08-1.79 (m, 6H), 1.21 (t, 3H).

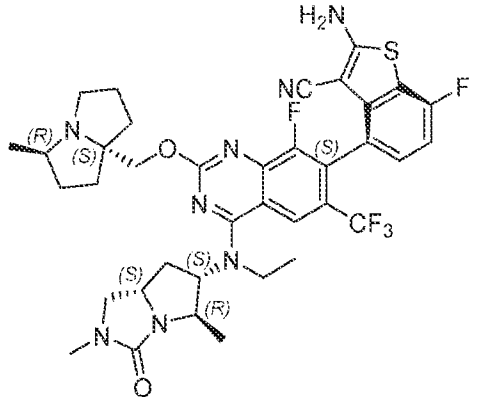
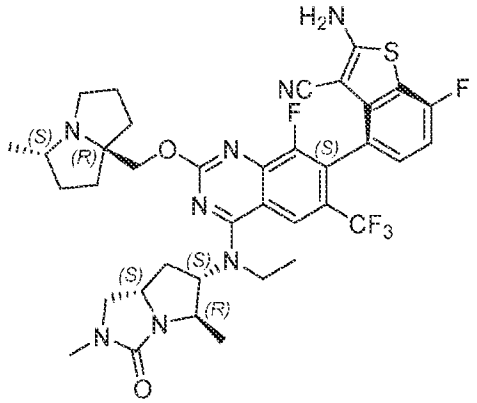
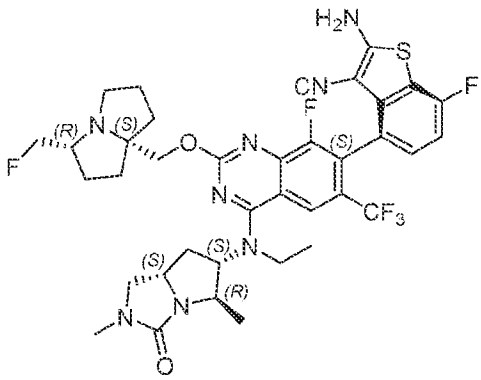
Cmpd. No.	Structure	Analytical Data
292		LCMS m/z [M+1]: 755.3 1H NMR (400 MHz, CD3OD) 8.69 (m, 2H), 8.33 (s, 1H), 7.25-7.22 (m, 2H), 7.05-7.01 (m, 1H), 5.57 (m, 1H), 5.29 (m, 1H), 4.83-4.71 (m, 2H), 4.66-3.83 (m, 9H), 3.47–3.03 (m, 1H), 2.67–2.60 (m, 4H), 2.58-2.53 (m, 3H), 2.37-2.31 (m, 1H), 1.53-1.51 (m, 3H).
293		LCMS m/z [M+1]: 761.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.22 (dd, J = 8.3, 5.0 Hz, 1H), 7.02 (t, J = 8.9 Hz, 1H), 5.40 (s, 0.5H), 5.26 (s, 0.5H), 5.03-4.98 (m, 1H), 4.46-4.39 (m, 1H), 4.33-4.20 (m, 2H), 4.07 – 3.94 (m, 2H), 3.93 – 3.73 (m, 4H), 3.29 – 3.20 (m, 3H), 3.15 (s, 3H), 3.10-3.01 (m, 1H), 2.44 – 2.11 (m, 5H), 2.09 – 1.83 (m, 3H), 1.49 (t, J = 6.9 Hz, 3H).
294		LCMS m/z [M+1]: 760.1 1H NMR (400 MHz, CD3OD) δ 8.20 (s, 1H), 7.21-7.24 (m, 1H), 7.01 (t, 1H), 5.40 (s, 0.5H), 5.27 (s, 0.5H), 4.69-4.72 (m, 1H), 4.53-4.58 (m, 1H), 4.46-4.53 (m, 1H), 4.26-4.28 (m, 1H), 4.16-4.19 (m, 1H), 3.93-3.99 (m, 1H), 3.73-3.79 (m, 1H), 3.30-3.47 (m, 2H), 3.18-3.21 (m, 2H), 3.03-3.12 (m, 2H), 2.57-2.65 (m, 1H), 2.38-2.45 (m, 2H), 2.21-2.29 (m, 3H), 1.94-2.02 (m, 4H), 1.49-1.60 (m, 6H).

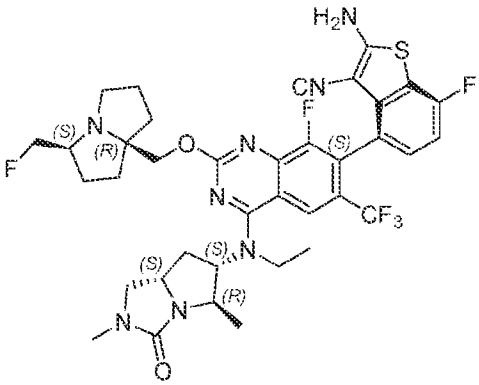
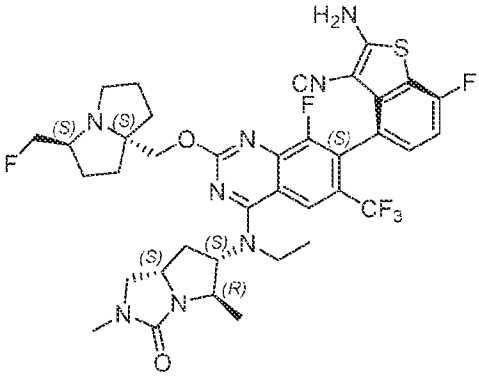
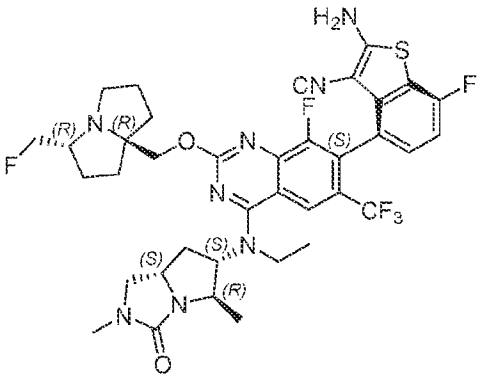
Cmpd. No.	Structure	Analytical Data
295		LCMS m/z [M+1]: 700.2 1H NMR (400 MHz, CD3OD) δ 7.78-7.69(m, 1H), 7.19-7.17 (m, 1H), 7.05-7.01(m, 1H), 5.35 (m, 1.5H), 5.23 (s, 0.5H), 4.3-4.23 (m, 2H),3.78-3.59 (m, 2H), 3.45 (s, 3H), 3.59-3.45 (m, 3H), 3.22-3.19 (m, 2H), 2.99-2.77(m, 1H), 2.21-2.14(m, 3H), 2.02-1.89 (m, 3H), 1.88-1.60 (m, 4H), 1.17 (s, 3H).
296		LCMS m/z [M+1]: 745.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.24-7.23 (m, 1H), 7.03-6.99 (m, 1H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 4.62 (m, 1H), 4.22 (m, 1H), 3.93 (m, 2H), 3.86 (m, 1H), 3.72 (m, 2H), 3.59(s, 3H), 3.46 (m, 1H), 3.31-3.29 (m, 3H), 2.99 (m,1H), 2.46-2.16 (m, 6H), 1.97-1.93(m, 3H), 1.52(m, 3H), 0.98-1.23 (m, 3H).
297		LCMS m/z [M+1]: 730.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.28 – 7.19 (m, 1H), 7.03 (t, J = 8.8 Hz, 1H), 5.08 – 4.99 (m, 1H), 4.74 – 4.51 (m, 2H), 4.08 – 3.75 (m, 5H), 3.72 (s, 3H), 3.65 – 3.54 (m, 1H), 3.50 – 3.42 (m, 2H), 3.25 – 3.19 (m, 1H), 2.55 – 2.33 (m, 3H), 2.27 – 2.13 (m, 3H), 2.09 – 1.96 (m, 4H), 1.48 (t, J = 6.8 Hz, 3H), 1.41 (d, J = 6.8 Hz, 3H).

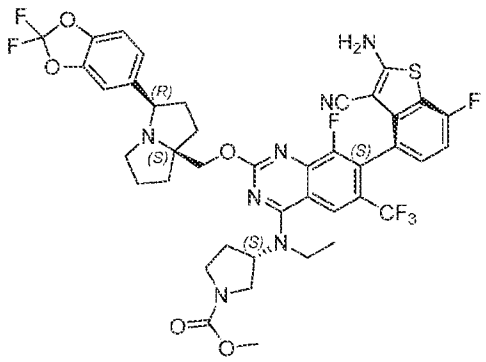
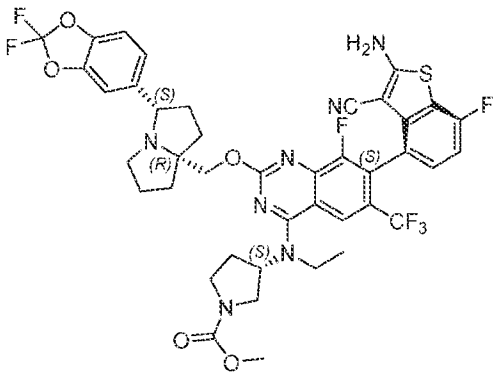
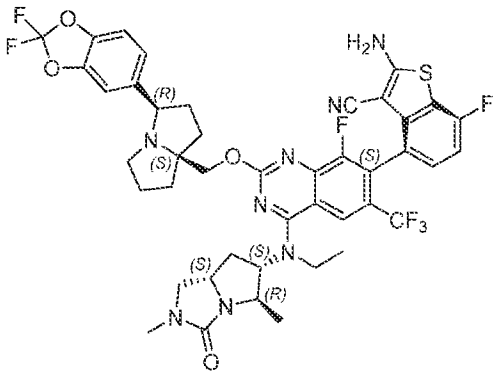
Cmpd. No.	Structure	Analytical Data
298		LCMS m/z [M+1]: 730.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.27 – 7.19 (m, 1H), 7.03 (t, J = 8.8 Hz, 1H), 5.07 – 4.97 (m, 1H), 4.74 – 4.50 (m, 2H), 4.09 – 3.76 (m, 5H), 3.73 (s, 3H), 3.66 – 3.57 (m, 1H), 3.50 – 3.43 (m, 2H), 3.25 – 3.18 (m, 1H), 2.59 – 2.33 (m, 3H), 2.28 – 2.12 (m, 3H), 2.09 – 1.95 (m, 4H), 1.49 (t, J = 6.8 Hz, 3H), 1.42 (d, J = 6.4 Hz, 3H).
299		LCMS m/z [M+1]: 745.2 1HNMR (400 MHz, CD3OD) δ 8.36 (s, 1H), 7.30 – 7.14 (m, 1H), 7.01 (t, J = 8.9 Hz, 1H), 5.45 (s, 0.5H), 5.32 (s, 0.5H), 5.10 – 4.97 (m, 1H), 4.77 – 4.64 (m, 1H), 4.46 – 4.19 (m, 3H), 3.67 (t, J = 8.9 Hz, 1H), 3.62 – 3.46 (m, 4H), 3.45 – 3.34 (m, 3H), 3.18 – 3.07 (m, 1H), 2.84 (s, 3H), 2.76 – 2.64 (m, 1H), 2.57 – 2.37 (m, 1H), 2.35 – 2.21 (m, 2H), 2.13 – 1.90 (m, 4H), 1.11 (d, J = 7.1 Hz, 3H).
300		LCMS m/z [M+1]: 768.2 1H NMR (400 MHz, CD3OD) δ 9.04 (d, J = 3.7 Hz, 1H), 8.77 (d, J = 9.2 Hz, 1H), 8.32 (s, 1H), 7.76 (dd, J = 9.1, 4.7 Hz, 1H), 7.25 (dd, J = 8.2, 5.0 Hz, 1H), 7.06 – 6.98 (m, 1H), 5.43 (d, J = 52.4 Hz, 1H), 4.69 (t, J = 10.5 Hz, 1H), 4.51 – 4.03 (m, 6H), 3.97 – 3.63 (m, 4H), 2.79 – 2.66 (m, 2H), 2.49 – 2.21 (m, 3H), 2.18 – 2.04 (m, 2H), 1.92 (d, J = 7.0 Hz, 1H), 1.70 (t, J = 7.0 Hz, 3H), 1.63 – 1.20 (m, 3H).

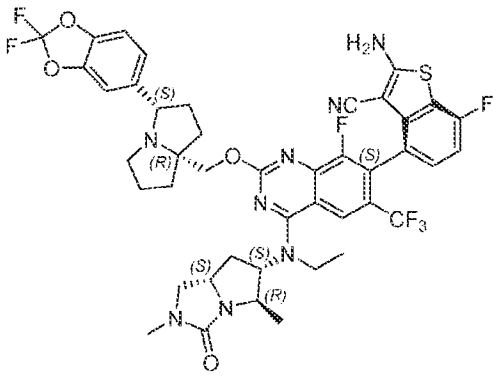
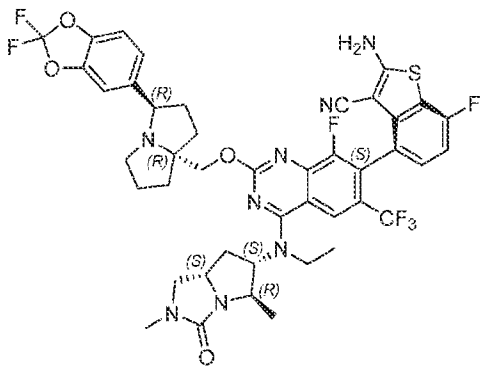
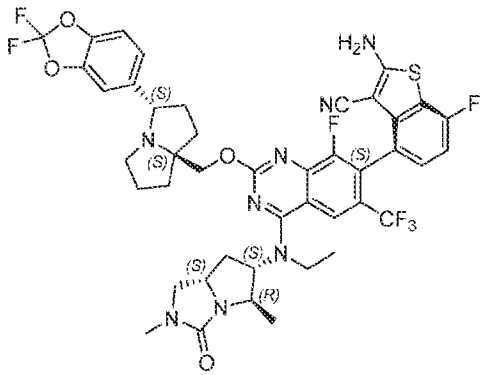
Cmpd. No.	Structure	Analytical Data
301		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.27 – 7.17 (m, 1H), 7.02 (t, J = 9.0 Hz, 1H), 5.07 – 4.99 (m, 1H), 4.83 – 4.72 (m, 1H), 4.71 – 4.61 (m, 1H), 4.38 – 4.29 (m, 1H), 4.00 – 3.81 (m, 3H), 3.80 – 3.74 (m, 1H), 3.72 (s, 3H), 3.63 – 3.55 (m, 1H), 3.47 – 3.39 (m, 1H), 3.19 – 3.00 (m, 3H), 3.00 – 2.89 (m, 1H), 2.56 – 2.43 (m, 1H), 2.42 – 2.33 (m, 1H), 2.15 – 1.86 (m, 5H), 1.84 – 1.71 (m, 2H), 1.70 – 1.61 (m, 1H), 1.52 – 1.39 (m, 3H).
302		LCMS m/z [M+1]: 748.3 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.26 – 7.18 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 5.08 – 4.98 (m, 1H), 4.83 – 4.72 (m, 1H), 4.65 (d, J = 10.8 Hz, 1H), 4.36 – 4.28 (m, 1H), 3.99 – 3.79 (m, 3H), 3.79 – 3.73 (m, 1H), 3.72 (s, 3H), 3.64 – 3.56 (m, 1H), 3.49 – 3.40 (m, 1H), 3.17 – 2.99 (m, 3H), 2.98 – 2.87 (m, 1H), 2.55 – 2.43 (m, 1H), 2.43 – 2.31 (m, 1H), 2.15 – 1.97 (m, 3H), 1.97 – 1.70 (m, 4H), 1.70 – 1.61 (m, 1H), 1.50 – 1.39 (m, 3H).
303		LCMS m/z [M+1]: 748.3 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.27 – 7.17 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 5.07 – 4.95 (m, 1H), 4.81 – 4.54 (m, 2H), 4.40 – 4.27 (m, 1H), 4.02 – 3.79 (m, 3H), 3.79 – 3.63 (m, 4H), 3.63 – 3.51 (m, 1H), 3.51 – 3.38 (m, 1H), 3.37 – 3.32 (m, 1H), 3.20 (s, 1H), 3.17 – 2.94 (m, 2H), 2.55 – 2.29 (m, 2H), 2.14 – 1.64 (m, 8H), 1.52 – 1.38 (m, 3H).

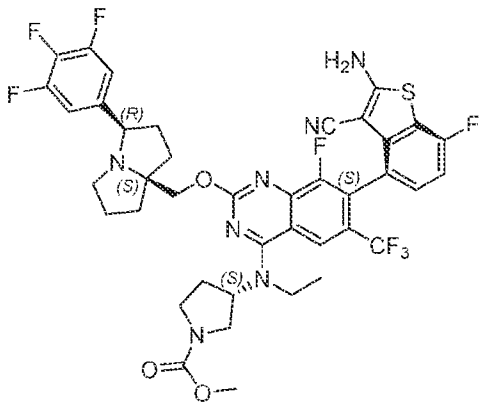
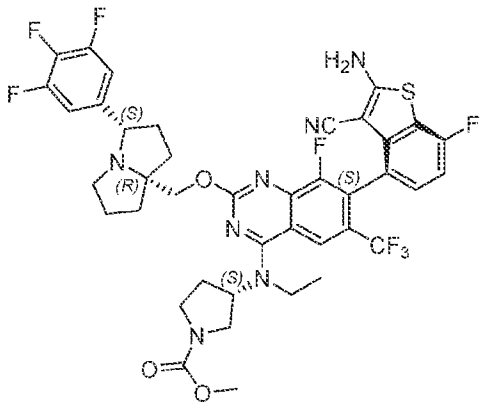
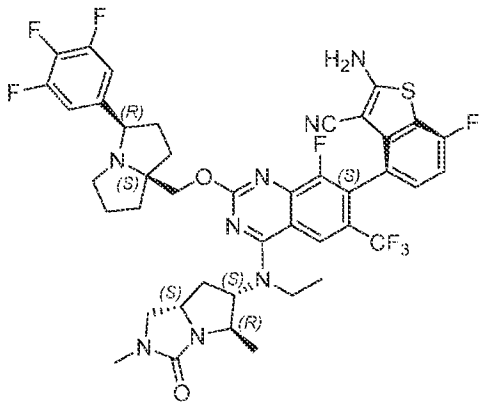
Cmpd. No.	Structure	Analytical Data
304		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.26 – 7.19 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 5.05 – 4.95 (m, 1H), 4.78 (s, 0.5H), 4.66 (s, 0.5H), 4.63 – 4.56 (m, 1H), 4.38 – 4.30 (m, 1H), 3.97 – 3.79 (m, 3H), 3.79 – 3.66 (m, 4H), 3.63 – 3.55 (m, 1H), 3.49 – 3.41 (m, 1H), 3.36 – 3.32 (m, 1H), 3.19 (s, 1H), 3.17 – 3.03 (m, 2H), 2.53 – 2.33 (m, 2H), 2.10 – 1.73 (m, 8H), 1.45 (t, J = 6.2 Hz, 3H).
305		LCMS m/z [M+1]: 755.3 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.25 (s, 1H), 7.04 (s, 1H), 4.73 – 4.54 (m, 3H), 4.20 (s, 1H), 4.09 – 3.86 (m, 2H), 3.75 – 3.59 (m, 2H), 3.55 – 3.39 (m, 4H), 2.87 (s, 3H), 2.56 – 2.42 (m, 1H), 2.37 – 1.92 (m, 9H), 1.51 – 1.41 (m, 6H), 1.32 (s, 3H).
306		LCMS m/z [M+1]: 755.3 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.24 (s, 1H), 7.11 – 6.95 (m, 1H), 4.72 – 4.47 (m, 3H), 4.29 – 4.17 (m, 1H), 4.07 – 3.87 (m, 2H), 3.75 – 3.67 (m, 1H), 3.64 – 3.58 (m, 1H), 3.55 – 3.42 (m, 4H), 2.87 (s, 3H), 2.53 – 2.44 (m, 1H), 2.37 – 2.05 (m, 8H), 1.89 (s, 1H), 1.51 – 1.41 (m, 6H), 1.34 (s, 3H).

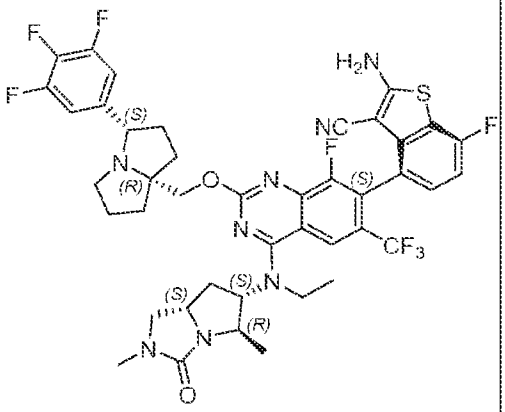
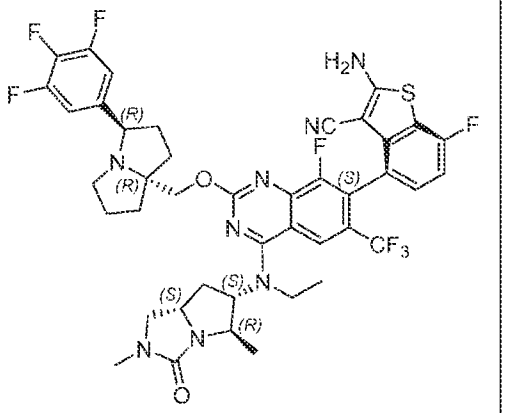
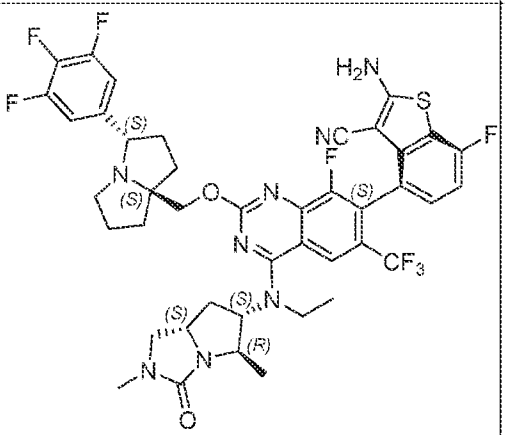
Cmpd. No.	Structure	Analytical Data
307		
308		
309		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.27 – 7.17 (m, 1H), 7.02 (t, J = 9.0 Hz, 1H), 5.07 – 4.99 (m, 1H), 4.83 – 4.72 (m, 1H), 4.71 – 4.61 (m, 1H), 4.38 – 4.29 (m, 1H), 4.00 – 3.81 (m, 3H), 3.80 – 3.74 (m, 1H), 3.72 (s, 3H), 3.63 – 3.55 (m, 1H), 3.47 – 3.39 (m, 1H), 3.19 – 3.00 (m, 3H), 3.00 – 2.89 (m, 1H), 2.56 – 2.43 (m, 1H), 2.42 – 2.33 (m, 1H), 2.15 – 1.86 (m, 5H), 1.84 – 1.71 (m, 2H), 1.70 – 1.61 (m, 1H), 1.52 – 1.39 (m, 3H).

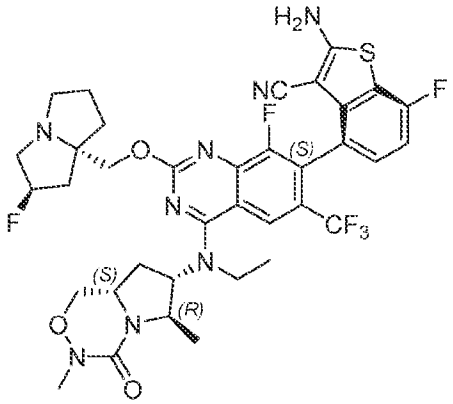
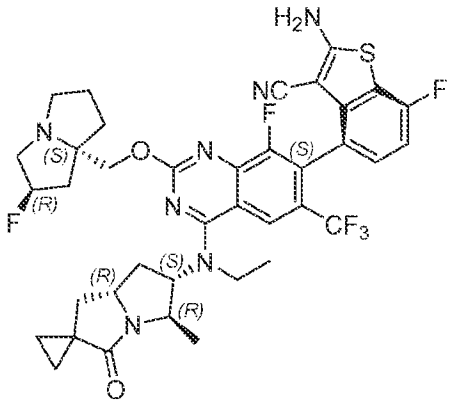
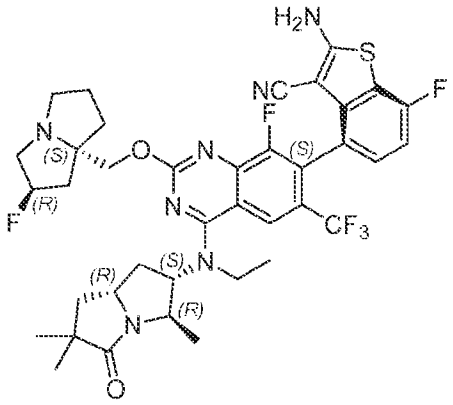
Cmpd. No.	Structure	Analytical Data
310		LCMS m/z [M+1]: 748.3 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.26 – 7.18 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 5.08 – 4.98 (m, 1H), 4.83 – 4.72 (m, 1H), 4.65 (d, J = 10.8 Hz, 1H), 4.36 – 4.28 (m, 1H), 3.99 – 3.79 (m, 3H), 3.79 – 3.73 (m, 1H), 3.72 (s, 3H), 3.64 – 3.56 (m, 1H), 3.49 – 3.40 (m, 1H), 3.17 – 2.99 (m, 3H), 2.98 – 2.87 (m, 1H), 2.55 – 2.43 (m, 1H), 2.43 – 2.31 (m, 1H), 2.15 – 1.97 (m, 3H), 1.97 – 1.70 (m, 4H), 1.70 – 1.61 (m, 1H), 1.50 – 1.39 (m, 3H).
311		LCMS m/z [M+1]: 773.2 1H NMR (400 MHz, CD3OD) δ 8.22 (d, 1H), 7.28-7.18 (m, 1H), 7.07-6.96 (m, 1H), 4.81-4.59 (m, 3H), 4.23-4.09 (m, 1H), 4.24-4.09 (m, 1H), 4.03-3.94 (m, 1H), 3.91-3.79 (m, 1H), 3.69-3.55 (m, 3H), 3.49-3.33 (m, 2H), 3.21-3.10 (m, 2H), 2.85 (s, 3H), 2.34-1.54 (m, 10H), 1.46-1.37 (m, 3H), 1.34-1.31 (m, 3H).
312		

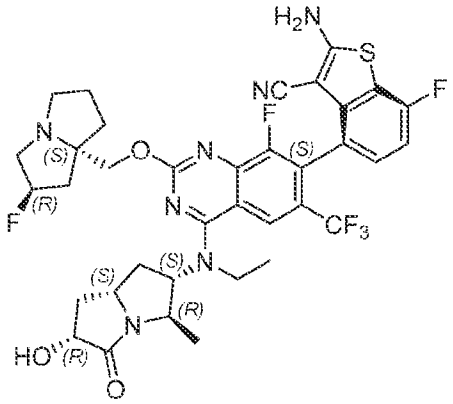
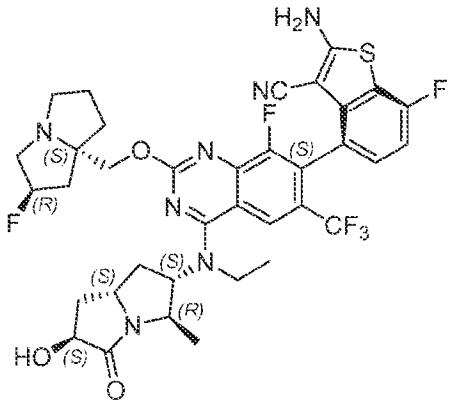
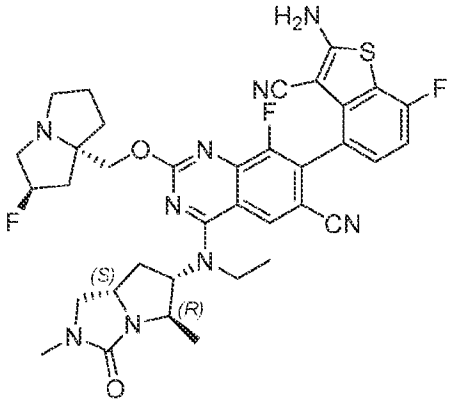
Cmpd. No.	Structure	Analytical Data
313		LCMS m/z [M+1]: 872.2 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.27-7.18 (m, 2H), 7.16-7.11 (m, 1H), 7.08-7.00 (m, 2H), 5.03-4.92 (m, 1H), 4.46-4.34 (m, 2H), 3.97-3.90 (m, 1H), 3.90-3.81 (m, 3H), 3.78-3.72 (m, 1H), 3.66 (d, 3H), 3.57-3.39 (m, 2H), 2.93-2.87 (m, 1H), 2.67 (s, 1H), 2.53-2.43 (m, 1H), 2.33-2.20 (m, 3H), 2.04-1.95 (m, 3H), 1.90-1.77 (m, 3H), 1.48-1.42 (m, 3H).
314		LCMS m/z [M+1]: 872.2 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.25-7.20 (m, 1H), 7.19-7.12 (m, 1H), 7.11-7.05 (m, 1H), 7.04-6.98 (m, 2H), 5.04-4.96 (m, 1H), 4.49 (d, 1H), 4.41-4.33 (m, 1H), 3.95-3.81 (m, 4H), 3.78-3.71 (m, 1H), 3.70 (s, 3H), 3.62-3.54 (m, 1H), 3.45-3.38 (m, 1H), 2.93-2.85 (m, 1H), 2.66 (s, 1H), 2.52-2.42 (m, 1H), 2.38-2.28 (m, 2H), 2.22-2.16 (m, 1H), 2.07-1.89 (m, 4H), 1.87-1.78 (m, 2H), 1.45 (t, 3H).
315		LCMS m/z [M+1]: 897.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.30-7.19 (m, 2H), 7.14 (d, 1H), 7.08-6.98 (m, 2H), 4.86-4.82 (m, 1H), 4.46-4.33 (m, 2H), 4.14-4.06 (m, 1H), 3.96 (s, 1H), 3.87-3.66 (m, 3H), 3.60 (t, 1H), 3.44 (d, 1H), 2.90 (s, 1H), 2.85 (s, 3H), 2.67 (s, 1H), 2.33-2.10 (m, 4H), 2.05-1.79 (m, 6H), 1.40-1.30 (m, 6H).

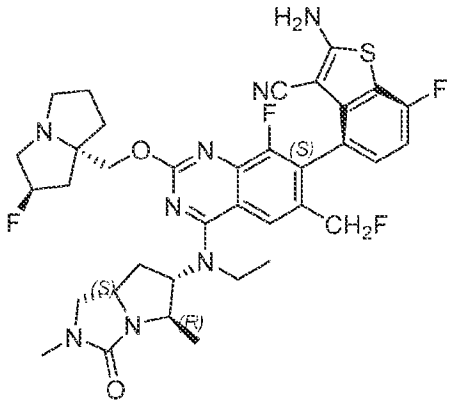
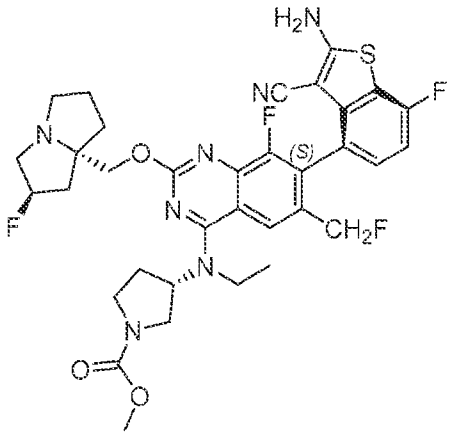
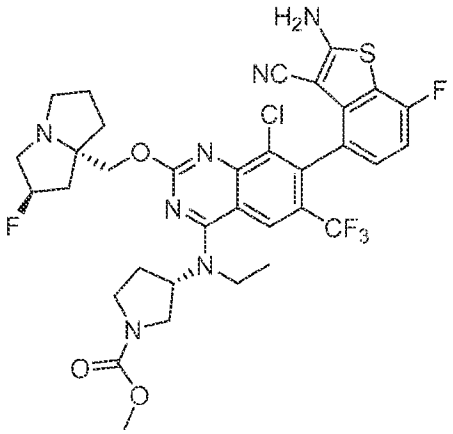
Cmpd. No.	Structure	Analytical Data
316		LCMS m/z [M+1]: 897.3 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.27-7.22 (m, 1H), 7.16 (s, 1H), 7.10-6.97 (m, 3H), 4.85-4.79 (m, 1H), 4.52 (d, 1H), 4.36 (d, 1H), 4.11-4.05 (m, 1H), 3.98-3.91 (m, 1H), 3.89-3.78 (m, 2H), 3.67-3.56 (m, 2H), 3.44-3.38 (m, 1H), 2.95-2.87 (m, 1H), 2.83 (s, 3H), 2.69-2.61 (s, 1H), 2.35-2.27 (m, 2H), 2.22-2.12 (m, 2H), 2.05-1.78 (m, 6H), 1.40-1.35 (m, 3H), 1.30-1.23 (m, 3H).
317		LCMS m/z [M+1]: 897.3 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.42-7.37 (m, 1H), 7.33-7.29 (m, 1H), 7.27-7.17 (m, 2H), 7.05-6.99 (m, 1H), 4.74-4.68 (m, 1H), 4.58-4.43 (m, 2H), 4.24-4.16 (m, 1H), 4.04-3.97 (m, 1H), 3.96-3.87 (m, 1H), 3.72-3.67 (m,1H), 3.62-3.57 (m, 1H), 3.48-3.44 (m, 1H), 2.84 (s, 3H), 2.77-2.63 (m, 2H), 2.54-2.45 (m, 1H), 2.38-2.20 (m, 5H), 2.11-2.05 (m, 1H), 2.03-1.81 (m, 4H), 1.45 (t, 3H), 1.33 (d, 3H).
318		LCMS m/z [M+1]: 897.3 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.44-7.40 (m, 1H), 7.35-7.32 (m, 1H), 7.28-7.23 (m, 1H), 7.22-7.16 (m, 1H), 7.02 (t, 1H), 4.75-4.58 (m, 2H), 4.51-4.41 (m, 1H), 4.24-4.17 (m, 1H), 4.05-3.89 (m, 2H), 3.72-3.68 (m, 1H), 3.60 (t, 1H), 3.48-3.44 (m, 1H), 2.84 (s, 3H), 2.80-2.68 (m, 2H), 2.58-2.48 (m, 1H), 2.38-2.19 (m, 5H), 2.15-2.08 (m, 1H), 2.01-1.79 (m, 4H), 1.45 (t, 3H), 1.33 (d, 3H).

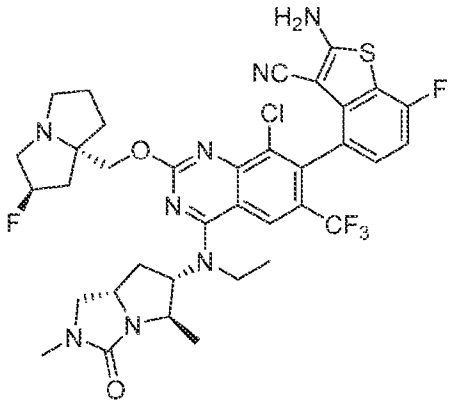
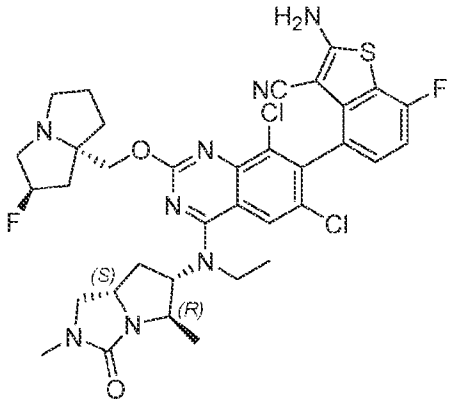
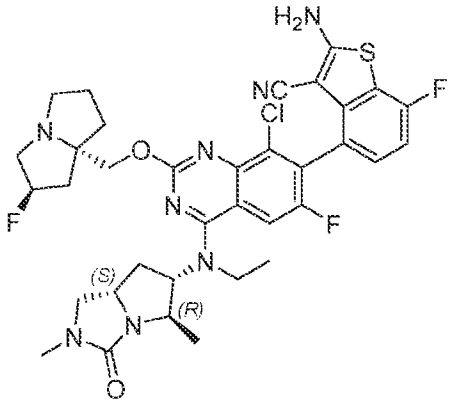
Cmpd. No.	Structure	Analytical Data
319		LCMS m/z [M+1]: 846.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.24-7.20 (m, 1H), 7.08-7.00 (m, 3H), 5.05-4.98 (m, 1H), 4.49-4.46 (m,1H), 4.38-4.32 (m, 1H), 3.96-3.85 (m, 3H), 3.81-3.77 (m, 1H), 3.71 (s, 3H), 3.64-3.56 (m, 1H), 3.49-3.39 (m, 2H), 2.96-2.88 (m, 1H), 2.66-2.60 (m, 1H), 2.53-2.44 (m, 1H),2.39-2.33 (m, 1H), 2.31-2.26 (m, 1H),2.23-2.19 (m, 1H), 2.02-1.89 (m, 4H), 1.86-1.77 (m, 2H), 1.48-1.45 (m, 3H) .
320		LCMS m/z [M+1]: 846.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.26-7.23 (m, 1H), 7.17-7.12 (m, 2H), 7.03 (t, 1H), 5.00-4.94 (m,1H), 4.39-4.37 (m, 2H), 3.95-3.81(m, 4H), 3.78-3.73 (m, 1H), 3.66 (d, 3H), 3.56-3.49 (m, 1H), 3.45-3.38 (m, 1H), 2.96-2.89 (m, 1H), 2.67-2.59 (m, 1H), 2.53-2.46 (m, 1H), 2.32-2.20 (m,3H), 2.04-1.77 (m, 6H),1.49-1.44 (m, 3H).
321		LCMS m/z [M+1]: 871.2 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.25-7.21 (m, 1H), 7.05-7.00 (m, 3H), 4.84-4.82 (m, 1H), 4.49-4.47 (m,1H), 4.35-4.32 (m, 1H), 4.11 (t, 1H), 3.99-3.93 (m, 1H), 3.87-3.79 (m, 2H), 3.70-3.65 (m, 1H), 3.59 (t, 1H), 3.43-3.40 (m, 1H), 2.95-2.90 (m, 1H), 2.84 (s, 3H),2.64-2.59 (m, 1H), 2.34-2.27 (m, 2H),2.20-2.13 (m, 2H), 1.99-1.90 (m, 4H), 1.84-1.77 (m, 2H),1.39 (t, 3H), 1.32-1.30 (m, 3H).

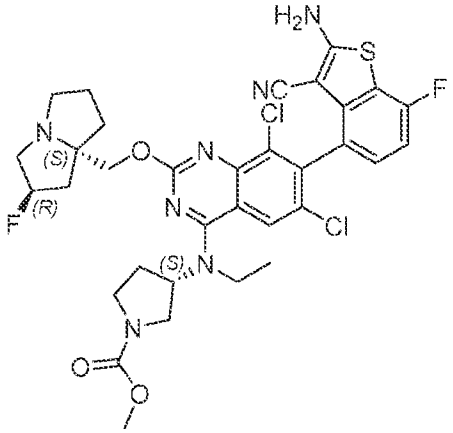
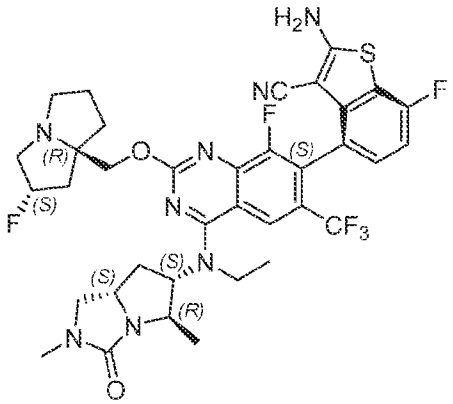
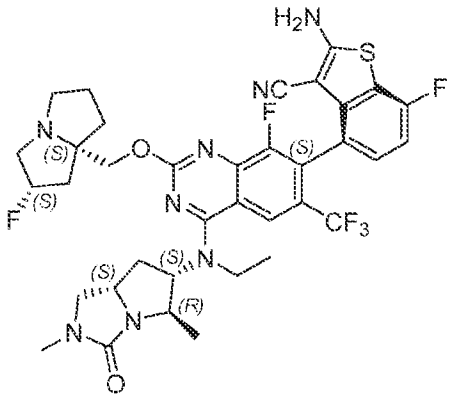
Cmpd. No.	Structure	Analytical Data
322		LCMS m/z [M+1]: 871.2 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.27-7.23 (m, 1H), 7.16 (t, 2H), 7.03 (t, 1H), 4.85-4.83 (m,1H), 4.39-4.31 (m, 2H), 4.09(t, 1H), 3.98-3.93 (m,1H), 3.85-3.80 (m,2H), 3.73-3.68 (m,1H), 3.60 (t,1H), 3.46-3.43 (m, 1H), 2.97-2.91 (m, 1H), 2.85 (s, 3H),2.68-2.61 (m,1H), 2.31-2.13 (m, 4H), 2.05-1.92 (m,4H), 1.87-1.78 (m, 2H), 1.38 (t, 3H), 1.33 (d, 3H).
323		LCMS m/z [M+1]: 871.3 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.34-7.22 (m, 3H), 7.03 (t, 1H), 4.82-4.76 (m, 1H), 4.47 (d, 2H), 4.33 (d, 1H), 4.20-4.13 (m, 1H), 4.04-3.97 (m, 1H), 3.92-3.84 (m, 1H), 3.72-3.58 (m, 2H), 3.49-3.44 (m, 1H), 2.86 (s, 3H), 2.57-2.39 (m, 2H), 2.37-2.20 (m, 4H), 2.14-1.96 (m, 3H), 1.86-1.71 (m, 3H), 1.42 (t, 3H), 1.34 (d, 3H).
324		LCMS m/z [M+1]: 871.2 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.36-7.20 (m, 3H), 7.03 (t, 1H), 4.82-4.76 (m, 1H), 4.55-4.32 (m, 3H), 4.20-4.13 (m, 1H), 4.04-3.97 (m, 1H), 3.93-3.85 (m, 1H), 3.72-3.58 (m, 2H), 3.49-3.44 (m, 1H), 2.85 (s, 3H), 2.62-2.45 (m, 2H), 2.38-2.09 (m, 6H), 2.06-1.99 (m, 1H), 1.91-1.75 (m, 3H), 1.42 (t, 3H), 1.33 (d, 3H).

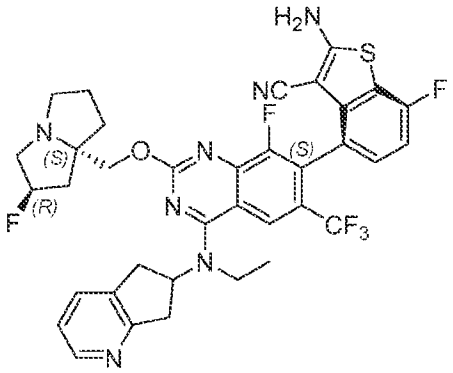
Cmpd. No.	Structure	Analytical Data
325		LCMS m/z [M+1]: 775.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.21-7.25 (m, 1H), 7.02 (t, J = 9.2 Hz, 1H), 5.42 (s, 0.5H), 5.28 (s, 0.5H), 4.66-4.74 (m, 1H), 4.39-4.51 (m, 2H), 4.27 (s, 2H), 4.05 – 4.13 (m, 1H), 3.70 –4.03 (m, 4H), 3.36 – 3.52 (m, 2H), 3.06 – 3.16 (m, 4H), 2.39 – 2.57 (m, 2H), 2.16 – 2.38 (m, 4H), 1.95 – 2.07 (m, 2H), 1.54 (t, J = 6.8 Hz,3H), 1.42 (d, J = 6.4 Hz, 3H).
326		LCMS m/z [M+1]: 770.2 1H-NMR (400 MHz, CD_3OD): 8.25(s, 1 H), 7.21-7.24 (m, 1 H), 7.02-7.07 (m, 1 H), 5.47-5.52 (m, 0.5 H), 5.35-5.40 (m, 0.5 H), 4.44-4.51 (m, 1 H), 4.30-4.41 (m, 2 H), 3.87-3.96 (m, 1 H), 3.50-3.81 (m, 5 H), 3.17-3.26 (m, 2 H), 2.38-2.50 (m, 2 H), 2.11-2.32 (m, 7 H), 1.98-2.08(m, 4 H), 1.43-1.52 (m, 4 H), 1.16-1.21 (m, 3 H).
327		LCMS m/z [M+1]: 772.2 1HNMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.22-7.27 (m, 1H), 6.99-7.07 (m, 1H), 5.40 (s, 0.5H), 5.27 (s, 0.5H), 4.79-4.85 (m, 2H), 4.22-4.37 (m, 3H), 4.08-4.15 (m, 1H), 3.89-3.98 (m, 1H), 3.75-3.83 (m, 1H), 3.01-3.23 (m, 3H), 2.37-2.44 (m, 1H), 2.24-2.31 (m, 2H), 2.09-2.23 (m, 3H), 1.94-2.08 (m, 3H), 1.80-1.87 (m, 1H), 1.42-1.50 (m, 3H), 1.34 – 1.37 (m, 3H), 1.19-1.27 (m, 6H).

Cmpd. No.	Structure	Analytical Data
328		LCMS m/z [M+1]: 760.2 1HNMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.28-7.19 (m, 1H), 7.03 (t, 1H), 5.39 (s, 0.5H), 5.25 (s, 0.5H), 4.78-4.69 (m, 1H), 4.61 (t, 1H), 4.40-4.29 (m, 1H), 4.14 (s, 2H), 4.07-3.91 (m, 2H), 3.87-3.71 (m, 1H), 3.40 (s, 1H), 3.22 (s, 2H), 3.02 (d, 1H), 2.95-2.81 (m, 1H), 2.67 (q, 1H), 2.47-2.22 (m, 4H), 1.99 (s, 3H), 1.84-1.71 (m, 1H), 1.62 (t, 3H), 1.39 (d, 3H).
329		LCMS m/z [M+1]: 760.2 1HNMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.30-7.19 (m, 1H), 7.03 (t, 1H), 5.44 (s, 0.5H), 5.30 (s, 0.5H), 4.59-4.48 (m, 1H), 4.43 (t, 2H), 4.37-4.18 (m, 3H), 4.00-3.86 (m, 1H), 3.86-3.72 (m, 1H), 3.65 (s, 1H), 3.41 (s, 2H), 3.14 (s, 1H), 2.44-2.16 (m, 7H), 2.07 (s, 2H), 1.95 (s, 1H), 1.55 (t, 3H), 1.41 (d, 3H).
330		LCMS m/z [M+1]: 716.2 1H NMR (400 MHz, CD3OD) δ 8.14 (d, 1H), 7.19 (s, 1H), 6.94 (d, 1H), 5.19 (s, 2H), 4.61 (s, 1H), 4.22 (d, 2H), 3.97 (s, 1H), 3.86 (s, 1H), 3.49-3.40 (m, 2H), 3.31 (d, 3H), 2.98 (s, 1H), 2.70 (s, 2H), 2.23 (s, 2H), 2.07-2.00 (m, 3H), 1.95 (s, 1H), 1.87 (s, 4H), 1.45 (s, 3H), 0.74 (d, 4H).

Cmpd. No.	Structure	Analytical Data
331		LCMS m/z [M+1]: 723.3 1H NMR (400 MHz, CD3OD) δ 7.98 (s, 1H), 7.28-7.22 (m, 1H), 7.09-7.03 (m, 1H), 5.50-5.35 (s, 1H), 5.29 (d, 1H), 5.18(d, 1H), 4.50-4.32 (m, 3H), 4.15-4.10 (m, 1H), 4.05-3.90 (m, 3H), 3.65-3.55 (m, 3H), 3.50-3.45 (m, 2H), 3.15 (s, 1H), 2.87 (s, 3H), 2.45-2.35 (m, 2H), 2.28-2.20 (m, 2H), 2.13 (s, 2H), 2.05-1.95 (m, 2H), 1.41-1.35 (m, 3H), 1.30 (d, 3H).
332		LCMS m/z [M+1]: 698.1 1H NMR (400 MHz, CD3OD) δ 7.98 (s, 1H), 7.24-7.18 (m, 1H), 7.08 – 7.00 (m, 1H), 5.48-5.30 (m, 1H), 5.28-5.12 (m, 1H), 5.17-5.12 (m, 1H), 5.02 (s, 1H), 4.39 (dd, 2H), 3.96-3.80 (m, 3H), 3.73 (s, 3H), 3.60-3.37 (m, 5H), 3.27 – 3.12 (m, 2H), 2.47-2.40 (m, 1H), 2.40-2.32 (m, 2H), 2.26 – 2.20 (m, 1H), 2.11 (s, 2H), 2.0-1.85 (m, 2H), 1.44-1.35 (m, 3H).
333		LCMS m/z [M+1]: 750.3 1H-NMR (400 MHz, CD3OD): 8.34 (s, 1 H), 7.11-7.17 (m, 1 H), 6.97-7.04 (m, 1 H), 5.42 (s, 0.5 H), 5.28 (s, 0.5 H), 4.91-4.97 (m, 1 H), 4.32.4.48 (m, 2 H), 3.74-3.98 (m, 4 H), 3.71 (s, 3 H), 3.54-3.60 (m, 1 H), 3.33-3.49 (m, 4 H), 3.06-3.16 (m, 1 H), 2.27-2.49 (m, 4 H), 2.16-2.21 (m, 1 H), 1.99-2.09 (m, 3 H), 1.39-1.45 (m, 3 H).

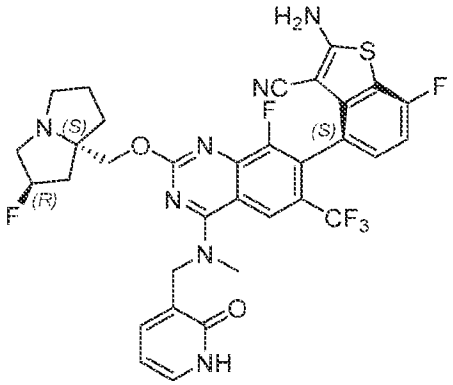
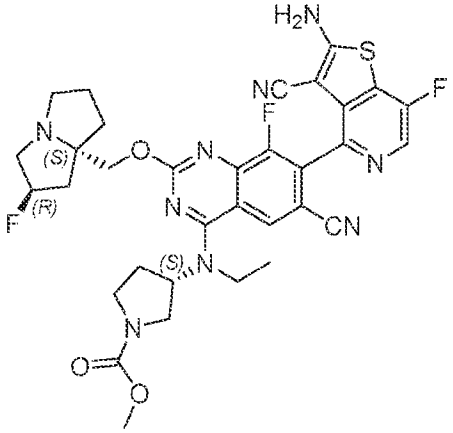
Cmpd. No.	Structure	Analytical Data
334		LCMS m/z [M+1]: 775.2 1H-NMR (400 MHz, CD_3OD): 8.30-8.36 (m, 1 H), 7.13-7.18 (m, 1 H), 6.98-7.04 (m, 1 H), 5.48 (s, 0.5 H), 5.35 (s, 0.5 H), 4.43-4.60 (m, 3 H), 4.10-4.20 (m, 2 H), 3.80-3.99 (m, 2 H), 3.62-3.69 (m, 1 H), 3.52-3.61 (m, 3 H), 3.41-3.50 (m, 2 H), 3.18-3.23 (m, 1 H), 2.83-2.87 (m, 3 H), 2.09-2.46 (m, 8 H), 1.37-1.45 (m, 3 H), 1.29-1.33 (m, 3 H).
335		LCMS m/z [M+1]: 741 1H NMR (400 MHz, CD3OD) δ8.06 (s, 1H), 7.20-7.11 (m, 1H), 7.09-6.99 (m, 1H), 5.51-5.44 (m, 0.5H), 5.37-5.31 (m, 0.5H), 4.63-4.49 (m, 2H), 4.46-4.38 (m, 1H), 4.19-4.05 (m, 1H), 4.03-3.94 (m, 1H), 3.92-3.79 (m, 1H), 3.61-3.51 (m, 4H), 3.45-3.39 (m, 1H), 3.28-3.16 (m, 2H), 2.85 (s, 3H), 2.58-2.44 (m, 1H), 2.43-2.28 (m, 3H), 2.23-2.09 (m, 3H), 2.00-1.90 (m, 1H), 1.36-1.32 (m, 3H), 1.29-1.25 (m, 3H).
336		LCMS m/z [M+1]: 725.2 1H NMR (400 MHz, CD3OD) δ 7.72-7.7 (m, 1H), 7.25-7.23 (m, 1H), 7.07-7.03 (m, 1H), 5.39 (s, 0.5H), 5.25(s, 0.5H), 4.64 (m, 1H), 4.27-4.24 (m, 2H), 4.22-3.87 (m, 3H), 3.65-3.54 (m, 1H), 3.54-3.46 (m, 2H), 3.32-3.20 (m, 3H), 3.09 (s, 1H), 3.76 (m, 3H), 2.51-1.90 (m, 8H), 1.43-1.25 (m, 6H).

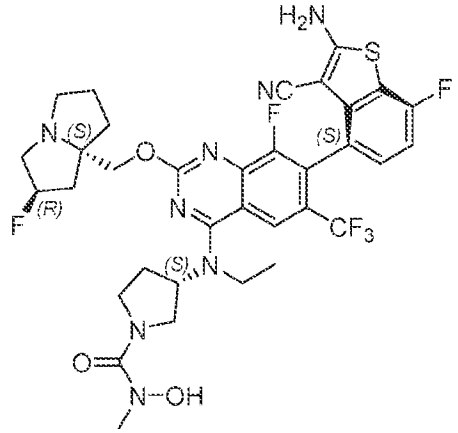
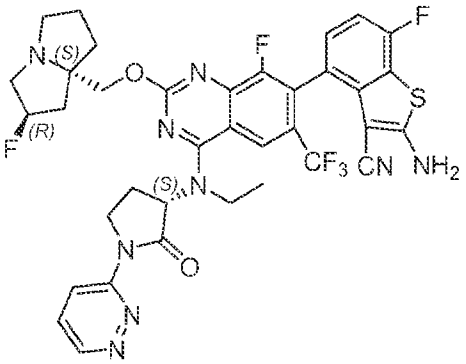
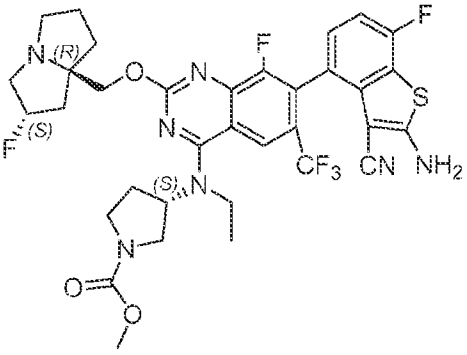
Cmpd. No.	Structure	Analytical Data
337		LCMS m/z [M+1]: 716.2 1H NMR (400 MHz, CD3OD) δ8.09 (s, 1H), 7.18-7.10 (m, 1H), 7.08-6.98 (m, 1H), 5.56-5.48 (m, 0.5H), 5.43-5.35 (m, 0.5H), 4.97-4.86 (m, 3H), 4.72-4.37 (m, 2H), 3.96-3.74 (m, 4H), 3.71 (s, 3H), 3.70-3.59 (m, 2H), 3.57-3.39 (m, 2H), 2.66-2.28 (m, 5H), 2.26-2.17 (m, 2H), 2.07-1.97 (m, 1H), 1.37-1.32 (m, 3H).
338		LCMS m/z [M+1]: 759.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.25-7.23 (m, 1H), 7.05-7.00 (m, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 4.79-4.78 (m, 1H), 4.28 (m, 2H), 4.05-4.03(m, 1H), 3.86-3.82 (m, 1H), 3.69-3.63 (m, 1H), 3.63-6.47 (m, 2H), 3.58-3.31(m, 1H), 3.36-3.31 (m, 1H), 3.19-3.09(m, 3H), 3.00 (m, 1H), 2.69 (s, 3 H), 2.26-2.02 (m, 5H), 2.02-1.89 (m, 3H). 1.47-1.34 (m, 3H), 1.34-1.30 (m, 3H).
339		LCMS m/z [M+1]: 759.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.27-7.25 (m, 1H), 7.05-7.00 (m, 1H), 5.41 (s, 0.5H), 5.27(s, 0.5H), 4.88 (m, 1H), 4.41-4.25 (m, 2H), 4.05-4.03 (m, 1H), 4.03-4.00 (m, 1H), 3.85-3.83(m, 2H), 3.67-3.44 (m, 3H), 3.36-3.12 (m, 1H), 3.11-2.96 (m, 3H), 2.75 (m,1H), 2.51-2.45 (m, 1H), 2.31-2.23(m, 1H), 2.25-1.75 (m, 6H), 1.43-1.25 (m, 6H).

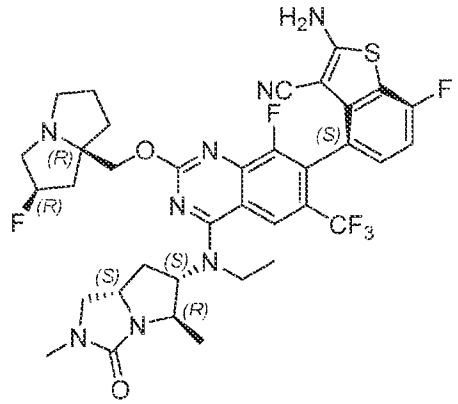
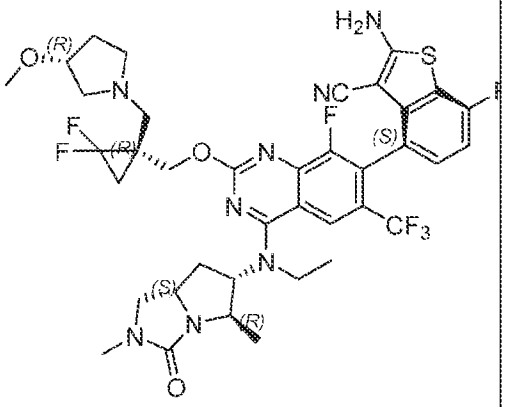
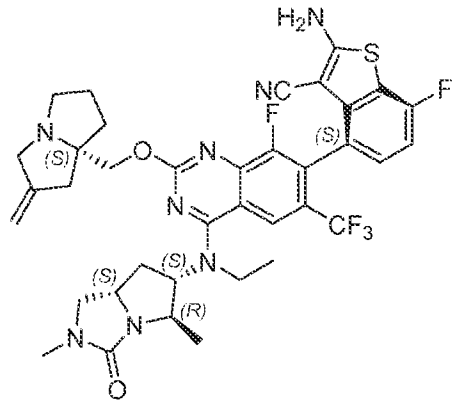
Cmpd. No.	Structure	Analytical Data
340		LCMS m/z [M+1]: 724.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, J = 5.7 Hz, 1H), 8.35 (d, J = 7.7 Hz, 1H), 8.28 (s, 1H), 7.87 – 7.81 (m, 1H), 7.23 (dd, J = 8.3, 5.0 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.46 (d, J = 51.9 Hz, 1H), 5.15 (t, J = 7.5 Hz, 1H), 4.43 (t, J = 11.9 Hz, 1H), 4.29 (dd, J = 12.6, 7.0 Hz, 1H), 4.04 – 3.97 (m, 2H), 3.87 – 3.63 (m, 7H), 3.41 – 3.34 (m, 1H), 2.50 – 2.34 (m, 2H), 2.27 – 2.12 (m, 3H), 1.94 – 1.84 (m, 1H), 1.63 (t, J = 7.0 Hz, 3H).

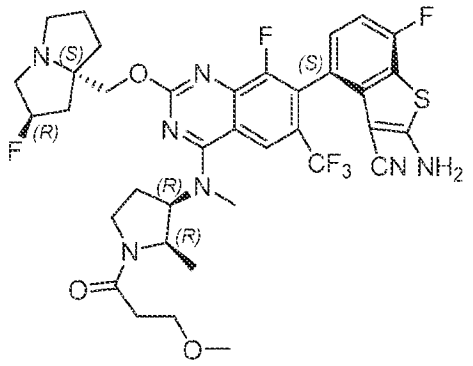
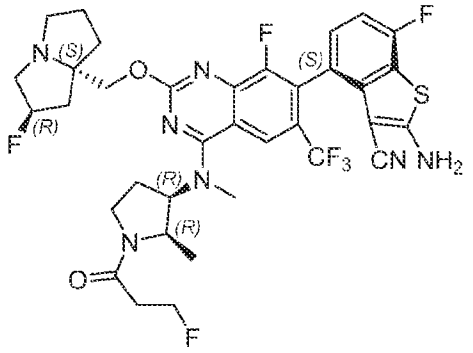
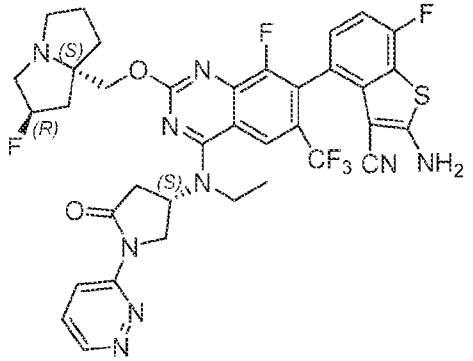
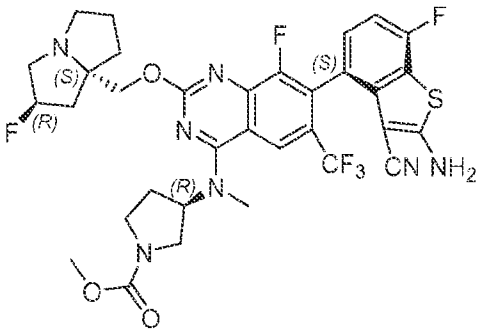
[0873] Table 3b includes selected compounds of the present disclosure.

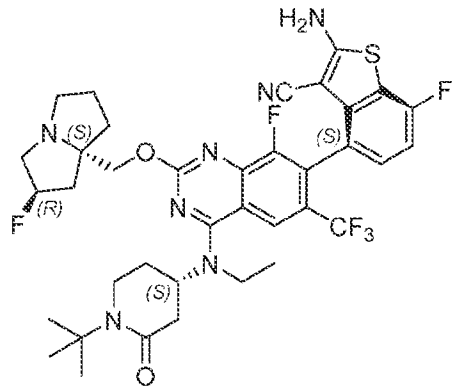
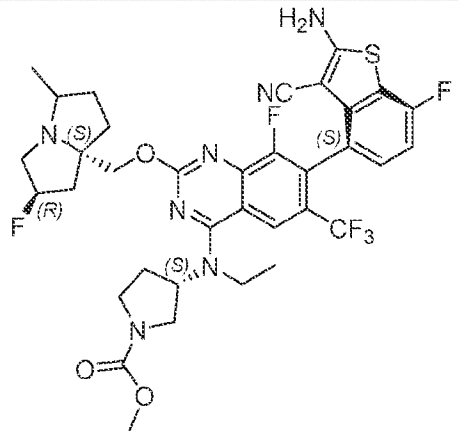
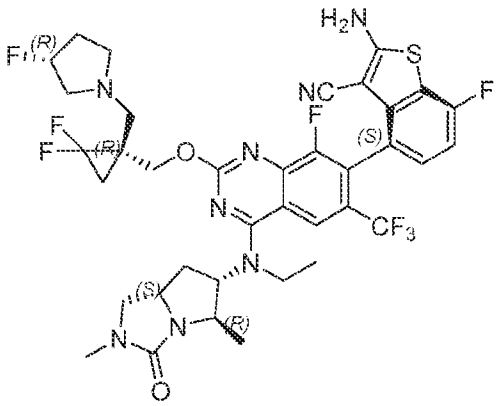
Table 3b. Selected compounds of the present disclosure.

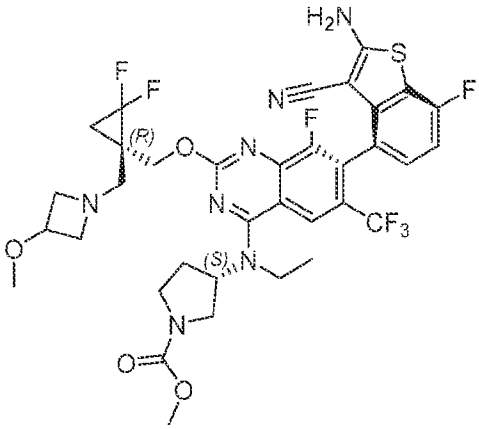
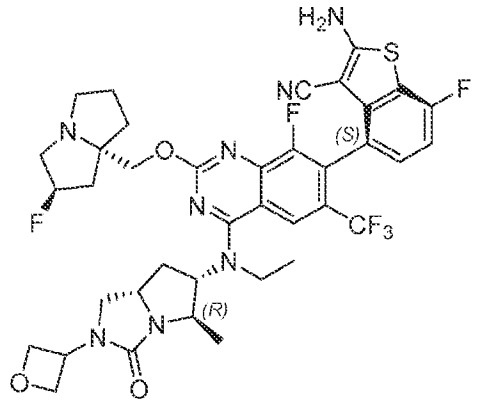
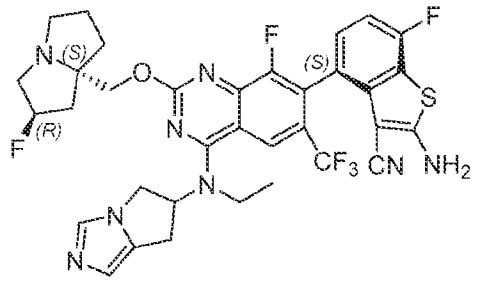
Cmpd. No.	Structure	Analytical Data
341		LCMS m/z [M+1]: 700.0 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.65 (d, 1H), 7.46 (d, 1H), 7.25-7.16 (m, 1H), 7.01 (t, 1H), 6.46 (t, 1H), 5.36-5.41 (m, 0.5H), 5.28-5.22 (m, 0.5H), 4.91 (s, 2H), 4.36-4.20 (dq, 2H), 3.56 (s, 3H), 3.29-3.21 (m, 3H), 3.09-3.01 (m, 1H), 2.36-2.12 (m, 3H), 2.05-1.85 (m, 3H).
342		LCMS m/z [M+1]: 692.3 1H NMR (400 MHz, CD3OD) δ 8.36 (d, 2H), 5.44 (s, 0.5H), 5.31 (s, 0.5H), 5.11-5.02 (m, 1H), 4.45-4.31 (m, 2H), 3.99-3.84 (m, 3H), 3.83-3.66 (m, 4H), 3.62-3.35 (m, 5H), 3.17-3.09 (m, 1H), 2.52-2.28 (m, 4H), 2.22-2.16 (m, 1H), 2.12-1.94 (m, 3H), 1.43 (t, 3H).

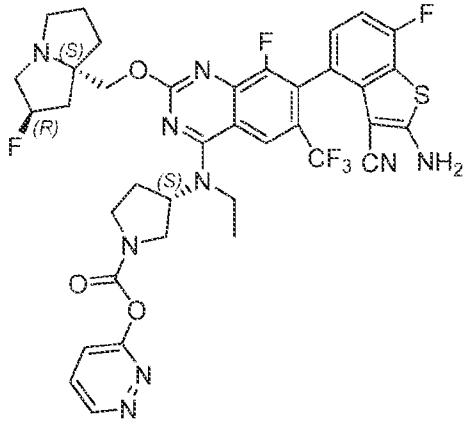
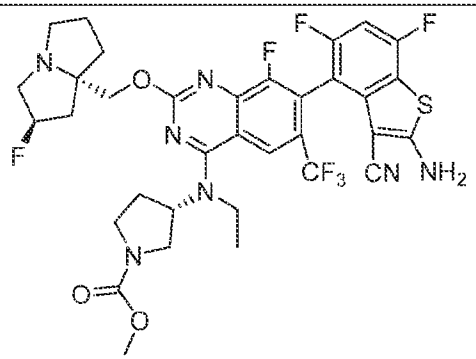
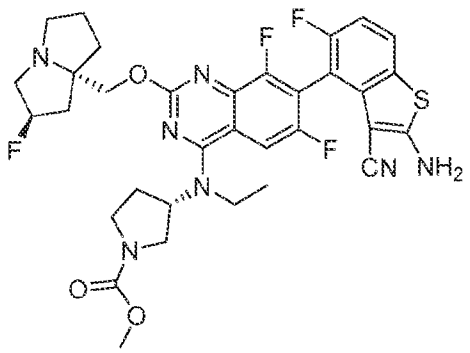
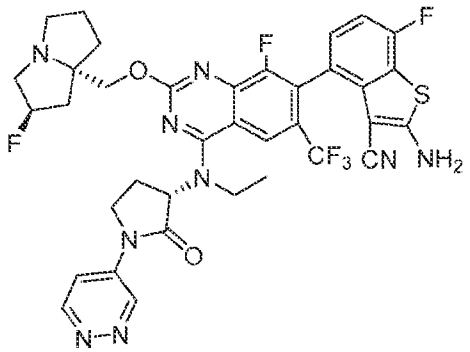
Cmpd. No.	Structure	Analytical Data
343		LCMS m/z [M+1]: 749.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.25-7.22 (m, 1H), 7.03 (t, 1H), 5.44 (s, 0.5H), 5.31 (s, 0.5H), 4.85-4.81 (m, 1H), 4.41-4.32 (m, 2H), 4.06-4.01 (m, 1H), 3.94-3.84 (m, 2H), 3.82-3.73 (m, 2H), 3.62-3.54 (m, 1H), 3.22-3.08 (m, 4H), 3.03 (s, 3H), 2.46-2.44 (m, 1H), 2.34-2.30 (m, 1H), 2.20 (t,1H),2.09-2.02 (m,3H), 1.96-1.92 (m,1H), 1.48 (t,3H).
344		LCMS m/z [M+1]: 768.3 1H NMR (400 MHz, CD3OD) δ 9.06 – 9.01 (m, 1H), 8.81 – 8.75 (m, 1H), 8.32 (s, 1H), 7.79 – 7.74 (m, 1H), 7.28 – 7.18 (m, 1H), 7.08 – 6.98 (m, 1H), 5.46 (d, J = 48.8 Hz, 1H), 4.94 – 4.89 (m, 1H), 4.67 – 4.58 (m, 1H), 4.50 – 4.26 (m, 2H), 4.21 – 4.03 (m, 3H), 3.80 – 3.58 (m, 3H), 3.39 – 3.34 (m, 1H), 2.78 – 2.64 (m, 2H), 2.55 – 2.30 (m, 2H), 2.20 – 1.80 (m, 4H), 1.69 (t, J = 7.2 Hz, 3H).
345		LCMS m/z [M+1]: 734.3 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.21-7.24 (m, 1H), 7.02 (t, 1H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 4.97-5.06 (m, 1H), 4.21-4.32 (m, 2H), 3.81-3.95 (m, 3H), 3.73-3.79 (m, 4H), 3.57-3.62 (m, 1H), 3.42-3.49 (m, 1H), 3.13-3.27 (m, 3H), 2.99-3.05 (m, 1H), 2.21-2.52 (m, 4H), 2.10-2.17 (m, 1H), 1.96-2.04 (m, 2H), 1.87-1.93 (m, 1H), 1.43-1.48 (m, 3H).

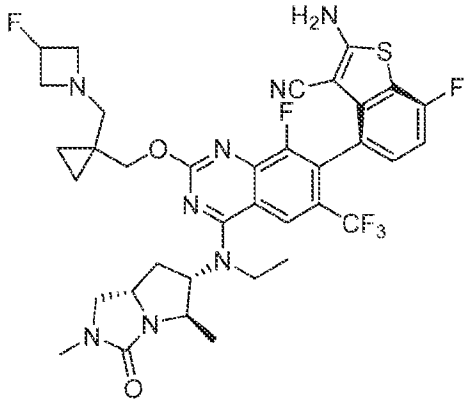
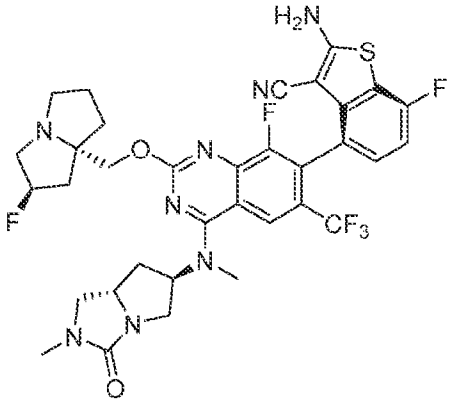
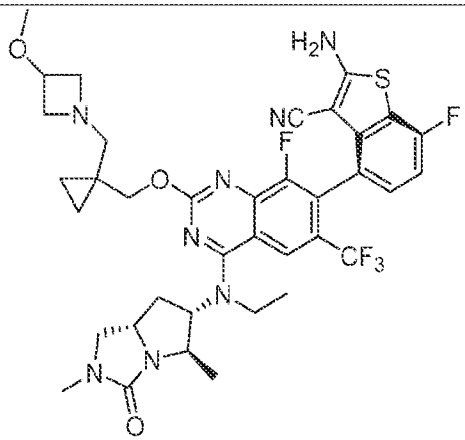
Cmpd. No.	Structure	Analytical Data
346		LCMS m/z [M+1]: 759.26 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.27-7.25 (m, 1H), 7.05-7.00 (m, 1H), 5.41 (s, 0.5H), 5.27(s, 0.5H), 4.88 (m, 1H), 4.41-4.25 (m, 2H), 4.05-4.03 (m, 1H), 4.03-4.00 (m, 1H), 3.85-3.83(m, 2H), 3.67-3.44 (m, 3H), 3.36-3.12 (m, 1H), 3.11-2.96 (m, 3H), 2.75 (m,1H), 2.51-2.45 (m, 1H), 2.31-2.23(m, 1H), 2.25-1.75 (m, 6H), 1.43-1.25 (m, 6H).
347		LCMS m/z [M+1]: 821.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.30 – 7.20 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 4.71 – 4.59 (m, 2H), 4.55 (d, J = 11.4 Hz, 1H), 4.28 – 4.19 (m, 1H), 4.03 – 3.85 (m, 3H), 3.73 – 3.59 (m, 2H), 3.46 (d, J = 9.8 Hz, 1H), 3.25 (s, 3H), 2.89 – 2.70 (m, 7H), 2.67 – 2.55 (m, J = 29.2, 8.7 Hz, 2H), 2.35 – 2.29 (m, 1H), 2.08 – 2.02 (m, J = 13.5, 6.3 Hz, 1H), 1.80 – 1.65 (m, 2H), 1.46 (t, J = 6.8 Hz, 3H), 1.35 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 50.6 Hz, 2H).
348		LCMS m/z [M+1]: 753.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.27-7.22 (m, 1H), 7.03 (t, 1H), 5.02 (s, 2H), 4.84-4.80 (m, 1H), 4.37-4.25 (m, 2H), 4.14-4.09 (m, 1H), 4.03-3.97 (m, 1H), 3.91-3.78 (m, 2H), 3.69-3.58 (m, 2H), 3.47-3.37 (m, 2H), 3.29-3.18 (m, 2H), 2.88-2.78 (m, 4H), 2.52 (d, 1H), 2.37-2.29 (m, 1H), 2.23-2.14 (m, 2H), 2.03-1.87 (m, 3H), 1.40 (t, 3H), 1.34-1.30 (m, 3H).

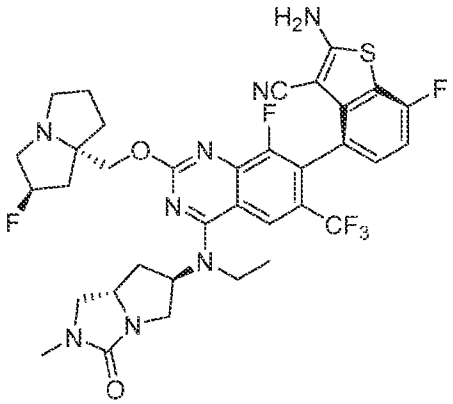
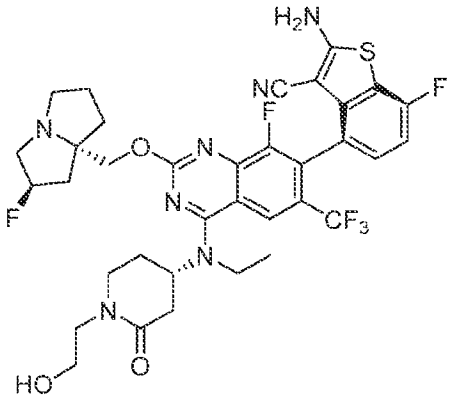
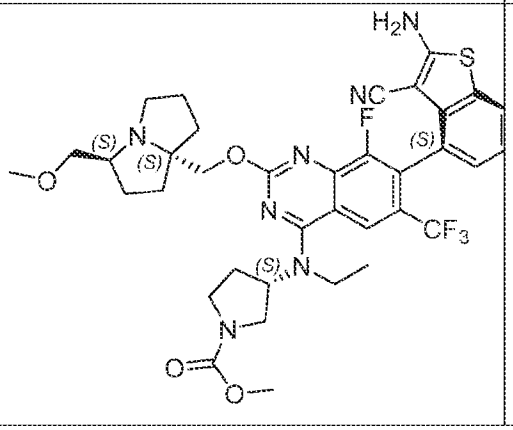
Cmpd. No.	Structure	Analytical Data
349		LCMS m/z [M+1]: 762.1 1H NMR (400 MHz, CD3OD) δ 8.38-7.48 (m, 1H), 7.18-7.27 (m, 1H), 6.99-7.08 (m, 1H), 5.56 (d, J = 52.0 Hz, 1H), 4.92-5.11 (m, 1H), 4.55-4.80 (m, 3H), 3.82-4.07 (m, 4H), 3.58-3.77 (m, 6H), 3.42-3.54 (m, 1H), 3.33-3.38 (m, 3H), 2.53-2.80 (m, 5H), 2.26-2.50 (m, 4H), 2.03-2.20 (m, 1H), 0.99-1.19 (m, 3H).
350		LCMS m/z [M+1]: 750.1 1H NMR (400 MHz, CD3OD) δ 8.42 (s, 1H), 7.19-7.28 (m, 1H), 6.97-7.09 (m, 1H), 5.62 (d, J = 48 Hz,1H), 4.98-5.09 (m, 1H), 4.57-4.85 (m, 5H), 3.82-4.10 (m, 4H), 3.42-3.74 (m, 5H), 2.27-2.82 (m, 9H), 2.06-2.21 (m, 1H), 1.00-1.18 (m, 3H).
351		LCMS m/z [M+1]: 768.3 1H NMR (400 MHz, CD3OD) δ 9.01 (s, 1H), 8.76 (d, J = 8.9 Hz, 1H), 8.26 (s, 1H), 7.80 (s, 1H), 7.23 (s, 1H), 7.03 (t, J = 8.8 Hz, 1H), 5.47 (s, 1H), 4.81 – 4.27 (m, 5H), 4.15 – 3.56 (m, 6H), 3.20 (ddd, J = 31.1, 18.4, 10.8 Hz, 2H), 2.49 – 2.27 (m, 2H), 2.24 – 1.88 (m, 4H), 1.65 (t, J = 6.1 Hz, 3H).
352		LCMS m/z [M+1]: 720.1 1H NMR (400 MHz, CD3OD) δ 8.37 (s, 1H), 7.23 (dd, J = 8.4, 4.9 Hz, 1H), 6.95 – 7.08(m, 1H), 5.56 – 5.63 (m, 1H), 5.29 – 5.37 (m, 1H), 4.68 (dd, J = 54.1, 12.5 Hz, 2H), 3.83 – 4.09(m, 4H), 3.69 – 3.79 (m, 4H), 3.42 – 3.59 (m, 6H), 2.54 – 2.73(m, 2H), 2.27 – 2.48 (m, 5H), 2.06 – 2.18 (m, 1H).

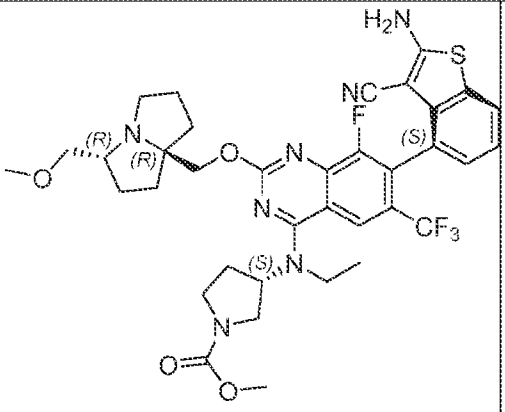
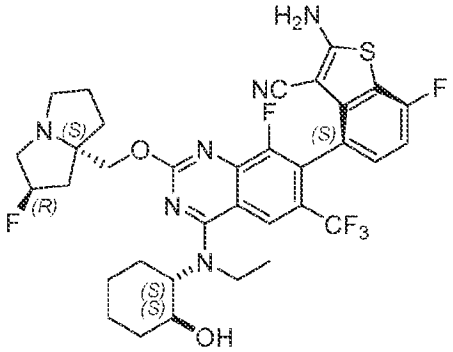
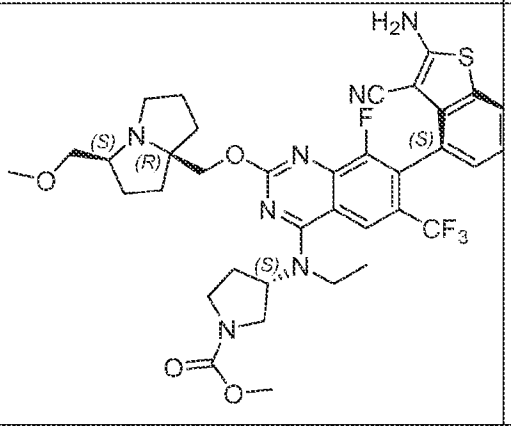
Cmpd. No.	Structure	Analytical Data
353		LCMS m/z [M+1]: 760.2 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.23-7.20 (m, 1H), 7.03-6.99 (m, 1H), 5.45 (s, 0.5H), 5.31 (s, 0.5H), 4.76-4.68 (m, 1H), 4.47-4.32 (m, 2H), 3.90-3.77 (m, 2H), 3.76-3.69 (m, 1H), 3.61-3.54 (m, 1H), 3.49-3.38 (m, 3H), 3.18-3.12 (m, 1H), 2.98-2.90 (m, 1H), 2.82-2.75 (m, 1H), 2.43-2.31 (m, 2H), 2.28-2.18 (m, 2H), 2.16-2.05 (m, 2H), 2.04-1.89 (m, 2H), 1.52-1.43 (m, 9H), 1.34-1.25 (m, 3H).
354		LCMS m/z [M+1]: 748.1 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.26-7.17 (m, 1H), 7.01 (t, 1H), 5.36 (s, 0.5H), 5.22 (s, 0.5H), 5.00 (s, 1H), 4.35 (s, 2H), 3.96-3.82 (m, 3H), 3.79-3.73 (s, 1H), 3.72 (s, 3H), 3.63-3.56 (m, 1H), 3.51-3.41 (m, 2H), 3.29-3.21 (m, 2H), 2.62-2.41 (m, 2H), 2.39-2.31 (m, 1H), 2.16-1.89 (m, 4H), 1.85-1.73 (m, 1H), 1.45 (t, 3H), 1.28 (s, 3H).
355		LCMS m/z [M+1]: 808.26 1H NMR (400 MHz, CD3OD) δ 8.22 (d, J = 12.3 Hz, 1H), 7.35 (s, 0.5H), 7.24 (s, 1H), 7.02 (t, J = 8.8 Hz, 1H), 5.20 (s, 0.5H), 5.06 (s, 0.5H), 4.68 – 4.55 (m, 3H), 4.27 – 4.18 (m, 1H), 3.99 (d, J = 7.1 Hz, 1H),3.92 – 3.83 (m, J = 14.4, 7.4 Hz, 1H), 3.75 – 3.65 (m, 1H), 3.60 (t, J = 8.8 Hz, 1H), 3.45 (d, J = 9.6 Hz, 1H), 2.99 – 2.69 (m, 9H), 2.52 (d, J = 6.9 Hz, 1H), 2.32 (t, J = 9.7 Hz, 2H), 2.19 – 2.09 (m, 1H), 2.03 – 1.87 (m, J = 19.4, 11.4 Hz, 1H), 1.71 (s, 1H), 1.44 (d, J = 6.3 Hz, 3H), 1.32 (d, J = 15.2 Hz, 3H).

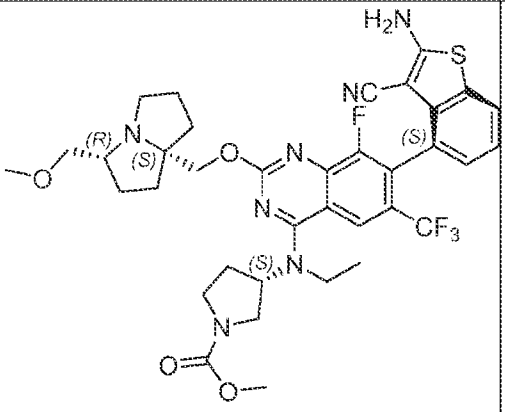
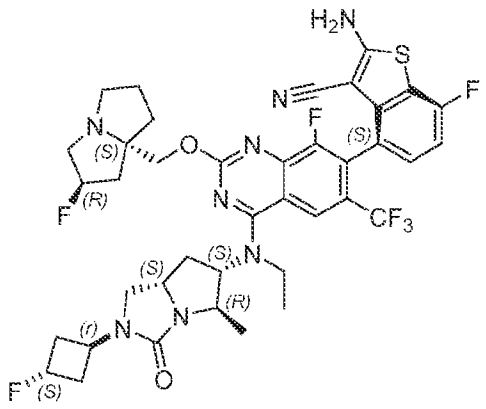
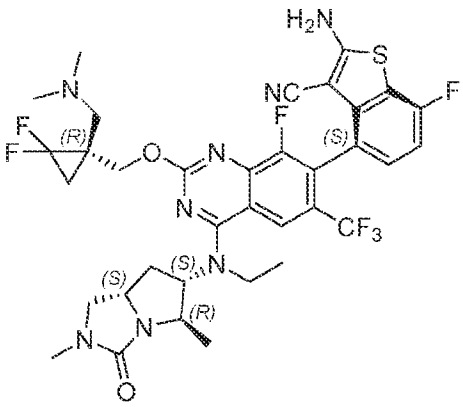
Cmpd. No.	Structure	Analytical Data
356		LCMS m/z [M+1]: 781.23 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.25 – 7.18 (m, 1H), 7.01 (t, J = 8.9 Hz, 1H), 5.02 (d, J = 7.1 Hz, 1H), 4.60 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 11.1 Hz, 1H), 4.04 – 3.99 (m, 1H), 3.94 – 3.82 (m, 3H), 3.77 – 3.68 (m, 6H), 3.59 (d, J = 9.3 Hz, 1H), 3.44 (d, J = 9.2 Hz, 1H), 3.22 (s, 3H), 3.08 (d, J = 6.4 Hz, 2H), 2.94 – 2.80 (m, J = 32.0, 12.9 Hz, 2H), 2.42 (d, J = 45.1 Hz, 2H), 1.62 – 1.55 (m, 1H), 1.45 (t, J = 6.8 Hz, 3H), 1.33 (s, 1H).
357		LCMS m/z [M+1]: 801.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.23 (s, 1H), 7.03 (s, 1H), 5.42-5.29 (m, 1H), 5.12 (s, 2H), 4.80-4.75 (m, 1H), 4.40-4.25 (m, 2H), 4.14 (s, 2H), 3.99 – 3.55 (m, 6H), 3.50-3.35(m, 3H), 3.12 (s, 2H), 2.40-2.25 (m, 3H), 2.20 (s, 2H), 2.05 (s, 2H), 1.93 (s, 1H), 1.39 (s, 3H), 1.33-1.34-1.31 (m, 3H).
358		LCMS m/z [M+1]: 713.2 1H NMR (400 MHz, CD3OD) δ 8.31 (s,1H), 7.73 (m,1H),7.27-7.19 (m,1H), 7.05-7.01 (m,1H), 6.89 (s,1H), 6.00-6.90 (m,1H), 5.53-5.32 (m,1H), 4.64-4.16 (m, 4H), 3.70-3.45 (m,6H) ,3.28-2.88 (m,3H), 2,54-1.93 (m,7H), 1.41-1.38 (m,3H).

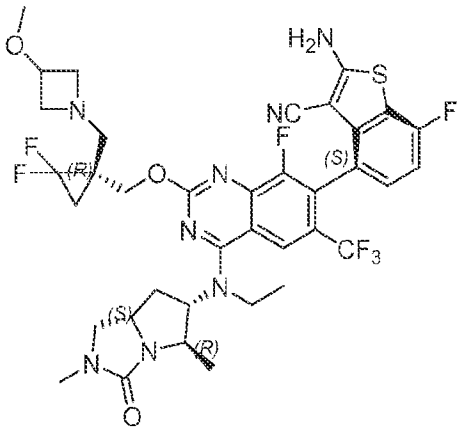
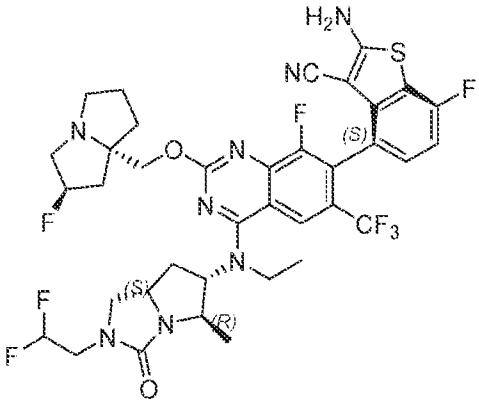
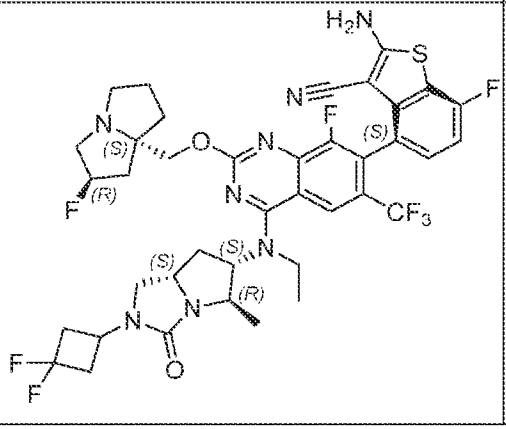
Cmpd. No.	Structure	Analytical Data
359		LCMS m/z [M+1]: 798.2 1H NMR (400 MHz, CD3OD) δ 8.16-8.35 (m, 1H), 7.82-8.08 (m, 1H), 7.41-7.69 (m, 1H), 7.16-7.25 (m, 1H), 6.96-7.25 (m, 2H), 5.58 (d, J = 52.3 Hz, 1H), 4.58-4.71 (m, 1H), 3.61-4.35 (m, 9H), 3.39-3.53 (m, 2H), 2.13-2.84 (m, 9H), 1.38-1.59 (m, 3H).
360		LCMS m/z [M+1]: 752.0 1H NMR (400 MHz, Methanol-d4) δ 8.30 (s, 1H), 6.97 (t, J = 9.6 Hz, 1H), 5.57 (d, J = 51.7 Hz, 1H), 5.04 (p, J = 7.9 Hz, 1H), 4.76 – 4.55 (m, 2H), 4.10 – 3.82 (m, 6H), 3.73 (s, 4H), 3.68 – 3.40 (m, 3H), 2.81 – 2.02 (m, 9H), 1.48 (td, J = 6.9, 3.4 Hz, 3H).
361		LCMS m/z [M+1]: 684.1 1H NMR (400 MHz, CD3OD) δ 7.75 – 7.64 (m, 2H), 7.08 (t, J = 9.2 Hz, 1H), 5.41 (d, J = 53.1 Hz, 1H), 5.03-4.90 (m, 2H), 4.47 – 4.33 (m, 2H), 3.95 – 3.73 (m, 7H), 3.58 – 3.45 (m, 4H), 3.23-3.15 (m, 1H), 2.44 – 1.97 (m, 8H), 1.47-1.21 (m, 3H).
362		LCMS m/z [M+1]: 768.3 1H NMR (400 MHz, CD3OD) δ 9.92 (d, J = 22.8 Hz, 1H), 9.21 – 9.15 (m, 1H), 8.32 (s, 1H), 8.11 – 8.03 (m, 1H), 7.28 – 7.23 (m, 1H), 7.03 (t, J = 9.2 Hz,1H), 5.38 (d, J = 54.4 Hz, 1H), 4.90 – 4.86 (m, 1H), 4.49 – 4.42 (m, 1H), 4.34 – 4.18 (m, 2H), 4.15 – 3.99 (m, 3H), 3.90 – 3.55

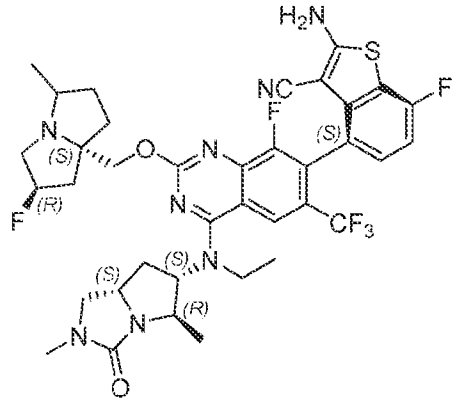
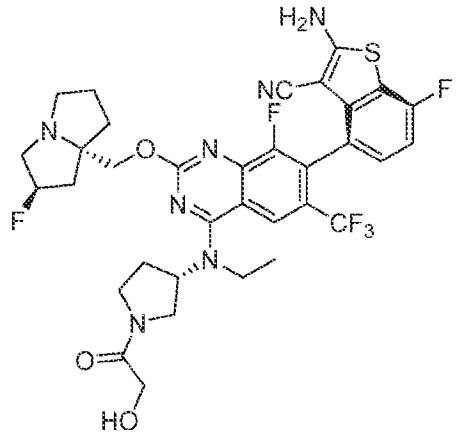
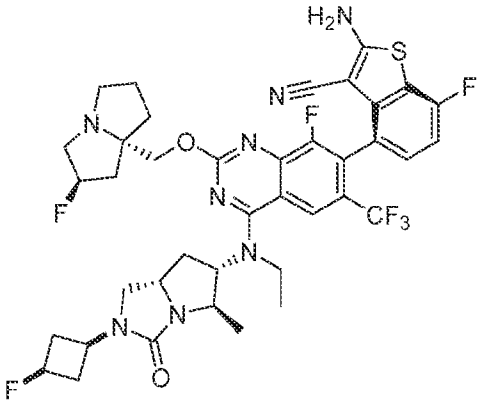
Cmpd. No.	Structure	Analytical Data
		(m, 4H), 2.84 – 2.68 (m, 2H), 2.52 – 2.28 (m, 2H), 2.24 – 1.80 (m, 4H), 1.74 – 1.64 (m, 3H).
363		LCMS m/z [M+1]: 801.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.23 (s, 1H), 7.03 (s, 1H), 5.42-5.29 (m, 1H), 5.12 (s, 2H), 4.80-4.75 (m, 1H), 4.40-4.25 (m, 2H), 4.14 (s, 2H), 3.99 – 3.55 (m, 6H), 3.50-3.35(m, 3H), 3.12 (s, 2H), 2.40-2.25 (m, 3H), 2.20 (s, 2H), 2.05 (s, 2H), 1.93 (s, 1H), 1.39 (s, 3H), 1.33-1.34-1.31 (m, 3H).
364		LCMS m/z [M+1]: 731.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.19-7.22 (m, 1H), 7.00 (t, 1H), 5.38 (s, 0.5H), 5.18-5.24 (s, 1.5H), 4.22-4.36 (s, 3H), 4.15-4.20 (m, 1H), 3.65 (t, 1H), 3.46 (s, 3H), 3.36-3.39 (m, 1H), 3.12-3.26 (m, 4H), 2.99-3.05 (m, 1H), 2.84 (s, 3H), 2.30-2.46 (m, 2H), 2.21-2.27 (m, 1H), 2.13-2.17 (m, 1H), 1.96-2.08 (m, 3H), 1.87-1.94 (m, 1H).
365		LCMS m/z [M+1]: 801.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.23 (s, 1H), 7.03 (s, 1H), 5.42-5.29 (m, 1H), 5.12 (s, 2H), 4.80-4.75 (m, 1H), 4.40-4.25 (m, 2H), 4.14 (s, 2H), 3.99 – 3.55 (m, 6H), 3.50-3.35(m, 3H), 3.12 (s, 2H), 2.40-2.25 (m, 3H), 2.20 (s, 2H), 2.05 (s, 2H), 1.93 (s, 1H), 1.39 (s, 3H), 1.33-1.34-1.31 (m, 3H).

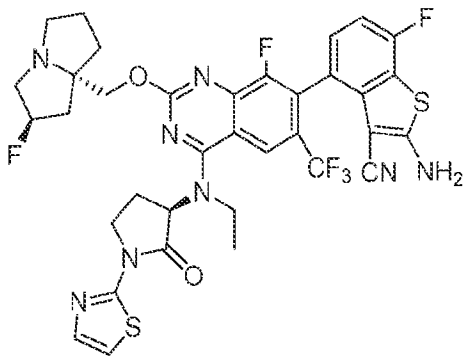
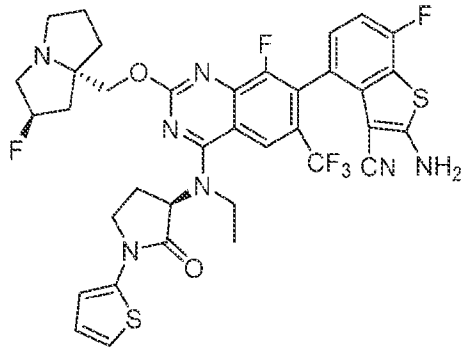
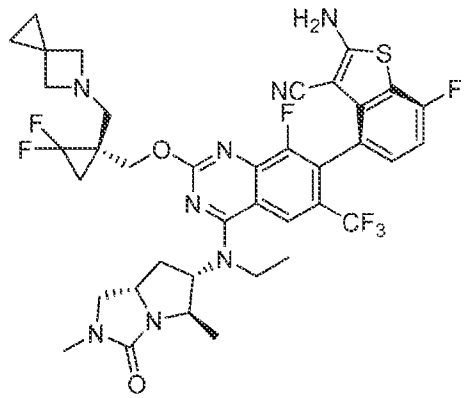
Cmpd. No.	Structure	Analytical Data
366		LCMS m/z [M+1]: 745.3 1H NMR (400 MHz, CD3OD) δ 8.18 (s, 1H), 7.20 (s, 1H), 7.00 (t, 1H), 5.37 (s, 0.5H), 5.24 (s, 0.5H), 4.69 (s, 1H), 4.46-4.49 (m, 1H), 4.24-4.37 (m, 2H), 4.08-4.15 (m, 1H), 3.82-3.87 (m, 2H), 3.61-3.67 (m, 1H), 3.35-3.47 (m, 2H), 3.13-3.26 (m, 3H), 3.02 (s, 1H), 2.83 (s, 3H), 2.20-2.45 (m, 3H), 2.12-2.14 (m, 1H), 1.90-2.00 (m, 4H), 1.46 (t, 3H).
367		LCMS m/z [M+1]: 745.24 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.22-7.20 (s, 1H), 7.05-7.00 (m, 1H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 4.29-4.23 (m, 2H), 3.85-3.60 (m, 7H), 3.25-3.03 (m, 4H), 3.03-2.95(m, 2H), 2.78-2.69 (m, 1H), 2.53-2.46 (m, 1H), 2.45-1.75 (m, 8H), 1.52-1.38 (s, 3H).
368		LCMS m/z [M+1]: 760.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.23 (d, J = 2.4 Hz, 1H), 7.11 – 6.96 (m, 1H), 5.10 – 4.97 (m, 1H), 4.73 – 4.47 (m, 2H), 4.24 – 4.04 (m, 1H), 4.03 – 3.56 (m, 10H), 3.56 – 3.34 (m, 6H), 2.56 – 1.94 (m, 10H), 1.55 – 1.42 (s, 3H).

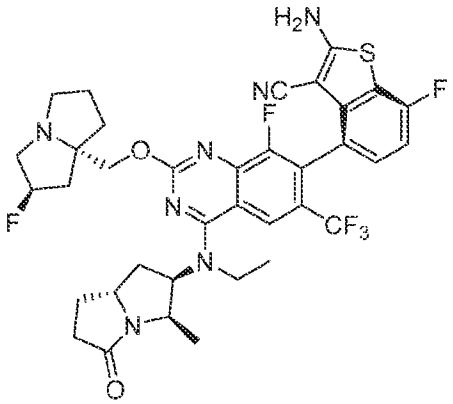
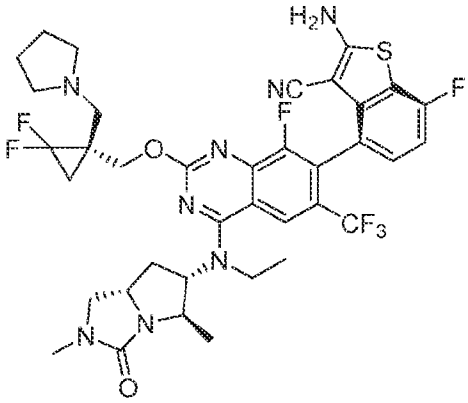
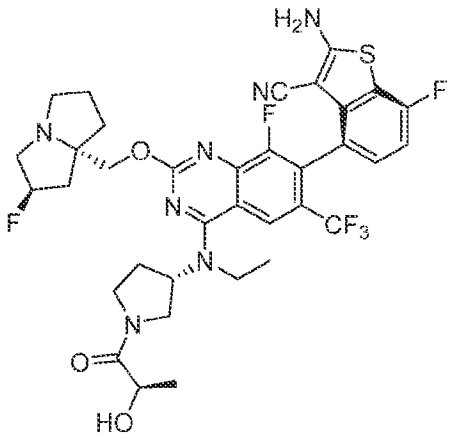
Cmpd. No.	Structure	Analytical Data
369		LCMS m/z [M+1]: 760.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.23 (s, 1H), 7.11 – 6.95 (m, 1H), 5.00 (s, 1H), 4.70 – 4.50 (m, 2H), 4.22 – 4.03 (m, 1H), 4.01 – 3.57 (m, 10H), 3.57 – 3.35 (m, 6H), 2.63 – 1.92 (m, 10H), 1.55 – 1.40 (m, 3H).
370		LCMS m/z [M+1]: 705.1 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.25-7.22 (m, 1H), 7.03 (t, 1H), 5.44 (s, 0.5H), 5.31 (s,0.5H), 4.85-4.81 (m, 1H), 4.41-4.32 (m, 2H), 4.06-4.01 (m,1H), 3.94-3.84 (m,2H), 3.82-3.73 (m,2H), 3.62-3.54 (m,1H), 3.22-3.08 (m, 4H), 3.03 (s, 3H), 2.46-2.44 (m, 1H),2.34-2.30 (m, 1H), 2.20 (t, 1H),2.09-2.02 (m, 3H), 1.96-1.92 (m, 1H). 1.48 (t, 3H).
371		LCMS m/z [M+1]: 760.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.30 – 7.18 (m, 1H), 7.03 (t, J = 8.8, 1H), 5.08 – 4.99 (m, 1H), 4.70 – 4.23 (m, 2H), 3.99 – 3.83 (m, 3H), 3.81 – 3.70 (m, 4H), 3.65 – 3.37 (m, 6H), 3.29 – 3.05 (m, 4H), 2.61 – 1.76 (m, 10H), 1.48 (t, J = 6.8 Hz, 3H).

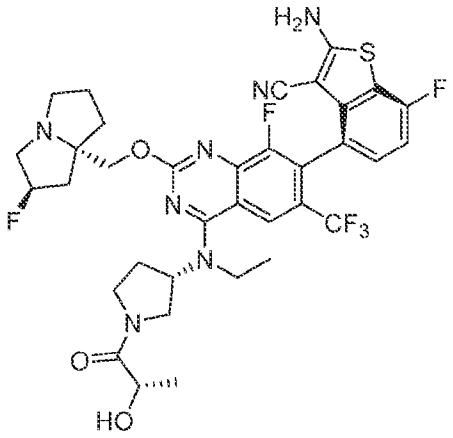
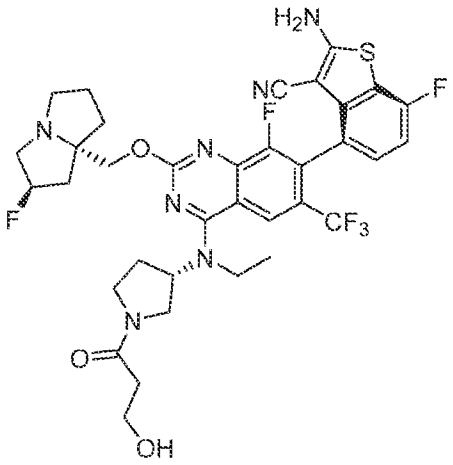
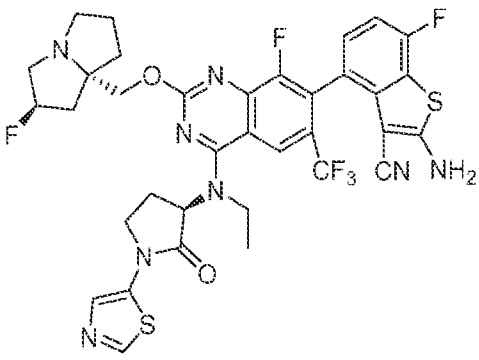
Cmpd. No.	Structure	Analytical Data
372		LCMS m/z [M+1]: 760.3 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.30 – 7.16 (m, 1H), 7.08 – 6.98 (m, 1H), 5.11 – 4.97 (m, 1H), 4.62 – 4.36 (m, 2H), 3.98 – 3.82 (m, 3H), 3.80 – 3.70 (m, 4H), 3.67 – 3.32 (m, 10H), 2.58 – 1.83 (m, 10H), 1.48 (t, J = 7.0 Hz, 3H).
373		LCMS m/z [M+1]: 817.2 1H-NMR (400 MHz, CD_3OD): 8.32 (s, 1 H), 7.19-7.25 (m, 1 H), 6.97-7.04 (m, 1 H), 5.39 (s, 0.5 H), 5.20-5.27 (m, 1 H), 5.05-5.11 (m, 0.5 H), 4.66-4.83 (m, 3 H), 4.22-4.36 (m, 2 H), 4.08-4.18 (m, 1 H), 3.98-4.07 (m, 1 H), 3.77-3.89 (m, 1 H), 3.59-3.73 (m, 2 H), 3.48-3.55 (m, 1 H), 3.19-3.27 (m, 2 H), 3.00-3.10 (m, 1 H), 2.56-2.73 (m, 2 H), 2.24-2.54 (m, 5 H), 1.99-2.20 (m, 4 H), 1.88-1.96 (m, 1 H), 1.38 (t, J=7 Hz, 3 H), 1.32 (d, J=6 Hz, 3 H).
374		LCMS m/z [M+1]: 765.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.27 – 7.21 (m, J = 8.3, 5.0 Hz, 1H), 7.06 – 6.97 (m, 1H), 4.67 – 4.48 (m, 3H), 4.28 – 4.18 (m, 1H), 4.01 – 3.94 (m, 1H), 3.93 – 3.84 (m, J = 14.8, 7.2 Hz, 1H), 3.71 – 3.64 (m, J = 14.8, 7.2 Hz, 1H), 3.58 (d, J = 8.8 Hz, 1H), 3.46 – 3.42 (m, J = 9.5, 2.5 Hz, 1H), 3.297 (s, 2H), 2.85 (s, 3H), 2.42 – 2.26 (m, J = 17.1, 11.6 Hz, 8H), 1.82 – 1.47 (m, 2H), 1.44 (t, J = 7.0 Hz, 3H), 1.33 (d, J = 6.5 Hz, 3H).

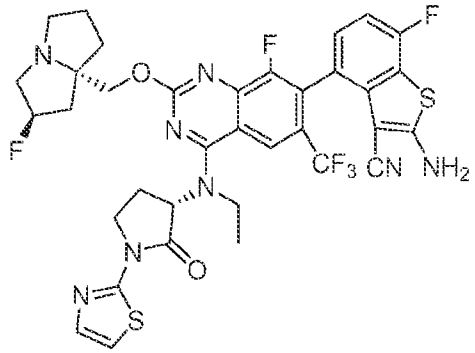
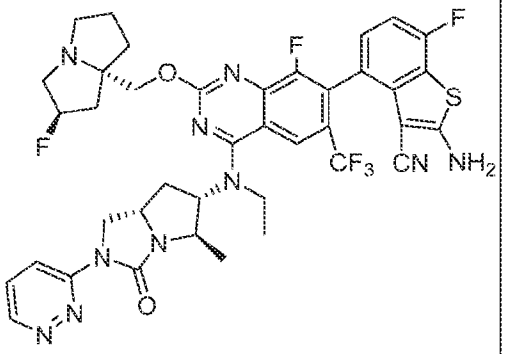
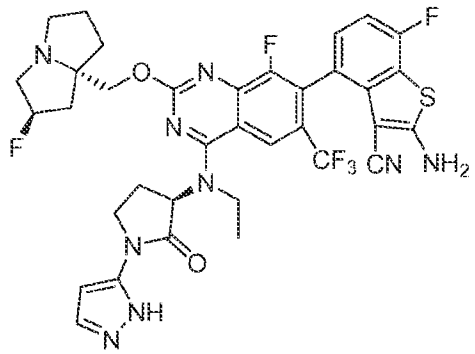
Cmpd. No.	Structure	Analytical Data
375		LCMS m/z [M+1]: 807.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.28 – 7.20 (m, J = 8.4, 5.0 Hz, 1H), 7.05 – 6.96 (m, J = 9.4, 8.5 Hz, 1H), 4.68 – 4.55 (m, 2H), 4.41 (d, J = 11.7 Hz, 1H), 4.27 – 4.20 (m, 1H), 4.05 – 3.96 (m, J = 15.8, 6.9 Hz, 2H), 3.91 – 3.83 (m, J = 14.0, 7.0 Hz, 1H), 3.75 – 3.57 (m, 4H), 3.47 – 3.43 (m, J = 9.5, 2.4 Hz, 1H), 3.22 (s, 3H), 3.17 – 2.87 (m, 4H), 2.85 (s, 3H), 2.39 – 2.25 (m, 2H),1.76 – 1.48 (m, 2H), 1.44 (d, J = 7.0 Hz, 3H), 1.33 (d, J = 6.5 Hz, 4H).
376		LCMS m/z [M+1]: 809.3 1HNMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.23 (dd, J = 8.5, 5.0 Hz, 1H), 7.05 – 6.98 (m, 1H), 6.00 (td, J = 55.5, 27.8 Hz, 1H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 4.84 – 4.79 (m, 1H), 4.28 (dd, J = 32.9, 10.6 Hz, 2H), 4.15 (t, J = 6.6 Hz, 1H), 4.11 – 3.99 (m, 1H), 3.90 – 3.75 (m, 2H), 3.72 – 3.62 (m, 2H), 3.61 – 3.50 (m, 2H), 3.28 – 3.18 (m, 3H), 3.11 – 2.95 (m, 1H), 2.41 – 2.28 (m, 2H), 2.27 – 2.11 (m, 3H), 2.05 – 1.96 (m, 2H), 1.92 (d, J = 14.5 Hz, 1H), 1.38 (t, J = 6.9 Hz, 3H), 1.33 (d, J = 6.5 Hz, 3H).
377		LCMS m/z [M+1]: 835.27 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.25-7.21 (m, 1H), 7.04-6.99 (m, 1H), 5.37 (s, 0.5H), 5.24 (s, 0.5H), 4.30-4.28 (m, 2H),4.28-4.25 (m, 1H), 4.21-3.99 (m, 2H), 3.80-3.65 (m, 1H), 3.80-3.65(m, 2H), 3.53-3.36 (m, 1H), 3.30-3.13 (m, 3H), 3.13-2.81 (m, 6H), 2.25-1.60 (m, 8H), 1.52-1.38 (m, 3H), 1.38-1.28 (m, 3H).

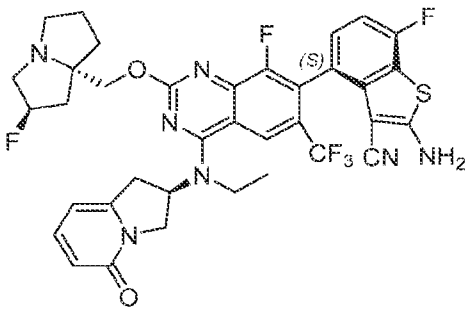
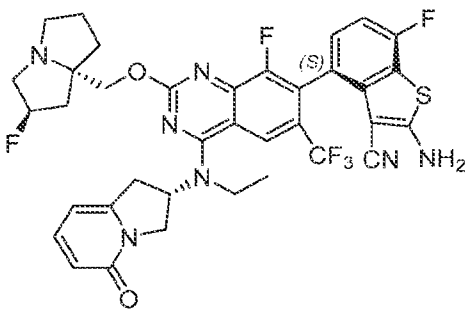
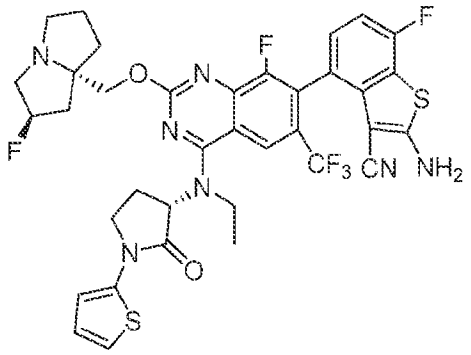
Cmpd. No.	Structure	Analytical Data
378		LCMS m/z [M+1]: 773.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.29-7.19 (m, 1H), 7.09-6.97 (m, 1H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 4.78-4.68 (m, 1H), 4.37 (s, 2H), 4.23-4.12 (m, 1H), 4.05-3.95 (m, 1H), 3.92-3.80 (m, 1H), 3.70-3.52 (m, 3H), 3.47-3.35 (m, 2H), 2.85 (s, 3H), 2.67-2.52 (m, 1H), 2.38-1.76 (m, 8H), 1.41 (t, 3H), 1.34-1.27 (m, 6H).
379		LCMS m/z [M+1]: 734.2 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.26 – 7.17 (m, 1H), 7.06 – 6.98 (m, 1H), 5.51 (s, 0.5 H), 5.36 (s, J = 16.7 Hz, 0.5 H), 5.05 – 4.94 (m, J = 15.7, 7.8 Hz, 1H), 4.56 – 4.35 (m, 2H), 4.26 (dd, J = 18.0, 13.0 Hz, 1H), 4.17 (s, 1H), 4.04 – 3.45 (m, 10H), 2.58 – 2.37 (m, 4H), 2.27 (d, J = 6.4 Hz, 1H), 2.18 (d, J = 5.6 Hz, 2H), 2.03 (s, 1H), 1.53 – 1.46 (m, J = 7.1 Hz, 3H).
380		LCMS m/z [M+1]: 817.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.25 – 7.18 (m, J = 8.3, 5.0 Hz, 1H), 7.05 – 6.97 (m, 1H), 5.40 (s, 0.5H), 5.26 (s, 0.5H), 4.89 (d, J = 6.8 Hz, 0.5H), 4.82 – 4.73 (m, 1.5H), 4.35 (d, J = 10.8 Hz, 1H), 4.27 (d, J = 10.8 Hz, 1H), 4.15 – 4.09 (m, J = 13.2, 6.6 Hz, 1H), 4.08 – 3.98 (m, 2H), 3.89 – 3.79 (m, J = 14.0, 7.0 Hz, 1H), 3.75 – 3.63 (m, J = 14.7, 8.3 Hz, 2H), 3.57 – 3.53 (m, 1H), 3.41 (d, J = 14.7 Hz, 1H), 3.10 – 3.02 (m, J = 15.1, 9.7 Hz, 1H), 2.67 – 2.59 (m, 2H), 2.52 – 1.86 (m, J = 44.6, 38.2, 21.4, 12.6, 7.8 Hz, 12H), 1.38 (t, J = 6.9 Hz, 3H), 1.33 – 1.28 (m, 3H).

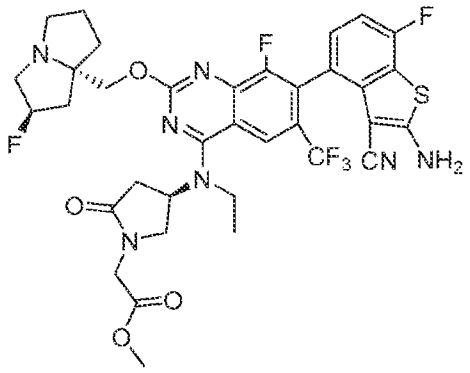
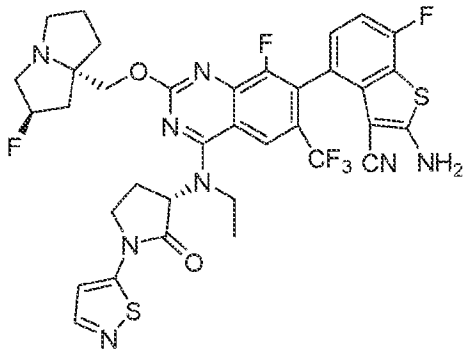
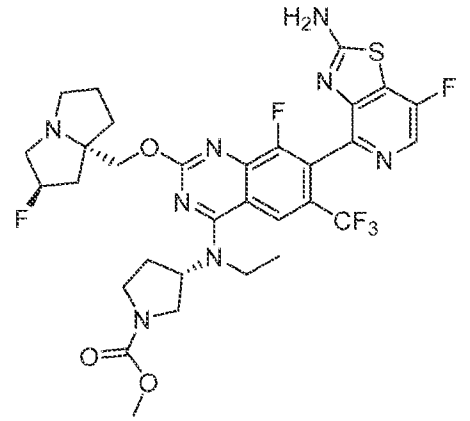
Cmpd. No.	Structure	Analytical Data
381		LCMS m/z [M+1]: 773.2 1H NMR (400 MHz, CD3OD) δ 8.31 (s, 1H), 7.60 (d, J = 3.2 Hz, 1H), 7.38 – 7.16 (m, 2H), 7.03 (t, J = 8.9 Hz, 1H), 5.39 (dd, J = 52.2, 10.4 Hz, 1H), 4.93 (s, 1H), 4.58 – 4.32 (m, 2H), 4.15 (dd, J = 28.6, 8.4 Hz, 3H), 3.99 (t, J = 11.6 Hz, 1H), 3.68 (ddd, J = 82.0, 47.0, 18.8 Hz, 4H), 2.92 – 2.62 (m, 2H), 2.53 – 2.23 (m, 2H), 2.03 (d, J = 38.6 Hz, 3H), 1.70 (t, J = 6.8 Hz, 3H), 1.56 (s, 1H).
382		LCMS m/z [M+1]: 772.2 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.20-7.32 (m, 1H), 6.98-7.14 (m, 3H), 6.76-6.86 (m, 1H), 5.44 (d, J = 56 Hz, 1H), 4.78-4.85 (m, 1H), 4.19-4.39 (m, 2H), 3.98-4.15 (m, 4H), 3.58-3.93 (m, 3H), 3.20-3.27 (m, 1H), 2.64-2.93 (m, 2H), 2.26-2.58 (m, 2H), 1.98-2.08 (m, 2H), 1.66-1.74 (m, 3H), 1.48-1.62 (m, 2H).
383		LCMS m/z [M+1]: 803.3 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.27-7.19 (m, 1H), 7.01 (t, 1H), 4.66-4.50 (m, 2H), 4.42 (d, 1H), 4.32-4.24 (m, 1H), 4.04-3.54 (m, 8H), 3.47-3.43 (m, 1H), 2.85 (s, 3H), 2.43-2.33 (m, 1H), 2.31-2.23 (m, 1H), 1.83-1.73 (m, 1H), 1.67-1.58 (m, 1H), 1.47 (t, 3 H) 1.37-1.22 (m, 5 H), 0.62 (s, 4H).

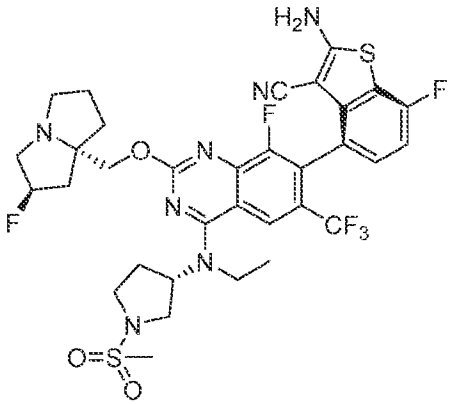
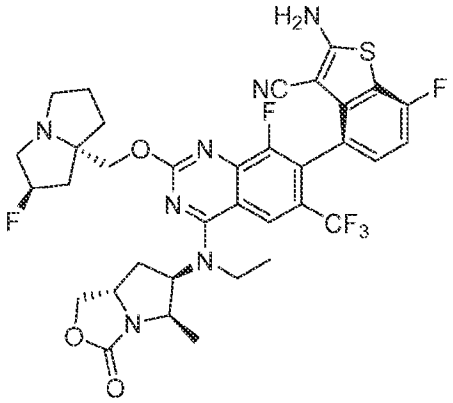
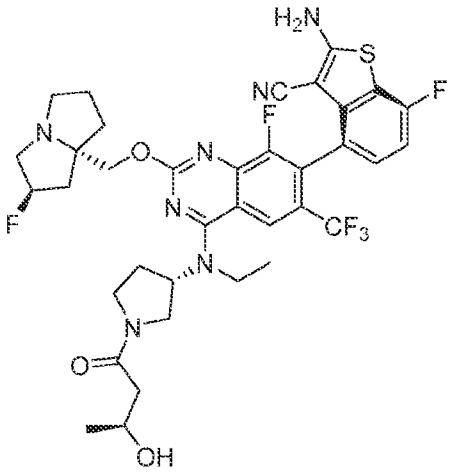
Cmpd. No.	Structure	Analytical Data
384		LCMS m/z [M+1]: 744.3 1HNMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.26 – 7.18 (m, 1H), 7.07 – 6.97 (m, 1H), 5.48 (s, 0.5H), 5.35 (s, 0.5H), 4.51 – 4.30 (m, 3H), 4.09 – 3.88 (m, 2H), 3.66 – 3.39 (m, 3H), 3.21 – 3.10 (m, 2H), 2.82 – 2.64 (m, 2H), 2.53 – 2.24 (m, 5H), 2.20 – 1.94 (m, 5H), 1.90 – 1.78 (m, J = 21.2, 12.3, 9.0 Hz, 1H), 1.45 (t, J = 6.9 Hz, 4H), 1.07 (d, J = 6.8 Hz, 3H).
385		LCMS m/z [M+1]: 791.3 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.25-7.20 (m, 1H), 7.01 (t, 1H), 4.67 (d, 1H), 4.59-4.48 (m, 2H), 4.31-4.23 (m, 1H), 4.02-3.95 (m, 1H), 3.92-3.85 (m, 1H), 3.72-3.65 (m, 1H), 3.59 (t, 1H), 3.47-3.42 (m, 1H), 2.98-2.90 (m, 1H), 2.85 (s, 3H), 2.43-2.16 (m, 3H), 1.99-1.77 (m, 5H), 1.64-1.56 (m, 1H), 1.47 (t, 3 H) 1.35-1.26 (m, 7 H).
386		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.30 (d, J = 9.9 Hz, 1H), 7.27 – 7.18 (m, J = 8.3, 5.0 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 5.62 (s, 0。5H), 5.49 (s, 0.5H), 5.08 (d, J = 8.4 Hz, 0.5H), 5.00 – 4.94 (m, 0.5H), 4.75 – 4.57 (m, J = 18.2, 17.4, 9.1 Hz, 2H), 4.57 – 4.15 (m, J = 55.3, 18.5, 8.6, 5.1 Hz, 2H), 4.09 – 3.83 (m, 7H), 3.80 – 3.52 (m, 2H), 3.51 – 3.42 (m, J = 15.2, 6.7, 3.1 Hz, 1H), 2.73 – 2.50 (m, 3H), 2.46 – 2.39 (m, 2H), 2.34 – 2.26 (m, 2H), 2.14 (d, J = 21.7 Hz, 1H), 1.53 – 1.47 (m, J = 6.9, 2.6 Hz, 3H), 1.35 (d, J = 5.7 Hz, 3H).

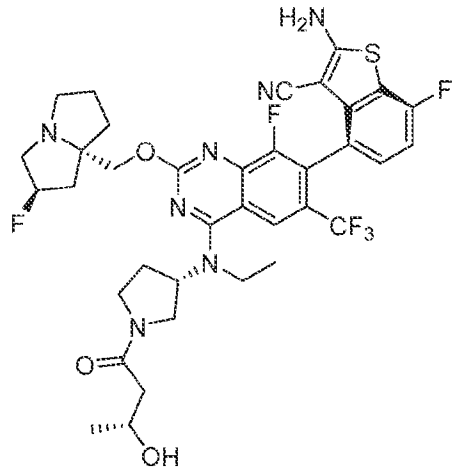
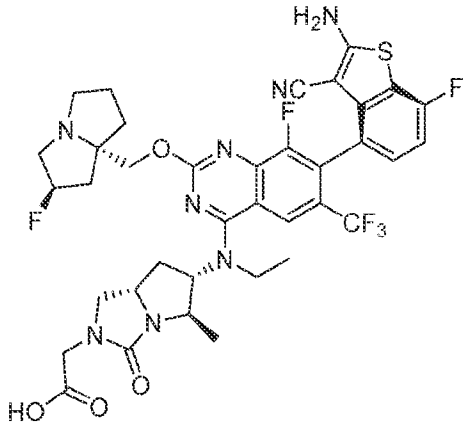
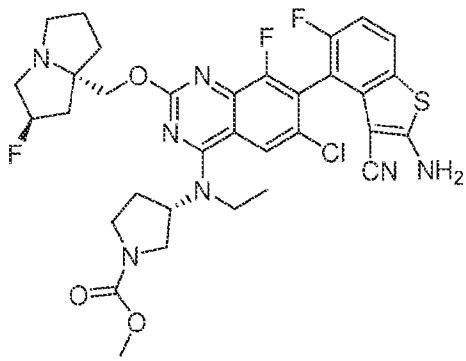
Cmpd. No.	Structure	Analytical Data
387		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.28 (d, J = 23.6 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.07 – 6.98 (m, 1H), 5.62 (s, 0.5H), 5.49 (s, 0.5H), 5.10 – 4.90 (m, J = 40.7, 31.8 Hz, 1H), 4.80 – 4.71 (m, J = 18.1, 12.3 Hz, 1H), 4.62 – 4.40 (m, 2H), 4.14 – 3.32 (m, 11H), 2.70 – 2.50 (m, 3H), 2.43 – 2.26 (m, 4H), 2.19 – 2.06 (m, J = 23.1, 6.0 Hz, 1H), 1.55 – 1.45 (m, 3H), 1.40 – 1.32 (m, J = 13.1, 6.5 Hz, 3H).
388		LCMS m/z [M+1]: 748.3 1H NMR (400 MHz, CD3OD) δ 8.29 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 6.0 Hz, 1H), 7.07 – 6.98 (m, 1H), 5.62 (s, 0.5H), 5.49 (s, 0.5H), 5.10 – 4.98 (m, 1H), 4.77 – 4.68 (m, J = 12.3, 3.7 Hz, 1H), 4.63 – 4.50 (m, J = 27.1, 12.3 Hz, 1H), 4.10 – 3.83 (m, 10H), 3.71 – 3.57 (m, 1H), 3.49 – 3.39 (m, 1H), 2.65 – 2.50 (m, 5H), 2.44 – 2.29 (m, 4H), 2.12 (s, 1H), 1.54 – 1.45 (m, J = 14.9, 7.8 Hz, 3H).
389		LCMS m/z [M+1]: 773.1 1H NMR (400 MHz, CD3OD) δ 8.73 (s, 1H), 8.30 (s, 1H), 7.76 (s, 1H), 7.25 (m, 1H), 6.99 – 7.08 (m, 1H), 5.30 – 5.46 (m, 1H), 4.83 (s, 1H), 4.39 (d, J = 11.7 Hz, 1H), 4.22 – 4.30 (m, 1H), 4.02 – 4.13 (m, 4H), 3.71 – 3.89 (m, 2H), 3.61 – 3.66 (m, 1H), 3.27 (d, J = 5.9 Hz, 2H), 2.71 – 2.89 (m, 2H), 2.32 – 2.52(m, 2H), 2.15 – 2.02 (m, 2H), 1.69 (t, J = 7.1 Hz, 3H), 1.52 – 1.58 (m, 1H).

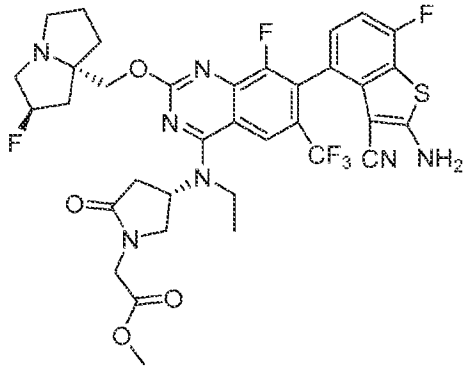
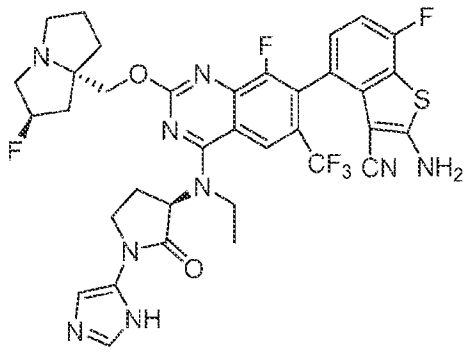
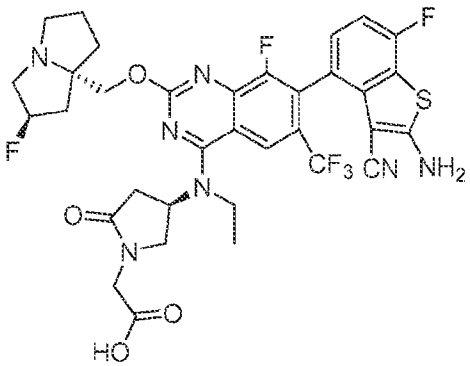
Cmpd. No.	Structure	Analytical Data
390		LCMS m/z [M+1]: 773.2 1H NMR (400 MHz, CD3OD) δ 8.31 (s, 1H), 7.61 (d, J = 3.4 Hz, 1H), 7.44 – 7.15 (m, 2H), 7.03 (t, J = 8.8 Hz, 1H), 5.38 (d, J = 51.0 Hz, 1H), 4.98 (s, 1H), 4.44 (dt, J = 33.0, 16.3 Hz, 2H), 4.27 – 3.90 (m, 4H), 3.88 – 3.37 (m, 4H), 2.90 – 2.61 (m, 2H), 2.53 – 2.27 (m, 2H), 2.05 (d, J = 29.0 Hz, 3H), 1.70 (t, J = 6.9 Hz, 3H), 1.58 (s, 1H).
391		LCMS m/z [M+1]: 823.3 1H NMR (400 MHz, CD3OD) δ 8.84 (d, J = 4.0 Hz, 1H), 8.62 (d, J = 9.2 Hz, 1H), 8.22 (s, 1H), 7.68 – 7.62 (m, 1H), 7.25 – 7.20 (m, 1H), 7.01 (t, J = 8.8 Hz, 1H), 5.19 (d, J = 52.8 Hz, 1H) , 4.60 – 4.50 (m, 1H), 4.40 – 4.34 (m, 1H), 4.29 – 4.18 (m, 2H), 4.15 – 4.10 (m, 1H), 4.03 – 3.89 (m, 1H), 3.81 – 3.61 (m, 1H), 3.50 – 3.38 (m, 1H) , 3.20 – 3.12 (m, 1H), 2.98 – 2.86 (m, 1H), 2.71 – 2.58 (m, 1H), 2.53 – 2.43 (m, 1H), 2.34 – 2.21 (m, 1H), 2.18 – 2.02 (m, 2H), 1.95 –1.90 (m, 1H), 1.84 – 1.66 (m, 3H), 1.52 (t, J = 6.8 Hz, 3H), 1.46 – 1.38 (m, 3H), 1.34 – 1.25 (m, 2H).
392		LCMS m/z [M+1]: 756.3 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.03 (t, J = 9.0 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 5.42 (d, J = 52.5 Hz, 1H), 4.84 – 4.74 (m, 2H), 4.40 – 4.26 (m, 2H), 4.13 – 3.96 (m, 4H), 3.88 – 3.63 (m, 3H), 2.89 – 2.81 (m, 1H), 2.68 – 2.26 (m, 5H), 2.10 – 2.02 (m, 2H), 1.72 – 1.67 (m, 3H).

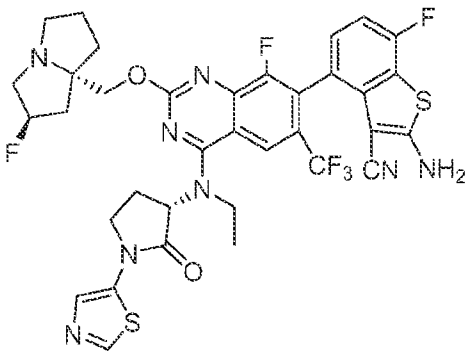
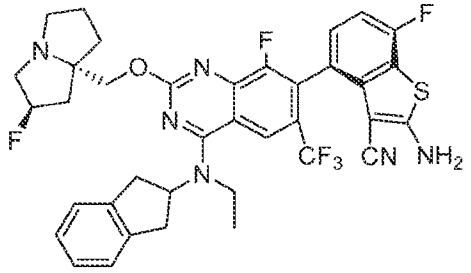
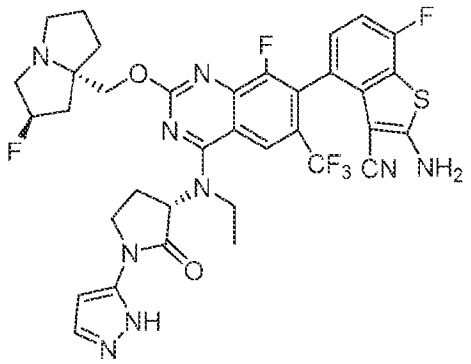
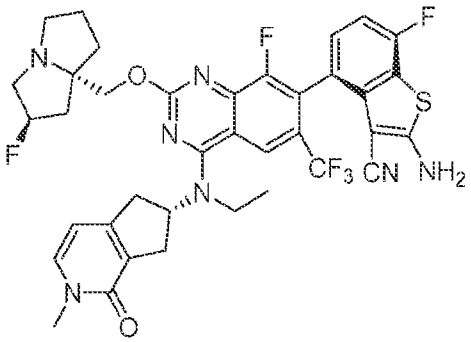
Cmpd. No.	Structure	Analytical Data
393		LCMS m/z [M+1]: 740.2 1H NMR (400 MHz, CD3OD) δ 8.61 (s, 1H), 7.74 – 7.48 (m, 1H), 7.33 – 7.16 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 6.48 (d, J = 8.0 Hz, 2H), 5.56 (d, J = 52.0 Hz, 1H), 5.08 – 4.90 (m, 1H), 4.75 – 4.51 (m, 2H), 4.26 (dd, J = 13.6, 4.0 Hz, 1H), 4.11 – 3.80 (m, 3H), 3.73 – 3.56 (m, 1H), 3.52 – 3.39 (m, 1H), 2.79 – 2.54 (m, 2H), 2.48 – 2.26 (m, 2H), 2.20 – 2.01 (m, 2H), 2.01 – 1.83 (m, 2H), 1.43 – 1.24 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H).
394		LCMS m/z [M+1]: 740.2 1H NMR (400 MHz, CD3OD) δ 8.62 (s, 1H), 7.74 – 7.51 (m, 1H), 7.35 – 7.13 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 6.48 (d, J = 8.0 Hz, 2H), 5.56 (d, J = 52.0 Hz, 1H), 5.11 – 4.92 (m, 1H), 4.75 – 4.55 (m, 2H), 4.24 (dd, J = 13.6, 4.0 Hz, 1H), 4.09 – 3.82 (m, 3H), 3.65 – 3.56 (m, 1H), 3.52 – 3.41 (m, 1H), 2.78 – 2.52 (m, 2H), 2.46 – 2.27 (m, 2H), 2.23 – 2.01 (m, 2H), 2.00 – 1.85 (m, 2H), 1.37 – 1.25 (m, 2H), 1.14 (t, J = 7.6 Hz, 3H).
395		LCMS m/z [M+1]: 772.3 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.18-7.32 (m, 1H), 6.98-7.15 (m, 3H), 6.75-6.88 (m, 1H), 5.23-5.45 (m, 1H), 4.77-4.85 (m, 1H), 3.99-4.40 (m, 6H), 3.40-3.83 (m, 3H), 3.22-3.29 (m, 1H), 2.67-2.90 (m, 2H), 1.90-2.40 (m, 5H), 1.61-1.83 (m, 4H).

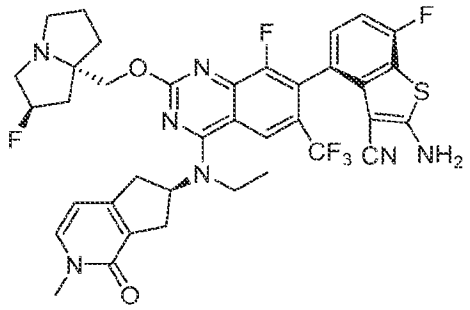
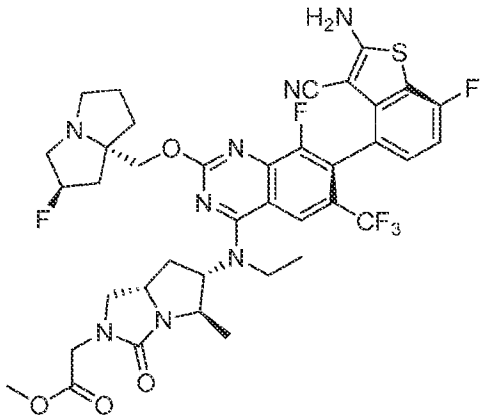
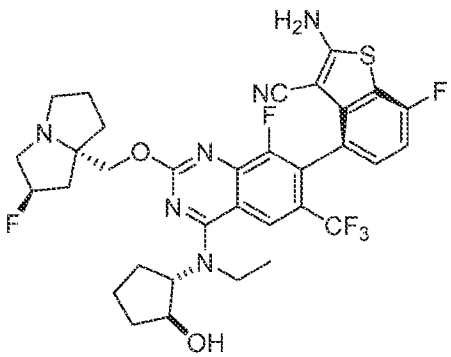
Cmpd. No.	Structure	Analytical Data
396		LCMS m/z [M+1]: 762.3 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.24 – 7.20 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 5.57 (d, J = 52.4 Hz, 1H), 4.83 – 4.81 (m, 1H), 4.72 – 4.49 (m, 2H), 4.20 (s, 2H), 4.12 – 3.83 (m, 7H), 3.75 (s, 3H), 3.47 – 3.42 (m, 1H), 3.16 – 3.08 (m, 1H), 2.92 – 2.16 (m, 7H), 1.58 – 1.55 (m, 3H).
397		1H NMR (400 MHz, CD3OD) δ 8.50 (d, J = 8.9 Hz, 1H), 8.36 (s, 1H), 8.28 (s, 1H), 7.28 – 7.20 (m, 1H), 7.03 (dd, J = 26.0, 11.3 Hz, 2H), 5.27 (s, 1H), 4.34 – 4.18 (m, 2H), 4.08 (t, J = 15.3 Hz, 3H), 3.89 (dd, J = 14.0, 12.4 Hz, 2H), 3.05 (dd, J = 17.8, 8.9 Hz, 1H), 2.87 – 2.68 (m, 2H), 2.19-1.90 (m, 4H), 1.74 – 1.61 (m, 3H), 1.31 (dd, J = 16.2, 1.3 Hz, 3H), 0.94-0.75(m, 2H).
398		LCMS m/z [M+1]: 711.1 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 8.24 (s, 1H), 5.57 (s,0.5H), 5.44 (s,0.5H), 5.04 (t, 1H), 4.62-4.53 (m,2H), 3.95-3.86 (m, 3H), 3.77-3.72 (m, 6H), 3.61-3.55 (m,1H), 3.49-3.45 (m,1H), 3.40-3.34 (m,1H), 3.26-3.24 (m,1H), 2.26-2.45 (m, 3H), 2.41-2.32 (m, 2H), 2.30-2.24 (m, 2H),2.11-2.05 (m,1H), 1.46 (t,3H).

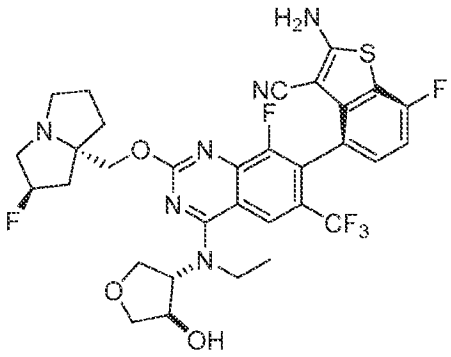
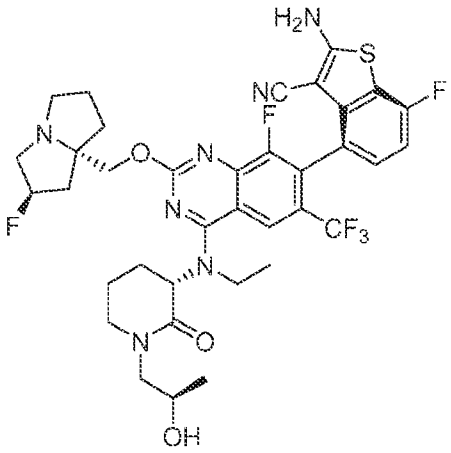
Cmpd. No.	Structure	Analytical Data
399		LCMS m/z [M+1]: 754.1 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.27-7.16 (m, 1H), 7.07-6.96 (m, 1H), 5.39 (s, 0.5H), 5.25 (s, 0.5H), 5.04-4.94 (m, 1H), 4.38 (d, 1H), 4.28 (d, 1H), 3.97-3.75 (m, 3H), 3.74-3.66 (m, 1H), 3.62-3.54 (m, 1H), 3.42-3.36 (m, 1H), 3.29-3.18 (m, 3H), 3.10-3.00 (m, 1H), 2.97 (s, 3H), 2.62-2.50 (m,1H), 2.44-2.17 (m, 4H), 2.04-1.91 (m, 3H), 1.47 (t, 3H).
400		LCMS m/z [M+1]: 746.3 1HNMR (400 MHz, CD3OD) δ 8.39 (s, 1H), 7.30 – 7.16 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.65 (s, 0.5H), 5.52 (s, 0.5H), 4.87 – 4.79 (m, 2H), 4.77 – 4.66 (m, 2H), 4.63 – 4.47 (m, 2H), 4.31 – 4.22 (m, 1H), 4.17 – 3.82 (m, 5H), 3.52 – 3.39 (m, 1H), 2.87 – 2.50 (m, 4H), 2.41 – 2.13 (m, 4H), 1.53 (t, J = 6.9 Hz, 3H), 1.11 (d, J = 6.5 Hz, 3H).
401		LCMS m/z [M+1]: 762.2 1H NMR (400 MHz, CD3OD) δ 8.29 (d, J = 12.4 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.07 – 6.98 (m, J = 9.4, 8.5 Hz, 1H), 5.62 (s, 0.5 H), 5.50 (s, 0.5 H), 5.09 – 4.96 (m, 1H), 4.72 (d, J = 12.8 Hz, 1H), 4.61 – 4.49 (m, 1H), 4.28 – 4.18 (m, 1H), 4.10 – 3.86 (m, 7H), 3.70 – 3.40 (m, J = 22.1, 15.6, 9.3, 5.3 Hz, 3H), 2.63 – 2.37 (m, 7H), 2.34 (d, J = 6.8 Hz, 2H), 2.14 (d, J = 21.7 Hz, 1H), 1.55 – 1.45 (m, J = 15.6, 7.0 Hz, 3H), 1.24 (dt, J = 19.1, 9.5 Hz, 3H).

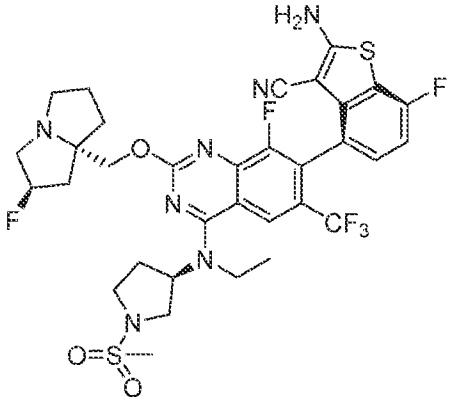
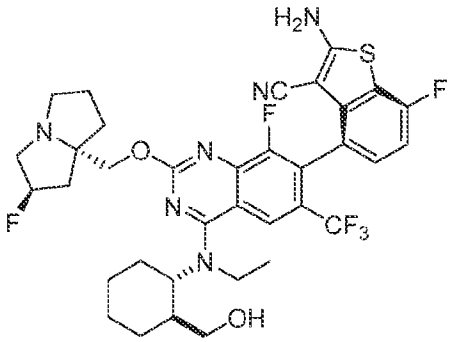
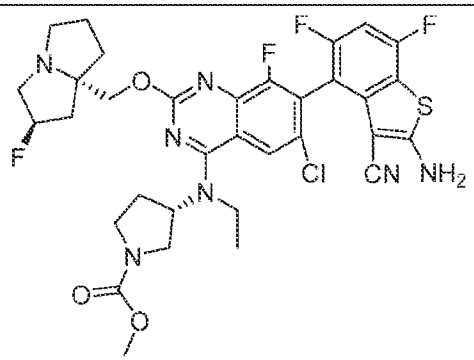
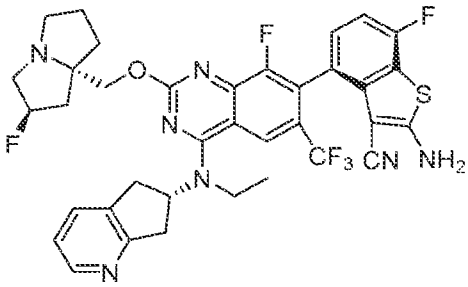
Cmpd. No.	Structure	Analytical Data
402		LCMS m/z [M+1]: 762.2 1H NMR (400 MHz, CD3OD) δ 8.29 (d, J = 12.4 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.07 – 6.98 (m, J = 9.4, 8.5 Hz, 1H), 5.62 (s, 0.5 H), 5.50 (s, 0.5 H), 5.09 – 4.96 (m, 1H), 4.72 (d, J = 12.8 Hz, 1H), 4.61 – 4.49 (m, 1H), 4.28 – 4.18 (m, 1H), 4.10 – 3.86 (m, 7H), 3.70 – 3.40 (m, J = 22.1, 15.6, 9.3, 5.3 Hz, 3H), 2.63 – 2.37 (m, 7H), 2.34 (d, J = 6.8 Hz, 2H), 2.14 (d, J = 21.7 Hz, 1H), 1.55 – 1.45 (m, J = 15.6, 7.0 Hz, 3H), 1.24 (dt, J = 19.1, 9.5 Hz, 3H).
403		LCMS m/z [M+1]: 803.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.28 – 7.21 (m, J = 8.3, 5.0 Hz, 1H), 7.06 – 6.97 (m, 1H), 5.62 (s, 0.5H), 5.49 (s, 0.5H), 4.70 – 4.50 (m, 3H), 4.31 – 4.23 (m, J = 6.6 Hz, 1H), 4.11 – 3.86 (m, 7H), 3.77 – 3.67 (m, 2H), 3.56 – 3.51 (m, 1H), 3.50 – 3.42 (m, 1H), 2.75 – 2.56 (m, 2H), 2.47 – 2.16 (m, 6H), 1.52 – 1.44 (m, J = 7.0 Hz, 3H), 1.33 (d, J = 6.5 Hz, 3H).
404		LCMS m/z [M+1]: 701.2

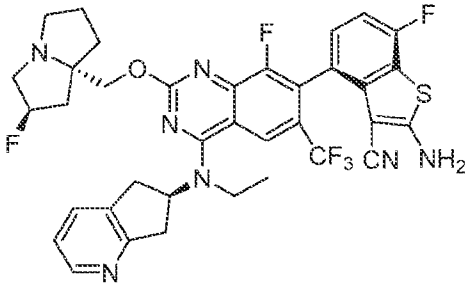
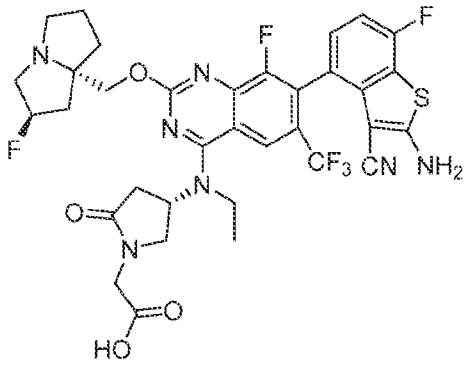
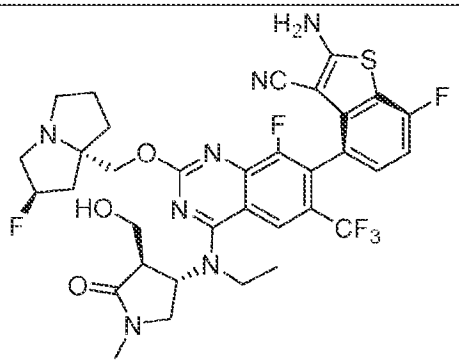
Cmpd. No.	Structure	Analytical Data
405		LCMS m/z [M+1]: 762.2 1H NMR (400 MHz, CD3OD) δ8.22 (s, 1H), 7.25 – 7.20 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 5.57 (d, J = 51.6 Hz, 1H), 5.37 – 5.31 (m, 1H), 4.81 – 4.73 (m, 2H), 4.50 – 4.41 (m, 1H),4.22 (s, 2H), 3.97 – 3.86 (m, 5H), 3.76 (s, 3H),3.49 – 3.44 (m, 1H), 3.23 – 3.11 (m, 1H), 2.93 – 2.84 (m, 1H), 2.80 – 2.48 (m, 2H), 2.43 – 2.47 (m, 3H), 2.22 – 2.16 (m, 1H), 2.06– 2.00 (m, 1H), 1.57 (t, J = 6.8 Hz, 3H).
406		LCMS m/z [M+1]: 756.3 1H NMR (400 MHz, CD3OD) δ 8.31 (s, 1H), 8.08 (s, 1H), 7.55 (d, J = 1.1 Hz, 1H), 7.25 (dd, J = 8.3, 5.0 Hz, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.33 – 5.53 (m, 1H), 4.82 (d, J = 9.7 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 4.15 – 4.30 (m, 2H), 3.68 – 4.12 (m, 6H), 3.35 – 4.12 (m, 1H), 2.78 – 2.88 (m, 1H), 2.65 – 2.72 (m, 1H), 2.32 – 2.58 (m, 2H), 2.09 – 2.17 (m, 2H), 1.78 – 1.85 (m, 1H), 1.60 – 1.69 (m, 4H).
407		LCMS m/z [M+1]: 748.3 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.23 – 7.20 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 5.59 (d, J = 52.4 Hz, 1H), 4.72 – 4.48 (m, 2H), 4.21 – 3.81 (m, 10H), 3.47 – 3.42 (m, 1H), 3.18 – 3.10 (m, 1H), 2.91 – 2.15 (m, 7H), 1.59 – 1.55 (m, 3H).

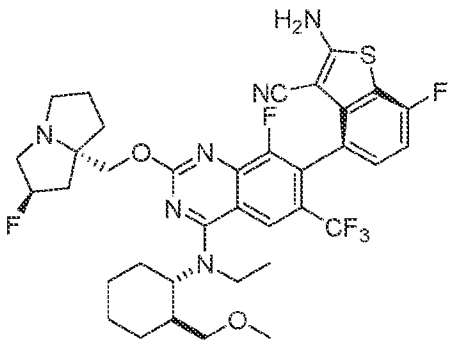
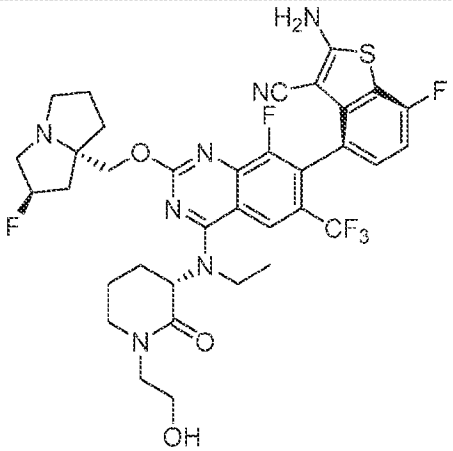
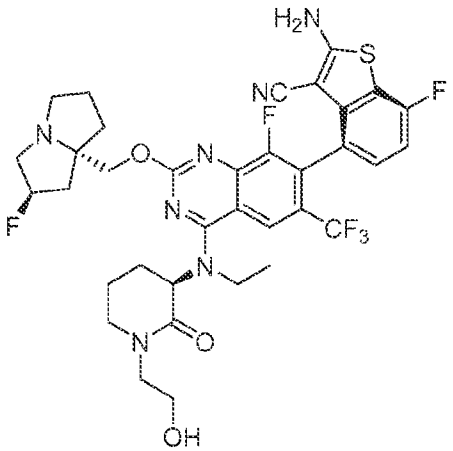
Cmpd. No.	Structure	Analytical Data
408		LCMS m/z [M+1]: 773.3 1H NMR (400 MHz, CD3OD) δ 8.74 (s, 1H), 8.30 (s, 1H), 7.76 (s, 1H), 7.19 – 7.28 (m, 1H), 7.00 – 7.05(m, 1H), 5.29 – 5.48 (m, 1H), 4.36 – 4.47 (m, 1H), 4.01 – 4.29 (m, 6H), 3.61 – 3.88 (m, 3H), 3.40 – 3.52 (m, 1H), 2.72 – 2.88 (m, 2H), 2.28 – 2.49 (m, 2H).1.91 – 2.20 (m, 3H), 1.63 – 1.74 (m, 4H).
409		LCMS m/z [M+1]: 723.2 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 7.29 (s, 2H), 7.24 (d, J = 3.5 Hz, 3H), 7.03 (t, J = 8.9 Hz, 1H), 5.49 (d, J = 51.8 Hz, 1H), 5.07 (t, J = 7.2 Hz, 1H), 4.11 (d, J = 12.2 Hz, 1H), 4.04-3.92(m, 3H), 3.89 – 3.62 (m, 4H), 3.52-3.33 (m, 3H), 2.59 – 2.34 (m, 2H), 2.28-2.00 (m, 3H), 1.95-1.81 (m, 2H), 1.57 (t, J = 7.0 Hz, 3H).
410		LCMS m/z [M+1]: 756.3 1H NMR (400 MHz, CD3OD) δ 8.31 (s, 1H), 7.70 (dd, J = 5.2, 2.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 6.88 (d, J = 2.2 Hz, 1H), 5.42 (d, J = 51.3 Hz, 1H), 4.82 – 4.76 (m, 2H), 4.41 – 4.25 (m, 2H), 4.13 – 3.94 (m, 4H), 3.86 – 3.60 (m, 3H), 2.89 – 2.79 (m, 1H), 2.74 – 2.53 (m, 2H), 2.49 – 2.17 (m, 3H), 2.11 – 1.98 (m, 2H), 1.70 (t, J = 7.0 Hz, 3H).
411		LCMS m/z [M+1]: 754.3 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.62 (d, J = 6.7 Hz, 1H), 7.24 (dd, J = 8.2, 5.1 Hz, 1H), 7.03 (t, J = 8.9 Hz, 1H), 6.46 (d, J = 6.8 Hz, 1H), 5.51 (d, J = 51.6 Hz, 1H), 5.14 (t, J = 7.6 Hz, 1H), 4.40 (d, J = 12.2 Hz, 1H), 4.26 (d, J = 12.2 Hz, 1H), 4.02 – 3.81 (m, 5H), 3.61 (s, 3H), 3.58 – 3.51 (m, 1H), 3.49 – 3.32 (m,

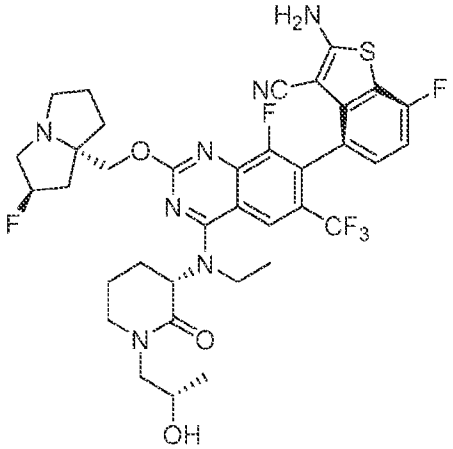
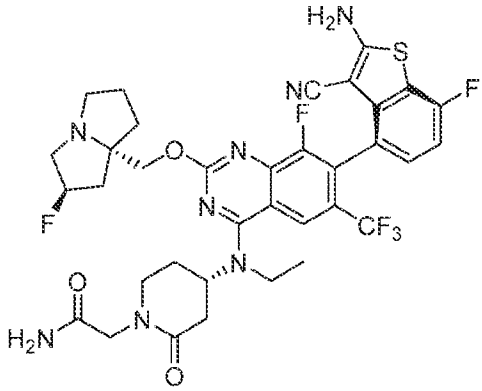
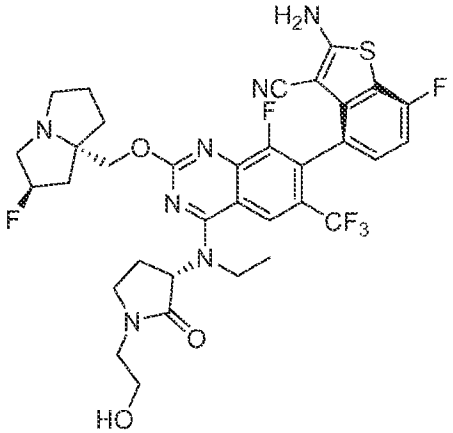
Cmpd. No.	Structure	Analytical Data
		4H), 2.62 – 2.46 (m, 2H), 2.32 – 2.22 (m, 2H), 2.11 – 1.95 (m, 2H), 1.54 (t, J = 7.0 Hz, 3H).
412		LCMS m/z [M+1]: 754.3 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.59 (d, J = 6.8 Hz, 1H), 7.22 (dd, J = 8.1, 4.9 Hz, 1H), 7.01 (t, J = 8.9 Hz, 1H), 6.43 (d, J = 6.8 Hz, 1H), 5.33 (d, J = 53.6 Hz, 1H), 5.11 – 5.03 (m, 1H), 4.07 – 3.97 (m, 2H), 3.94 – 3.84 (m, 2H), 3.63 – 3.57 (m, 3H), 3.57 – 3.35 (m, 5H), 3.29 – 3.21 (m, 2H), 3.14 – 3.07 (m, 1H), 2.37 – 2.20 (m, 2H), 2.08 – 1.79 (m, 4H), 1.54 (t, J = 7.0 Hz, 3H).
413		LCMS m/z [M+1]: 816.26 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.28 – 7.19 (m, J = 8.4, 5.0 Hz, 1H), 7.05 – 6.98 (m, 1H), 5.49 (s, 0 .5H), 5.39 – 5.30 (m, J = 12.5, 7.8 Hz, 1.5H), 4.50 (d, J = 11.5 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 4.19 (t, J = 6.6 Hz, 1H), 4.05 (s, 2H), 3.95 – 3.89 (m, J = 14.7, 7.0 Hz, 1H), 3.76 (d, J = 6.2 Hz, 3H), 3.73 – 3.43 (m, 8H), 2.43 – 2.34 (m, 2H), 2.33 – 2.27 (m, 2H), 2.21 – 2.16 (m, 2H), 2.03 (d, J = 5.7 Hz, 2H), 1.42 (t, J = 6.9 Hz, 3H), 1.34 (s, 3H).
414		LCMS m/z [M+1]: 690.22 1H NMR (400 MHz, CD3OD) δ 8.54 (s, 1H), 7.24 – 7.17 (m, J = 8.2, 5.1 Hz, 1H), 7.05 – 6.96 (m, 1H), 5.46 (s, 0.5H), 5.33 (s, 0.5H), 4.64 – 4.53 (m, J = 16.8, 8.7 Hz, 1H), 4.53 – 4.40 (m, J = 13.5, 6.4 Hz, 2H), 4.36 (d, J = 11.2 Hz, 1H), 3.92 – 3.69 (m, J = 35.5, 14.1, 7.0 Hz, 2H), 3.48 (s, 2H), 3.20 – 3.08 (m, 2H), 2.50 – 2.30 (m, 2H), 2.27 – 2.19 (m, 1H), 2.15 – 1.93 (m, 6H),

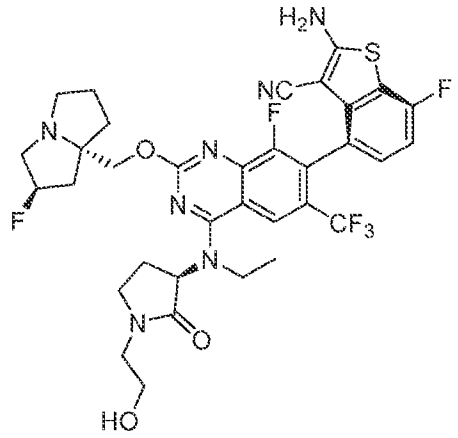
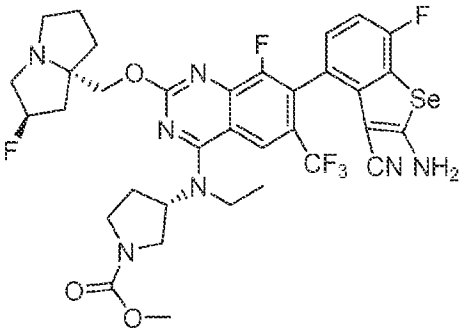
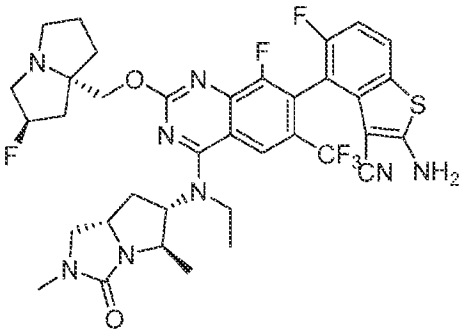
Cmpd. No.	Structure	Analytical Data
		1.87 – 1.77 (m, 2H), 1.65 – 1.58 (m, J = 12.6, 8.1 Hz, 1H), 1.44 (t, J = 6.9 Hz, 3H).
415		LCMS m/z [M+1]: 693.1 1H NMR (400 MHz, CD3OD) δ 8.54 (d, J = 12.0 Hz, 1H), 7.24 – 7.20 (m, J = 8.4, 4.6 Hz, 1H), 7.01 (t, J = 8.9 Hz, 1H), 5.47 (s, 0.5H), 5.34 (s, 0.5H), 4.80 (dt, J = 9.6, 4.5 Hz, 2H), 4.54 (d, J = 11.3 Hz, 0.5H), 4.46 (s, 1H), 4.38 (d, J = 11.3 Hz, 0.5H), 4.31 – 4.23 (m, 1H), 4.20 – 4.12 (m, J = 9.7, 6.4 Hz, 1H), 4.07 – 3.94 (m, J = 21.7, 12.1, 6.0 Hz, 2H), 3.90 – 3.81 (m, J = 14.3, 7.0 Hz, 1H), 3.67 – 3.46 (m, 4H), 3.23 – 3.14 (m, J = 15.1, 9.9 Hz, 1H), 2.51 – 2.34 (m, J = 23.5, 15.1, 10.7 Hz, 2H), 2.28 – 2.21 (m, 1H), 2.16 – 2.08 (m, J = 15.3, 7.8 Hz, 2H), 2.04 – 1.96 (m, 1H), 1.47 – 1.42 (m, 3H).
416		LCMS m/z [M+1]: 762.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.24-7.19 (m, 1H), 7.01 (t, 1H), 5.36 (s, 0.5H), 5.23 (s, 0.5H), 4.31 (d, 1H), 4.15 (d, 1H), 4.11-4.05 (m, 1H), 3.96 (s, 1H), 3.82-3.75 (m, 1H), 3.56-3.40 (m, 3H), 3.38-3.31 (m, 3H), 3.25-3.21 (m, 1H), 3.04 (s, 1H), 2.60 (s, 1H), 2.34-1.85 (m, 10H), 1.66-1.53 (m, 3H), 1.18 (d, 3H).

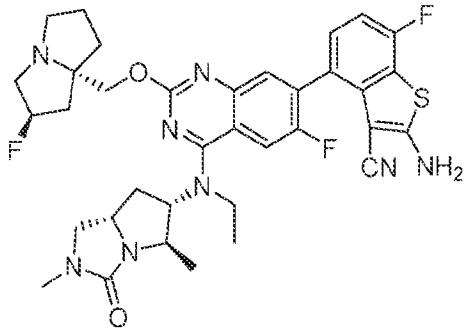
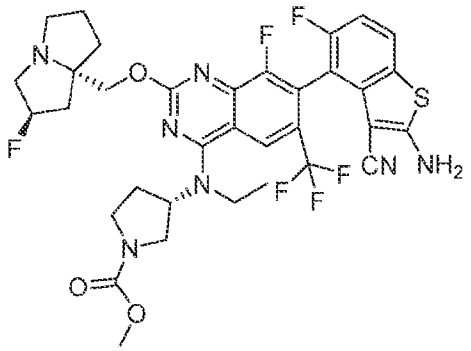
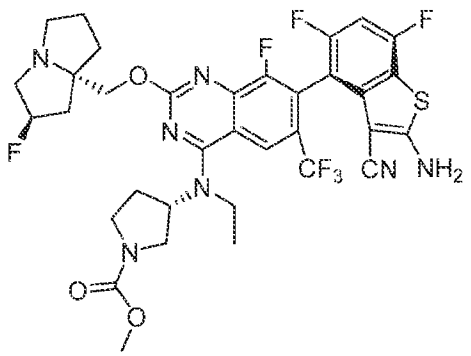
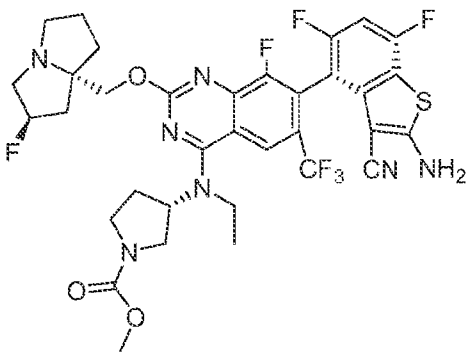
Cmpd. No.	Structure	Analytical Data
417		LCMS m/z [M+1]: 754.1 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.25-7.18 (m, 1H), 7.01 (t, 1H), 5.44-5.38 (m, 0.5H), 5.31-5.25 (m, 0.5H), 5.01-4.92 (m, 1H), 4.41-4.27 (m, 2H), 3.99-3.68 (m, 4H), 3.62-3.54 (m, 1H), 3.48-3.31 (m, 4H), 3.14-3.05 (m, 1H), 2.95 (s, 3H), 2.61-2.52 (m, 1H), 2.48-2.18 (m, 4H), 2.08-1.89 (m, 3H), 1.47 (t, 3H).
418		LCMS m/z [M+1]: 719.3 1H NMR (400 MHz, CD3OD) δ 8.31 (s, 1H), 7.19-7.23 (m, 1H), 7.02 (t, 1H), 5.36 (s, 0.5H), 5.23 (s, 0.5H), 4.66-4.82 (m, 2H), 4.29-4.41 (m, 2H), 3.54-3.75 (m, 1H), 3.12-3.26 (m, 5H), 2.93-3.04 (m, 3H), 2.12-2.32 (m, 5H), 1.96-2.02 (m, 3H), 1.85-1.89 (m, 3H), 1.66-1.75 (m, 2H), 1.42-1.47 (m, 3H).
419		LCMS m/z [M+1]: 718.3 1H NMR (400 MHz, CD3OD): δ 8.02 (s, 1H), 6.99 (t, J = 9.6 Hz, 1H), 5.56 (d, J = 52.2Hz, 1H), 5.05 - 4.97 (m, 1H), 4.71 - 4.57 (m, 2H), 4.06 - 3.75 (m, 10H), 3.61 - 3.44 (m, 1H), 2.76 - 2.53 (m, 2H), 2.40 - 2.31 (m, 5H), 2.20 - 2.15 (m, 3H), 1.41 (t, J = 6.6 Hz, 3H).
420		LCMS m/z [M+1]: 724.1 1H NMR (400 MHz, CD3OD) δ 8.35 (d, J = 4.6 Hz, 1H), 8.23 (s, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.30 – 7.19 (m, 2H), 7.04 – 6.98 (m, 1H), 5.21 (d, J = 55.2 Hz, 1H), 5.10 – 5.04 (m, 1H), 3.95 – 3.88 (m, 2H), 3.86 – 3.73 (m, 3H), 3.70 – 3.64 (m, 1H), 3.52 – 3.40 (m, 3H), 3.10 (dd, J = 11.8, 3.9 Hz, 2H), 2.95 – 2.88 (m, 1H), 2.10 – 1.98

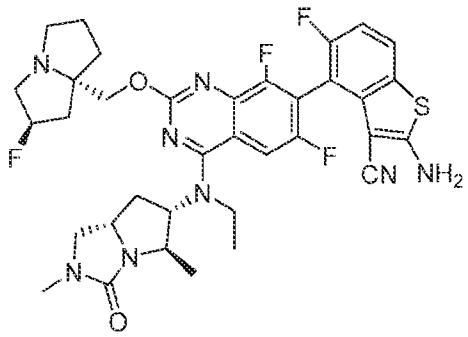
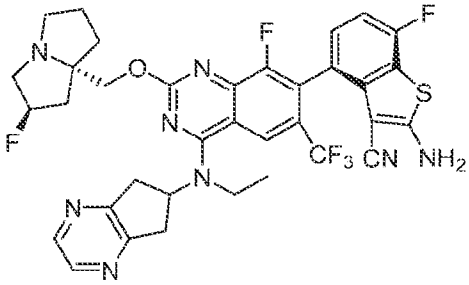
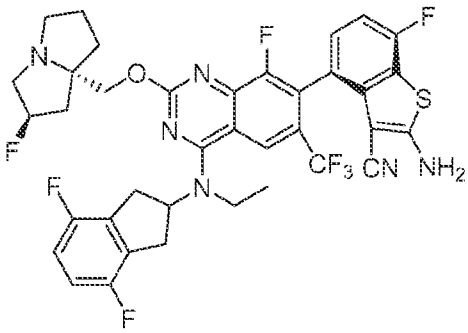
Cmpd. No.	Structure	Analytical Data
		(m, 2H), 1.91 – 1.79 (m, 2H), 1.75 – 1.66 (m, 2H), 1.55 (t, J = 7.0 Hz, 3H).
421		LCMS m/z [M+1]: 724.1 1H NMR (400 MHz, CD3OD) δ 8.35 (d, J = 4.9 Hz, 1H), 8.24 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.29 – 7.19 (m, 2H), 7.04 – 6.98 (m, 1H), 5.19 (d, J = 52.6 Hz, 2H), 3.94 – 3.60 (m, 7H), 3.51 – 3.44 (m, 2H), 3.16 – 3.10 (m, 2H), 2.97 – 2.88 (m, 1H), 2.12 – 2.02 (m, 2H), 1.92 – 1.74 (m, 4H), 1.54 (t, J = 7.0 Hz, 3H).
422		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.26 – 7.19 (m, 1H), 7.02 (t, J = 8.4 Hz, 1H), 5.56 (d, J = 52.8 Hz, 1H), 5.34 (t, J = 4.4 Hz, 1H), 4.78 – 4.76 (m, 1H), 4.46 – 4.38(m, 1H), 4.26 – 4.06 (m, 2H), 3.97 – 3.89 (m, 4H), 3.49 – 3.47 (m, 1H), 3.14 – 3.11 (m, 1H), 2.92- 2.83 (m, 1H), 2.80 – 2.48 (m, 2H), 2.46 – 2.24 (m, 3H), 2.18 (t, J = 7.6 Hz, 2H), 2.06 – 2.00 (m, 2H), 1.58 (t, J = 6.8 Hz, 3H).
423		LCMS m/z [M+1]: 734.1 1H-NMR (400 MHz, CD_3OD): 8.21 (s, 1 H), 7.18-7.25 (m, 1 H), 6.98-7.05 (m, 1 H), 5.55 (s, 0.5 H), 5.42 (s, 0.5 H), 4.54-4.67 (m, 1 H), 4.22-4.42 (m, 2 H), 3.52-4.08 (m, 9 H), 3.22-3.29 (m, 2 H), 2.95 (s, 3 H), 2.67-2.28 (m, 3 H), 2.01-2.22 (m, 3 H), 1.63 (t, J=7 Hz, 3 H).

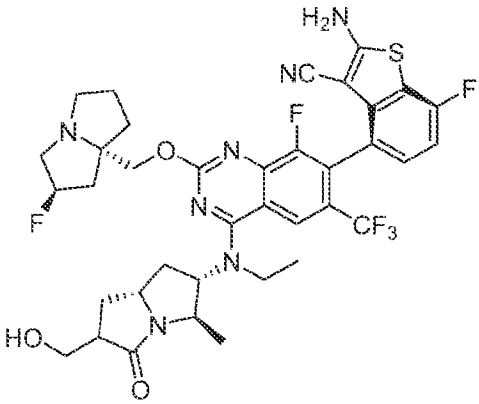
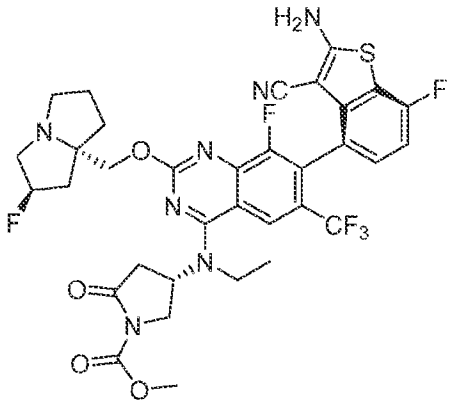
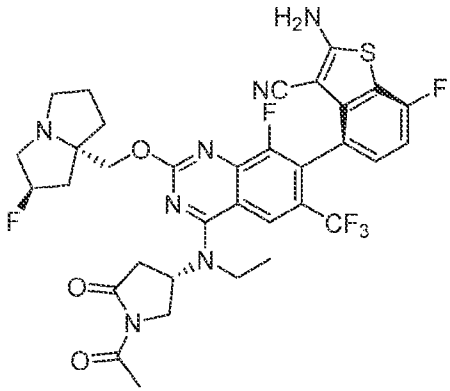
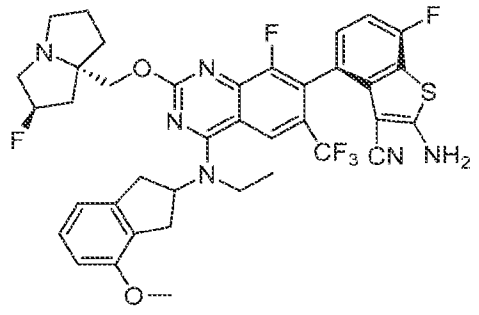
Cmpd. No.	Structure	Analytical Data
424		LCMS m/z [M+1]:733.3 1H NMR (400 MHz, CD3OD) δ 8.10 (d, 1H), 7.18-7.27 (m, 1H), 6.97-7.03 (m, 1H), 5.36 (s, 0.5H), 5.23 (s, 0.5H), 4.19-4.39 (m, 4H), 3.40-3.47 (m, 1H), 3.19-3.24 (m, 3H), 2.98-3.09 (m, 3H), 2.93 (s, 1H), 2.76 (s , 2H), 2.27-2.37 (m, 1H), 2.12-2.24 (m, 3H), 1.89-2.01 (m, 6H), 1.74-1.82 (m, 2H), 1.28-1.38 (m, 6H).
425		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.27-7.20 (m, 1H), 7.03 (t, 1H), 5.59 (s, 0.5H), 5.46 (s, 0.5H), 4.83-4.78 (m, 1H), 4.75-4.65 (m, 1H), 4.62-4.55 (m, 1H), 4.07-3.80 (m, 5H), 3.78-3.63 (m, 3H), 3.61-3.40 (m, 4H), 2.69-2.50 (m, 3H), 2.45-2.27 (m, 3H), 2.24-2.18 (m, 1H), 2.13-2.00 (m, 3H), 1.64-1.53 (m, 3H).
426		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.24-7.17 (m, 1H), 7.02 (t, 1H), 5.61 (s, 0.5H), 5.48 (s, 0.5H), 4.86-4.83 (m, 1H), 4.73 (d, 1H), 4.57-4.52 (m, 1H), 4.10-3.85 (m, 5H), 3.79-3.68 (m, 3H), 3.57-3.41 (m, 4H), 2.69-2.51 (m, 3H), 2.47-2.29 (m, 3H), 2.24-2.17 (m, 1H), 2.11-2.00 (m, 3H), 1.64-1.55 (m, 3H).

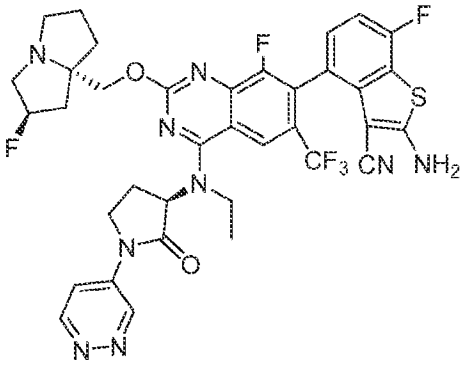
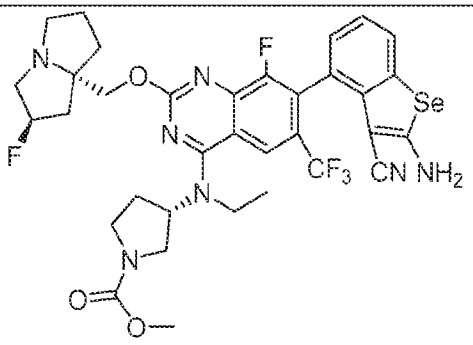
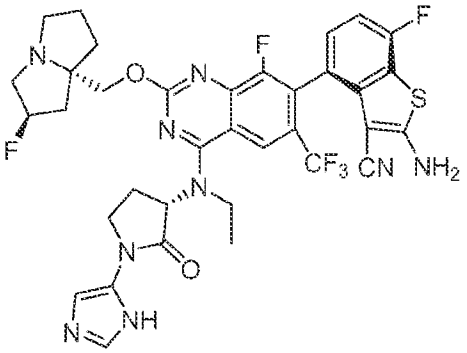
Cmpd. No.	Structure	Analytical Data
427		LCMS m/z [M+1]: 762.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.26-7.20 (m, 1H), 7.02 (t, 1H), 5.54 (s, 0.5H), 5.41 (s, 0.5H), 4.58-4.46 (m, 2H), 4.12-3.94 (m, 3H), 3.78-3.70 (m, 2H), 3.67-3.56 (m, 3H), 3.39-3.31 (m, 3H), 3.14-3.08 (m, 1H), 2.61-2.44 (m, 3H), 2.36-2.17 (m, 4H), 2.10-1.99 (m, 3H), 1.66-1.54 (m, 3H), 1.19 (d, 3H).
428		LCMS m/z [M+1]: 761.2 1H NMR (400 MHz, CD3OD): 8.21 (s, 1H), 7.20-7.22 (m, 1H), 7.03-7.07(m, 1H), 5.34-5.49 (m, 2H), 4.08-4.24 (m, 4H), 3.86-3.89 (m, 2H), 3.49-3.57 (m, 3H),3.25-3.31 (m, 4H), 3.03-3.20 (m, 2H), 2.61-2.89 (m, 1H), 2.20-2.25 (m, 1H), 2.32-2.16 (m, 1H), 2.04-2.13 (m, 1H), 14.83-1.97 (m, 3H), 1.49-1.53(m, 3H).
429		LCMS m/z [M+1]: 734.1 1H NMR (400 MHz, CD3OD): 8.31 (s, 1H), 7.25-7.22 (m, 1H), 705-7.00(m, 1H), 5.61-5.59 (m, 0.5H), 5.48-5.46 (m, 0.5H), 5.34 (t, 1H), 4.67-4.64 (m, 1H), 4.58-4.55 (m, 1H), 4.08-3.96 (m, 2H), 3.91-3.84 (m, 3H), 3.78-3.75 (m, 1H), 3.74-3.70 (m, 1H), 3.60-3.55 (m, 1H), 3.48-3.43 (m, 1H), 3.42-3.36 (m, 1H), 3.23-3.19(m, 1H), 2.69-2.52 (m, 4H), 2.42-2.28 (m, 3H), 2.03-2.02 (m, 1H), 1.56 (t, 3H).

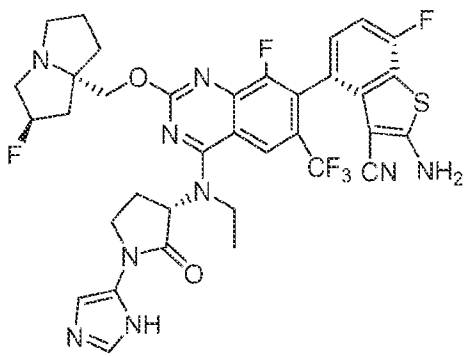
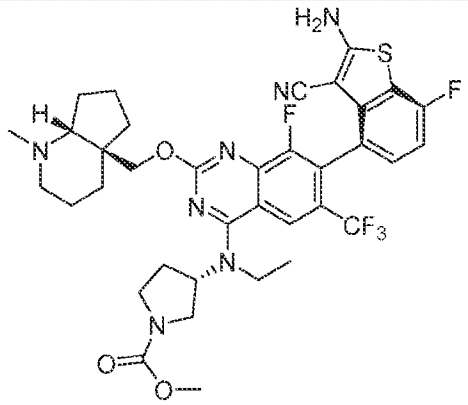
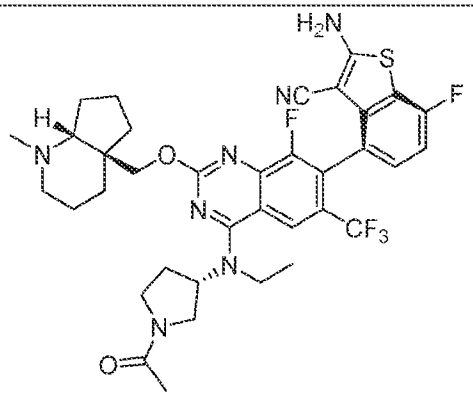
Cmpd. No.	Structure	Analytical Data
430		LCMS m/z [M+1]: 734.3 1H NMR (400 MHz, CD3OD) : 8.33 (s, 1H),7.22-7.17 (m, 1H), 7.04-6.99 (m, 1H), 5.62-5.61 (m, 0.5H), 5.49-5.48 (m, 0.5H), 5.34 (t, 1H), 4.81-4.78 (m, 1H), 4.69 (t,1H), 4.52-4.49 (m, 1H), 4.10-4.02 (m, 1H), 3.94-3.87 (m, 3H), 3.78-3.57 (m, 4H), 3.50-3.36 (m,2H), 3.23-3.21 (m,1H), 2.66-2.52 (m, 3H), 2.44-2.29 (m, 3H), 2.05-2.00(m, 2H), 1.61-1.53 (m, 3H).
431		LCMS m/z [M+1]: 782.1 1H NMR (400 MHz, CD3OD): δ 8.27 (s, 1H), 7.23 - 7.19 (m, 1H), 6.98 (t, J = 8.4 Hz, 1H), 5.62 (d, J = 53.2 Hz, 1H), 5.08 - 5.00 (m, 1H), 4.69 - 4.58 (m, 2H), 4.06 - 3.79 (m, 7H), 3.64 - 3.53 (m, 1H), 3.49 - 3.42 (m, 2H), 2.71 - 2.33 (m, 8H), 2.20 - 2.14 (m, 1H), 1.50 - 1.46 (m, 3H), 1.33 - 1.29 (m, 2H).
432		LCMS m/z [M+1]: 759.2 1H NMR (400 MHz,CD3OD) δ 8.29 – 8.25 (m, 1H), 7.70 (dd, J = 8.6, 4.7 Hz, 1H), 7.04 (t, J = 9.2 Hz, 1H), 5.50 (d, J = 52.0 Hz,1H), 4.66 – 4.60 (m, 2H), 4.28 – 4.22 (m, 1H), 4.02 – 3.87 (m, 5H), 3.76 – 3.69 (m, 1H), 3.61 (t, J = 9.0 Hz, 1H), 3.49 – 3.44 (m, 2H), 2.86 (s, 3H), 2.62 – 2.57 (m, 1H), 2.45 – 2.30 (m, 4H), 2.16 – 2.04 (m, 2H), 1.35 – 1.29 (m, 6H).

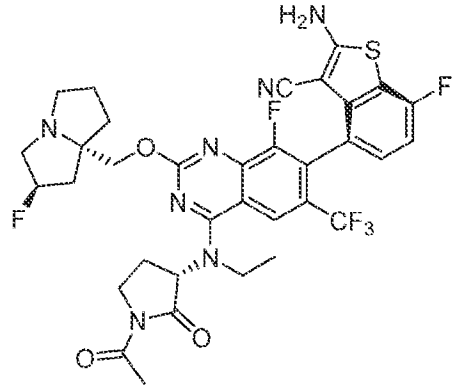
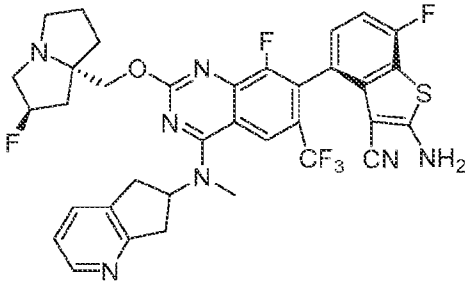
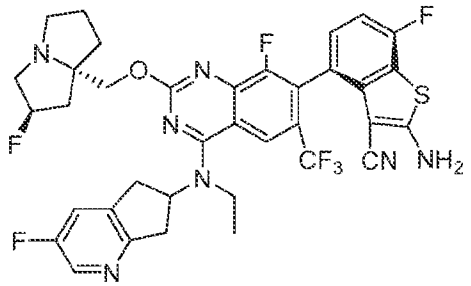
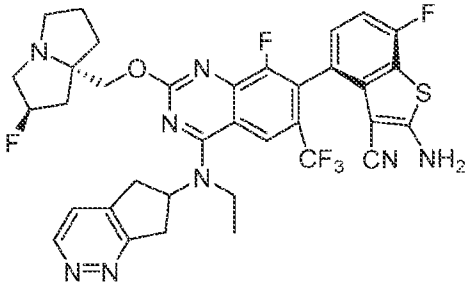
Cmpd. No.	Structure	Analytical Data
433		LCMS m/z [M+1]: 691.2 1H NMR (400 MHz, CD3OD) δ 7.69 - 7.78 (m, 1H), 7.62 (d, J = 7 Hz, 1H), 7.24 - 7.30 (m, 1H), 7.02 (t, J = 9.3 Hz, 1H), 5.49 (d, J = 53.6 Hz, 1H), 4.36 – 4.70(m, 3H), 3.85 – 4.15 (m, 3H), 3.42 – 3.76 (m, 6H), 2.75 – 2.88 (m, 3H), 2.02 – 2.54 (m, 7H), 1.14 – 1.53(m, 6H).
434		LCMS m/z [M+1]: 734.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.68 (dd, J = 8.7, 4.7 Hz, 1H), 7.03 (t, J = 9.1 Hz, 1H), 5.44 (d, J = 53.0 Hz, 1H), 5.08 – 4.98 (m, 1H), 4.53 – 4.40 (m, 2H), 3.97 – 3.68 (m, 7H), 3.72– 3.58 (m, 5H), 3.27 – 3.19 (s, 1H), 2.56 – 2.33 (m, 4H), 2.30 – 2.23 (m, 1H), 2.21 – 2.10 (m, 2H), 2.07 – 1.97 (s, 1H), 1.51 – 1.41 (m, 3H).
435		LCMS m/z [M+1]: 752.3 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 6.92-7.03 (m, 1H), 5.30 (d, J = 53.9 Hz, 1H), 4.95-5.07 (s, 1H), 4.20-4.33 (m, 2H), 3.68-3.98 (m, 7H), 3.53-3.64 (m, 1H), 3.37-3.49 (m, 1H), 3.10-3.25 (m, 3H), 2.92-3.07 (m, 1H), 2.06-2.53 (m, 5H), 1.81-2.05 (m, 3H), 1.38-1.51 (t, J = 6.9 Hz, 3H).
436		LCMS m/z [M+1]: 752.3 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 6.95 (t, J = 9.6 Hz, 1H), 5.29 (d, J = 53.9 Hz, 1H), 4.98-5.06 (m, 1H), 4.19-4.33 (m, 2H), 3.69-3.95 (m, 7H), 3.52-3.64 (m, 1H), 3.38-3.50 (m, 1H), 3.13-3.26 (m, 3H), 2.93-3.06 (m, 1H), 2.08-2.52 (m, 5H), 1.84-2.05 (m, 3H), 1.38-1.48 (m, 3H).

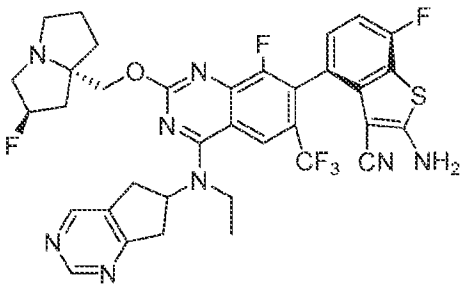
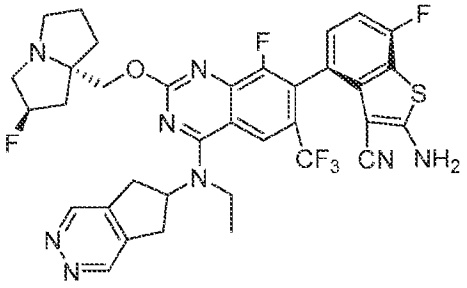
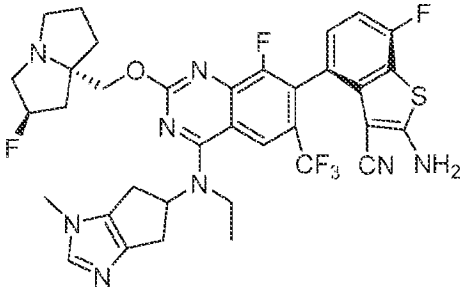
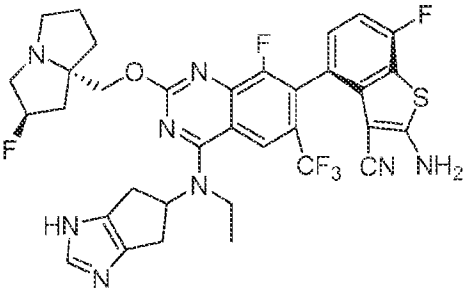
Cmpd. No.	Structure	Analytical Data
437		LCMS m/z [M+1]: 710.2 1H.NMR (400 MHz, CD3OD) δ 7.76 – 7.65 (m, 2H), 7.07 (t, J = 9.1 Hz, 1H), 5.55 (d, J = 52.2 Hz, 1H), 4.70 – 4.57 (m, 2H), 4.19 – 3.85 (m, 6H), 3.65 – 3.60 (m, 1H), 3.48 – 3.45 (m, 1H), 3.38 – 3.34 (m, 1H), 3.21 (q, J = 7.55 Hz, 1H), 2.86 (s, 2H), 2.70 – 2.55 (m, 2H), 2.47 – 2.27 (m, 5H), 2.15 – 2.06 (m, 1H), 1.40 – 1.27 (m, 6H).
438		LCMS m/z [M+1]: 725.4 1H NMR (400 MHz, CD3OD): δ 8.42 (s, 2H), 8.18 (s, 1H), 7.28-7.21 (m, 1H),7.05-7.00 (m, 1H), 5.48 (d, J = 51.2Hz, 1H), 5.08 - 5.00 (m, 1H), 4.21 - 4.18 (m, 1H), 4.04 - 3.95 (m, 3H), 3.86 - 3.54 (m, 7H), 3.40 - 3.33 (m, 1H), 2.48 - 2.41 (m, 2H), 2.29 - 2.15 (m, 2H), 2.04 - 1.85 (m, 2H), 1.64 (t, J = 7.2 Hz, 3H).
439		LCMS m/z [M+1]: 759.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.23 (dd, J = 8.2, 5.0 Hz, 1H), 7.02 (dd, J = 13.8, 7.6 Hz, 3H), 5.50 (d, J = 51.6 Hz, 1H), 5.18 – 5.11 (m, 1H), 4.21 (d, J = 12.0 Hz, 1H), 4.11 (d, J = 12.1 Hz, 1H), 3.99 – 3.77 (m, 5H), 3.71 – 3.61 (m, 2H), 3.55 – 3.47 (m, 2H), 3.43 – 3.35 (m, 1H), 2.62 – 2.43 (m, 2H), 2.29 – 2.15 (m, 2H), 2.01 – 1.87 (m, 2H), 1.59 (t, J = 7.0 Hz, 3H).

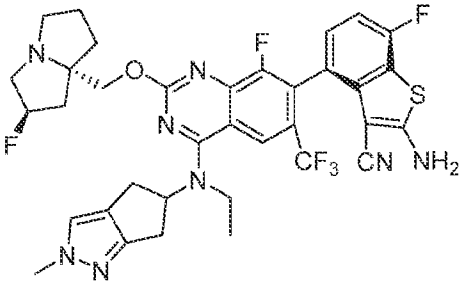
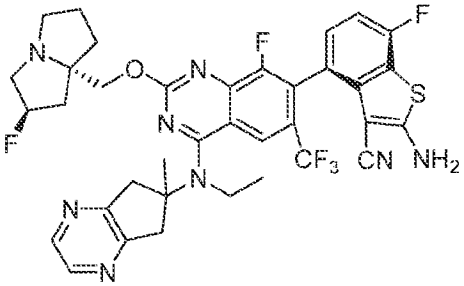
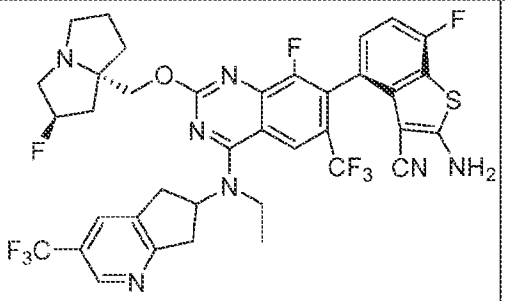
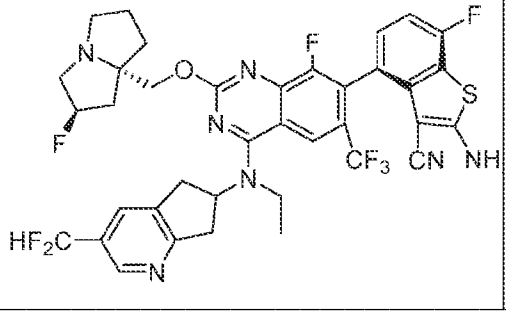
Cmpd. No.	Structure	Analytical Data
440		LCMS m/z [M+1]: 774.3 1HNMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.30 – 7.19 (m, 1H), 7.02 (m, 1H), 5.41 (s, 0.5H), 5.28 (s, 0.5H), 4.61 – 4.49 (m, 1H), 4.49 – 4.35 (m, 1H), 4.36 – 4.14 (m, 3H), 4.03 – 3.69 (m, 4H), 3.53 – 3.37 (m, 2H), 3.16 – 3.03 (m, 1H), 2.91 – 2.74 (m, 1H), 2.51 – 1.86 (m, 11H), 1.52 (t, J = 7.0 Hz, 3H), 1.36 (d, J = 6.4 Hz, 3H).
441		LCMS m/z [M+1]: 748.1 1H NMR (400 MHz, CD3OD) : 8.17 (s, 1H), 7.22-7.19 (m, 1H), 7.03-6.99 (m, 1H), 5.53-5.34 (m, 1H), 4.56-4.50 (m, 1H), 4.37-4.25 (m, 3H), 4.04-4.00 (m, 1H), 3.89-3.80 (m, 5H), 3.75-3.61 (m, 1H), 3.55-3.43 (m, 2H), 3.22-3.15 (m, 1H), 3.01-2.92 (m, 2H), 2.56-2.42 (m, 1H), 2.33-2.25 (m, 1H), 2.20-2.17 (m, 1H), 2.14-2.07 (m, 2H), 2.03-1.95 (m, 1H), 1.62-1.55 (m, 3H).
442		LCMS m/z [M+1]: 732.2 1H NMR (400 MHz, CD3OD) : 8.18 (s, 1H), 7.23-7.19 (m, 1H), 7.03-6.99 (m, 1H), 5.42-5.29 (m, 1H), 4.61 (d, 1H), 4.40-4.19 (m, 4H), 4.05-4.01 (m, 1H), 3.88 (d, 2H), 3.12-3.08 (m, 3H), 2.57 (s, 3H), 2.40-2.15 (m, 4H), 2.06 (s, 2H), 1.92 (s, 2H), 1.57-1.54 (m, 3H).
443		LCMS m/z [M+1]: 753.3 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 7.23 (dd, J = 7.9, 5.6 Hz, 2H), 7.06 – 6.99 (m, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 5.50 (d, J = 51.5 Hz, 1H), 5.10 – 5.00 (m, 1H), 4.15 – 3.62 (m, 11H), 3.55 – 3.35 (m,

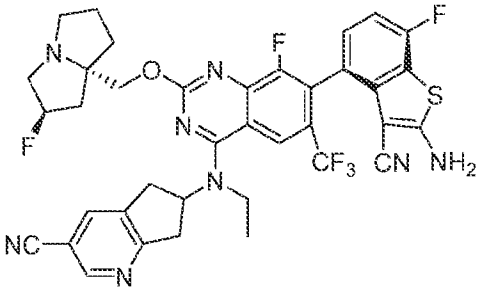
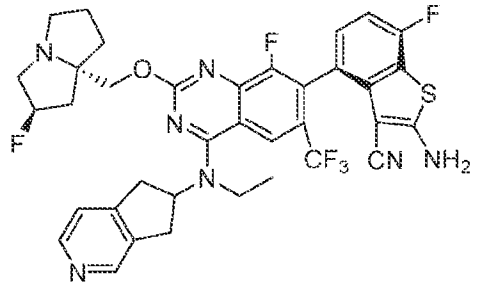
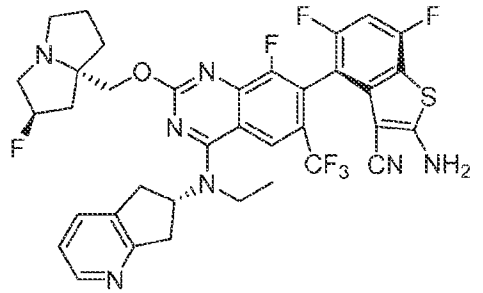
Cmpd. No.	Structure	Analytical Data
		4H), 2.57 – 2.36 (m, 2H), 2.27 – 2.09 (m, 2H), 1.96 – 1.84 (m, 2H), 1.61 – 1.53 (m, 3H).
444		LCMS m/z [M+1]: 768.3 1H NMR (400 MHz, CD3OD) δ 9.92 (d, J = 26.4 Hz, 1H), 9.17 (s, 1H), 8.32 (s, 1H), 8.08 – 7.98 (m, 1H), 7.28 – 7.22 (m, 1H), 7.03 (t, J = 9.2 Hz, 1H), 5.38 (d, J = 47.6 Hz, 1H), 4.49-- 4.39 (m, 1H), 4.25 – 4.00 (m, 4H), 3.92 – 3.60 (m, 3H), 2.87 – 2.67 (m, 2H), 2.60 – 2.24 (m, 3H), 2.22 – 1.90(m, 4H), 1.73 – 1.64 (m, 2H), 1.35 – 1.29(m, 3H).
445		LCMS m/z [M+1]: 764.2 1H NMR (400 MHz, CD3OD, ppm): δ 7.85-7.82 (m, 1H), 7.65-7.64 (m, 1H), 7.29-7.26 (m, 1H), 7.06-7.04 (m, 1H), 5.65-5.63 (m, 1H), 5.10-5.01 (m, 1H), 4.67-4.61 (m, 2H), 3.93-3.88 (m, 6H), 3.72-3.48 (m, 8H), 2.65-2.39 (m, 8H), 1.43-1.39 (m, 3H).
447		LCMS m/z [M+1]: 756.3 1H NMR (400 MHz, CD3OD) δ 8.31 (s, 1H), 7.90 (d, J = 16.0 Hz, 1H), 7.54 (s, 1H), 7.21 – 7.29 (m, 1H), 7.03 (t, J = 8.0 Hz, 1H), 5.32 – 5.55 (m, 1H), 4.18 – 4.47 (m, 3H), 3.91 – 4.16 (m, 4H), 3.64 – 3.87 (m, 3H), 3.34 – 3.41 (m, 1H), 2.74 – 2.89 (m, 1H), 2.61 – 2.74 (m, 1H), 2.30 – 2.58 (m, 2H), 1.91 – 2.24 (m, 3H), 1.73 – 1.80 (m, 1H), 1.68 (t, J = 8.0 Hz, 3H).

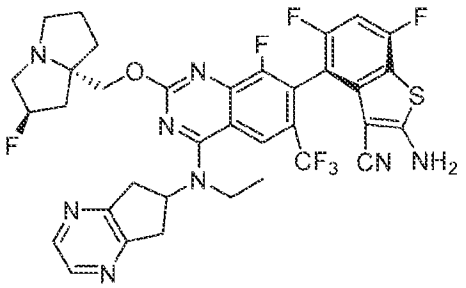
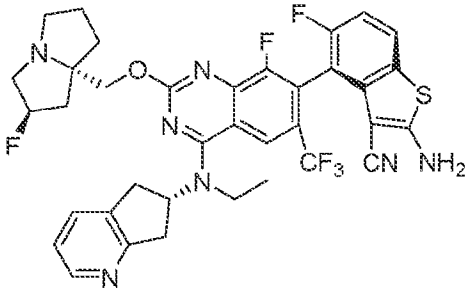
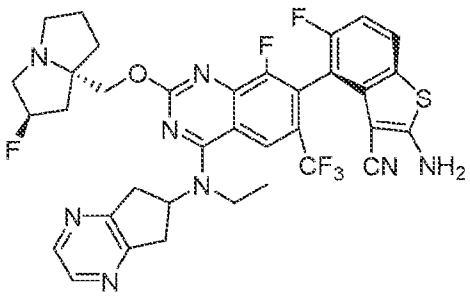
Cmpd. No.	Structure	Analytical Data
448		LCMS m/z [M+1]: 756.3 1H NMR (400 MHz, CD3OD) δ 8.32 (s, 1H), 7.88 (s, 1H), 7.53 (s, 1H), 7.17 – 7.24 (m, 1H), 7.02 (t, J = 8.0 Hz, 1H), 5.42 (d, J = 52.0 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 4.19 – 4.26 (m, 2H), 3.95 – 4.14 (m, 3H), 3.57 – 3.83 (m, 3H), 3.32 – 3.41 (m, 2H), 2.63 – 2.77 (m, 2H), 2.28 – 2.48 (m, 2H), 2.16 – 2.22 (m, 1H), 1.94– 2.07 (m, 2H), 1.74 – 1.83 (m, 1H), 1.67 (t, J = 8.0 Hz, 3H)
449		LCMS m/z [M+1]: 744.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.23 (dd, 1H), 7.04-6.99 (m, 1H), 5.01 (d, 1H), 4.38 (d, 2H), 3.87 (dd, 3H), 3.72 (d, 4H), 3.65 (s, 1H), 3.48-3.44 (m, 2H), 3.13 (s, 1H), 2.71 (d, 3H), 2.51-2.30 (m, 3H), 2.10 (s, 2H), 1.94 (s, 2H), 1.75 (d, 6H), 1.47 (t, 3H).
450		LCMS m/z [M+1]: 728.2 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.23 (dd, 1H), 7.05-7.00 (m, 1H), 5.02 (d, 1H), 4.39 (d, 1H), 4.04-3.81 (m, 5H), 3.61 (dd, 2H), 3.45 (dd, 2H), 2.83 (s, 3H), 2.46 (s, 1H), 2.20-2.14 (m, 2H), 2.10 (d, 3H), 2.03 (s, 2H), 1.83 (d, 6H), 1.67-1.60 (m, 2H), 1.49 (dd, 3H).

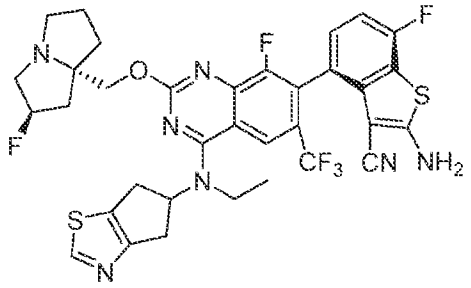
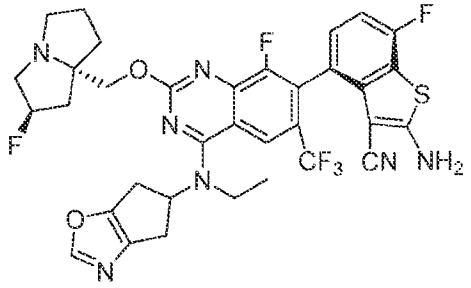
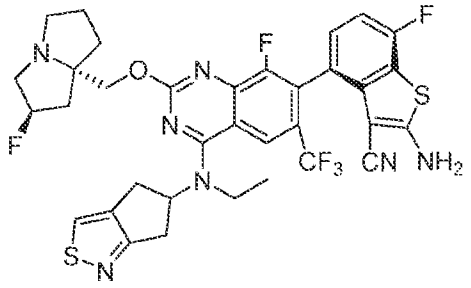
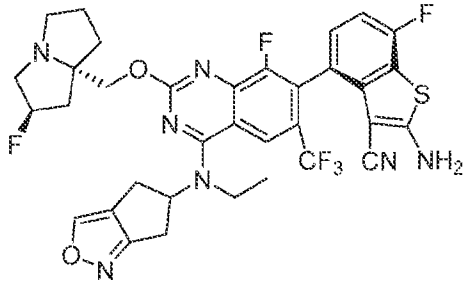
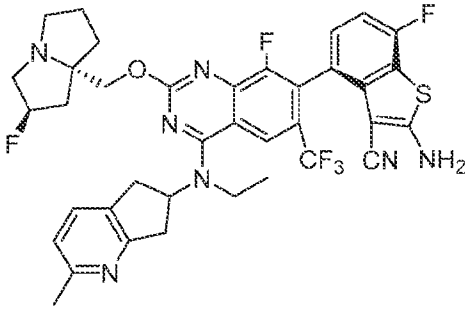
Cmpd. No.	Structure	Analytical Data
451		LCMS m/z [M+1]: 732.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.25-7.21 (m, 1H), 7.01 (t, 1H), 5.34 (s, 0.5H), 5.20 (s,0.5H), 4.68 (t, 1H), 4.15-3.94 (m, 5H), 3.77-3.70 (m,1H), 3.24-3.12 (m, 3H), 3.02-2.96 (m, 1H), 2.62-2.40 (m, 5H), 2.30-2.12 (m, 2H), 2.01-1.90 (m, 3H), 1.86-1.78 (m, 1H), 1.63 (t, 3H).
452		LCMS m/z [M+1]: 711.2 H NMR (400 MHz, CD3OD) δ 8.52 (d, J = 5.5 Hz, 1H), 8.40 (s, 1H), 8.13 (d, J = 7.7 Hz, 1H), 7.66 – 7.52 (m, 1H), 7.23 (dd, J = 8.2, 5.2 Hz, 1H), 7.09 – 6.97 (m, 1H), 5.74 (d, J = 5.0 Hz, 1H), 5.54 (d, J = 51.9 Hz, 1H), 4.67 (dd, J = 12.5, 5.7 Hz, 1H), 4.53 (dd, J = 12.5, 6.7 Hz, 1H), 4.06 – 3.94 (m, 1H), 3.87 (t, J = 16.3 Hz, 2H), 3.67 (ddd, J = 28.3, 20.9, 13.8 Hz, 3H), 3.55 – 3.49 (m, 3H), 3.45 (dd, J = 14.4, 8.5 Hz, 2H), 2.70 – 2.51 (m, 2H), 2.44 – 2.20 (m, 3H), 2.05 (d, J = 12.3 Hz, 1H).
453		
454		

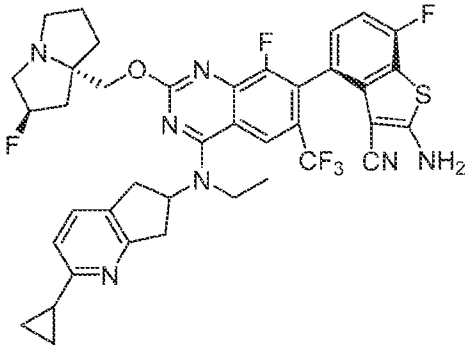
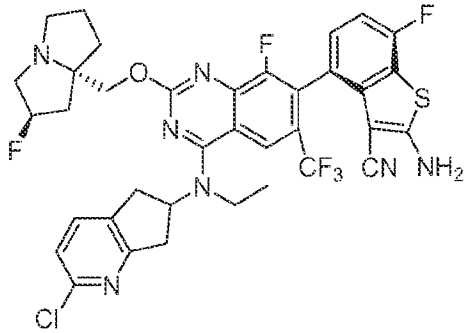
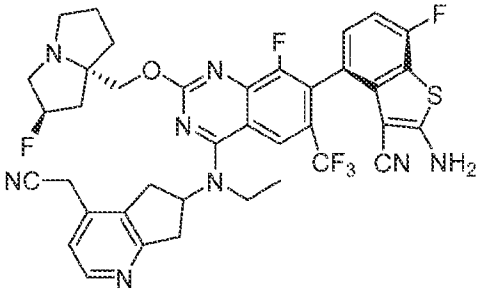
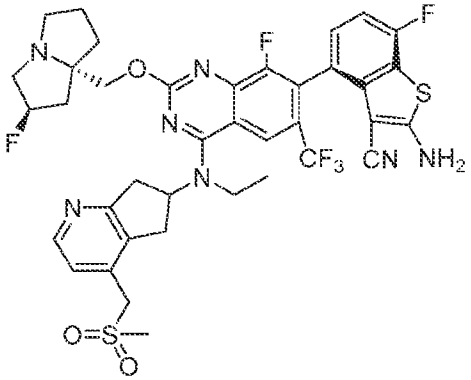
Cmpd. No.	Structure	Analytical Data
455		LCMS m/z [M+1]: 725.3 1H NMR (400 MHz, CD3OD) δ 9.00 (s, 1H), 8.61 (s, 1H), 8.30 (s, 1H), 7.22 – 7.19 (m, 1H), 7.01 (t, J = 8.9 Hz, 1H), 5.98 – 5.85 (m, 1H), 5.35 (d, J = 52.8 Hz, 1H), 4.79 – 3.59 (m, 1H), 4.12 – 3.79 (m, 4H), 3.38 – 3.36 (m, 3H), 3.32 – 3.12 (m, 2H), 2.16 – 1.87 (m, 8H), 1.58 – 1.55 (m, 3H).
456		LCMS m/z [M+1]: 725.2 1H NMR (400 MHz, CD3OD) δ 9.25 (s, 2H), 8.26 (s, 1H), 7.22 (dd, J = 8.3, 5.1 Hz, 1H), 7.06 – 6.99 (m, 1H), 5.48 (d, J = 52.5 Hz, 1H), 5.06 – 5.02 (m, 1H), 4.22 – 4.17 (m, 1H), 4.09 – 4.04 (m, 1H), 4.01 – 3.94 (m, 2H), 3.81 – 3.73 (m, 2H), 3.68 – 3.63 (m, 3H), 3.41 – 3.36 (m, 1H), 2.46 – 2.13 (m, 5H), 2.06 – 1.81 (m, 3H), 1.64 (t, J = 7.0 Hz, 3H).
457		
458		

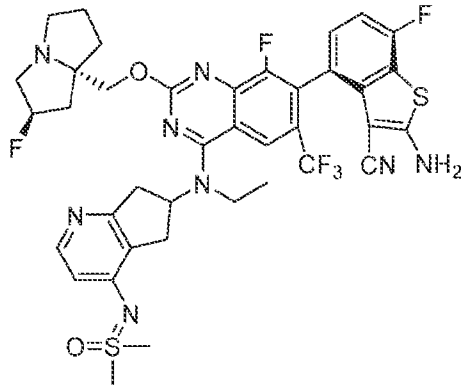
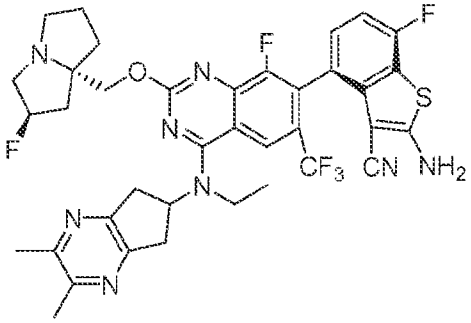
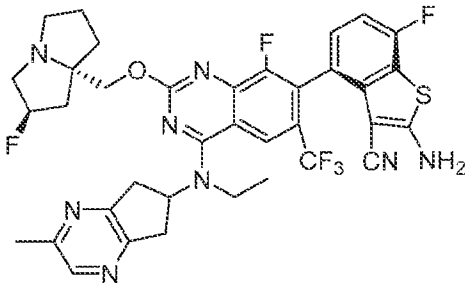
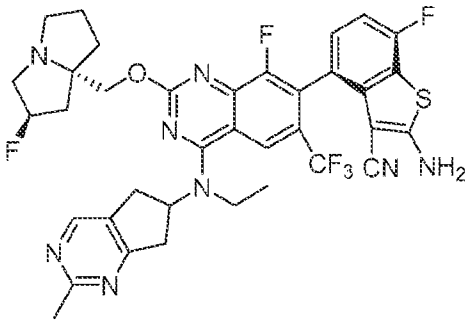
Cmpd. No.	Structure	Analytical Data
459		LCMS m/z [M+1] 727.1. ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 7.68 – 7.28 (m, 1H), 7.22 (dd, *J* = 8.5, 5.0 Hz, 1H), 7.02 (t, *J* = 8.9 Hz, 1H), 5.35 (d, *J* = 53.3 Hz, 1H), 5.22 – 4.95 (m, 1H), 4.46 – 4.36 (m, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 3.84 – 3.76 (m, 3H), 3.70 (q, *J* = 7.1 Hz, 2H), 3.46 (d, *J* = 14.0 Hz, 1H), 3.11 (d, *J* = 10.0 Hz, 2H), 3.05 (m, 1H), 2.95 – 2.93 (m, 2H), 2.81 – 2.66 (m, 1H), 2.66 – 2.38 (m, 1H), 2.39 – 2.23 (m, 4H), 2.19 (d, *J* = 9.3 Hz, 1H), 2.05 (s, 2H), 1.93 (s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H).
460		
461		
462		

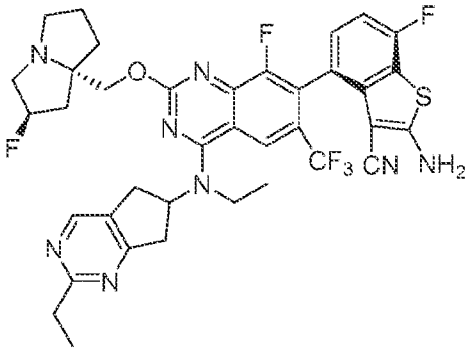
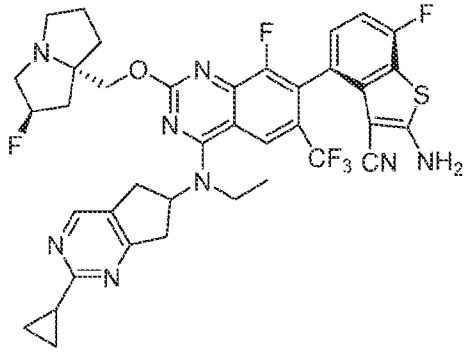
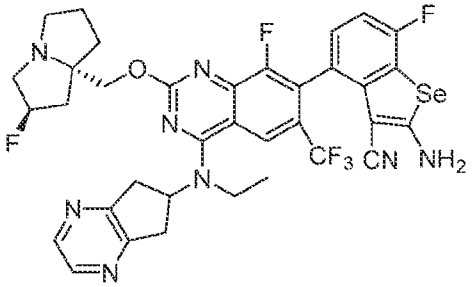
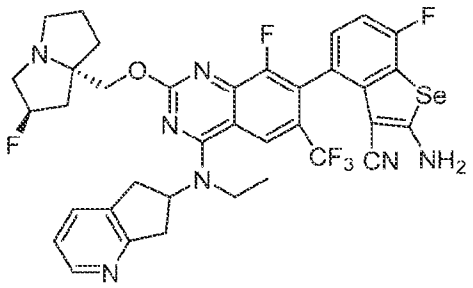
Cmpd. No.	Structure	Analytical Data
463		LCMS m/z [M+1] 749.3 1H NMR (400 MHz, CD3OD) δ 8.77 (s, 1H), 8.28 (s, 1H), 8.07 (s, 1H), 7.23 (dd, J = 8.4, 5.0 Hz, 1H), 7.11 – 6.96 (m, 1H), 5.49 (d, J = 50.7 Hz, 1H), 5.17 – 5.07 (m, 1H), 4.29 (dd, J = 11.9, 9.3 Hz, 1H), 4.13 (dd, J = 18.0, 12.3 Hz, 1H), 3.96 (q, J = 6.9 Hz, 2H), 3.89 – 3.71 (m, 4H), 3.67 – 3.52 (m, 3H), 3.44 – 3.34 (m, 1H), 2.58 – 2.42 (m, 2H), 2.32 – 2.18 (m, 2H), 2.11 – 1.98 (m, 1H), 1.95 – 1.86 (m, 1H), 1.59 (t, J = 7.0 Hz, 3H).
464		
465		LCMS m/z [M+1]: 743.2 1H NMR (400 MHz, CD3OD) δ 8.57 (d, J = 5.4 Hz, 1H), 8.30 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 7.74 – 7.64 (m, 1H), 6.98 (t, J = 9.6 Hz, 1H), 5.54 (s, 1H), 5.41 (s, 1H), 5.15 (s, 1H), 4.31 (dd, J = 63.5, 12.5 Hz, 2H), 4.04 – 3.58 (m, 8H), 3.39 (dd, J = 13.6, 7.2 Hz, 2H), 2.49 (s, 1H), 2.40 (dd, J = 14.7, 10.7 Hz, 1H), 2.30 – 2.17 (m, 2H), 2.12 (t, J = 12.0 Hz, 1H), 1.88 (s, 1H), 1.61 (t, J = 7.0 Hz, 3H).

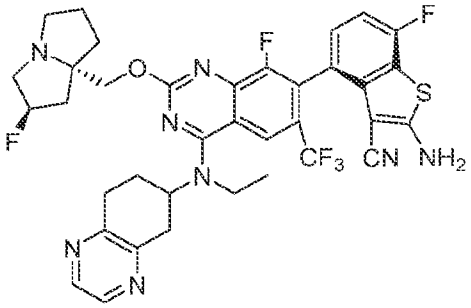
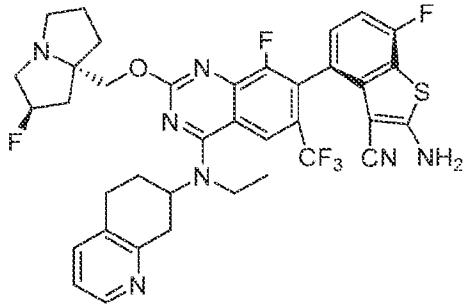
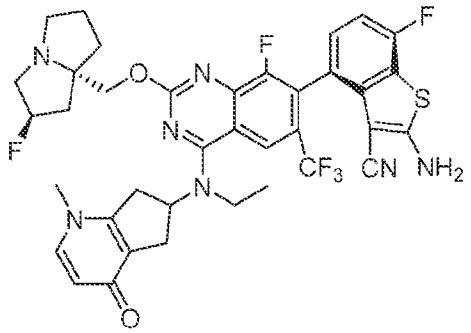
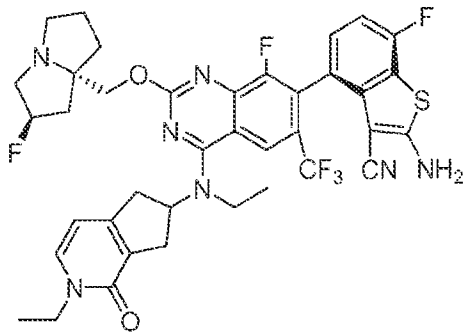
Cmpd. No.	Structure	Analytical Data
466		LCMS m/z [M+1]: 773.1 1H NMR (400 MHz, CD3OD): δ 8.42 (s, 2H), 8.27 (s, 1H), 7.23 - 7.19 (m, 1H), 6.96 (t, J = 8.6 Hz, 1H), 5.47 (d, J = 52.0 Hz, 1H), 5.08 - 5.00 (m, 1H), 4.21 - 3.93 (m, 4H), 3.84 - 3.53 (m, 7H), 3.40 - 3.33 (m, 1H), 2.49 - 2.41 (m, 2H), 2.28 - 2.15 (m, 2H), 2.04 - 1.84 (m, 2H), 1.64 (t, J = 7.0 Hz, 3H).
467		LCMS m/z [M+1]: 725.2 1H NMR (400 MHz, CD3OD) δ 8.54 (d, J = 5.3 Hz, 1H), 8.30 (s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.70 (dd, J = 8.7, 4.8 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.08 – 7.00 (m, 1H), 5.48 (d, J = 52.0 Hz, 1H), 5.18 – 5.11 (m, 1H), 4.37 (d, J = 12.5 Hz, 1H), 4.20 (d, J = 12.5 Hz, 1H), 3.99 (q, J = 6.8 Hz, 2H), 3.88 – 3.62 (m, 6H), 3.43 – 3.36 (m, 1H), 2.43 (dd, J = 23.3, 15.2 Hz, 2H), 2.20 (dd, J = 16.9, 8.4 Hz, 2H), 2.14 – 2.05 (m, 1H), 1.88 (s, 1H), 1.61 (t, J = 7.0 Hz, 3H).
468		LCMS m/z [M+1]: 725.4 1H NMR (400 MHz, CD3OD): δ 8.42 (s, 2H), 8.18 (s, 1H), 7.71-7.267 (m, 1H), 7.03 (t, J = 9.1Hz, 1H), 5.48 (d, J = 50.8 Hz, 1H), 5.06 - 5.00 (m, 1H), 4.21 - 3.97 (m, 4H), 3.83 - 3.64 (m, 4H), 3.60 - 3.59 (m, 2H), 3.40 - 3.33 (m, 1H), 2.49 - 2.41 (m, 2H), 2.26 - 1.85 (m, 4H), 1.64 (t, J = 7.0 Hz, 3H).

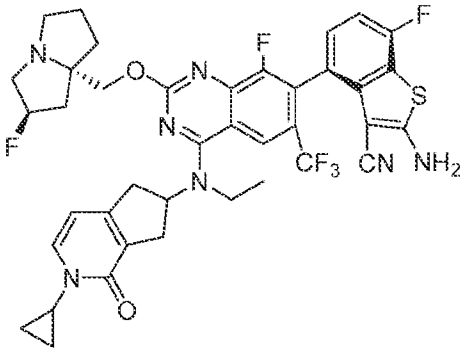
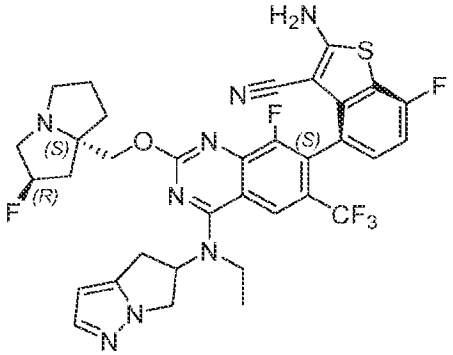
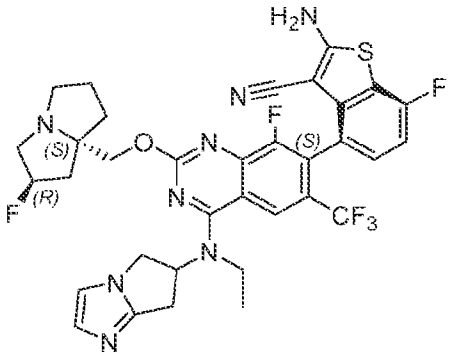
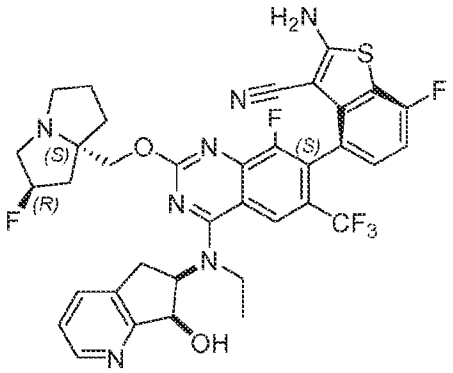
Cmpd. No.	Structure	Analytical Data
469		
470		
471		
472		
473		

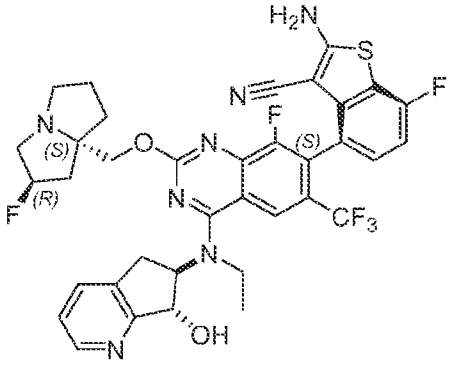
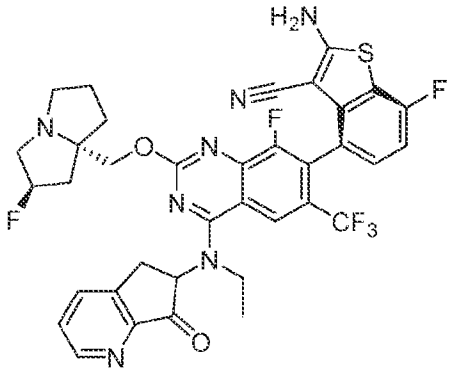
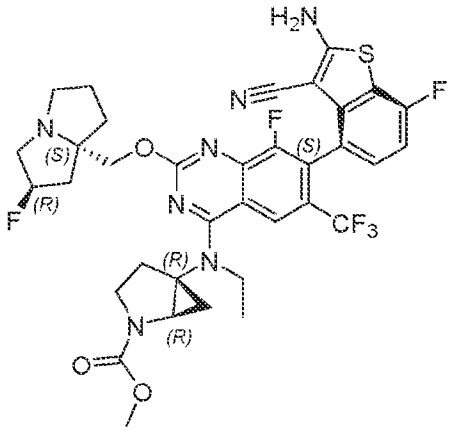
Cmpd. No.	Structure	Analytical Data
474		
475		
476		
477		

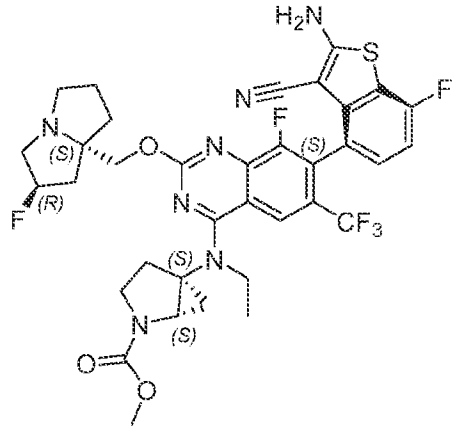
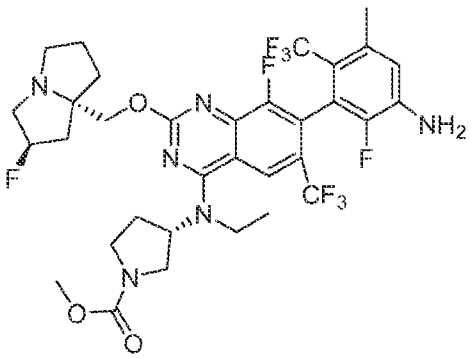
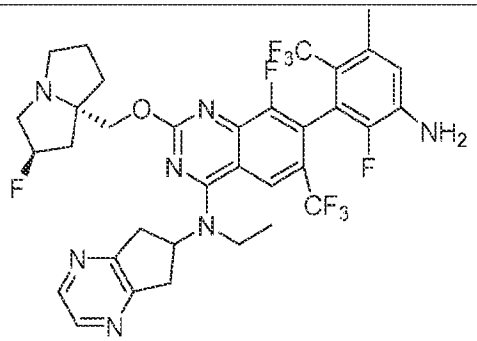
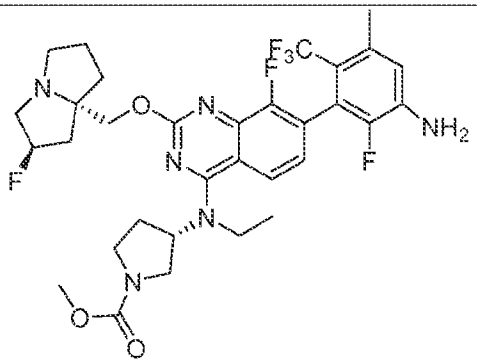
Cmpd. No.	Structure	Analytical Data
478		
479		
480		
481		LCMS m/z [M+1]: 739.4 1H NMR (400 MHz, CD3OD) δ8.53 (s, 1H), 8.33 (s, 1H), 7.23 – 7.20 (m, 1H), 7.02 (t, J = 8.9 Hz, 1H), 5.93 – 5.89 (m, 1H), 5.35 (d, J = 52.0 Hz, 1H), 4.53 – 3.77 (m, 7H), 3.47 – 3.40 (m, 2H), 3.19 – 3.11 (m, 1H), 2.79 – 2.03 (m, 11H), 1.56 – 1.53 (m, 3H).

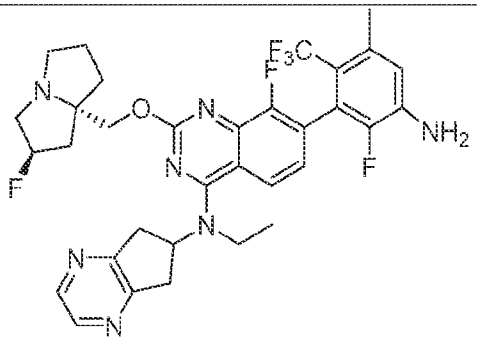
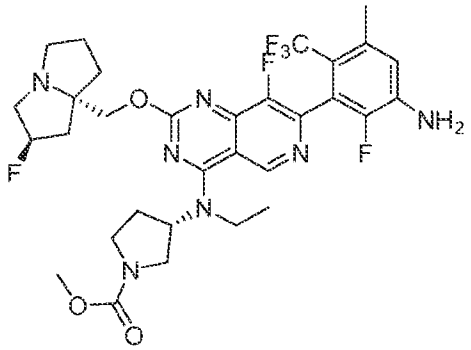
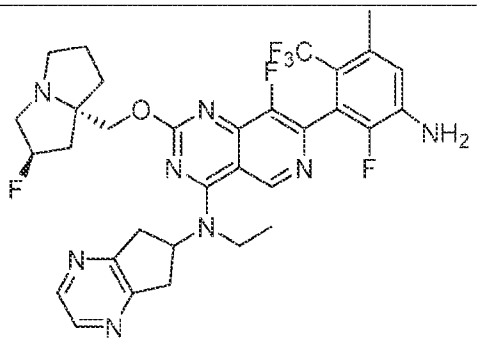
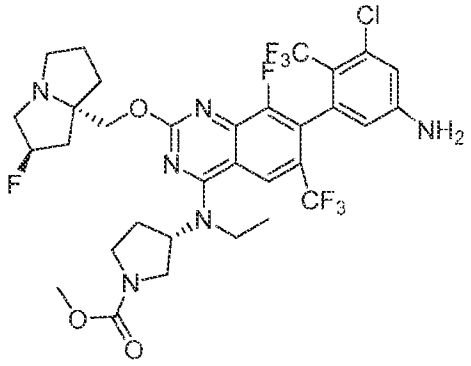
Cmpd. No.	Structure	Analytical Data
482		
483		
484		LCMS m/z [M+1]: 773.1 1H NMR (400 MHz, CD3OD): δ 8.42 (s, 2H), 8.27 (s, 1H), 7.23 - 7.19 (m, 1H), 6.96 (t, J = 8.6 Hz, 1H), 5.47 (d, J = 52.0 Hz, 1H), 5.08 - 5.00 (m, 1H), 4.21 - 3.93 (m, 4H), 3.84 - 3.53 (m, 7H), 3.40 - 3.33 (m, 1H), 2.49 - 2.41 (m, 2H), 2.28 - 2.15 (m, 2H), 2.04 - 1.84 (m, 2H), 1.64 (t, J = 7.0 Hz, 3H).
485		

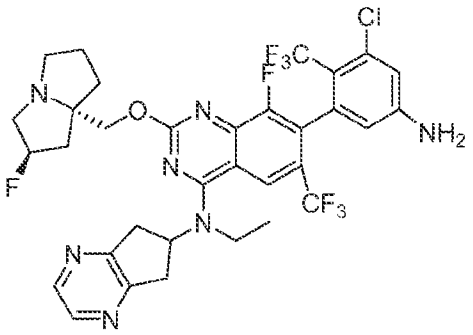
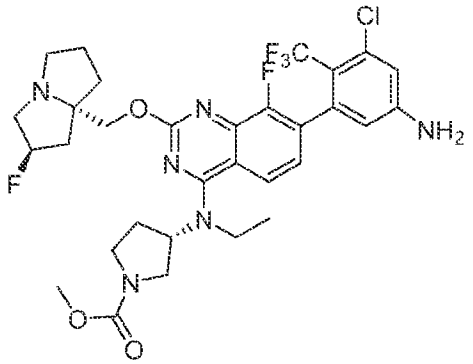
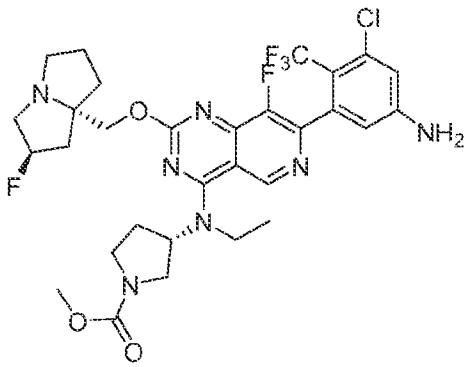
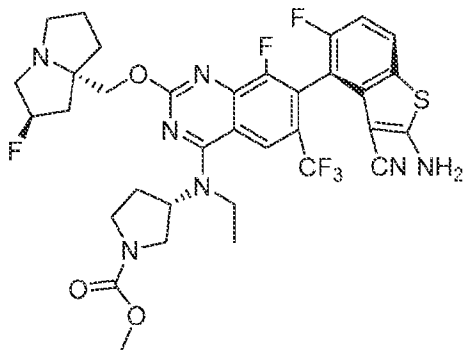
Cmpd. No.	Structure	Analytical Data
486		
487		LCMS m/z [M+1]: 738.2 1H NMR (400 MHz, CD3OD) δ 8.36-8.29 (m, 1H), 8.28-8.20 (m, 1H), 7.66-7.59 (m, 1H), 7.28-7.16 (m, 2H), 7.00 (t, 1H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 4.98-4.90 (m, 1H), 4.38-4.23 (m, 2H), 4.00-3.86 (m, 2H), 3.58-3.40 (m, 2H), 3.38-3.31 (m, 3H), 3.10-2.95 (m, 3H), 2.45-2.22 (m, 4H), 2.13-1.98 (m, 3H), 1.90-1.82 (m, 1H), 1.52 (t, 3H).
488		LCMS m/z [M+1]: 755.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 8.14 (t, J = 6.8 Hz, 1H), 7.56 – 7.16 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 6.84 (t, J = 7.3 Hz, 1H), 5.55 (s, 0.5H), 5.42 (s, 0.5H), 5.15 (t, J = 8.2 Hz, 1H), 4.61 – 4.16 (m, 2H), 4.07 – 3.64 (m, 11H), 3.61 – 3.37 (m, 4H), 2.84 – 1.88 (m, 6H), 1.60 (q, J = 7.0 Hz, 3H).
489		

Cmpd. No.	Structure	Analytical Data
490		
491		
492		
493		

Cmpd. No.	Structure	Analytical Data
494		
495		
496		LCMS m/z [M+1]: 746.2 1H NMR (400 MHz, CD3OD) δ 8.38 (s, 1H), 7.20-7.24 (m, 1H), 7.01 (t, 1H), 5.42 (s, 0.5H), 5.28 (s, 0.5H), 4.28-4.39 (m, 2H), 3.96-4.01 (m, 1H), 3.79-3.85 (m, 1H), 3.70 (s, 3H), 3.34-3.36 (m, 1H), 3.18-3.26 (m, 2H), 3.07-3.13 (m, 1H), 2.76-2.84 (m, 1H), 2.63-2.69 (m, 1H), 2.27-2.44 (m, 2H), 2.15-2.23 (m, 2H), 1.90-2.09 (m, 4H), 1.55-1.65 (m, 1H), 1.47 (t, 3H), 0.85-0.91 (m, 2H).

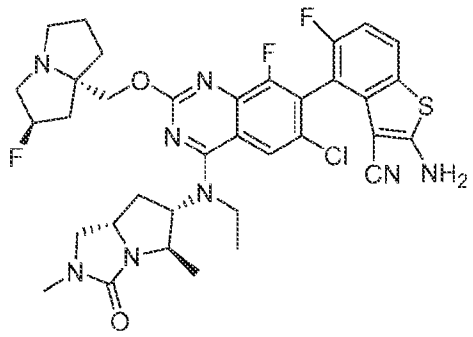
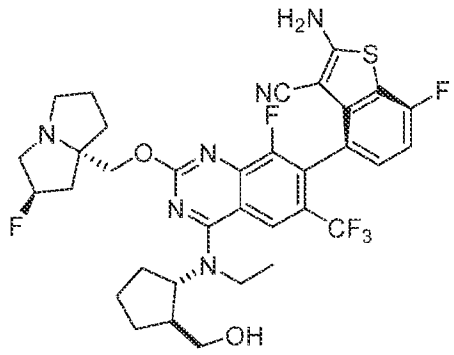
Cmpd. No.	Structure	Analytical Data
497		LCMS m/z [M+1]: 746.2 1H NMR (400 MHz, CD3OD) δ 8.37 (s, 1H), 7.20-7.24 (m, 1H), 7.01 (t, 1H), 5.41 (s, 0.5H), 5.28 (s, 0.5H), 4.28-4.37 (m, 2H), 3.95-4.01 (m, 1H), 3.85-3.87 (m, 1H), 3.68 (s, 3H), 3.34-3.36 (m, 1H), 3.06-3.26 (m, 3H), 2.74-2.82 (m, 1H), 2.63-2.68 (m, 1H), 2.25-2.43 (m, 2H), 2.14-2.21 (m, 2H), 1.90-2.08 (m, 4H), 1.56-1.66 (m, 1H), 1.47 (t, 3H), 0.87-0.94 (m, 2H).
498		LCMS m/z [M+1]: 735.2 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.57 (d, J = 52.0 Hz, 1H), 5.17 – 4.97 (m, 1H), 4.79 – 4.50 (m, 2H), 4.12 – 3.79 (m, 6H), 3.73 (s, 3H), 3.65 – 3.42 (m, 3H), 2.83 – 2.52 (m, 2H), 2.41 (s, 3H), 2.38 – 2.31 (m, 2H), 2.21 - 1.98 (m, 2H), 1.48 (t, J = 6.8 Hz, 3H), 1.39 – 1.26 (m, 3H).
499		
500		LCMS m/z [M+1]: 667.2 1H NMR (400 MHz, CD3OD) δ 7.98 (d, J = 8.8 Hz, 1H), 7.35 (dd, J = 8.8, 7.2 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.70 – 5.47 (m, 1H), 5.25 – 5.10 (m, 1H), 4.77 – 4.64 (m, 2H), 4.10 – 3.74 (m, 7H), 3.72 (s, 3H), 3.69 – 3.53 (m, 1H), 3.55 – 3.39 (m, 2H), 2.78 - 2.78 (m, 2H), 2.54 – 2.43

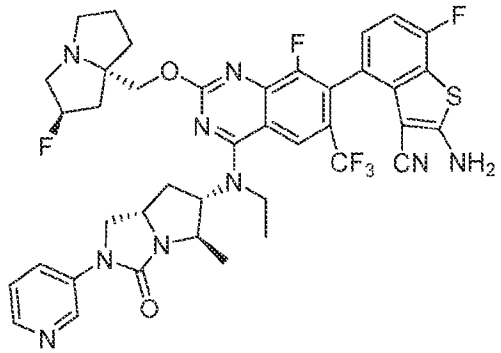
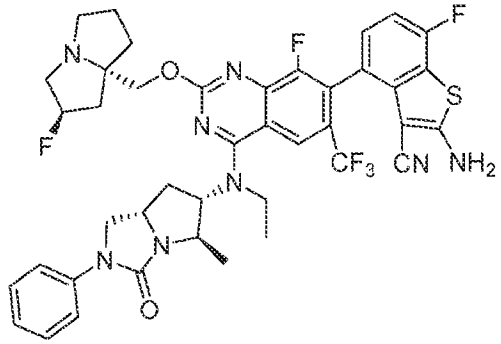
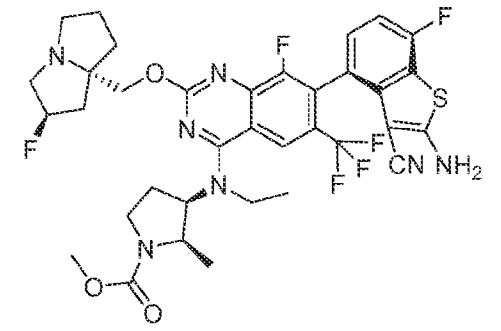
Cmpd. No.	Structure	Analytical Data
		(m, 2H), 2.41 (s, 3H), 2.40 – 2.08 (m, 4H), 1.46 (t, J = 7.2 Hz, 3H).
501		
502		LCMS m/z [M+1]: 668.3 1H NMR (400 MHz, CD3OD) δ 9.14 (s, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.58 (d, J = 52.0 Hz, 1H), 5.26 – 5.09 (m, 1H), 4.78 – 4.58 (m, 2H), 4.17 – 3.76 (m, 7H), 3.73 (s, 3H), 3.67 – 3.41 (m, 3H), 2.84 – 2.46 (m, 3H), 2.42 (s, 3H), 2.40 – 2.31 (m, 2H), 2.27 – 2.10 (m, 1H), 1.49 (t, J = 6.8 Hz, 3H).
503		
504		

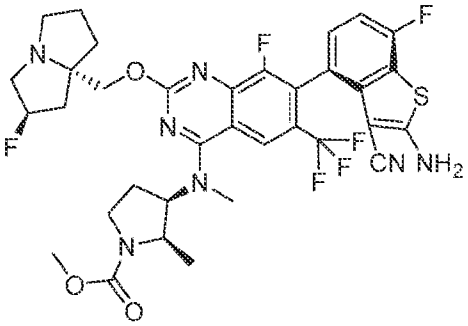
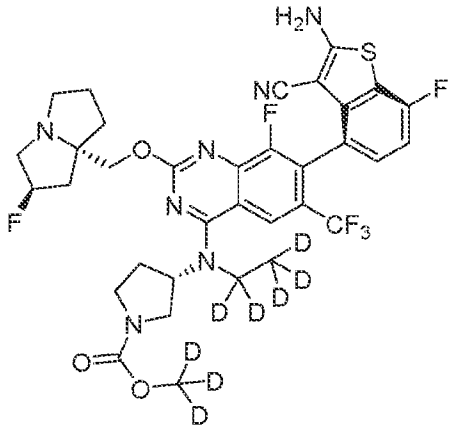
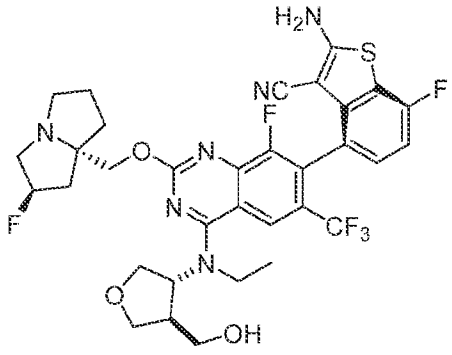
Cmpd. No.	Structure	Analytical Data
505		
506		LCMS m/z [M+1]: 669.3 1H NMR (400 MHz, CD3OD) δ 7.92 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 7.3 Hz, 1H), 6.89 (s, 1H), 6.42 (s, 1H), 5.56 (d, J = 51.5 Hz, 1H), 5.09 (s, 1H), 4.62 – 4.74 (m, 2H), 3.81 – 4.09 (m, 6H), 3.68 – 3.80 (m, 4H), 3.40 – 3.64 (m, 3H), 2.52 – 2.77 (m, 2H), 2.28 – 2.51 (m, 5H), 2.10 – 2.40 (m, 1H), 1.41 (t, J = 6.7 Hz, 3H).
507		LCMS m/z [M+1]: 670.2 1H NMR (400 MHz, CD3OD) δ 9.03 (s, 1H), 6.91 (s, 1H), 6.50 (s, 1H), 5.32 (d, J = 53.2 Hz, 1H), 5.07 – 5.18 (m, 1H), 4.26 – 4.34 (m, 2H), 3.68 – 4.00 (m, 8H), 3.40 – 3.64 (m, 3H), 3.20 – 3.27 (m, 1H), 3.00 – 3.10 (m, 1H), 1.84 – 2.53 (m, 10H), 1.46 (t, J = 6.5 Hz, 3H).
508		LCMS m/z [M+1]: 734.3 1HNMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.57 (m, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 5.38 – 52.5 (m, 3H), 4.96 (t, *J* = 7.2 Hz, 1H), 4.33 – 4.25 (m, 2H), 3.94 – 3.91 (m, 1H), 3.75 – 3.71 (s, 5H), 3.43 – 3.23 (m, 5H), 3.02 (m, 1H), 2.32 – 2.18 (m, 5H), 1.98 –1.91 (m, 4H), 1.38 (t, *J* = 7.6 Hz, 3H).

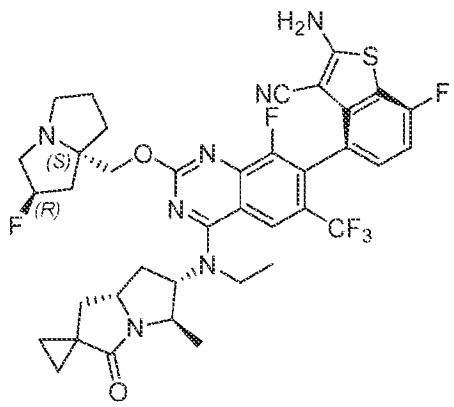
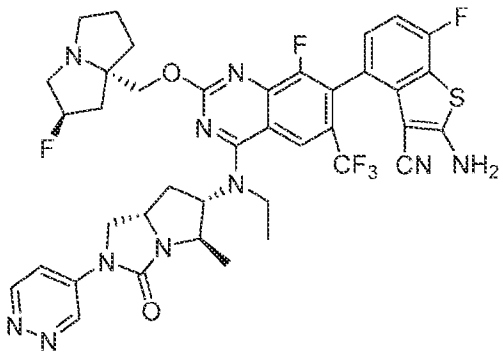
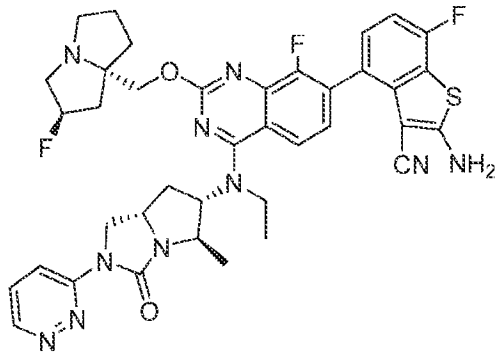
[0874] Table 3c includes selected compounds of the present disclosure.

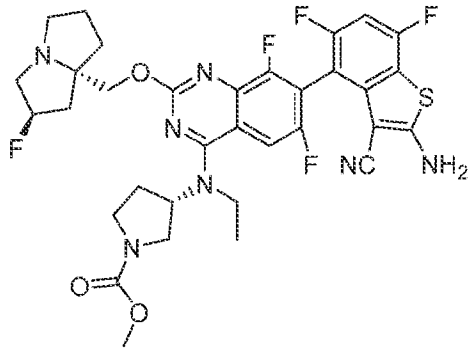
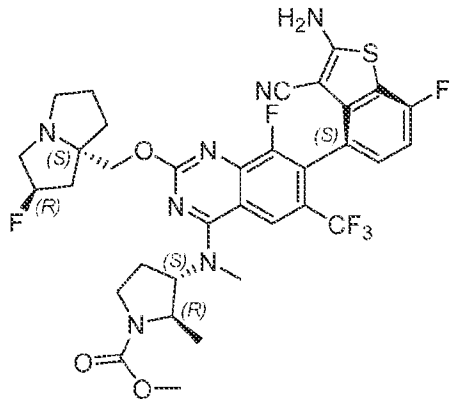
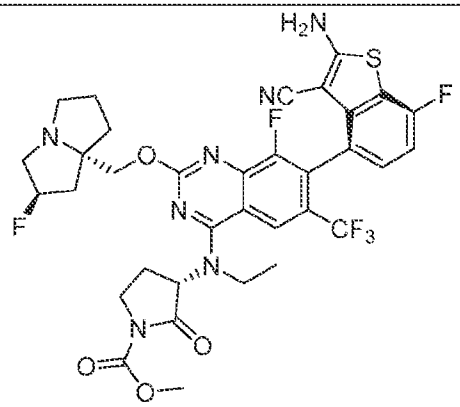
Table 3c. Selected compounds of the present disclosure.

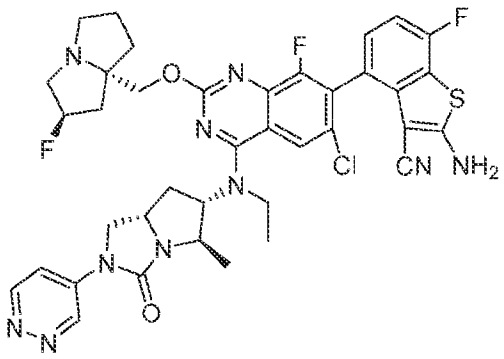
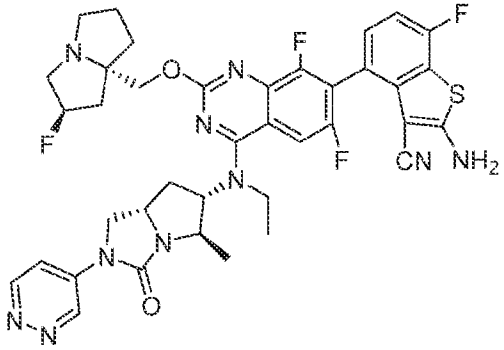
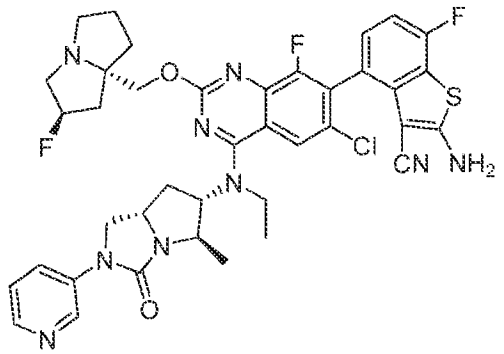
Cmpd. No.	Structure	Analytical Data
509		LCMS m/z [M+1]: 725.2 1H NMR (400 MHz, CD3OD) δ 8.06 – 7.95 (m, 1H), 7.76 – 7.66 (dd, J = 8.7, 4.7 Hz, 1H), 7.06 (t, J = 9.1 Hz, 1H), 5.55 (d, J = 51.9 Hz, 1H), 4.72 – 4.42 (m, 3H), 4.24 – 3.78 (m, 6H), 3.71 – 3.55 (m, 2H), 3.53 – 3.40 (m, 2H), 2.93 – 2.75 (m, 3H), 2.77 – 2.24 (m, 7H), 2.19 – 2.05 (m, 1H), 1.60 – 1.38 (m, 4H), 1.34 – 1.22 (m, 2H).
510		LCMS m/z [M+1]: 705.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.30 – 7.21 (m, J = 8.0, 5.0 Hz, 1H), 7.06 – 6.97 (m, J = 8.9 Hz, 1H), 5.62 (s, 0.5H), 5.49 (s, 0.5H), 5.36 – 5.28 (m, J = 4.8 Hz, 1H), 4.72 – 4.58 (m, 3H), 4.52 – 4.43 (m, J = 7.0 Hz, 1H), 4.12 – 4.02 (m, J = 14.0, 7.3 Hz, 1H), 3.94 – 3.82 (m, J = 15.1 Hz, 3H), 3.67 – 3.60 (m, J = 14.2, 7.1 Hz, 1H), 3.50 – 3.43 (m, J = 11.2, 5.4 Hz, 1H), 3.46 – 3.35 (m, 1H), 2.72 – 2.53 (m, 2H), 2.44 (d, J = 15.4 Hz, 2H), 2.35 – 2.27 (m, J = 19.0, 13.5 Hz, 2H), 2.22 – 2.16 (m, 3H), 2.05 – 1.97 (m, 3H), 1.61 (d, J = 8.6 Hz, 3H).

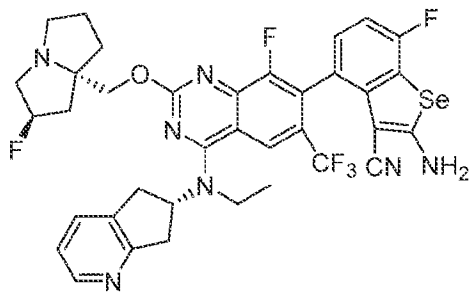
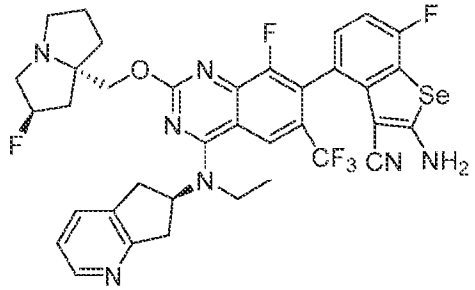
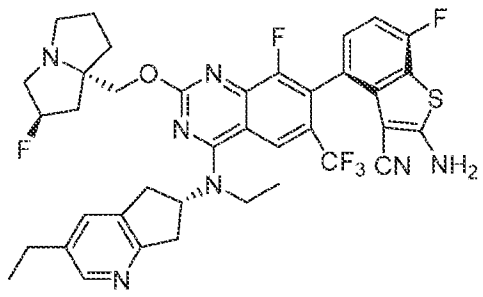
511		LCMS m/z [M+1]: 822.4 1H NMR (400 MHz, CD3OD) δ 9.26 (s, 1H), 8.38 – 8.48 (m, 2H), 8.24 - 8.30 (m, 1H), 7.82 – 7.90 (m, 1H), 7.21 – 7.29 (m, 1H), 7.03 (t, J = 8.4 Hz, 1H), 5.44 (d, J = 51.7 Hz, 1H), 4.28 – 4.69(m, 5H), 4.15 – 4.23 (m, 1H), 3.72 – 4.10 (m, 6H), 2.40 – 2.70 (m, 5H), 2.12 – 2.29 (m, 3H), 1.48 – 1.58(m, 3H), 1.36 – 1.46 (m, 3H).
512		LCMS m/z [M+1]: 821.4 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.58 – 7.68 (m, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.20 – 7.28 (m, 1H), 7.11 (t, J = 7.3 Hz, 1H), 7.02 (t, J = 8.4 Hz, 1H), 5.04 – 5.25 (m, 1H), 3.94 – 4.60 (m, 7H), 3.60 – 3.92 (m, 4H), 2.68 – 2.79 (m, 1H), 1.85 – 2.57 (m, 7H), 1.55 – 1.68(m, 3H), 1.36 – 1.46 (m, 3H).
513		LCMS m/z [M+1]: 748.3 1H NMR (400 MHz, CD3OD) δ 8.45 – 8.22(m 1H), 7.29 – 7.18 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.57 (d, J = 52.0 Hz, 1H), 5.06 – 4.92 (m, 1H),4.84 – 4.51 (m, 4H), 4.17 – 3.82 (m, 5H), 3.78 – 3.60 (m, 4H), 3.53 – 3.40 (m, 2H), 2.77 – 2.52 (m, 3H), 2.46 – 2.27 (m, 4H), 2.22 – 2.07 (m, 1H), 1.54 – 1.36 (m, 3H), 1.01 (d, J = 6.0 Hz, 2H).

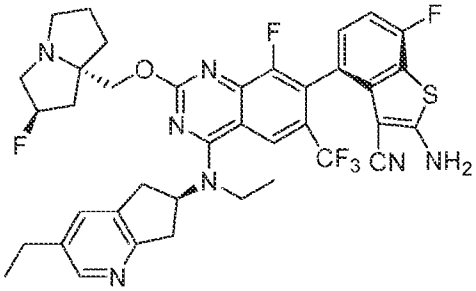
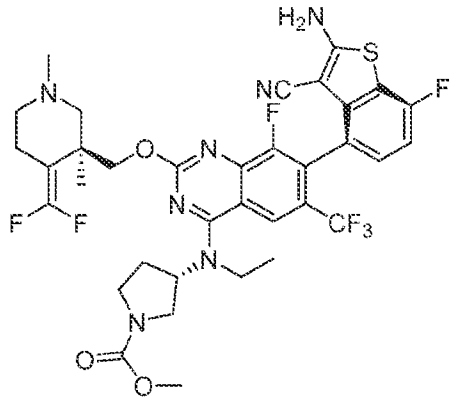
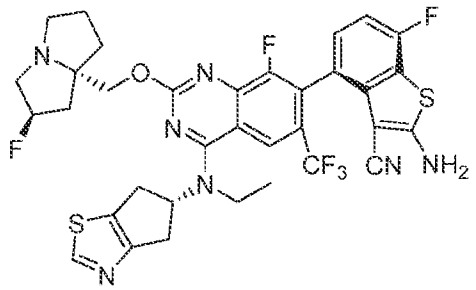
514		LCMS m/z [M+1]: 734.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.22 (dd, *J* = 8.3, 5.1 Hz, 1H), 7.01 (t, *J* = 12.0 Hz, 1H), 5.39 (d, *J* = 53.0 Hz, 1H), 4.70 – 4.85 (m, 2H), 4.32 – 4.52 (m, 2H), 3.57 – 3.77 (m, 7H), 3.31 – 3.51 (m, 4H), 3.10 – 3.22 (m, 1H), 2.35 – 2.46 (m, 1H), 2.31 – 2.41 (m, 2H), 2.06 – 2.26 (m, 3H), 1.87 – 2.01 (m, 1H), 1.06 (d, *J* = 6.5 Hz, 3H).
515		LCMS m/z [M+1]: 742.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.24-7.18 (m, 1H), 7.01 (t, 1H), 5.36 (s, 0.5H), 5.22 (s, 0.5H), 5.04-4.95 (m, 1H), 4.29-4.20 (m, 2H), 3.94-3.87 (m, 1H), 3.77-3.71 (m, 1H), 3.60-3.53 (m, 1H), 3.48-3.40 (m, 1H), 3.28-3.15 (m, 3H), 3.03-2.95 (m, 1H), 2.51-2.41 (m, 1H), 2.36-2.08 (m, 4H), 2.01-1.83 (m, 3H).
516		LCMS m/z [M+1]: 707.1 1H NMR (400 MHz, CD3OD) δ 8.25 (d, J = 16.5 Hz, 1H), 7.27 – 7.18 (m, J = 8.5, 4.4 Hz, 1H), 7.02 – 6.96 (m, J = 8.0, 1.5 Hz, 1H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 4.99 – 4.90 (m, 1H), 4.36 – 4.23 (m, J = 12.1, 9.8, 4.2 Hz, 3H), 4.35 – 4.24 (m, 2H), 4.13 – 4.07 (m, 1H), 4.04 – 3.96 (m, J = 14.4, 7.1 Hz, 1H), 3.89 – 3.74 (m, J = 29.7, 14.7, 7.2 Hz, 1H), 3.72 – 3.58 (m, 3H), 3.24 (d, J = 13.4 Hz, 2H), 3.05 – 2.98 (m, J = 9.8, 6.1 Hz, 1H), 2.85 – 2.76 (m,

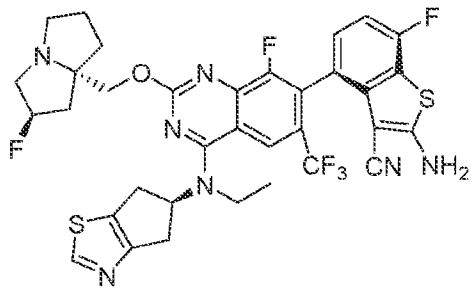
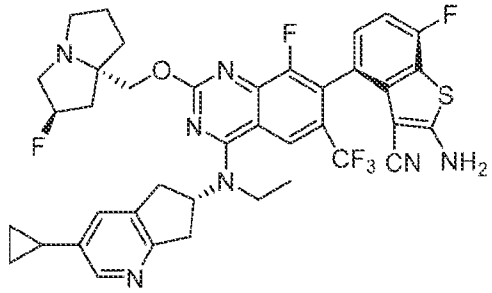
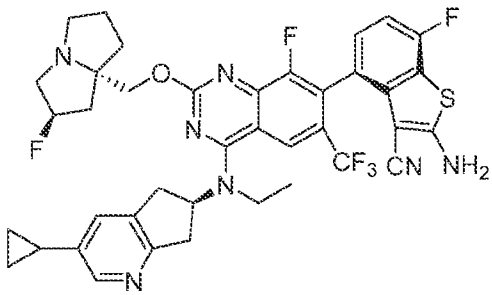
		1H), 2.40 – 1.82 (m, 7H), 1.46 – 1.39 (m, J = 6.9, 2.3 Hz, 3H).
517		LCMS m/z [M+1]: 770.2 1H-NMR (400 MHz, CD_3OD): 8.25(s, 1 H), 7.21-7.24 (m, 1 H), 7.02-7.07 (m, 1 H), 5.47-5.52 (m, 0.5 H), 5.35-5.40 (m, 0.5 H), 4.44-4.51 (m, 1 H), 4.30-4.41 (m, 2 H), 3.87-3.96 (m, 1 H), 3.50-3.81 (m, 5 H), 3.17-3.26 (m, 2 H), 2.38-2.50 (m, 2 H), 2.11-2.32 (m, 7 H), 1.98-2.08(m, 4 H), 1.43-1.52 (m, 4 H), 1.16-1.21 (m, 3 H).
518		LCMS m/z [M+1]: 823.2 1H NMR (400 MHz, CD3OD) δ 9.86 (s, 1H), 9.12 (d, J = 6.4 Hz, 1H), 8.37 – 8.16 (m, 1H), 8.02 – 7.80 (m, 1H), 7.27 – 7.21 (m, 1H), 7.03 (t, J = 8.8 Hz, 1H), 5.46 (d, J = 52.0 Hz, 1H), 4.67 – 4.56 (m, 1H), 4.50 – 4.33 (m, 2H), 4.30 – 4.13 (m, 2H), 4.11 – 3.72 (m, 6H), 3.46 – 3.36 (m, 1H), 2.65 – 2.53 (m, 2H), 2.53 – 2.39 (m, 1H), 2.30 – 1.90 (m, 6H), 1.62 – 1.49 (m, 3H), 1.48 – 1.38 (m, 3H).
519		LCMS m/z [M+1]: 755.4 1H NMR (400 MHz, CD3OD) δ 8.88 (d, J = 4.6 Hz, 1H), 8.66 (t, J = 8.1 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.05 (t, J = 8.7 Hz, 1H), 5.49 – 5.33 (m, 2H), 4.58 – 4.28 (m, 5H), 4.09 – 3.74 (m, 5H), 3.45 – 3.28 (m, 1H), 2.62 – 2.58

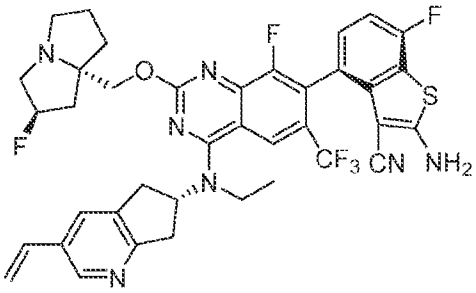
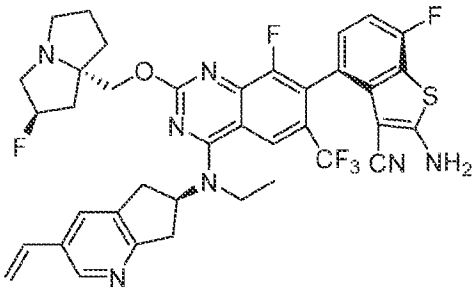
		(m, 2H), 2.30 – 2.02 (m, 7H), 1.58 – 1.55 (m, 3H), 1.41 (t, J = 7.2 Hz, 3H).
520		LCMS m/z [M+1]: 702.3 1H NMR (400 MHz, CD3OD) δ 7.77 – 7.70 (m, 1H), 7.04 (t, J = 9.6 Hz, 1H), 5.58 (d, J = 51.9 Hz, 1H), 5.06 – 5.01 (m, 1H), 4.75 – 4.60 (m, 2H), 4.06 – 3.88 (m, 5H), 3.80 – 3.70 (m, 4H), 3.65 – 3.42 (m, 4H), 2.78 – 2.59 (m, 2H), 2.51 – 2.31 (m, 5H), 2.25 – 2.10 (m, 1H), 1.44 – 1.38 (m, 3H).
521		LCMS m/z [M+1]: 734.2 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.24-7.18 (m, 1H), 7.00 (t, 1H), 5.41-5.35 (m, 0.5H), 5.27-5.22 (m, 0.5H), 5.08-4.99 (m, 1H), 4.34 (d, 1H), 4.25 (d, 1H), 4.20-4.13 (m, 1H), 3.87-3.78 (m, 1H), 3.72 (s, 3H), 3.57-3.48 (m, 1H), 3.44 (s, 3H), 3.10-3.31 (m, 1H), 3.28-3.19 (m, 2H), 3.08-3.01 (m, 1H), 2.51-2.42 (m, 1H), 2.5136-2.12 (m, 4H), 2.05-1.97 (m, 2H), 1.95-1.86 (m, 1H), 1.41 (d, 3H).
522		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.24-8.21 (m, 1H), 7.22 (s, 1H), 7.04-6.99 (m, 1H), 5.33-5.32 (m, 1H), 4.66-4.64 (m, 1H), 4.24-3.98 (m, 5H), 3.88-3.85 (m, 3H), 3.59-3.39 (m, 4H), 3.20-3.13(m,1H), 2.50-2.37 (m, 2H), 2.18-1.94 (m, 6H), 1.65-1.58(m, 3H).

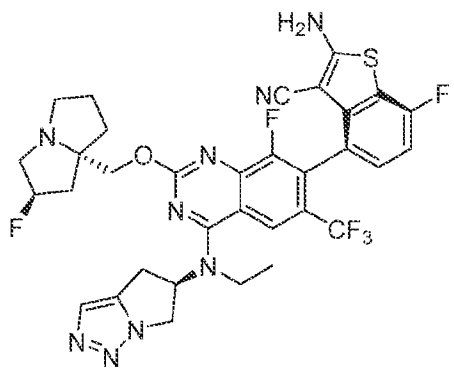
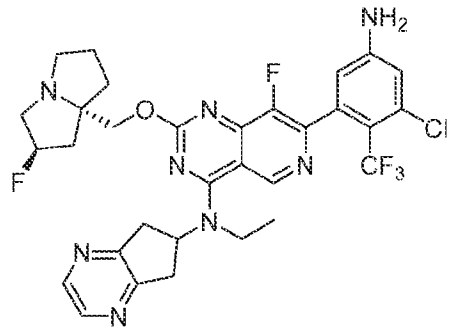
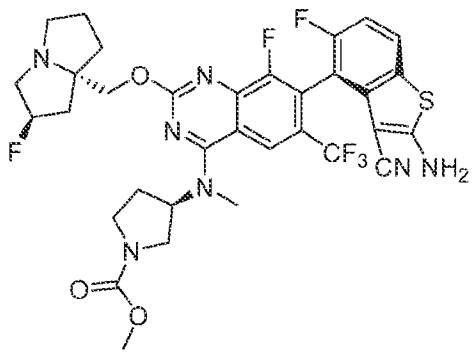
523		LCMS m/z [M+1]: 790.2 1H NMR (400 MHz, CD3OD) δ 9.87 (s, 1H), 9.12 (d, J = 6.4 Hz, 1H), 8.09 – 7.80 (m, 2H), 7.24 (dd, J = 8.4, 5.2 Hz, 1H), 7.06 (t, J = 8.8 Hz, 1H), 5.46 (d, J = 52.0 Hz, 1H), 4.72 – 4.52 (m, 1H), 4.50 – 4.33 (m, 3H), 4.27 (t, J = 9.6 Hz, 1H), 4.11 – 3.72 (m, 6H), 3.50 – 3.35 (m, 1H), 2.71 – 2.54 (m, 2H), 2.53 – 2.39 (m, 2H), 2.34 – 1.89 (m, 5H), 1.51 (t, J = 7.0 Hz, 3H), 1.43 (d, J = 6.4 Hz, 3H).
524		LCMS m/z [M+1]: 774.2 1H NMR (400 MHz, CD3OD) δ 9.87 (s, 1H), 9.11 (d, J = 6.4 Hz, 1H), 7.99 – 7.83 (m, 1H), 7.67 (d, J = 11.2 Hz, 1H), 7.32 (dd, J = 8.4, 5.2 Hz, 1H), 7.14 – 6.94 (m, 1H), 5.47 (d, J = 52.4 Hz, 1H), 5.38 – 5.32 (m, 1H), 4.64 – 4.47 (m, 1H), 4.44 – 4.24 (m, 3H), 4.10 – 3.76 (m, 6H), 3.46 – 3.36 (m, 1H), 2.65 – 2.54 (m, 2H), 2.52 – 2.40 (m,2H), 2.23 – 1.95 (m, 5H), 1.51 (t, J = 6.8 Hz, 3H), 1.41 (d, J = 6.8 Hz, 3H).
525		LCMS m/z [M+1]: 788.4 1H NMR (400 MHz, CD3OD) δ 9.24 (s, 1H), 8.38 – 8.48 (m, 2H), 7.96 (d, J = 12.2 Hz, 1H), 7.78 – 7.86 (m, 1H), 7.20 – 7.27 (m, 1H), 7.05 (t, J = 8.4 Hz, 1H), 5.44 (d, J = 52.2 Hz, 1H), 4.12 – 4.66(m, 7H), 3.67 – 4.09 (m, 6H), 2.37 – 2.63 (m, 4H), 2.11 – 2.30

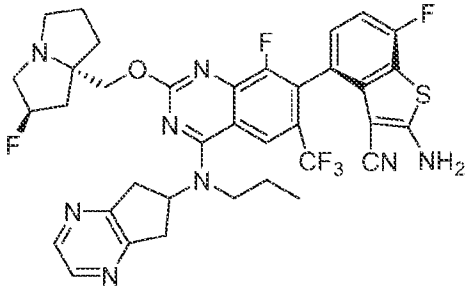
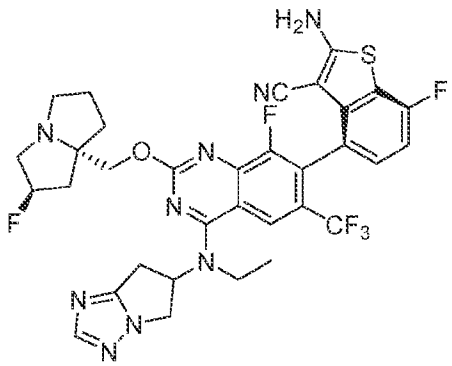
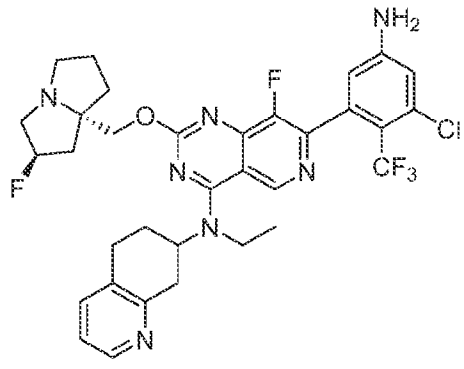
		(m, 3H), 1.90 – 2.11 (m, 1H), 1.43 – 1.54 (m, 3H), 1.34 – 1.43 (m, 3H).
526		LCMS m/z [M+1]: 772.1 1H NMR (400 MHz, CD3OD) δ 8.49 (s, 1H), 8.27 (s, 1H), 7.99 (s, 1H), 7.52 (s, 1H), 7.26 – 7.18 (m, 1H), 6.97 (t, J = 8.5 Hz, 1H), 5.47 (d, J = 50.8 Hz, 1H), 5.11 (s, 1H), 4.31 – 4.01 (m, 2H), 3.91 – 3.73 (m, 4H), 3.59 – 3.53 (m, 3H), 3.37 (m, 2H), 2.49– 2.42 (m, 1H), 2.22– 2.17 (m, 3H), 2.03– 1.79 (m, 3H), 1.61 (t, J = 6.3 Hz, 3H).
527		LCMS m/z [M+1]: 772.1 1H NMR (400 MHz, CD3OD) δ 8.48 (s, 1H), 8.27 (s, 1H), 7.99 (d, J = 6.3 Hz, 1H), 7.52 (s, 1H), 7.25 – 7.18 (m, 1H), 6.97 (t, J = 8.5 Hz, 1H), 5.48 (d, J = 48.5 Hz, 1H), 5.11 (s, 1H), 3.98 (d, J = 6.7 Hz, 2H), 3.78 (d, J = 12.6 Hz, 4H), 3.66 – 3.58 (m, 2H), 3.59 – 3.54 (m, 1H), 3.39 –3.31(m, 1H), 2.52 – 2.40 (m, 2H), 2.31 – 2.13 (m, 3H), 2.03 – 1.89 (m, 3H), 1.61 (t, J = 6.3 Hz, 3H).
528		1H NMR (400 MHz, CD3OD) δ 8.47 (s, 1H), 8.29 (s, 1H), 8.18 (s, 1H), 7.29 – 7.17 (m, 1H), 7.09 – 6.98 (m, 1H), 5.47 (d, J = 53.4 Hz, 2H), 5.23 – 5.13 (m, 1H), 4.45 (d, J = 12.6 Hz, 1H), 4.28 (d, J = 12.8 Hz, 1H), 4.03 – 3.92 (m, 2H), 3.92 – 3.74 (m, 4H), 3.74 – 3.60 (m, 3H), 3.44 – 3.34 (m, 2H), 2.86 (q, J = 7.5 Hz, 2H), 2.54 –

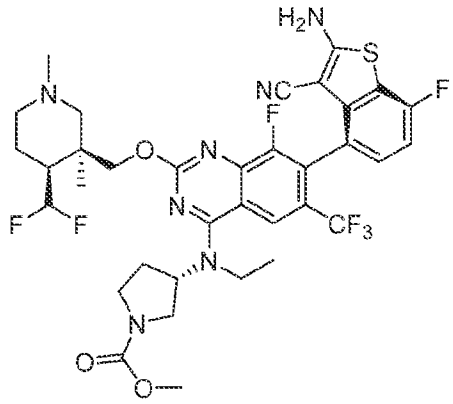
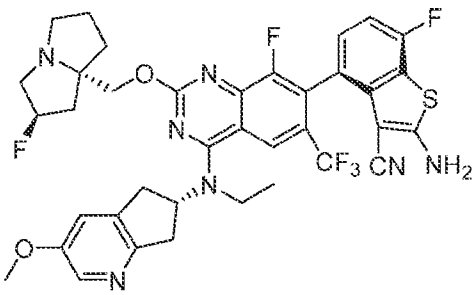
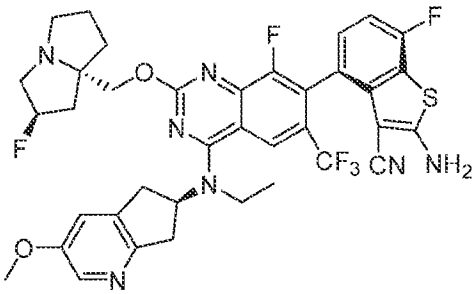
		2.37 (m, 2H), 2.29 – 2.08 (m, 3H), 1.89 (ddd, J = 16.5, 11.6, 4.6 Hz, 1H), 1.60 (t, J = 7.0 Hz, 3H), 1.35 (t, J = 7.6 Hz, 3H).
529		1H NMR (400 MHz, CD3OD) δ 8.44 (s, 1H), 8.29 (s, 1H), 8.11 (s, 1H), 7.23 (dd, J = 8.2, 4.8 Hz, 1H), 7.10 – 6.99 (m, 1H), 5.48 (d, J = 51.3 Hz, 2H), 5.24 – 5.09 (m, 1H), 4.37 (d, J = 12.5 Hz, 1H), 4.21 (d, J = 12.5 Hz, 1H), 4.04 – 3.92 (m, 2H), 3.93 – 3.72 (m, 4H), 3.66 (t, J = 11.0 Hz, 3H), 3.44 – 3.35 (m, 1H), 2.84 (q, J = 7.6 Hz, 2H), 2.46 (d, J = 28.9 Hz, 2H), 2.22 (dt, J = 15.1, 10.8 Hz, 2H), 2.08 (t, J = 10.5 Hz, 1H), 1.95 – 1.84 (m, 1H), 1.61 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.6 Hz, 3H).
530		LCMS m/z [M+1]: 765.3 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.25-7.17 (m, 1H), 7.01 (t, 1H), 5.02-4.89 (m, 1H), 4.55 (d, 1H), 4.47 (d, 1H), 3.96-3.84 (m, 3H), 3.76-3.69 (m, 4H), 3.66-3.60 (m, 6H), 3.57-3.54 (m, 1H), 3.48-3.41 (m, 2H), 2.42-2.40 (m, 1H), 2.26-2.23 (m, 1H), 2.20-2.17 (m, 1H), 2.03-2.01 (m, 1H), 1.62-1.57 (m, 3H), 1.46 (t, 3H).
531		LCMS m/z [M+1]: 730.3 1H NMR (400 MHz, CD3OD) δ 9.00 (s, 1H), 8.27 (s, 1H), 7.24 (dd, J = 8.2, 5.1 Hz, 1H), 7.08 – 6.99 (m, 1H), 5.51 (d, J = 51.7 Hz, 1H), 5.33 (t, J = 6.3 Hz, 1H), 4.10 – 3.79 (m, 7H), 3.68 –

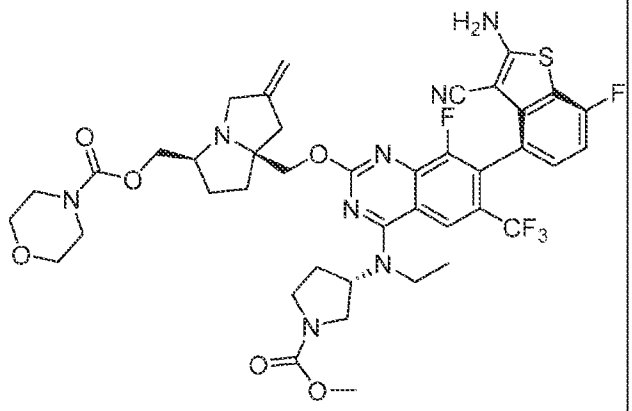
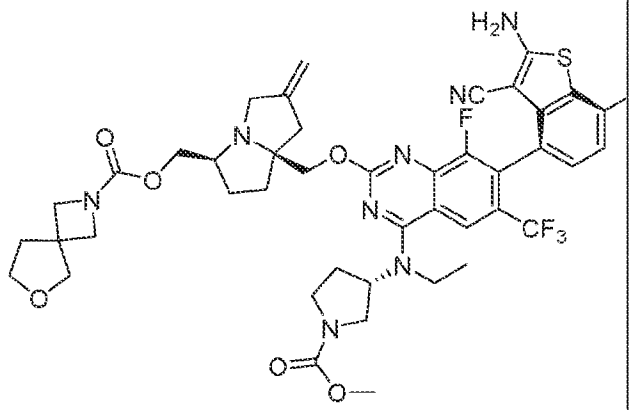
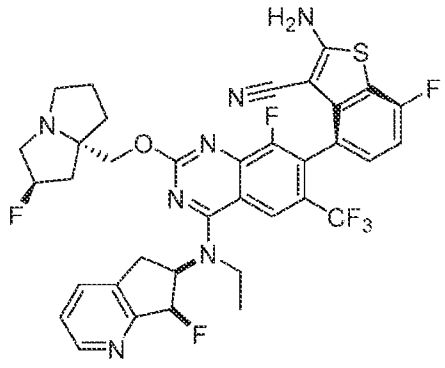
		3.32 (m, 6H), 2.61 – 2.41 (m, 2H), 2.32 – 2.16 (m, 2H), 2.06 – 1.92 (m, 2H), 1.63 (t, J = 7.0 Hz, 3H).
532		LCMS m/z [M+1]: 730.3 1H NMR (400 MHz, CD3OD) δ 8.96 (s, 1H), 8.24 (s, 1H), 7.22 (dd, J = 8.3, 5.0 Hz, 1H), 7.05 – 6.99 (m, 1H), 5.38 (d, J = 51.0 Hz, 2H), 4.59 (s, 1H), 3.99 – 3.82 (m, 4H), 3.65 – 3.39 (m, 7H), 3.20 – 3.13 (m, 1H), 2.39 – 2.21 (m, 2H), 2.12 – 1.98 (m, 2H), 1.92 – 1.81 (m, 2H), 1.61 (t, J = 7.0 Hz, 3H).
533		1H NMR (400 MHz, CD3OD) δ 8.43 (s, 1H), 8.27 (s, 1H), 7.93 (s, 1H), 7.23 (dd, J = 8.3, 5.0 Hz, 1H), 7.10 – 6.98 (m, 1H), 5.48 (d, J = 52.1 Hz, 1H), 5.17 – 5.07 (m, 1H), 4.38 (d, J = 12.5 Hz, 1H), 4.23 (d, J = 12.5 Hz, 1H), 3.98 (q, J = 7.0 Hz, 2H), 3.89 – 3.74 (m, 4H), 3.72 – 3.57 (m, 3H), 3.43 – 3.35 (m, 1H), 2.52 – 2.35 (m, 2H), 2.29 – 2.07 (m, 4H), 1.94 – 1.83 (m, 1H), 1.61 (t, J = 7.0 Hz, 3H), 1.26 – 1.19 (m, 2H), 0.95 – 0.88 (m, 2H).
534		1H NMR (400 MHz, CD3OD) δ 8.42 (s, 1H), 8.27 (s, 1H), 7.89 (s, 1H), 7.23 (dd, J = 8.3, 5.1 Hz, 1H), 7.08 – 6.98 (m, 1H), 5.48 (d, J = 51.9 Hz, 1H), 5.13 (dt, J = 16.8, 8.3 Hz, 1H), 4.34 (d, J = 12.4 Hz, 1H), 4.19 (d, J = 12.4 Hz, 1H), 3.96 (tt, J = 9.8, 4.7 Hz, 2H), 3.90 – 3.56 (m, 7H), 3.44 – 3.35 (m, 1H), 2.53 – 2.38 (m, 2H), 2.31 – 2.02 (m, 4H), 1.94 – 1.84 (m, 1H),

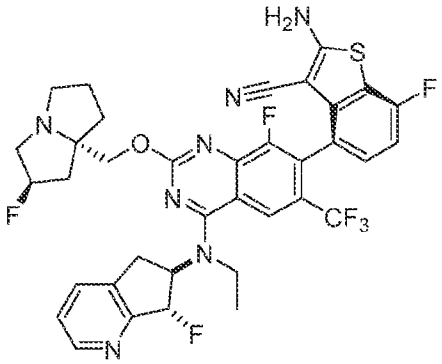
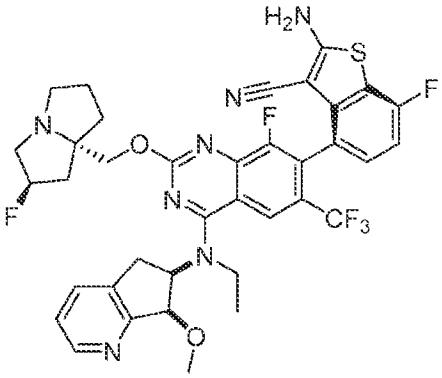
		1.61 (t, J = 7.0 Hz, 3H), 1.22 (td, J = 6.3, 4.6 Hz, 2H), 0.94 – 0.87 (m, 2H).
535		1H NMR (400 MHz, CD3OD) δ 8.57 (s, 1H), 8.26 (d, J = 20.0 Hz, 2H), 7.23 (dd, J = 8.3, 5.1 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.88 (dd, J = 17.6, 11.2 Hz, 1H), 6.08 (d, J = 17.7 Hz, 1H), 5.51 (dd, J = 39.0, 31.7 Hz, 2H), 5.15 – 5.05 (m, 1H), 4.28 (d, J = 12.4 Hz, 1H), 4.12 (d, J = 12.5 Hz, 1H), 3.99 (q, J = 6.9 Hz, 2H), 3.88 – 3.73 (m, 4H), 3.70 – 3.56 (m, 3H), 3.36 (dd, J = 15.5, 9.4 Hz, 1H), 2.51 – 2.34 (m, 2H), 2.26 – 2.12 (m, 2H), 2.02 (dd, J = 14.0, 8.9 Hz, 1H), 1.83 (dd, J = 18.2, 10.5 Hz, 1H), 1.63 (t, J = 7.0 Hz, 3H).
536		1H NMR (400 MHz, CD3OD) δ 8.55 (s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 7.23 (dd, J = 8.4, 5.0 Hz, 1H), 7.08 – 6.99 (m, 1H), 6.87 (dd, J = 17.7, 11.1 Hz, 1H), 6.07 (d, J = 17.6 Hz, 1H), 5.49 (t, J = 32.2 Hz, 3H), 5.14 – 5.07 (m, 1H), 4.23 (d, J = 12.3 Hz, 1H), 4.07 (d, J = 12.3 Hz, 1H), 3.99 (dt, J = 9.7, 7.0 Hz, 2H), 3.76 (dt, J = 12.7, 12.2 Hz, 4H), 3.69 – 3.55 (m, 3H), 3.41 – 3.34 (m, 1H), 2.52 – 2.37 (m, 2H), 2.26 – 2.12 (m, 2H), 1.98 (dd, J = 12.0, 4.8 Hz, 1H), 1.89 – 1.80 (m, 1H), 1.63 (t, J = 7.0 Hz, 3H).

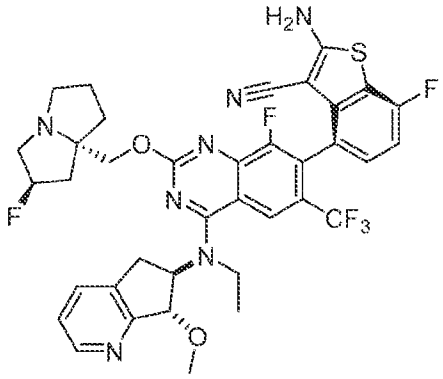
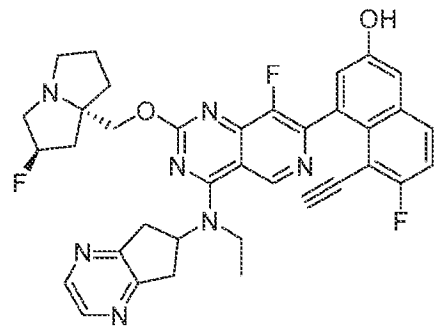
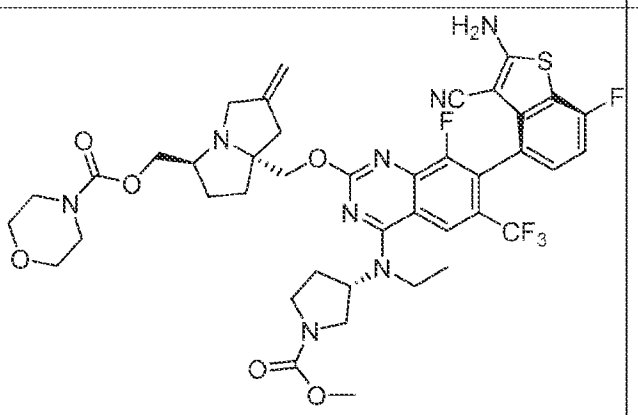
537		LCMS m/z [M+1]: 714.2 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.55 (s, 1H), 7.24-7.19 (m, 1H), 7.01 (t, 1H), 5.44-5.34 (m, 1H), 5.33 (s, 0.5H), 5.19 (s, 0.5H), 5.00-4.93 (m, 1H), 4.78-4.71 (m, 1H), 3.99-3.88 (m, 2H), 3.64-3.43 (m, 4H), 3.20-3.07 (m, 3H), 3.00-2.92 (m, 1H), 2.21-1.99 (m, 2H), 1.96-1.79 (m, 4H), 1.63 (t, 3H).
538		LCMS m/z [M+1]: 661.2 1H NMR (400 MHz, CD3OD) δ 9.02 (s, 1H), 8.39 (s, 1H), 6.90 (d, 1H), 6.50 (d, 1H), 5.28-5.24 (m, 0.5H), 5.15-5.10 (m, 0.5H), 5.05-4.98 (m, 1H), 4.68-4.60 (m, 1H), 4.05-3.97 (m, 2H), 3.77-3.64 (m, 4H), 3.57-3.49 (m, 2H), 3.16-3.10 (m, 2H), 2.98-2.90 (m, 1H), 2.10-2.05 (m, 1H), 2.02-1.97 (m, 1H), 1.94-1.87 (m, 1H), 1.85-1.65 (m, 1H), 1.60 (t, 3H).
539		LCMS m/z [M+1]: 748.3 1H NMR (400 MHz, CD3OD) δ 8.36(m 1H), 7.23 – 7.21 (m, 1H), 7.05-7.01 (m. 1H), 5.62-5.50 (m, 1H), 5.38 – 5.24 (m, 1H),4.76 – 4.59 (m, 2H), 4.07 – 3.87 (m, 4H), 3.76 – 3.73 (m, 4H), 3.63 – 3.43 (m, 6H), 2.72 – 2.58 (m, 2H), 2.42 – 2.34 (m, 5H), 2.15 – 1.99 (m, 1H).

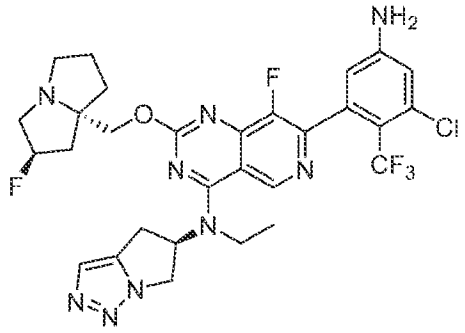
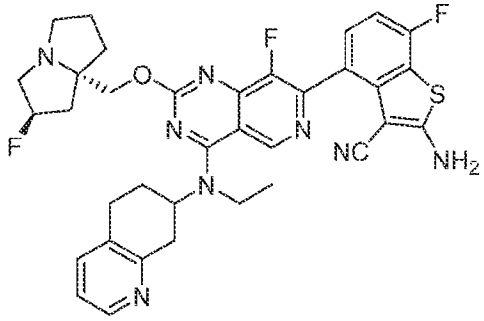
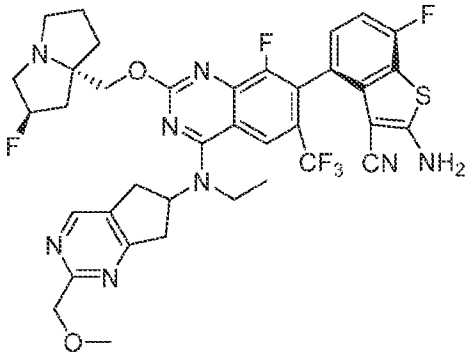
540		LCMS m/z [M+1]: 839 1H NMR (400 MHz, CD3OD): δ 8.40 (s, 2H), 8.18 (s, 1H), 7.24 - 7.21 (m, 1H), 7.01 (t, J = 9.0 Hz, 1H), 5.48 (d, J = 53.6 Hz, 1H), 5.04 - 4.95 (m, 1H), 3.89 - 3.80 (m, 4H), 3.72 - 3.47 (m, 4H), 3.34 - 3.18 (m, 1H), 3.15-3.25 (m, 1H), 3.09 - 3.02 (m, 1H). 2.24 - 1.73 (m, 8H), 1.70 (t, J = 7.2 Hz, 3H).
541		LCMS m/z [M+1]: 714.3 1H NMR (400 MHz, CD3OD) δ 8.20 (s, 1H), 8.04 (s, 1H), 7.19-7.23 (m, 1H), 7.01 (t, 1H), 5.26-5.34 (m, 1.5H), 5.19 (s, 0.5H), 4.63-4.69 (m, 1H), 4.51-4.56 (m, 1H), 3.92-3.97 (m, 2H), 3.58-3.69 (m, 3H), 3.52-3.56 (m, 1H), 3.36-3.43 (m, 1H), 3.16-3.21 (m, 2H), 2.95-3.01 (m, 1H), 2.16-2.20 (m, 1H), 2.02-2.11 (m, 2H), 1.88-1.91 (m, 2H), 1.76-1.82 (m, 1H), 1.63 (t, 3H).
542		LCMS m/z [M+1]: 674.3 1H NMR (400 MHz, CD3OD) δ 9.05 (s, 1H), 8.33 (d, 1H), 7.65 (d, 1H), 7.25 (dd, 1H), 6.90 (d, 1H), 6.50 (d, 1H), 5.40-5.27 (m, 1H), 5.08 (s, 1H), 4.31 (dt, 2H), 4.01-3.98 (m, 2H), 3.52-3.37 (m, 3H), 3.15-3.01 (m, 3H), 2.42-2.24 (m, 4H), 2.23-2.16 (m, 1H), 2.15-1.95 (m, 4H), 1.87 (s, 1H), 1.53 (t, 3H).

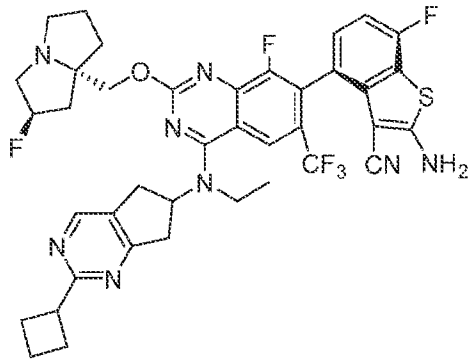
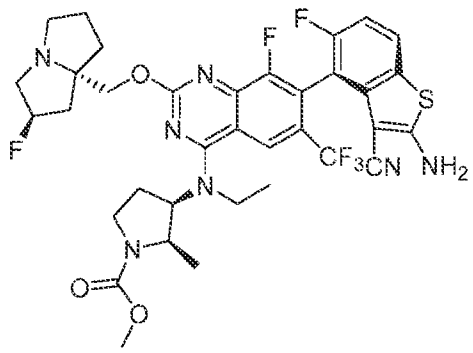
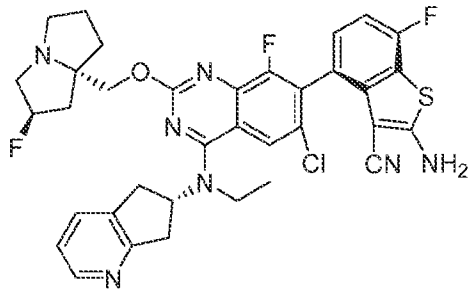
543		LCMS m/z [M+1]: 652.2 1H NMR (400 MHz, CD3OD) δ 9.02 (s, 1H), 8.40 (s, 2H),7.86-7.83 (m, 1H), 7.34-7.29 (m, 2H), 7.20 (d, 1H), 5.24 (s, 0.5H), 5.10 (s, 0.5H), 5.06-5.00 (m, 1H), 4.05-4.02 (m, 2H), 3.78-3.67 (m, 4H), 3.58-3.48 (m, 2H), 3.12-3.03 (m, 3H), 2.99-2.88 (m, 2H), 2.05-2.00 (m, 3H), 1.97 (s, 1H), 1.90-1.85 (m, 1H), 1.81-1.76 (m, 1H), 1.64 (t, 3H).
545		1H NMR (400 MHz, CD3OD) δ 8.57 (s, 1H), 8.26 (d, J = 20.0 Hz, 2H), 7.23 (dd, J = 8.3, 5.1 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.88 (dd, J = 17.6, 11.2 Hz, 1H), 6.08 (d, J = 17.7 Hz, 1H), 5.51 (dd, J = 39.0, 31.7 Hz, 2H), 5.15 – 5.05 (m, 1H), 4.28 (d, J = 12.4 Hz, 1H), 4.12 (d, J = 12.5 Hz, 1H), 3.99 (q, J = 6.9 Hz, 2H), 3.88 – 3.73 (m, 4H), 3.70 – 3.56 (m, 3H), 3.36 (dd, J = 15.5, 9.4 Hz, 1H), 2.51 – 2.34 (m, 2H), 2.26 – 2.12 (m, 2H), 2.02 (dd, J = 14.0, 8.9 Hz, 1H), 1.83 (dd, J = 18.2, 10.5 Hz, 1H), 1.63 (t, J = 7.0 Hz, 3H).
546		1H NMR (400 MHz, CD3OD) δ 8.55 (s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 7.23 (dd, J = 8.4, 5.0 Hz, 1H), 7.08 – 6.99 (m, 1H), 6.87 (dd, J = 17.7, 11.1 Hz, 1H), 6.07 (d, J = 17.6 Hz, 1H), 5.49 (t, J = 32.2 Hz, 3H), 5.14 – 5.07 (m, 1H), 4.23 (d, J = 12.3 Hz, 1H), 4.07 (d, J = 12.3 Hz, 1H), 3.99 (dt, J =

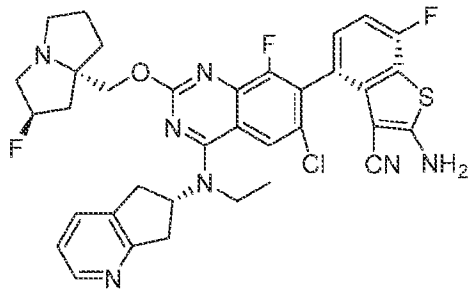
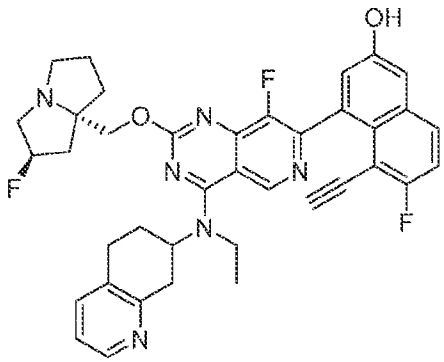
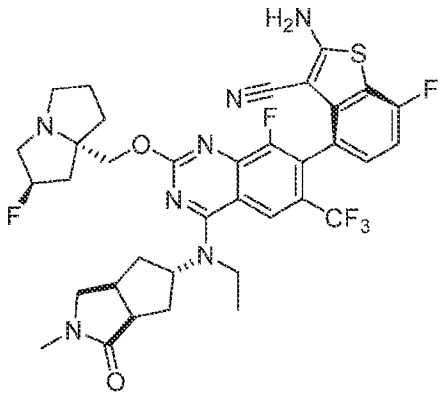
		9.7, 7.0 Hz, 2H), 3.76 (dt, J = 12.7, 12.2 Hz, 4H), 3.69 – 3.55 (m, 3H), 3.41 – 3.34 (m, 1H), 2.52 – 2.37 (m, 2H), 2.26 – 2.12 (m, 2H), 1.98 (dd, J = 12.0, 4.8 Hz, 1H), 1.89 – 1.80 (m, 1H), 1.63 (t, J = 7.0 Hz, 3H).
547		LCMS m/z [M+1]: 871.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.26-7.20 (m, 1H), 7.01 (t, 1H), 5.05-4.93 (m, 3H), 4.28-4.20 (m, 1H), 4.18-4.15 (m, 1H) 4.12-4.06 (m, 1H), 4.01-3.64 (m, 9H), 3.64-3.40 (m, 5H), 3.48-3.36 (m, 5H), 3.12-3.05 (m, 1H), 2.68 (d, 1H), 2.50-2.16 (m, 5H), 2.08-2.02 (m, 1H), 1.85-1.74 (m, 2H), 1.43 (t, 3H).
549		LCMS m/z [M+1]: 897.3 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.26-7.20 (m, 1H), 7.01 (t, 1H), 5.04-4.94 (m, 3H), 4.32-4.25 (m, 1H), 4.20-4.14 (m, 1H) 4.10-4.04 (m, 1H), 4.01-3.80 (m, 8H), 3.79-3.69 (m, 8H), 3.61-3.35 (m, 4H), 3.12-3.02 (m, 1H), 2.70 (d, 1H), 2.48-2.32 (m, 3H), 2.28-2.21 (m, 1H), 2.14-2.02 (m, 3H). 1.85-1.75 (m, 2H), 1.44 (t, 3H).
550		LCMS m/z [M+1]: 742.2 1H NMR (400 MHz, CD3OD) δ 8.56 (d, 1H), 8.38 (s, 1H), 7.94 (d, 1H), 7.50-7.53 (m, 1H), 7.21-7.24 (m, 1H), 7.01 (t, 1H), 6.25 (d, 0.5H), 6.10 (d, 0.5H), 5.37-5.44 (m, 1.5H), 5.26 (s, 0.5H), 4.20-4.31 (m, 2H), 4.07-4.13 (m, 1H), 3.94-4.02 (m, 1H), 3.69-3.77

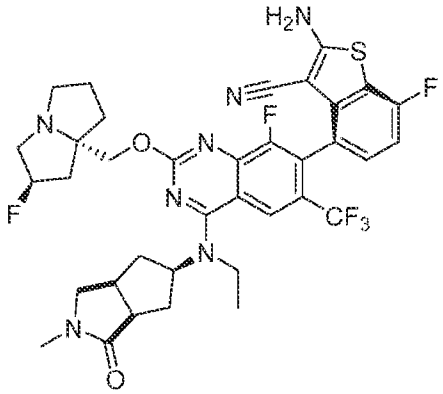
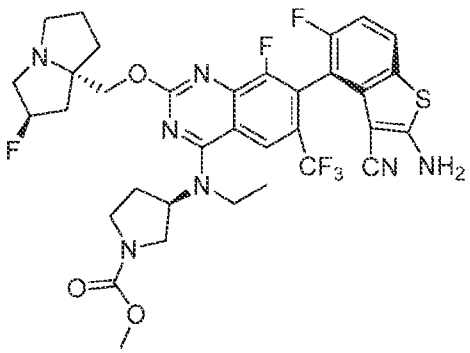
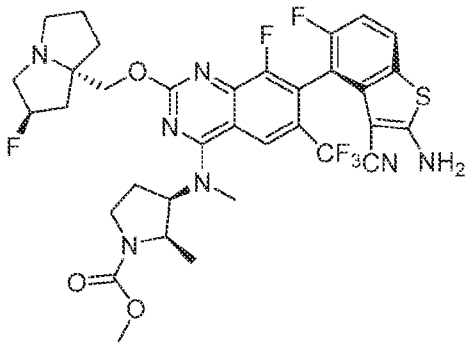
		(m, 1H), 3.43-3.47 (m, 2H), 3.35-3.37 (m, 1H), 3.04-3.09 (m, 2H), 2.21-2.30 (m, 2H), 2.01-2.12 (m, 3H), 1.82-1.93 (m, 1H), 1.50 (t, 3H).
551		LCMS m/z [M+1]:742.2 1H NMR (400 MHz, CD3OD) δ 8.56 (d, 1H), 8.38 (s, 1H), 7.94 (d, 1H), 7.49-7.53 (m, 1H), 7.19-7.24 (m, 1H), 6.98-7.04 (m, 1H), 6.25 (d, 0.5H), 6.10 (d, 0.5H), 5.35-5.44 (m, 1.5H), 5.26 (s, 0.5H), 4.20-4.30 (m, 2H), 4.07-4.11 (m, 1H), 3.94-4.00 (m, 1H), 3.70-3.77 (m, 1H), 3.40-3.51 (m, 2H), 3.35-3.37 (m, 1H), 3.04-3.12 (m, 2H), 2.10-2.36 (m, 3H), 1.87-2.03 (m, 3H), 1.50 (t, 3H).
552		LCMS m/z [M+1]:754.3 1H NMR (400 MHz, CD3OD) δ, 8.51 (d, J = 4.1 Hz, 1H), 8.35 (s, 1H), 7.78 (d, J = 7.1 Hz, 1H), 7.43 – 7.35 (m, J = 7.7, 4.9 Hz, 1H), 7.25 – 7.19 (m, J = 8.4, 5.0 Hz, 1H), 7.01 (s, 1H), 5.63 (d, J = 5.5 Hz, 1H), 5.29 (s, 0H), 5.15 (s, 0H), 4.63 – 4.53 (m, 1H), 4.06 – 3.96 (m, J = 14.7, 7.6 Hz, 2H), 3.73 (d, J = 10.7 Hz, 1H), 3.69 (s, 3H), 3.63 (d, J = 10.6 Hz, 1H), 3.59 – 3.52 (m, J = 16.5, 7.1 Hz, 1H), 3.46 – 3.39 (m, J = 16.5, 9.4 Hz, 1H), 3.26 – 3.10 (m, 3H), 3.01 – 2.93 (m, J = 14.9, 9.2 Hz, 1H), 2.21 – 1.75 (m, 5H), 1.66 (d, J = 6.9 Hz, 3H).

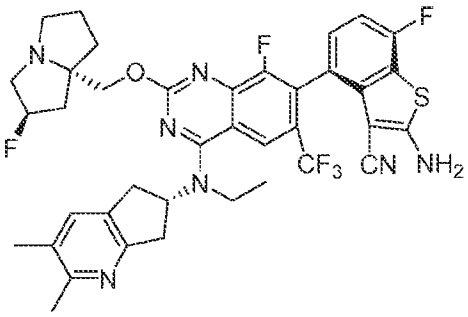
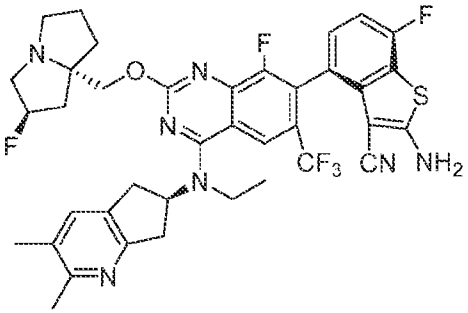
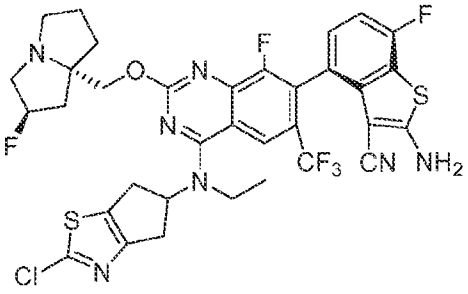
553		LCMS m/z [M+1]:754.2 1H NMR (400 MHz, CD3OD) δ 8.51 (d, J = 4.0 Hz, 1H), 8.37 (s, 1H), 7.78 (d, J = 7.0 Hz, 1H), 7.41 – 7.36 (m, J = 11.0, 6.1 Hz, 1H), 7.25 – 7.18 (m, J = 8.4, 5.1 Hz, 1H), 5.62 (d, J = 5.3 Hz, 1H), 5.34 (s, J = 4.5 Hz, 0.5H), 5.21 (s, 0.5H), 4.65 – 4.53 (m, 1H), 4.07 – 3.96 (m, 2H), 3.80 – 3.72 (m, J = 11.0 Hz, 2H), 3.69 (s, 3H), 3.50 (ddd, J = 21.8, 16.6, 7.0 Hz, 2H), 3.37 (s, 1H), 3.11 – 3.04 (m, 1H), 2.27 – 1.70 (m, 8H), 1.66 (t, J = 7.0 Hz, 3H).
554		LCMS m/z [M+1]: 752.2 1H NMR (400 MHz, CD3OD) δ 9.02 (s, 1H), 8.40 (s, 2H), 7.01 (t, 1H), 7.86-7.83 (m,1H), 7.34-7.28 (m,2H), 7.20 (d,1H), 5.24 (s, 0.5H), 5.10(s, 0.5H), 5.05-4.99 (m, 1H), 4.07-4.00 (m, 2H), 3.77-3.67 (m, 4H), 3.58-3.51 (m, 2H), 3.12-3.03 (m, 3H), 2.99-2.89 (m, 2H), 2.06-2.00 (m, 3H), 1.98-1.95 (m, 1H), 1.90-1.85 (m, 1H), 1.81-1.76 (m, 1H), 1.64 (t, 3H).
555		LCMS m/z [M+1]:891.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.23-7.20 (m, 1H), 7.03-6.99 (m, 1H), 4.87 (d, 2H), 4.44-4.25 (m, 4H), 3.86-3.29 (m, 20H), 2.80 (d, 1H), 2.62 (d, 1H), 2.50-2.30 (m, 2H), 2.21-2.13 (m, 1H), 2.08-2.01 (m, 1H), 1.98-1.85 (m, 2H), 1.45 (t, 3H).

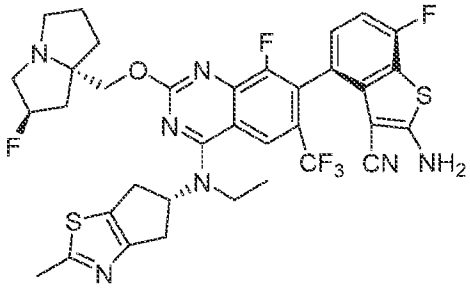
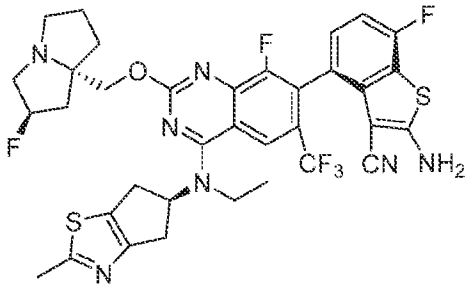
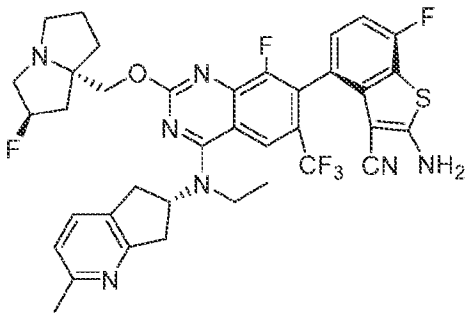
556		LCMS m/z [M+1]: 650.1 1H NMR (400 MHz, CD3OD) δ 9.05 (s, 1H), 7.58 (s, 1H), 6.91 (d, 1H), 6.50 (d, 1H), 5.47 (s, 0.5H), 5.39 (m, 1H), 5.33 (s, 0.5H), 4.98-4.91 (m, 1H), 4.79-4.73 (m, 1H), 4.10-4.00 (m, 2H), 3.72 (s, 2H), 3.56-3.41 (m, 5H), 3.21-3.14 (m, 1H), 2.27-2.20 (m, 1H), 2.17-1.96 (m, 4H), 1.94-1.85 (m, 1H), 1.63 (t, 3H).
557		LCMS m/z [M+1]: 671.3 1H NMR (400 MHz, CD3OD) δ 9.12 (s, 1H), 8.33 (d, 1H), 7.63 (d, 1H), 7.40 (d, 1H), 7.26-7.23 (m, 1H), 7.05 (t, 1H), 5.48 (s, 0.5H), 5.35 (s, 0.5H), 5.14-5.04 (m, 1H), 4.55-4.32 (m, 2H), 4.10-3.94 (m, 2H), 3.79-3.37 (m, 6H), 3.38-3.32 (m, 2H), 3.08-3.01 (m, 2H), 2.56-2.34 (m, 3H), 2.33-2.25 (m, 1H), 2.21-2.09 (m, 3H), 2.02-1.92 (m, 1H), 1.55 (t, 3H).
558		LCMS m/z [M+1]: 769.3 1H NMR (400 MHz, CD3OD) δ 8.58 (s, 1H), 8.33 (s, 1H), 7.23 – 7.20 (m, 1H), 7.02 (t, J = 8.9 Hz, 1H), 5.88 – 5.84 (m, 1H), 5.56 (d, J = 52.4 Hz, 1H), 4.64 (s, 2H), 4.40 – 4.37 (m, 1H), 4.16 – 3.845 (m, 6H), 3.52 (s, 3H), 3.47 – 3.35 (m, 2H), 3.21 – 3.12 (m, 1H), 2.80 – 2.06 (m, 8H), 1.62 – 1.58 (m, 3H).

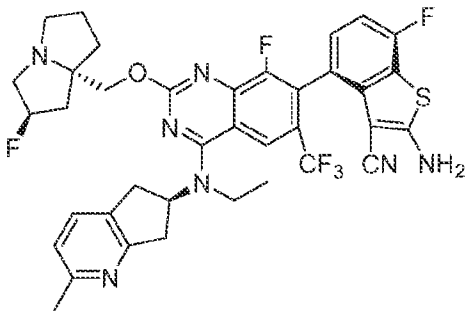
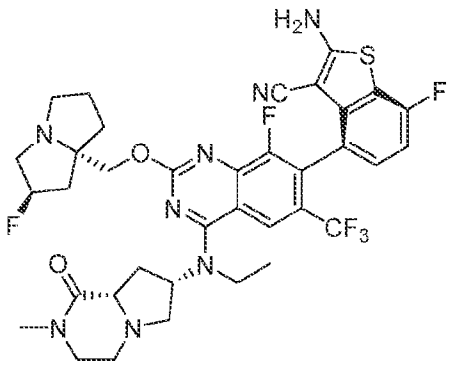
559		LCMS m/z [M+1]: 779.3 1H NMR (400 MHz, CD3OD) δ 8.55 (s, 1H), 8.34 (s, 1H), 7.23 – 7.20 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 5.97 – 5.93 (m, 1H), 5.56 (d, J = 52.0 Hz, 1H), 4.56 – 3.76 (m, 8H), 3.48 – 3.35 (m, 2H), 3.21 – 3.12 (m, 1H), 2.80 – 1.93 (m, 14H), 1.54 – 1.51 (m, 3H).
560		LCMS m/z [M+1]: 748.3 1H NMR (400 MHz, CD3OD) δ 8.38 (s, 1H), 7.23 – 7.26 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.57 (d, J = 52.0 Hz, 1H), 4.65 – 4.72 (m, 4H), 4.01 – 4.09 (m, 1H), 3.87 – 4.06 (m, 4H), 3.62 – 3.69 (m, 4H), 3.38 – 3.50 (m, 2H), 2.53 – 2.75 (m, 3H), 2.25 – 2.49 (m, 4H), 2.07 – 2.22 (m, 1H), 1.48 (t, J = 8.0 Hz, 3H), 1.01 (d, J = 8.0 Hz, 3H).
561		LCMS m/z [M+1]: 690.2 1H NMR (400 MHz, CD3OD) δ 8.51 (s, 1H), 8.11 (d, J = 7.5 Hz, 1H), 8.00 (s, 1H), 7.65 – 7.57 (m, 1H), 7.22 (dd, J = 8.3, 5.1 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 5.48 (d, J = 51.2 Hz, 1H), 5.13 (m, 1H), 4.39 (d, J = 12.5 Hz, 1H), 4.19 (d, J = 12.6 Hz, 1H), 3.97 (q, J = 7.1 Hz, 2H), 3.84 – 3.39 (m, 8H), 2.51 – 2.38 (m, 2H), 2.26 – 2.09 (m, 3H), 1.87 (s, 1H), 1.56 (t, J = 7.0 Hz, 3H).

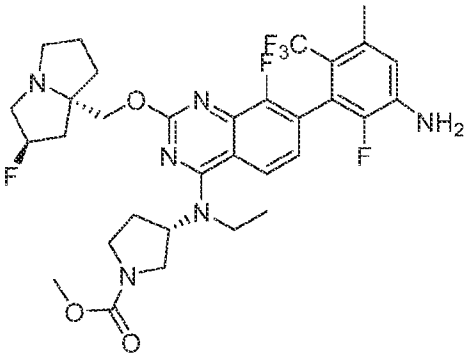
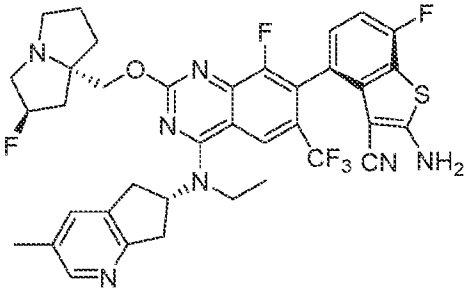
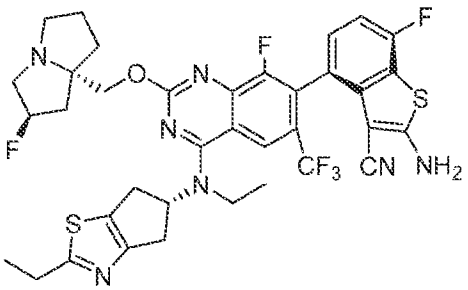
562		LCMS m/z [M+1]: 690.2 1H NMR (400 MHz, CD3OD) δ 8.55 (s, 1H), 8.18 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 1.5 Hz, 1H), 7.74 – 7.63 (m, 1H), 7.23 (dd, J = 8.4, 5.1 Hz, 1H), 7.10 – 7.02 (m, 1H), 5.46 (d, J = 50.5 Hz, 1H), 5.13 (d, J = 6.1 Hz, 1H), 4.31 (s, 2H), 4.03 – 3.92 (m, 2H), 3.86 – 3.53 (m, 7H), 3.44 – 3.37 (m, 1H), 2.51 – 2.37 (m, 2H), 2.22 (m, 2H), 2.12 (m, 1H), 1.95 (m, 1H), 1.56 (t, J = 7.0 Hz, 3H).
563		LCMS m/z [M+1]: 665.3 1H NMR (400 MHz, CD3OD) δ 9.07 (d, 1H), 8.34 (d, 1H), 7.87-7.83 (m, 1H), 7.65 (d, 1H), 7.37-7.28 (m, 2H), 7.28-7.18 (m, 2H). 5.35 (s, 0.5H), 5.22 (s, 0.5H), 5.16-5.07 (m, 1H), 4.34-4.19 (m, 2H), 4.09-3.96 (m, 2H), 3.59-3.31 (m, 5H), 3.26-3.14 (m, 2H), 3.11-2.97 (m, 3H), 2.41-2.18 (m, 4H), 2.06-1.92 (m, 3H), 1.86-1.76 (m, 1H), 1.57 (t, 3H)
564		LCMS m/z [M+1]: 744.3 1H NMR (400 MHz, CD3OD) δ 8.20 (s, 1H), 7.22-7.19 (m, 1H), 7.00 (t, 1H), 5.39 (s, 0.5H), 5.26 (s,0.5H), 4.36-4.24 (m, 2H), 3.76-3.65 (m, 3H), 3.32-3.31 (m,1H), 3.28-3.26 (m,2H), 3.08-3.01 (m,2H), 2.88 (t,3H), 2.78-2.74 (m, 1H), 2.51-2.16 (m, 6H), 2.07-1.79 (m, 6H),1.40 (t,3H).

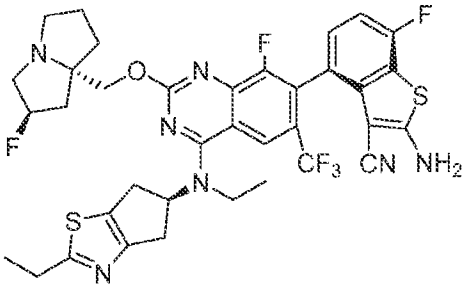
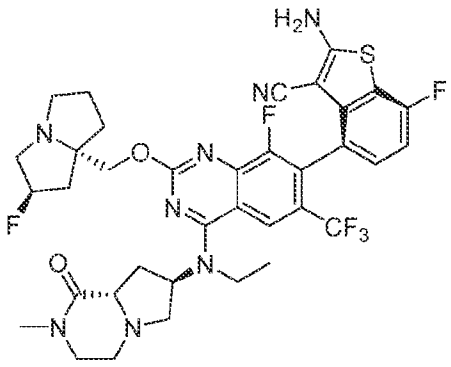
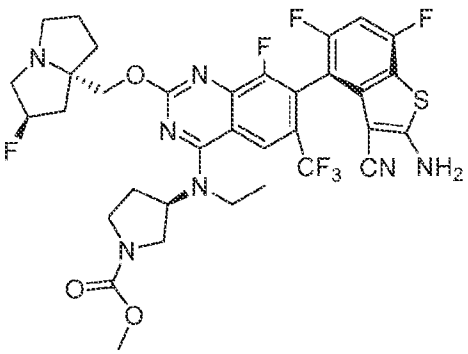
565		LCMS m/z [M+1]: 744.3 1H NMR (400 MHz, CD3OD) δ 8.20 (s, 1H), 7.22-7.19 (m, 1H), 7.00 (t, 1H), 5.41 (s, 0.5H), 5.27 (s,0.5H), 4.38-4.36 (m, 1H), 4.29-4.26 (m, 1H) 3.82-3.78 (m, 1H), 3.74-3.66 (m,2H), 3.48-3.32 (m,3H), 3.12-3.07 (m,1H), 3.05-2.99(m, 1H), 2.88 (t,3H), 2.80-2.76 (m, 1H), 2.49-2.17 (m, 6H), 2.09-1.81 (m, 6H),1.39 (t,3H) .
566		LCMS m/z [M+1]: 734.2 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 7.25-7.21 (m, 1H), 7.03 (t, J = 8.0 Hz, 1H), 5.56 (d, J = 52.0 Hz, 1H), 5.04 (t, J = 8.0 Hz, 1H), 4.73 – 4.57 (m, 2H), 3.95 – 3.67 (m, 13H), 3.49 – 3.45 (m, 2H), 2.60 – 2.30 (m, 7H), 1.51 – 1.47 (t, J = 8.0 Hz, 3H).
567		LCMS m/z [M+1]: 734.3 1H NMR (400 MHz, CD3OD) δ 8.41 (s, 1H), 7.20 – 7.26 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.57 (d, J = 52.0 Hz, 1H), 4.68-4.74 (m, 2H), 4.62 (d, J = 12.4 Hz, 1H), 3.87 – 4.06 (m, 3H), 3.73 (s, 3H), 3.62 – 3.69 (m, 4H), 3.38 – 3.50 (m, 3H), 2.53 – 2.70 (m, 3H), 2.29 – 2.46 (m, 4H), 2.07 – 2.18 (m, 1H), 1.08 (d, J = 6.6 Hz, 3H).

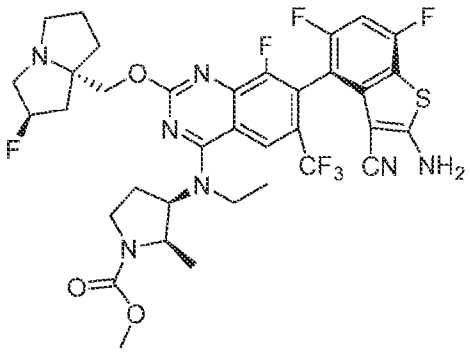
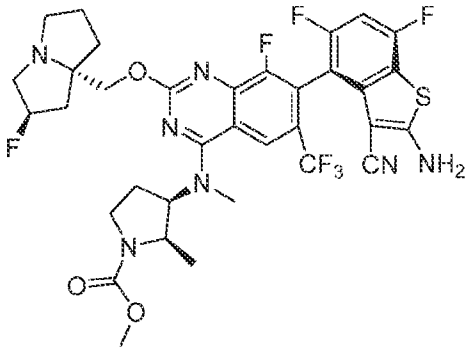
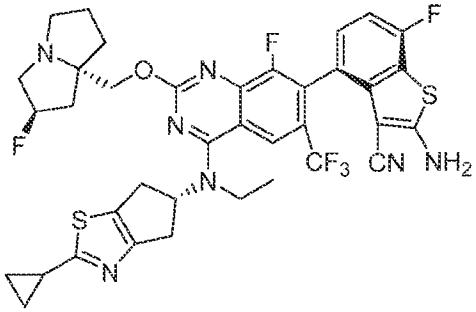
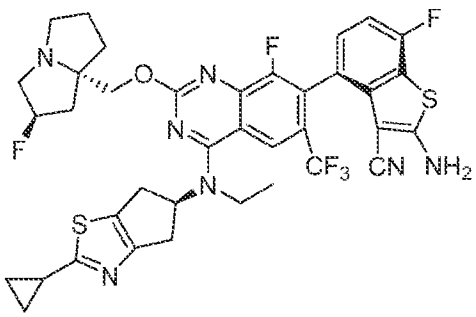
568		LCMS m/z [M+1]: 752.3 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 8.19 (s, 1H), 7.18-7.28 (m, 1H), 7.03 (dd, J = 9.4, 8.4 Hz, 1H), 5.40 (d, J = 52 Hz, 1H), 5.17-5.30 (m, 1H), 4.40 (dd, J = 72.3, 12.6 Hz, 2H), 3.65-4.02 (m, 7H), 3.60 (d, J = 7.7 Hz, 2H), 3.34-3.45 (m, 1H), 2.71 (s, 3H), 2.40-2.54 (m, 5H), 2.09-2.31 (m, 3H), 1.83-1.94 (m, 1H), 1.54-1.62 (m, 3H).
569		LCMS m/z [M+1]: 752.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 8.12 (s, 1H), 7.18-7.29 (m, 1H), 7.03 (dd, J = 9.4, 8.4 Hz, 1H), 5.40 (d, J = 52 Hz, 1H), 5.16-5.32 (m, 1H), 4.40 (dd, J = 72.3, 12.6 Hz, 2H), 3.66-4.02 (m, 7H), 3.60 (d, J = 7.7 Hz, 2H), 3.35-3.45 (m, 1H), 2.71 (s, 3H), 2.39-2.56 (m, 5H), 2.10-2.30 (m, 3H), 1.82-1.95 (m, 1H), 1.53-1.65 (m, 3H).
570		LCMS m/z [M+1]: 764.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.23 (dd, J = 8.3, 5.1 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.54 (d, J = 52.5 Hz, 1H), 5.26 – 5.17 (m, 1H), 4.22 – 3.77 (m, 8H), 3.65 – 3.36 (m, 5H), 2.68 – 2.46 (m, 2H), 2.35 – 2.22 (m, 2H), 2.11 – 1.94 (m, 2H), 1.67 – 1.60 (m, 3H).

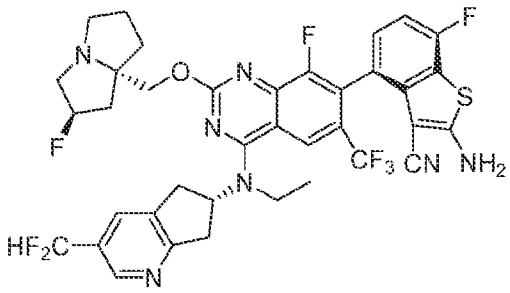
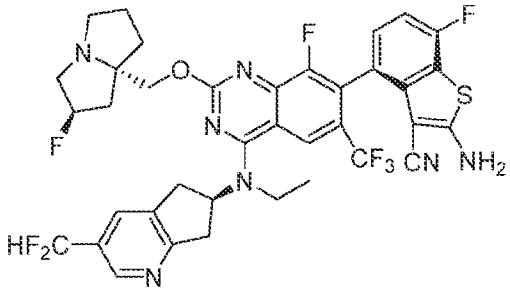
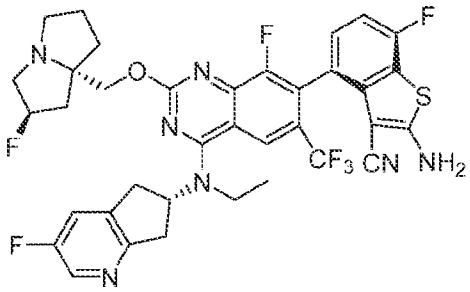
571		LCMS m/z [M+1]: 744.3 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.26 – 7.21 (m, 1H), 7.04 (d, J = 9.1 Hz, 1H), 5.52 (d, J = 51.5 Hz, 1H), 5.32 – 5.25 (m, 1H), 4.20 – 4.14 (m, 1H), 4.04 – 3.92 (m, 4H), 3.89 – 3.81 (m, 2H), 3.58 – 3.48 (m, 2H), 3.44 – 3.37 (m, 2H), 3.28 – 3.22 (m, 1H), 2.73 (s, 3H), 2.59 – 2.45 (m, 2H), 2.32 – 2.20 (m, 2H), 2.04 – 1.94 (m, 2H), 1.61 (t, J = 6.9 Hz, 3H).
572		LCMS m/z [M+1]: 744.3 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.23 (dd, J = 8.4, 5.0 Hz, 1H), 7.07 – 6.99 (m, 1H), 5.54 (d, J = 51.7 Hz, 1H), 5.28 – 5.21 (m, 1H), 4.11 – 3.79 (m, 7H), 3.62 – 3.49 (m, 2H), 3.44 – 3.35 (m, 2H), 3.29 – 3.22 (m, 1H), 2.73 (s, 3H), 2.67 – 2.44 (m, 2H), 2.34 – 2.18 (m, 2H), 1.99 – 1.85 (m, 2H), 1.62 (t, J = 7.0 Hz, 3H).
573		LCMS m/z [M+1]: 738.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.20 – 7.25 (m, 1H), 7.03 (t, J = 8.4 Hz, 1H), 5.47 (d, J = 52.0 Hz, 1H), 5.15 – 5.25 (m, 1H), 4.48 (d, J = 12.8 Hz, 1H), 4.29 (d, J = 12.8 Hz, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.68 – 3.91 (m, 5H), 3.55 – 3.66 (m, 2H), 3.35 – 3.44 (m, 1H), 2.75 (s, 3H), 2.39 – 2.54 (m, 2H), 2.06 – 2.29 (m, 3H), 1.83 – 1.95 (m, 1H), 1.59 (t, J = 6.8 Hz, 3H).

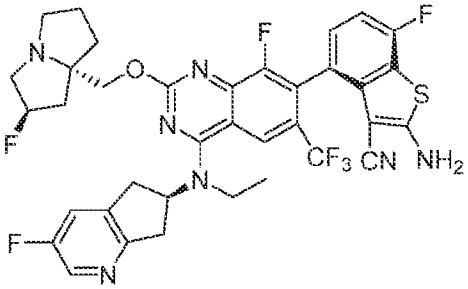
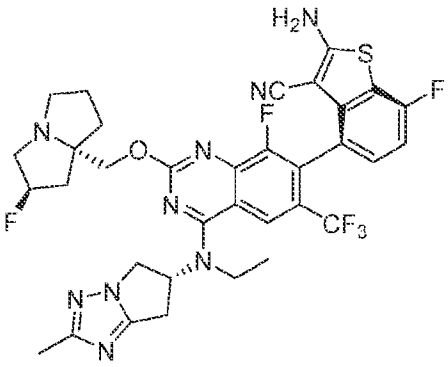
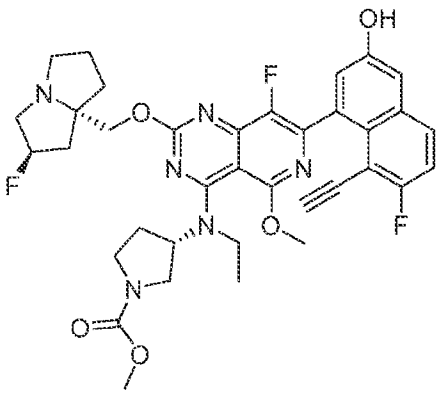
574		LCMS m/z [M+1]: 738.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.20 – 7.25 (m, 1H), 7.03 (t, J = 8.0 Hz, 1H), 5.47 (d, J = 53.6 Hz, 1H), 5.14 – 5.24 (m, 1H), 4.41 (d, J = 12.4 Hz, 1H), 4.28 (d, J = 12.4 Hz, 1H), 3.94 – 4.02 (m, 2H), 3.68 – 3.91 (m, 5H) , 3.62 (d, J = 7.6 Hz, 2H), 3.35 – 3.43 (m, 1H), 2.73 (s, 3H) , 2.40 – 2.52 (m, 2H) , 2.06 – 2.30 (m, 3H), 1.85 – 1.97 (m, 1H) , 1.60 (t, J = 7.2 Hz, 3H).
575		LCMS m/z [M+1]: 759.1 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 7.26 – 7.20 (m, J = 8.3, 4.9 Hz, 1H), 7.07 – 7.00 (m, 1H), 5.62 (s, 0.5 H), 5.49 (s, 0.5 H), 5.13 – 5.03 (m, J = 16.1, 8.1 Hz, 1H), 4.79 (d, J = 12.6 Hz, 1H), 4.64 (d, J = 12.6 Hz, 1H), 4.24 (d, J = 20.1 Hz, 1H), 4.07 – 3.79 (m, 8H), 3.68 (s, 3H), 3.59 – 3.41 (m, J = 21.3, 16.7, 8.1 Hz, 4H), 3.07 (s, 3H), 2.93 – 2.70 (m, 2H), 2.71 – 2.62 (m, 1H), 2.58 (s, 1H), 2.47 (d, J = 7.6 Hz, 1H), 2.37 – 2.29 (m, 2H), 2.15 (d, J = 14.9 Hz, 1H), 1.45 (t, J = 6.9 Hz, 3H).

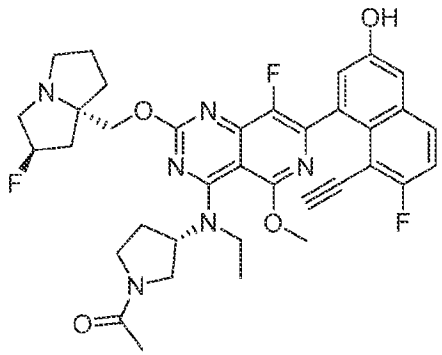
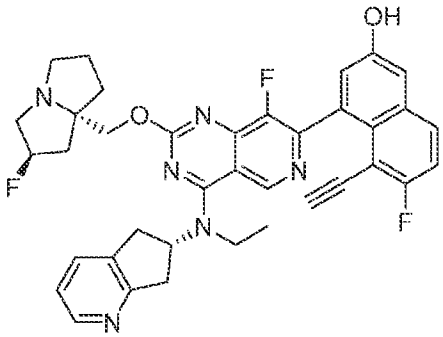
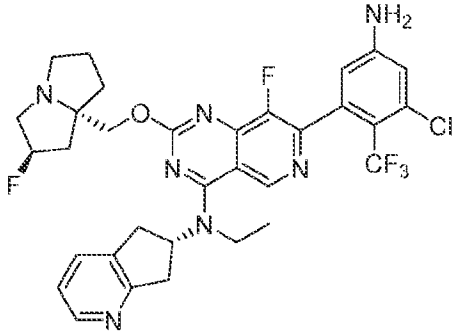
576		LCMS m/z [M+1]: 667.2 1H NMR (400 MHz, CD3OD) δ 7.98 (d, J = 8.8 Hz, 1H), 7.35 (dd, J = 8.8, 7.2 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.70 – 5.47 (m, 1H), 5.25 – 5.10 (m, 1H), 4.77 – 4.64 (m, 2H), 4.10 – 3.74 (m, 7H), 3.72 (s, 3H), 3.69 – 3.53 (m, 1H), 3.55 – 3.39 (m, 2H), 2.78 - 2.78 (m, 2H), 2.54 – 2.43 (m, 2H), 2.41 (s, 3H), 2.40 – 2.08 (m, 4H), 1.46 (t, J = 7.2 Hz, 3H).
577		LCMS m/z [M+1]: 739.2 1H NMR (400 MHz, CD3OD) δ 8.44 (s, 1H), 8.28 (s, 1H), 8.10 (s, 1H), 7.23 (dd, J = 8.2, 5.2 Hz, 1H), 7.13 – 6.95 (m, 1H), 5.47 (d, J = 53.2 Hz, 1H), 5.25 – 5.08 (m, 1H), 4.49 – 4.20 (m, 2H), 4.06 – 3.92 (m, 2H), 3.92 – 3.53 (m, 7H), 3.46 – 3.32 (m, 1H), 2.51 (s, 3H), 2.50 – 2.35 (m, 2H), 2.30 – 2.16 (m, 2H), 2.12 – 2.04 (m, 1H), 1.95 – 1.79 (m, 1H), 1.61 (t, J = 7.2 Hz, 3H).
578		LCMS m/z [M+1]: 758.3 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.24 (dd, J = 8.3, 5.1 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.52 (d, J = 51.4 Hz, 1H), 5.36 – 5.29 (m, 1H), 4.22 (d, J = 12.0 Hz, 1H), 4.08 (d, J = 12.0 Hz, 1H), 4.02 – 3.81 (m, 5H), 3.59 – 3.49 (m, 2H), 3.45 – 3.37 (m, 2H), 3.26 (dd, J = 13.2, 3.8 Hz, 1H), 3.10 – 3.02 (m, 2H), 2.61 – 2.45 (m, 2H), 2.33 – 2.20 (m, 2H), 2.05 – 1.95 (m, 2H),

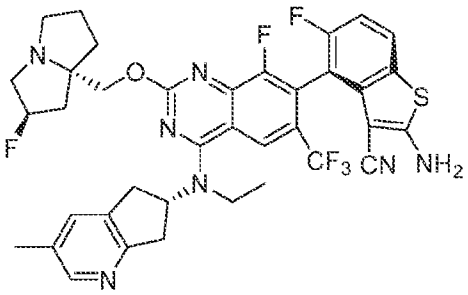
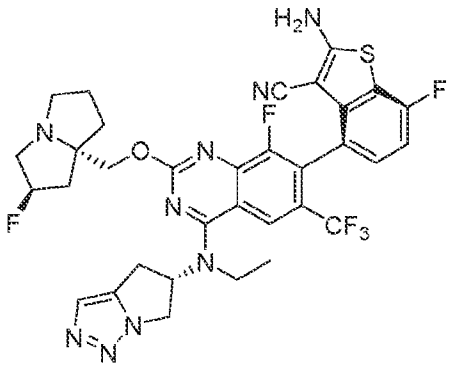
		1.60 (t, J = 7.0 Hz, 3H), 1.40 (t, J = 7.6 Hz, 3H).
579		LCMS m/z [M+1]: 758.3 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.23 (dd, J = 8.1, 5.1 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.53 (d, J = 51.8 Hz, 1H), 5.32 – 5.26 (m, 1H), 4.15 (d, J = 12.1 Hz, 1H), 4.07 – 3.81 (m, 6H), 3.62 – 3.50 (m, 2H), 3.44 – 3.37 (m, 2H), 3.29 – 3.23 (m, 1H), 3.09 – 3.01 (m, 2H), 2.65 – 2.45 (m, 2H), 2.32 – 2.18 (m, 2H), 1.98 – 1.88 (m, 2H), 1.62 (t, J = 7.0 Hz, 3H), 1.40 (t, J = 7.5 Hz, 3H).
580		LCMS m/z [M+1]: 760.2 1H NMR (400 MHz, CD3OD) δ 8.17 (s, 1H), 7.23-7.19 (m, 1H), 7.00 (t, 1H), 5.38 (s, 0.5H), 5.25 (s,0.5H), 4.98-4.90 (m, 2H), 4.34-4.27 (m, 2H), 3.97-3.82 (m,3H), 3.65-3.58 (m,1H), 3.35-3.33 (m,1H), 3.25-3.21 (m,2H), 3.17-3.12 (m,2H), 3.07-3.01 (m, 2H), 2.96 (s,3H), 2.55-2.44 (m, 2H), 2.30-2.15 (m, 3H), 2.03-1.84 (m, 4H), 1.43 (t.3H) .
581		LCMS m/z [M+1]: 752.3 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 6.98 (t, J = 8.0 Hz, 1H), 5.56 (d, J = 52.0 Hz, 1H), 5.02 (t, J = 8.0 Hz, 1H), 4.73 – 4.57 (m, 2H), 3.93 – 3.67 (m, 11H), 3.49 – 3.44 (m, 2H), 2.7 – 2.32 (m, 7H), 2.25 – 2.0 (m, 1H) 1.49 (t, J = 8.0 Hz, 3H).

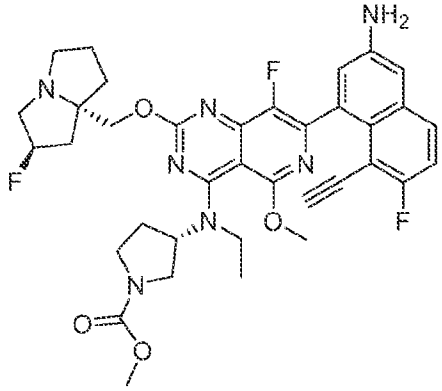
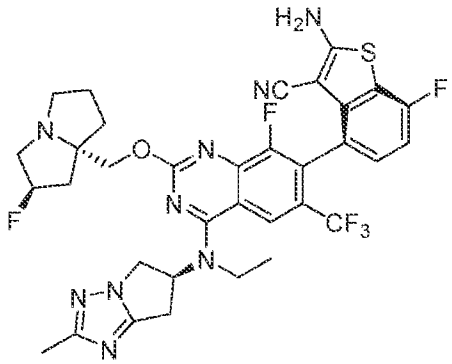
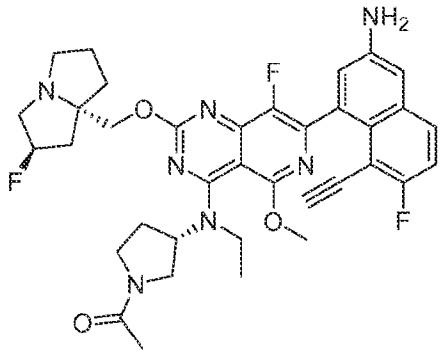
582		LCMS m/z [M+1]: 766.3 1H NMR (400 MHz, CD3OD) δ 8.40 (s, 1H), 6.98 (t, J = 8.0 Hz, 1H), 5.56 (d, J = 52.0 Hz, 1H), 4.76 – 4.63 (m, 2H), 4.02 – 3.55 (m, 11H), 3.48 – 3.44 (m, 2H), 2.66 – 2.03 (m, 8H), 1.47 (t, J = 8.0 Hz, 3H), 1.01 (d, J = 4.0 Hz, 3H).
583		LCMS m/z [M+1]: 752.3 1H NMR (400 MHz, CD3OD) δ 8.42 (s, 1H), 6.99-6.95 (m, 1H), 5.63-5.50 (m, 1H), 4.76-4.73 (m, 1H), 4.63-4.60 (m, 1H), 3.92-3.89 (m, 3H), 3.72 (s, 3H), 3.63 (s, 3H) , 3.48-3.43 (m, 2H) , 2.70-2.58 (m, 3H), 2.40-2.31 (m, 4H), 1.08-1.07 (d, J=7.3Hz, 3 H).
584		LCMS m/z [M+1]: 770.3 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.23 (dd, J = 8.3, 5.0 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.53 (d, J = 51.6 Hz, 1H), 5.28 – 5.20 (m, 1H), 4.12 (d, J = 12.0 Hz, 1H), 4.02 – 3.81 (m, 6H), 3.57 – 3.35 (m, 4H), 3.27 – 3.20 (m, 1H), 2.64 – 2.44 (m, 2H), 2.39 – 2.21 (m, 3H), 2.09 – 1.97 (m, 2H), 1.62 (t, J = 7.0 Hz, 3H), 1.24 – 1.19 (m, 2H), 1.11 – 0.98 (m, 2H).
585		LCMS m/z [M+1]: 770.3 1H NMR (400 MHz, CD3OD) δ 8.26 (s, 1H), 7.23 (dd, J = 8.3, 5.1 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.54 (d, J = 51.4 Hz, 1H), 5.26 – 5.17 (m, 1H), 4.09 – 3.92 (m, 5H), 3.89 – 3.79 (m, 2H), 3.61 – 3.35 (m, 4H), 3.27 – 3.19 (m,

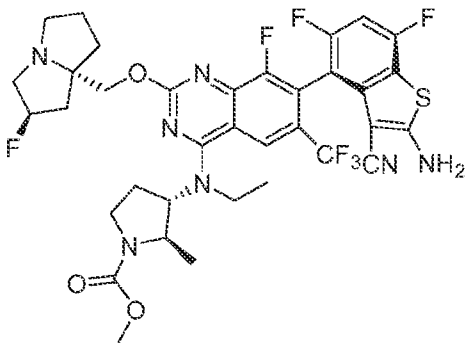
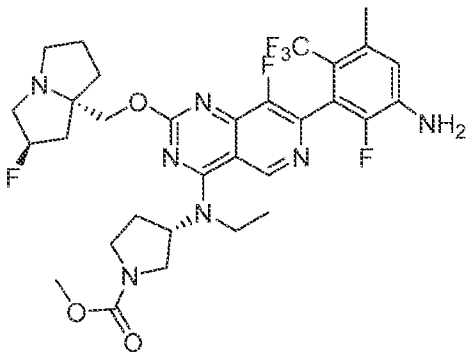
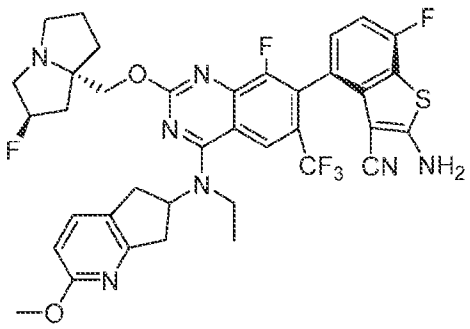
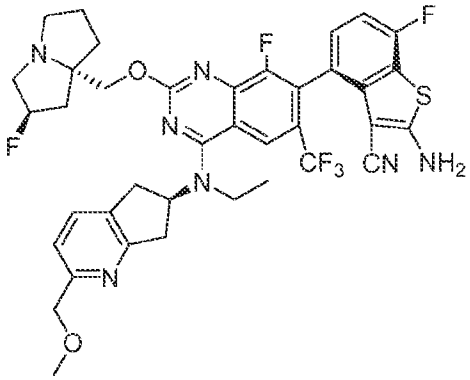
		1H), 2.68 – 2.45 (m, 2H), 2.40 – 2.20 (m, 3H), 2.06 – 1.90 (m, 2H), 1.63 (t, J = 7.0 Hz, 3H), 1.25 – 1.18 (m, 2H), 1.13 – 1.06 (m, 1H), 1.03 – 0.96 (m, 1H).
586		LCMS m/z [M+1]: 774.4 1H NMR (400 MHz, CD3OD) δ 8.58 (s, 1H), 8.29 (s, 1H), 7.94 (s, 1H), 7.27 – 7.20 (m, 1H), 7.08 (s, 1H), 7.06 – 7.00 (m, 1H), 6.94 (s, 1H), 6.80 (s, 1H), 5.54 (s, 1H), 5.11 (d, J = 0.9 Hz, 1H), 4.13 (d, J = 12.6 Hz, 1H), 4.04 – 3.89 (m, 3H), 3.78 (ddd, J = 33.9, 15.2, 10.8 Hz, 4H), 3.60 – 3.35 (m, 4H), 2.42 (dd, J = 16.1, 11.3 Hz, 2H), 2.26 – 2.13 (m, 2H), 1.93 – 1.81 (m, 2H), 1.62 (t, J = 7.1 Hz, 3H).
587		LCMS m/z [M+1]: 774.4
588		LCMS m/z [M+1]: 742.3 1H NMR (400 MHz, CD3OD) δ 8.31 (s, 1H), 8.28 (s, 1H), 7.58 (dd, J = 2.3 Hz, 8.6 Hz, 1H), 7.20-7.26 (m, 1H), 7.03 (t, J = 9.4 Hz, 1H), 5.50 (d, J = 51.3 Hz, 1H), 5.12-5.22 (m, 1H), 4.22 – 4.29 (m, 1H), 4.08 – 4.15 (m, 1H), 3.92 – 4.00 (m, 2H), 3.76 – 3.84 (m, 2H), 3.35 – 3.72 (m, 6H), 2.42 – 2.60 (m, 2H), 2.14 – 2.32 (m, 2H), 1.84-2.12 (m, 2H), 1.58 (t, J = 7.0 Hz, 3H).

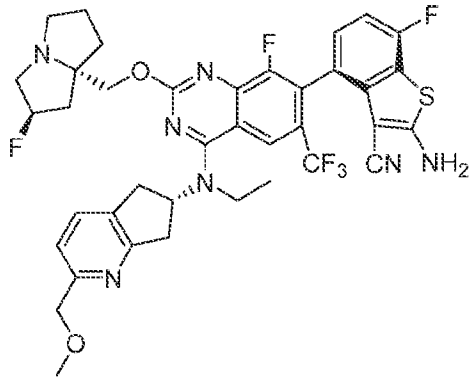
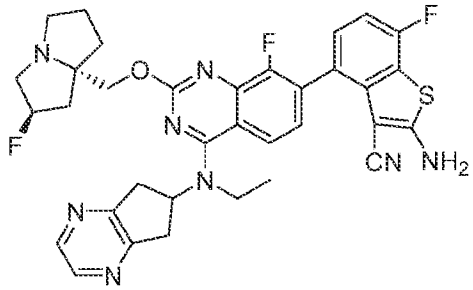
589		LCMS m/z [M+1]: 742.3
590		LCMS m/z [M+1]: 728.3 1H NMR (400 MHz, CD3OD) δ 8.20 (s, 1H), 7.23-7.19 (m, 1H),7.01 (t, 1H), 5.35-5.31 (m, 1.5H), 5.28-5.22 (m, 1H), 5.17 (s, 0.5H), 4.66-4.62 (m, 1H), 4.46 (t, 1H), 3.93 (d, 2H), 3.72-3.69 (m, 1H), 3.63-3.61 (m, 1H), 3.59-3.54 (m, 1H), 3.37-3.33 (m, 1H), 3.23-3.16 (m, 2H), 3.01-3.29 (m, 1H), 2.39 (s, 3H), 2.20-2.16 (m, 1H), 2.07-2.02 (m, 2H), 1.94-1.85 (m,2H), 1.82-1.77 (m,1H) , 1.63 (t,3H).
591		LCMS m/z [M+1]: 691.3 1H NMR (400 MHz, CD3OD) δ 7.81-7.85 (m, 1H), 7.27-7.32 (m, 2H), 7.22 (t, 1H), 5.38 (s, 0.5H), 5.25 (s, 0.5H), 4.65 (s, 1H), 4.23-4.32 (m, 2H), 4.01 (s, 3H), 3.67-3.84 (m, 7H), 3.55-3.61 (m, 1H), 3.34-3.47 (m, 3H), 3.19-3.25 (m, 2H), 3.01-3.07 (m, 1H), 2.25-2.39 (m, 4H), 2.11-2.22 (m, 1H), 1.97-2.04 (m, 2H), 1.86-1.94 (m, 1H), 1.30 (t, 3H).

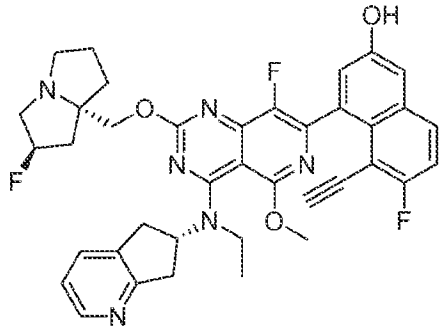
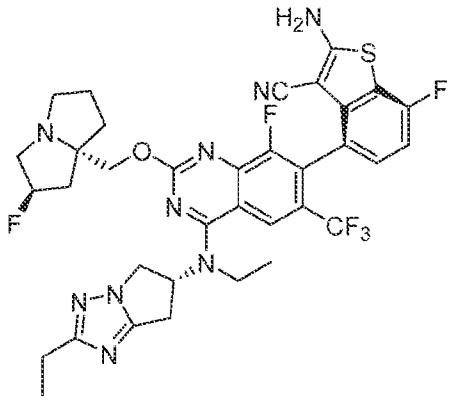
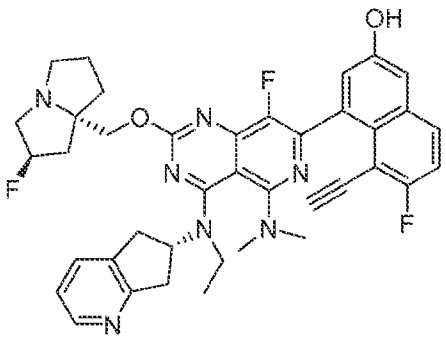
592		LCMS m/z [M+1]: 675.3 1H NMR (400 MHz, CD3OD) δ 7.86-7.80 (m, 1H), 7.34-7.26 (m, 2H), 7.24-7.20 (m, 1H), 5.38 (s, 0.5H), 5.25 (s, 0.5H), 4.74-4.65 (m, 1H), 4.32-4.21 (m, 2H), 4.06-3.98 (m, 3H), 3.94-3.73 (m, 4H), 3.66-3.48 (m, 2H), 3.42-3.33 (m, 2H), 3.26-3.21 (m, 2H), 3.08-3.01 (m, 1H), 2.43-2.22 (m, 4H), 2.17-2.11 (m, 1H), 2.08 (s, 3H), 2.04-1.97 (m, 2H), 1.94-1.86 (m, 1H)1.32-1.28 (m, 3H).
593		LCMS m/z [M+1]: 651.2 1H NMR (400 MHz, CD3OD) δ 9.05 (d, J = 1.5 Hz, 1H), 8.37 (d, J = 4.5 Hz, 1H), 7.88 – 7.81 (m, J = 9.1, 5.7 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 2.6 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.22 (d, J = 2.3 Hz, 1H), 5.30 (s, 0.5H), 5.14 (d, J = 16.1 Hz, 1.5H), 4.02 – 3.97 (m, 2H), 3.85 – 3.68 (m, 4H), 3.53 – 3.45 (m, 3H), 3.15 (d, J = 19.1 Hz, 3H), 2.95 (d, J = 5.8 Hz, 1H), 2.23 – 2.10 (m, 1H), 2.04 (d, J = 8.7 Hz, 1H), 1.95 – 1.82 (m, 1H), 1.75 – 1.63 (m, 2H), 1.59 (t, J = 6.8 Hz, 3H).
594		LCMS m/z [M+1]: 660.0 1H NMR (400 MHz, CDCl3) δ 9.05 (d, J = 12.9 Hz, 1H), 8.36 (d, J = 4.7 Hz, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.32 – 7.22 (m, 1H), 6.90 (s, 1H), 6.50 (s, 1H), 5.31 (s, 0.5H), 5.15 (d, J = 12.0 Hz, 1.5H), 4.02 – 3.91 (m, J =

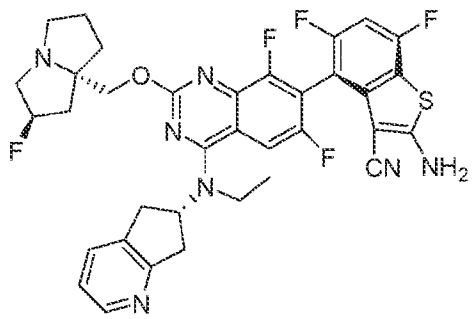
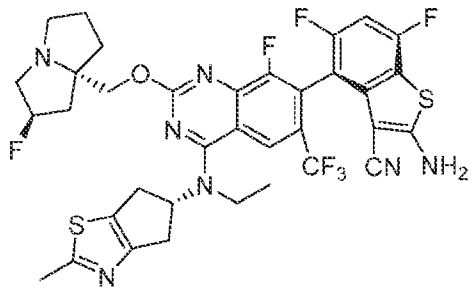
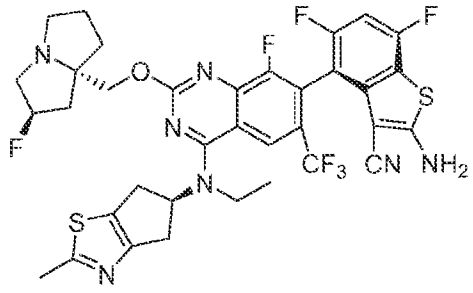
		13.7, 6.8 Hz, 2H), 3.85 – 3.63 (m, 5H), 3.50 – 3.36 (m, J = 19.1, 8.8 Hz, 3H), 3.16 (s, 2H), 2.27 – 1.81 (m, J = 76.6, 47.1, 14.4 Hz, 6H), 1.55 (t, J = 6.9 Hz, 3H).
595		LCMS m/z [M+1]: 739.2 1H NMR (400 MHz, CD3OD) δ 8.42 (s, 1H), 8.30 (s, 1H), 8.06 (s, 1H), 7.70 (dd, J = 8.8, 4.8 Hz, 1H), 7.04 (t, J = 9.2 Hz, 1H), 5.48 (d, J = 50.0 Hz, 1H), 5.28 – 5.09 (m, 1H), 4.41-4.21 (m, 2H), 4.06 – 3.90 (m, 2H), 3.90 – 3.59 (m, 7H), 3.45 – 3.33 (m, 1H), 2.50 (s, 3H), 2.50 – 2.36 (m, 2H), 2.30 – 2.17 (m, 2H), 2.16 – 2.02 (m, 1H), 1.96 – 1.78 (m, 1H), 1.60 (t, J = 7.2 Hz, 3H).
596		LCMS m/z [M+1]: 714.2 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.56 (s, 1H), 7.25-7.17 (m, 1H), 7.06-6.97 m, 1H), 5.43-5.34 (m, 1H), 5.33 (s, 0.5H), 5.19 (s, 0.5H), 5.00-4.94 (m, 1H), 4.78-4.72 (m, 1H), 3.94 (q, 2H), 3.60-3.41 (m, 4H), 3.20-3.09 (m, 3H), 2.99-2.91 (m, 1H). 2.21-1.99 (m, 2H), 1.95-1.74 (m, 4H), 1.63 (t, 3H).

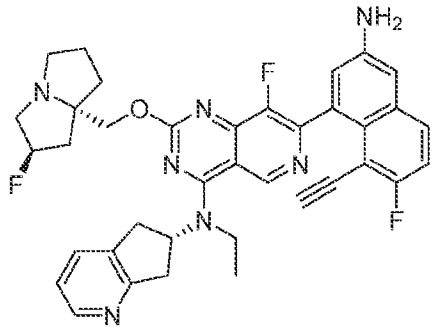
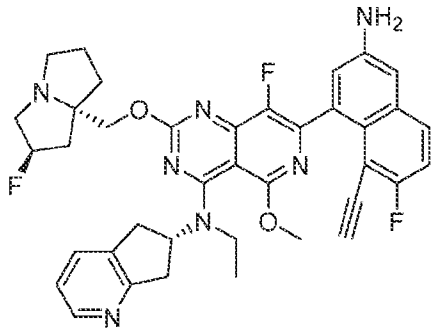
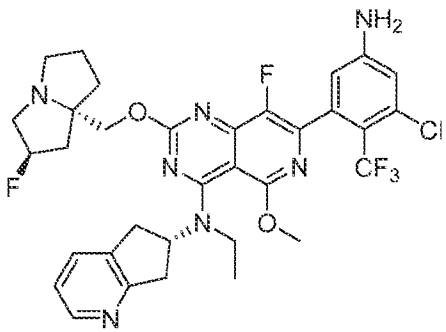
597		LCMS m/z [M+1]: 690.2 1H NMR (400 MHz, CD3OD) δ 7.70-7.74 (m, 1H), 7.22 (t, 1H), 7.15 (s, 2H), 5.41 (s, 0.5H), 5.28 (s, 0.5H), 4.63-4.68 (m, 1H), 4.26-4.35 (m, 2H), 4.01 (s, 3H), 3.76-3.84 (m, 2H), 3.67-3.74 (m, 5H), 3.54-3.63 (m, 2H), 3.31-3.42 (m, 4H), 3.06-3.12 (m, 1H), 2.26-2.44 (m, 4H), 2.14-2.22 (m, 1H), 2.01-2.08 (m, 2H), 1.91-1.97 (m, 1H), 1.30 (t, 3H).
598		LCMS m/z [M+1]: 728.2 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.24-7.18 (m, 1H), 7.01 (t, 1H), 5.38-5.34 (m, 0.5H), 5.30-5.21 (m, 1.5H), 4.68-4.60 (m, 1H), 4.51-4.44 (m, 1H), 4.00-3.89 (m, 2H), 3.81-3.74 (m, 1H), 3.72-3.66 (m, 1H), 3.58-3.52 (m, 1H), 3.48-3.31 (m, 4H), 3.09-3.02 (m, 1H), 2.39 (s, 3H), 2.26-2.12 (m, 2H), 2.06-1.89 (m, 3H), 1.85-1.78 (m, 1H), 1.63 (t, 3H).
599		LCMS m/z [M+1]: 674.2 1H NMR (400 MHz, CD3OD) δ 7.75-7.71 (m, 1H), 7.22 (t, 1H),7.16-7.15 (m, 1H), 5.48 (s, 0.5H), 5.35 (s, 0.5H), 4.76-4.66 (m, 1H), 4.44-4.38 (m, 2H), 4.03-4.02 (m, 3H), 3.82-.71 (m, 4H), 3.64-3.47 (m, 5H), 3.24-3.16 (m, 2H), 2.43-2.34 (m, 4H), 2.26-2.21 (m, 1H), 2.18-2.11 (m, 2H), 2.09 (s, 3H), 2.03-1.98 (m, 1H), 1.35-1.32 (m, 3H).

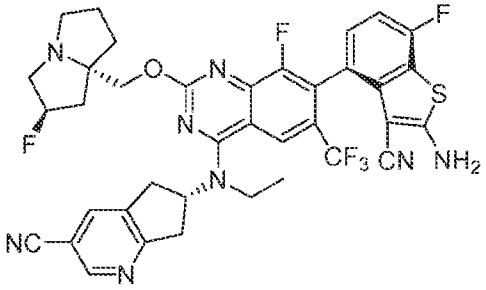
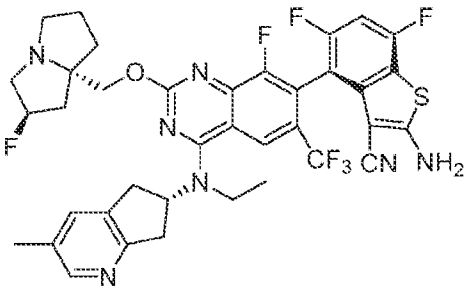
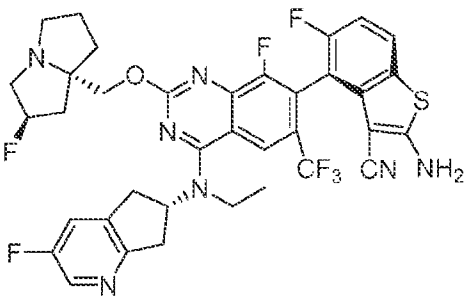
607		LCMS m/z [M+1]: 766.2 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 6.98 (t, J = 9.6 Hz, 1H), 5.57 ((t, J = 52 Hz, 1H), 4.55 – 4.72 (m, 3H), 4.25 - 4.31 (m, 1H), 3.84 – 4.06 (m, 6H), 3.74 (s, 3H), 3.44 – 3.52 (m, 2H), 2.33 – 2.65 (m, 7 H), 2.10 – 2.21 (m, 1H), 1.47 (t, J = 6.9 Hz, 3H), 1.37 (d, J = 6.3 Hz, 3H).
608		LCMS m/z [M+1]: 668.3 1H NMR (400 MHz, CD3OD) δ 9.14 (s, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.58 (d, J = 52.0 Hz, 1H), 5.26 – 5.09 (m, 1H), 4.78 – 4.58 (m, 2H), 4.17 – 3.76 (m, 7H), 3.73 (s, 3H), 3.67 – 3.41 (m, 3H), 2.84 – 2.46 (m, 3H), 2.42 (s, 3H), 2.40 – 2.31 (m, 2H), 2.27 – 2.10 (m, 1H), 1.49 (t, J = 6.8 Hz, 3H).
609		LCMS m/z [M+1]: 754.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.25 - 7.22 (m, 1H), 7.03 (t, J = 9.1 Hz, 1H), 6.75 - 6.72 (m, 1H), 5.51 (d, J = 51.4 Hz, 1H), 5.14 - 5.02 (m ,1H), 4.21 - 3.37 (m, 15H), 2.60 - 1.90 (m, 6H), 1.63 - 1.58 (m, 3H).
610		LCMS m/z [M+1]: 768.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.21 – 7.25 (m, 1H), 7.03 (t, J = 9.2 Hz, 1H), 5.47 (d, J = 51.2 Hz, 1H), 5.07 – 5.17 (m, 1H), 4.63 (s, 2H), 4.19 (dd, J = 50.0, 12.0 Hz, 2H), 3.98 (q, J = 7.2 Hz, 2H),

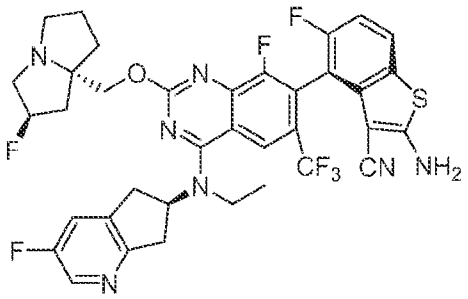
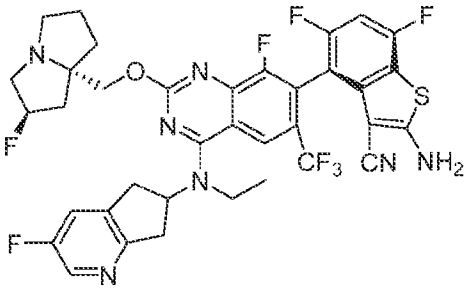
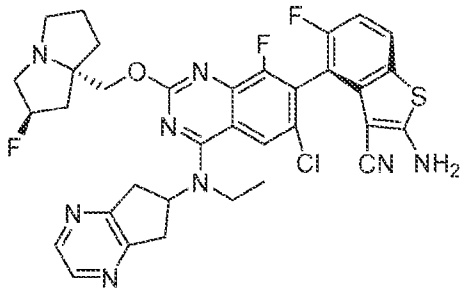
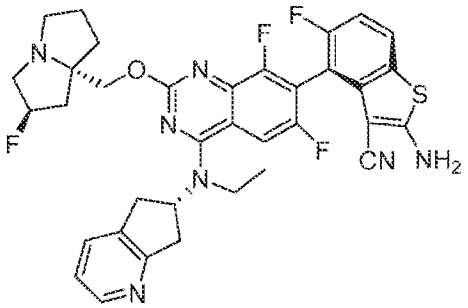
		3.70 – 3.90 (m, 4H), 3.55 – 3.69 (m, 3H), 3.53 (s, 3H), 3.34 – 3.42 (m, 1H), 2.37 – 2.49 (m, 2H), 2.14 – 2.27 (m, 2H), 1.98 – 2.07 (m, 1H), 1.83 – 1.95 (m, 1H), 1.60 (t, J = 6.8 Hz, 3H).
611		LCMS m/z [M+1]: 768.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.20 – 7.25 (m, 1H), 7.03 (t, J = 9.2 Hz, 1H), 5.47 (d, J = 52.4 Hz, 1H), 5.07 – 5.17 (m, 1H), 4.65 (s, 2H), 4.20 (dd, J = 60.8, 12.0 Hz, 2H), 3.84 – 4.02 (m, 3H), 3.72 – 3.82 (m, 3H), 3.57 – 3.69 (m, 3H), 3.54 (s, 3H), 3.34 – 3.41 (m, 1H), 2.39 – 2.54 (m, 2H), 2.13 – 2.26 (m, 2H), 1.97 – 2.04 (m, 1H), 1.81 – 1.91 (m, 1H), 1.61 (t, J = 6.8 Hz, 3H).
612		LCMS m/z [M+1]: 657.3 1H NMR (400 MHz, CD3OD): δ 8.38 (s, 2H), 7.91 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 7.1 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.03 (t, J = 9.2 Hz, 1H), 5.37 (t, J = 53.6 Hz, 1H), 5.06 – 4.98 (m, 1H),4.55- 4.45 (m, 1H), 4.15 - 3.94 (m, 4H), 3.66 - 3.49 (m, 6H), 3.24 - 3.17 (m, 1H), 2.41 - 1.79 (m, 6H), 1.56 (t, J = 6.8 Hz, 3H).

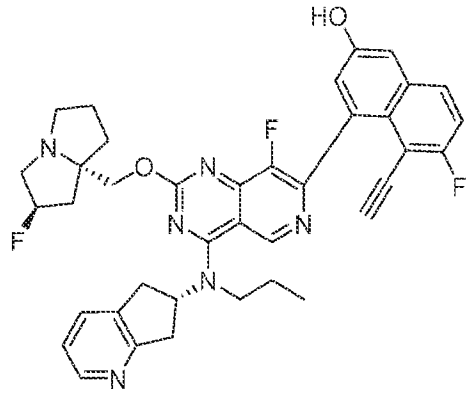
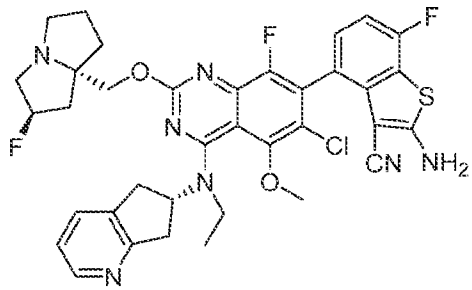
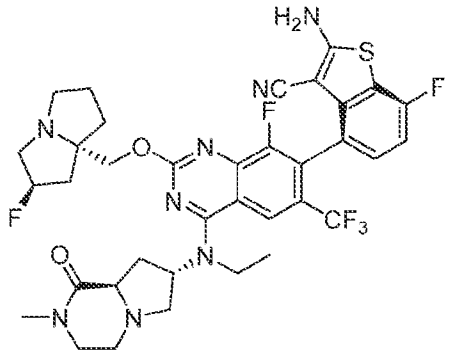
614		LCMS m/z [M+1]: 681.3 1H NMR (400 MHz, CD3OD) δ 8.35 (d, 1H), 7.81-7.85 (m, 1H), 7.73 (d, 1H), 7.22-7.32 (m, 4H), 5.35 (s, 0.5H), 5.21 (s, 0.5H), 4.91-4.95 (m, 1H), 4.05 (s, 3H), 3.88-4.01 (m, 2H), 3.54-3.69 (m, 3H), 3.43-3.53 (m, 3H), 3.32-3.40 (m, 1H), 3.20-3.25 (m, 3H), 2.98-3.04 (m, 1H), 2.08-2.20 (m, 2H), 1.88-1.99 (m, 3H), 1.74-1.80 (m, 1H), 1.35 (t, 3H).
615		LCMS m/z [M+1]: 742.2 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.24-7.19 (m, 1H), 7.01 (t, 1H), 5.33 (s, 0.5H), 5.31-5.23 (m, 1H), 5.19 (s, 0.5H), 4.68-4.59 (m, 1H), 4.48 (t, 1H), 4.01-3.86 (m, 2H), 3.81-3.73 (m, 1H), 3.72-3.65 (m, 1H), 3.61-3.55 (m, 1H), 3.39-3.33 (m, 1H), 3.28-3.20 (m, 3H), 3.06-2.97 (m, 1H), 2.83-2.69 (m, 2H), 2.27-2.10 (m, 2H), 2.07-1.88 (m, 3H), 1.84-1.76 (m, 1H), 1.62 (t, 3H), 1.35-1.32 (m, 3H).
616		LCMS m/z [M+1]: 694.2 1H NMR (400 MHz, CD3OD) δ 8.37 (s, 1H), 7.84-7.80 (m, 1H), 7.76 (s, 1H), 7.35 7.26 (m,2H), 5.42 (s, 0.5H), 5.28 (s,0.5H), 5.09-5.00 (m, 1H), 3.96-3.36 (m, 10H), 3.17-2.81 (m,8H), 2.31-2.15 (m,2H), 2.07-1.87 (m,3H), 1.59 (s,1H), 1.28 (s,3H) .

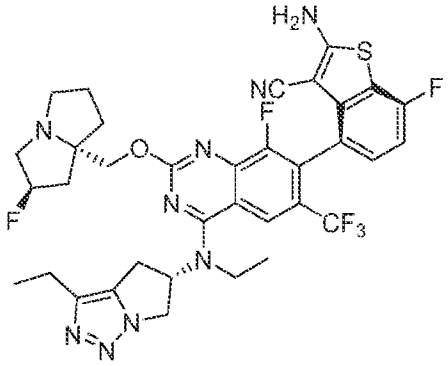
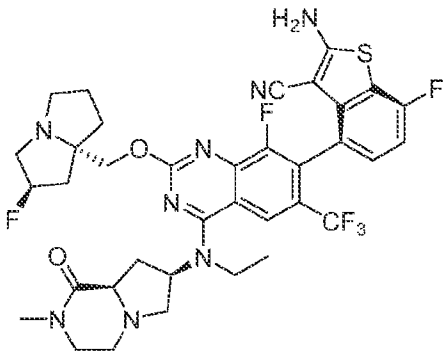
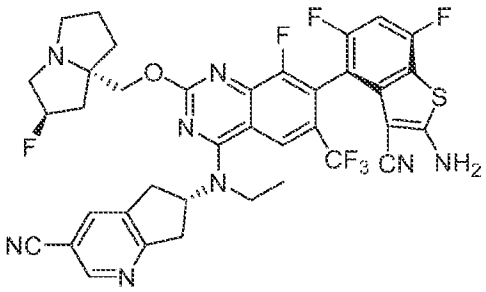
617		LCMS m/z [M+1]: 692.2 1H NMR (400 MHz, CD3OD) δ 8.55 (s, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.01 (t, J = 9.7 Hz, 1H), 5.49 (d, J = 51.0 Hz, 1H), 5.11 – 5.17 (m, 1H), 4.42 (d, J = 12.7 Hz, 1H), 4.21 (d, J = 12.6 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.54 – 3.86 (m, 7H), 3.36 – 3.42 (m, 1H), 2.37 – 2.50 (m, 2H), 2.19 (m, 3H), 1.84 – 1.94 (m, 1H), 1.55 (t, J = 7.0 Hz, 3H).
618		LCMS m/z [M+1]: 762.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 6.97 (t, J = 9.6 Hz, 1H), 5.53 (d, J = 51.4 Hz, 1H), 5.32 – 5.25 (m, 1H), 4.21 – 4.14 (m, 1H), 4.06 – 3.81 (m, 6H), 3.59 – 3.37 (m, 4H), 3.28 – 3.23 (m, 1H), 2.73 (s, 3H), 2.62 – 2.45 (m, 2H), 2.33 – 2.21 (m, 2H), 2.04 – 1.95 (m, 2H), 1.61 (t, J = 7.0 Hz, 3H).
619		LCMS m/z [M+1]: 762.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 6.97 (t, J = 9.6 Hz, 1H), 5.54 (d, J = 51.7 Hz, 1H), 5.30 – 5.21 (m, 1H), 4.11 – 3.80 (m, 7H), 3.61 – 3.48 (m, 2H), 3.44 – 3.36 (m, 2H), 3.29 – 3.21 (m, 1H), 2.73 (s, 3H), 2.65 – 2.42 (m, 2H), 2.34 – 2.19 (m, 2H), 1.99 – 1.87 (m, 2H), 1.62 (t, J = 7.0 Hz, 3H).

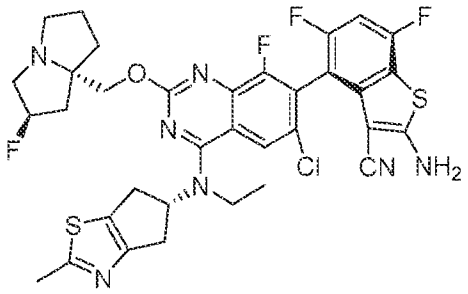
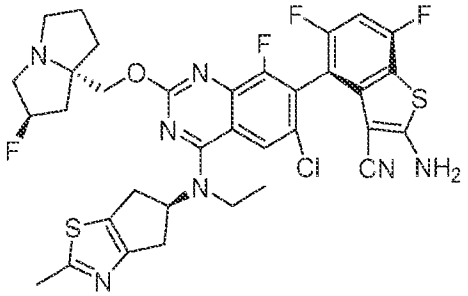
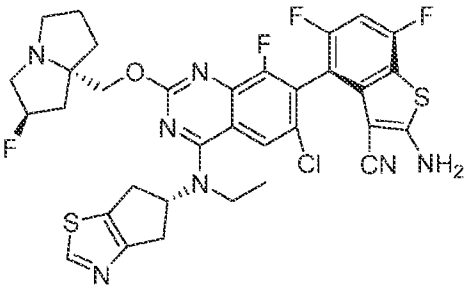
620		LCMS m/z [M+1]: 651.3 1H NMR (400 MHz, CD3OD) δ 9.03 (d, 1H), 8.36 (d, 1H),7.75-7.71 (m, 2H), 7.29-7.14 (m, 4H), 5.29 (s, 0.5H), 5.15-5.13 (s, 1.5H), 4.03-3.98 (m, 2H), 3.81-3.67(m, 4H), 3.52-3.42 (m, 3H), 3.23-3.12 (m, 3H), 2.98-2.94 (m, 1H), 2.13-2.03 (m, 2H), 1.92-1.81 (m, 2H), 1.70-1.63 (m, 2H), 1.58 (t,3H).
621		LCMS m/z [M+1]: 680.1 1H NMR (400 MHz, CD3OD) δ 8.35 (d, 1H), 7.69-7.73 (m, 2H), 7.15-7.27 (m, 4H), 5.33 (s, 0.5H), 5.20 (s, 0.5H), 4.90-4.94 (m, 1H), 4.04 (s, 3H), 3.85-3.98 (m, 2H), 3.53-3.72 (m, 3H), 3.41-3.50 (m, 3H), 3.32-3.39 (m, 1H), 3.26-3.27 (m, 1H), 3.15-3.20 (m, 2H), 2.94-3.00 (m, 1H), 2.09-2.27 (m, 2H), 1.83-1.95 (m, 3H), 1.69-1.78 (m, 1H), 1.35 (t, 3H).
622		LCMS m/z [M+1]: 690.3 1H NMR (400 MHz, CD3OD) δ 8.34 (d, 1H), 7.72 (d, 1H), 7.24-7.27 (m, 1H), 6.86 (d, 1H), 6.55 (d, 1H), 5.37 (s, 0.5H), 5.24 (s, 0.5H), 4.87-4.91 (m, 1H), 4.07 (s, 3H), 3.92-4.03 (m, 2H), 3.61-3.63 (m, 2H), 3.37-3.48 (m, 5H), 3.22-3.29 (m, 2H), 2.91-3.06 (m, 1H), 2.11-2.35 (m, 2H), 1.88-1.98 (m, 3H), 1.75-1.81 (m, 1H), 1.32 (m, 3H).

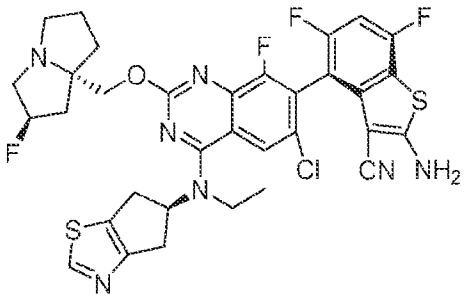
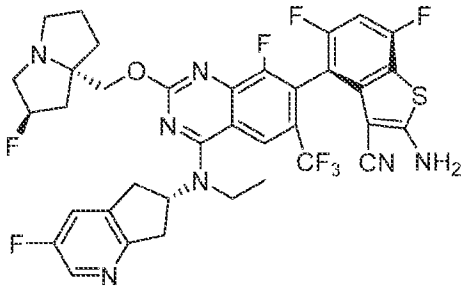
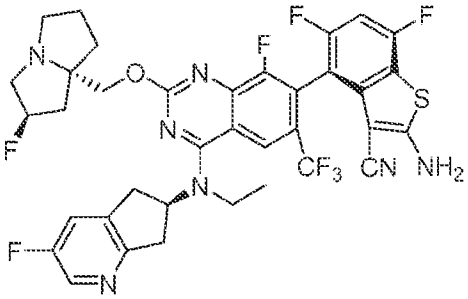
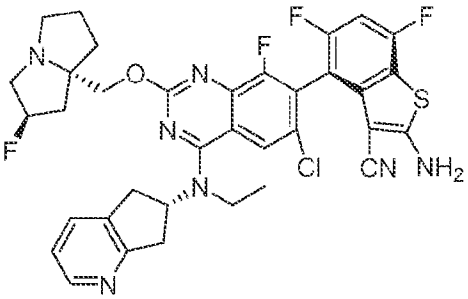
623		LCMS m/z [M+1]: 749.2 1H NMR (400 MHz, CD3OD) δ 8.78 (s, 1H), 8.28 (s, 1H), 8.06 (s, 1H), 7.23 (dd, J = 8.4, 5.2 Hz, 1H), 7.11 – 6.96 (m, 1H), 5.49 (d, J = 52.0 Hz, 1H), 5.20 – 5.06 (m, 1H), 4.33-4.12 (m, 2H), 4.01 – 3.70 (m, 6H), 3.68 – 3.53 (m, 3H), 3.46 – 3.36 (m, 1H), 2.60 – 2.41 (m, 2H), 2.32 – 2.17 (m, 2H), 2.11 – 1.85 (m, 2H), 1.59 (t, J = 7.2 Hz, 3H).
624		LCMS m/z [M+1]: 757.3 1H NMR (400 MHz, CD3OD) δ 8.45 (s, 1H), 8.30 (s, 1H), 8.13 (s, 1H), 6.98 (t, J = 9.6 Hz, 1H), 5.48 (d, J = 52.0 Hz, 1H), 5.28 – 5.10 (m, 1H), 4.48 – 4.22 (m, 2H), 4.05 – 3.91 (m, 2H), 3.90 – 3.55 (m, 7H), 3.46 – 3.35 (m, 1H), 2.52 (s, 3H), 2.48 – 2.37 (m, 1H), 2.32 – 1.97 (m, 4H), 2.00 – 1.84 (m, 1H), 1.60 (t, J = 7.2 Hz, 3H).
625		LCMS m/z [M+1]: 742.2 1H NMR (400 MHz, CD3OD) δ 8.32 (s, 1H), 8.30 (s, 1H), 7.67-7.73 (m, 1H), 7.60 (d, J = 7.0 Hz, 1H), 7.03 (t, J = 9.2 Hz, 1H), 5.50 (d, J = 50.7 Hz, 1H), 5.12-5.22 (m, 1H), 3.75 – 4.34 (m, 6H), 3.40 – 3.74 (m, 5H), 1.85 – 2.60 (m, 6H), 1.58 (t, J = 6.9 Hz, 3H).

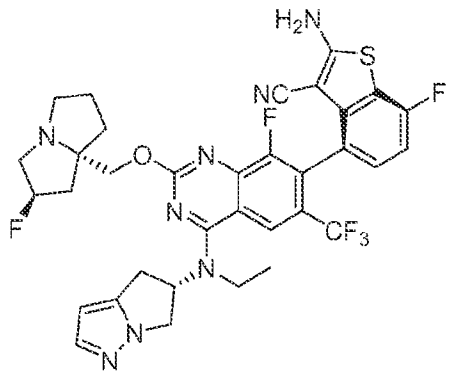
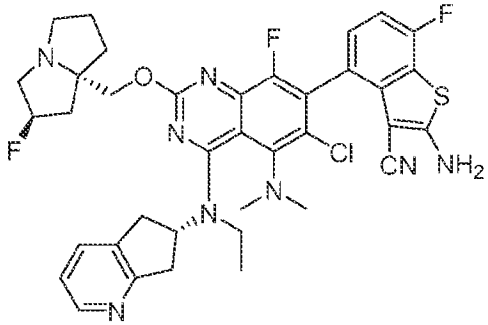
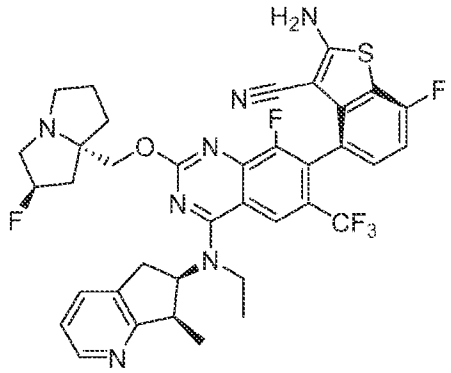
626		LCMS m/z [M+1]: 742.2 1H NMR (400 MHz, CD3OD) δ 8.38 – 8.26 (m, 2H), 7.73-7.67 (m, 1H), 7.60 (d, J = 7.0 Hz, 1H), 7.03 (t, J = 9.2 Hz, 1H), 5.50 (d, J = 50.7 Hz, 1H), 5.22-5.12 (m, 1H), 3.75 – 4.34 (m, 7H), 3.74 – 3.40 (m, 5H), 2.60–1.85 (m, 6H), 1.58 (t, J = 6.9 Hz, 3H).
627		LCMS m/z [M+1]: 760.3 1H NMR (400 MHz, CD3OD) δ 8.55 (s, 1H), 7.58 – 7.56 (m, 1H), 6.97 (t, J = 9.5 Hz, 1H), 5.52 (d, J = 52.0 Hz, 1H), 5.16 – 5.15 (m, 1H), 4.27 – 3.39 (m, 12H), 2.58 – 1.90 (m, 6H), 1.59 – 1.56 (m, 3H).
628		LCMS m/z [M+1]: 691 1H NMR (400 MHz, CD3OD): δ 8.42 (s, 2H), 8.0 (s, 1H), 7.24 - 7.21 (m, 1H), 7.05 (t, J = 9.2 Hz, 1H), 5.25 (d, J = 52.9 Hz, 1H), 5.06 - 5.0 (m, 1H), 4.20 - 3.96 (m, 4H), 3.86 - 3.52 (m, 8H), 3.40 - 3.35 (m, 1H), 2.50 - 2.41 (m, 2H), 2.23 - 2.18 (m, 2H), 2.07 - 2.02 (m, 1H), 1.92 - 1.82 (m, 1H), 1.58 (t, J = 6.9 Hz, 3H).
629		LCMS m/z [M+1]: 674.3 1H NMR (400 MHz, CD3OD) δ 8.58 (d, J = 5.1 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.72 – 7.78 (m, 3H), 7.09 (t, J = 8.0 Hz, 1H), 5.36 (d, J = 52.0 Hz, 1H), 5.15 – 5.25 (m, 1H) 4.36 (d, J = .6 Hz, 1H), 4.00 (d, J = 8.0 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.60 – 3.89 (m, 7H), 3.32 – 3.48 (m, 1H), 2.39 –

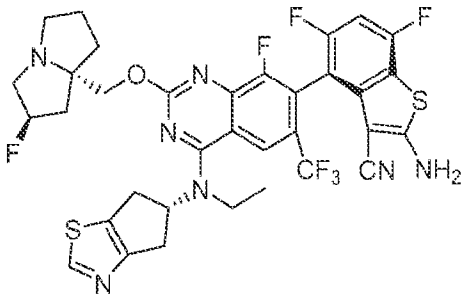
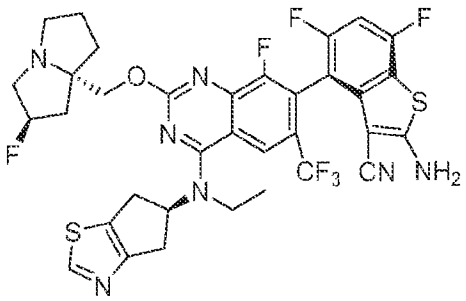
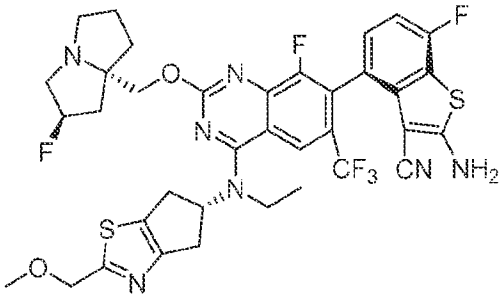
		2.51 (m, 2H), 2.17 – 2.31 (m, 3H), 1.84 – 1.94 (m, 1H), 1.52 – 1.68 (m, 3H)
630		LCMS m/z [M+1]: 665.2 1H NMR (400 MHz, CD3OD) δ 8.98 (d, 1H), 8.36 (d, 1H), 7.88-7.83 (m, 1H), 7.74 (d, 1H), 7.35-7.34 (m, 1H), 7.33-7.25 (m, 2H), 7.24-7.20 (m, 1H), 5.28 (s, 0.5H), 5.19-5.12 (m, 1.5H), 3.87-3.83 (m, 2H), 3.81-3.67 (m, 4H), 3.53-3.43 (m, 3H), 3.21-3.14 (m, 1H), 3.13-3.07 (m, 2H), 2.96-2.89 (m, 1H), 2.22-2.09 (m, 1H), 2.07-2.00 (m, 3H), 1.90-1.79 (m, 2H), 1.71-1.62 (m, 2H), 1.04 (t, 3H).
633		LCMS m/z [M+1]: 720.1 1H NMR (400 MHz, CD3OD) δ 8.32 (d, 1H), 7.70 (d, 1H), 7.26-7.17 (m, 2H), 7.05-7.00 (m, 1H), 5.35 (s, 0.5H), 5.22 (s, 0.5H), 5.00-4.95 (m, 1H), 4.09 (dd, 2H), 3.82 (s, 3H), 3.72 – 3.57 (m, 2H), 3.39 (s, 3H), 3.19 (s, 4H), 3.00 (s, 1H), 2.39 – 2.30 (m, 1H), 2.29-2.1 (m, 2H), 1.96 (d, 2H), 1.81 (s, 1H), 1.35 (t, 3H).
634		LCMS m/z [M+1]: 759.1 1H NMR (400 MHz, CD3OD) δ 8.18 (s, 1H), 7.24-7.18 (m, 1H), 7.04-6.98 (m, 1H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 4.99-4.95 (m, 1H), 4.40-4.30 (d, 1H), 4.26-4.19 (d, 1H), 4.03-3.93 (m, 1H), 3.92-3.8 (m, 2H), 3.65-3.58 (m, 1H), 3.42-3.34 (m, 2H), 3.27-3.18 (m, 3H), 3.16-3.12 (m, 2H), 3.07-2.99

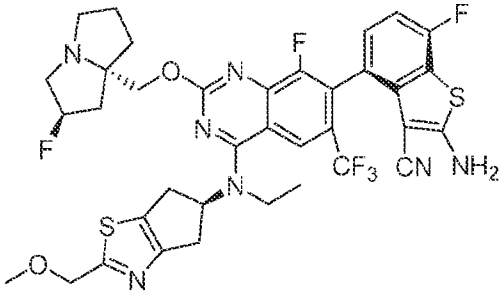
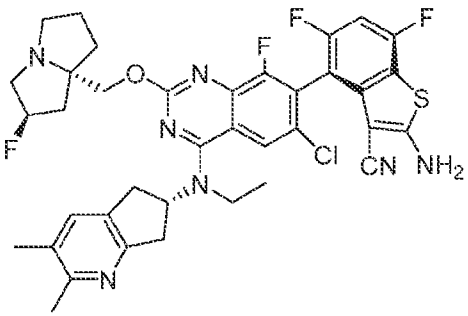
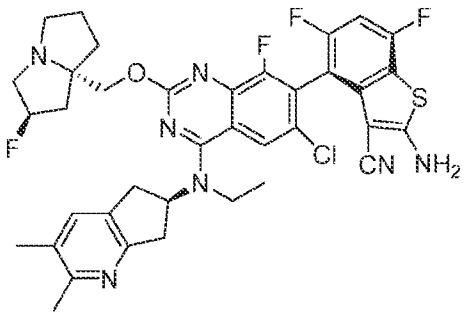
		(m, 2H), 2.96 (s, 3H), 2.57-2.44 (m, 2H), 2.35-2.11 (m, 3H), 2.03-1.96 (m, 2H), 1.93-1.84 (m, 1H), 1.42 (t, 3H).
636		LCMS m/z [M+1]: 742.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.25-7.20 (m, 1H), 7.02 (t, 1H), 5.40-5.34 (m, 0.5H), 5.35-5.32 (m, 0.5H), 5.33 (t, 1H), 5.00-4.93 (m, 2H), 4.76-4.70 (m, 1H), 4.64-4.56 (m, 1H), 4.01-3.92 (m, 2H), 3.78-3.70 (m, 2H), 3.63-3.57 (m, 1H), 3.49-3.44 (m, 1H), 3.38-3.32 (m, 2H), 2.79-2.69 (m, 2H), 2.18 (s, 3H), 2.05-2.03 (m, 1H), 2.02-1.99 (m, 2H), 1.68-1.55 (m, 6H).
637		LCMS m/z [M+1]: 759.2 1H NMR (400 MHz, CD3OD) δ 8.18 (s, 1H), 7.21 (dd, 1H), 7.00 (dd, 1H), 5.38 (s, 0.5H), 5.24 (s, 0.5H), 5.14-5.06 (m, 1H), 4.29 (dd, 2H), 4.06-3.90 (m, 2H), 3.72-3.65 (m, 1H), 3.36-3.33 (m, 2H), 3.26-3.18 (m, 3H), 3.12 (t, 1H), 3.03-2.93 (m, 4H), 2.85 (t, 1H), 2.79-2.71 (m, 2H), 2.45-2.08 (m, 5H), 2.05-1.86 (m, 3H). 1.35 (t, 3H).
638		LCMS m/z [M+1]: 767.2 1H NMR (400 MHz, CD3OD) δ 8.78 (s, 1H), 8.30 (s, 1H), 8.07 (s, 1H), 6.98 (t, J = 9.6 Hz, 1H), 5.50 (d, J = 52.0 Hz, 1H), 5.20 – 5.06 (m, 1H), 4.37 – 4.12 (m, 2H), 4.01 – 3.89 (m, 2H), 3.89 – 3.71 (m, 4H), 3.65 – 3.47 (m, 3H), 2.56 – 2.39 (m, 2H), 2.32 –

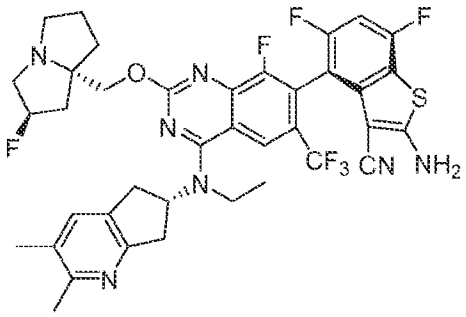
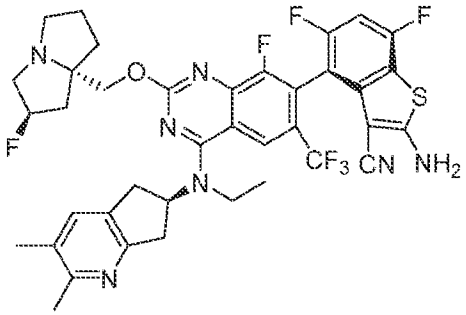
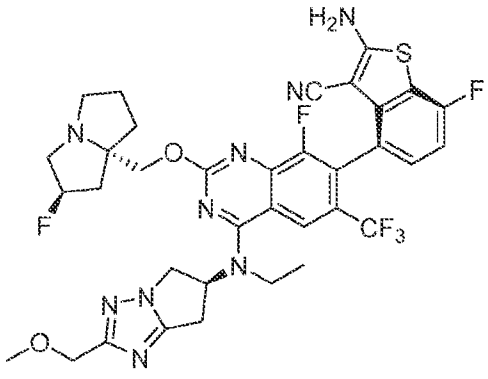
		2.16 (m, 2H), 2.11 – 1.86 (m, 3H), 1.59 (t, J = 6.8 Hz, 3H).
639		LCMS m/z [M+1]: 728.2 1H NMR (400 MHz, CD3OD) δ 7.99 (s, 1H), 7.00 (t, J = 9.6 Hz, 1H), 5.52 (d, J = 50.7 Hz, 1H), 5.31 – 5.26 (m, 1H), 4.20 (d, J = 12.2 Hz, 1H), 4.06 – 3.83 (m, 6H), 3.52 – 3.39 (m, 4H), 3.26 – 3.21 (m, 1H), 2.73 (s, 3H), 2.59 – 2.45 (m, 2H), 2.33 – 2.21 (m, 2H), 2.06 – 1.96 (m, 2H), 1.56 (t, J = 7.0 Hz, 3H).
640		LCMS m/z [M+1]: 728.2 1H NMR (400 MHz, CD3OD) δ 7.99 (s, 1H), 6.99 (t, J = 9.6 Hz, 1H), 5.54 (d, J = 51.7 Hz, 1H), 5.29 – 5.23 (m, 1H), 4.11 (d, J = 11.9 Hz, 1H), 4.04 – 3.80 (m, 6H), 3.57 – 3.36 (m, 4H), 3.28 – 3.20 (m, 1H), 2.72 (s, 3H), 2.64 – 2.44 (m, 2H), 2.34 – 2.20 (m, 2H), 2.01 – 1.89 (m, 2H), 1.57 (t, J = 7.0 Hz, 3H).
641		LCMS m/z [M+1]: 714.2 1H NMR (400 MHz, CD3OD) δ 8.98 (s, 1H), 8.01 (d, J = 1.4 Hz, 1H), 6.99 (t, J = 9.6 Hz, 1H), 5.52 (d, J = 51.7 Hz, 1H), 5.38 – 5.30 (m, 1H), 4.13 (d, J = 12.0 Hz, 1H), 4.03 – 3.92 (m, 4H), 3.86 – 3.79 (m, 2H), 3.60 – 3.35 (m, 5H), 2.58 – 2.42 (m, 2H), 2.30 – 2.17 (m, 2H), 2.09 – 1.96 (m, 2H), 1.58 (t, J = 7.0 Hz, 3H).

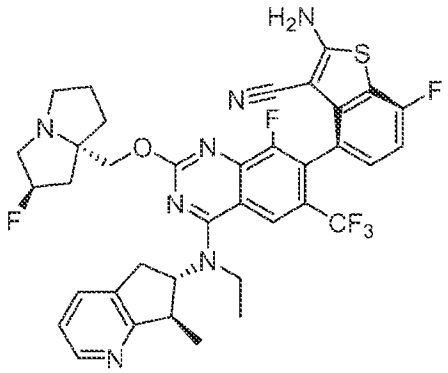
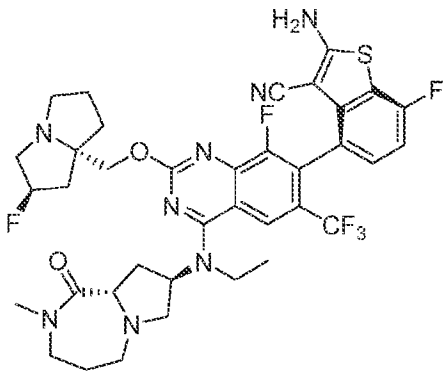
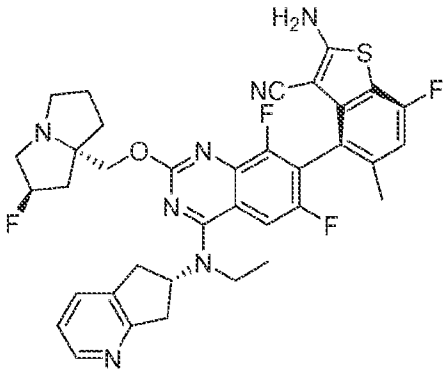
642		LCMS m/z [M+1]: 714.2 1H NMR (400 MHz, CD3OD) δ 9.00 (s, 1H), 8.03 (s, 1H), 7.02 (t, J = 9.6 Hz, 1H), 5.55 (d, J = 51.4 Hz, 1H), 5.37 – 5.30 (m, 1H), 4.08 – 3.78 (m, 7H), 3.64 – 3.36 (m, 5H), 2.65 – 2.44 (m, 2H), 2.32 – 2.18 (m, 2H), 2.07 – 1.91 (m, 2H), 1.61 (t, J = 7.0 Hz, 3H).
643		LCMS m/z [M+1]: 760.2 1H NMR (400 MHz, CD3OD) δ 8.33 – 8.30 (m, 2H), 7.61 – 7.59 (m, 1H), 6.97 (t, J = 9.5 Hz, 1H), 5.50 (d, J = 52.4 Hz, 1H), 5.18 – 5.14 (m, 1H), 4.27 – 3.38 (m, 12H), 2.55 – 1.90 (m, 6H), 1.59 – 1.56 (m, 3H).
644		LCMS m/z [M+1]: 760.2 1H NMR (400 MHz, CD3OD) δ 8.28 – 8.27 (m, 2H), 7.56 – 7.55 (m, 1H), 6.96 (t, J = 9.5 Hz, 1H), 5.35 (d, J = 52.4 Hz, 1H), 5.14 – 5.05 (m, 1H), 4.02 – 3.47 (m, 12H), 2.40 – 1.87 (m, 6H), 1.59 – 1.55 (m, 3H).
645		LCMS m/z [M+1]: 708.2 1H NMR (400 MHz, CD3OD) δ 8.51 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 7.2 Hz, 1H), 8.03 (s, 1H), 7.62 – 7.56 (m, 1H), 7.00 (t, J = 9.7 Hz, 1H), 5.42 (s, 1H), 5.13 (s, 1H), 4.38 (d, J = 12.6 Hz, 1H), 4.19 (d, J = 12.6 Hz, 1H), 3.98 – 3.51 (m, 10H), 2.53 – 2.40 (m, 2H), 2.24 – 2.08 (m, 3H), 1.89 (s, 1H), 1.55 (t, J = 7.0 Hz, 3H).

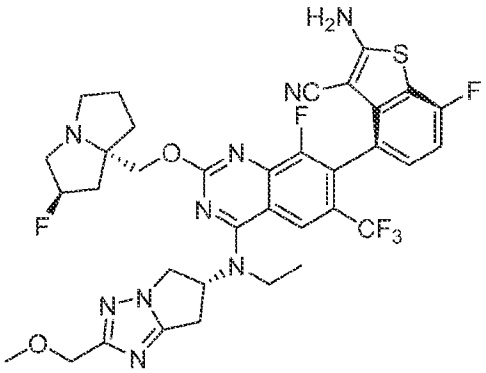
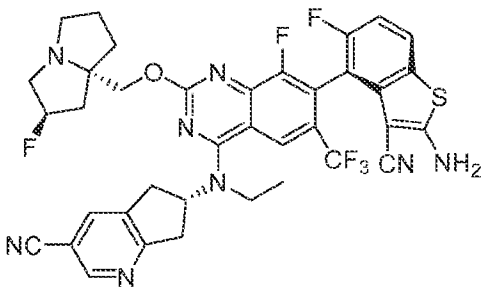
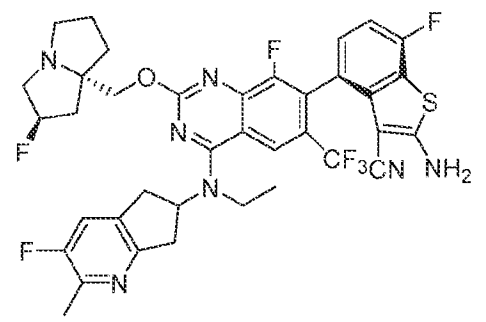
646		LCMS m/z [M+1]: 713.1 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.55 (d, 1H), 7.20-7.23 (m, 1H), 7.01 (t, 1H), 6.11 (s, 1H), 5.24-5.32 (m, 1.5H), 5.19 (m, 0.5H), 4.73-4.78 (m, 1H), 4.50 (t, 1H), 3.90-3.96 (m, 2H), 3.56-3.63 (m, 3H), 3.35-3.41 (m, 1H), 3.12-3.17 (m, 3H), 2.95-2.96 (m, 1H), 1.97-2.25 (m, 2H), 1.75-1.87 (m, 4H), 1.60 (t, 3H).
647		LCMS m/z [M+1]: 733.1 1H NMR (400 MHz, CD3OD) δ 8.34 (d, 1H), 7.74 (d, 1H), 7.68-7.54 (m, 1H), 7.23 (dd, 1H), 7.01 (t, 1H), 5.34-5.19 (m, 2H), 4.59 (s, 3H), 4.32-4.25 (m, 1H), 3.83 (dd,1H), 3.70 (s, 2H), 3.58-3.48 (m, 2H), 3.15 (d, 2H), 3.08 (s, 6H), 2.95 (d, 1H), 2.05 (t, 4H), 1.87 (d, 2H), 1.64-1.54 (m, 3H).
649		LCMS m/z [M+1]: 738.1 1H NMR (400 MHz, CD3OD) δ 8.36 (d, 1H), 8.33 (s, 1H), 7.77 (d, 1H), 7.29-7.21 (m, 2H), 7.01 (t, 1H), 5.42-5.37 (m, 1H), 5.37 (s, 0.5H), 5.25 (s, 0.5H), 4.32-4.22 (m, 2H), 3.91-3.83 (m, 2H), 3.72-3.64 (m, 2H), 3.54-3.45 (m, 3H), 3.15-3.00 (m, 3H), 2.32-2.23 (m, 2H), 2.16-2.09 (m, 1H), 2.06-1.96 (m, 3H), 1.94-1.84 (m, 2H), 1.42-1.35 (m, 3H).

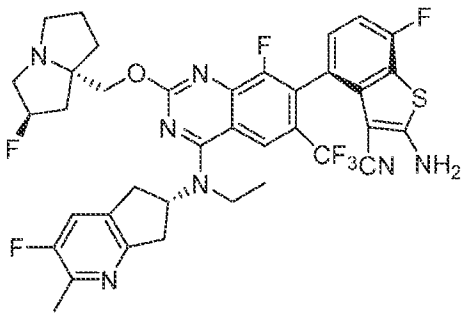
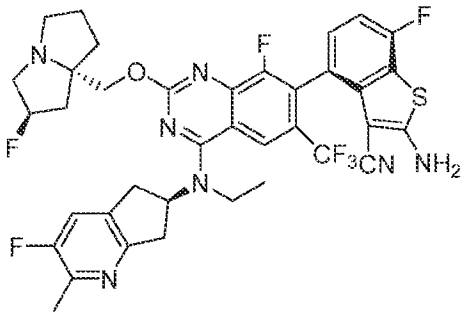
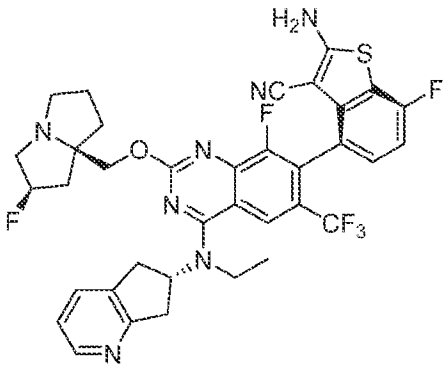
650		LCMS m/z [M+1]: 748.1 1H NMR (400 MHz, CD3OD) δ 8.99 (s, 1H), 8.29 (s, 1H), 6.98 (t, J = 9.6 Hz, 1H), 5.52 (d, J = 51.9 Hz, 1H), 5.36 – 5.30 (m, 1H), 4.09 (d, J = 11.9 Hz, 1H), 4.00 – 3.92 (m, 3H), 3.86 – 3.79 (m, 2H), 3.66 – 3.34 (m, 6H), 2.58 – 2.43 (m, 2H), 2.29 – 2.18 (m, 2H), 2.05 – 1.95 (m, 2H), 1.63 (t, J = 7.0 Hz, 3H).
651		LCMS m/z [M+1]: 748.1 1H NMR (400 MHz, CD3OD) δ 8.86 (s, 1H), 8.16 (s, 1H), 6.86 (t, J = 9.6 Hz, 1H), 5.35 – 5.20 (m, 2H), 3.89 – 3.72 (m, 4H), 3.55 – 3.45 (m, 3H), 3.40 – 3.26 (m, 4H), 3.08 – 3.02 (m, 1H), 2.28 – 2.12 (m, 2H), 2.00 – 1.90 (m, 2H), 1.83 – 1.73 (m, 2H), 1.51 (t, J = 7.0 Hz, 3H).
652		LCMS m/z [M+1]: 774.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.24 (dd, J = 8.3, 5.1 Hz, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.39 – 5.22 (m, 2H), 4.75 – 4.68 (m, 2H), 4.62 – 4.55 (m, 2H), 3.98 – 3.76 (m, 4H), 3.65 – 3.56 (m, 2H), 3.52 (s, 3H), 3.46 – 3.38 (m, 1H), 3.28 – 3.21 (m, 2H), 3.08 – 2.99 (m, 1H), 2.28 – 2.08 (m, 2H), 2.02 – 1.89 (m, 2H), 1.87 – 1.77 (m, 2H), 1.61 (t, J = 7.0 Hz, 3H).

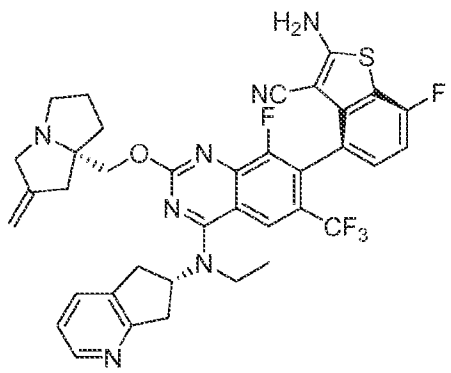
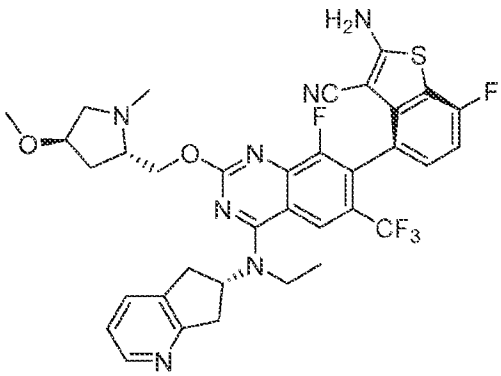
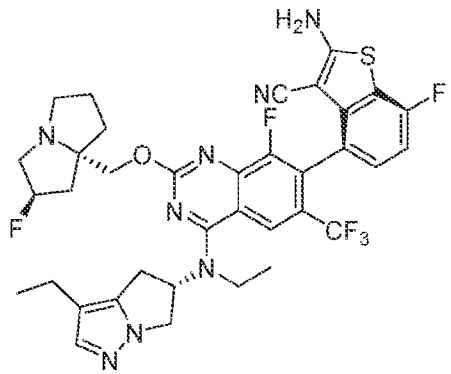
654		LCMS m/z [M+1]: 774.2 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 7.25 (dd, J = 8.6, 5.1 Hz, 1H), 7.08 – 7.02 (m, 1H), 5.54 (d, J = 51.4 Hz, 1H), 5.32 – 5.26 (m, 1H), 4.76 – 4.69 (m, 2H), 4.12 – 4.07 (m, 1H), 4.04 – 3.97 (m, 3H), 3.94 – 3.79 (m, 3H), 3.69 – 3.57 (m, 2H), 3.54 (s, 3H), 3.51 – 3.38 (m, 3H), 2.63 – 2.47 (m, 2H), 2.32 – 2.20 (m, 2H), 2.04 – 1.91 (m, 2H), 1.65 (t, J = 7.0 Hz, 3H).
655		LCMS m/z [M+1]: 736.2 1H NMR (400 MHz, CD3OD) δ 8.11 (s, 1H), 7.99-8.05 (m, 1H), 7.00 (t, J = 9.7 Hz, 1H), 5.38-5.57 (m, 2H), 5.17-5.25 (s, 1H), 4.46-4.57(m, 1H), 4.25-4.36(m, 1H), 3.88-4.00 (m, 2H), 3.36-3.88 (m, 8H), 2.70 (s, 3H), 2.42-2.55 (m, 4H), 2.12-2.31 (m, 3H), 1.81-1.96 (m, 1H), 1.46-1.59 (m, 3H).
656		LCMS m/z [M+1]: 736.2 1H NMR (400 MHz, CD3OD) δ 8.14 (s, 1H), 8.01-8.06 (m, 1H), 7.02 (t, J = 9.6 Hz, 1H), 5.35-5.62 (m, 2H), 5.17-5.30 (m, 1H), 4.29-4.54 (m, 2H), 3.92-4.02 (m, 2H), 3.37-3.91 (m, 8H), 2.71 (s, 3H), 2.42-2.56 (m, 4H), 2.09-2.33 (m, 3H), 1.88-2.05 (m, 1H), 1.47-1.63 (m, 3H).

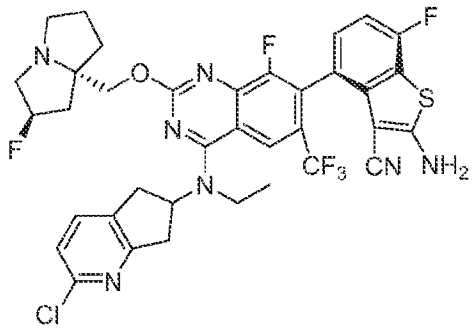
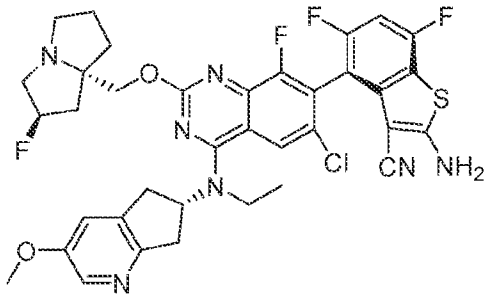
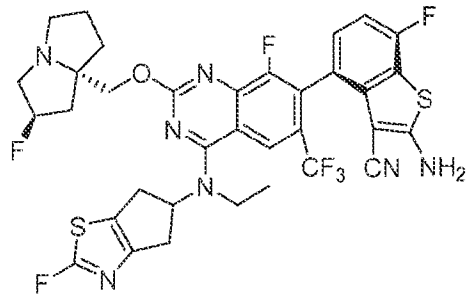
657		LCMS m/z [M+1]: 770.2 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 8.17 (s, 1H), 6.98 (t, J = 9.6 Hz, 1H), 5.48 (d, J = 51.8 Hz, 1H), 5.20-5.30 (m, 1H), 4.31-4.54 (m, 2H), 3.86-4.01 (m, 3H), 3.57-3.85 (m, 6H), 3.34-3.46 (m, 1H), 2.71 (s, 3H), 2.43-2.56 (m, 5H), 2.17-2.32 (m, 2H), 2.08-2.16 (m, 1H), 1.86-1.97 (m, 1H), 1.48-1.63 (m, 3H).
658		LCMS m/z [M+1]: 770.2 1H NMR (400 MHz, CD3OD) δ δ 8.30 (s, 1H), 8.16 (s, 1H), 6.98 (t, J = 9.6 Hz, 1H), 5.48 (d, J = 51.6 Hz, 1H), 5.17-5.28 (m, 1H), 4.31-4.47 (m, 2H), 3.86-4.01 (m, 3H), 3.60-3.84 (m, 6H), 3.36-3.45 (m, 1H), 2.71 (s, 3H), 2.44-2.55 (m, 5H), 2.17-2.32 (m, 2H), 2.08-2.16 (m, 1H), 1.86-1.97 (m, 1H), 1.47-1.65 (m, 3H).
659		LCMS m/z [M+1]: 758.0 1H NMR (400 MHz, CD3OD) δ 8.20 (s, 1H), 7.19-7.23 (m, 1H), 7.01 (t, 1H), 5.25-7.23 (m, 1.5H), 5.17 (s, 0.5H), 4.65-4.69 (m, 1H), -4.45-4.55 (m, 3H), 3.91-3.97 (m, 2H), 3.68-3.76 (m, 2H), 3.56-3.62 (m, 1H), 3.45 (s, 3H), 3.34-3.38 (m, 1H), 3.21 (s, 2H), 3.15 (m, 1H), 2.95-3.01 (m, 1H), 2.13-2.20 (m, 1H), 2.07-2.10 (m, 1H), 1.88-1.95 (m, 3H),1.77-1.81 (m, 1H), 1.63 (t, 3H).

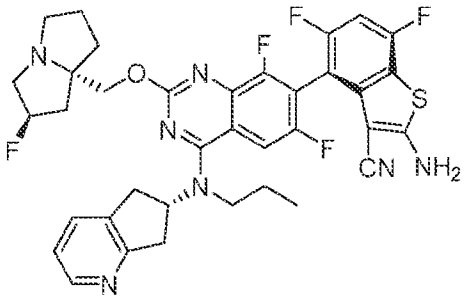
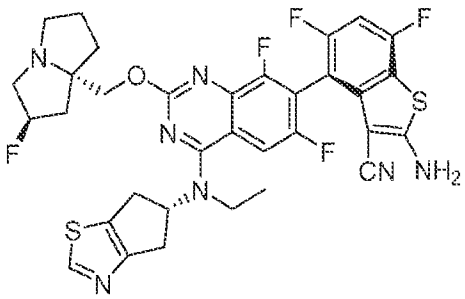
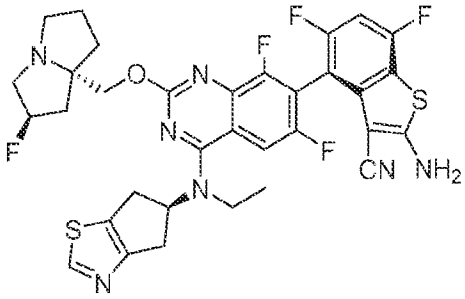
660		LCMS m/z [M+1]: 738.2 1H NMR (400 MHz, CD3OD) δ 8.38 (d, 1H), 8.25 (s, 1H), 7.74 (d, 1H), 7.27 (dd, 1H), 7.22 (dd, 1H), 7.00 (t, 1H), 5.30 (s, 0.5H), 5.16 (s, 0.5H), 4.60-4.51 (m, 1H), 4.10-4.02 (m, 2H), 3.90-3.76 (m, 3H), 3.70-3.63 (m, 2H), 3.47-3.36 (m, 1H), 3.22-3.12 (m, 2H), 3.01-2.93 (m, 1H), 2.21-2.04 (m, 2H), 1.93-1.80 (m, 2H), 1.75-1.64 (m, 2H), 1.59 (t, 3H), 1.48 (d, 3H).
661		LCMS m/z [M+1]: 773.3 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.20-7.23 (m, 1H), 7.00 (t, 1H), 5.39 (s, 0.5H), 5.26 (s, 0.5H), 4.92-4.96 (m, 1H), 4.33-4.40 (m, 2H), 3.76-3.95 (m, 4H), 3.31-3.40 (m, 3H), 3.11-3.28 (m, 4H), 2.93-3.05 (m, 5H), 2.64-2.71 (m, 1H), 2.16-2.40 (m, 4H), 1.93-2.03 (m, 3H), 1.81-1.89 (m, 2H), 1.43 (t, 3H).
662		LCMS m/z [M+1]: 688.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (d, 1H), 7.73 (d, 1H), 7.61-7.64 (m, 1H), 7.25-7.28 (m, 1H), 6.97 (d, 1H), 5.35 (s, 0.5H), 5.21 (s, 0.5H), 5.04-5.08 (m, 1H), 3.81-3.94 (m, 4H), 3.68-3.74 (m, 1H), 3.57-3.63 (m, 1H), 3.41-3.48 (m, 2H), 3.24-3.26 (m, 3H), 2.99-3.05 (m, 1H), 2.20-2.29 (m, 1H), 2.16 (s, 3H), 1.89-2.03 (m, 3H), 1.71-1.82 (m, 2H), 1.48 (t, 3H).

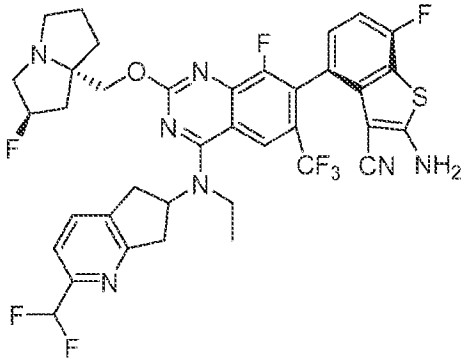
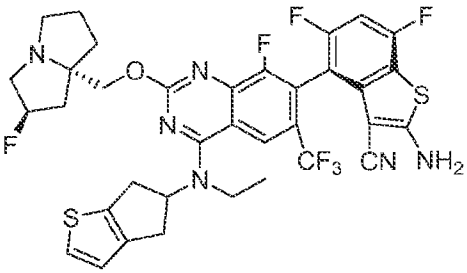
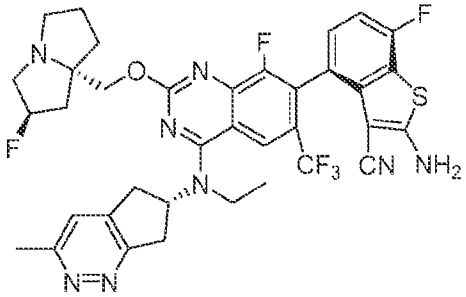
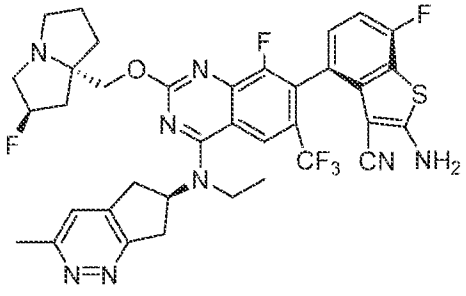
663		LCMS m/z [M+1]: 759.1 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.23-7.20 (m, 1H), 7.03-6.99 (m, 1H), 5.37 (s, 0.5H), 5.32-5.25(m,1H), 5.24 (s, 0.5H), 4.69-4.65 (m, 1H), 4.55-4.45 (m, 3H), 3.98-3.93 (m, 2H), 3.82-3.72 (m, 2H), 3.61-3.55 (m, 1H), 3.46 (s, 3H), 3.42-3.34 (m, 3H), 3.24-3.21 (m, 1H), 3.10-3.04 (m, 1H), 2.25-2.16 (m, 2H), 2.04-1.94 (m, 3H), 1.85-1.78 (m, 1H), 1.63 (t, 3H).
664		LCMS m/z [M+1]: 750.2 1H NMR (400 MHz, CD3OD) δ 8.78 (s, 1H), 8.30 (s, 1H), 8.07 (s, 1H), 7.70 (dd, J = 8.8, 4.8 Hz, 1H), 7.04 (t, J = 9.2 Hz, 1H), 5.49 (d, J = 52.0 Hz, 1H), 5.23 – 5.05 (m, 1H), 4.37 – 4.12 (m, 2H), 4.04 – 3.91 (m, 2H), 3.91 – 3.72 (m, 4H), 3.66 – 3.52 (m, 3H), 3.46 – 3.35 (m, 1H), 2.58 – 2.41 (m, 2H), 2.34 – 2.16 (m, 2H), 2.13 – 2.00 (m, 1H), 1.99 – 1.84 (m, 1H), 1.59 (t, J = 7.2 Hz, 3H).
665		LCMS m/z [M+1]: 756.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.59 (d, J = 9.4 Hz, 1H), 7.28 – 7.20 (m, 1H), 7.03 (t, J = 8.7 Hz, 1H), 5.49 (d, J = 54.9 Hz, 1H), 5.24 - 5.12 (m, 1H), 4.36 – 3.98 (m, 2H), 4.02 – 3.76 (m, 5H), 3.73 – 3.35 (m, 5H), 2.65 – 1.84 (m, 9H), 1.566– 1.52 (m, 3H).

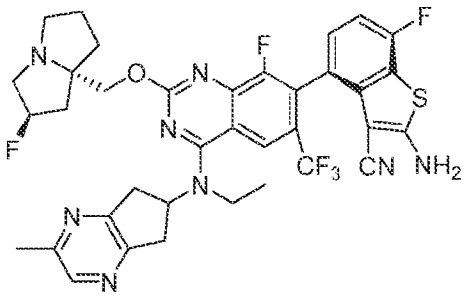
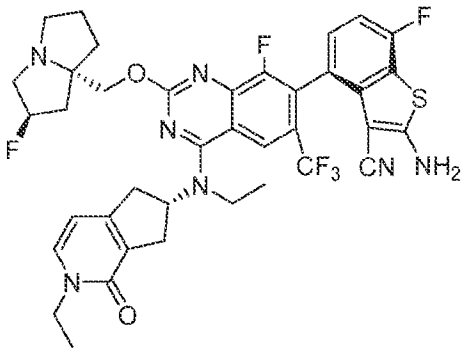
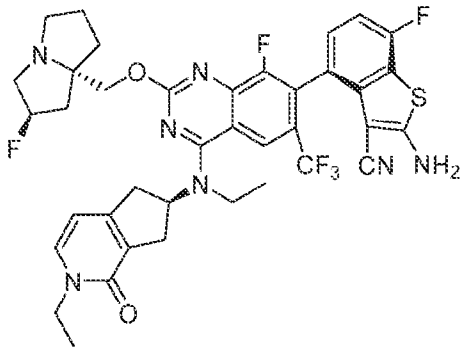
666		LCMS m/z [M+1]: 756.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.59 (d, J = 9.4 Hz, 1H), 7.28 – 7.20 (m, 1H), 7.03 (t, J = 9.2 Hz, 1H), 5.49 (d, J = 52.2 Hz, 1H), 5.24 - 5.12 (m, 1H), 4.36 – 4.14 (m, 2H), 4.02 – 3.76 (m, 5H), 3.73 – 3.35 (m, 5H), 2.62 – 1.84 (m, 9H), 1.57 (t, J = 7.0 Hz, 3H).
667		LCMS m/z [M+1]: 756.2 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.57 (d, J = 9.4 Hz, 1H), 7.28 – 7.20 (m, 1H), 7.03 (t, J = 9.3 Hz, 1H), 5.50 (d, J = 51.8 Hz, 1H), 5.24 – 5.10 (m, 1H), 4.28 – 3.98 (m, 2H), 4.02 – 3.76 (m, 5H), 3.73 – 3.35 (m, 5H), 1.84 – 2.64 (m, 9H), 1.58 (t, J = 7.0 Hz, 3H).
668		LCMS m/z [M+1]: 724.3 1H NMR (400 MHz, CD3OD) δ 8.33 (d, 1H), 8.24 (s, 1H), 7.72 (d, 1H), 7.20-7.27 (m, 2H), 7.00 (t, 1H), 5.31 (s, 0.5H), 5.21-5.24 (m, 1H), 5.18 (s, 0.5H), 4.04-4.11 (m, 2H), 3.85-3.90(m, 2H), 3.53-3.66 (m, 2H), 3.44-3.50 (m, 2H), 3.31-3.37 (m, 1H), 3.00-3.06 (m, 1H), 2.77-2.90 (m, 1H), 2.65-2.70 (m, 1H), 2.19-2.27 (m, 1H), 1.97-2.04 (m, 1H), 1.80-1.94 (m, 3H), 1.68-1.74 (m, 1H), 1.49 (t, 3H).

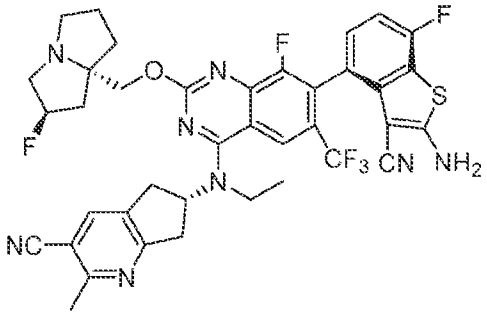
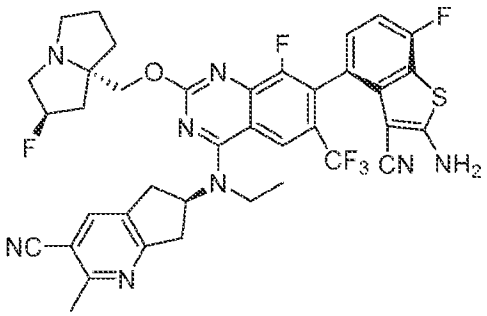
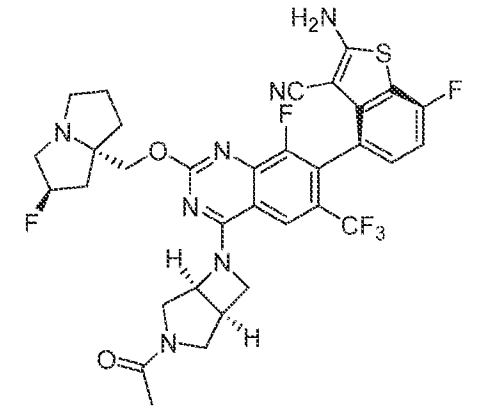
669		LCMS m/z [M+1]: 718.2 1H NMR (400 MHz, CD3OD) δ 8.33 (d, 1H), 8.24 (s, 1H), 7.72 (d, 1H), 7.20-7.28 (m, 2H), 7.00 (t, 1H), 5.12-5.16 (m, 1H), 4.95 (s, 2H), 3.87-3.97 (m, 4H), 3.58-3.74 (m, 3H), 3.42-3.48 (m, 2H), 3.24-3.28 (m, 1H), 3.04-3.08 (m, 1H), 2.55-2.66 (m, 2H), 2.34 (d, 1H), 1.87-1.92 (m, 2H), 1.68-1.79 (m, 2H), 1.52 (t, 3H).
670		LCMS m/z [M+1]: 710.3 1H NMR (400 MHz, CD3OD) δ 8.35 (d, 1H), 8.24 (s, 1H), 7.73 (d, 1H), 7.20-7.28 (m, 2H), 7.00 (t, 1H), 5.13-5.18 (m, 1H), 4.06-4.08 (m, 2H), 3.86-3.90 (m, 3H), 3.66-3.72 (m, 1H), 3.57-3.62 (m, 1H), 3.44-3.50 (m, 2H), 3.33-3.35 (m, 1H), 3.28 (s, 3H), 2.86-2.92 (m, 1H), 2.38-2.43 (m, 4H), 1.92-1.98 (m, 1H), 1.69-1.76 (m, 1H), 1.52 (t, 3H).
671		LCMS m/z [M+1]: 741.1 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.39 (s, 1H), 7.28 – 7.17 (m, J = 8.4, 5.0 Hz, 1H), 7.06 – 6.98 (m, J = 9.3, 8.5 Hz, 1H), 5.36 (s, 0.5H), 5.32 – 5.23 (m, 1H), 5.23 (s, 0.5H), 4.77 – 4.71 (m, J = 10.4, 6.1 Hz, 1H), 4.45 (t, J = 9.9 Hz, 1H), 3.97 – 3.91 (m, 2H), 3.67 (d, J = 10.8 Hz, 1H), 3.55 (d, J = 10.8 Hz, 1H), 3.50 – 3.44 (m, 1H), 3.40 – 3.34 (m, 1H), 3.21 (s, 3H), 3.08 – 3.00 (m, J = 15.5, 9.4 Hz, 1H), 2.54 – 2.47 (m, J = 7.6 Hz, 2H), 2.29

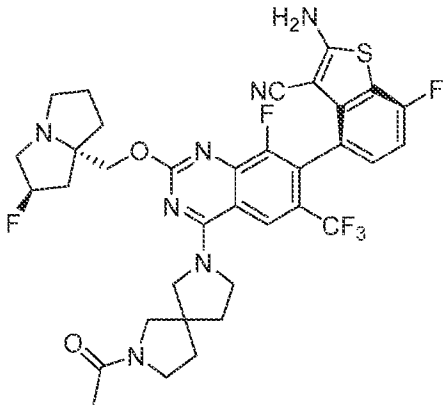
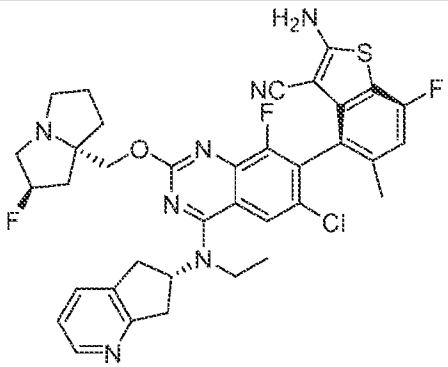
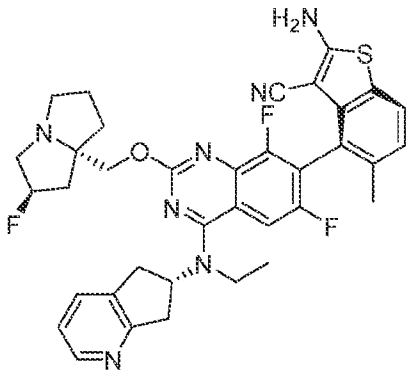
		– 2.05 (m, 2H), 1.99 – 1.85 (m, 3H), 1.84 – 1.75 (m, J = 18.1, 8.3 Hz, 1H), 1.62 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.6 Hz, 3H).
672		LCMS m/z [M+1]: 758.2 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 6.35 – 7.31 (m, 1H), 7.25 – 7.20 (m, 1H), 7.02 (t, J = 9.6 Hz, 1H), 5.49 (d, J = 51.6 Hz, 1H), 5.13 – 4.99 (m, 1H), 4.26 – 3.94 (m, 4H), 3.89 – 3.73 (m, 3H), 3.68 – 3.34 (m, 5H), 2.62 – 2.42 (m, 2H), 2.32 – 2.14 (m, 2H), 2.09 – 1.87 (m, 2H), 1.64 – 1.57 (m, 3H).
673		LCMS m/z [M+1]: 738.4 1H NMR (400 MHz, CD3OD) δ 8.27 (s, 1H), 8.02 (d, J = 1.2 Hz, 1H), 7.82 (s, 1H), 7.00 (t, J = 9.6 Hz, 1H), 5.48 (d, J = 52.0 Hz, 1H), 5.25 – 5.08 (m, 1H), 4.46 – 4.18 (m, 2H), 3.98 (s, 3H), 3.97 – 3.85 (m, 3H), 3.84 – 3.76 (m, 2H), 3.73 – 3.52 (m, 4H), 3.47 – 3.35 (m, 1H), 2.60 – 2.37 (m, 2H), 2.32 – 2.06 (m, 3H), 2.01 – 1.84 (m, 1H), 1.55 (t, J = 7.2 Hz, 3H).
674		LCMS m/z [M+1]: 748.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.22 (dd, J = 8.3, 5.0 Hz, 1H), 7.05 – 6.99 (m, 1H), 5.38 (d, J = 53.4 Hz, 1H), 5.20 – 5.13 (m, 1H), 4.59 – 4.51 (m, 1H), 4.07 – 3.88 (m, 4H), 3.56 – 3.39 (m, 5H), 3.25 – 3.14 (m, 2H), 2.43 – 2.26 (m, 2H), 2.13 – 1.87 (m, 4H), 1.63 – 1.56 (m, 3H).

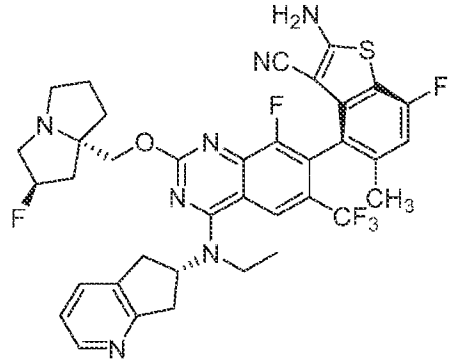
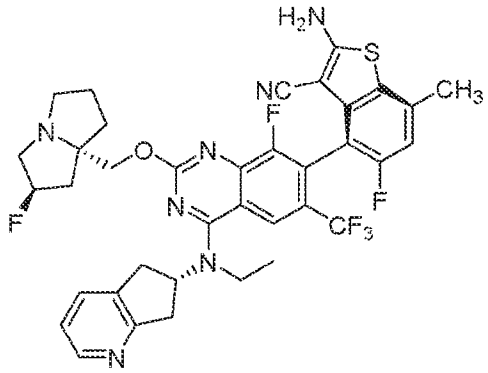
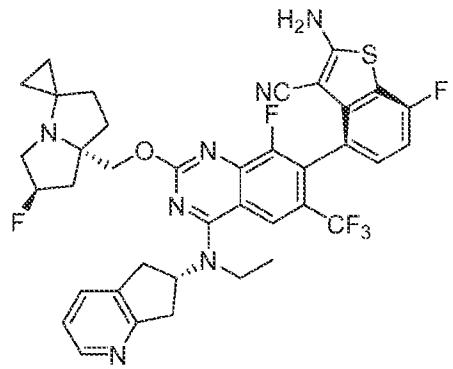
675		LCMS m/z [M+1]: 706.3 1H NMR (400 MHz, CD3OD) δ 8.49 (s, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 9.6 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.01 (t, J = 9.7 Hz, 1H), 5.55 (d, d, J = 53.4 Hz, 1H), 5.15 (m, 1H), 4.42 (d, J = 12.6 Hz, 1H), 4.22 (d, J = 12.7 Hz, 1H), 3.86 (m, 4H), 3.71 – 3.57 (m, 3H), 3.40 (m, 1H), 2.51 (s, 1H), 2.45 – 2.40 (m, 1H), 2.31 – 2.11 (m, 4H), 1.97 (dd, J = 15.6, 7.9 Hz, 4H), 1.03 (t, J = 7.4 Hz, 3H).
676		LCMS m/z [M+1]: 698.1 1H NMR (400 MHz, CD3OD) δ 8.98 (s, 1H), 7.68 (d, J = 10.2 Hz, 1H), 7.01 (t, J = 9.7 Hz, 1H), 5.52 (d, J = 51.8 Hz, 1H), 5.37 – 5.30 (m, 1H), 4.18 – 4.11 (m, 1H), 4.04 – 3.80 (m, 6H), 3.62 – 3.36 (m, 5H), 2.56 – 2.42 (m, 2H), 2.31 – 2.19 (m, 2H), 2.09 – 1.96 (m, 2H), 1.61 – 1.51 (m, 3H).
677		LCMS m/z [M+1]: 698.1 1H NMR (400 MHz, CD3OD) δ 8.98 (s, 1H), 7.69 (d, J = 10.3 Hz, 1H), 7.01 (t, J = 9.7 Hz, 1H), 5.53 (d, J = 51.7 Hz, 1H), 5.37 – 5.29 (m, 1H), 4.13 – 3.78 (m, 7H), 3.63 – 3.34 (m, 5H), 2.61 – 2.43 (m, 2H), 2.31 – 2.16 (m, 2H), 2.08 – 1.92 (m, 2H), 1.61 – 1.53 (m, 3H).

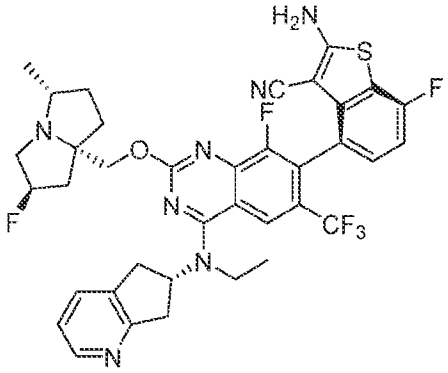
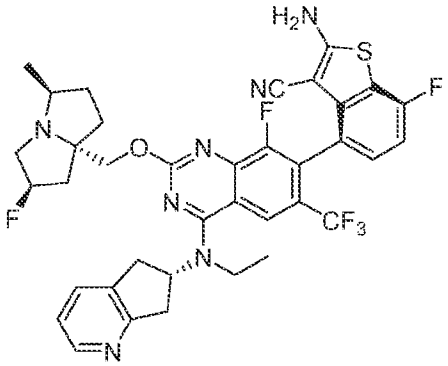
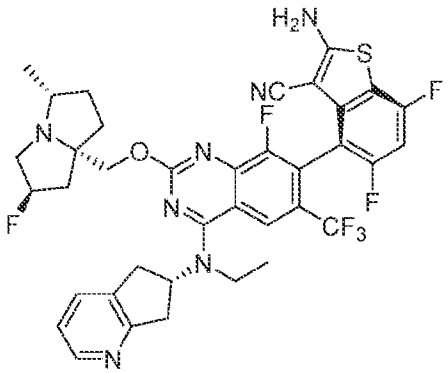
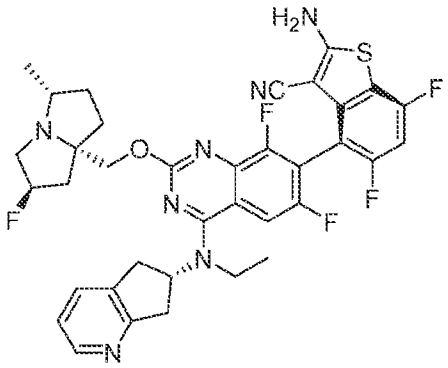
678		LCMS m/z [M+1]: 774.2 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.25 - 7.22 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 6.89-6.60 (m, 1H), 5.56 - 5.40 (m, 1H), 5.15 - 5.08 (m , 1H), 4.21 - 3.34 (m, 12H), 2.57 - 1.83 (m, 6H), 1.63 - 1.58 (m, 3H).
679		LCMS m/z [M+1]: 747.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.33 – 7.32 (m, 1H), 6.95 (t, J = 9.5 Hz, 1H), 6.90 – 6.89 (m, 1H), 5.41 – 5.28 (m, 2H), 3.96 – 3.86 (m, 4H), 3.58 – 3.35 (m, 6H), 3.24 – 3.10 (m, 2H), 2.39 – 1.84 (m, 6H), 1.59 – 1.55 (m, 3H),
680		LCMS m/z [M+1]: 739.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.71 (s, 1H), 7.26 - 7.20 (m, 1H), 7.03 (t, J = 8.4 Hz, 1H), 5.47 (d, J = 51.3 Hz, 1H), 5.05 - 5.00 (m, 1H), 4.25 (dd, J = 44.0, 8.4 Hz, 2H), 4.01 - 3.96 (m, 2H), 3.82 - 3.60 (m, 7H), 2.75 (s, 3H), 2.47 - 2.42 (m, 1H), 2.28 - 2.17 (m, 3H), 2.10 - 2.01 (m, 2H), 1.89 - 1.84 (m, 1H), 1.67 - 1.61 (m, 3H).
681		LCMS m/z [M+1]: 739.3 1H NMR (400 MHz, CD3OD) δ 8.28 (s, 1H), 7.61 (s, 1H), 7.26 - 7.19 (m, 1H), 7.02 (t, J = 9.6, 8.8 Hz, 1H), 5.48 (d, J = 51.9 Hz, 1H), 5.03 - 4.98 (m, 1H), 4.19 - 4.14 (m, 1H), 4.05 - 4.00

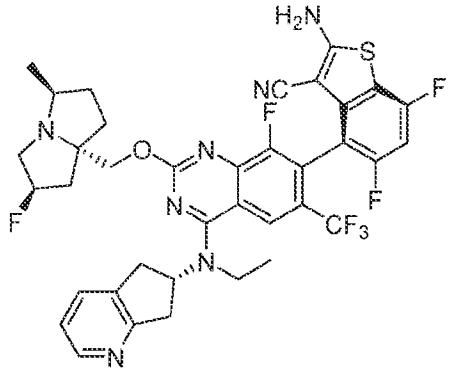
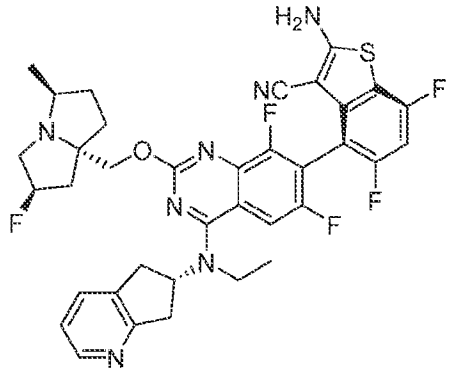
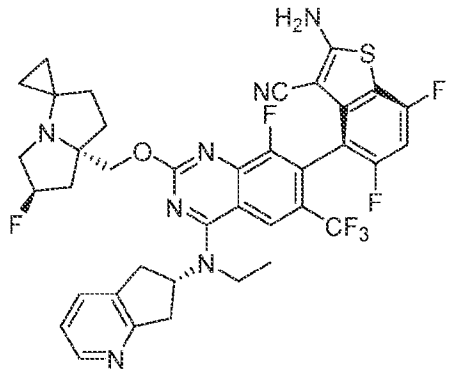
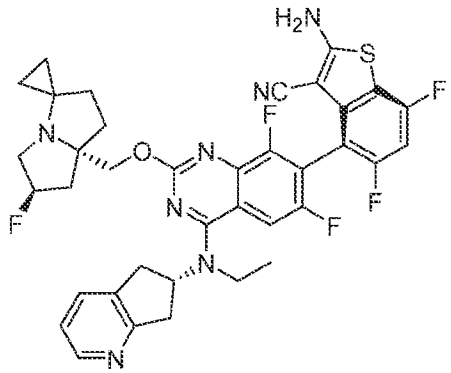
		(m, 1H), 3.99 - 3.95 (m, 1H), 3.84 - 3.62 (m, 8H), 2.72 (s, 3H), 2.42 - 2.40 (m, 1H), 2.24 - 2.16 (m, 3H), 2.10 - 2.01 (m, 2H), 1.90 - 1.84 (m, 1H), 1.68 - 1.60 (m, 3H).
682		LCMS m/z [M+1]: 739.2 1H NMR (400 MHz, CD3OD): δ 8.30 (s, 1H), 8.23 (s, 1H), 7.23 - 7.19 (m, 1H), 7.01 (t, J = 9.4 Hz, 1H), 5.21 (d, J = 53.5 Hz, 1H), 5.02 - 4.91 (m, 1H), 3.96 - 3.92 (m, 2H), 3.81 - 3.63 (m, 4H), 3.52 - 3.43 (m, 2H), 3.21 - 3.09 (m, 3H), 3.01 - 2.94 (m, 1H), 2.55 (s, 3H), 2.14 - 1.66 (m, 6H), 1.61 (t, J = 7.0 Hz, 3H).
683		LCMS m/z [M+1]: 768.2 1H NMR (400 MHz, CD3OD, ppm): δ 8.37 (s, 1H), 8.29 (s, 1H), 7.91 (s, 1H), 7.27-7.21 (m, 1H), 7.08-6.97 (m, 1H),5.59-5.38 (m, 1H), 5.24-5.11 (m, 1H), 4.41-4.13 (m, 2H), 4.04-3.68 (m, 6H), 3.65-3.37 (m, 5H), 2.85-2.71 (m, 2H), 2.55-2.39 (m, 2H), 2.32-1.79 (m, 4H),1.66-1.54 (m, 3H),1.38-1.27 (m, 3H).
684		LCMS m/z [M+1]: 768.2 1H NMR (400 MHz, CD3OD, ppm): δ 8.37-8.34 (m, 1H), 8.29 (s, 1H), 7.91 (s, 1H), 7.27-7.21 (m, 1H), 7.08-6.97 (m, 1H),5.59-5.38 (m, 1H), 5.24-5.11 (m, 1H), 4.41-4.13 (m, 2H), 4.04-3.68 (m, 6H), 3.65-3.37 (m, 5H), 2.85-2.71 (m, 2H), 2.55-2.39 (m, 2H),

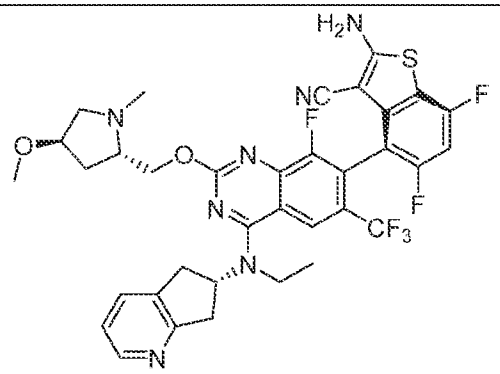
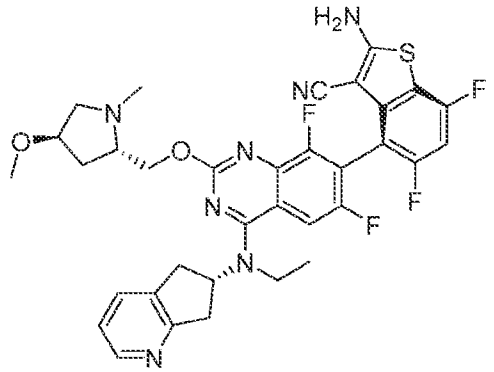
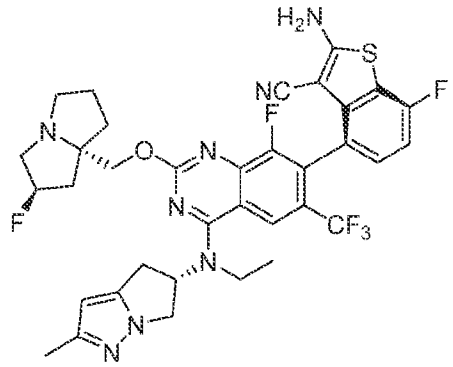
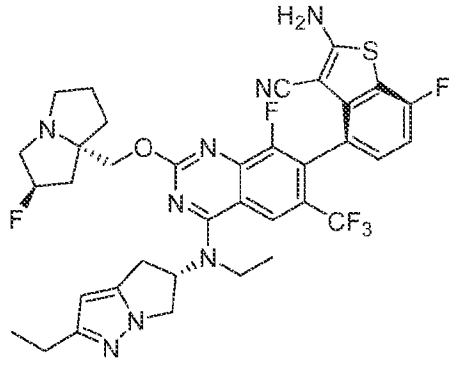
		2.32-1.79 (m, 4H), 1.59-1.57 (m, 3H), 1.34-1.20 (m, 3H).
685		LCMS m/z [M+1]: 763.2 1H NMR (400 MHz, CD3OD): δ 8.28 (s, 1H), 7.98 (s, 1H), 7.24 - 7.21 (m, 1H), 7.00 (t, J = 9.52 Hz, 1H), 5.55 (d, J = 52.1Hz, 1H), 5.18 - 5.10 (m, 1H), 4.34 - 4.15 (m, 2H), 3.97-3.69 (m, 7H), 3.56 - 3.47 (m, 3H), 3.42 - 3.37 (m, 1H), 2.74 (s, 3H), 2.59-2.46 (m, 2H), 2.31-2.20 (m, 2H), 2.02-1.99 (m, 1H), 1.92-1.88 (m, 1H) 1.57 (t, J = 7.05 Hz, 3H).
686		LCMS m/z [M+1]: 763.2 1H NMR (400 MHz, CD3OD): δ 8.28 (s, 1H), 7.98 (s, 1H), 7.24 - 7.21 (m, 1H), 7.00 (t, J = 9.52 Hz, 1H), 5.55 (d, J = 52.1Hz, 1H), 5.18 - 5.10 (m, 1H), 4.34 - 4.15 (m, 2H), 3.97-3.69 (m, 7H), 3.56 - 3.47 (m, 3H), 3.42 - 3.37 (m, 1H), 2.74 (s, 3H), 2.59-2.46 (m, 2H), 2.31-2.20 (m, 2H), 2.02-1.99 (m, 1H), 1.92-1.88 (m, 1H) 1.57 (t, J = 7.05 Hz, 3H).
687		LCMS m/z [M+1]: 702.2 1H NMR (400 MHz, CD3OD) δ 8.03 (d, 1H), 7.20-7.17 (m,1H), 6.99 (t, 1H), 5.38 (s, 1.5H), 5.26 (s, 0.5H), 4.50-4.44 (m, 1H), 4.34-4.21 (m, 3H), 4.07-4.05 (m, 1H), 3.68-3.61 (m, 1H), 3.55-3.34 (m, 3H), 3.24-3.18 (m, 2H), 3.08-3.00 (m, 1H), 2.41-2.28 (m, 1H), 2.27-2.10 (m, 5H), 2.07-1.80 (m, 4H).

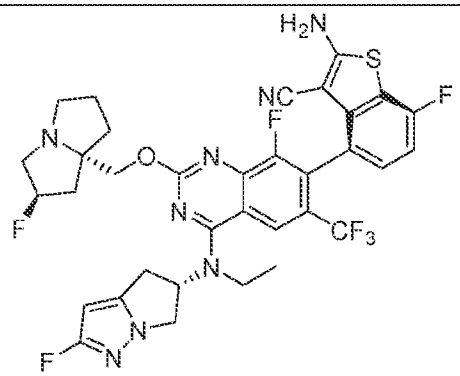
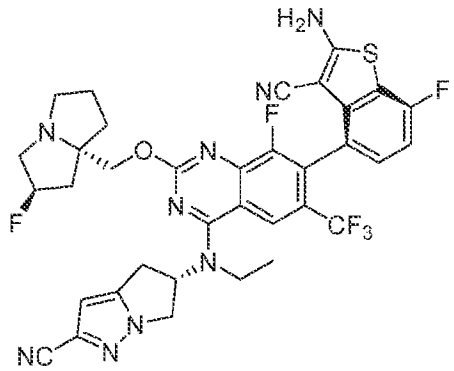
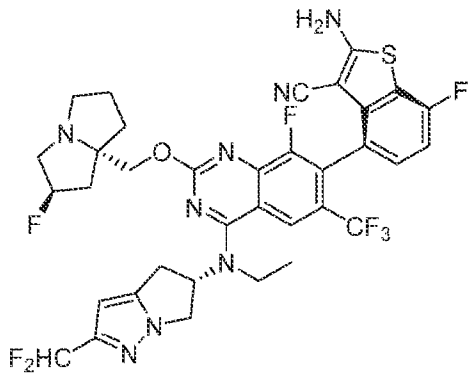
688		LCMS m/z [M+1]: 730.0 1H NMR (400 MHz, CD3OD) δ 8.42 (s, 1H), 7.18-7.21 (m, 1H), 7.00 (t, 1H), 5.38 (s, 0.5H), 5.25 (s, 0.5H), 4.34-4.37 (m, 1H), 4.20-4.27 (m, 3H), 4.00 (s, 2H), 3.71 (t, 1H), 3.58-3.60 (m, 2H), 3.52 (s, 1H), 3.30-3.31 (m, 1H), 3.29-3.30 (m, 2H), 3.05 (m, 1H), 2.23-2.36 (m, 2H), 2.06-2.08 (m, 4H), 2.01-2.06 (m, 3H), 1.90-2.01 (m, 4H).
689		
690		LCMS m/z [M+1]: 670.3 1H NMR (400 MHz, CD3OD) δ 8.33 (d, 1H), 7.72 (d, 1H), 7.56-7.63 (m, 2H), 7.24-7.27 (m, 1H), 7.15 (d, 1H), 5.32 (s, 0.5H), 5.19 (s, 0.5H), 5.05-5.09 (m, 1H), 3.80-3.92 (m, 4H), 3.68-3.85 (m, 1H), 3.57-3.63 (m, 1H), 3.39-3.50 (m, 2H), 3.18-3.23 (m, 2H), 2.95-3.02 (m, 1H), 2.13-2.31 (m, 5H), 2.04-2.10 (m, 1H), 1.84-1.94 (m, 2H), 1.70-1.81 (m, 2H), 1.48 (t, 3H).

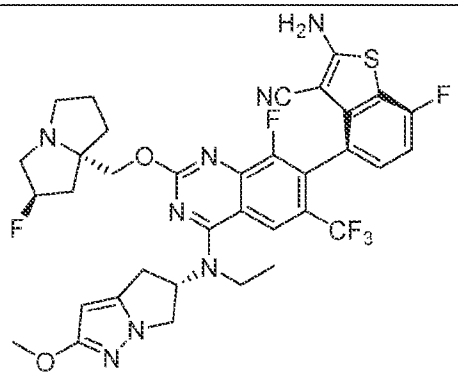
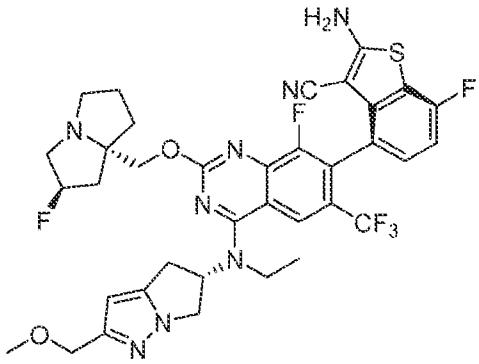
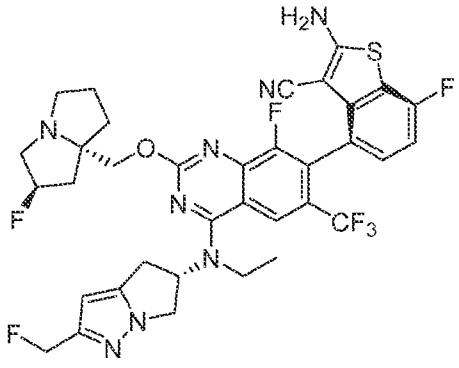
691		
692		LCMS m/z [M+1]: 738.3 1H NMR (400 MHz, CD3OD) δ 8.35 (d, 1H), 8.25 (s,1H), 7.73 (d, 1H), 7.28-7.25 (m,1H), 6.89 (d, 1H), 5.32 (s, 0.5H), 5.18 (s, 0.5H), 5.11-5.03 (s, 1H), 3.94-3.87 (m, 3H), 3.81-3.74 (m, 2H), 3.68-3.62 (m, 1H), 3.49-3.42 (m, 2H), 3.29-3.16 (m, 3H), 3.02-2.96 (m, 1H), 2.47 (s, 3H), 2.26-2.16 (m, 1H), 2.14-2.08 (m, 1H), 1.95-1.84 (m, 2H), 1.78-1.68 (m, 2H), 1.55 (t,3H).
693		LCMS m/z [M+1]: 750.1 1H NMR (400 MHz, CD3OD) δ 8.34 (d, 1H), 8.24 (s, 1H), 7.74 (d, 1H), 7.25 (ddd, 2H), 7.04-6.98 (m, 1H), 5.12 (dd, 2H), 4.00-3.86 (m, 4H), 3.78 (dd, 1H), 3.66 (dd, 1H), 3.51-3.40 (m, 2H), 3.20-3.05 (m, 2H), 2.44-2.31 (m, 2H), 2.24-1.97 (m, 2H), 1.95-1.85 (m, 1H), 1.77-1.66 (m, 1H), 1.55 (t, 3H), 0.89-0.45 (m, 4H).

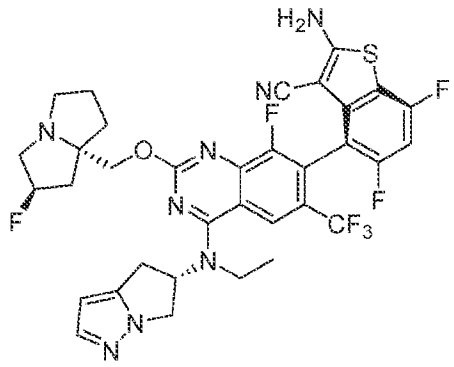
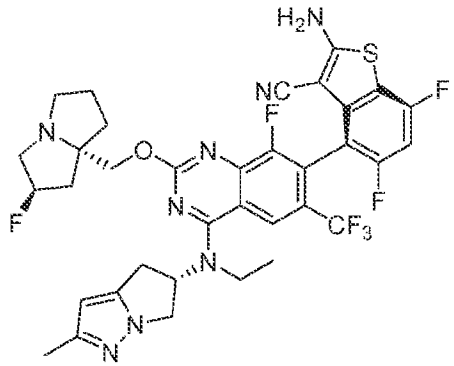
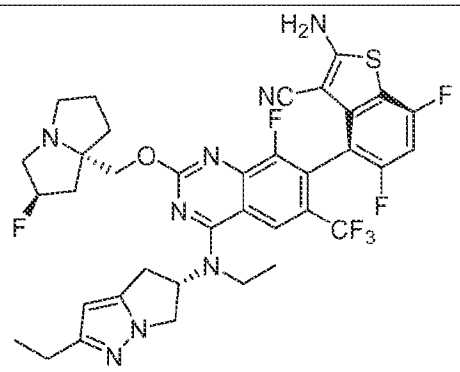
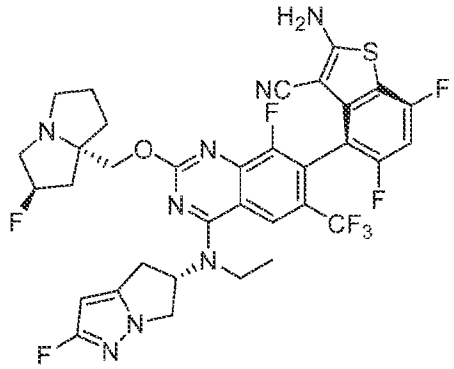
694		
695		
696		
697		

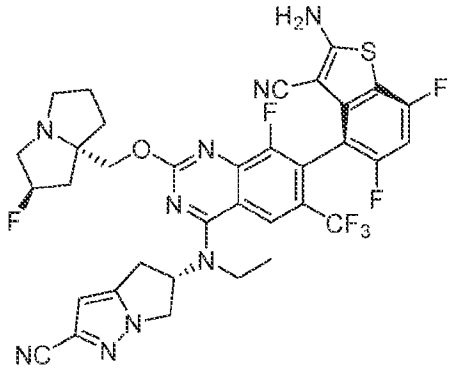
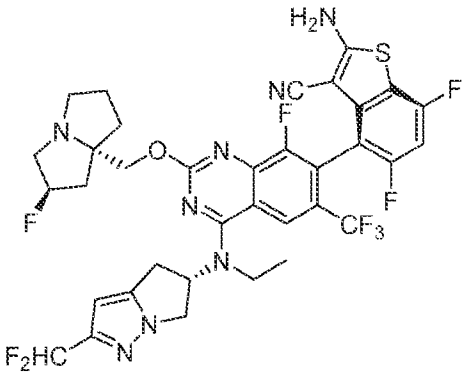
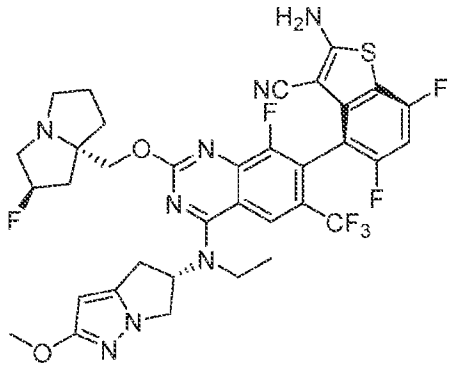
698		
699		
700		
701		

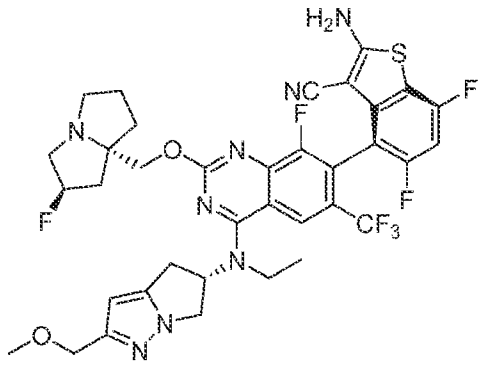
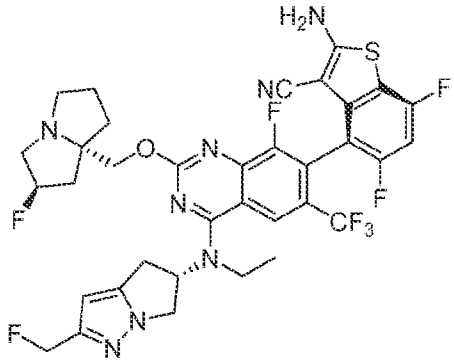
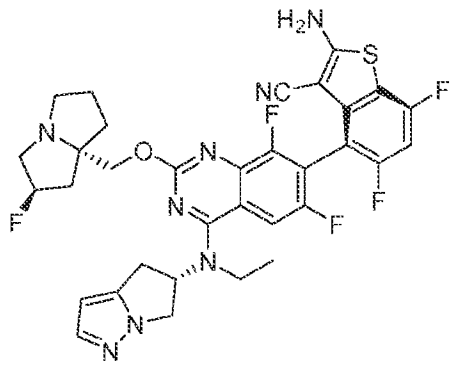
702		
703		
704		
705		

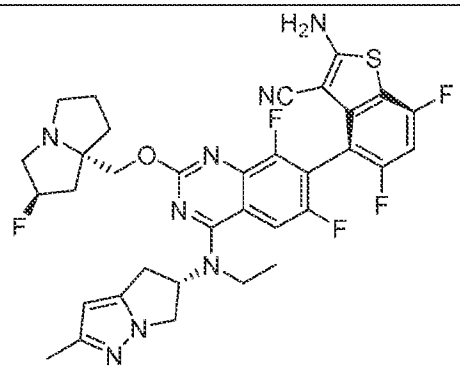
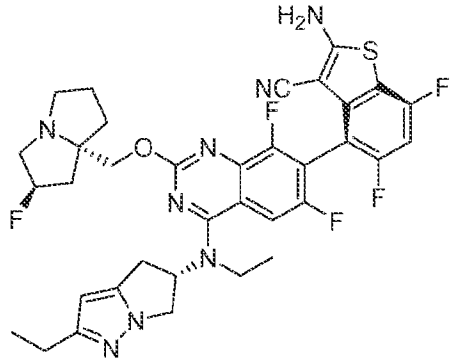
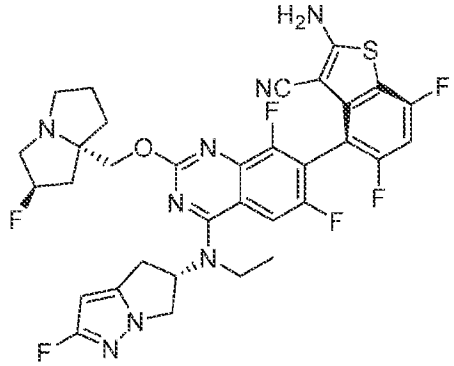
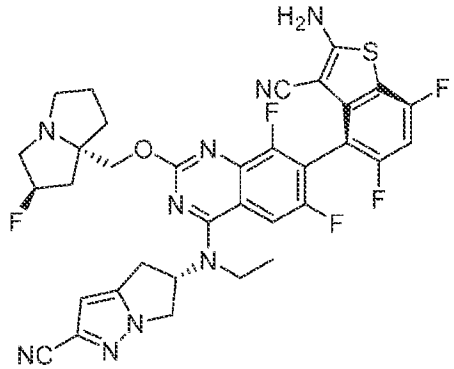
706		
707		LCMS m/z [M+1]: 738.2 1H NMR (400 MHz, CD3OD) δ 8.35 (d, 1H), 8.25 (s,1H), 7.73 (d, 1H), 7.28-7.25 (m,1H), 6.89 (d, 1H), 5.32 (s, 0.5H), 5.18 (s, 0.5H), 5.11-5.03 (s, 1H), 3.94-3.87 (m, 3H), 3.81-3.74 (m, 2H), 3.68-3.62 (m, 1H), 3.49-3.42 (m, 2H), 3.29-3.16 (m, 3H), 3.02-2.96 (m, 1H), 2.47 (s, 3H), 2.26-2.16 (m, 1H), 2.14-2.08 (m, 1H), 1.95-1.84 (m, 2H), 1.78-1.68 (m, 2H), 1.55 (t,3H).
708		LCMS m/z [M+1]: 763.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.23-7.20 (m, 1H), 7.01(t, 1H), 6.87-6.60 (m, 1H), 6.34 (s, 1H), 5.35 (s, 0.5H), 5.32-5.24 (m, 1H), 5.22 (s, 0.5H), 4.83-4.78 (m, 1H), 4.52 (t, 1H), 3.99-3.90 (m, 2H), 3.78-3.71 (m, 2H), 3.65-3.60 (m, 1H), 3.43-3.32 (m, 2H), 3.28-3.22 (m, 1H), 3.07-3.01 (m, 1H), 2.20-2.11 (m, 1H), 2.10-1.95 (m, 2H), 1.93-1.76 (m, 3H), 1.62 (t,3H).

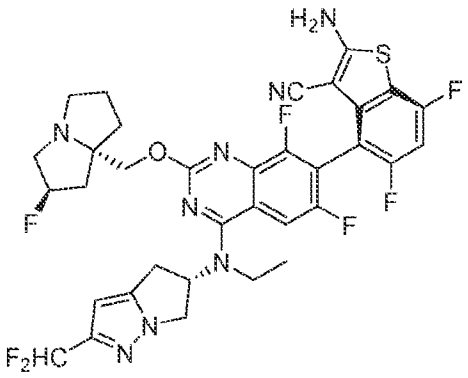
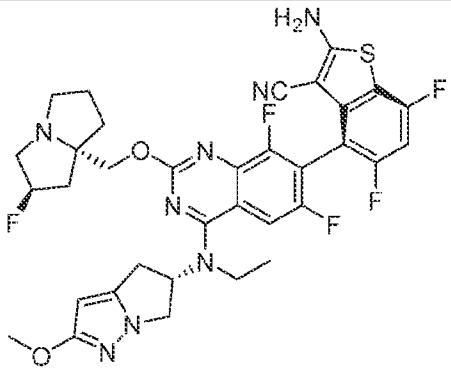
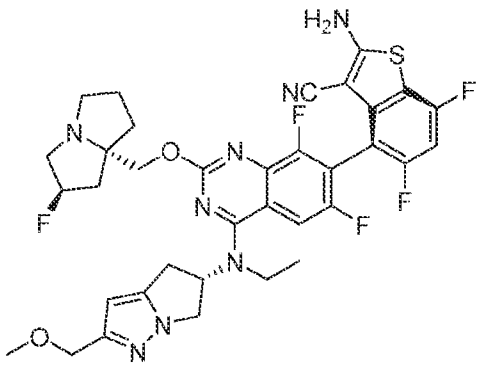
709		
710		LCMS m/z [M+1]: 757.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.20-7.23 (m, 1H), 7.01(t, 1H), 6.12 (s, 1H), 5.37 (s, 0.5H), 5.25-5.29 (m, 1.5H), 4.72-4.75 (m, 1H), 4.38-4.50 (m, 3H), 3.91-3.97 (m, 2H), 3.68-3.72 (m, 2H), 3.54-3.60 (m, 1H), 3.34-3.47 (m, 6H), 3.20-3.29 (m, 1H), 3.03-3.09 (m, 1H), 3.05 (m, 1H), 2.23-2.32 (m, 1H), 2.08-2.19 (m, 1H), 1.79-2.00 (m, 4H), 1.61 (t, 3H).
711		LCMS m/z [M+1]: 745.2 1H NMR (400 MHz, CD3OD) δ 8.21 (s, 1H), 7.23-7.20 (m,1H), 7.01(t, 1H), 6.24 (s,1H), 5.37 (s, 1H), 5.32 (s, 0.5H), 5.29-5.23 (m,2H), 5.18 (s, 0.5H), 4.81-4.76 (m, 1H), 4.50 (t, 1H), 3.96-3.91 (m, 2H), 3.71-3.58 (m, 3H), 3.41-3.37 (m, 1H), 3.26-3.11 (m, 3H), 3.01-2.95 (m, 1H), 2.26-2.14 (m, 1H), 2.11-2.04 (m, 1H), 1.97-1.91 (m, 1H), 1.88-1.74 (m, 3H), 1.61 (t,3H).

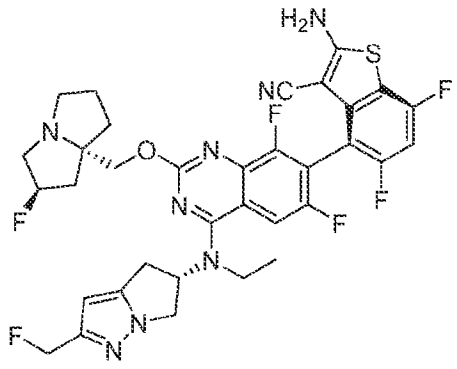
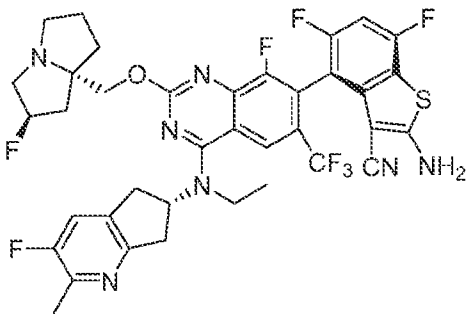
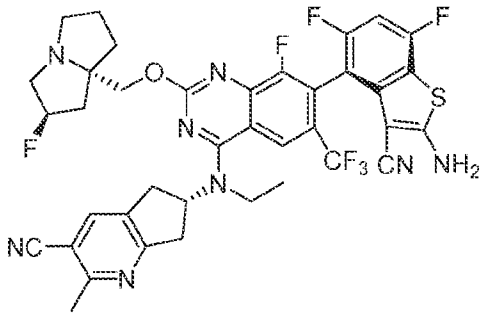
712		LCMS m/z [M+1]: 731.1 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.57 (d, 1H), 6.97 (t, 1H), 6.13 (s, 1H), 5.38 (s, 0.5H), 5.34-5.27 (m, 1H), 5.24 (s, 0.5H), 4.78 (dd, 1H), 4.52 (t, 1H), 3.95 (q, 2H), 3.68-3.51 (m, 3H), 3.44-3.35 (m, 2H), 3.28-3.20 (m, 2H), 3.09-2.98 (m, 1H), 2.35-2.20 (m, 1H), 2.10-1.90 (m, 4H), 1.86-1.76 (m, 1H), 1.63 (t, 3H).
713		
714		
715		

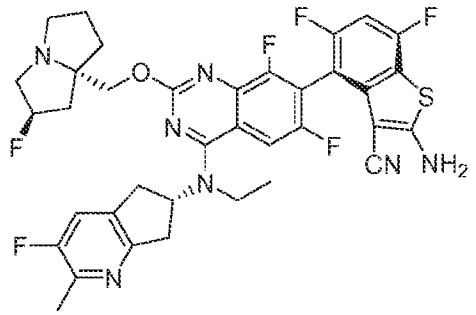
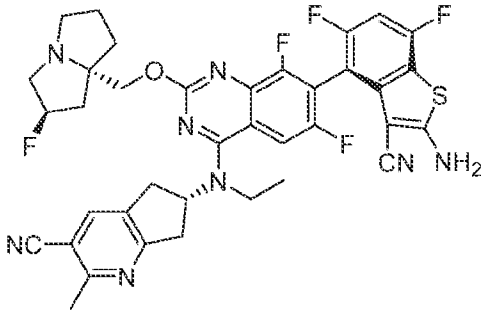
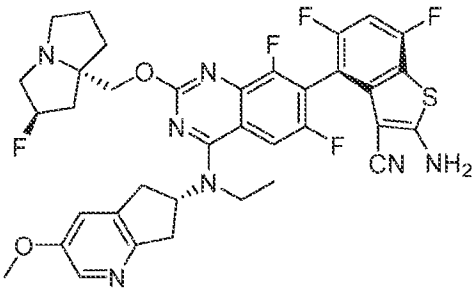
716		LCMS m/z [M+1]: 756.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 6.96 (t, 1H), 6.62 (s, 1H), 5.34 (s, 0.5H), 5.31-5.22 (m, 1H), 5.21 (s, 0.5H), 4.57 (t, 1H), 3.93 (q, 2H), 3.69-3.41 (m, 4H), 3.27-3.10 (m, 4H), 3.02-2.95 (m, 1H), 2.25-2.16 (m, 1H), 2.15-2.02 (m, 2H), 1.94-1.87 (m, 2H), 1.83-1.73 (m, 1H), 1.62 (t, 3H).
717		LCMS m/z [M+1]: 781.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 6.95 (t, 1H), 6.87-6.59 (m,1H), 6.33 (s, 1H), 5.33 (s,0.5H),5.30-5.24 (m,1H), 5.20 (s,0.5H),4.82-4.78(m, 1H), 4.51 (t, 1H), 3.97-3.91 (m, 2H), 3.74 (s, 2H), 3.66-3.60 (m, 1H), 3.43-3.36 (m, 1H), 3.27-3.21 (m, 3H), 3.04-2.98 (m, 1H), 2.24-2.07 (m, 2H), 2.03-1.90 (m, 2H), 1.88-1.77(m, 2H), 1.61 (t, 3H).
718		

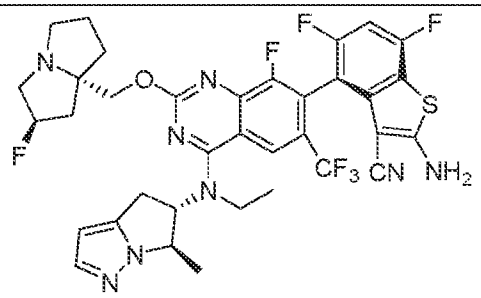
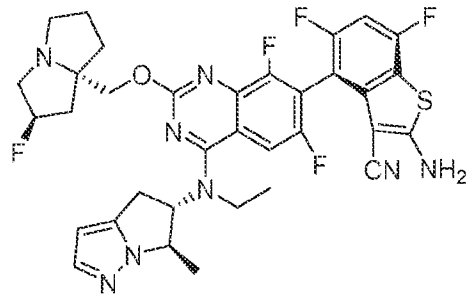
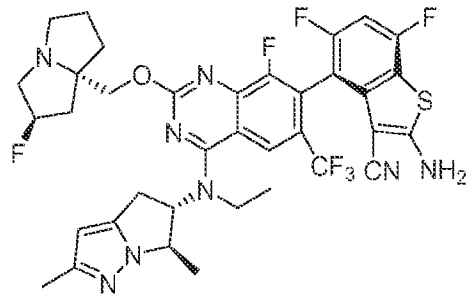
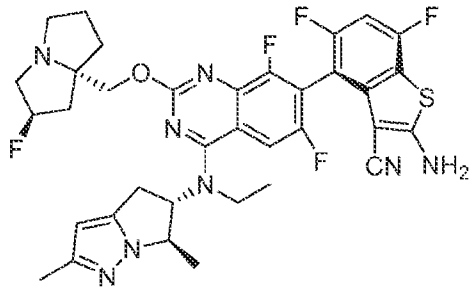
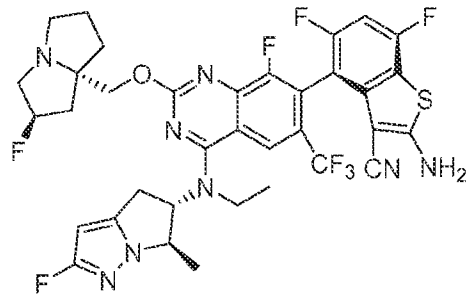
719		LCMS m/z [M+1]: 775.1 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 6.96 (t, J = 9.6 Hz, 1H), 6.12 (s, 1H), 5.34 (s, J = 12.0 Hz, 0.5H), 5.31 – 5.24 (m, 1H), 5.22 (s, 0.5H), 4.79 – 4.71 (m, J = 10.4, 6.3 Hz, 1H), 4.52 – 4.37 (m, 3H), 3.94 (q, J = 7.0 Hz, 2H), 3.61 – 3.53 (m, J = 15.9, 6.1 Hz, 2H), 3.40 (s, 3H), 3.37 (d, J = 6.4 Hz, 1H), 3.23 (d, J = 27.3 Hz, 3H), 3.09 – 2.97 (m, J = 15.2, 9.2 Hz, 1H), 2.31 – 2.08 (m, 2H), 2.06 – 1.92 (m, 2H), 1.90 – 1.78 (m, 2H), 1.61 (t, J = 7.0 Hz, 3H).
720		LCMS m/z [M+1]: 763.2 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 6.95 (t, 1H), 6.24 (s,1H), 5.37 (s, 1H), 5.32 (s,0.5H),5.25 (s,1H), 5.18 (s,0.5H), 4.83-4.75(m, 2H), 4.49 (t, 1H), 3.96-3.91 (m,2H), 3.68-3.58 (m, 3H), 3.41-3.35 (m, 1H), 3.24-3.12 (m, 3H), 3.01-2.95 (m, 1H), 2.21-2.03(m, 2H), 1.96-1.90 (m, 1H), 1.87-1.73 (m, 3H), 1.61 (t,3H).
721		LCMS m/z [M+1]: 681.3 1H NMR (400 MHz, CD3OD) δ 7.63 (d, 1H), 7.51 (d, 1H), 7.16 (t, 1H), 6.06 (s, 1H), 5.31-5.36 (m, 1.5H), 5.21 (s, 0.5H), 4.46-4.60 (m, 2H), 3.70-3.86 (m, 4H), 3.32-3.40 (m, 2H), 3.04-3.17 (m, 3H), 2.88-2.94 (m, 1H), 2.13-2.23 (m, 1H), 1.99-2.09 (m, 1H), 1.76-1.92 (m, 4H), 1.43 (t, 3H).

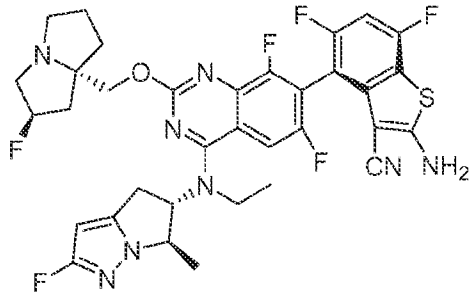
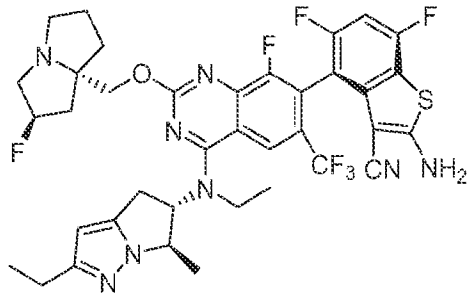
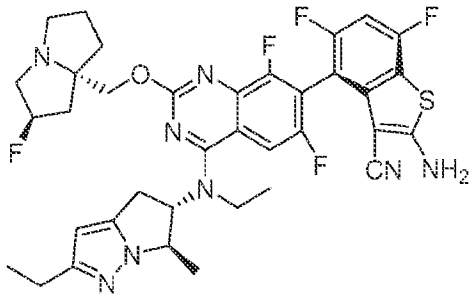
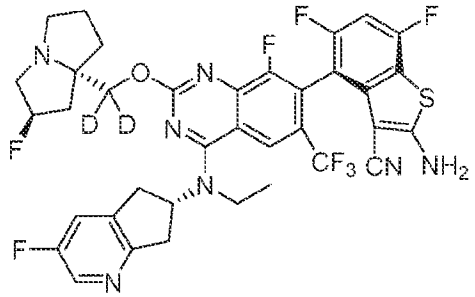
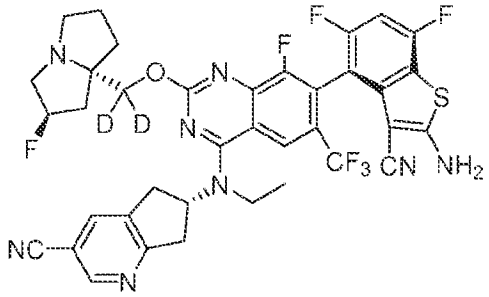
722		
723		
724		
725		LCMS m/z [M+1]: 706.2 1H NMR (400 MHz, CD3OD) δ 7.60 (d, 1H), 6.99 (t, 1H), 6.61 (s, 1H), 5.36 (s, 0.5H), 5.20-5.28 (m, 1.5H), 4.56 (t, 1H), 3.88-3.93 (m, 2H), 3.71-3.76 (m, 1H), 3.61-3.65 (m, 1H), 3.39-3.51 (m, 3H), 3.18-3.25 (m, 3H), 3.01-3.08 (m, 1H), 2.09-2.18 (m, 2H), 1.93-2.03 (m, 3H), 1.77-1.86 (m, 1H), 1.55 (t, 3H).

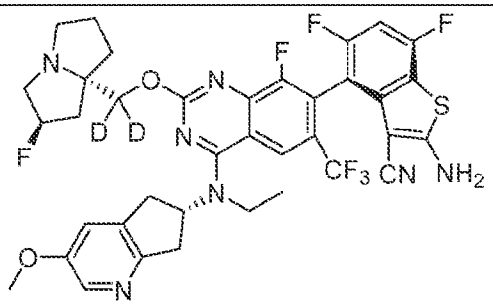
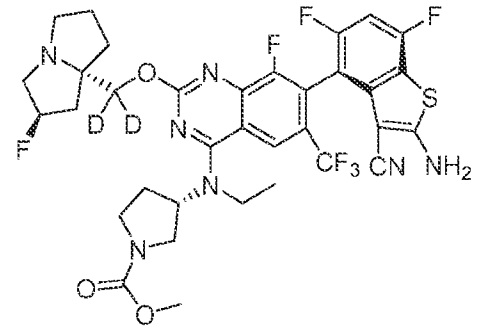
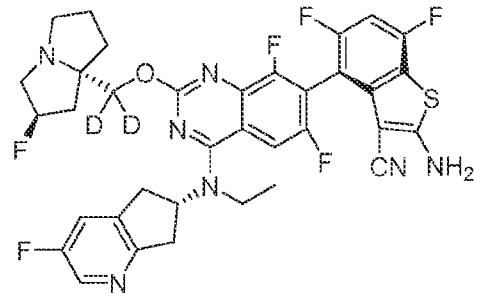
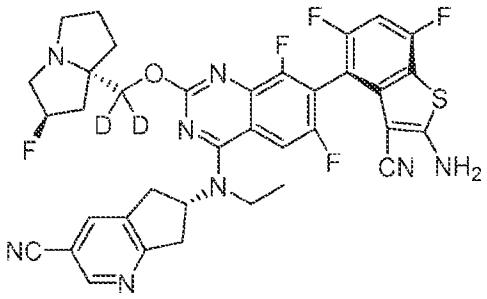
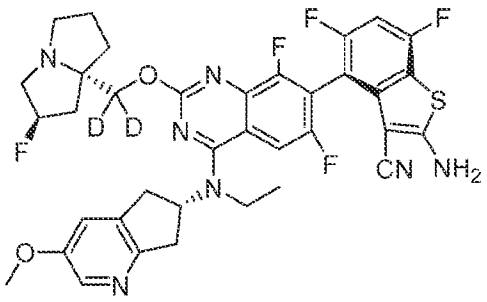
726		LCMS m/z [M+1]: 731.1 1H NMR (400 MHz, CD3OD) δ 7.61 (d, 1H), 6.99 (t, 1H), 6.86-6.58 (m,1H), 6.32(s, 1H), 5.34 (s, 0.5H), 5.32-5.24 (m,1H), 5.20 (s, 0.5H),4.78-4.73 (m, 1H), 4.51 (t, 1H), 3.93-3.88 (m, 2H), 3.78-3.71 (m, 2H), 3.61-3.34 (m, 3H), 3.25-3.20 (m, 2H), 3.04-2.97 (m, 1H), 2.31-2.20 (m, 1H), 2.18-2.00 (m, 2H), 1.97-1.92 (m, 1H), 1.88-1.75 (m, 2H), 1.54 (t, 3H).
727		
728		LCMS m/z [M+1]: 725.3 1H NMR (400 MHz, CD3OD) δ 7.61 (d, 1H), 6.99 (t, 1H), 6.11 (s, 1H), 5.35 (s, 0.5H), 5.22-5.28 (m, 1.5H), 4.67-4.72 (m, 1H), 4.36-4.49 (m, 3H), 3.87-3.92 (m, 2H), 3.68-3.75 (m, 2H), 3.47-3.55 (m, 1H), 3.34-3.39 (m, 4H), 3.12-3.24 (m, 3H), 2.97-3.04 (m, 1H), 2.16-2.32 (m, 1H), 2.03-2.12 (m, 1H), 1.76-1.95 (m, 4H), 1.52 (t, 3H).

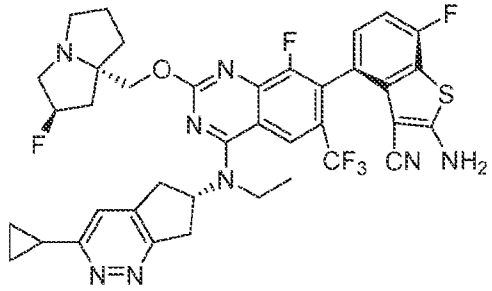
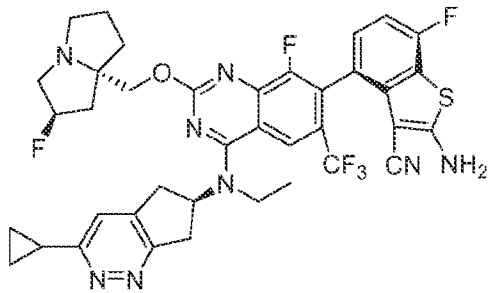
729		LCMS m/z [M+1]: 713.3 1H NMR (400 MHz, CD3OD) δ 7.63 (d, 1H), 7.00 (t, 1H), 6.25 (s,1H), 5.42-5.36 (s, 1.5H), 5.30-5.21 (m, 2.5H), 4.79-4.72 (m, 1H), 4.50 (t, 1H), 3.95-3.90 (m, 2H), 3.84-3.75 (m, 2H), 3.58-3.47 (m, 2H), 3.45-3.34 (m, 3H), 3.15-3.10 (m, 1H), 2.30-2.13 (m, 2H), 2.08-1.93 (m, 3H), 1.87-1.81 (m, 1H), 1.55 (t,3H).
730		LCMS m/z [M+1]: 774.2 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.55 (d, J = 9.2 Hz, 1H), 6.97 (t, J = 9.6 Hz, 1H), 5.50 (d, J = 51.9 Hz, 1H), 5.10 - 5.24 (m, 1H), 4.10 – 4.36 (m, 2H), 3.76 – 4.02 (m, 5H), 3.35 – 3.73 (m, 5H), 2.40 – 2.65 (m, 5H), 2.16 – 2.32 (m, 2H), 1.82 – 2.06 (m, 2H), 1.57 (t, J = 6.8 Hz, 3H).
731		LCMS m/z [M+1]: 781.2 1H NMR (400 MHz, CD3OD) δ 8.30 (s, 1H), 7.99 (s, 1H), 7.00-6.95 (m, 1H), 5.49 (d, J = 52.0 Hz, 1H), 5.16 – 5.12 (m, 1H), 4.34 – 4.17 (m, 2H), 4.03 – 3.55 (m, 9H), 2.77 – 2.70 (m, 3H), 2.60 – 2.46 (m, 2H), 2.27 – 2.23 (m, 2H), 2.03 – 1.71 (m, 2H), 1.59 – 1.56 (m, 3H).

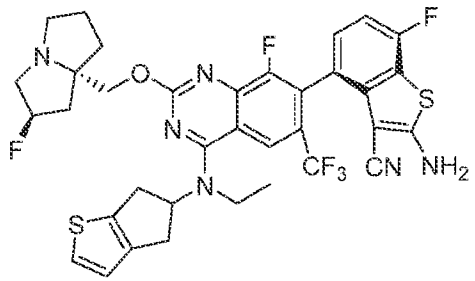
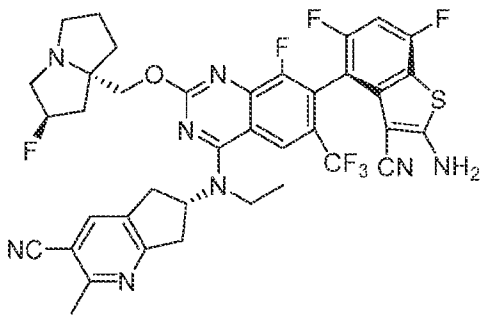
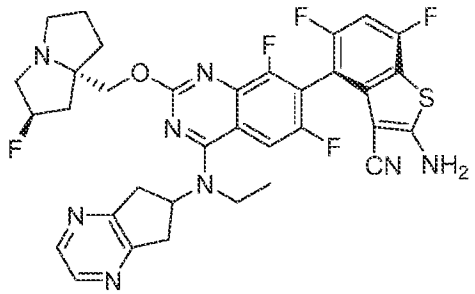
732		LCMS m/z [M+1]: 724.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (dd, *J* =10.3, 1.5 Hz, 1H), 7.44 (d, *J* = 9.6 Hz, 1H), 6.99 (t, *J* = 9.6 Hz, 1H), 5.30 (d, *J* = 53.5 Hz, 1H), 5.01 – 5.12 (m, 1H), 3.83 – 3.99 (m, 4H), 3.52 – 3.66 (m, 2H), 3.32 – 3.47 (m, 5H), 3.03 – 3.14 (m, 1H), 2.48 (s, 3H), 2.11 – 2.38 (m, 2H), 1.90 – 2.08 (m, 2H), 1.70 – 1.88 (m, 2H), 1.49 (t, *J* = 7.0 Hz, 3H).
733		LCMS m/z [M+1]: 731.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (s, 1H),7.63 (d, *J* = 6.0 Hz,1H), 7.02-6.97 (m. 1H), 5.31 (d, *J* = 56.0 Hz, 1H), 5.04 – 4.99 (m, 1H), 3.92 – 3.86 (m, 4H), 3.52 – 3.36 (m, 6H), 3.14 – 3.09 (m, 1H), 2.73 (s, 3H), 2.30 – 1.76 (m, 7H). 1.52 – 1.49 (m, 3H).
734		LCMS m/z [M+1]: 723.2 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.77 – 7.60 (m, 2H), 7.01 (t, J = 9.6 Hz, 1H), 5.49 (d, J = 52.0 Hz, 1H), 5.19 – 5.06 (m, 1H), 4.37 (d, J = 12.4 Hz, 1H), 4.18 (d, J = 12.4 Hz, 1H), 3.96 (s, 3H), 3.95 – 3.90 (m, 2H), 3.89 – 3.77 (m, 3H), 3.69 – 3.60 (m, 1H), 3.59 – 3.48 (m, 3H), 3.44 – 3.36 (m, 1H), 2.54 – 2.42 (m, 2H), 2.29 – 2.09 (m, 3H), 1.94 – 1.83 (m, 1H), 1.53 (t, J = 7.2 Hz, 3H).

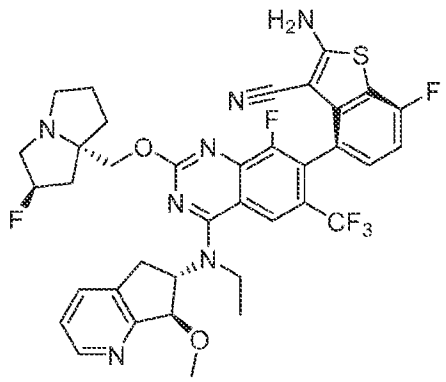
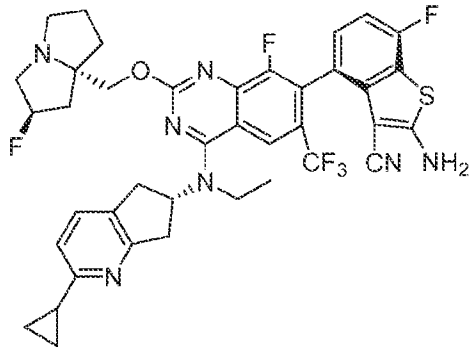
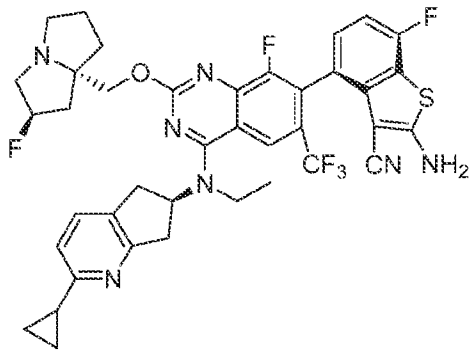
735		
736		
737		
738		
739		

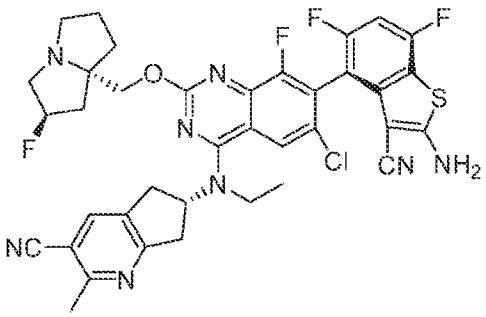
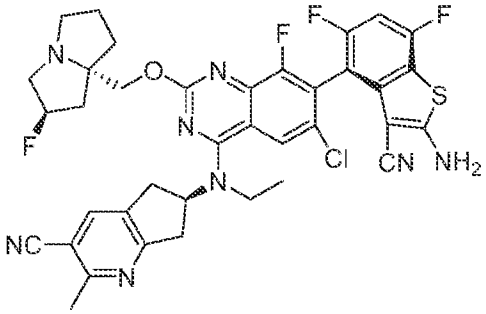
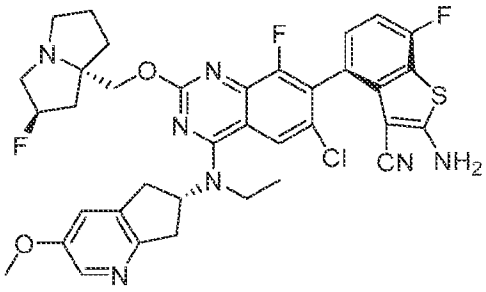
740		
741		
742		
743		
744		LCMS m/z [M+1]: 769.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.77 (s, 1H), 8.29 (s, 1H), 8.06 (s, 1H), 6.97 (t, *J* = 9.6 Hz, 1H), 5.49 (d, *J* = 51.1 Hz, 1H), 5.13 – 5.09 (m, 1H), 3.98 – 3.36 (m, 10H), 2.52 – 2.03 (m, 6H), 1.60 – 1.57 (m, 3H).

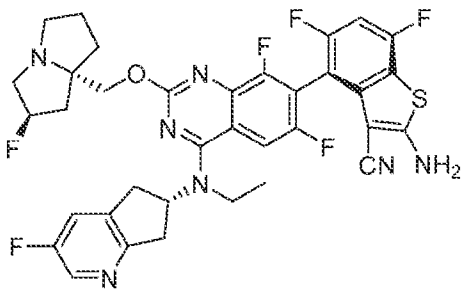
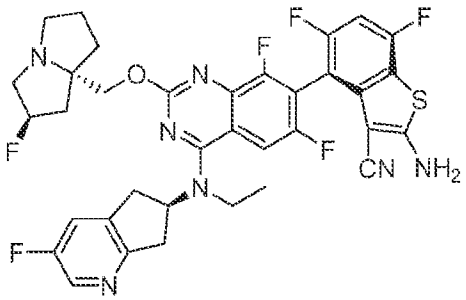
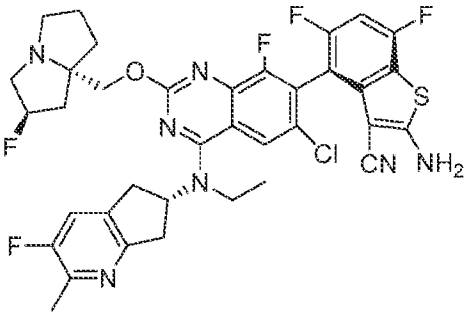
745		
746		LCMS m/z [M+1]: 754.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 6.97 (t, *J* = 9.6 Hz, 1H), 5.56 (d, *J* = 51.4 Hz, 1H), 5.06 – 5.02 (m, 1H), 4.02 – 3.47 (m, 13H), 2.74 – 2.14 (m, 8H), 1.50 – 1.46 (m, 3H).
747		
748		
749		LCMS m/z [M+1]: 725.2 1H NMR (400 MHz, CD3OD) δ 8.25 (s, 1H), 7.77 (s, 1H), 7.70 (d, J = 9.6 Hz, 1H), 7.02 (t, J = 9.6 Hz, 1H), 5.49 (d, J = 52.0 Hz, 1H), 5.18 – 5.06 (m, 1H), 3.97 (s, 3H), 3.95 – 3.89 (m, 2H), 3.88 – 3.76 (m, 3H), 3.69 – 3.52 (m, 4H), 3.43 – 3.35 (m, 1H), 2.52 –

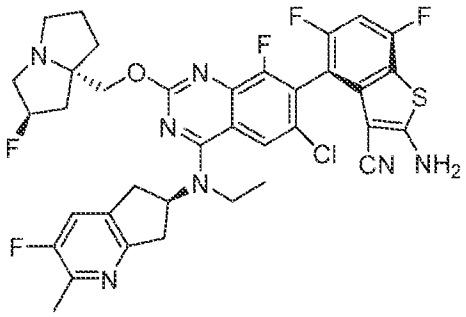
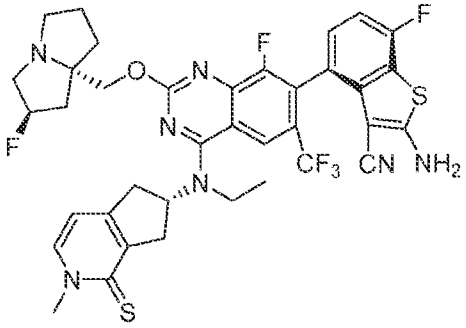
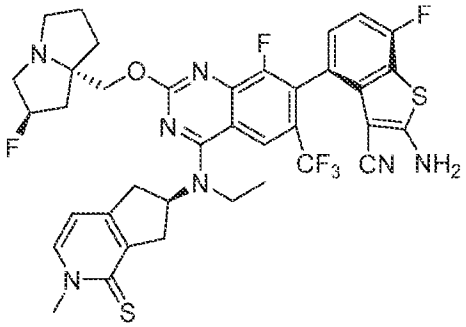
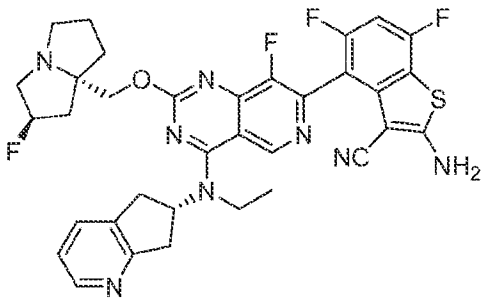
		2.41 (m, 2H), 2.27 – 2.10 (m, 3H), 1.95 – 1.84 (m, 1H), 1.54 (t, J = 7.2 Hz, 3H).
750		LCMS m/z [M+1]: 765.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.55 (s, 1H), 7.25 - 7.19 (m, 1H), 7.03 (t, *J* = 8.4 Hz, 1H), 5.49 (d, *J* = 52.5 Hz, 1H), 5.01 - 4.95 (m, 1H), 4.34 - 4.28 (m, 1H), 4.16 - 4.12 (m, 1H), 4.03 - 3.96 (m, 2H), 3.85 - 3.81 (m, 1H), 3.80 - 3.60 (m, 5H), 3.57 - 3.52 (m, 1H), 2.52 - 2.47 (m, 1H), 2.46 - 2.33 (m, 3H), 2.29 - 2.18 (m, 2H), 2.16 - 2.09 (m, 1H), 1.90 - 1.83 (m, 1H), 1.65 (t, *J* = 7.0 Hz, 3H), 1.38 - 1.32 (m, 2H), 1.27 - 1.21 (m, 1H), 1.17 - 1.10 (m, 1H).
751		LCMS m/z [M+1]: 765.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.54 (s, 1H), 7.25 - 7.19 (m, 1H), 7.03 (dd, *J* = 9.4, 8.4 Hz, 1H), 5.55 (d, *J* = 52.5 Hz, 1H), 5.00 - 4.96 (m, 1H), 4.29 - 4.23 (m, 1H), 4.09 - 3.98 (m, 3H), 3.89 - 3.84 (m, 1H), 3.80 - 3.61 (m, 6H), 2.51 - 2.47 (m, 1H), 2.44 - 2.32 (m, 3H), 2.28 - 2.19 (m, 2H), 2.06 - 2.06 (m, 1H), 1.88 - 1.81 (m, 1H), 1.65 (t, *J* = 7.0 Hz, 3H), 1.38 - 1.33 (m, 2H), 1.26 - 1.21 (m, 1H), 1.16 - 1.11 (m, 1H).

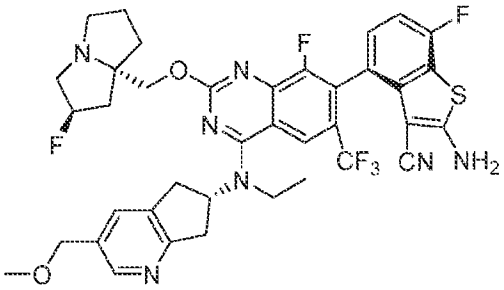
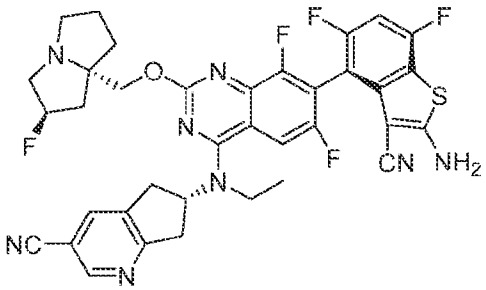
752		LCMS m/z [M+1]: 729.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 7.37 – 7.36 (m, 1H), 7.25 – 7.21 (m, 1H), 7.02 (t, J = 8.8 Hz, 1H), 6.93 – 6.92 (m, 1H), 5.52 (d, J = 52.6 Hz, 1H), 5.27 – 5.23 (m, 1H), 4.07 – 3.77 (m, 7H), 3.61 – 3.35 (m, 4H), 3.27 – 3.21 (m, 1H), 2.61 – 1.91 (m, 6H), 1.64 – 1.60 (m, 3H).
753		LCMS m/z [M+1]: 781.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 7.99 (s, 1H), 7.00-6.95 (m, 1H), 5.49 (d, *J* = 52.0 Hz, 1H), 5.16 – 5.12 (m, 2H), 4.34 – 4.17 (m, 2H), 4.03 – 3.55 (m, 9H), 2.77 – 2.70 (m, 3H), 2.60 – 2.46 (m, 2H), 2.27 – 2.23 (m, 2H), 2.03 – 1.71 (m, 2H),1.59 – 1.56 (m, 3H).
754		LCMS m/z [M+1]: 693.2 ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.37 (s, 2H), 8.33 (s, 2H), 7.66 (d, *J* = 10.3 Hz, 1H), 7.33 (t, *J* = 9.8 Hz, 1H), 5.24 (d, *J* = 54.6 Hz, 1H), 5.00 (t, *J* = 7.8 Hz, 1H), 3.83 - 3.70 (m, 4H), 3.47 - 3.43 (m, 4H), 3.09 - 2.79 (m, 4H), 2.03 - 1.66 (m, 6H), 1.40 (t, *J* = 6.8 Hz, 3H).

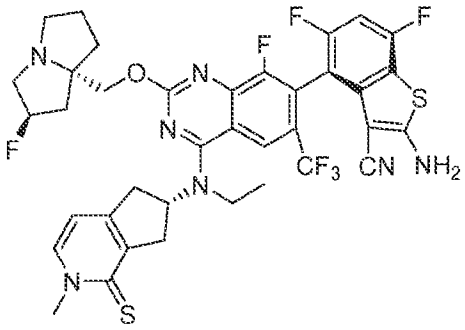
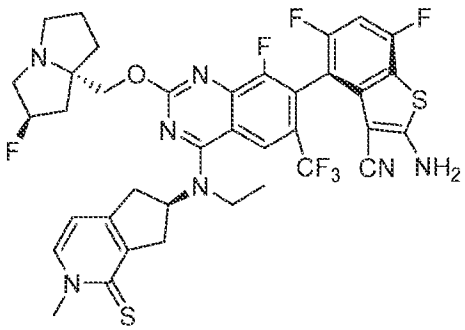
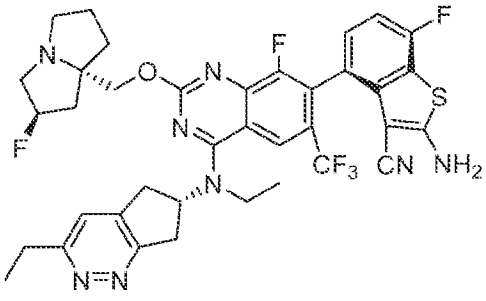
755		LCMS m/z [M+1]: 754.2 1H NMR (400 MHz, CD3OD) δ 8.50 (d, 1H), 8.35 (s, 1H), 7.77 (d, 1H), 7.38 (dd. 1H), 7.22 (dd, 1H), 7.01 (t, 1H), 7.62 (d, 1H), 5.28 (s, 0.5H), 5.14 (s, 0.5H), 4.61-4.55 (m, 1H), 4.07-3.95 (m, 2H), 3.74-3.34 (m, 7H), 3.25-3.10 (m, 3H), 3.02-2.90 (m, 1H), 2.21-1.78 (m, 5H), 1.68-1.64 (t, 3H), 1.64-1.58 (m, 1H).
756		LCMS m/z [M+1]: 764.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.03 (t, *J* = 8.4 Hz, 1H), 5.48 (d, *J* = 50.8 Hz, 1H), 5.21 – 5.11 (m, 1H), 4.41 (d, *J* = 12.4 Hz, 1H), 4.23 (d, *J* = 12.4 Hz, 1H), 4.01 – 3.75 (m, 6H), 3.70 – 3.62 (m, 1H), 3.57 (d, *J* = 7.6 Hz, 2H), 3.43 – 3.34 (m, 1H), 2.53 – 2.41 (m, 2H), 2.33 – 2.19 (m, 3H), 2.16 – 2.07 (m, 1H), 1.97 – 1.83 (m, 1H), 1.59 (t, *J* = 6.8 Hz, 3H), 1.36 – 1.34 (m, 2H), 1.15 – 1.14 (m, 2H).
757		LCMS m/z [M+1]: 764.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.03 (t, J = 8.4 Hz, 1H), 5.48 (d, J = 51.2 Hz, 1H), 5.19 – 5.11 (m, 1H), 4.35 (d, J = 12.4 Hz, 1H), 4.22 (d, J = 12.4 Hz, 1H), 4.03 – 3.73 (m, 6H), 3.70 – 3.56 (m,3H), 3.44 – 3.35 (

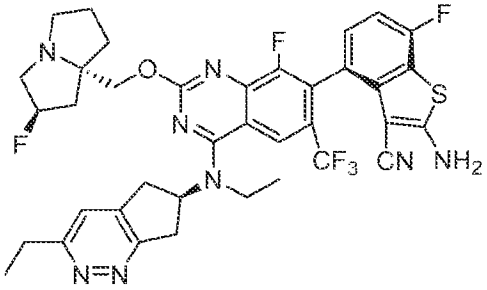
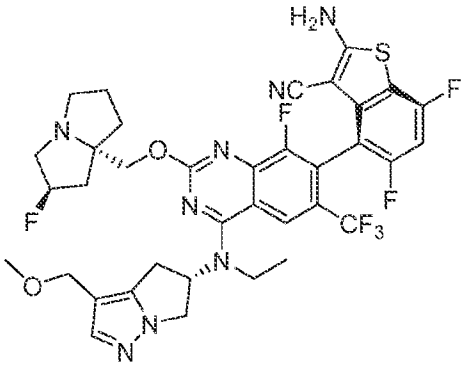
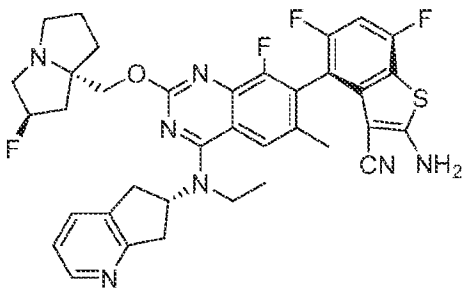
		m, 1H), 2.53 – 2.41 (m, 2H), 2.32 – 2.18 (m, 3H), 2.14 – 2.05 (m, 1H), 1.97 – 1.86 (m, 1H), 1.61 (t, J = 6.8 Hz, 3H), 1.37 – 1.32 (m, 2H), 1.17 – 1.11 (m, 2H).
758		LCMS m/z [M+1]: 747.1 ^{1}H NMR (400 MHz, CD_3OD): δ 8.02 (s, 1H), 7.97 (s, 1H), 6.99 (t, *J* = 9.71 Hz, 1H), 5.55(d, *J* = 51.7 Hz, 1H), 5.14 - 5.10 (m, 1H), 4.36 - 4.12 (m, 2H), 3.94-3.82 (m, 5H), 3.71 - 3.64 (m, 1H), 3.54 - 3.37 (m, 5H), 2.74 (s, 3H), 2.59-2.46 (m, 2H), 2.30-2.21 (m, 2H), 2.10-2.03 (m, 1H), 1.93-1.89 (m, 1H),1.51 (t, *J* = 6.86 Hz, 3H).
759		LCMS m/z [M+1]: 747.2 ^{1}H NMR (400 MHz, CD_3OD): δ 8.02 (s, 1H), 7.97 (s, 1H), 6.99 (t, *J* = 9.71 Hz, 1H), 5.55 (d, *J* = 51.7 Hz, 1H), 5.16 - 5.07 (m, 1H), 4.32 - 4.12 (m, 2H), 3.98-3.79 (m, 5H), 3.72 - 3.36 (m, 6H), 2.73 (s, 3H), 2.57-2.46 (m, 2H), 2.29-2.22 (m, 2H), 2.04-1.87 (m, 2H), 1.52 (t, *J* = 7.05 Hz, 3H).
760		LCMS m/z [M+1]: 721.3 LCMS m/z [M+1]: ^{1}H NMR (400 MHz, CD_3OD): δ 8.02 (s, 1H), 7.97 (s, 1H), 6.99 (t, *J* = 9.71 Hz, 1H), 5.55 (d, *J* = 51.7 Hz, 1H), 5.16 - 5.07 (m, 1H), 4.32 - 4.12 (m, 2H), 3.98-3.79 (m, 5H), 3.72 - 3.36 (m, 6H), 2.73 (s, 3H), 2.57-2.46 (m, 2H), 2.29-

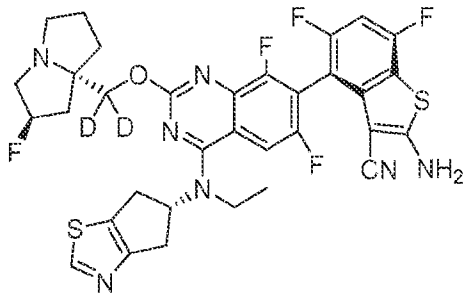
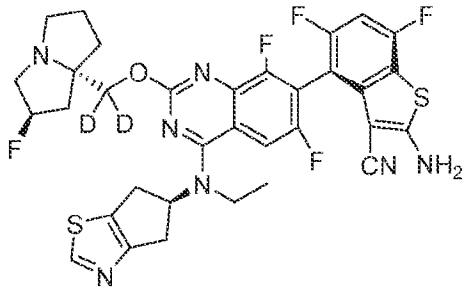
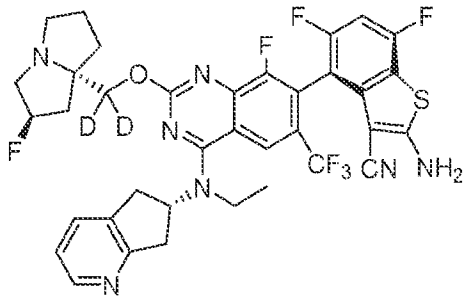
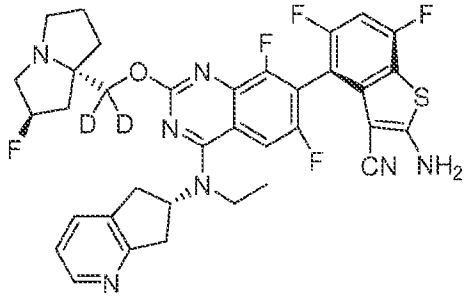
		2.22 (m, 2H), 2.04-1.87 (m, 2H), 1.52 (t, *J* = 7.05 Hz, 3H).
761		LCMS m/z [M+1]: 710.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 7.70 (d, *J* = 9.3 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 9.6 Hz, 1H), 5.50 (d, *J* = 52.2 Hz, 1H), 5.12-5.22 (m, 1H), 4.14 – 4.36 (m, 2H), 3.76 – 3.98 (m, 5H), 3.34 – 3.66 (m, 6H), 1.87 – 2.62 (m, 6H), 1.50 (t, *J* = 6.9 Hz, 3H).
762		LCMS m/z [M+1]: 710.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 7.70 (d, *J* = 10.1 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.01 (t, *J* = 9.6 Hz, 1H), 5.50 (d, *J* = 52.2 Hz, 1H), 5.12-5.22 (m, 1H), 4.14 – 4.36 (m, 2H), 3.76 – 3.98 (m, 5H), 3.34 – 3.66 (m, 5H), 1.87 – 2.62 (m, 6H), 1.51 (t, *J* = 7.0 Hz, 3H).
763		LCMS m/z [M+1]: 740.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (s, 1H), 7.53 (d, J = 9.5 Hz, 1H), 7.00 (t, *J* = 9.6 Hz, 1H), 5.50 (d, *J* = 52.2 Hz, 1H), 5.11 - 5.22 (m, 1H), 4.14 – 4.36 (m, 2H), 3.76 – 3.98 (m, 5H), 3.36 – 3.66 (m, 5H), 1.87 – 2.62 (m, 9H), 1.51 (t, *J* = 7.0 Hz, 3H).

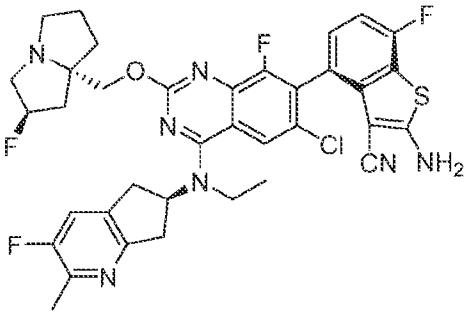
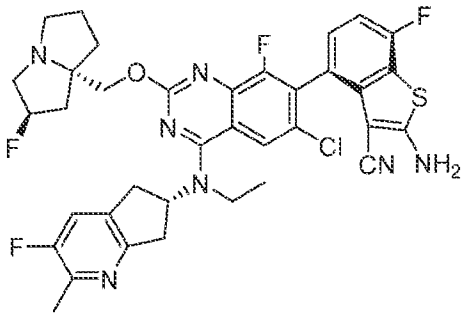
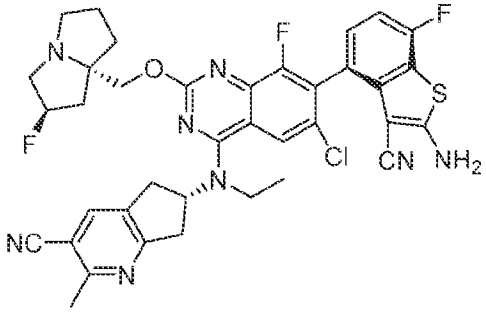
764		LCMS m/z [M+1]: 740.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (s, 1H), 7.50 (d, *J* = 9.5 Hz, 1H), 6.99 (t, *J* = 9.6 Hz, 1H), 5.50 (d, *J* = 52.2 Hz, 1H), 5.08 - 5.18 (m, 1H), 4.06 – 4.28 (m, 2H), 3.76 – 4.02 (m, 5H), 3.35 – 3.66 (m, 5H), 1.87 – 2.65 (m, 9H), 1.52 (t, *J* = 7.0 Hz, 3H).
765		LCMS m/z [M+1]: 770.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 7.62-7.51 (m, 1H), 7.29-7.18 (m, 1H), 7.03-6.98 (m, 1H), 6.48-6.36 (m, 1H),,5.59-5.38 (m, 1H), 5.14-5.00 (m, 1H), 4.04-3.82 (m, 4H),3.60 (s, 3H), 3.55-2.55 (m, 7H), 2.27-2.04 (m, 2H), 2.01-1.71 (m, 4H),1.60-1.45 (m, 3H).
766		LCMS m/z [M+1]: 770.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 7.62-7.51 (m, 1H), 7.29-7.18 (m, 1H), 7.03-6.98 (m, 1H), 6.48-6.36 (m, 1H),,5.59-5.38 (m, 1H), 5.14-5.00 (m, 1H), 4.04-3.82 (m, 4H), 3.60 (s, 3H), 3.55-2.55 (m, 7H), 2.27-2.04 (m, 2H), 2.01-1.71 (m, 4H),1.60-1.45 (m, 3H).
767		LCMS m/z [M+1]: 676.2 1H NMR (400 MHz, CD3OD) δ 9.14 (s, 1H), 8.37 (d, J = 4.9 Hz, 1H), 7.74 (s, 1H), 7.32 – 7.24 (m, 1H), 6.98 (t, J = 9.7 Hz, 1H), 5.34 (d, J = 9.5 Hz, 0.5H), 5.22 (s, 0.5H), 5.18 – 5.11 (m, 1H), 4.07 – 3.96 (m, J = 7.0 Hz, 2H), 3.91 (d, J = 10.9 Hz, 1H), 3.84 (d, J =

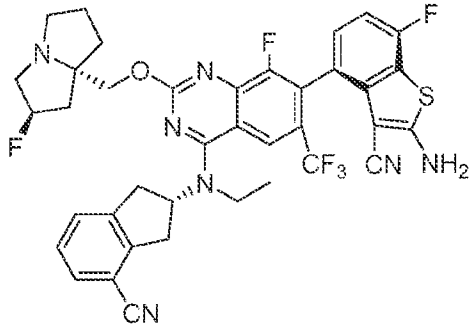
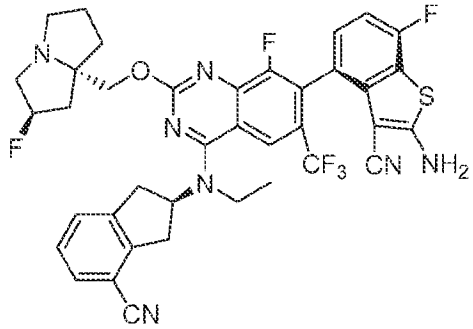
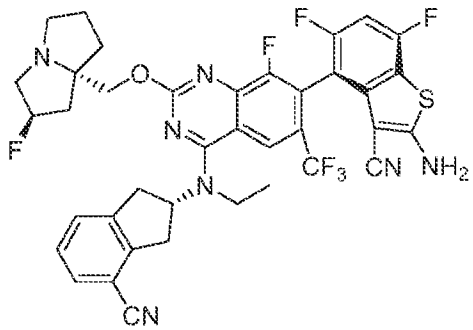
		10.9 Hz, 1H), 3.82 – 3.75 (m, J = 17.2, 7.1 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.53 – 3.39 (m, J = 17.4, 10.6 Hz, 3H), 3.27 – 3.23 (m, 2H), 3.08 – 2.99 (m, 1H), 2.24 – 2.11 (m, 2H), 1.99 – 1.88 (m, J = 23.8, 12.5 Hz, 2H), 1.74 (t, J = 10.7 Hz, 2H), 1.56 (t, J = 7.0 Hz, 3H).
768		LCMS m/z [M+1]: 768.2 1H NMR (400 MHz, CD3OD) δ 8.50 (s, 1H), 8.28 (s, 1H), 8.06 (s, 1H), 7.23 (dd, J = 8.5, 5.0 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.47 (d, J = 51.3 Hz, 1H), 5.16 – 5.08 (m, 1H), 4.58 (s, 2H), 4.32 (d, J = 12.4 Hz, 1H), 4.15 (d, J = 12.4 Hz, 1H), 4.02 – 3.95 (m, 2H), 3.85 – 3.74 (m, 4H), 3.68 – 3.60 (m, 3H), 3.52 – 3.46 (m, 3H), 3.41 – 3.35 (m, 1H), 2.50 – 2.37 (m, 2H), 2.27 – 2.15 (m, 2H), 2.10 – 2.04 (m, 1H), 1.91 – 1.82 (m, 1H), 1.62 (t, J = 7.0 Hz, 3H).
771		LCMS m/z [M+1]: 717.2 1H NMR (400 MHz, CD3OD) δ 8.76 (s, 1H), 8.05 (s, 1H), 7.70 (d, J = 10.4 Hz, 1H), 7.01 (t, J = 9.6 Hz, 1H), 5.50 (d, J = 52 Hz, 1H), 5.17 – 5.05 (m, 1H), 4.38 – 4.14 (m, 2H), 4.00 – 3.78 (m, 4H), 3.75 – 3.66 (m, 1H), 3.63 – 3.48 (m, 4H), 3.46 – 3.35 (m, 1H), 2.57 – 2.40 (m, 2H), 2.31 – 2.09 (m, 3H), 1.98 – 1.86 (m, 1H), 1.52 (t, J = 6.8 Hz, 3H).

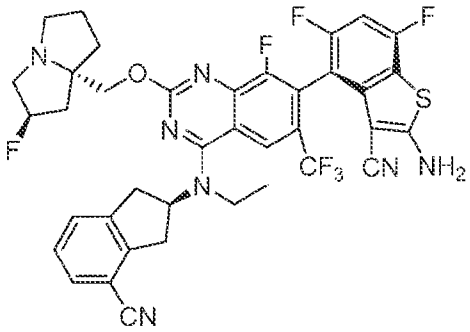
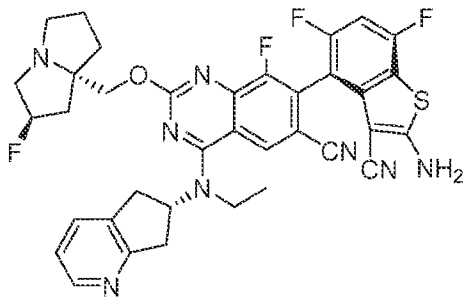
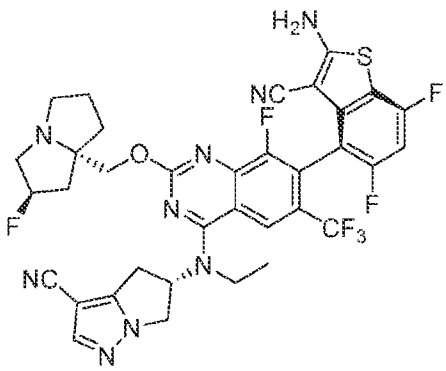
772		LCMS m/z [M+1]: 768.2 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.24 (dd, J = 8.3, 5.1 Hz, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.39 – 5.22 (m, 2H), 4.75 – 4.68 (m, 2H), 4.62 – 4.55 (m, 2H), 3.98 – 3.76 (m, 4H), 3.65 – 3.56 (m, 2H), 3.52 (s, 3H), 3.46 – 3.38 (m, 1H), 3.28 – 3.21 (m, 2H), 3.08 – 2.99 (m, 1H), 2.28 – 2.08 (m, 2H), 2.02 – 1.89 (m, 2H), 1.87 – 1.77 (m, 2H), 1.61 (t, J = 7.0 Hz, 3H).
773		LCMS m/z [M+1]: 768.2 1H NMR (400 MHz, CD3OD) δ 8.29 (s, 1H), 7.25 (dd, J = 8.6, 5.1 Hz, 1H), 7.08 – 7.02 (m, 1H), 5.54 (d, J = 51.4 Hz, 1H), 5.32 – 5.26 (m, 1H), 4.76 – 4.69 (m, 2H), 4.12 – 4.07 (m, 1H), 4.04 – 3.97 (m, 3H), 3.94 – 3.79 (m, 3H), 3.69 – 3.57 (m, 2H), 3.54 (s, 3H), 3.51 – 3.38 (m, 3H), 2.63 – 2.47 (m, 2H), 2.32 – 2.20 (m, 2H), 2.04 – 1.91 (m, 2H), 1.65 (t, J = 7.0 Hz, 3H).
774		LCMS m/z [M+1]: 753.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.81 (s, 1H), 7.25 - 7.21 (m, 1H), 7.03 (t, *J* = 8.9 Hz, 1H), 5.47 (d, *J* = 51.7 Hz, 1H), 5.07 - 5.01 (m, 1H), 4.37 - 4.19 (m, 2H), 4.02 - 3.99 (m, 2H), 3.86 - 3.59 (m, 7H), 3.43 - 3.32 (m, 2H), 3.13 - 3.04 (m, 2H), 2.50 - 2.39 (m, 2H), 2.30 - 2.20 (m, 2H), 1.94 - 1.86 (m, 2H), 1.68 - 1.60 (m, 2H), 1.46 - 1.38 (m, 3H).

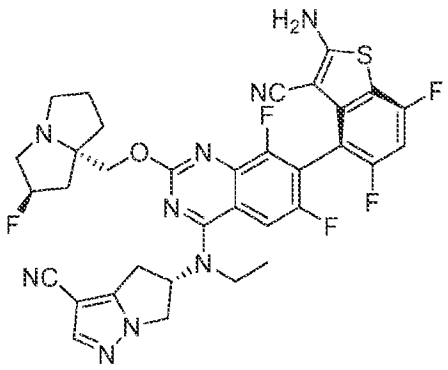
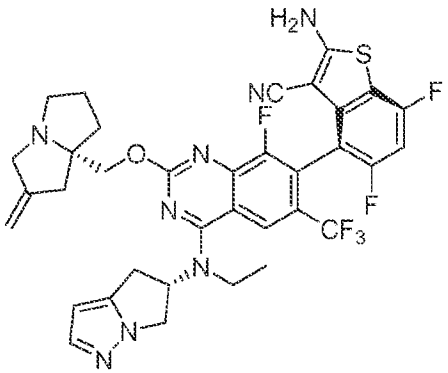
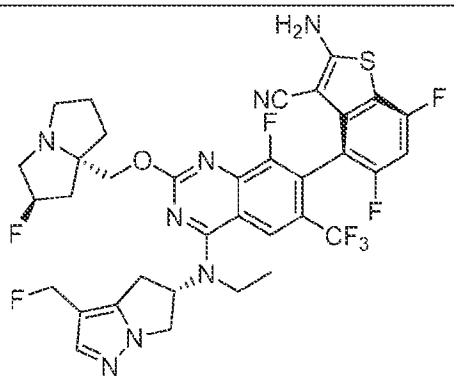
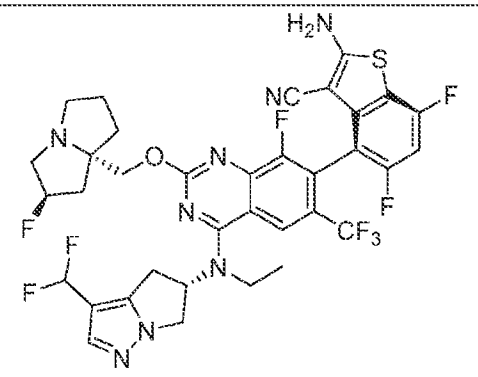
775		LCMS m/z [M+1]: 753.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.72 (s, 1H), 7.27 - 7.19 (m, 1H), 7.03 (t, J = 8.9 Hz, 1H), 5.48 (d, J = 51.6 Hz, 1H), 5.07 - 5.01 (m, 1H), 4.27 - 4.07 (m, 2H), 4.05 - 3.58 (m, 9H), 3.38 - 3.32 (m, 2H), 3.13 - 3.00 (m, 2H), 2.51 - 2.37 (m, 2H), 2.29 - 2.16 (m, 2H), 1.96 - 1.77 (m, 2H), 1.68 - 1.59 (m, 2H), 1.45 - 1.34 (m, 3H).
776		LCMS m/z [M+1]: 775.1 1H NMR (400 MHz, CD3OD) δ 8.23 (s, 1H), 7.52 (s, 1H), 6.95 (t, 1H), 5.35-5.25 (m, 1.5H), 5.18 (s, 0.5H), 4.77-4.70 (m, 1H), 4.49 (t, 1H), 4.35 (q, 2H), 3.93 (q, 2H), 3.62 (q, 2H), 3.55-3.46 (m, 1H), 3.42-3.33 (m, 4H), 3.25-3.08 (m, 3H), 3.00-2.93 (m, 1H), 2.28-2.08 (m, 2H), 2.05-1.97 (m, 1H), 1.97-1.84 (m, 2H), 1.83-1.73 (m, 1H), 1.60 (t, 3H).
777		LCMS m/z [M+1]: 689.3 1H NMR (400 MHz, CD3OD) δ 8.54 (s, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.82 (s, 1H), 7.72 – 7.61 (m, 1H), 7.00 (t, J = 9.6 Hz, 1H), 5.47 (d, J = 52.4 Hz, 1H), 5.20 – 5.07 (m, 1H), 4.43 (d, J = 12.8 Hz, 1H), 4.20 (d, J = 12.8 Hz, 1H), 3.99 (q, J = 6.8 Hz, 2H), 3.91 – 3.70 (m, 5H), 3.69 – 3.62 (m, 1H), 3.61 – 3.51 (m, 1H), 3.42 – 3.34 (m, 1H), 2.49 – 2.33 (m, 2H), 2.24 (s,

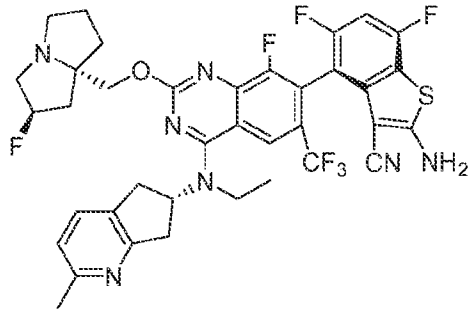
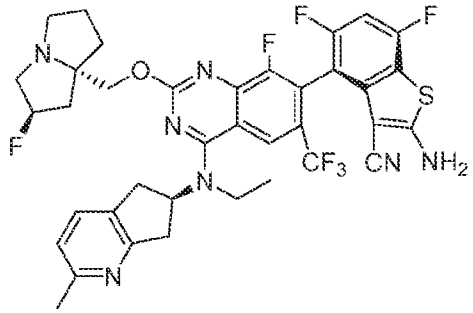
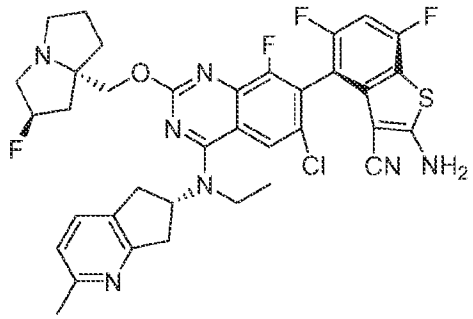
		3H), 2.23 – 2.10 (m, 3H), 1.92 – 1.78 (m, 1H), 1.57 (t, J = 7.2 Hz, 3H).
778		LCMS m/z [M+1]: 698.1 1H NMR (400 MHz, CD3OD) δ 8.98 (s, 1H), 7.68 (d, J = 10.2 Hz, 1H), 7.01 (t, J = 9.7 Hz, 1H), 5.52 (d, J = 51.8 Hz, 1H), 5.37 – 5.30 (m, 1H), 4.18 – 4.11 (m, 1H), 4.04 – 3.80 (m, 6H), 3.62 – 3.36 (m, 5H), 2.56 – 2.42 (m, 2H), 2.31 – 2.19 (m, 2H), 2.09 – 1.96 (m, 2H), 1.61 – 1.51 (m, 3H).
779		LCMS m/z [M+1]: 698.1 1H NMR (400 MHz, CD3OD) δ 8.98 (s, 1H), 7.69 (d, J = 10.3 Hz, 1H), 7.01 (t, J = 9.7 Hz, 1H), 5.53 (d, J = 51.7 Hz, 1H), 5.37 – 5.29 (m, 1H), 4.13 – 3.78 (m, 7H), 3.63 – 3.34 (m, 5H), 2.61 – 2.43 (m, 2H), 2.31 – 2.16 (m, 2H), 2.08 – 1.92 (m, 2H), 1.61 – 1.53 (m, 3H).
780		LCMS m/z [M+1]: 744.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 – 8.54 (m, 1H), 8.30 (s, 1H), 8.16 – 8.14 (m, 1H), 7.67 – 7.63 (m, 1H), 6.97 (t, *J* = 9.4 Hz, 1H), 5.47 (d, *J* = 51.2 Hz, 1H), 5.16 – 5.12 (m, 1H), 4.00 – 3.34 (m, 10H), 2.48 – 2.07 (m, 6H), 1.62 – 1.59 (m, 3H).
781		LCMS m/z [M+1]: 694.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (d, *J* = 5.6 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 10.5 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.02 (t, *J* = 9.7 Hz, 1H), 5.48 (d, *J* = 51.8 Hz, 1H),

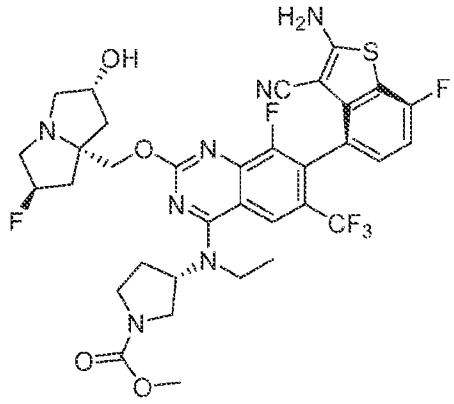
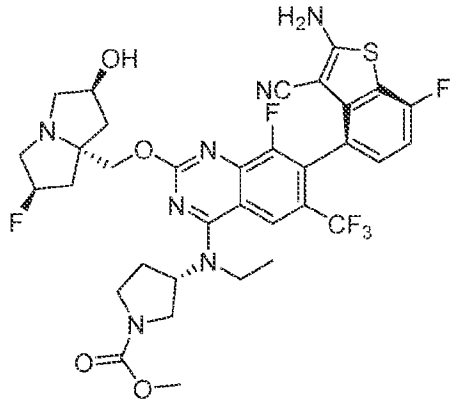
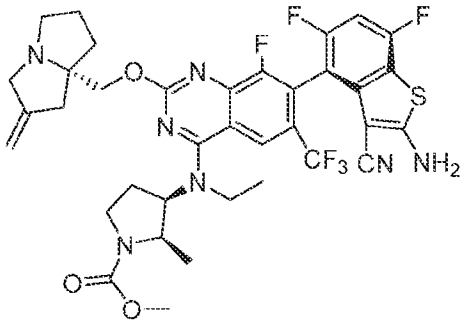
		5.17-5.09 (m, 1H), 3.97 (q, *J* = 6.9 Hz, 2H), 3.85 – 3.77 (m, 1H), 3.81 (s, 2H), 3.74 – 3.54 (m, 4H), 3.42 – 3.36 (m, 1H), 2.50 – 2.35 (m, 2H), 2.28 – 2.11 (m, 3H), 1.91 – 1.84 (m, 1H), 1.55 (t, *J* = 7.0 Hz, 3H).
782		LCMS m/z [M+1]: 722.2 1H NMR (400 MHz, CD3OD) δ 7.99 (s, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), 7.20 – 7.26 (m, 1H), 7.05 (t, *J* = 8.9 Hz, 1H), 5.49 (d, *J* = 52.1 Hz, 1H), 5.10 - 5.22 (m, 1H), 4.18 – 4.32 (m, 2H), 3.76– 4.00 (m, 4H), 3.34 – 3.66 (m, 6H), 2.43 – 2.54 (m, 5H), 2.18 – 2.32 (m, 2H), 1.90 – 2.07 (m, 2H), 1.51 (t, *J* = 6.9 Hz, 3H).
783		LCMS m/z [M+1]: 722.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (d, *J* = 1.2 Hz, 1H), 7.44 (d, *J* = 9.5 Hz, 1H), 7.18 – 7.24 (m, 1H), 7.03 (t, *J* = 8.9 Hz, 1H), 5.27 (d, *J* = 54.2 Hz, 1H), 5.01 - 5.12 (m, 1H), 3.76 – 3.92 (m, 4H), 3.52 – 3.68 (m, 2H), 3.22 – 3.46 (m, 5H), 2.99 – 3.09 (m, 1H), 2.48 (s, 3H), 1.65 – 2.35 (m, 6H), 1.51 (t, *J* = 6.9 Hz, 3H).
784		LCMS m/z [M+1]: 729.1 ^{1}H NMR (400 MHz, CD_3OD): δ 7.98 (d, *J* = 7.7 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.05 (t, *J* = 9.1 Hz, 1H), 5.55 (d, *J* = 51.4 Hz, 1H), 5.16 – 5.07 (m, 1H), 4.31 – 4 .11 (m, 2H), 3.98 – 3.79 (m, 5H), 371 –3.36 (m, 5H), 2.74 (s, 3H),

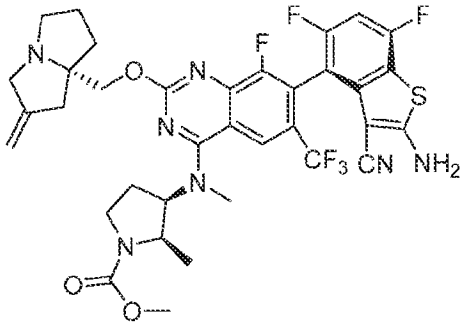
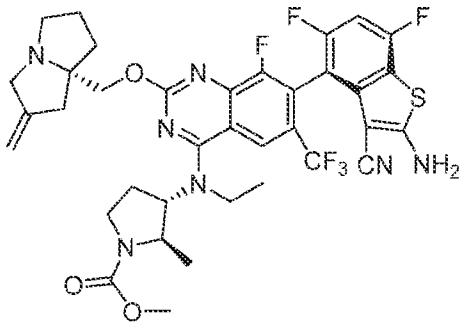
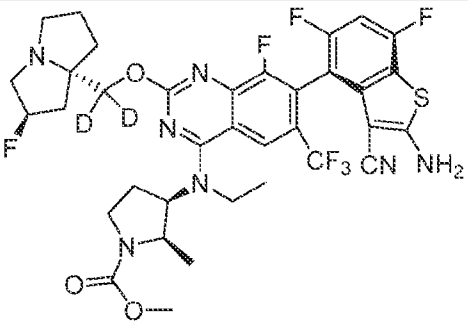
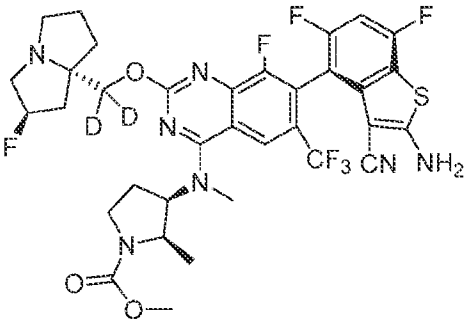
		2.60 – 2.46 (m, 4H), 2.27 – 1.89 (m, 2H), 1.52 (t, *J* = 7.5 Hz, 3H).
785		
786		
787		LCMS m/z [M+1]: 748.1 ^{1}H NMR (400 MHz, CD_3OD): δ 8.29 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 8.3 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.42 (t, *J* = 9.1 Hz, 1H) 5.50 (d, *J* = 51.4 Hz, 1H), 5.16 – 5.11 (m, 1H), 4.18 (d, *J* = 12.3 Hz, 2H), 4.03 – 3.90 (m, 3H), 3.84 – 3.74 (m, 5H), 3.64 – 3.49 (m, 3H), 3.41 – 3.35 (m, 2H), 2.59-2.11 (m, 5H), 1.93 – 1.85 (m, 2H), 1.59 (t, *J* = 7.5 Hz, 3H).

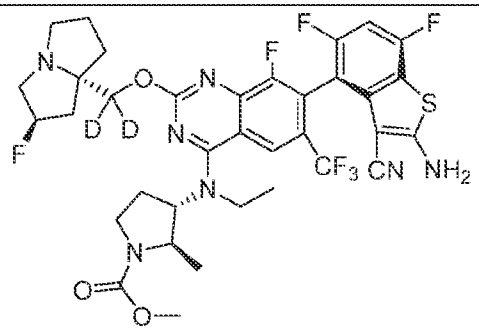
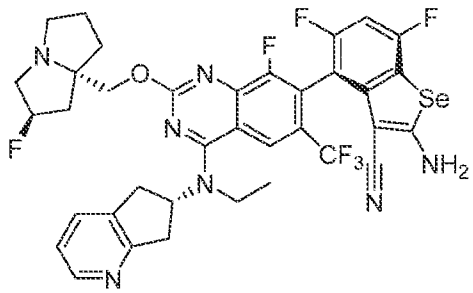
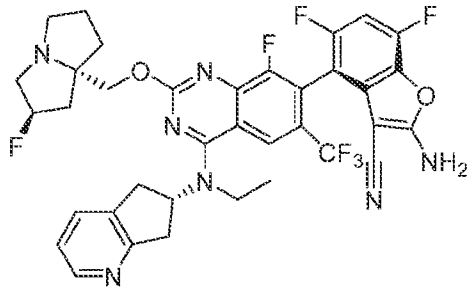
788		LCMS m/z [M+1]: 748.1 ^{1}H NMR (400 MHz, CD_3OD): δ 8.29 (s, 1H), 7.62 (d, *J* = 7.69 Hz, 1H), 7.42 (t, *J* = 8.3 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.42 (t, *J* = 9.1 Hz, 1H) 5.50 (d, *J* = 51.4 Hz, 1H), 5.16 –5.11 (m, 2H), 4.25 – 4.18 (m, 2H), 3.98 – 3.91 (m, 2H), 3.81-3.34 (m, 8H), 2.59 – 2.40 (m, 2H), 2.27 – 2.15 (m, 2H), 2.03 – 1.89 (m, 2H), 1.57 (t, *J* = 7.5 Hz, 3H).
789		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (d, *J* = 5.2 Hz, 1H), 8.35 (s, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 7.72 – 7.63 (m, 1H), 7.05 (t, *J* = 9.6 Hz, 1H), 5.48 (d, *J* = 52.0 Hz, 1H), 5.26 – 5.12 (m, 1H), 4.40 (d, *J* = 12.4 Hz, 1H), 4.26 (d, *J* = 12.4 Hz, 1H),4.02 – 3.97 (m, 2H), 3.88 – 3.76 (m, 4H), 3.75 – 3.58 (m, 3H), 3.43 –3.34 (m, 1H), 2.54 – 2.37 (m, 2H), 2.30 – 2.10 (m, 3H), 1.98 – 1.83 (m, 1H), 1.58 (t, *J* = 7.2 Hz, 3H).
790		LCMS m/z [M+1]: 776.0 1H NMR (400 MHz, CD3OD) δ 8.22 (s, 1H), 7.97 (s, 1H), 6.95 (t, 1H), 5.34 (s, 0.5H), 5.30-5.24 (m, 1H), 5.20 (s, 0.5H), 4.75-4.71 (m, 1H), 4.57 (t, 1H), 3.93 (q, 2H), 3.76-3.62 (m, 3H), 3.56-3.47 (m, 1H), 3.26-3.12 (m, 3H), 3.05-2.95 (m, 1H), 2.23-2.07 (m, 2H), 2.03-1.88 (m, 3H), 1.85-1.74 (m, 1H), 1.62 (t, 3H).

791		LCMS m/z [M+1]: 706.0 1H NMR (400 MHz, CD3OD) δ 7.97 (s, 1H), 7.60 (d, 1H), 6.99 (t, 1H), 5.37 (s, 0.5H), 5.32-5.20 (m, 1.5H), 4.74-4.67 (m, 1H), 4.60-4.54 (m, 1H), 3.91 (q, 2H), 3.81-3.73 (m, 2H), 3.66-3.46 (m, 3H), 3.26-3.18 (m, 2H), 3.07-3.00 (m, 1H), 2.26-2.13 (m, 2H), 2.03-1.93 (m, 3H), 1.85-1.77 (m, 1H), 1.56 (t, 3H).
792		
793		
794		

795		LCMS m/z [M+1]: 756.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 6.98 (t, *J* = 9.6 Hz, 1H), 5.48 (d, *J* = 51.6 Hz, 1H), 5.27 – 5.17 (m, 1H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.31 (d, *J* = 12.8 Hz, 1H), 4.01 – 3.93 (m, 2H), 3.89 – 3.65 (m, 5H), 3.64 – 3.59 (m, 2H), 3.46 – 3.36 (m, 1H), 2.75 (s, 3H), 2.54 – 2.40 (m, 2H), 2.30 – 2.10 (m, 3H), 1.95 – 1.85 (m, 1H), 1.59 (t, J = 6.8 Hz, 3H).
796		LCMS m/z [M+1]: 756.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 9.6 Hz, 1H), 5.48 (d, *J* = 52.0 Hz, 1H), 5.25 – 5.16 (m, 1H), 4.41 (d, *J* = 12.4 Hz, 1H), 4.30 (d, *J* = 12.4 Hz, 1H), 4.02 – 3.92 (m, 2H), 3.89 – 3.67 (m, 5H), 3.65 – 3.59 (m, 2H), 3.44 – 3.36 (m, 1H), 2.74 (s, 3H), 2.53 – 2.41 (m, 2H), 2.28 – 2.08 (m, 3H), 1.98 – 1.87 (m, 1H), 1.59 (t, *J* = 6.8 Hz, 3H).
797		LCMS m/z [M+1]: 722.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, *J* = 8.0 Hz, 1H), 8.02 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.00 (t, *J* = 9.6 Hz, 1H), 5.48 (d, *J* = 54.0 Hz, 1H), 5.22 – 5.15 (m, 1H), 4.49 (d, *J* = 12.8 Hz, 1H), 4.29 (d, *J* = 12.8 Hz, 1H), 3.98 – 3.92 (m, 2H), 3.90 – 3.66 (m, 5H), 3.62 – 3.53 (m, 2H), 3.44 – 3.37 (m, 1H), 2.73 (s, 3H), 2.53 – 2.42 (m,

		2H), 2.28 – 2.13 (m, 3H), 1.94 – 1.85 (m, 1H), 1.54 (t, *J* = 7.2 Hz, 3H).
798		LCMS m/z [M+1]: 750.3 1H NMR (400 MHz, CD3OD) δ 8.24 (s, 1H), 7.20-7.23 (m, 1H), 7.01 (t, 1H), 5.48 (s, 0.5H), 5.34 (m, 0.5H), 4.98-5.02 (m, 1H), 4.46-4.54 (m, 1H), 4.31 (m, 2H), 3.84-3.94 (m, 3H), 3.70-3.78 (m, 4H), 3.56-3.60 (m, 1H), 3.41-3.47 (m, 4H), 3.02-3.07 (m, 1H), 2.43-2.48 (m, 2H), 2.27-2.39 (m, 2H), 2.03-2.20 (m, 2H), 1.45 (t, 3H).
799		
800		

801		
802		
803		
804		

805		
806		
807		

Biological Example 1: Disrupting RAS-effector binding HTRF assay

[0875] A protein:protein interaction (PPI) Homogeneous Time Resolved Fluorescence (HTRF) assay was used to determine the effectiveness of compounds of the present disclosure in disrupting KRAS protein and effector RAF1 binding.

[0876] The HTRF assay used the following reagents and proteins: (i) 50 nM Avi-KRAS G12D (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); (ii) 50 nM Avi-KRAS G12C (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); (iii) 50 nM Avi-KRAS G12V (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); (iv) 50 nM Avi-KRAS WT (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); (v) 50 nM Avi-KRAS G12R (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); and (vi) 75 nM 3xFLAG-RAF1 RBD (51-131)-Avi. The assay buffer included: 50 mM Tris pH 7.5 (Invitrogen, 15567-027), 100 mM NaCl (Sigma, S5150-1L), 5 mM MgCl2 (Sigma, 63069), 0.1% BSA (Sigma, A7030), 0.01% Tween 20 (Sigma, P7949), and 10% DMSO (Cell Signaling, 12611). The bead buffer included: 50 mM Tris pH 7.5 (Invitrogen, 15567-027), and 0.01% Tween 20

(Sigma, P7949). Assay volume of 20 µL was used in a 384 well plate-low volume format. Compound titration: 30-0.0045 µM, 3x dilution series.

[0877] The HTRF assay employed the following protocol:

[0878] Compounds were dispensed in assay plate (384-well, Grenier Bione #784075) using Echo (model 555) with dose response settings: 200 nL final volume, titration from 30 µM as a 10-point dilution series. Protein mix was prepared in assay buffer, and dispensed on plates, 10 µL per well. Reagents mix was prepared and added to plates, 10 µL per well, then plates were incubated for 1 h at room temperature, with 700 rpm shaking.

[0879] Plates were analyzed on an Envision plate reader using the following setting: Excitation 320 nM, Bandwidth 75 nM; Emission 615 nM, Bandwidth 85 nM, Gain 100%, Flashes 100, Lag 60 µs. Data was reported as percentage of activity, with DMSO as 100%. Data was plotted and analyzed using Prism 8.

[0880] The biochemical Raf1-KRAS G12D/G12R/G12V/WT-GTP disruption assay IC_{50} of selected compounds described herein are shown in Table 4 (Compounds 1-667).

Biological Example 2: Cell-based pERK HTRF assay in GP2d cell

[0881] A pERK assay (Perkin Elmer) was used to determine the effectiveness of compounds in disrupting KRAS G12D protein/effector signaling in cells.

[0882] On Day 1, cells (GP2d) were seeded into 96-well plates at $3x10^4$ cells/well in 80 µL complete growth media (DMEM, 10% FBS).

[0883] On Day 2, cells were treated with compounds at 0.25% DMSO. The source plate was created with compounds diluted in media at 5-fold the final assay concentration. The compounds were run in a 9-point concentration curve starting at 1 µM or in a 9-point concentration curve starting at 1 µM, with a half-log dilution between concentrations. 20 µL was transferred onto the cell plates (final volume in wells was 100 µL). Plates were harvested after 60 min incubation by aspirating media and adding kit-supplied 1x supplemented lysis buffer to all wells (50 µL per well). Plates were then placed on a plate shaker and incubated at 850 rpm for an additional 30 min.

[0884] Antibody mixture solution was prepared by diluting aliquoted d2 and Eu Cryptate antibodies 1:20 in kit supplied detection buffer, and mixing the diluted antibodies solutions (1:1 v:v). 4 µL of this solution was then added to a 384-well detection plate (Perkin Elmer; 6008230).

[0885] Samples were homogenized by pipetting up and down and then transferred (16 µL of cell lysates) from the 96-well cell culture plate to two wells of the HTRF 384-well detection plate containing the antibody solution. Plates were centrifuged (524 g for 1 min) and allowed to incubate between 4 and 24 h at room temperature. Maximum signal is reached after 4 h incubation time and remains stable over a period

of 24 hours. Therefore, readings can be made between 4 and 24 h of incubation. Plates were centrifuged again (524 *g* for 1min), then analyzed on the EnVision plate reader using the following settings: Excitation 320 nm, Bandwidth 75 nm; Emission 615 nm, Bandwidth 85 nm; Gain 100%; Flashes 100; Lag 60 µs.

[0886] The Cell-based pERK HTRF assay in GP2d cell IC_{50} of selected compounds described herein are shown in Table 4.

Biological Example 3: Cell-based pERK HTRF assay in SW620 cell

[0887] A pERK assay (Perkin Elmer) was used to determine the effectiveness of compounds in disrupting KRAS G12V protein/effector signaling in cells.

[0888] On Day 1, cells (SW620) were seeded into 96-well plates at $3x10^4$ cells/well in 80 µL complete growth media (RPMI, 10% FBS).

[0889] On Day 2, cells were treated with compounds at 0.25% DMSO. The source plate was created with compounds diluted in media at 5-fold the final assay concentration. The compounds were run in a 9-point concentration curve starting at 100 nM, with a half-log dilution between concentrations. Twenty µL was transferred onto the cell plates (final volume in wells was 100 µL). Plates were harvested after 4 h incubation by aspirating media and adding kit-supplied 1x supplemented lysis buffer to all wells (50 µL per well). Plates were then placed on a plate shaker and incubated at 850 rpm for an additional 30 min.

[0890] Antibody mixture solution was prepared by diluting aliquoted d2 and Eu Cryptate antibodies 1:20 in kit supplied detection buffer and mixing the diluted antibodies solutions (1:1 v:v). Four µL of this solution was then added to a 384-well detection plate (Perkin Elmer; 6008230).

[0891] Samples were homogenized by pipetting up and down and then transferred (16 µL of cell lysates) from the 96-well cell culture plate to two wells of the HTRF 384-well detection plate containing the antibody solution. Plates were centrifuged (524 *g* for 1min) and allowed to incubate between 4 and 24 h at room temperature. Maximum signal was reached after 4 h incubation time and remained stable over a period of 24 hours. Therefore, readings could be made between 4 and 24 h of incubation. Plates were centrifuged again (524 *g* for 1min), then analyzed on the EnVision plate reader using the following settings: Excitation 320 nm, Bandwidth 75 nm; Emission 615 nm, Bandwidth 85 nm; Gain 100%; Flashes 100; Lag 60 µs.

[0892] The Cell-based pERK HTRF assay in SW620 cell IC_{50} of selected compounds described herein are shown in Table 4.

Biological Example 4: Cell-based pERK HTRF assay in PSN-1 cell and Hup-T3

[0893] pERK assay (Perkin Elmer) was used to determine the effectiveness of compounds in disrupting KRAS G12R protein/effector signaling in cells.

[0894] On Day 1, cells (PSN1 or Hup-T3) were seeded into 96-well plates at $2x10^4$ cells/well in 80 µl complete growth media (RPMI, 10% FBS).

[0895] On Day 2, cells were treated with compounds at 0.25% DMSO. The source plate was created with compounds diluted in media at 5-fold the final assay concentration. The compounds were run in a 9-point concentration curve starting at 10 µM, with a half-log dilution between concentrations. Twenty µL was transferred onto the cell plates (final volume in wells was 100 µL). Plates were harvested after 2h incubation by aspirating media and adding kit-supplied 1x supplemented lysis buffer to all wells (50 µl per well). Plates were then placed on a plate shaker and incubated at 850 rpm for an additional 30 min.

[0896] Antibody mixture solution is prepared by diluting aliquoted d2 and Eu Cryptate antibodies 1:20 in kit supplied detection buffer, mix the diluted antibodies solutions (1:1 v:v). Four µL of this solution is then added to a 384-well detection plate (Perkin Elmer; 6008230).

[0897] Samples were homogenized by pipetting up and down and then transferred (16 µL of cell lysates) from the 96-well cell culture plate to two wells of the HTRF 384-well detection plate containing the antibody solution. Plates were centrifuged (524 *g* for 1min) and allowed to incubate between 4 and 24 h at room temperature. Maximum signal is reached after 4 h incubation time and remains stable over a period of 24 hours. Therefore, readings can be made between 4 and 24 h of incubation. Plates were centrifuged again (524 *g* for 1min), then analyzed on the EnVision plate reader using the following settings: Excitation 320 nm, Bandwidth 75 nm; Emission 615 nm, Bandwidth 85 nm; Gain 100%; Flashes 100; Lag 60 µs.

[0898] The Cell-based pERK HTRF assay in PSN1 or Hup-T3 cell IC_{50} of selected compounds described herein are shown in Table 4.

Biological Example 5: Cell-based pERK HTRF assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080 cells

[0899] The inhibition of ERK phosphorylation, as measured using the HTRF Advanced Phospho-ERK1/2 (Thr202/Tyr204) Detection Assay kit (Perkin Elmer), was used to determine the effectiveness of test compounds in disrupting KRAS-driven protein/effector signaling in cells.

[0900] On day 1, cells were seeded into 96-well plates at $2.5x10^4$ cells/well in 100 µL of complete growth media supplemented with 10% fetal bovine serum (FBS) and incubated at 37 °C in the presence of 5% CO_2.

[0901] On day 2, cells were treated with compounds diluted in DMSO at 0.25% final DMSO concentration. Compounds were dosed in a 9-point concentration curve with three-fold dilution between concentrations. Cells were incubated in the presence of compound for two hours at 37 °C. Following this treatment period, cells were harvested by aspirating the media, adding 40 µL of kit-supplied 1x lysis buffer per well, and shaking for 30 minutes at 250 rpm at room temperature.

[0902] Following cell lysis, samples were homogenized by pipetting up and down twenty times and 16 µL of cell lysate per well was transferred from the 96-well cell culture plate to two wells of a 384-well detection plate. A complete detection buffer was prepared by diluting D2 and Eu Cryptate antibodies 1:20 in kit-provided detection solution. 4 µL of complete detection buffer was then added to each well with lysate. Plates were incubated with gentle rocking for 24 hours at 4 °C.

[0903] Following this incubation period, plates were centrifuged at 500 x g for one minute and analyzed on a CLARIOstar plate reader. Data was imported into Microsoft Excel and the signal from the 665 nm channel was divided by the signal from the 620 nm channel. % pERK was calculated as:

% Signal = 100*((Sample Value – average of positive control)/(Vehicle Value – average of positive control))

[0904] Data was imported to the Prism software package (Graphpad) and EC_{50} values were calculated using the log (inhibitor) vs. response -- variable slope (Four parameters) model.

[0905] The cell-based pERK HTRF assay in the titled cells IC_{50} of selected compounds described herein are shown in Table 5.

Biological Example 6: 3D Cell viability assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080 cells

[0906] The inhibition of cellular viability as a result of test compound treatment in a spheroid assay was measured using the CellTiter-Glo® 3D Cell Viability Assay (Promega).

[0907] On Day 1, 1000 cells per well were seeded in 150 µL of of complete growth media supplemented with 10% fetal bovine serum (FBS) and incubated at 37 °C in the presence of 5% CO_2 in 96-well ultra-low attachment microplates (Corning) for 48 hours undisturbed to allow spheroids to form.

[0908] Following spheroid formation, cells were treated with compounds diluted in DMSO at 0.25% final DMSO concentration. Compounds were dosed in a 9-point concentration curve with three-fold dilution between concentrations. Cells were incubated in the presence of compound for 72 hours at 37 °C in the presence of 5% CO_2.

[0909] Following this incubation period, the kit-provided CTG reagent was allowed to equilibrate for 30 minutes at room temperature. 150 µL of equilibrated CTG reagent was added to each well, and the plate was sealed before shaking at 250 rpm for 10 minutes at room temperature to lyse the cells. 150 µL of lysate per well was transferred to a 96-well plate and luminescence was read on a CLARIOstar plate reader.

[0910] Data was imported into the Prism software package (Graphpad) and EC_{50} values were calculated using the log (inhibitor) vs. response --variable slope (Four parameters) model.

[0911] The 3D viability assay in the titled cells IC_{50} of selected compounds described herein are shown in Table 6.

[0912] For Raf1-KRAS G12D-GTP disruption assay: A: $IC_{50} \leq 0.1$ μM; B: 0.1 μM< $IC_{50} \leq 1$ μM; C: 1 μM< $IC_{50} \leq 10$ μM; D: $IC_{50} > 10$ μM. For GP2d (KRAS G12D) pERK HTRF assay: A: $IC_{50} \leq 0.1$ μM; B: $IC_{50} > 0.1$ μM. For SW620 (KRAS G12V), PSN1 (KRAS G12R), AsPC-1 (KRAS G12D), SW1900 (KRAS G12D), HPAC (KRAS G12D), Capan-2 (KRAS G12V), RKN (KRAS G12V), H358 (KRAS G12C), HCT116 (KRAS G13D), MKN1 (KRAS amplification), and HT1080 (NRAS) pERK HTRF assay and 3-D viability assay: A: $IC_{50} \leq 0.1$ μM; B: 0.1 μM< $IC_{50} \leq 1$ μM; C: $IC_{50} > 1$ μM. Blanks in the table represent that a compound was not tested in the indicated assay.

Biological Example 7: Disrupting RAS-effector binding HTRF assay

[0913] A protein:protein interaction (PPI) Homogeneous Time Resolved Fluorescence (HTRF) assay was used to determine the effectiveness of compounds in disrupting KRAS protein and effector RAF1 binding. The HTRF assay used the following reagents and proteins: (i) 12.5 nM Avi-KRAS G12D (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); (ii) 12.5 nM Avi-KRAS G12C (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); (iii) 12.5 nM Avi-KRAS G12V (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); (iv) 12.5 nM Avi-KRAS WT (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); (v) 12.5 nM Avi-KRAS G12R (2-169) GTP/ RAF1 RBD-3xFLAG (51-131); and (vi) 12.5 nM 3xFLAG-RAF1 RBD (51-131)-Avi. The following reagents were used: 12.5 nM HTRF Streptavidin-XLent (Revvity, 611SAXLB), and 0.43 nM HTRF MAb Anti FLAG-Tb (Revvity, 61FGBTLB). The assay buffer included: 50 mM Tris pH 7.5 (Invitrogen, 15567-027), 100 mM NaCl (Sigma, S5150-1L), 5 mM $MgCl_2$ (Sigma, 63069), 0.1% BSA (Sigma, A7030), 0.01% Tween 20 (Sigma, P7949), and 10% DMSO (Cell Signaling, 12611). Assay volume of 20 μL was used in a 384 well plate-low volume format. Compound titration: 10-0.0015 μM, 3x dilution series.

[0914] The HTRF assay employed the following protocol: Compounds were dispensed in assay plate (384-well, Grenier Bione #784075) using Echo (model 555) with dose response settings: 200 nL final volume, titration from 30 μM as a 10-point dilution series. Protein and HTRF reagent mix was prepared in assay buffer, and dispensed on plates, 20 μL per well. Then plates were incubated for 1 h at room temperature, with 700 rpm shaking.

[0915] Plates were analyzed on an Envision plate reader using the following setting: Excitation 320 nm, Bandwidth 75 nm; Emission 615 nm, Bandwidth 8.5 nm, Emission 665 nm, band width 7.5 nm. Gain 100%, Flashes 100. Lag 60 μs. Data was reported as percentage of activity, with DMSO as 100%. Data was plotted and analyzed using a Python script.

[0916] The biochemical Raf1-KRAS G12D/G12V/G12C/WT-GTP disruption assay IC_{50} of selected compounds described herein are shown in Table 4 (Compounds 668-797).

Table 4. Biological characterization of selected compounds of the present disclosure.

Compound No.	Raf1-GTP-KRAS G12D disruption	Raf1-GTP-KRAS G12V disruption	Raf1-GTP-KRAS G12R disruption	Raf1-GTP-KRAS G12C disruption	Raf1-GTP-KRAS WT disruption	pERK-Gp2D	pERK-SW620	pERK-PSN1	pERK-Hup-T3
1	B	C	A	C	B	A	A	A	
2	C	C		C	C	A	A		
3	B	B		A	B	A	A		
4	B	B		B	B	A	A		
5	B	B		B	B	A	A		
6	B	B		B	B	A	A		
7	B	B		B	B	A	A		
8	B	B		B	B	A	A		
9	B	B		B	B	A	A		
10	B	B		B	B	A	A		
11	C	C		C	C	A	A		
12	C	D		D	D	A	A		
13	C	D		D	D	A	A		
13-1	A	B		A	B	A	A		
13-2	D	D		D	D	A	B		
14	D	D		D	D	A	B		
15	C	C		C	D	A	A		
16	C	C		C	C	A	A		
17	D	D		D	D	B	B		
18	B	B		B	B	A	A		
19	B	B		B	B	A	A		
20	C	D		D	C	B	B		
21	C	B		B	C	B	A		
22	A	A	A	A	A	A	A	A	
23	B	C		C	C	A	A		
24	C	D		D	D	A	B		

25	D	D		D	D	B	B		
26	B	C		D	C	A	A		
27	D	D		D	D	B	C		
28	B	B		B	B	A	A		
29	C	D		D	D	B	A		
30	C	D		D	D	A	B		
31	C	C		C	C	A	A		
32	C	D		D	C	A	A		
33	D	D		D	D	B	B		
34	C	D		D	D	A	B		
35	D	D		D	D	B	C		
36	C	D		C	C	A	B		
37	C	C		C	C	A	A		
38	C	C		C	D	A	A		
39	C	D		D	D	B	B		
40	B	B		B	B	A	A		
41	D	D		D	D	B	C		
42	B	B		B	B	A	A		
43	C	C		C	C	B	A		
44	B	B		C	C	A	A		
45	D	D		D	D	B	B		
46	D	D		D	D	B	A		
47	B	B		B	B	A	A		
48	B	B		B	B	A	A		
49	C	C		C	C	A	A		
50	C	D		D	D	A	A		
51	D	D		D	D	A	A		
52	C	D		D	D	A	A		
53	B	C		C	C	A	A		
54	C	C		C	C	A	A		
55	C	C		C	C	A	A		
56	C	D		D	C	A	A		
57	B	B		B	B	A	A		

58	C	D		C	D	A	A		
59	B	B		B	B	A	A		
60	C	C		C	C	B	A		
61	D	D		D	D	A	B		
62	B	B		C	C	A	A		
63	B	B		B	B	A	A		
64	C	C		C	C	A	A		
65	C	C		C	C	A	A		
66	C	D		D	D	A	B		
67	D	D		D	D	A	A		
68	C	D		D	D	A	A		
69	C	C		C	C	A	A		
70	C	C		C	D	A	A		
70-1	B	B		B	B	A	A		
71	B	C		C	C	A	A		
72	D	D		D	D	B	B		
73	C	C		C	C	A	A		
74	C	C		D	C	A	A		
75	B	C		C	C	A	A		
76	C	D		D	D	A	A		
77	B	C		B	C	A	A		
78	B	B		B	B	A	A		
79	C	C		C	C	A	A		
80	C	C		C	C	A	A		
81	A	A	B	A	A	A	A	A	
82	C	D		D	D	A	B		
83	C	C		D	D	A	A		
84	B	B		B	C	A	A		
85	C	C		C	C	B	B		
86	C	C		C	C	A	A		
87	C	C		C	C	A	A		
88	D	D		D	D	A	B		
89	B	C		B	C	A	A		

90	B	B		B	B	A	A		
91	C	C		C	C	A	A		
92	D	D		D	D	B	C		
93	B	B		B	C	A	A		
94	B	B		B	C	A	A		
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112	D	D		D	D	B	B		
113	D	D		D	D	B	B		
114	D	D		D	D	B	C		
115	B	B		B	B	A	A		
116	B	B		B	B	A	A		
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118	D	D		D	D	B	C		
119	D	D		D	D	B	A		
120	C	C		C	C	A	B		
121	B	B		B	B	A	A		
122	C	C		C	C	B	B		

123	B	B		B	C	A	A		
124	B	B		A	B	A	A		
125	B	C		C	C	A	A		
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127	B	B		B	B	A	A		
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133	D	D		D	D	B	C		
134	D	D		D	D	B	C		
135	C	D	D	D	D	A	B		
136	B	B	A	A	A	A	A	A	
137	D	D		D	D	B	C		
138	D	D		D	D	B	C		
139	C	C		C	C	A	A		
140	B	B		B	B	A	A		
141	C	C		C	C	A	A		
142	C	C		C	C	A	A		
143	A	A	B	A	B	A	A	A	
144	B	B	B	B	B	A	A	A	
145	B	C	C	C	C	A	B		
146	A	B	B		B	A	B		
147	D	D	D		D	A	B		
148	A	A	A		A	A	A	A	
149	C	D	C		D	A	B		
150	D	D	D		D	B	C		
151	B	B	B		B	A	A	B	
152	B	B	B		B	A	A		
153	C	D	D		D	A	A		
154	D	D	D		D	A	B		
155	C	C	C		C	A	A		

156	B	C	C		D	A	A		
157	C	D	D		D	A	B		
158	B	C	C		C	A	A		
159	C	D	C		C	A	A		
160	C	D	C		D	A	A		
161	B	B	B		B	A	A	C	
162	C	C	C		C	A	B		
163	B	B	B		C	A	A	C	
164	B	C	C		C	A	A		
165	D	D	D		D	B	C		
166	C	D	C		C	A	A		
167	D	D	D		D	B	C		
168	B	C	C		C	A	A		
169	C	D	D		D	A	B		
170	B	C	C		C	A	A		
171	D	D	D		D	B	B		
172	B	B	B		B	A	A	B	
173	C	C	C		D	A	A		
174	B	B	B		C	A	A		
175	B	B	B		B	A	A	B	
176	D	D	D		D	A	B		
177	C	D	D		C	A	B		
178	C	D	D		D	A	A		
179	C	C	C		C	A	A		
180	D	D	D		D	B	C		
181	B	C	C		C	A	A		
182	B	B	B		B	A	A		
183	A	A	A		A	A	A	B	
184	A	A	A		A	A	A	B	
185	B	C	C		B	A	A		
186	A	B	B		B	A	A		
187	B	B	B		B	A	A	B	
188	D	D	D		D	B	B		

189	B	B	B		B	A	A		
190	B	C	B		C	A	B		
191	A	A	A		A	A	A		
192	A	A	A		A	A	A		
193	B	B	B		B	A	A		
194	A	A	A		A	A	A		
195	A	A	A		A	A	A		
196	A	A	A		A	A	A		
197	A	A	A		A	A	A		
198	D	D	D		D	B	C		
202	D	D	D		D	B	C		
203	D	D	D		D	B	C		
205	B	A	A		A	A	A	B	
206	B	A	A		B	A	A	B	
207	B	C	C		C	A	A		
208	B	A	B		B	A	A	B	
209	C	D	D		D	A	B		
210	D	D	D		D	B	B		
211	B	B	B		B	A	A		
212	A	A	A		B	A	A	B	
213	A	A	A		B	A	A	B	
214	B	B	B		B	A	A	C	
215	B	A	A		B	A	A	C	
216	D	D	D		D	B	B		
217	A	A	A		A	A	A	B	
218	D	D	D		D	B	C		
219	B	B	B		B	A	A		
220	C	D	D		D	A	B		
221	B	B	B		B	A	B		
223	C	C	C		D	A	B		
224	B	B	B		B	A	B		
225	C	D	D		D	A	A		
227	C	C	C		C	A	B		

228	B	C	C		C	A	A		
230	D	D	D		D	B	B		
231	D	D	D		D	B	B		
232	D	D	D		D	B	C		
233	B	C	C		C	A	A		
234	C	C	B		C	A	A		
235	C	B	B		C	A	A		
236	C	C	C		C	A	A		
237	C	C	C		C	B	B		
239	D	D	D		D	B	C		
240	C	C	C		D	A	B		
241	B	C	B		C	A	A		
242	B	B	A		B	A	A		
243	B	B	A		B	A	A		
244	D	D	D		D	B	C		
245	A	A	A		B	A	A		
246	C	D	D		D	A	B		
247	B	B	B		C	A	A		
248	D	C	C		D	B	B		
249	D	D	D		D	B	B		
251	D	D	D		D	A	B		
252	A	A	A		B	A	A		
253	D	D	D		D	B	B		
254	B	B	B		B	A	A		
255	B	C	C		B	A	A		
256	B	A	A		A	A	A		
257	C	C	D		C	A	A		
258	B	C	C		C	A	A		
259	C	C	C		D	A	A		
260	C	D	D		D	A	A		
261	C	D	D		D	A	B		
262	D	D	C		B	A	B		
263	D	D	D		D	B	C		

264	C	C	C		C	A	A		
265	C	C	C		C	A	A		
267	C	D	D		D	A	A		
268	C	D	D		D	A	B		
269	B	B	B		B	A	A	C	
270	B	B	B		C	A	A	C	
271	B	B	C		B	B	C		
272	A	A	A		A	A	A		
273	D	D	D		D	B	B		
274	D	D	D		D	B	B		
275	B	B	B		B	A	A		
276	B	B	B		B	A	A	C	
277	B	B	B		B	A	A		
278	B	B	B		D	A	A		
279	B	C	B		C	A	A		
280	C	D	C		D	B	B		
281	B	B	B		C	A	A		
282	A	A	A		B	A	A		
283	B	C	C		C	A	A		
284	B	B	B		B	A	A		
285	B	C	B		B	B	B		
286	D	D	D		D	B	C		
287	A	A	A		A	A	A	B	
288	B	B	B		B	A	A	C	
289	B	B	B		C	A	A		
292	C	D	C		C	A	B		
293	A	B	B		B	A	A	B	
294	B	B	B		B	A	A	B	
295	D	D	D		D	A	B		
296	B	B	B		B	A	A	B	
297	B	B	B		B	A	A	B	
298	B	B	B		B	A	A	C	
299	B	B	B		B	A	A	C	

300	C	D	D		D	A	A	C	
301	C	C	C		D	A	A		
302	C	C	C		D	A	B		
303	C	C	C		D	A	A		
304	C	D	D		D	A	B		
305	A	A	A		B	A	A		
306	A	A	A		B	A	A	B	
307	B	B	B		B	A	A		
309	C	C	C		D	A	A		
310	C	C	C		D	A	B		
311	B	C	C		C	A	A	C	
313	D	D	D		D	B	C		
314	D	D	D		D	B	C		
315	D	D	D		D	B	B		
316	D	D	D		D	B	B		
317	B	B	B		B	A	A	B	
318	C	C	C		C	A	A		
319	D	D	D		D	B	C		
320	D	D	D		D	B	C		
321	D	D	D		D	B	B		
322	D	D	D		D	B	B		
323	B	B	B		B	A	A		
324	B	B	B		B	A	A		
325	A	A	A		A	A	A	A	
326	A	A	A		A	A	A		
327	A	B	A		A	A	A	B	
328	A	A	A		A	A	A		
329	A	A	A		A	A	A		
330	C	C	C		C	B	B		
331	A	A	A		A	A	A	B	
332	B	B	B		B	A	A		
333	B	B	B		C	A	A		
334	B	B	B		B	A	A	B	

335	B	B	D		B	A	A	B	
336	B	B	B		C	A	A		
337	B	C	C		C	A	A	C	
338	B	B	B		B	A	A	B	
339	B	B	B		B	A	A		
340	A	A	A		B	A	A		
341	C	C	C		C	B	B		
342	C	C	D		D	A	B		
343	A	B	A		B	A	A	C	
345	B	B	B		C	A	A	C	
346	B	B	A		B	A	A	B	
347	C	C	B		C	A	A		
348	A	A	A		A	A	A	B	
349	B	B	B		B	A	A		
350	B	B	B		B	A	A		
351	B	B	B		B	A	A	C	
352	C	C	C		B	A	A		
353	B	B	B		B	A	A	C	
354	A	B	B		B	A	A	B	
355	C	C	C		C	A	A		
356	C	C	C		D	A	A		
357	A	A	B		B	A	A	B	
358	B	B	B		B	A	B		
359	B	B	B		C	A	A	C	
360	B	B	B		B	A	A	B	
361	B	C	C		C	A	A		
362	B	D	D		D	A	B	C	
363	B	C	B		C	A	A		
364	B	B	B		B	A	A		
365	B	B	B		B	A	A		
366	B	B	B		B	A	A	C	
367	B	B	B		B	A	A		
368	B	B	B		B	A	A		

369	B	B	B		C	A	A		
370	C	C	C		C	A	A		
371	B	B	B		C	A	A		
372	B	B	B		B	A	A		
373	A	A	B		B	A	A	B	
374	B	B	B		B	A	A	B	
375	C	C	C		C	A	A		
376	B	B	B		B	A	A	B	
377	B	B	B		B	A	A	B	
378	A	A	B		B	A	A	B	
379	A	B	B		B	A	A	C	
380	B	B	B		B	A	A	B	
381	B	C	C		C	A	A		
382	D	D	D		D	A	B		
383	B	B	B		B	A	A	C	
384	B	B	B		B	A	A	B	
385	B	B	B		B	A	A	B	
386	A	B	A		B	A	A	B	
387	B	B	B		B	A	A	B	
388	A	B	B		B	A	A	C	
389	C	D	D		D	A	B	C	
390	C	D	C		D	A	A	C	
391	B	B	B		B	A	A	B	
392	C	C	C		D	A	A	C	
393	D	D	D		D	A	B		
394	B	B	B		B	A	B		
395	C	D	D		D	A	A		
396	B	B	B		B	A	A	C	
397	C	C	C		C	A	A	C	
398	D	D	D		D	A	B		
399	C	C	C		B	A	A	C	
400	B	A	B		B	A	A		
401	B	B	B		B	A	A	B	

402	B	B	B		B	A	A	B	
403	B	A	A		A	B	B		
404	B	B	B		C	A	A	B	
405	D	D	D		D	A	B		
406	C	D	D		D	B	C		
407	B	B	B		B	B	C		
408	C	C	D		D	A	A		
409	D	D	D		D	B	C		
410	C	C	C		C	B	B		
411	A	A	A		A	A	A	A	
412	C	C	C		C	A	B		
413	B	B	B		B	A	A		
414	B	C	B		B	A	A		
415	B	C	C		B	A	A		
416	C	D	D		C	A	A	C	
417	C	C	C		C	A	A	C	
418	C	D	D		C	B	B		
419	B	B	B		B	A	A	B	
420	B	B	A		B	A	A	B	A
421	D	D	D		D	B	B		
422	D	D	D		C	B	C		
423	C	C	C		C	B	C		
424	D	D	D		D	B	C		
425	C	C	D		C	A	A		
426	C	D	D		C	A	B		
427	C	D	D		D	A	A		
428	B	C	C		B	A	B		
429	C	D	D		D	A	B		
430	C	D	C		D	A	B		
431	B	B	B		B	A	A		
432	B	B	B		B	A	A		
433	C	C	C		C	A	A		
434	B	B	B		B	A	A		

435	B	B	B		B	A	A		
436	D	D	D		D	B	B		
437	B	B	B		B	A	A		
438	B	B	B		B	A	A		
439	D	D	D		D	A	B		
440	A	A	A		A	A	A		
441	B	B	B		B	A	A		
442	A	B	B		B	A	A		
443	D	D	D		D	B	B		
444	B	D	D		D	A	B		
445	C	C	D		C	B	B		
447	B	B	B		C	A	B		
448	C	C	C		D	B	C		
449	A	B	B		B	A	A		
450	B	B	B		B	A	A		
451	B	C	C		C	A	A		
452	B	B	B		B	A	A		
455	A	B	B		B	A	A		
456	C	C	C		C	A	A		C
459	D	D	D		D	B	B		
463	A	A	A		A	A	A		B
465	A	A	A		A	A	A		A
466	B	B	A		B	A	A		A
467	B	B	B		B	A	A		A
468	B	B	B		B	A	A		
481	A	B	B		B	A	A		
482	C	C	C		C	A	A		
483	C	C	C		D	A	B		
484	B	B	B		B	A	A		B
487	B	B	B		B	A	A		
488	A	A	B		A	A	A		
493	A	B	A		A	A	A		B
494	A	A	A		A	A	A		B

496	C	C	C		D	B	B		
497	B	B	B		B	A	A		
498	D	D	D		D	A	B		
500	D	D	D		D	B	C		
502	D	D	D		D	A	B		
506	D	D	D		D	B	C		
507	D	D	D		D	A	B		
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509	B	B	B		B	A	A		
510	C	C	C		C	A	B		
511	B	B	B		B	A	A		
512	C	B	B		C	A	A		
513	B	B	B		B	A	A		
514	C	C	B		C	A	A		
515	A	B	B		B	A	A		
516	B	B	B		B	A	A		
517	B	B	B		B	A	A		
518	B	B	B		B	A	A		
519	B	C	B		B	A	A		
520	B	C	C		C	A	A		
521	C	C	C		C	A	A		
522	B	B	C		B	A	A		C
523	B	A	A		A	A	A		
524	B	B	B		B	A	B		
525	B	B	B		B	A	A		
526	B	B	B		B	A	A		B
527	C	C	C		C	A	B		C
528	B	B	B		B	A	A		
529	C	C	C		D	B	A		
530	D	D	D		D	A	B		
531	B	B	B		B	A	A		
532	D	D	D		D	A	B		B
533	B	B	B		B	A	A		

534	D	D	C		D	A	B		
535	B	B	B		B	A	A		
536	C	C	C		D	A	A		
537	C	C	C		C	A	B		
538	D	D	D		D	A	B		
539	B	B	B		B	A	A		
540	B	B	B		C	A	A		
541	B	B	B		B	A	A		
542	D	D	D		D	B	C		
543	C	C	C		C	A	A		
545	B	B	B		B	A	A		B
546	C	C	C		C	A	A		
547	B	C	B		C	A	A		B
549	B	B	B		B	A	A		B
550	C	C	C		C	A	A		
551	C	C	C		C	A	A		
552	B	B	B		B	A	A		
553	C	D	D		D	B	B		
554	C	D	D		D	A	B		C
555	B	B	B		C	A	A		
556	D	D	D		D	B	C		
557	D	D	D		D	B	C		
558	B	B	B		C	A	A		
559	C	C	C		D	A	B		
560	B	B	B		B	A	A		
561	B	B	B		B	A	A		B
562	D	D	D		D	A	B		
563	D	D	D		D	A	B		
564	B	B	C		B	A	A		
565	C	C	C		C	A	A		
566	C	C	C		C	A	A		
567	C	C	C		C	A	A		
568	B	B	B		B	A	A		B

569	C	D	D		D	B	B		
570	B	C	B		C	A	A		
571	B	B	B		B	A	A		B
572	C	C	C		D	A	B		
573	B	B	B		B	A	A		B
574	C	D	C		D	A	B		
575	B	C	C		B	A	A		
576	D	D	D		D	B	C		
577	A	B	A		B	A	A		B
578	B	B	B		B	A	A		B
579	C	C	C		D	A	A		
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581	B	B	B		B	A	A		B
582	B	B	B		B	A	A		B
583	B	B	C		B	A	A		
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585	D	C	D		D	A	B		
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587	C	C	C		C	A	A		
588	B	B	B		B	A	A		B
589	C	C	C		D	A	A		
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591	C	C	C		D	A	B		C
592	B	C	D		D	A	B		
593	C	C	B		C	A	A		C
594	D	D	D		D	A	B		B
595	B	A	A		B	A	A		A
596	A	A	B		B	A	A		B
597	D	D	D		D	A	C		
598	A	B	B		B	A	A		B
599	D	D	D		D	A	C		
607	B	B	B		B	A	A		
608	D	D	D		D	A	B		

609	C	C	C		C	A	A		
610	C	C	C		C	A	A		
611	A	B	B		B	A	A		A
612	A	A	B		A	A	A		
614	C	C	C		C	A	B		
615	A	B	A		B	A	A		B
616	D	D	D		D	B	C		
617	B	B	A		B	A	A		B
618	B	B	A		B	A	A		A
619	C	C	C		C	A	A		
620	D	D	C		D	A	B		
621	D	D	D		D	A	B		
622	D	D	D		D	B	C		
623	B	B	B		B	A	A		B
624	B	B	B		B	A	A		
625	B	B	B		B	A	A		A
626	C	C	C		C	A	A		
627	B	B	B		B	A	A		B
628	B	B	B		B	A	A		B
629	B	B	A		B	A	A		B
630	C	C	C		D	A	A		C
633	D	D	D		D	B	B		
634	C	C	C		B	A	A		
636	B	B	B		B	A	A		
637	B	C	C		B	A	A		B
638	B	B	B		B	A	A		B
639	B	B	B		B	A	A		A
640	C	D	C		D	A	A		
641	B	B	B		B	A	A		A
642	C	C	C		C	A	A		
643	B	B	B		B	A	A		B
644	C	C	C		C	A	A		
645	B	B	B		B	A	A		B

646	A	A	A		A	A	A		A
647	D	D	C		D	A	B		
649	C	C	B		C	A	A		
650	A	B	B		A	A	A		A
651	C	C	C		C	A	A		
652	B	B	A		B	A	A		A
654	C	C	C		C	A	A		
655	B	B	B		B	A	A		B
656	C	D	D		D	A	B		
657	B	B	B		B	A	A		A
658	C	C	C		C	A	B		
659	A	A	A		B	A	A		B
660	B	B	B		B	A	A		
661	B	C	C		B	A	A		
662	B	C	B		C	A	A		
663	A	A	A		B	A	A		B
664	B	A	A		B	A	A		A
665	B	B	B		C	A	A		
666	B	B	B		B	A	A		B
667	C	C	C		C	A	A		
668	A	B	A		B	A	A		B
669	A	A	A		A	A	A		B
670	B	C	B		C	A	A		B
671	A	A	A		A	A	A		B
672	B	B	B		B	A	A		
673	A	A	A		A	A	A		B
674	B	B	B		B	A	A		B
675	B	B	B		C	A	B		
676	A	A	A		B	A	A		B
677	C	C	C		C	A	A		
678	B	B	B		B	A	A		B
679	C	D	C		D	A	B		
680	A	A	A		B	A	A		B

681	B	B	B		B	A	A		
682	A	B	A		A	A	A		B
683	A	A	A		A	A	A		B
684	C	C	C		C	A	B		
685	A	B	B		B	A	A		B
686	B	C	C		C	A	A		
687	C	C	D		C	A	B		
688	C	D	D		C	B	B		
690	B	C	B		C	A	A		
692	A	A	A		B	A	A		B
693	C	C	C		C	A	A		
707	A	A	A	A	A	A	A		
708	A	A	A		A	A	A		
710	A	A	A		A	A	A		
711	A	A	A		A	A	A		
712	A	A	A		A	A	A		
719	A	A	A		A	A	A		
721	A	A	A		A	A	A		
725	B	B	B	A	B	A	A		
726	A	A	A		B	A	A		
728	A	A	A	A	A	A	A		
729	A	A	A		A	A	A		
730	B	B	B		B	A	A		
731	A	B	B		B	A	A		B
732	B	B	B		C	A	A		
733	B	B	B		C	A	A		
734	A	B	A	A	B	A	A		
746	A	A	A	A	A	A	A		
750	A	B	A		A	A	A		
751	B	B	B		B	A	A		
752	D	D	D		D	B	B		
753	B	C	B		C	A	A		
754	A	B	B		B	A	A		

755	A	B	A		A	A	A		B
756	B	B	A		C	A	A		
757	C	C	C		D	A	B		
758	A	B	A		B	A	A		
759	C	C	C		C	A	B		
760	A	A	A		B	A	A		B
761	A	B	A		B	A	A		
762	C	D	C		D	A	B		
763	A	B	A		B	A	A		B
764	C	C	C		C	A	B		
765	A	A	A		B	A	A		B
766	C	C	C		C	A	A		
767	C	C	B		C	A	A		
768	A	A	A		B	A	A		
771	A	B	A		B	A	A		
772	A	A	A		B	A	A		
773	B	B	A		B	A	A		
774	A	A	A	A	B	A	A		
775	B	B	B	B	B	A	A		
776	A	A	A		B	A	A		
777	A	A	A		A	A	A		
778	A	A	A		B	A	A		
779	B	B	B		C	A	A		
780	A	A	A		A	A	A		
781	A	A	A		B	A	A		
782	B	C	B		C	A	A		
783	B	C	B		C	A	A		
784	B	C	B		B	A	A		
785	D	D	D		D	B	B		
786	C	D	C		D	A	B		
789	A	B	A		B	A	A		
790	A	A	A		A	A	A		
791	A	B	A		B	A	A		

795	A	A	A		A	A	A		
796	B	C	B		C	A	A		
797	A	A	A		B	A	A		

Table 5. Biological characterization of selected compounds of the present disclosure.

Compound No.	pERK-AsPC-1	pERK-SW1990	pERK-HPAC	pERK-Capan-2	pERK-RKN	pERK-H358	pERK-HCT116	pERK-MKN	pERK-HT1080
3	A	A	A	A	A	A	A	A	C
22		A	A	A	A	A	A	A	C
81		A	A	A	A	A	A	A	C
83		A	B	B	B	A	B	A	C
245	A			A				A	
420	A	A	A					A	
438	A	A	A					A	
465	A		A	A	A			A	
466	A		A	A	A			A	
468	A		A	A	A			A	
531	A		A	A	A			A	
591	A			A				A	
593	A			A				A	
615	A			A				A	
669	A			A				A	

Table 6. Biological characterization of selected compounds of the present disclosure in 3D cell viability assays.

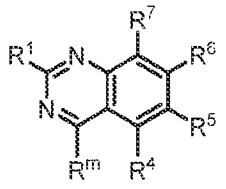
Compound No.	3D-viability AsPC-1	3D-viability SW1990	3D-viability HPAC	3D-viability Capan-2	3D-viability RKN	3D-viability H358	3D-viability HCT116	3D-viability MKN	3D-viability HT1080
3	A	A	A	A	A	A	A	A	C
22	A	A	A	A	A	A	A	A	C

81	A	A	A	A	A	A	A	A	C
83		A	B	A	A	A	C	B	C
245	A			A				A	
420	A	A	A					A	
438	A	A	A					A	
465	A		A	A	A			A	
466	A		A	A	A			A	
468	A		A	A	A			A	
531	A		A	A	A			A	
591	A			B				B	
593	A			B				B	
615	A			A				A	
669	A			A				A	

[0917] It should be understood from the foregoing that, while particular implementations have been illustrated and described, various modifications may be made thereto and are contemplated herein. It is also not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the preferable embodiments herein are not meant to be construed in a limiting sense. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. Various modifications in form and detail of the embodiments of the invention will be apparent to a person skilled in the art. It is therefore contemplated that the invention shall also cover any such modifications, variations, and equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

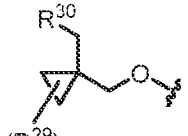
Claims

1. A compound represented by Formula A':



(A')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from H, $-OR^8$,  , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^m is selected from H and $-NR^2R^3$;

R^2 is selected from C_{1-6}alkyl which is optionally deuterated;

R^3 is selected from a C_{1-6}alkyl, 3- to 6-membered cycloalkyl optionally fused to a 5- or 6-membered heterocycle or heteroaryl, 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10}, or

R^2 and R^3, together with the atom they attach to, form a 4- to 10-membered heterocycle optionally substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle,

5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, $-N(R^{12})_2$, and -CN;

each R^{20} is independently selected from =O, -CN, -CN, $-OR^{12}$, and halogen;

each R^{28} is independently selected from halogen,$-OR^{12}$, C_{1-6}alkyl, and C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13};

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

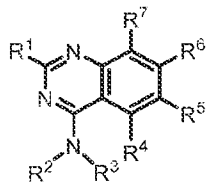
R^{30} is selected from $-N(R^{12})_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

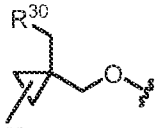
n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-4} alkenyl, , $-OR^{12}$, a 4- to 10-membered heterocycle, and a 4- to 10-membered aryl, wherein any 4- to 10-membered heterocycle or 4- to 10-membered aryl is optionally substituted with one or more R^{28}, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

2. The compound of claim 1, wherein the compound is a compound represented by Formula B:


(B)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:



R^1 is selected from H, $-OR^8$, , and a 6-10 membered heterocycle that is unsubstituted or substituted with one or more R^{31};

R^2 is selected from C_{1-6}alkyl;

R^3 is selected from a 4-10 membered heterocycle or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any heterocycle or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl, wherein the heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, =O, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently halogen;

each R^{14} is independently selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from halogen, -N(R^{12})$_2$, and -CN;

each R^{20} is independently selected from =O, -CN, and halogen;

each R^{28} is independently selected from halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

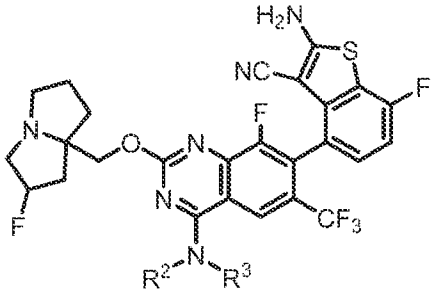
R^{30} is selected from -N(R^{12})$_2$ and a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, C_{2-4} alkenyl, and $-OR^{12}$, wherein any C_{1-6}alkyl or C_{2-4} alkenyl is unsubstituted or is substituted with one or more R^{13}.

3. The compound of claim 2, wherein the compound is of Formula B-a:



(B-a) or a salt (e.g., pharmaceutically acceptable salt) thereof.

4. The compound of any one of claims 1-3, wherein R^3 is a 4-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N.

5. The compound of claim 4, wherein R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

6. The compound of claim 4, wherein R^3 is a 4-7 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}.

7. The compound of any one of claims 1-6, wherein R^3 is a pyrrolidine that is substituted with 0-4 R^{10}.

8. The compound of any one of claims 1-6, wherein R^3 is a pyrrolidine that is substituted with 0-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}.

9. The compound of any one of claims 1-6, wherein R^3 is a 4-6 membered heterocycle that is substituted with one or more R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, and each R^{10} is independently selected from $-C(O)(C_{1-6}$alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), $-C(O)O(C_{1-6}$alkyl), $-C(O)N(R^{14})_2$, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

10. The compound of any one of claims 1-4, wherein R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N.

11. The compound of claim 10, wherein R^3 is an 8-10 membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

12. The compound of claim 10 or 11, wherein R^3 is an 8-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

13. The compound of claim 10 or 11, wherein R^3 is a 9-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

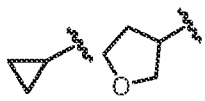
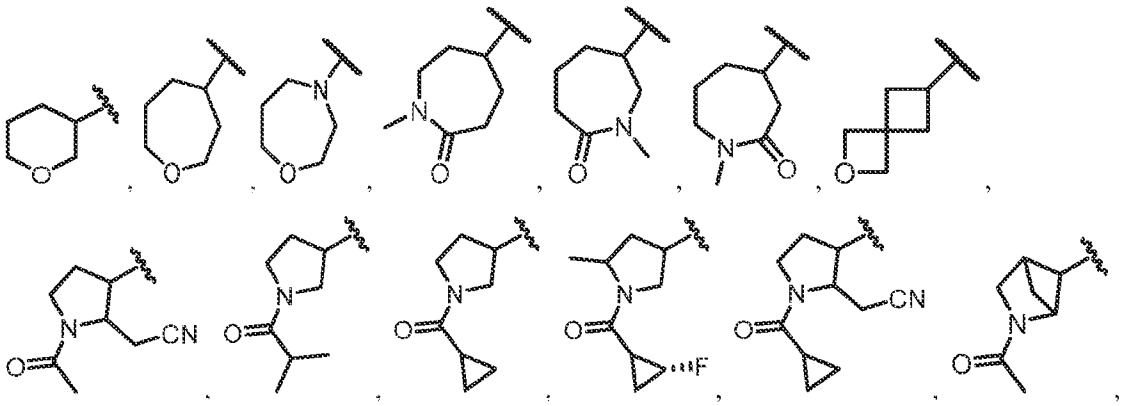
14. The compound of claim 10 or 11, wherein R^3 is a 10-membered heterocycle that includes 1-2 heteroatoms independently selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}.

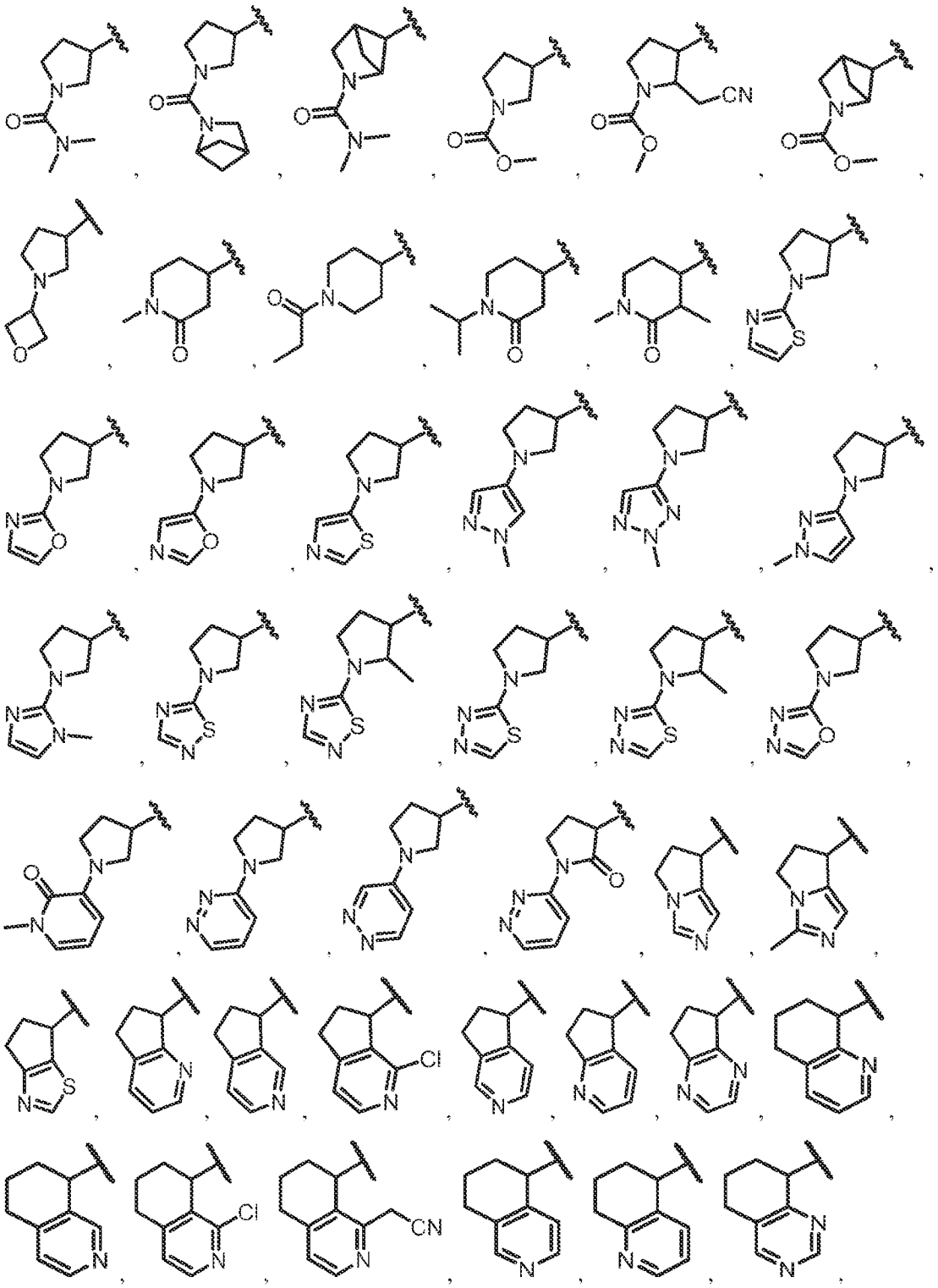
15. The compound of any one of claims 12-14, wherein R^{10} is selected from =O, C_{1-6}alkyl, a 3-6 membered carbocycle, and halogen.

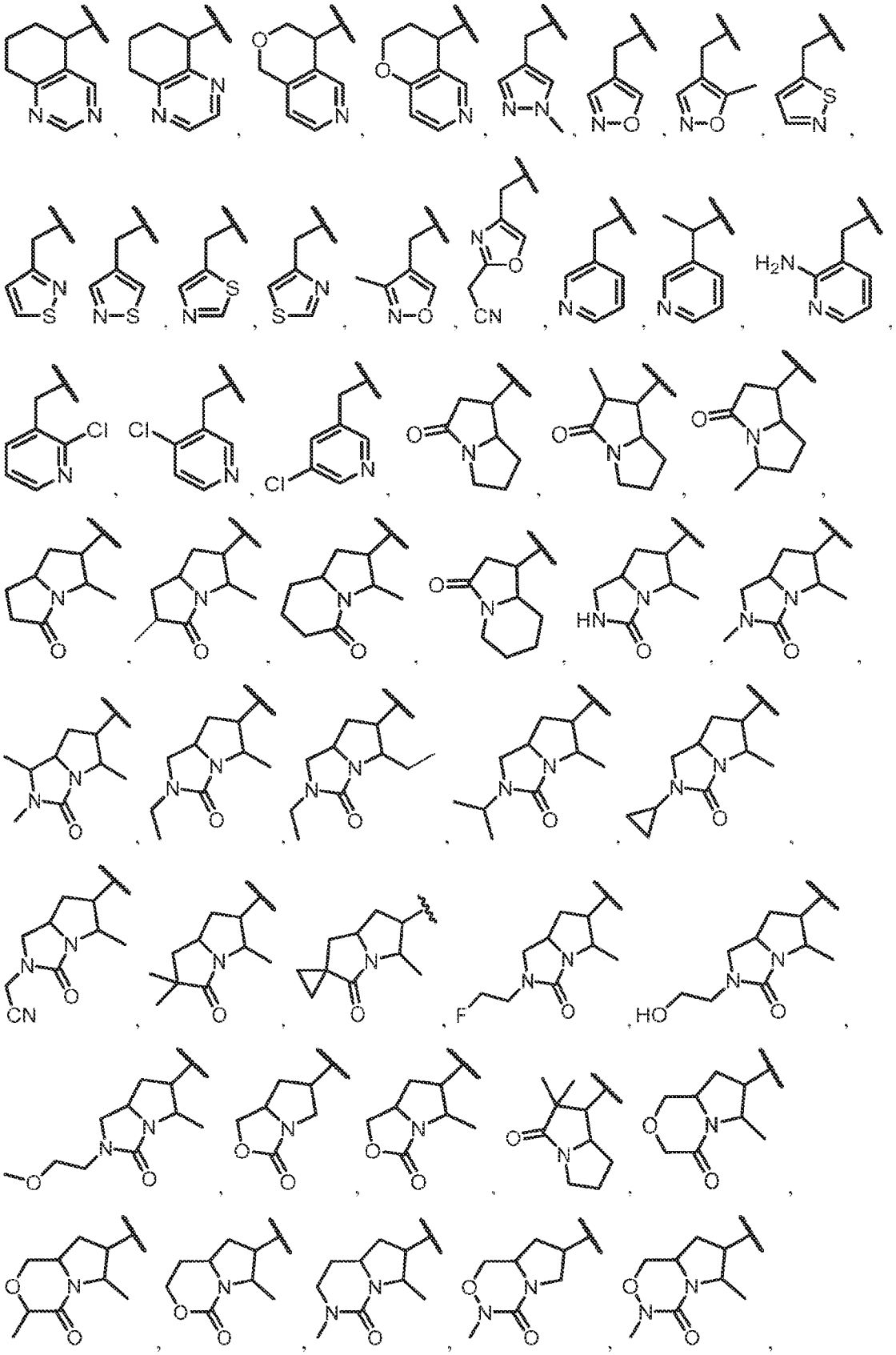
16. The compound of any one of claims 1-3, wherein R^3 is -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}.

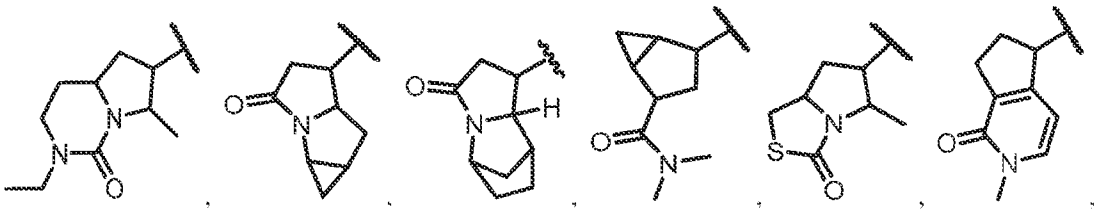
17. The compound of claim 16, wherein R^3 is -CH_2(5-6 membered heteroaryl), wherein the heteroaryl is unsubstituted or substituted with one or more R^{10}.

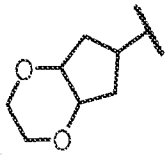
18. The compound of claim 17, wherein R^{10} is selected from halogen and C_{1-6}alkyl, wherein the C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}.

19. The compound of any one of claims 1-18, wherein R^3 is selected from: -CH_3,  , 

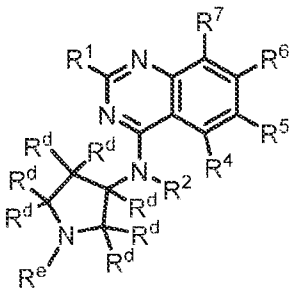




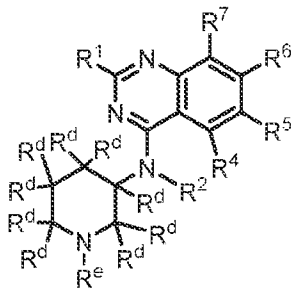


and  , any of which is optionally further substituted with one or more R^{10}.

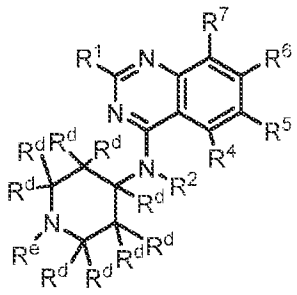
20. The compound of any one of claims 1-19, wherein the compound is a compound according to Formula BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, or BM:



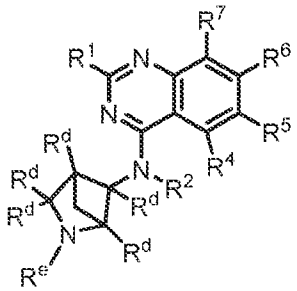
(BA),



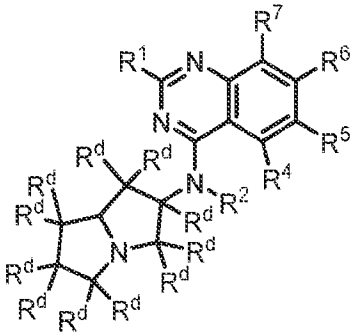
(BB),



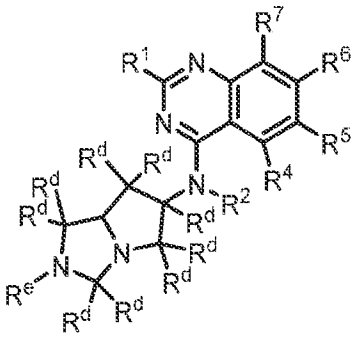
(BC),



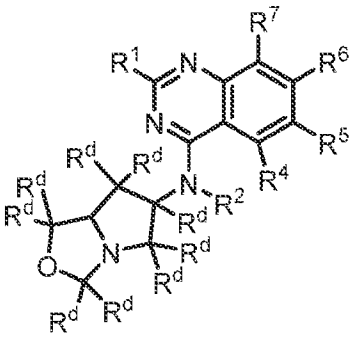
(BD),



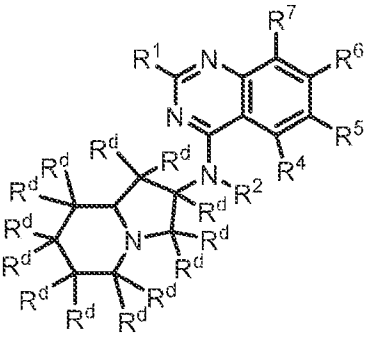
(BE),

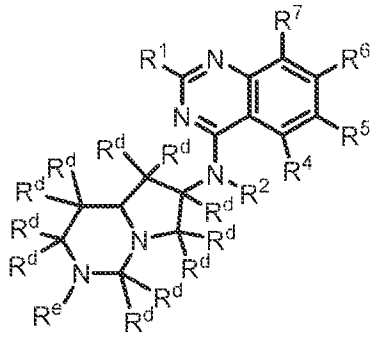


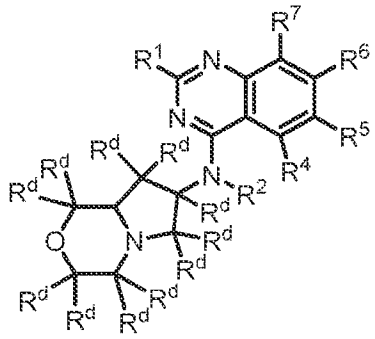
(BF),

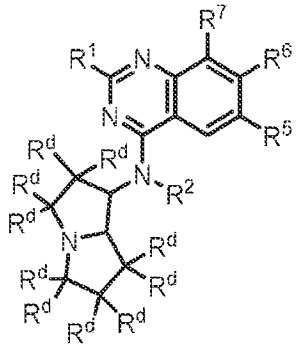


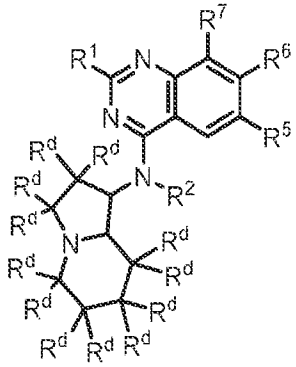
(BG),

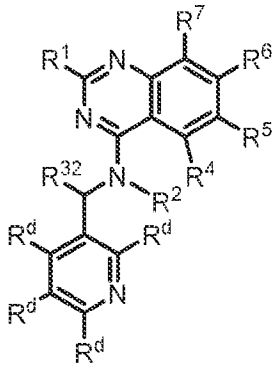

(BH),


(BI),


(BJ),


(BK),


(BL),

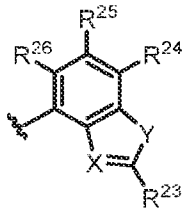

and (BM),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^{32}, if present, is selected from H and C_{1-5}alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}; and

R^e, if present, is selected from H, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

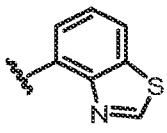
21. The compound of claim 20, wherein the compound is a compound according to Formula BA, or a salt (e.g., pharmaceutically acceptable salt) thereof.
22. The compound of claim 20, wherein the compound is a compound according to Formula BB, or a salt (e.g., pharmaceutically acceptable salt) thereof.
23. The compound of claim 20, wherein the compound is a compound according to Formula BC, or a salt (e.g., pharmaceutically acceptable salt) thereof.
24. The compound of claim 20, wherein the compound is a compound according to Formula BD, or a salt (e.g., pharmaceutically acceptable salt) thereof.
25. The compound of claim 20, wherein the compound is a compound according to Formula BE, or a salt (e.g., pharmaceutically acceptable salt) thereof.
26. The compound of claim 20, wherein the compound is a compound according to Formula BF, or a salt (e.g., pharmaceutically acceptable salt) thereof.
27. The compound of claim 20, wherein the compound is a compound according to Formula BG, or a salt (e.g., pharmaceutically acceptable salt) thereof.
28. The compound of claim 20, wherein the compound is a compound according to Formula BH, or a salt (e.g., pharmaceutically acceptable salt) thereof.
29. The compound of claim 20, wherein the compound is a compound according to Formula BI, or a salt (e.g., pharmaceutically acceptable salt) thereof.
30. The compound of claim 20, wherein the compound is a compound according to Formula BJ, or a salt (e.g., pharmaceutically acceptable salt) thereof.
31. The compound of claim 20, wherein the compound is a compound according to Formula BK, or a salt (e.g., pharmaceutically acceptable salt) thereof.
32. The compound of claim 20, wherein the compound is a compound according to Formula BL, or a salt (e.g., pharmaceutically acceptable salt) thereof.
33. The compound of claim 20, wherein the compound is a compound according to Formula BM, or a salt (e.g., pharmaceutically acceptable salt) thereof.
34. The compound of any one of claims 1-33, wherein (i) when R^3 includes a heterocycle or heteroaryl containing a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle or heteroaryl does not comprise an –NH- moiety.
35. The compound of any one of claims 1, 2, or 4-34, wherein R^6 is selected from:  , wherein:

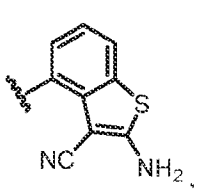
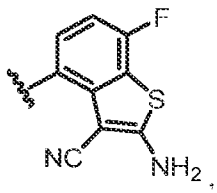
X is selected from N and C-CN;

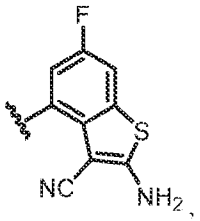
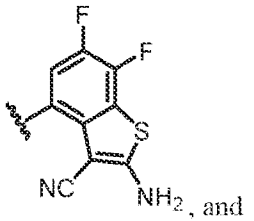
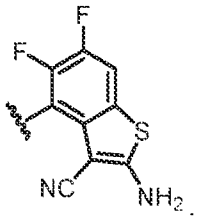
Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

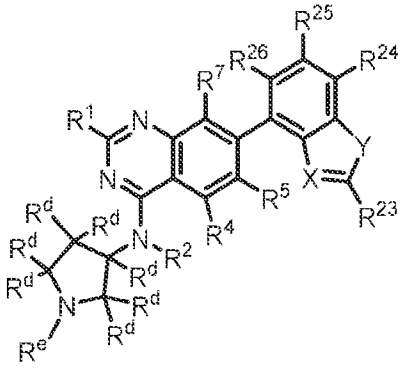
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

36. The compound of claim 35, wherein R^6 is selected from:  , which is substituted with one or more R^{15}.

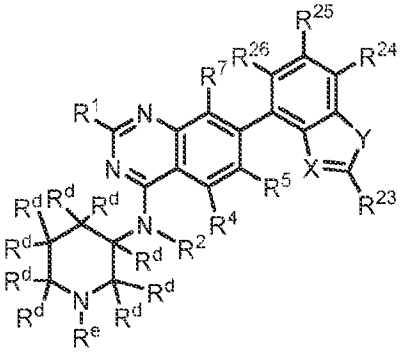
37. The compound of claim 36, wherein R^6 is selected from:  

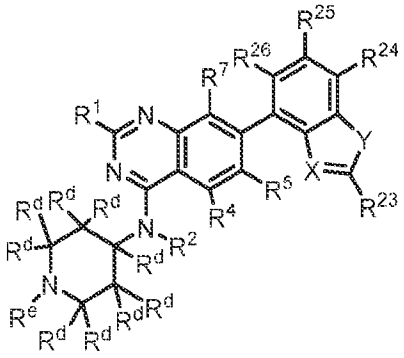
38. The compound of any one of claims 1, 2, or 4-37, wherein the compound is a compound according to Formula BA1, BB1, BC1, BD1, BE1, BF1, BG1, BH1, BI1, BJ1, BK1, BL1, or BM1:



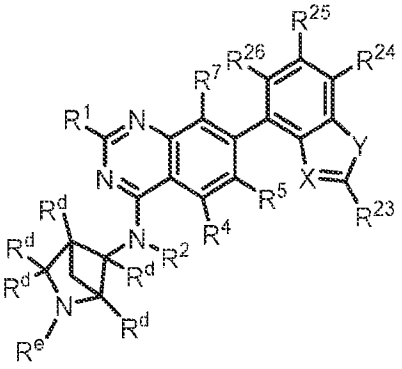
(BA1),



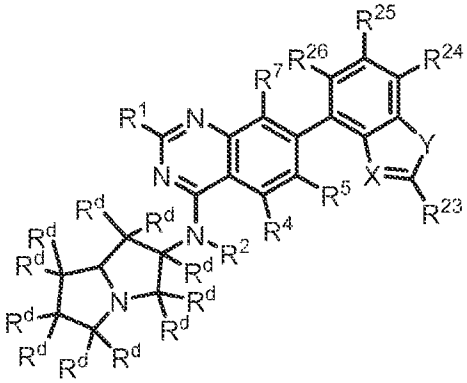
(BB1),



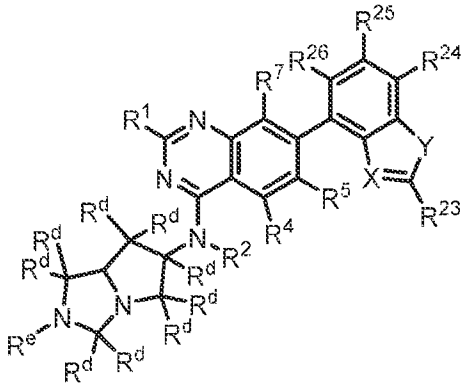
(BC1),



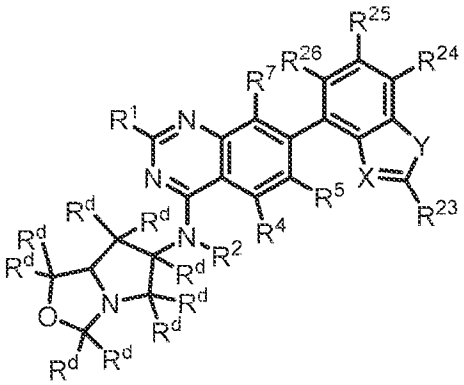
(BD1),



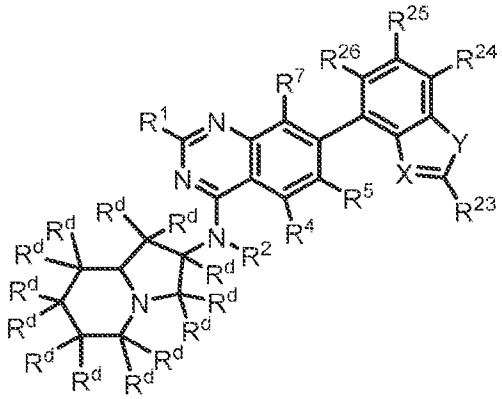
(BE1),



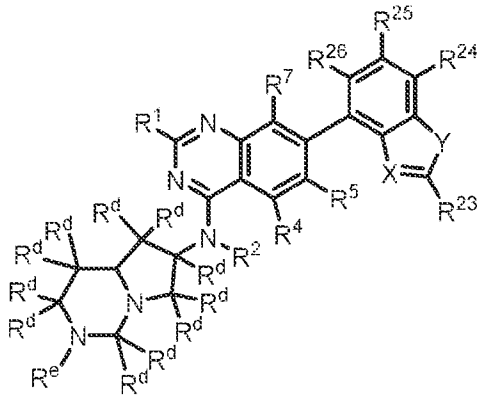
(BF1),



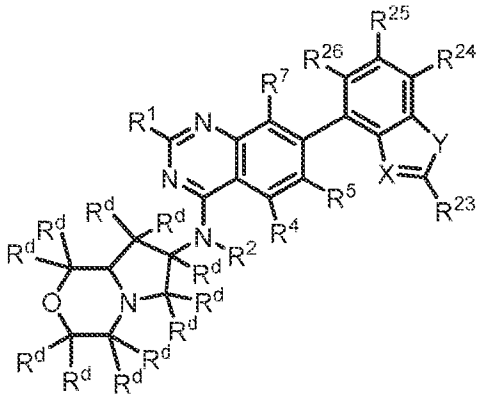
(BG1),



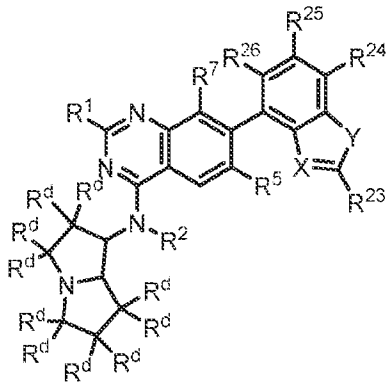
(BH1),



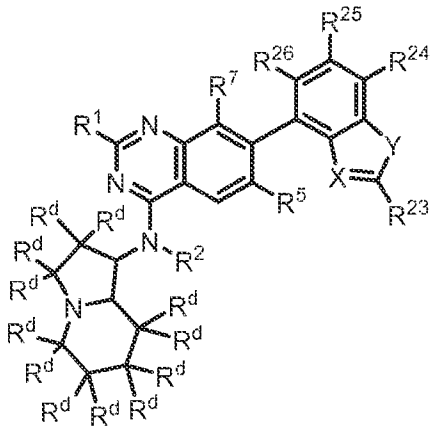
(BI1),



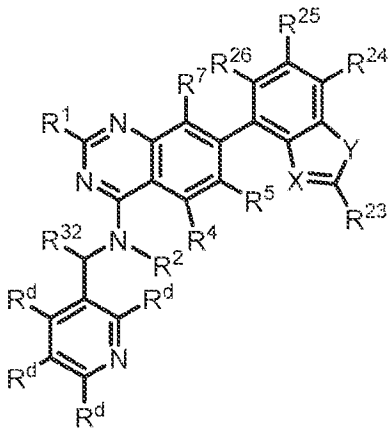
(BJ1),



(BK1),



(BL1), and



(BM1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^{32}, if present, is selected from H and C_{1-5}alkyl;

each R^d is independently selected from H, deuterium, =O, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20};

R^c, if present, is selected from -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-}

$_6$alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is C-CN;

Y is S;

R^{23} is selected from $-N(R^{12})_2$; and

R^{24}, R^{25}, and R^{26} are independently selected from H and halogen.

39. The compound of any one of claims 35-38, wherein one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

40. The compound of any one of claims 20-39, wherein R^e is -C(O)(3-6 membered carbocycle).

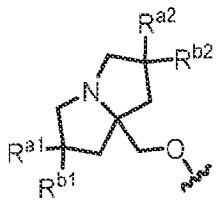
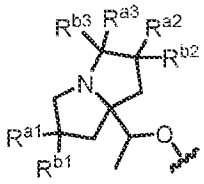
41. The compound of any one of claims 20-39, wherein R^e is selected from $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), and $-C(O)O(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

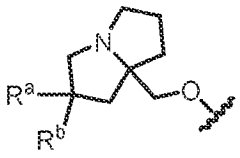
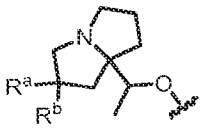
42. The compound of any one of claims 20-41, wherein each R^d is H.

43. The compound of any one of claims 1-42, wherein R^2 is H.

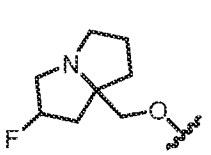
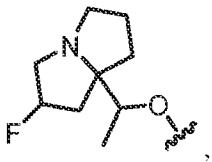
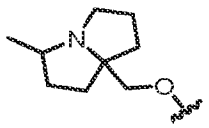
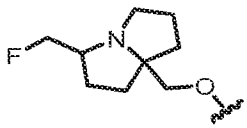
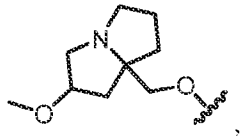
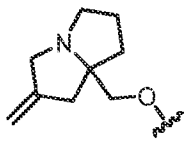
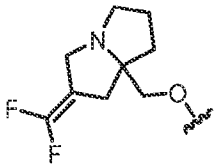
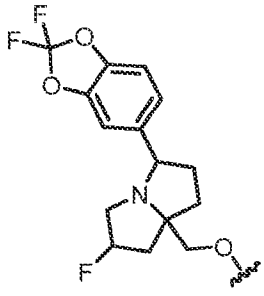
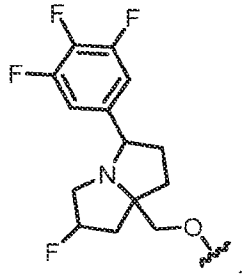
44. The compound of any one of claims 1-42, wherein R^2 is selected from C_{1-2}alkyl.

45. The compound of any one of claims 1, 2, or 4-44, wherein R^1 is selected from $-OR^8$.

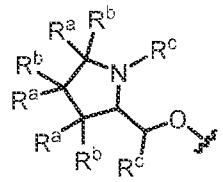
46. The compound of claim 45, wherein R^1 is selected from:  or  , wherein R^{a1}, R^{a2}, R^{b1}, R^{b2}, R^{a3}, and R^{b3} are each independently selected from deuterium, halogen, $-OR^{12}$, a 4- to 10-membered heterocycle, and a 4- to 10-membered aryl, wherein any 4- to 10-membered heterocycle or 4- to 10-membered aryl is optionally substituted with one or more R^{28}, and H, wherein R^{a1} and R^{b1} can optionally join together to form a exocyclic double bond that is unsubstituted or is substituted by halogen.

47. The compound of claim 46, wherein R^1 is selected from:  or  , wherein R^a and R^b are each independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen.

48. The compound of claim 47, wherein R^1 is selected from:

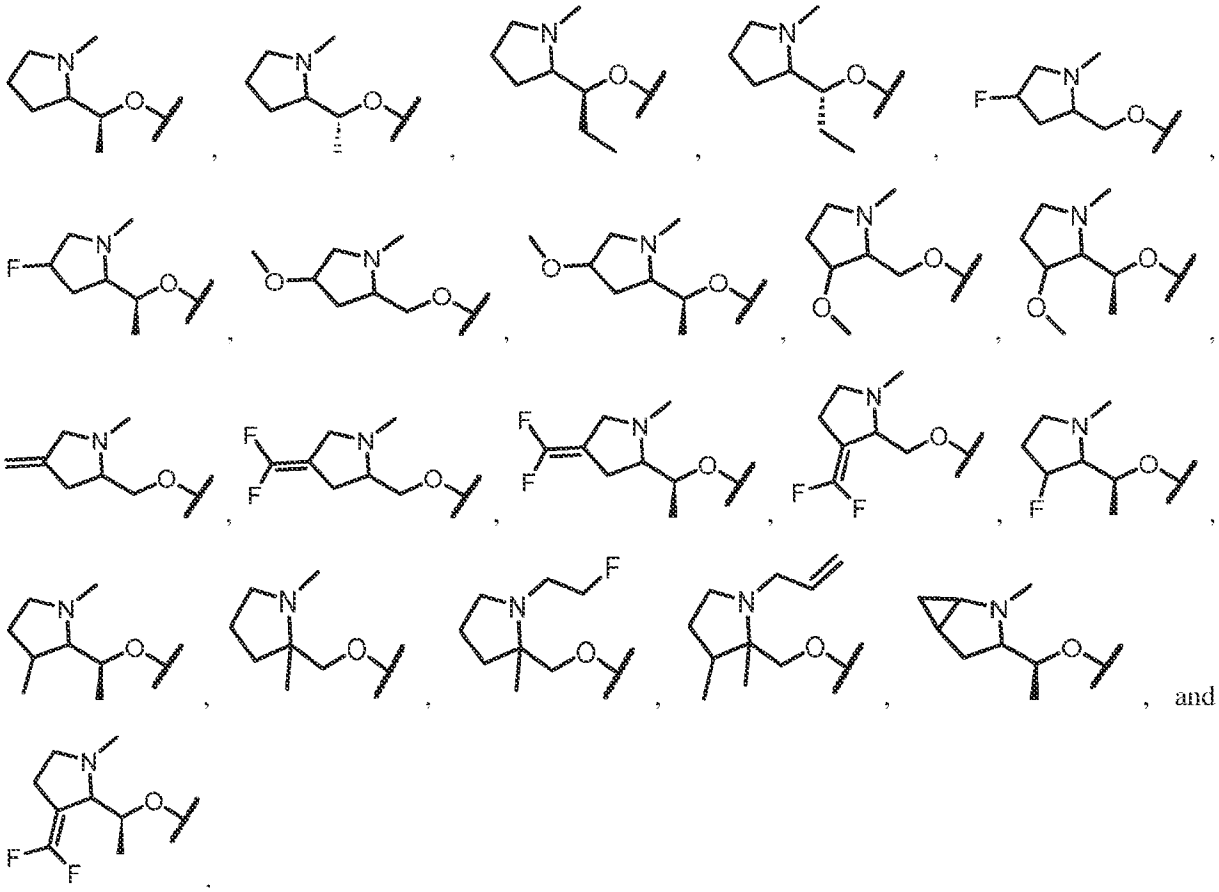
 ,  ,  ,  ,  ,  ,  ,  and  .

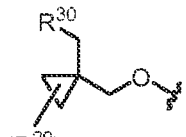
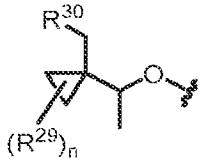
49. The compound of claim 45, wherein R^1 is:

 ,

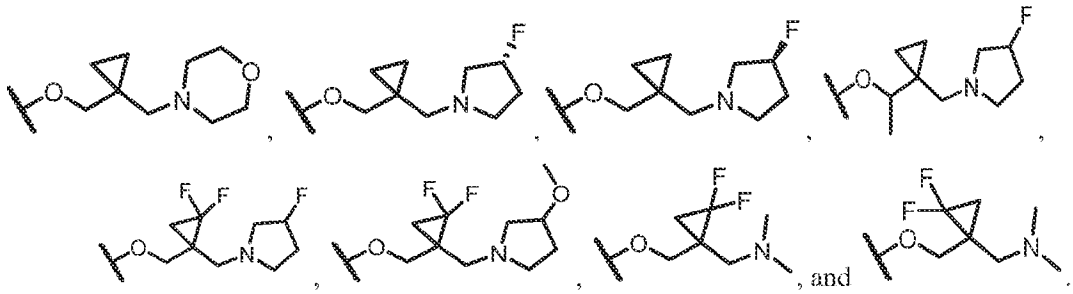
wherein each R^a and R^b is independently selected from halogen, $-OR^{12}$, C_{2-4} alkenyl, and H; and each R^c is independently selected from H and C_{1-6} alkyl, wherein any C_{2-4} alkenyl is unsubstituted or is substituted by halogen.

50. The compound of claim 49, wherein R^1 is selected from:



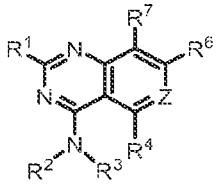
51. The compound of any one of claims 1, 2, or 4-44, wherein R^1 is  or  .

52. The compound of claim 51, wherein R^1 is selected from



53. The compound of any one of claims 1, 2, or 4-52, wherein R^5 is $-CF_3$.

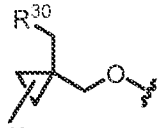
54. A compound represented by Formula II:



(II)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

Z is N or C-R^5;

R^1 is selected from H, -OR^8,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated;

R^3 is selected from 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, a 4-10 membered heterocycle, or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, -OC_{1-6}alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a phenyl or a bicyclic heteroaryl, wherein the phenyl or bicyclic heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen or H;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from deuterium, -OR^{12}, =O, =S, -CN, -N=S(=O)Me_2, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N(R^{14})$_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),-C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), -C(S)(C_{1-6}alkyl), -C(S)O(C_{1-6}

$_{6}$alkyl), -C(S)N(C_{1-6}alkyl)$_2$, -C(=N-OR^{12})(C_{1-6} alkyl), -C(O)N(R^{12})OR^{12}, halogen, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -CN, -N(R^{14})$_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{1-6} alkyl, -OR^{12}, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, halogen, -N(R^{12})$_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, =O, -CN, -NH_2, -NHC_{1-6}alkyl, -C(O)(C_{1-6}alkyl), -C(O)OR^{12}, -C(O)N(R^{12})$_2$, -S(O)$_2$R^{12}, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl, -OR^{12}, C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is N(R^{12})$_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

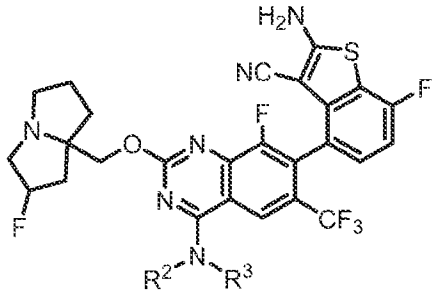
each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl,
,-C_{1-6} heteroalkyl, a 3-6 membered carbocycle, -OR^{12}, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

55. The compound of claim 54, wherein R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, or (ii) the heterocycle does not comprise an –NH- moiety.

56. The compound of claim 54 or 55, wherein the compound is of Formula II-a:



(II-a)

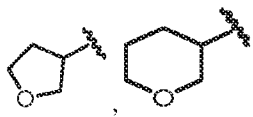
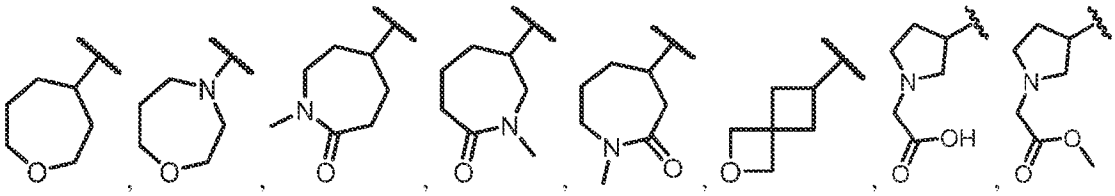
or a salt (e.g., pharmaceutically acceptable salt) thereof.

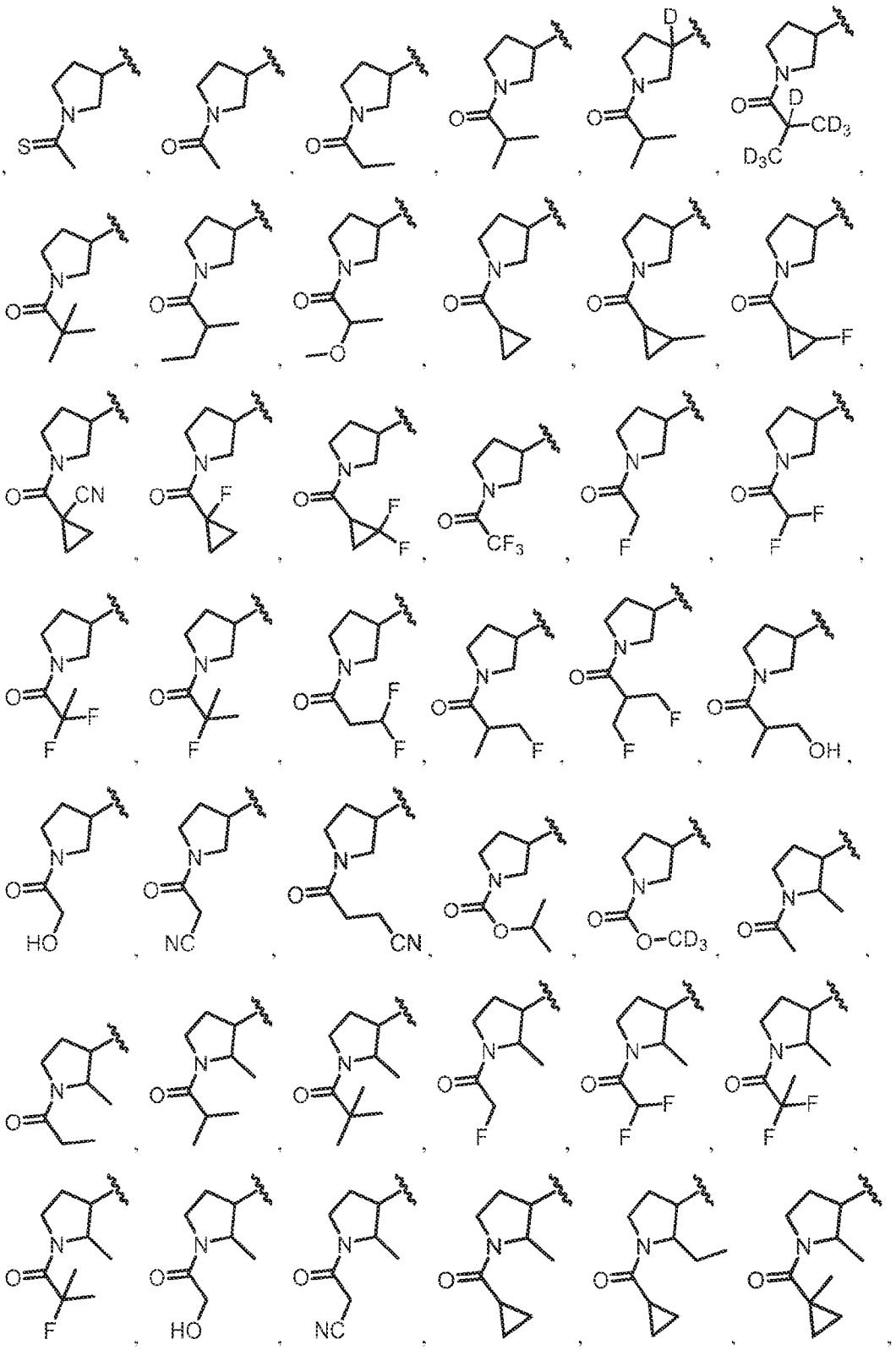
57. The compound of any one of claims 54-56, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N.

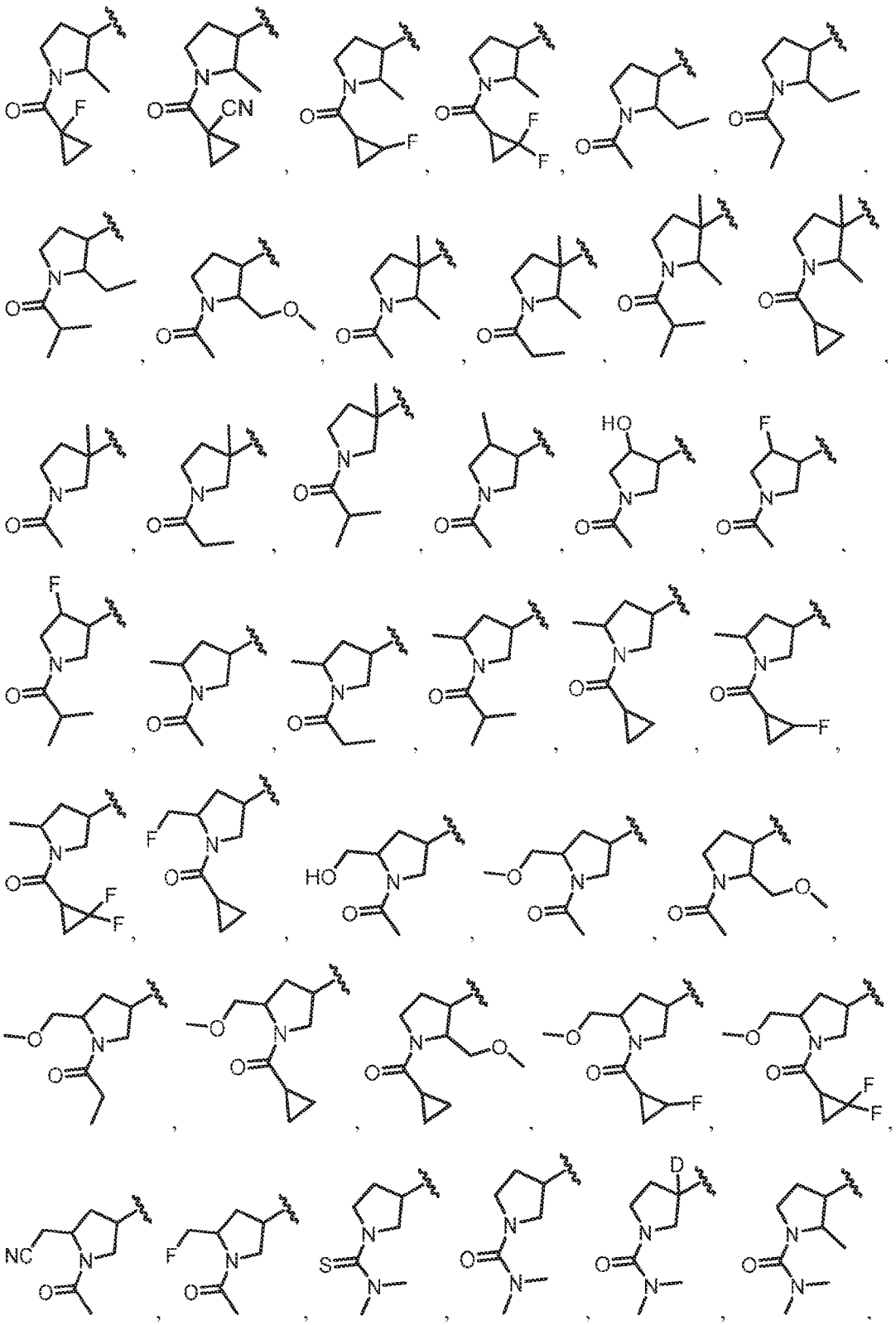
58. The compound of claim 57, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}.

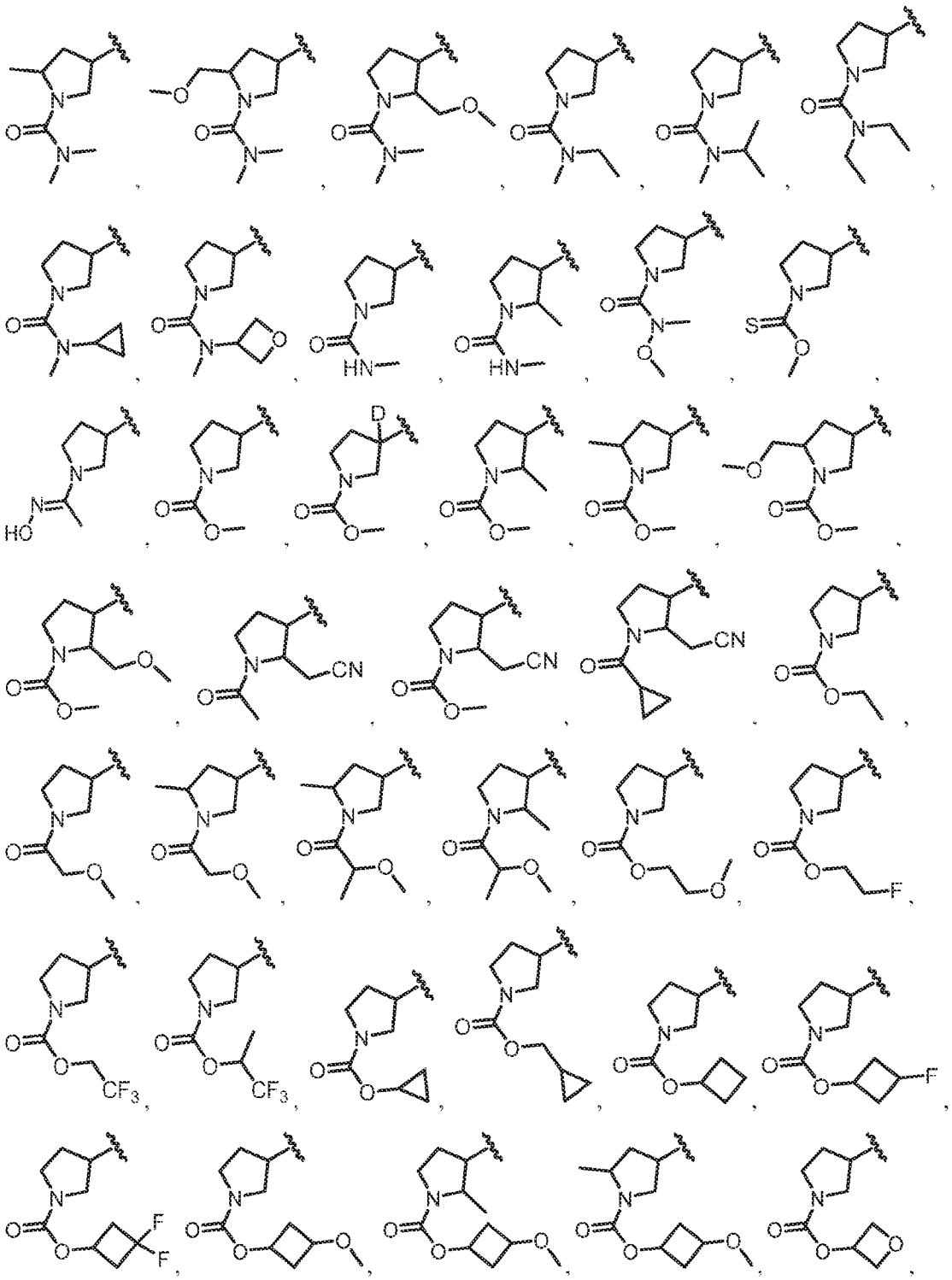
59. The compound of any one of claims 54-58, wherein R^3 is a pyrrolidine that is substituted with 1-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}.

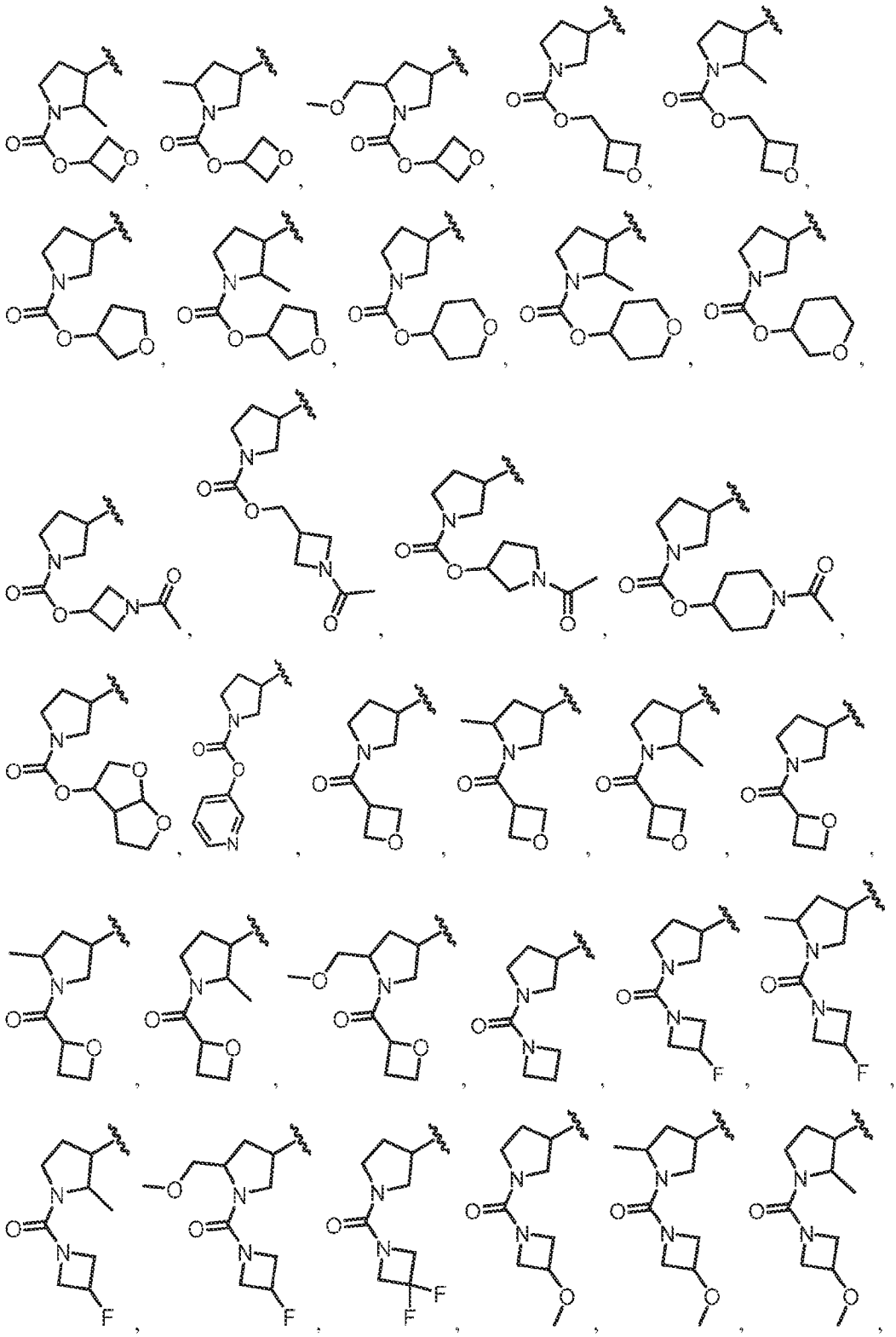
60. The compound of claim 59, wherein each R^{10} is independently selected from deuterium, -$C(O)N(R^{14})_2$, -$C(O)(C_{1\text{-}6}alkyl)$, -$C(O)O(C_{1\text{-}6}alkyl)$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), a 3-6 membered heterocycle, a 5-6 membered heteroaryl, halogen, and $C_{1\text{-}6}$alkyl, wherein any $C_{1\text{-}6}$alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

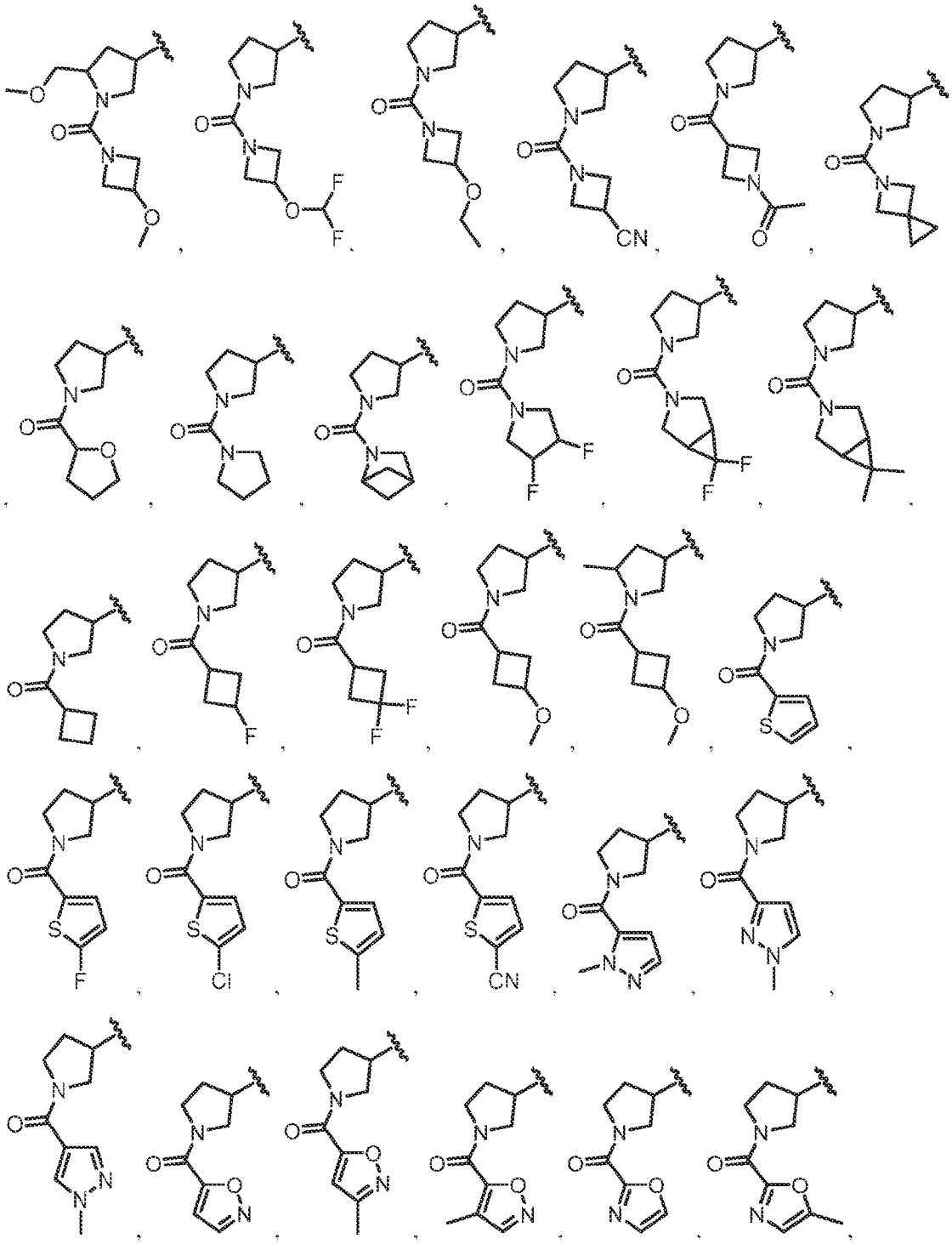
61. The compound of any one of claims 54-60, wherein R^3 is selected from:  , 

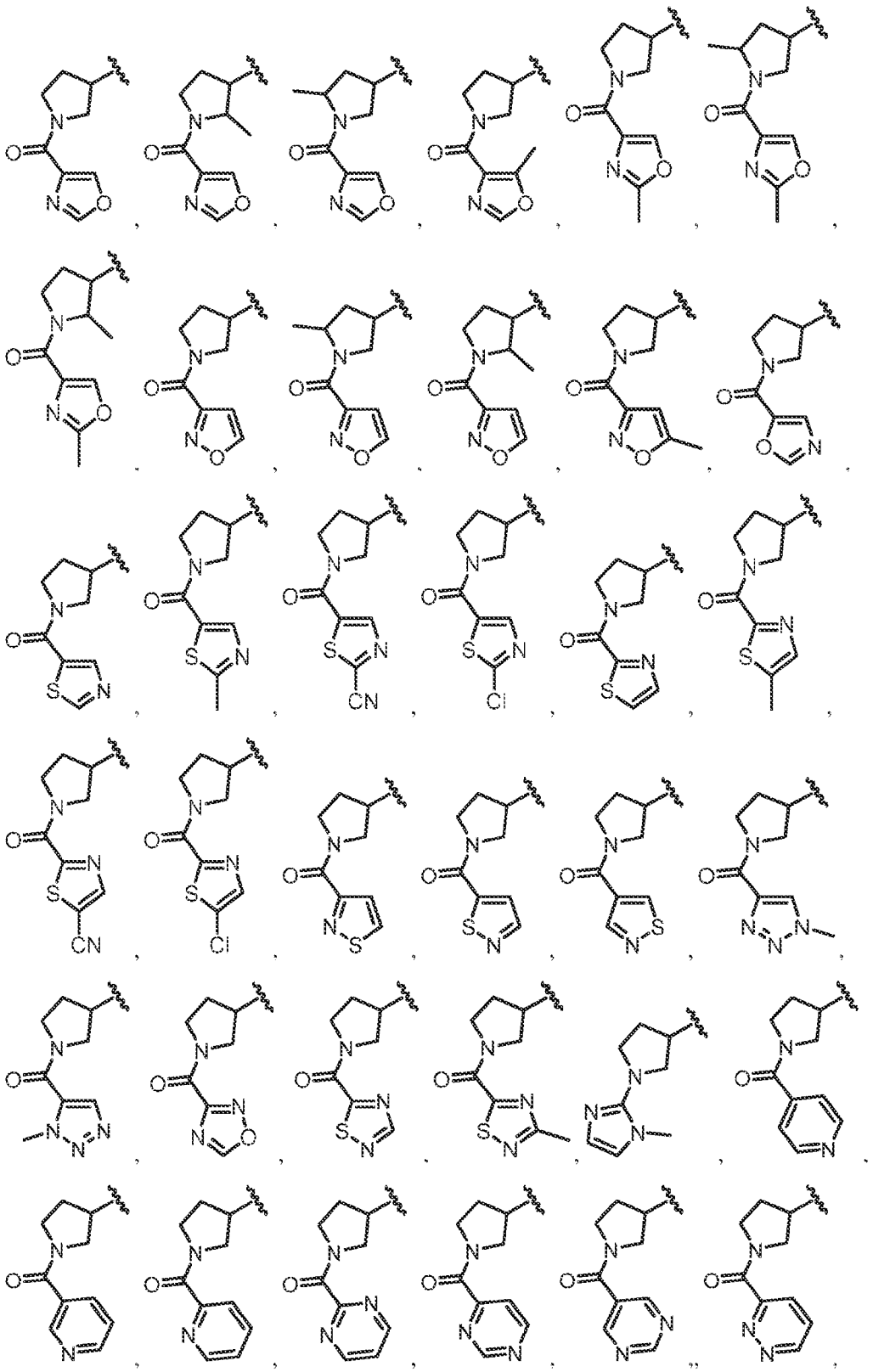


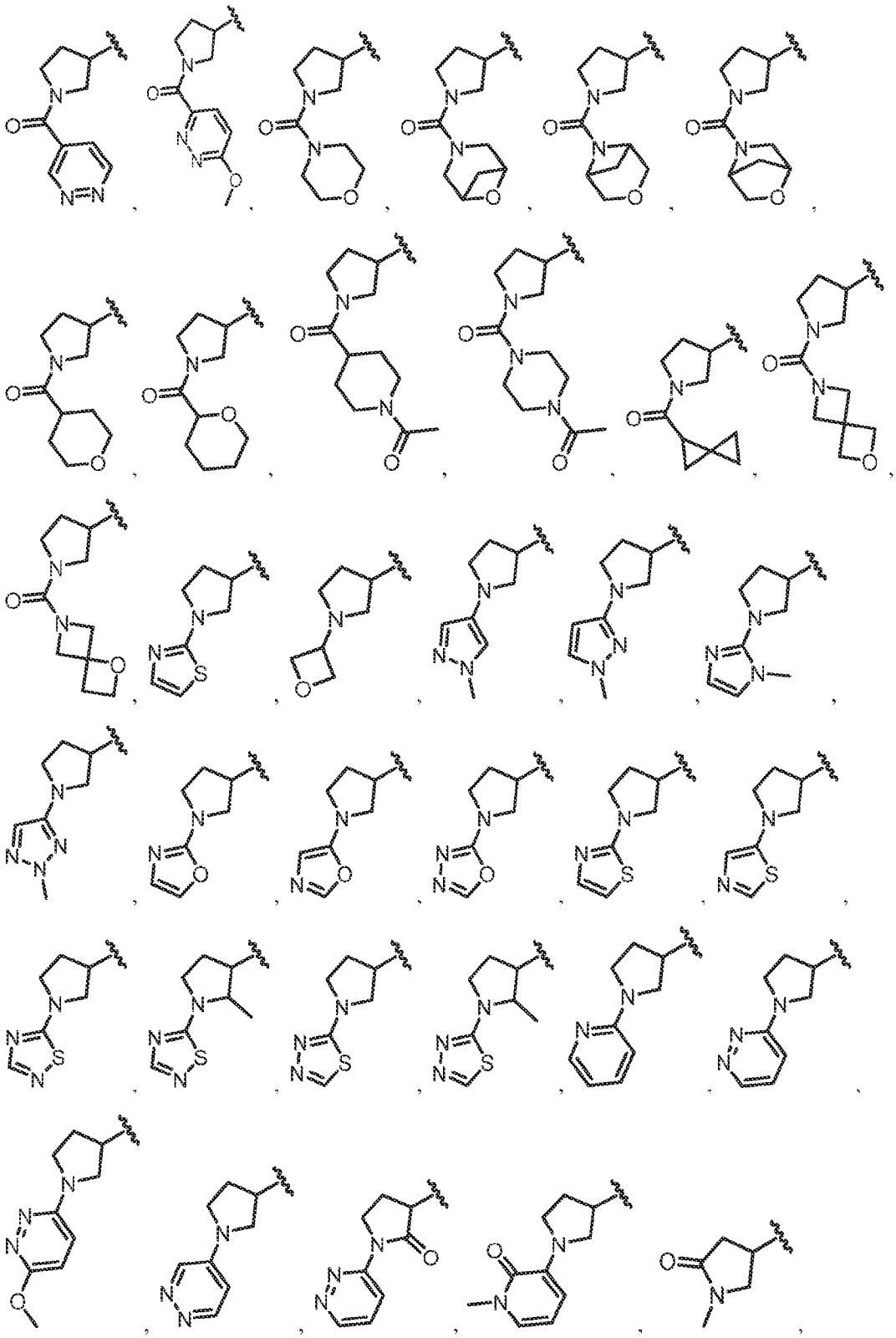


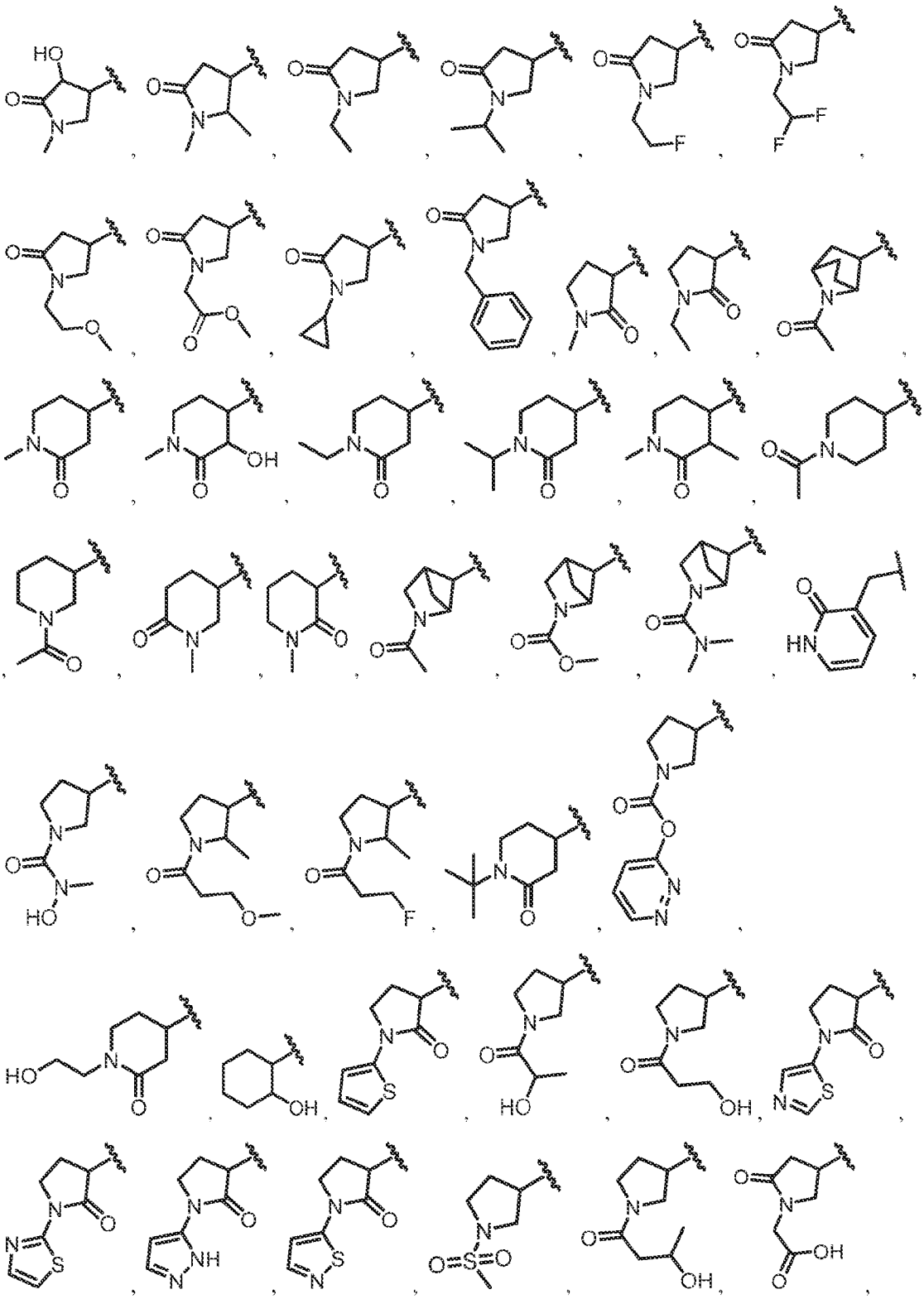


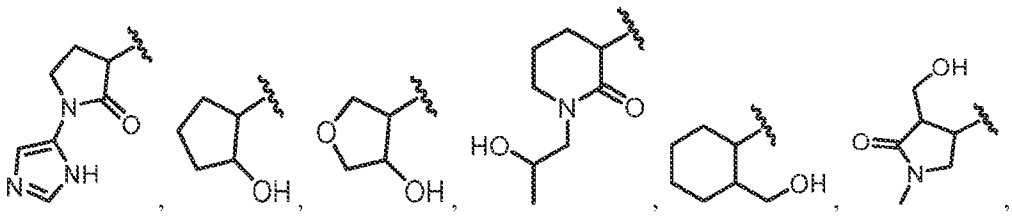


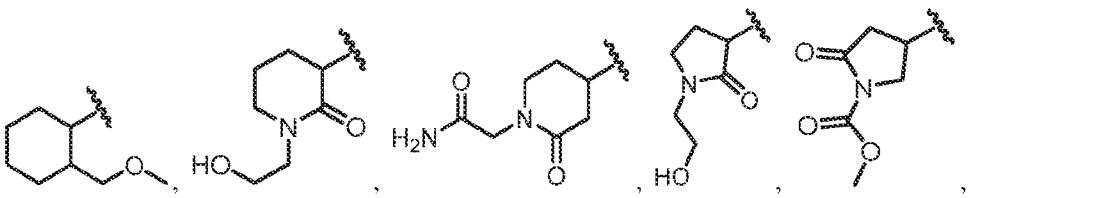


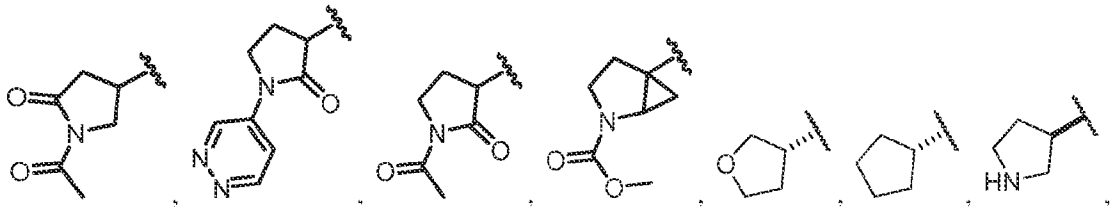


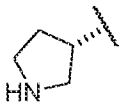




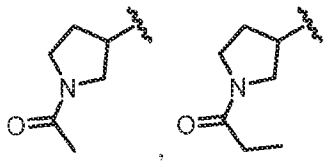


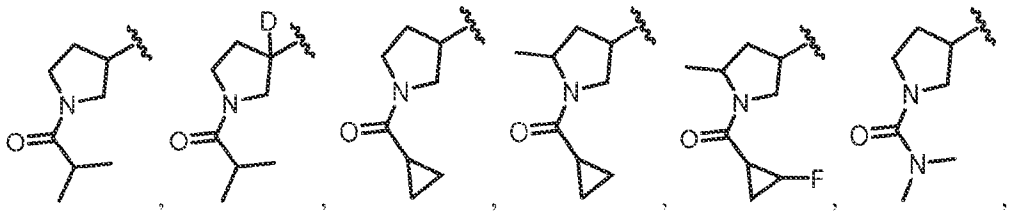


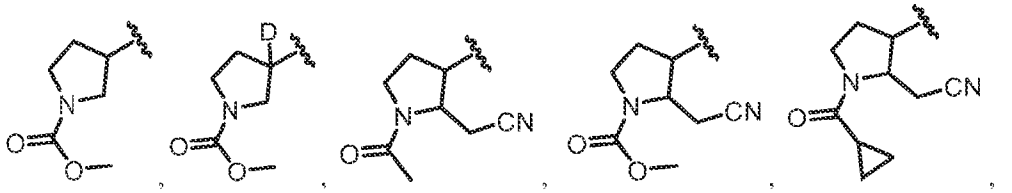


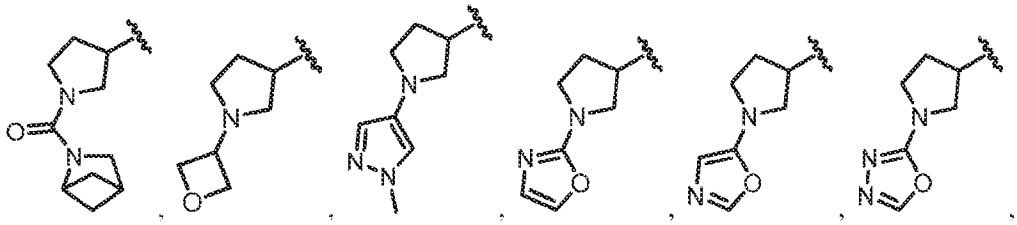


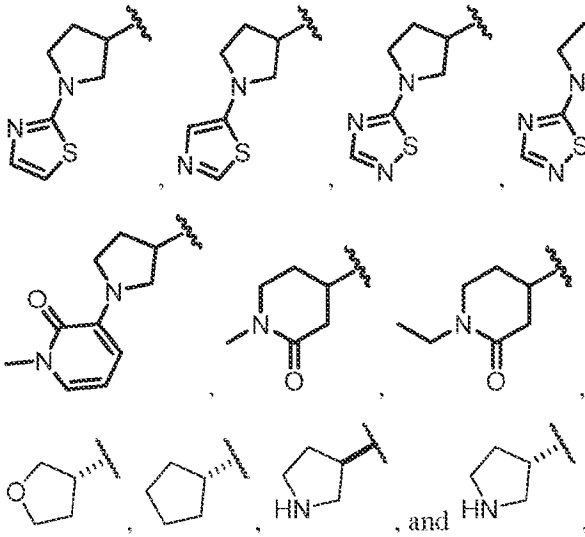
and , any of which is optionally further substituted with one or more R^{10}.

62. The compound of claim 61, wherein R^3 is selected from: 









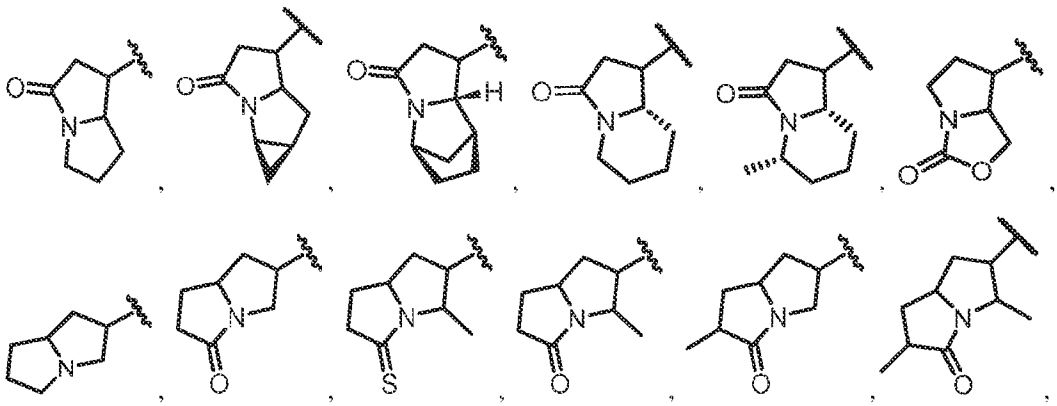
with one or more R^{10}.

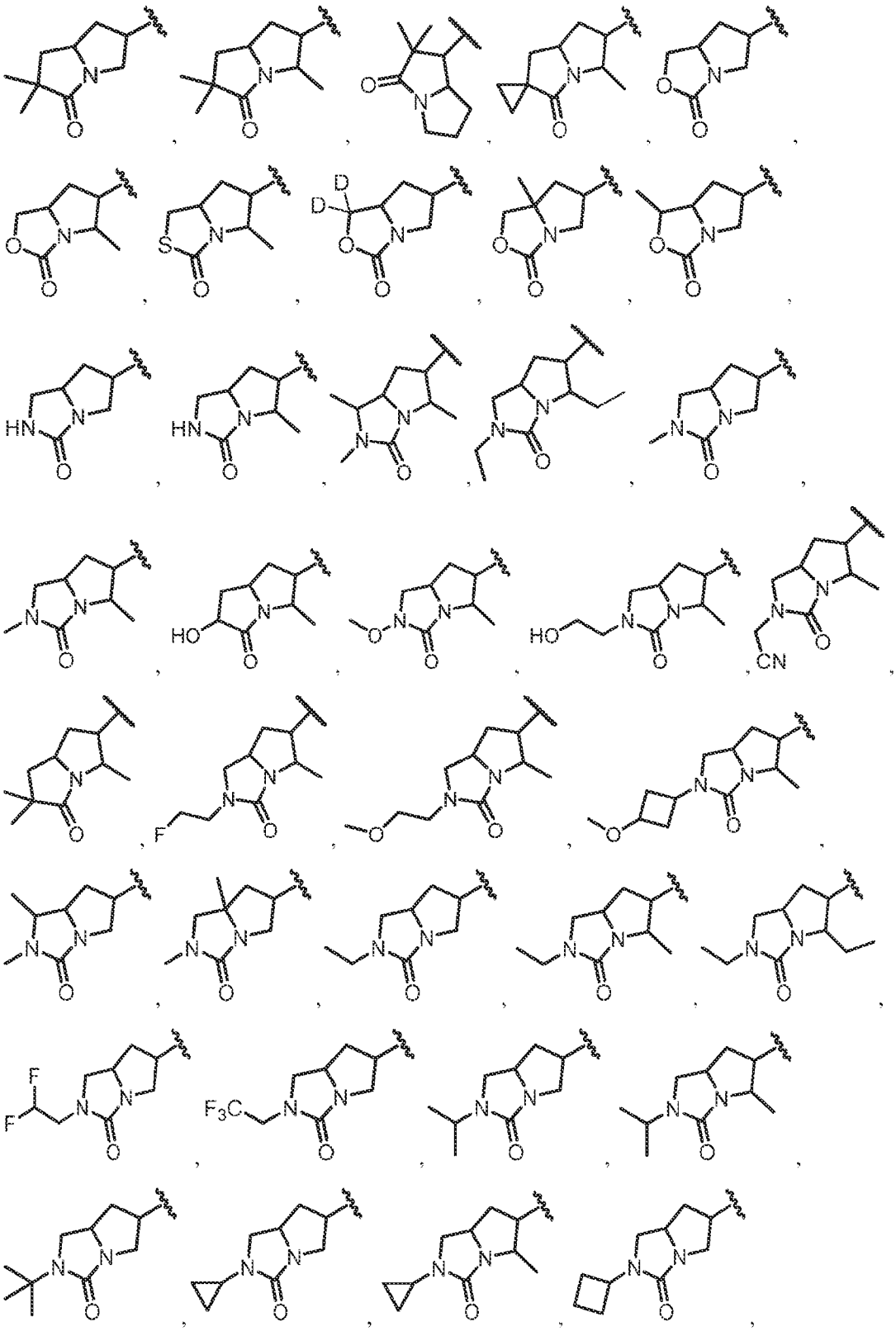
63. The compound of any one of claims 54-56, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

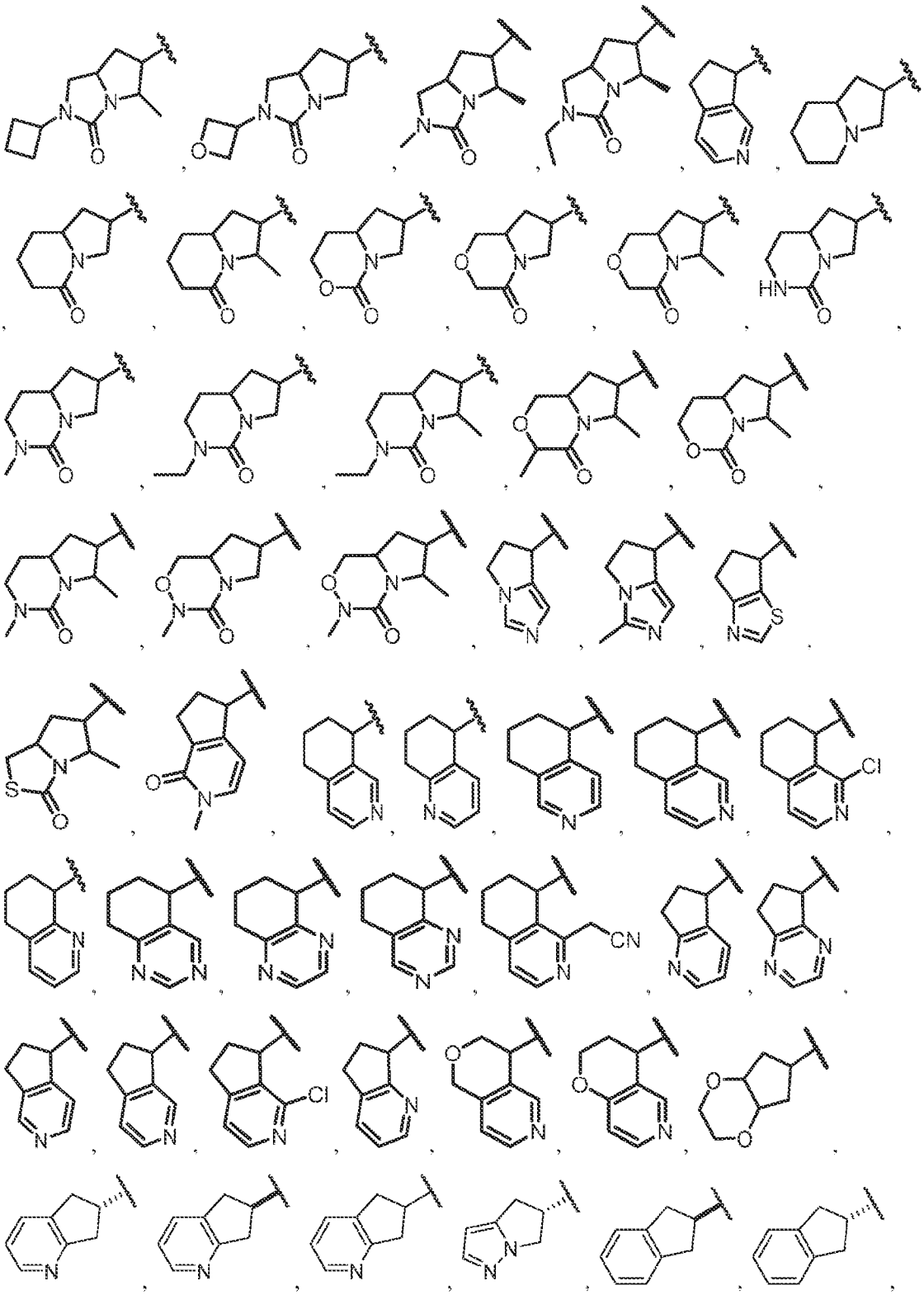
64. The compound of claim 63, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not comprise an –NH- moiety.

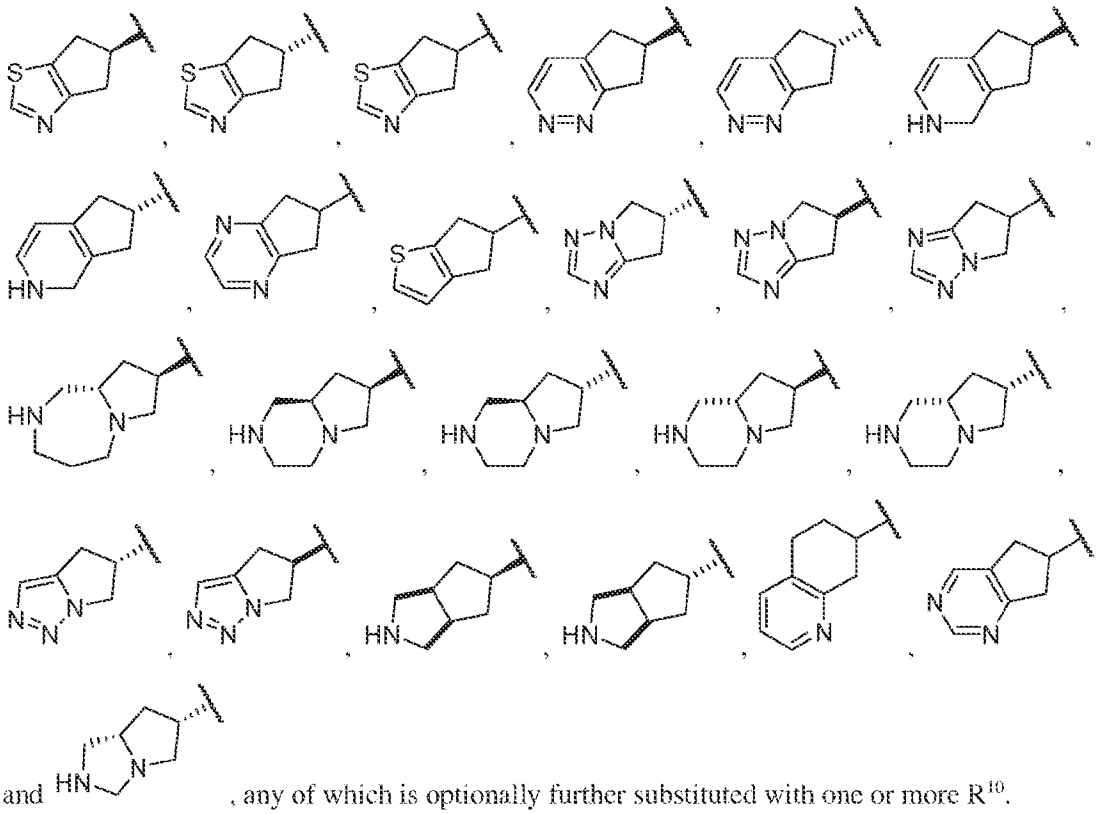
65. The compound of claim 63 or 64, wherein R^3 is a 7-10 membered heterocycle comprising a fused ring system that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

66. The compound of any one of claims 54-56 and 63-65, wherein R^3 is selected from: ,



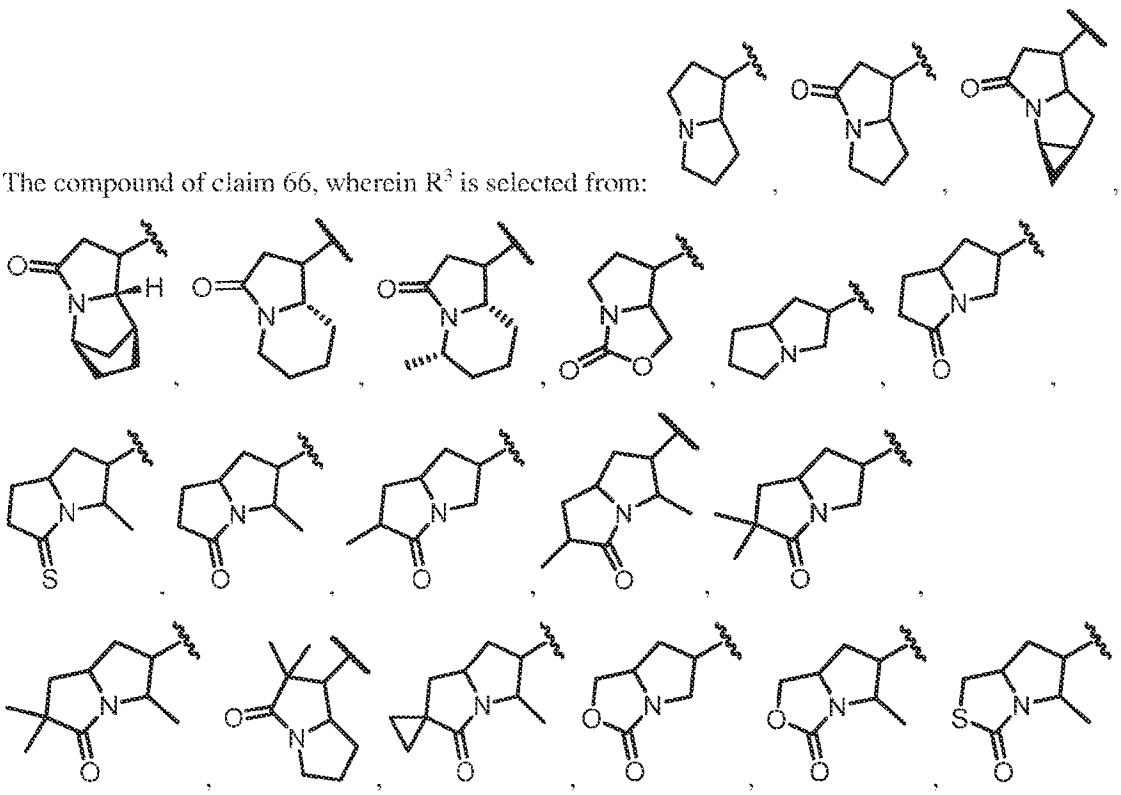


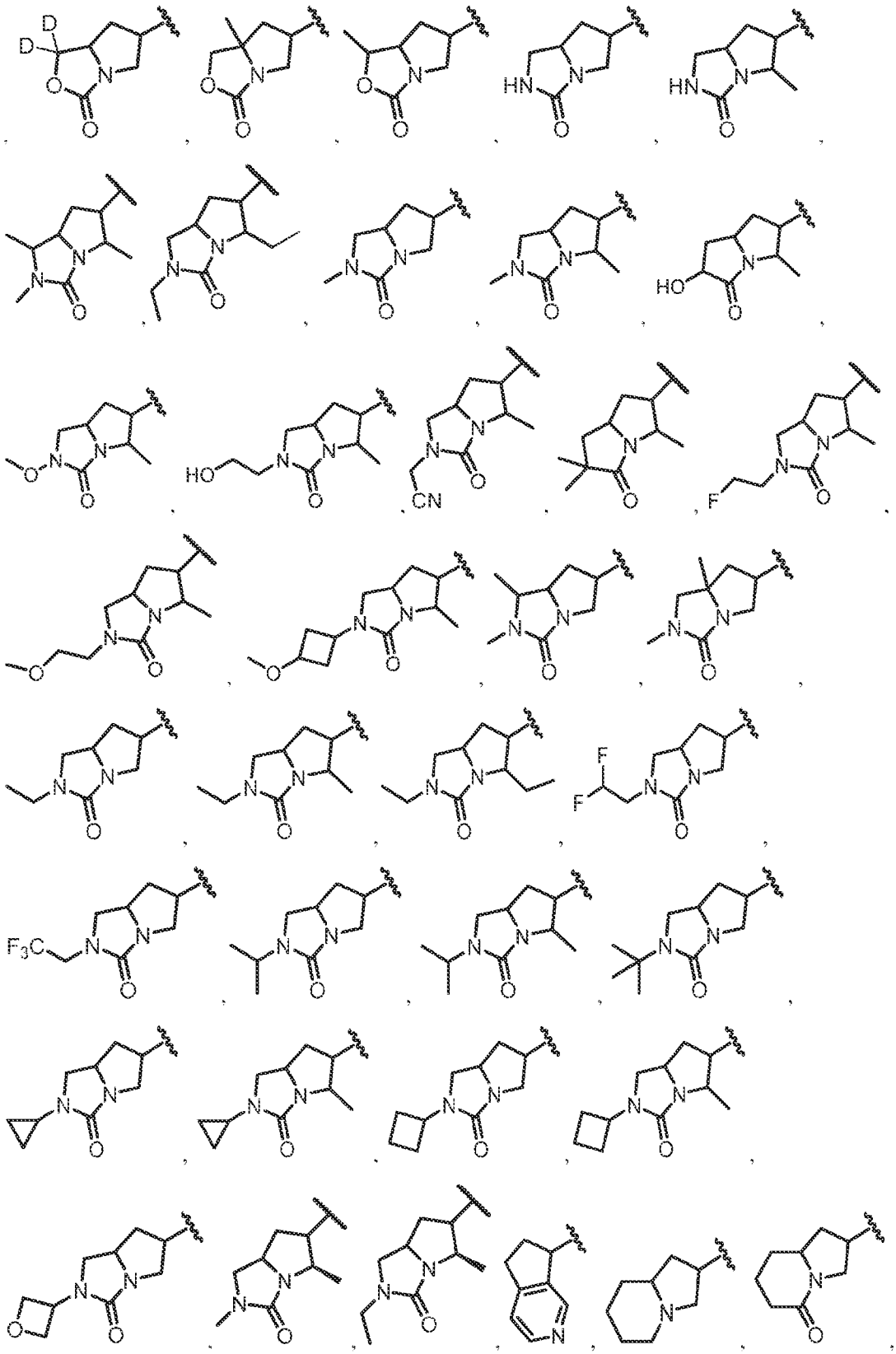


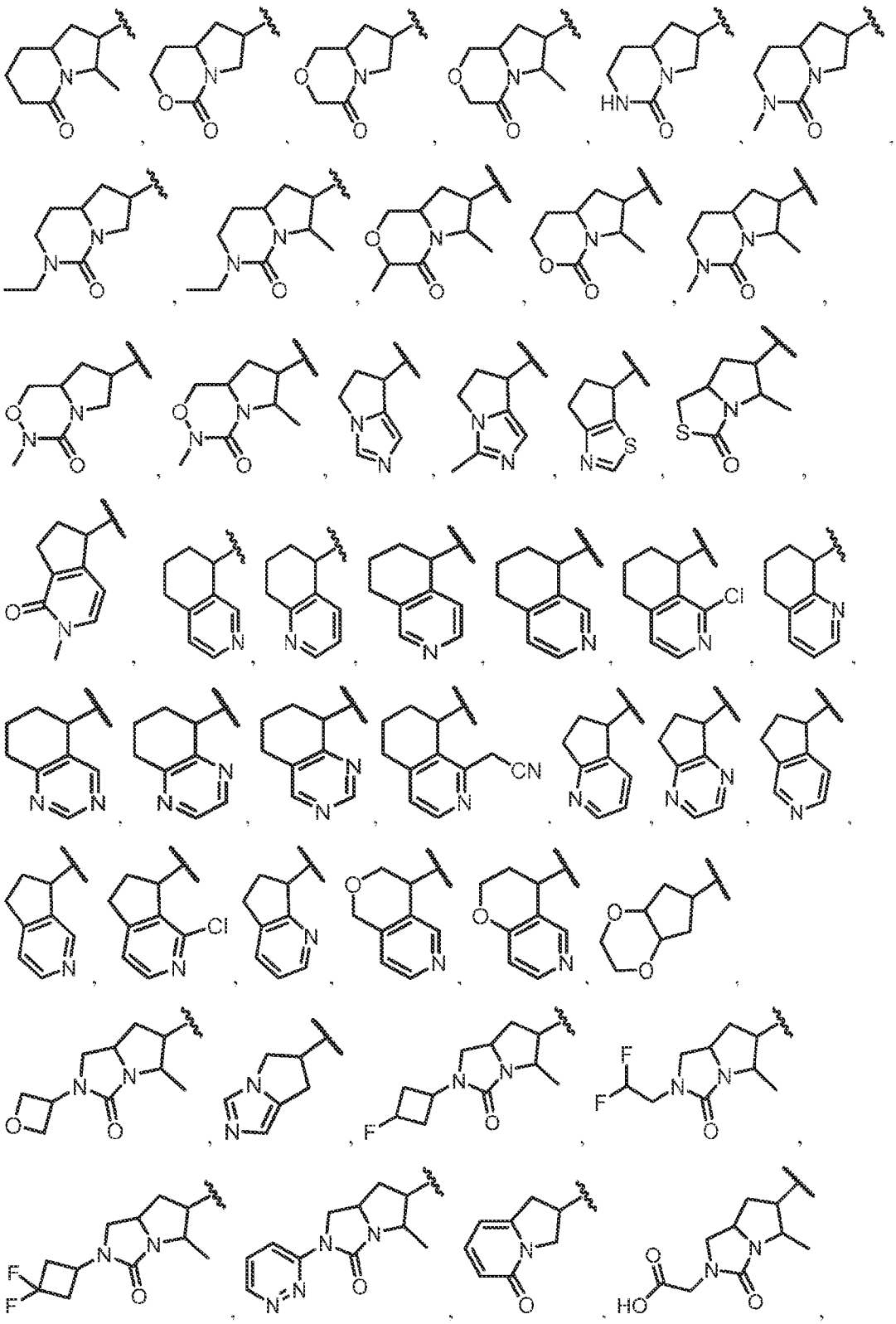


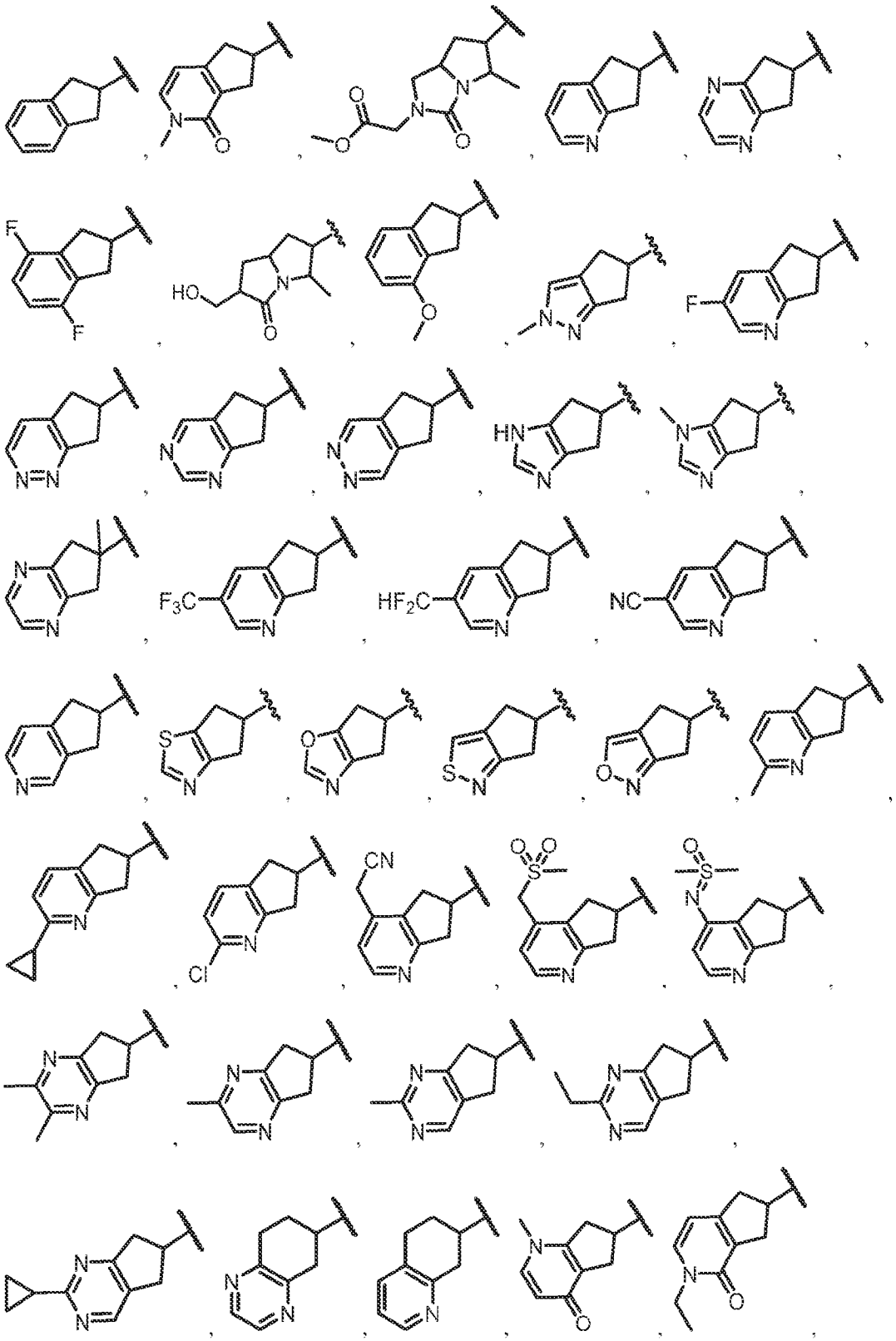
and , any of which is optionally further substituted with one or more R^{10}.

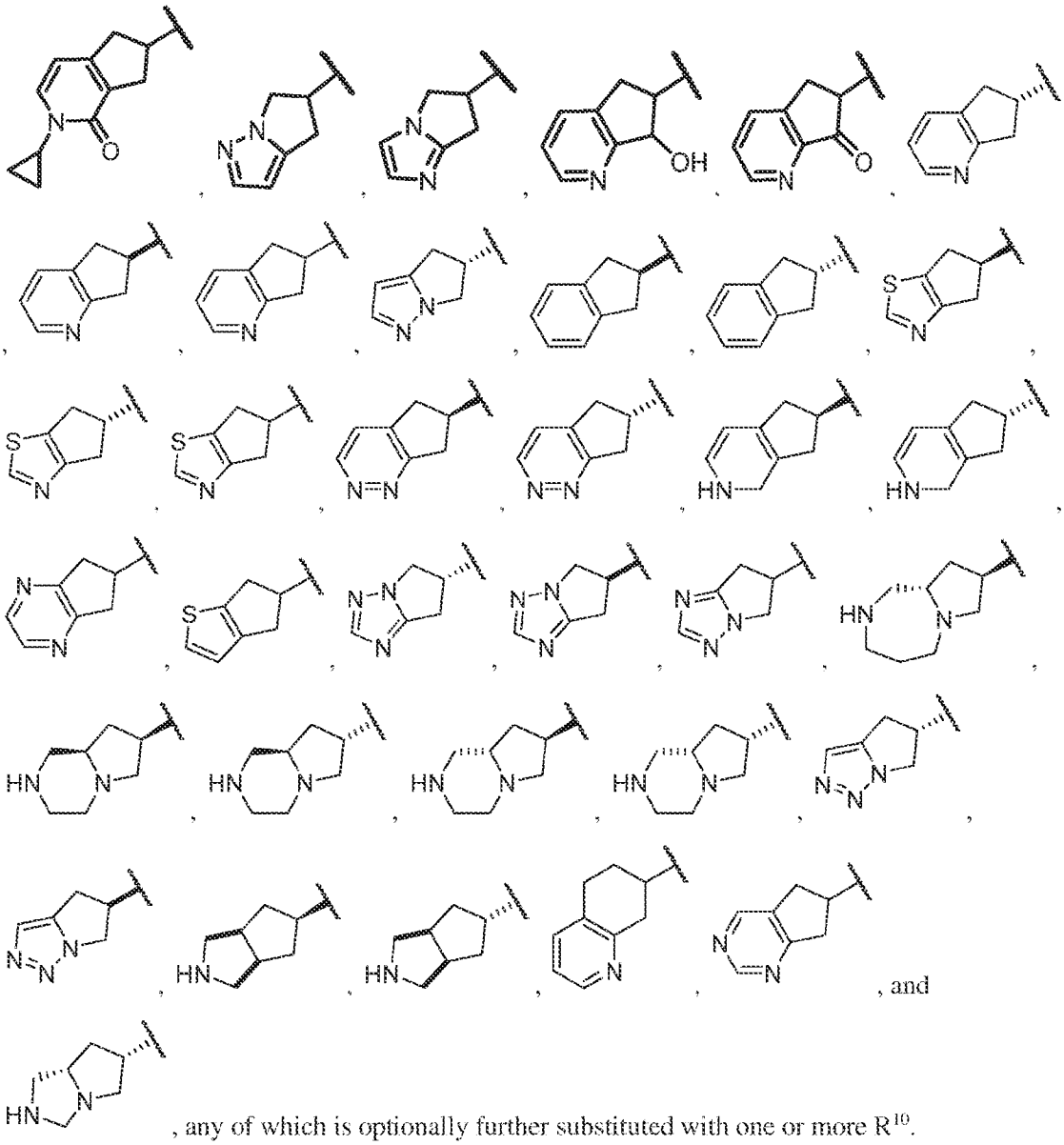
67. The compound of claim 66, wherein R^3 is selected from:





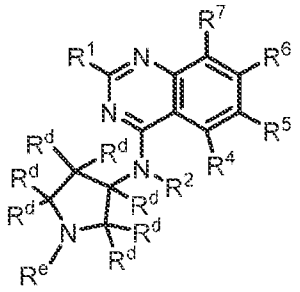
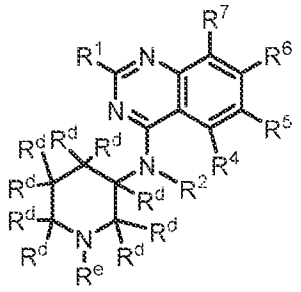
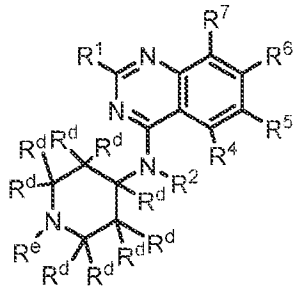
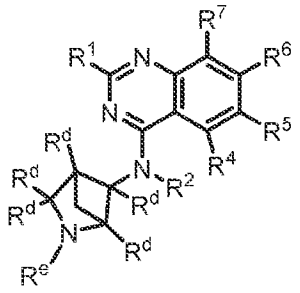






, any of which is optionally further substituted with one or more R^{10}.

68. The compound of any one of claims 54, 55, and 57-67, wherein the compound is a compound according to Formula IIR', IIU', IIV', or IIZ:

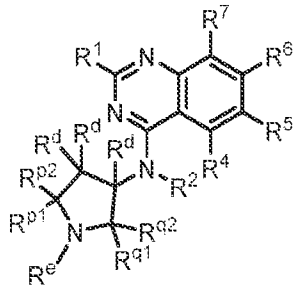

(IIR'),

(IIU'),

(IIV'), and

(IIZ),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^e is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

69. The compound of any one of claims 54, 55, and 57-67, wherein the compound is a compound according to Formula IIAA':



(IIAA'),

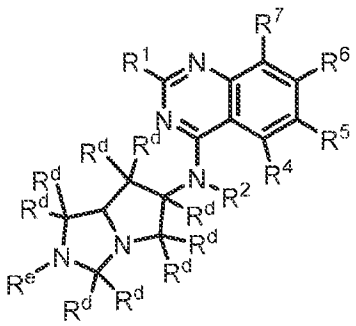
or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from deuterium, H, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)$(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, a 3-6 membered carbocycle, a 3-6 membered heterocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle or 3-6 membered heterocycle, is unsubstituted or substituted with one or more R^{12} or R^{20}; and

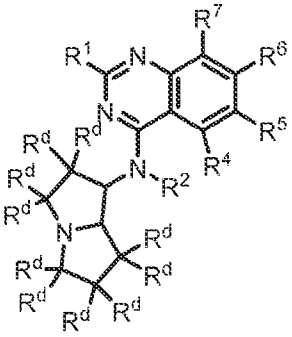
(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

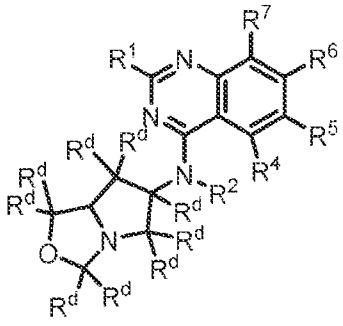
70. The compound of any one of claims 54, 55 and 69, wherein the compound is a compound according to Formula IIBB, IICC, IIDD, IIEE, IIFF, IIGG, IIHH, or IIJJ:



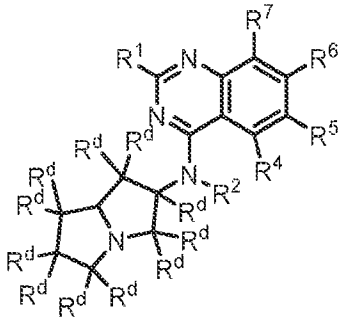
(IIBB),



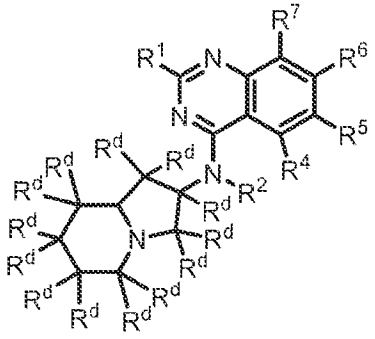
(IICC),



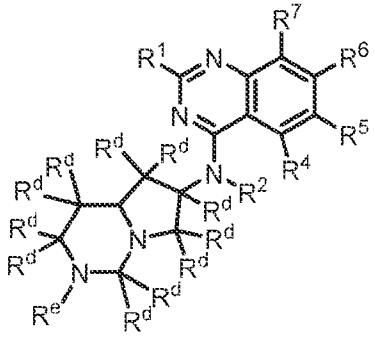
(IIDD),



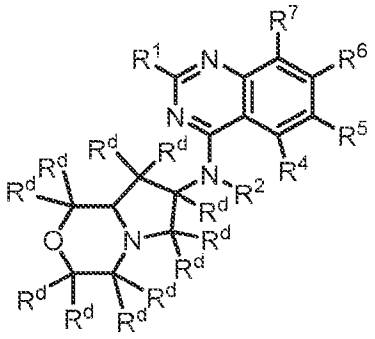
(IIEE),



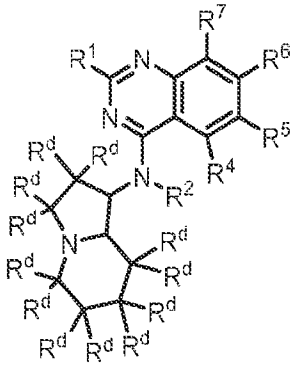
(IIFF),



(IIGG),



(IIHH), and



(IIJJ),

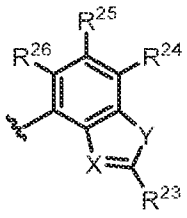
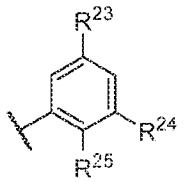
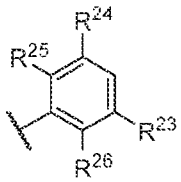
or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}; and

R^e, if present, is selected from $-C(O)(C_{1-6}alkyl)CN$, $-C(O)(C_{1-6}alkyl)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or

substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

71. The compound of any one of claims 54, 55, and 57-70, wherein R^6 is selected from:

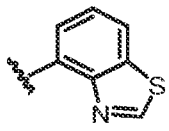


, or

, wherein:

X is selected from N and C-CN;

Y is selected from O, S, and Se;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

72. The compound of claim 71, wherein R^6 is selected from:

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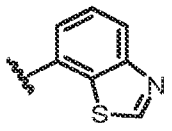
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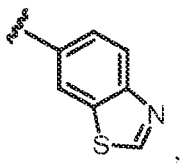
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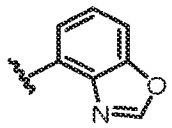
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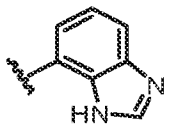
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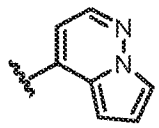
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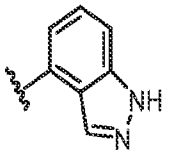
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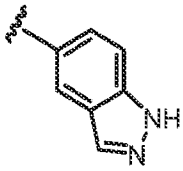
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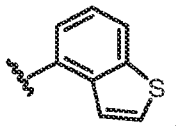
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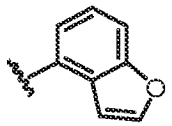
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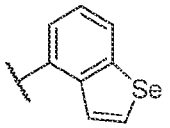
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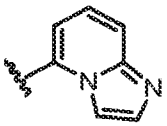
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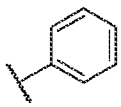
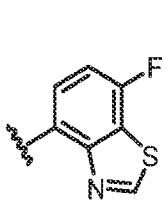

any of which is substituted with one or more R^{15}.

73. The compound of claim 71 or 72, wherein R^6 is selected from:

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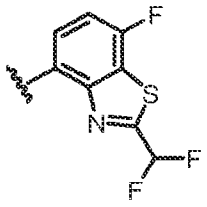
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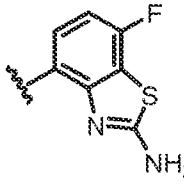
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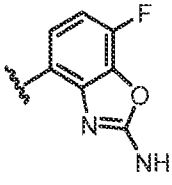
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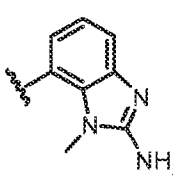
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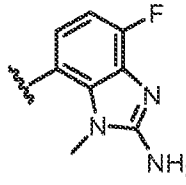
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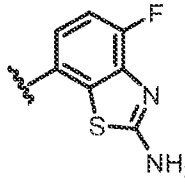
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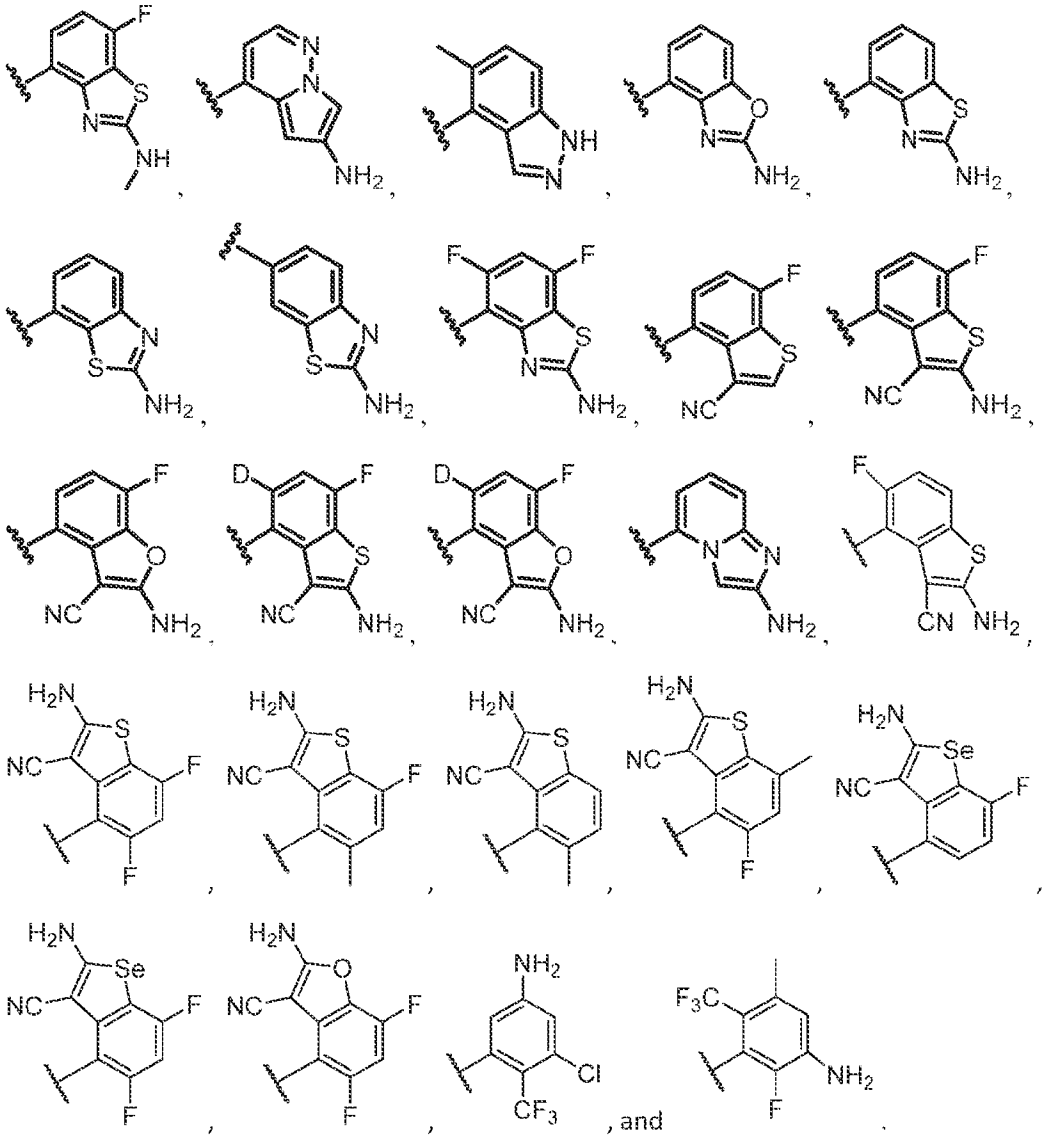
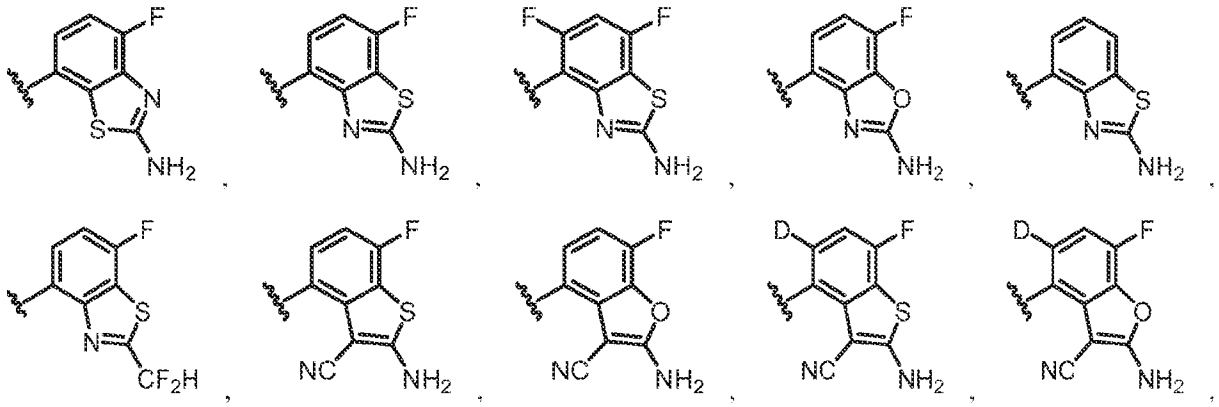
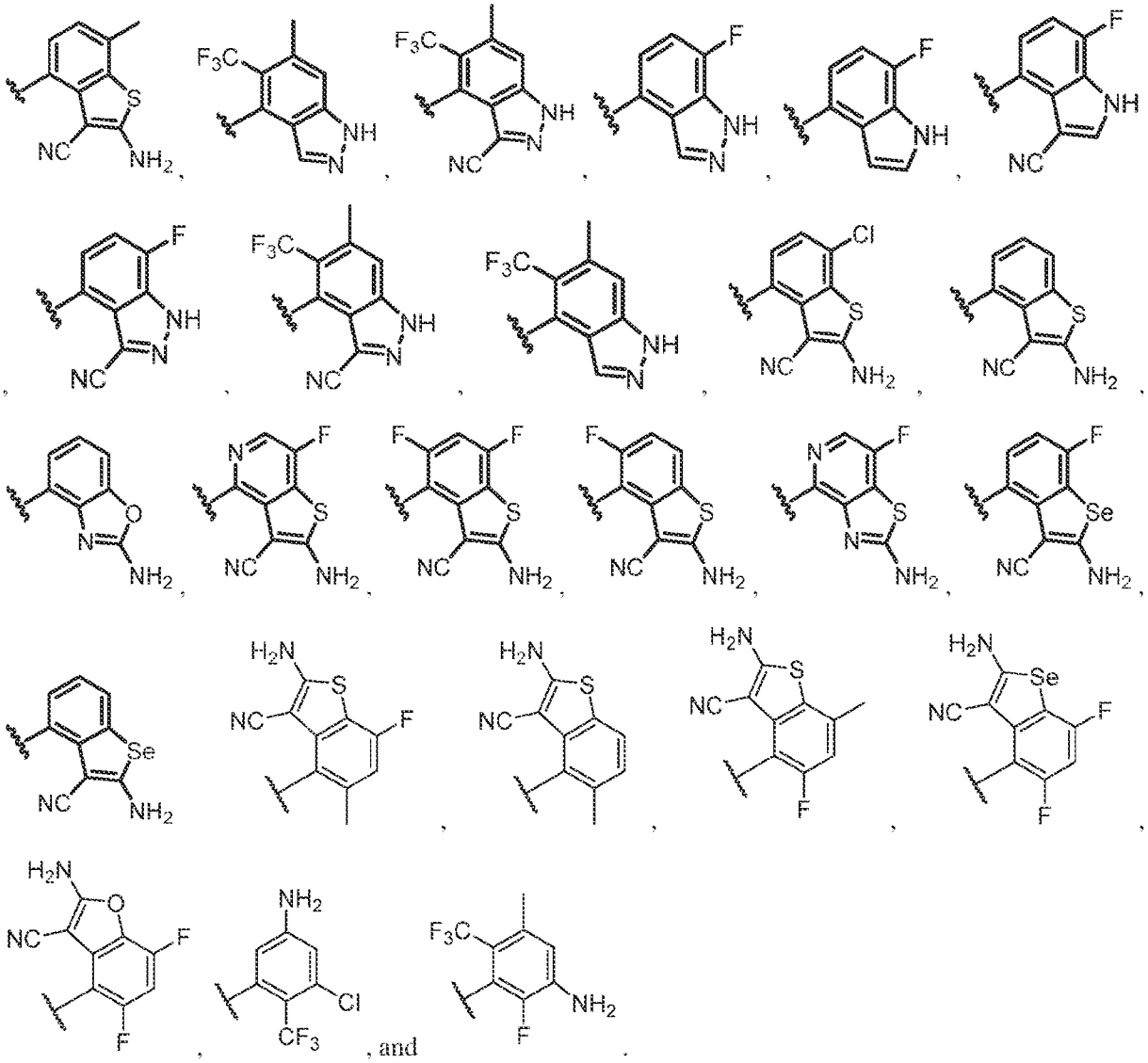
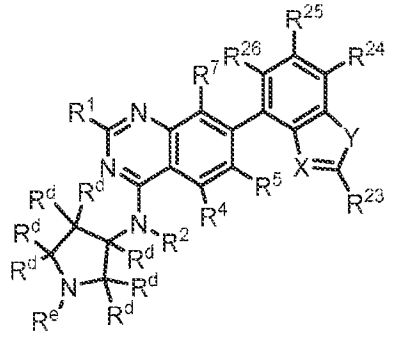


74. The compound of any one of claims 71-73, wherein R^6 is selected from:

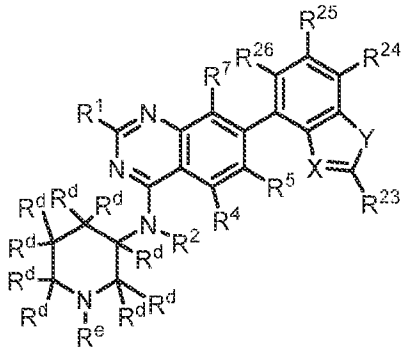




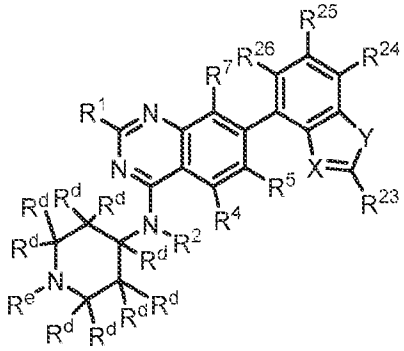
75. The compound of any one of claims 54, 55, and 57-70, wherein the compound is a compound according to Formula IIR1', IIU1', IIV1', or IIZ1:



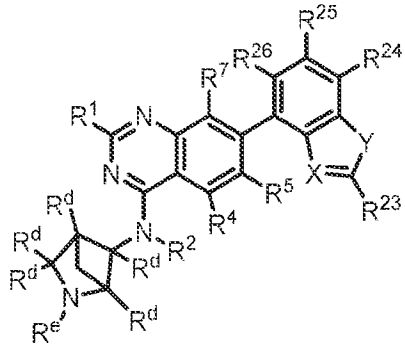
(IIR1'),



(IIU1'),



(IIV1'),



(IIZ1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, -C(O)(3-6 membered carbocycle), $-S(O)_2(C_{1-6}alkyl)$, halogen, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e is selected from $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)O(C_{1-6}alkyl)$, $-C(O)N(R^{14})_2$, $-C(O)OR^{14}$, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), $-C(O)O(C_{1-6}alkylene)$(3-6 membered heterocycle), $-S(O)_2(C_{1-6}alkyl)$, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and $C_{1-6}alkyl$, wherein any $C_{1-6}alkyl$ is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

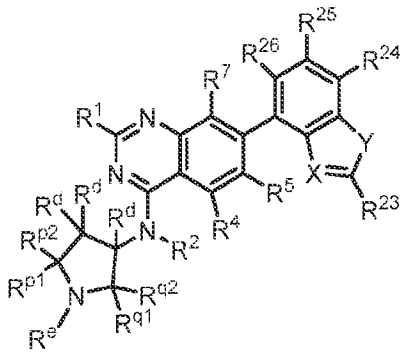
X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, $C_{1-6}alkyl$, and $C_{1-6}alkyl$-$N(R^{14})_2$, wherein any $C_{1-6}alkyl$ is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

76. The compound of any one of claims 54, 55, and 57-70, wherein the compound is a compound according to Formula IIAA1':



(IIAA1'),

or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, $-OR^{12}$, =O, $-C(O)(C_{1-6}alkylene)CN$, $-C(O)(C_{1-6}alkylene)OH$, $-C(O)(C_{1-6}alkyl)$, $-C(O)$(3-6 membered carbocycle), $-C(O)N(R^{14})_2$, $-S(O)_2(C_{1-6}alkyl)$, a 3-6 membered carbocycle, a 3-6 membered heterocycle, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle or 3-6 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

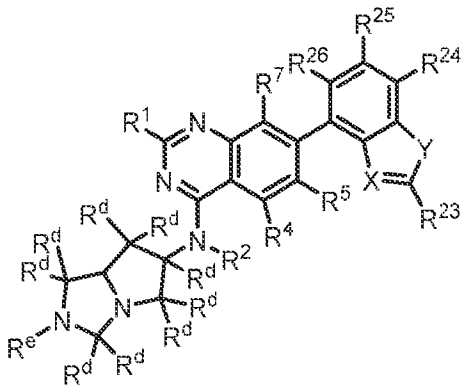
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

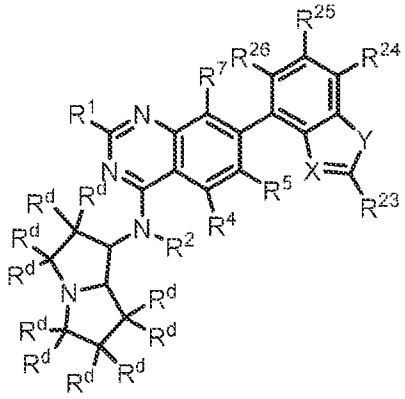
(i) R^{q1}, R^{q2}, and R^{p2} are each independently selected from R^d, and R^e and R^{p1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d; or

(ii) R^{p1}, R^{p2}, and R^{q2} are each independently selected from R^d, and R^e and R^{q1}, together with the atoms to which they are attached, form a 5-6 membered heterocycle that is unsubstituted or is substituted with one or more R^d.

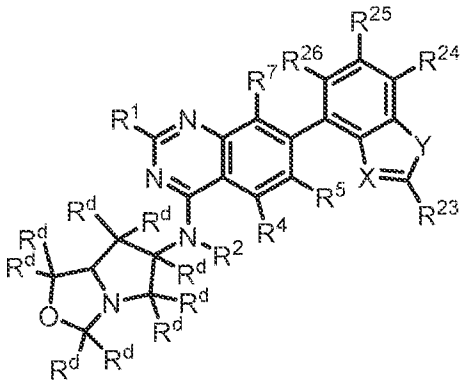
77. The compound of claim 76, wherein the compound is a compound according to Formula IIBB1, IICC1, IIDD1, IIEE1, IIFF1, IIGG1, IIHH1, or IIJJ1:



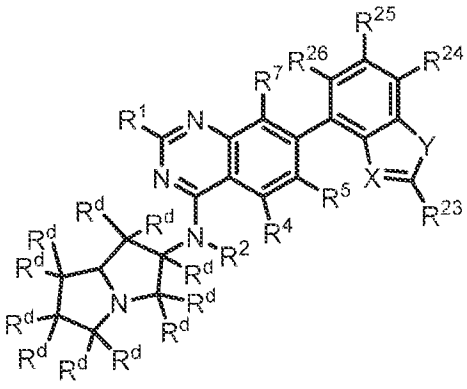
(IIBB1),



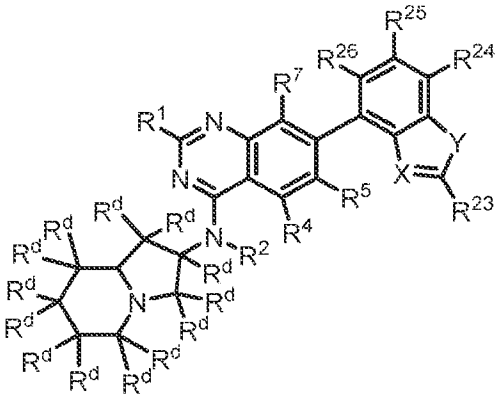
(IICC1),



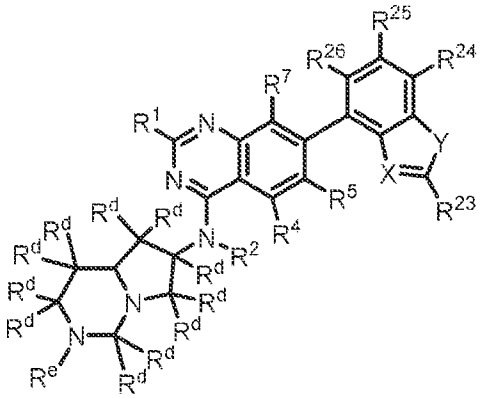
(IIDD1),



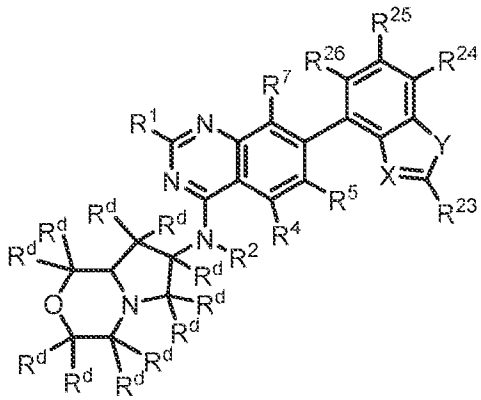
(IIEE1),



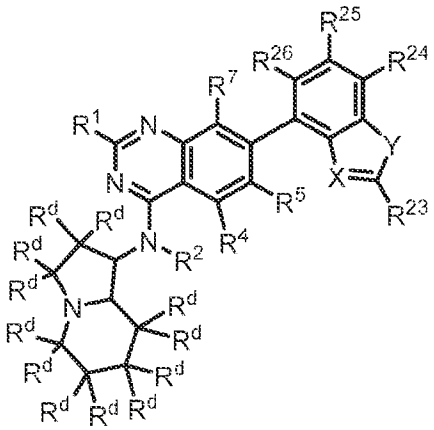
(IIFF1),



(IIGG1),



(IIHH1), and



(IIJJ1),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

each R^d is independently selected from H, deuterium, -OR^{12}, =O, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)$N(R^{14})_2$, -C(O)(3-6 membered carbocycle), -S(O)$_2$(C_{1-6}alkyl), halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

R^e, if present, is selected from -C(O)(C_{1-6}alkyl)CN, -C(O)(C_{1-6}alkyl)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)$N(R^{14})_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteraryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -S(O)$_2$(C_{1-6}alkyl), a 5-6 membered heteroaryl, a 3-6 membered carbocycle, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

78. The compound of any one of claims 75-77, wherein X is C-CN, Y is S, and R^{23} is -$N(R^{12})_2$.

79. The compound of any one of claims 75-78, wherein one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

80. The compound of any one of claims 68-79, wherein R^e is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{20}.

81. The compound of any one of claims 68-79, wherein R^e is -C(O)(3-6 membered carbocycle).

82. The compound of any one of claims 68-79, wherein R^e is selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), and -C(O)O(C_{1-6}alkyl), wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

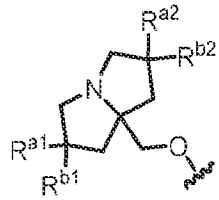
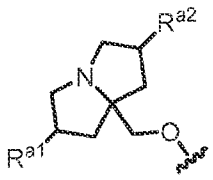
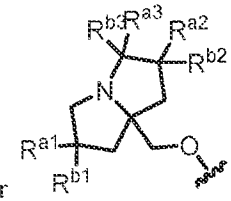
83. The compound of any one of claims 68-82, wherein each R^d is H.

84. The compound of any one of claims 54-83, wherein R^2 is H.

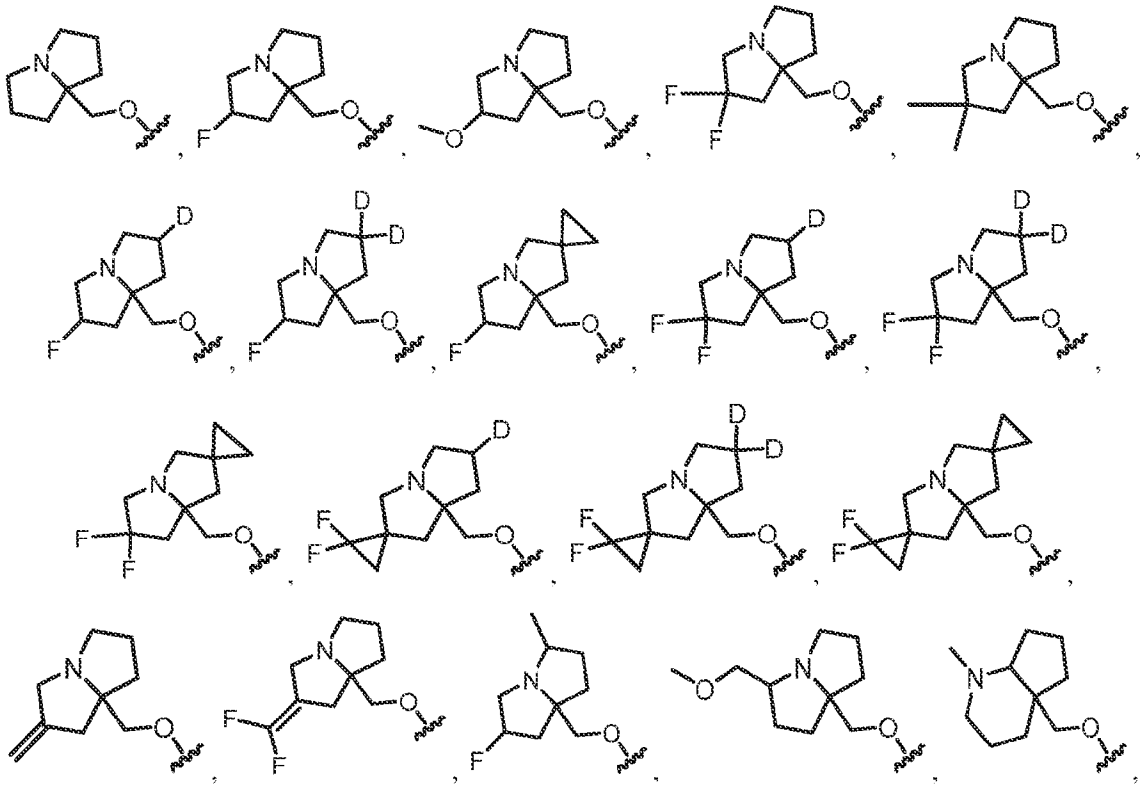
85. The compound of any one of claims 54-84, wherein R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated.

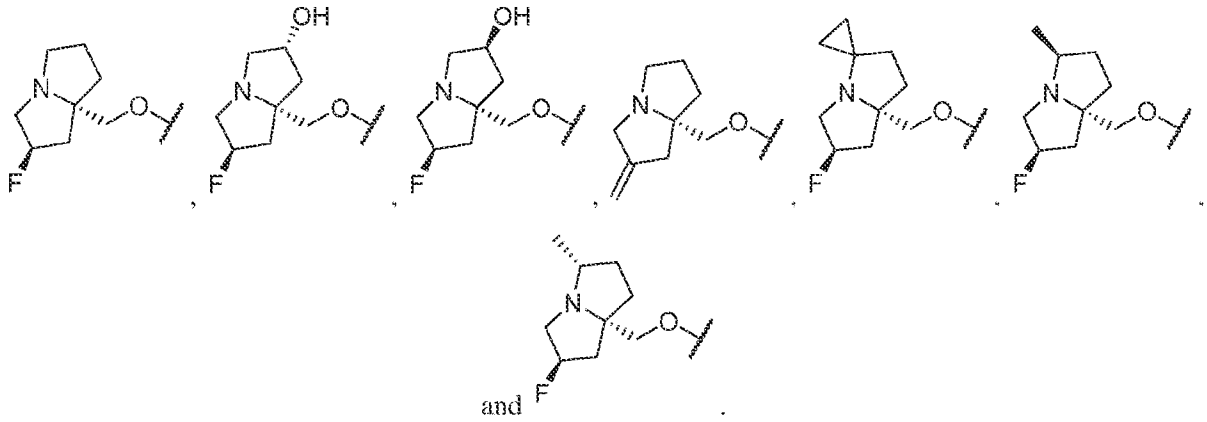
86. The compound of claim 85, wherein R^2 is selected from C_{1-3}alkyl and is optionally deuterated.

87. The compound of any one of claims 54, 55, and 57-86, wherein R^1 is selected from $-OR^8$.

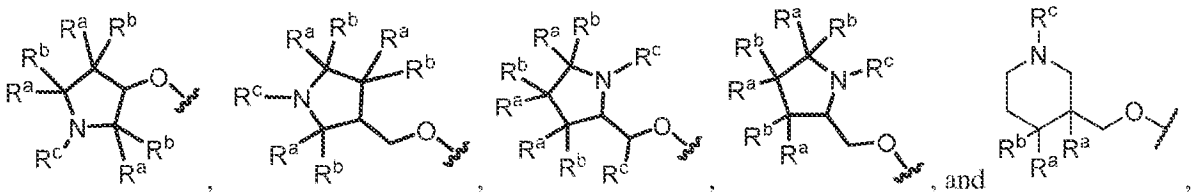
88. The compound of claim 87, wherein R^1 is selected from:  ,  ,  , or , R^{a1}, R^{a2}, R^{b1}, R^{b2}, R^{a3}, and R^{b3} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, , $-C_{1-6}$ heteroalkyl, $-OR^{12}$, and H, wherein R^{a2} and R^{b2} or R^{a3} and R^{b3} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}.

89. The compound of claim 88, wherein R^1 is selected from:



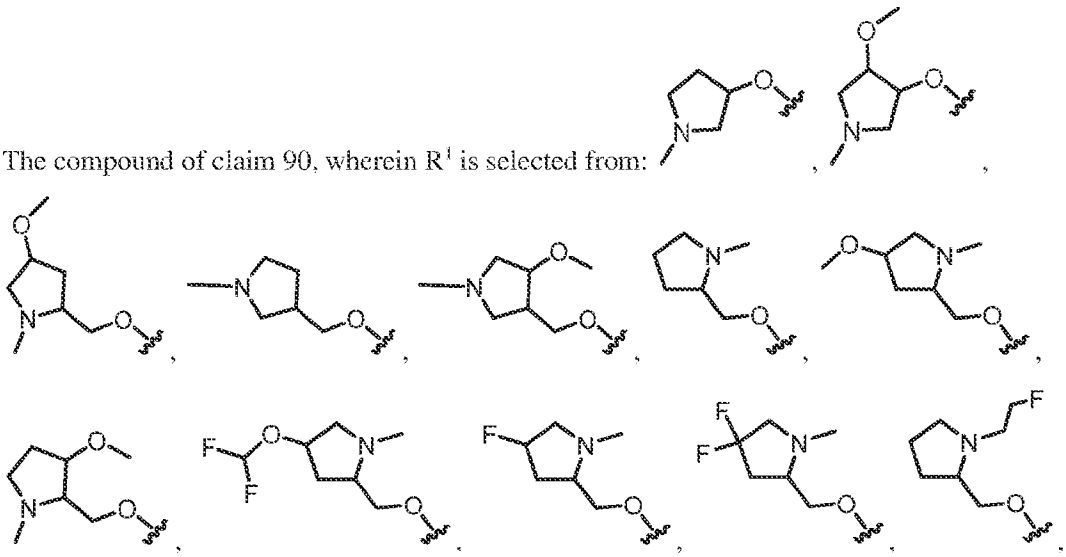


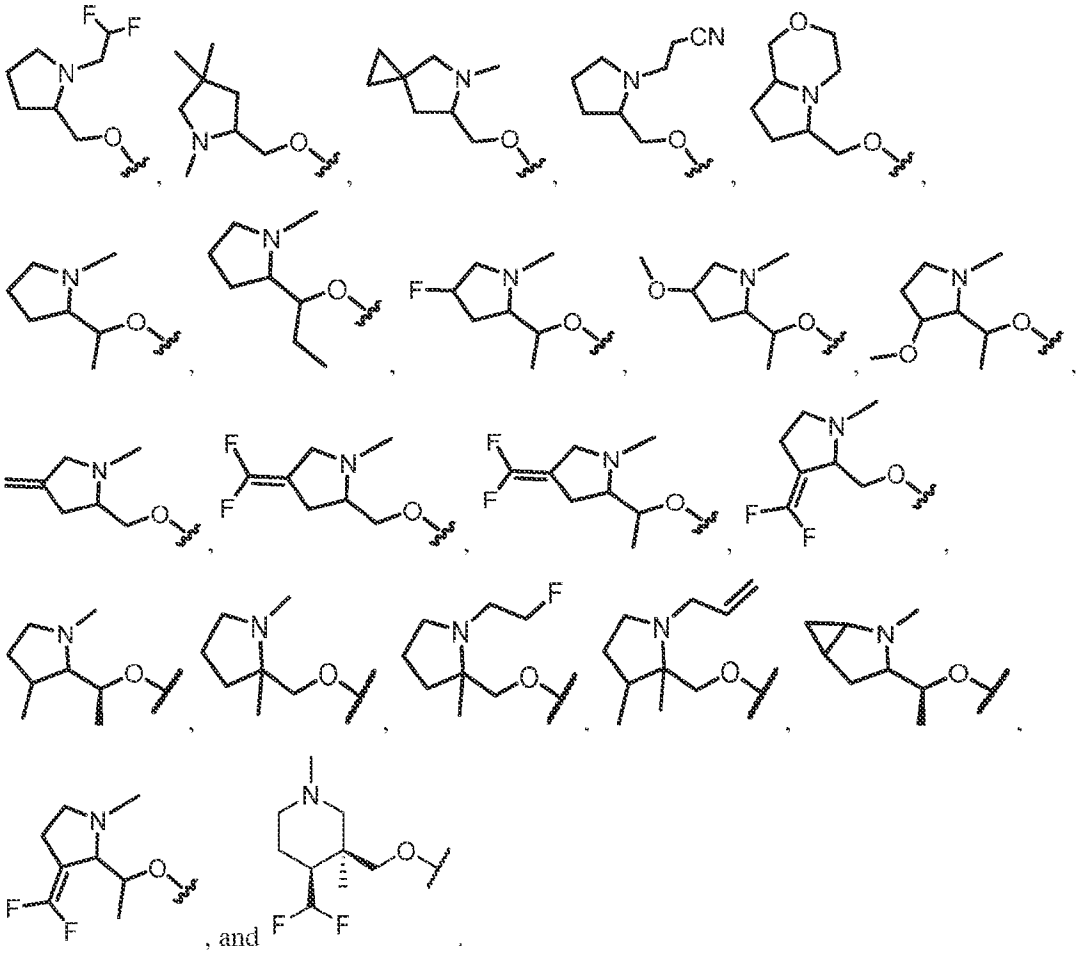
90. The compound of claim 87, wherein R^1 is selected from:



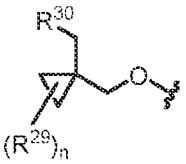
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H; and each R^c is independently selected from C_{1-6} alkyl and H, wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

91. The compound of claim 90, wherein R^1 is selected from:





92. The compound of any one of claims 54, 55, and 57-86, wherein R^1 is selected from



, wherein:

each R^{28} is independently selected from $C_{1\text{-}6}$alkyl and halogen; and

each R^{29} is independently selected from halogen and $C_{1\text{-}6}$alkyl;

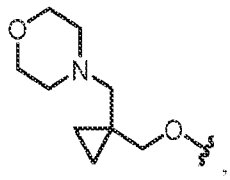
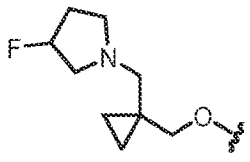
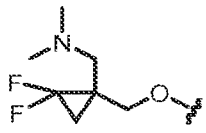
R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; and

n is 0-2.

93. The compound of claim 92, wherein R^{30} is $N(R^{14})_2$.

94. The compound of claim 92 or 93, wherein at least one R^{29} is a halogen such as F.

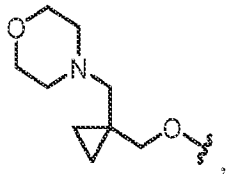
95. The compound of any one of claims 92-94, wherein R^1 is selected from:



, and 
.

96. The compound of any one of claims 54-86, wherein R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

97. The compound of claim 96, wherein R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

98. The compound of claim 96 or 97, wherein R^1 is selected from: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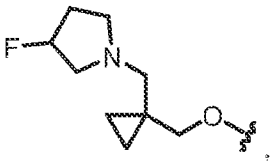
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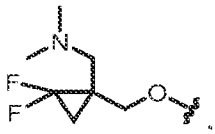
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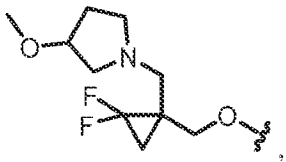
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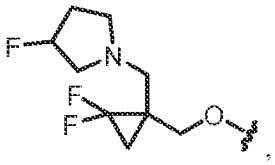
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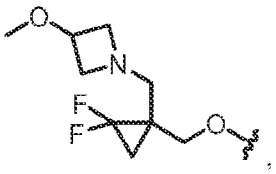
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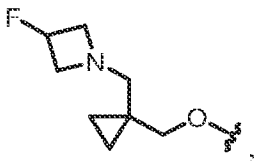
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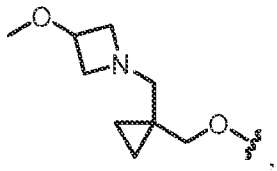
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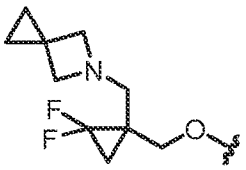
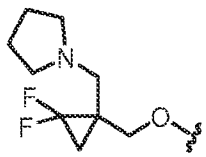

, and

.99.The compound of any one of claims 54, 55, and 57-86, wherein R^1 is H.

100. The compound of any one of claims 54, 55, and 57-99, wherein R^5 is a halogen (e.g., F or Cl).

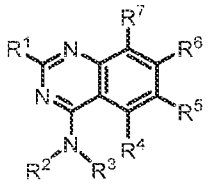
101. The compound of any one of claims 54, 55, and 57-99, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{43}.

102. The compound of claim 101, wherein R^5 is selected from - CH_3, -CF_2H, -CF_3, -CH_2CN, and -CH_2CH_3.

103. The compound of claim 102, wherein R^5 is -CF_3.

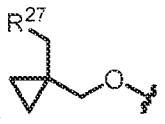
104. The compound of any one of claims 54-103, wherein the compound is not a compound included in Table 1.

105. A compound represented by Formula IV:



(IV)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from $-OR^8$ and  ;

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{15};

R^3 is selected from C_{1-6}alkyl that is substituted with one or more R^{10};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{15};

R^6 is a bicyclic heteroaryl substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{10} is independently selected from a 3-6 membered heterocycle, a 5-6 membered heteroaryl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13};

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

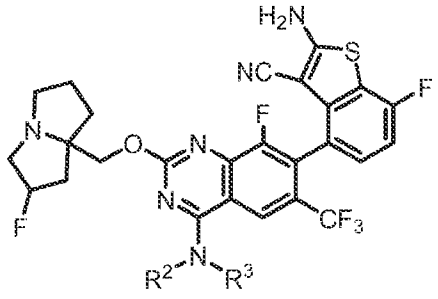
each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, and halogen;

R^{27} is a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{28} is independently selected from C_{1-6}alkyl and halogen; and

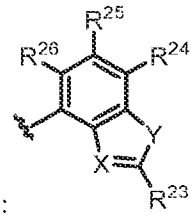
R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, -OR^{12}, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle.

106. The compound of claim 105, wherein the compound is of Formula IV-a:



(IV-a)

or a salt (e.g., pharmaceutically acceptable salt) thereof.



107. The compound of claim 105, wherein R^6 is selected from: , wherein:

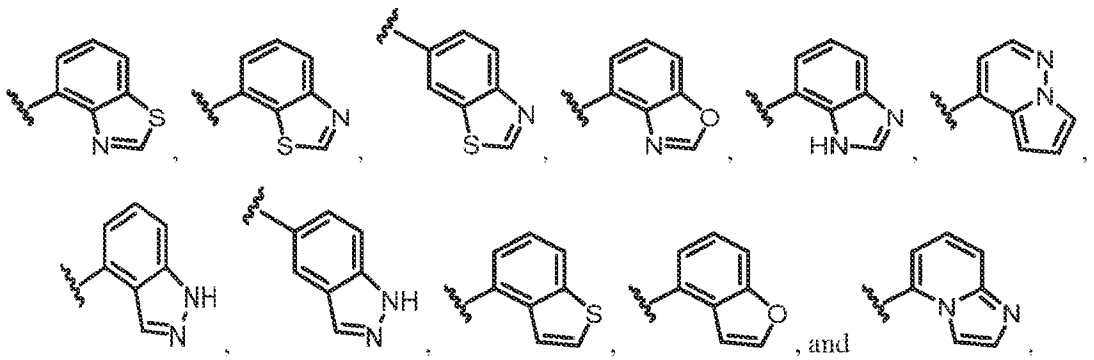
X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from -$N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

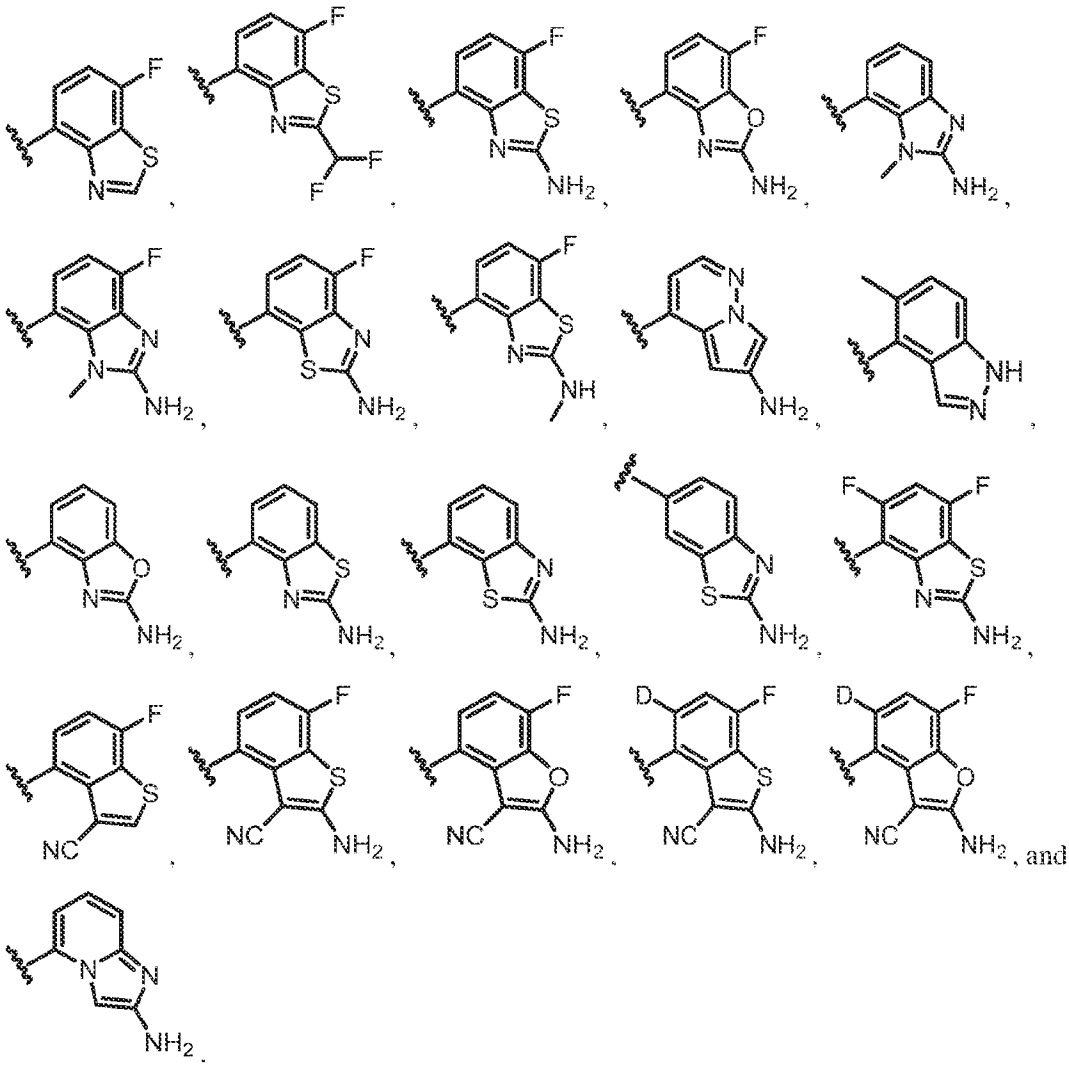
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

108. The compound of claim 105 or claim 107, wherein R^6 is selected from:

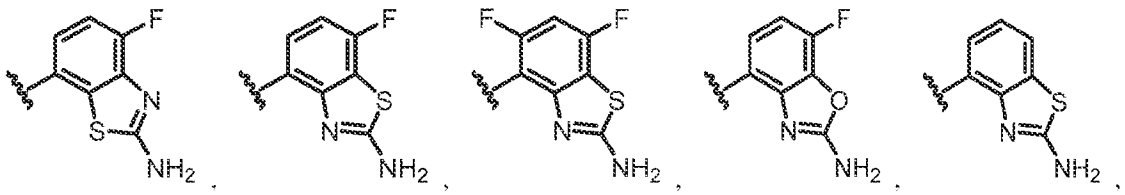


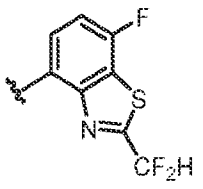
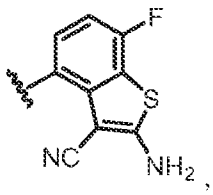
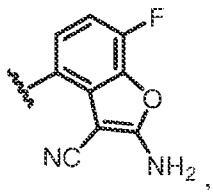
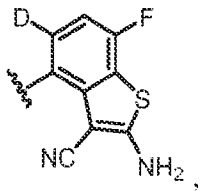
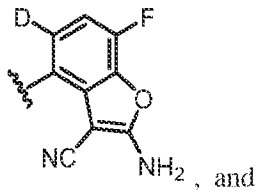
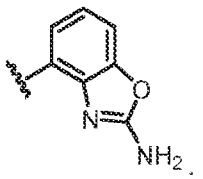
any of which is substituted with one or more R^{15}.

109. The compound of any one of claims 105, and 107-108, wherein R^6 is selected from:

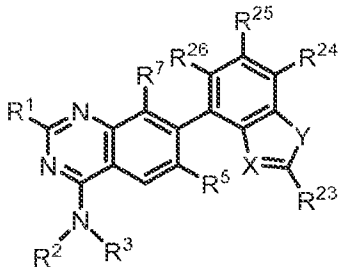


110. The compound of any one of claims 105, and 107-109, wherein R^6 is selected from:








, and

.

111. The compound of claim 105, wherein the compound is a compound according to Formula IVB:


(IVB),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

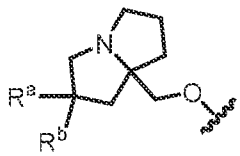
X is selected from N and C-CN;

Y is selected from O and S;

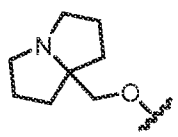
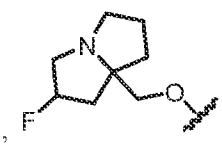
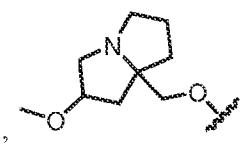
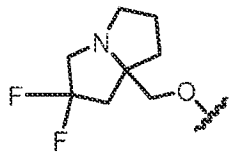
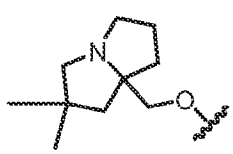
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

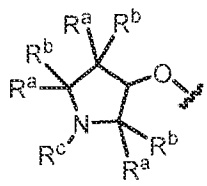
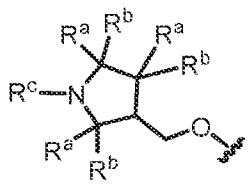
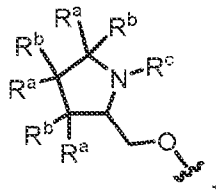
112. The compound of any one of claims 105, and 107-111, wherein R^1 is selected from $-OR^8$.

113. The compound of claim 112, wherein R^1 is selected from:  , wherein R^a and R^b are each independently selected from halogen, C_{1-6}alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13}.

114. The compound of claim 113, wherein R^1 is selected from:

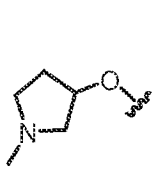
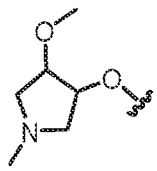




, and

.

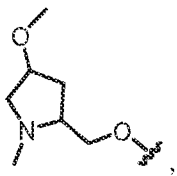
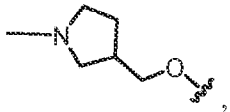
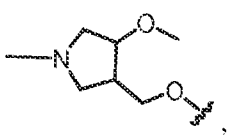
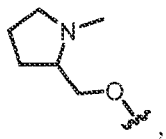
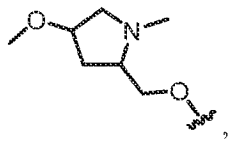
115. The compound of claim 112, wherein R^1 is selected from:

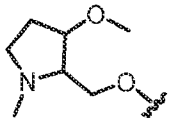
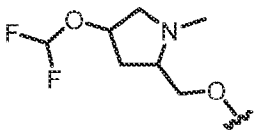
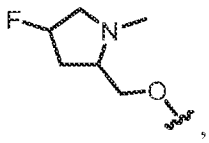
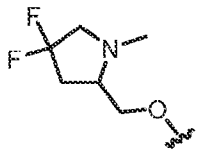
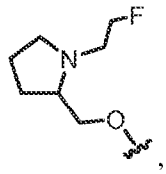




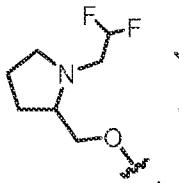
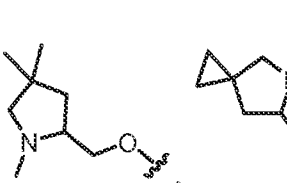
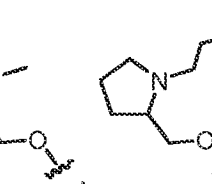
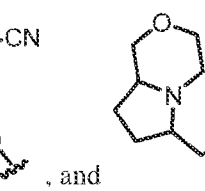
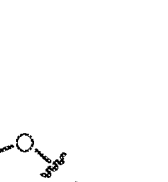
, and

wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H; and R^c is selected from C_{1-6} alkyl, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13}, and wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle.

116. The compound of claim 115, wherein R^1 is selected from:  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

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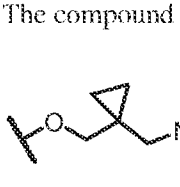
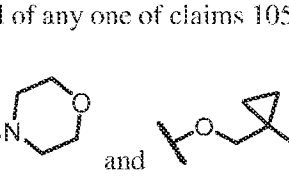
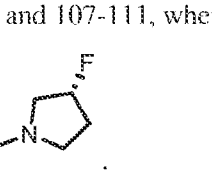
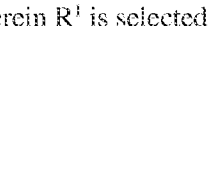
 ,  ,  ,  , ,

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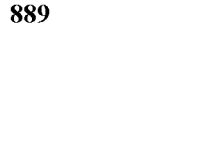
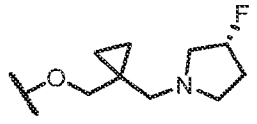
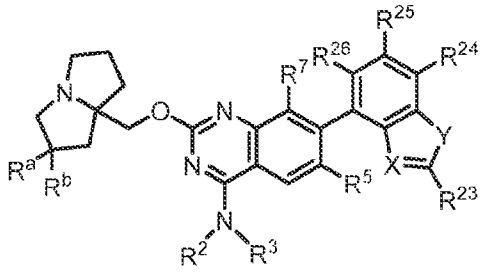
, ,  , , , and .

117. The compound of any one of claims 105, and 107-111, wherein R^1 is selected from

 and  .

118. The compound of claim 105, wherein the compound is a compound according to Formula IVC:



(IVC),

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^a and R^b are each independently selected from halogen, C_{1-6} alkyl, $-OR^{12}$, and H, wherein any C_{1-6}alkyl is unsubstituted or is substituted with one or more R^{13};

X is selected from N and C-CN;

Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

119. The compound of claim 118, wherein R^a is a halogen (e.g., F).

120. The compound of claim 118 or 119, wherein R^b is H.

121. The compound of any one of claims 111-120, wherein X is C-CN, Y is S, and R^{23} is selected from $-N(R^{12})_2$.

122. The compound of any one of claims 111-121, wherein at least one of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

123. The compound of any one of claims 105-122, wherein R^3 is selected from C_{1-3}alkyl that is substituted with one or more R^{10}.

124. The compound of claim 123, wherein each R^{10} is independently selected from 3-6 membered heterocycle and a 5-6 membered heteroaryl, wherein any 3-6 membered heterocycle or 5-6 membered heteroaryl is unsubstituted or substituted with one or more =O, R^{12}, or R^{13}.

125. The compound of claim 124, wherein each R^{10} is independently selected from thiazole, oxazole, isoxazole, isothiazole, pyrazole, and pyridine, any of which is unsubstituted or substituted with one or more R^{12}, or R^{13}.

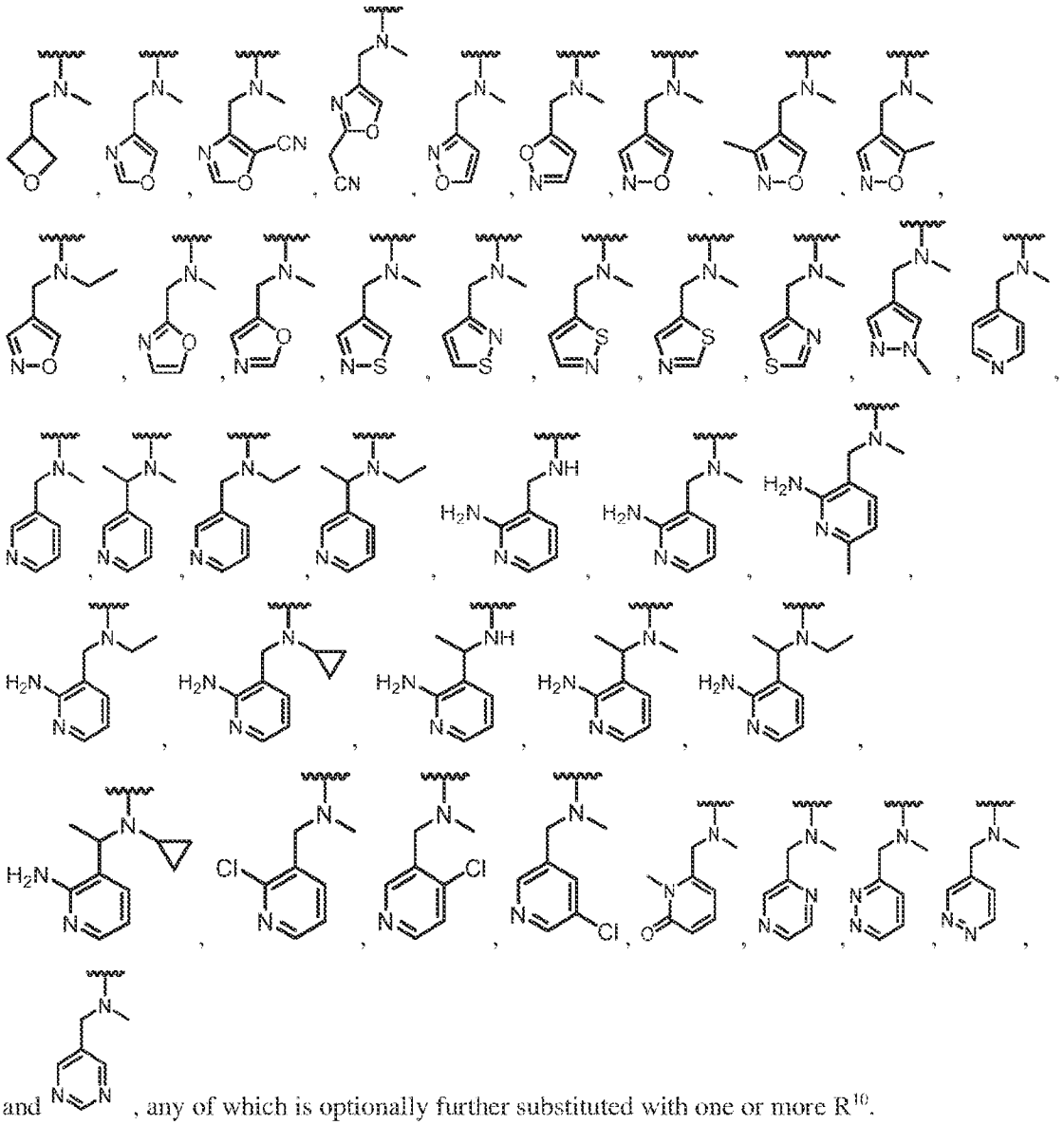
126. The compound of any one of claims 105-125, wherein R^2 is H.

127. The compound of any one of claims 105-125, wherein R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13}.

128. The compound of claim 127, wherein R^2 is selected from C_{1-2}alkyl that is unsubstituted.

129. The compound of any one of claims 105-125, wherein R^2 is a 3-6 membered carbocycle.

130. The compound of any one of claims 105-122, wherein the moiety is selected from:



and , any of which is optionally further substituted with one or more R^{10}.

131. The compound of any one of claims 105, and 107-130, wherein R^5 is a halogen (e.g., F or Cl).

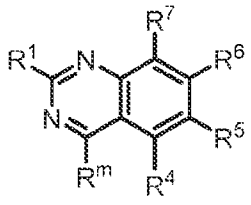
132. The compound of any one of claims 105, and 107-130, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

133. The compound of claim 132, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

134. The compound of claim 133, wherein R^5 is $-CF_3$.

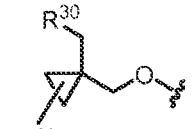
135. The compound of any one of claims 105, and 107-134, wherein R^7 is F.

136. A compound represented by Formula V':



(V')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

R^1 is selected from $-OR^8$,  , and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^m is selected from hydrogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^4 is H;

R^5 is selected from halogen and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a bicyclic heteroaryl that is substituted with one or more R^{15};

R^7 is selected from halogen;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-8 ring atoms and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from $-OR^{14}$, -CN, $-N(R^{14})_2$, and halogen;

each R^{14} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H;

each R^{15} is independently selected from deuterium, halogen, $-N(R^{12})_2$, -CN, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

n is 0-2;

each R^{31} is selected from C_{1-6} alkyl; and

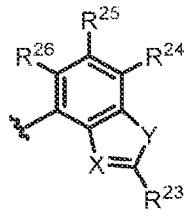
R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to

form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

137. The compound of claim 136, wherein R^m is hydrogen.

138. The compound of claim 136, wherein R^m is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

139. The compound of claim 138, wherein R^m is methyl that is unsubstituted.

140. The compound of any one of claims 136-139, wherein R^6 is  , wherein:

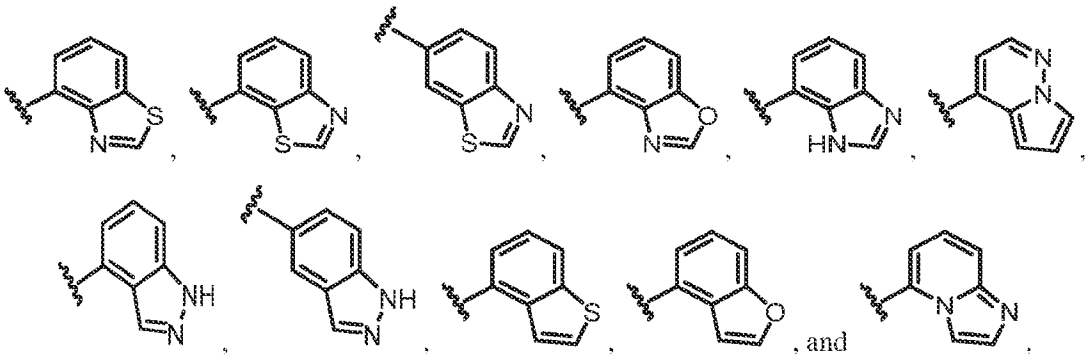
X is selected from N and C-CN;

Y is selected from O and S;

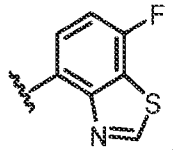
R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

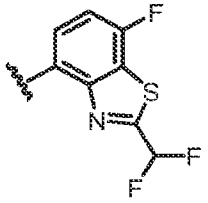
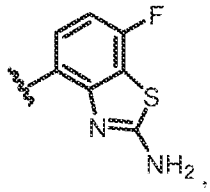
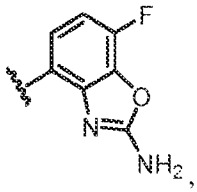
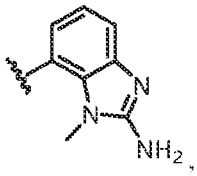
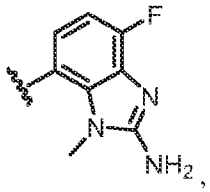
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

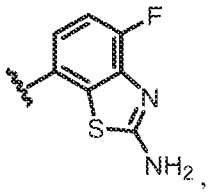
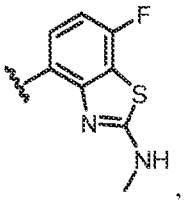
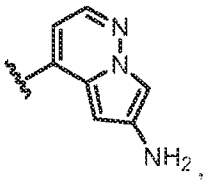
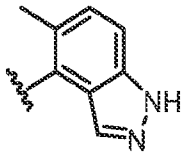
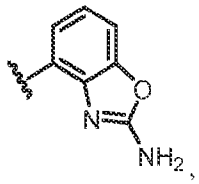
141. The compound of any one of claims 136-140, wherein R^6 is selected from:

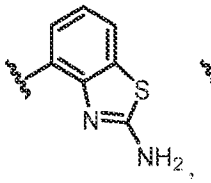
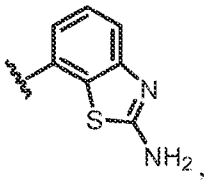
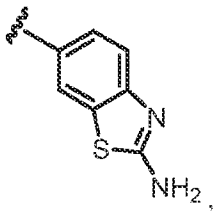
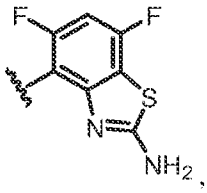
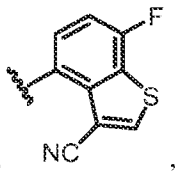


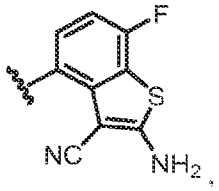
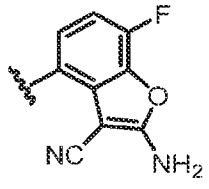
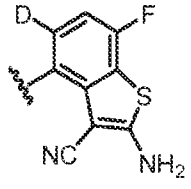
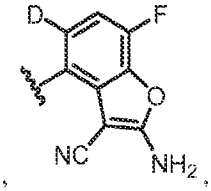
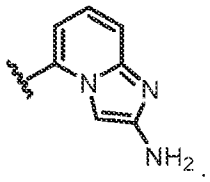
any of which is substituted with one or more R^{15}.

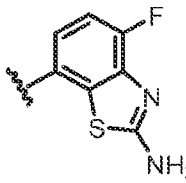
142. The compound of any one of claims 136-141, wherein R^6 is selected from:  ,

 ,  ,  ,  ,  ,

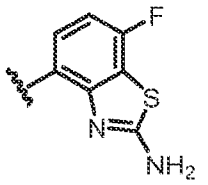
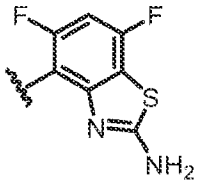
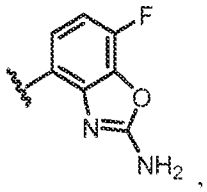
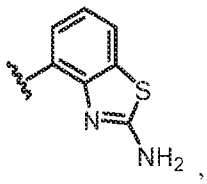
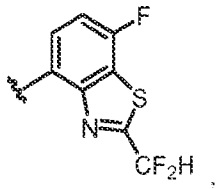
 ,  ,  ,  ,  ,

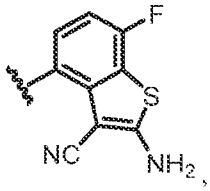
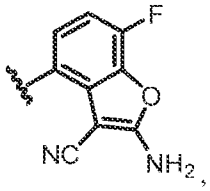
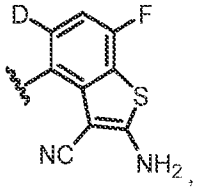
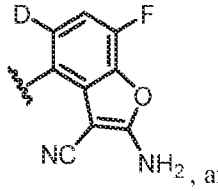
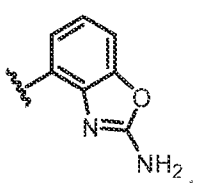
 ,  ,  ,  ,  ,

 ,  ,  ,  , and  .

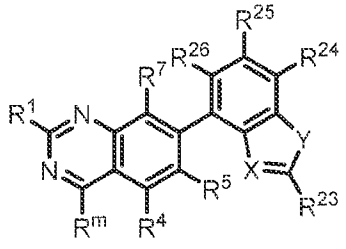
 ,

143. The compound of any one of claims 136-142, wherein R^6 is selected from:

 ,  ,  ,  ,  ,

 ,  ,  ,  , and  .

144. The compound of any one of claims 136-140, wherein the compound is a compound of Formula VC':



(VC')

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

X is selected from N and C-CN;

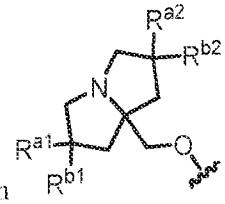
Y is selected from O and S;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, halogen, $-OR^{12}$, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

145. The compound of any one of claims 140-144, wherein X is C-CN, Y is S, R^{23} is $-N(R^{12})_2$, and one or more of R^{24}, R^{25}, and R^{26} is a halogen (e.g., F).

146. The compound of any one of claims 136-145, wherein R^1 is selected from $-OR^8$.

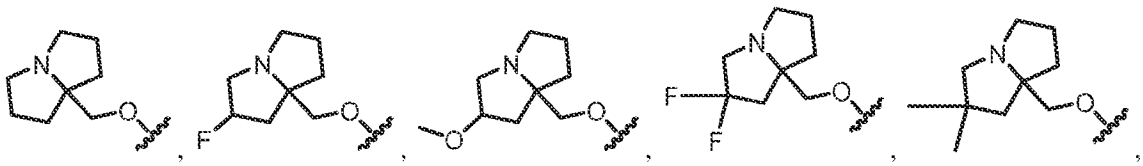
147. The compound of claim 146, wherein R^1 is selected from  , wherein:

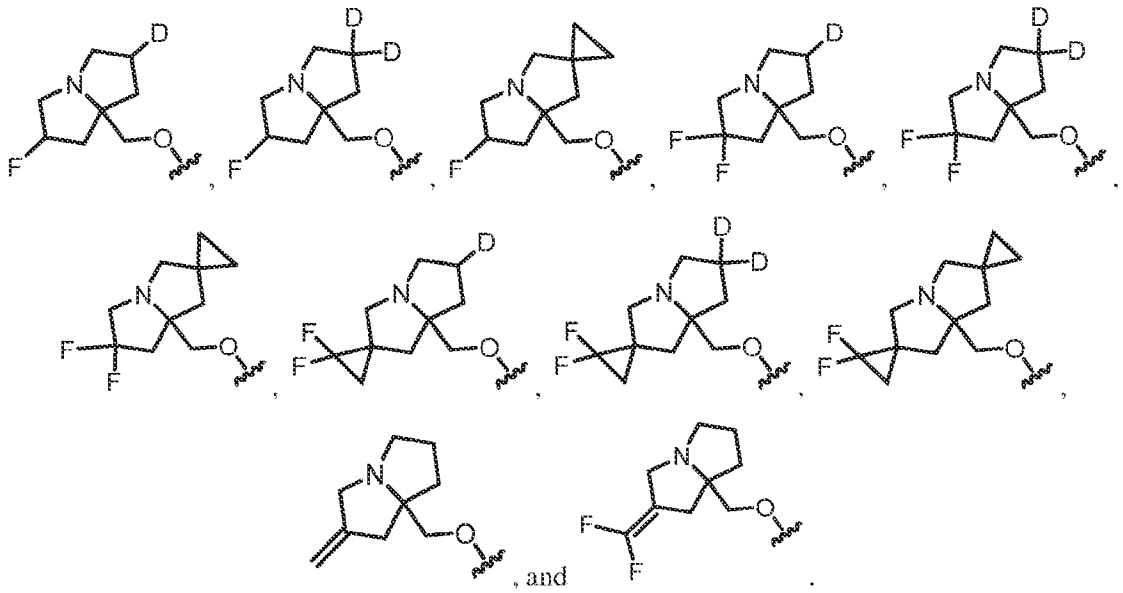
R^{a1}, R^{a2}, R^{b1}, and R^b are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H or are absent,

wherein R^{a2} and R^{b2} can optionally join together to form a 3-6 membered carbocycle, and

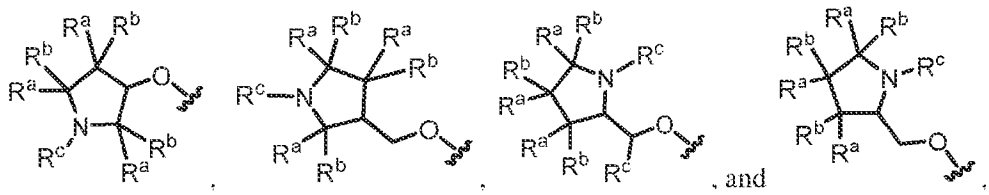
wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}.

148. The compound of claim 147, wherein R^1 is selected from:





149. The compound of claim 146, wherein R^1 is selected from:

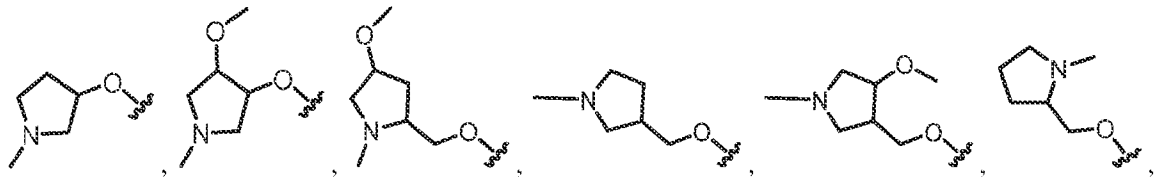


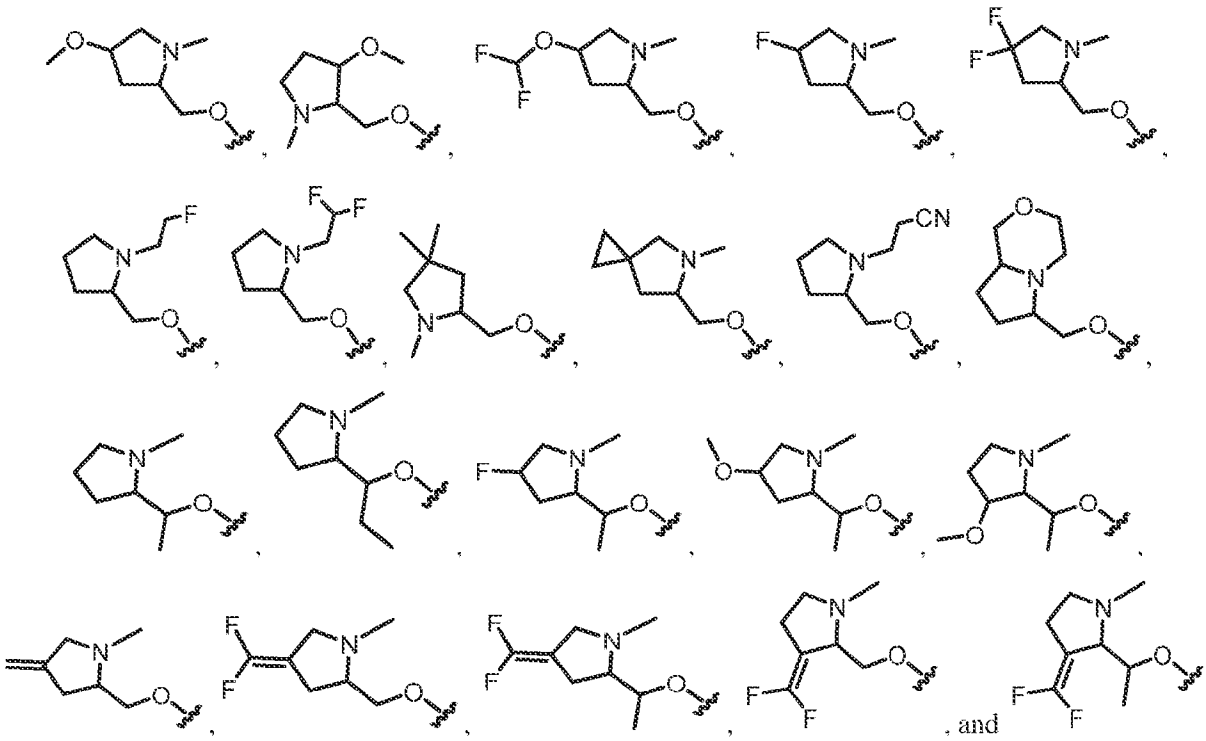
wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, $-OR^{12}$, and H; and each R^c is independently selected from H and C_{1-6} alkyl,

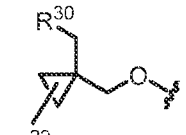
wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and

wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

150. The compound of claim 149, wherein R^1 is selected from:





151. The compound of any one of claims 136-145, wherein R^1 is selected from  , wherein:

each R^{28} is independently selected from C_{1-6}alkyl and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

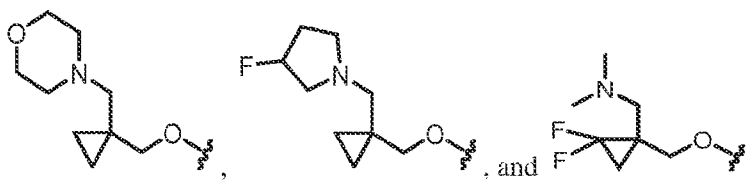
R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; and

n is 0-2.

152. The compound of claim 151, wherein R^{30} is $N(R^{14})_2$.

153. The compound of claim 151 or 152, wherein at least one R^{29} is a halogen such as F.

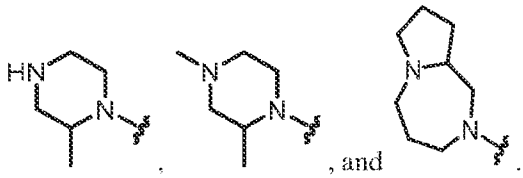
154. The compound of any one of claims 151-153, wherein R^1 is selected from:



155. The compound of any one of claims 136-145, wherein R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

156. The compound of claim 155, wherein R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

157. The compound of claim 156, wherein R^1 is selected from:



, , and .

158. The compound of any one of claims 136-157, wherein R^5 is a halogen (e.g., F or Cl).

159. The compound of any one of claims 136-157, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

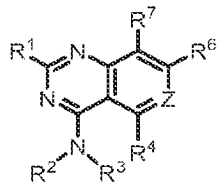
160. The compound of claim 159, wherein R^5 is selected from C_{1-6}alkyl that is substituted with one or more halogens or -CN.

161. The compound of claim 160, wherein R^5 is selected from $-CF_2H$, $-CF_3$, $-CH_2CN$, and $-CH_2CH_3$.

162. The compound of claim 161, wherein R^5 is $-CF_3$.

163. The compound of any one of claims 136-162, wherein R^7 is F.

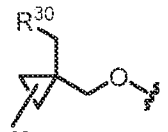
164. A compound represented by Formula III:



(III)

or a salt (e.g., pharmaceutically acceptable salt) thereof, wherein:

Z is N or C-R^5;

R^1 is selected from H, $-OR^8$, 

, and a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31};

R^2 is selected from H, C_{1-6}alkyl, and a 3-6 membered carbocycle, wherein any C_{1-6} alkyl is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated;

R^3 is selected from 3- to 12-membered cycloalkyl optionally fused to a 5- or 6-membered aryl, heterocycle, or heteroaryl, a 4-10 membered heterocycle, or -(C_{1-6} alkylenyl)(5-6 membered heteroaryl), wherein any cycloalkyl, aryl, heterocycle, or heteroaryl is unsubstituted or substituted with one or more R^{10};

R^4 is H, -OR^{12},or -$N(R^{14})_2$;

R^5 is selected from halogen, -CN, 5- to 6-membered heteroaryl, -OC_{1-6}alkyl, C_{1-6}alkyl, and H, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

R^6 is a phenyl, naphthyl, or bicyclic heteroaryl, wherein the phenyl, naphthyl, or bicyclic heteroaryl is substituted with one or more R^{15};

R^7 is selected from halogen or H;

R^8 is selected from a heterocycle and an alkylheterocycle, wherein any heterocycle comprises 4-9 members and is unsubstituted or is substituted with one or more R^a or R^b, and wherein an alkyl moiety of any alkylheterocycle is selected from C_{1-6}alkyl, and C_{1-6}alkyl is optionally deuterated (e.g. -CH_2- or -CD_2-);

each R^{10} is independently selected from deuterium, -OR^{12}, =O, =S, -CN, -$NSOMe_2$, -C(O)(C_{1-6}alkylene)CN, -C(O)(C_{1-6}alkylene)OH, -C(O)(C_{1-6}alkyl), -C(O)O(C_{1-6}alkyl), -C(O)N$(R^{14})_2$, -C(O)OR^{14}, -C(O)(3-6 membered carbocycle), -C(O)(3-8 membered heterocycle), -C(O)(5-6 membered heteroaryl), -C(O)O(3-6 membered carbocycle), -C(O)O(3-6 membered heterocycle), -C(O)O(5-6 membered heteroaryl),-C(O)O(C_{1-6}alkylene)(3-6 membered heterocycle), -$S(O)_2$(C_{1-6}alkyl), -C(S)(C_{1-6}alkyl), -C(S)O(C_{1-6}alkyl), -C(S)N$(C_{1-6}alkyl)_2$, -C(=N-OR^{12})(C_{1-6} alkyl), -C(O)N$(R^{12})OR^{12}$, halogen, phenyl, a 5-6 membered heteroaryl, a 3-6 membered carbocycle, a 3-6 membered heterocycle, C_{2-6} alkenyl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is optionally deuterated and is unsubstituted or substituted with one or more R^{20}, wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}, and wherein two R^{10}s optionally join together to form, together with the atom(s) to which they are attached, a 3-6 membered carbocycle or heterocycle;

each R^{12} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, and H, wherein any C_{1-6}alkyl or C_{2-6} alkenyl is unsubstituted or substituted with one or more R^{13};

each R^{13} is independently selected from -OR^{14}, -OC(O)R^{14}, -CN, -$N(R^{14})_2$, and halogen;

each R^{14} is independently selected from a 3-6 membered carbocycle, a 3-8 membered heterocycle, C_{1-6} alkyl, -OR^{12}, C_{2-6} alkenyl, and H, wherein any C_{1-6} alkyl is optionally deuterated;

each R^{15} is independently selected from deuterium, -OH, halogen, $-N(R^{12})_2$, -CN, C_{2-6} alkynyl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13};

each R^{20} is independently selected from -OH, $-OC_{1-6}$alkyl, $-OC_{1-6}$haloalkyl, =O, -CN, $-NH_2$, $-NHC_{1-6}$alkyl, $-C(O)(C_{1-6}$alkyl), $-C(O)OR^{12}$, $-C(O)N(R^{12})_2$, $-S(O)_2R^{12}$, a 3-6 membered carbocycle, phenyl, and halogen;

each R^{28} is independently selected from C_{1-6}alkyl, $-OR^{12}$, C_{1-6}heteroalkyl, wherein two heteroalkyl groups can optionally join together to form a 3-6 membered heterocycle that is unsubstituted or substituted with one or more R^{13} and halogen;

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

R^{30} is $N(R^{12})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28};

each R^{31} is selected from C_{1-6} alkyl;

n is 0-2; and

R^a and R^b are each independently selected from deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, , , $-C_{1-6}$ heteroalkyl, a 3-6 membered carbocycle, $-OR^{12}$, and H, wherein an R^a and R^b optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6}alkyl, C_{2-6} alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

165. The compound of claim 164, wherein R^3 is selected from a 4-10 membered heterocycle that is unsubstituted or substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}, or (ii) the heterocycle does not comprise an –NH- moiety.

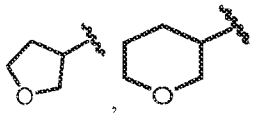
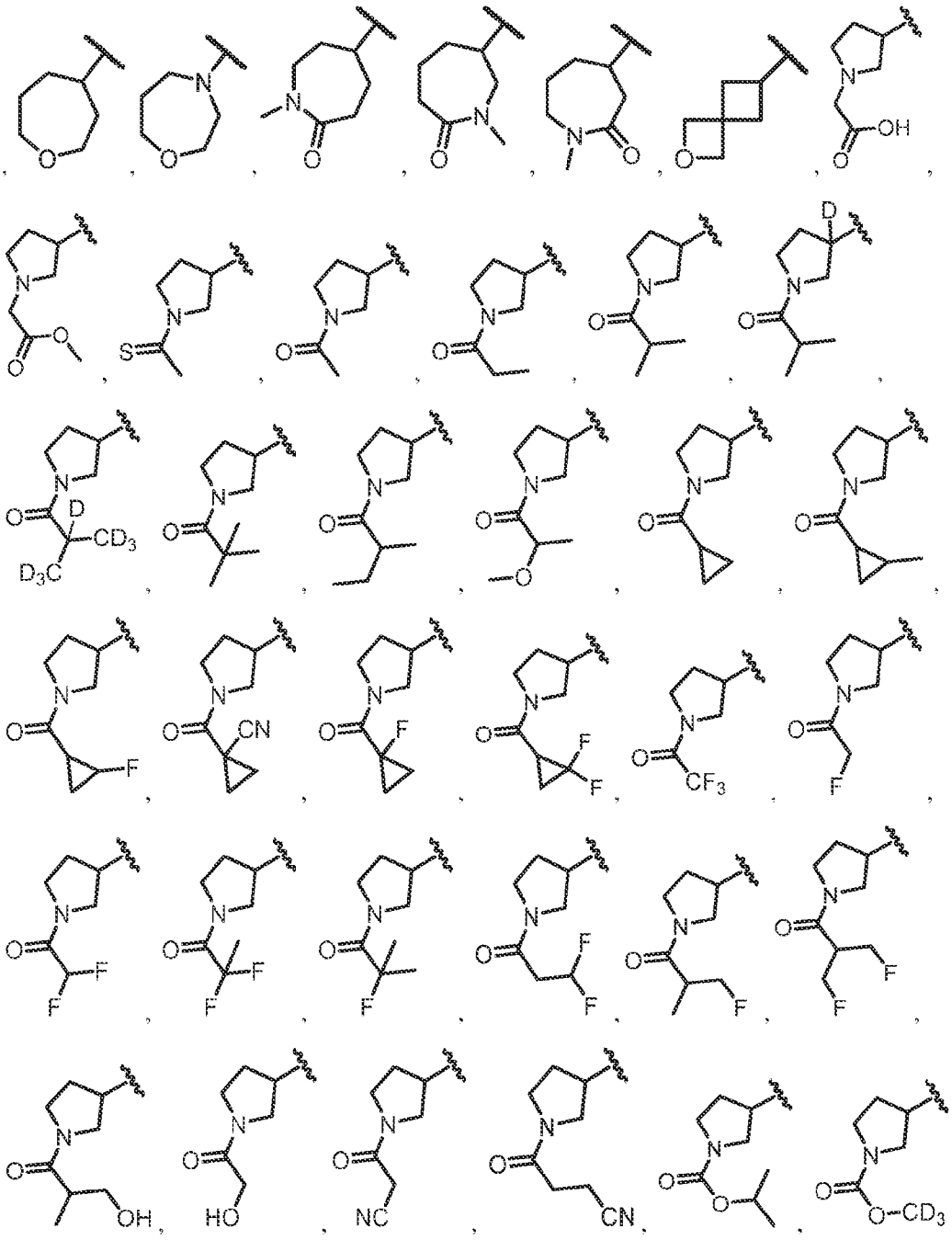
166. The compound of any one of claims 164-165, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N.

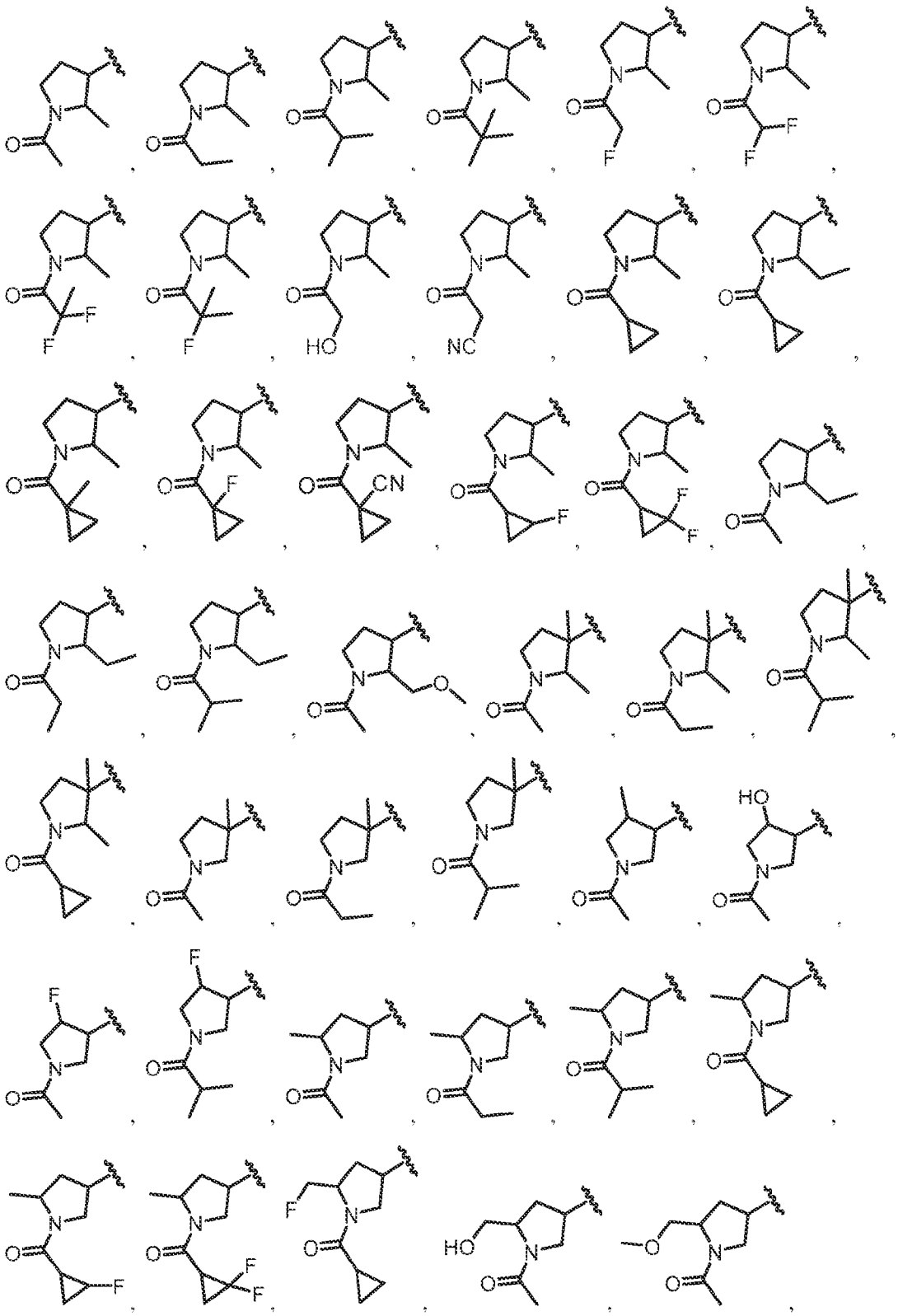
167. The compound of claim 166, wherein R^3 is a 4-6 membered heterocycle that includes 1 heteroatom selected from O, S, and N, wherein the heterocycle is substituted with 1-4 R^{10}, provided that when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10}.

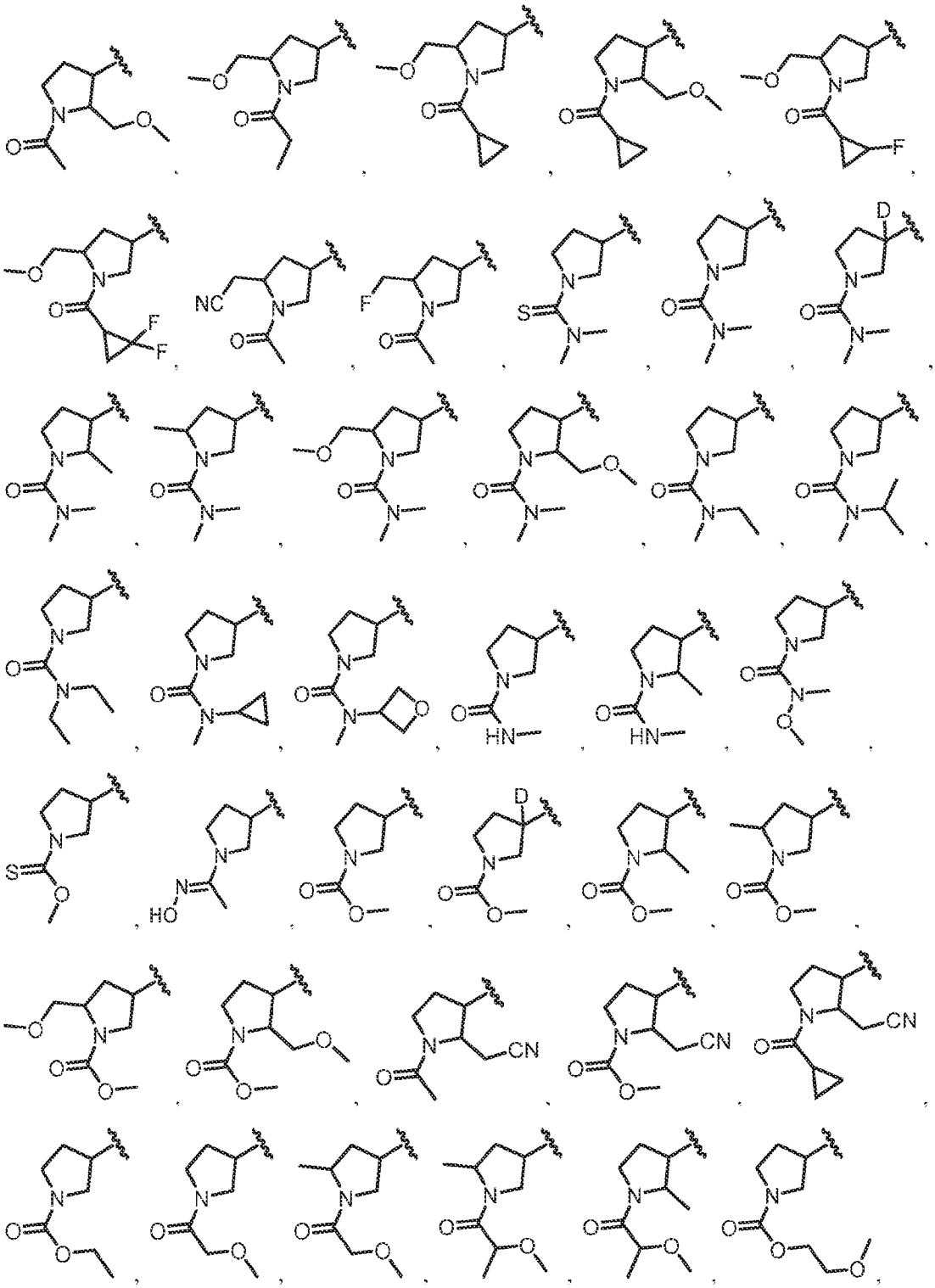
168. The compound of any one of claims 164-167, wherein R^3 is a pyrrolidine that is substituted with 1-4 R^{10}, provided that the nitrogen atom is substituted with R^{10}.

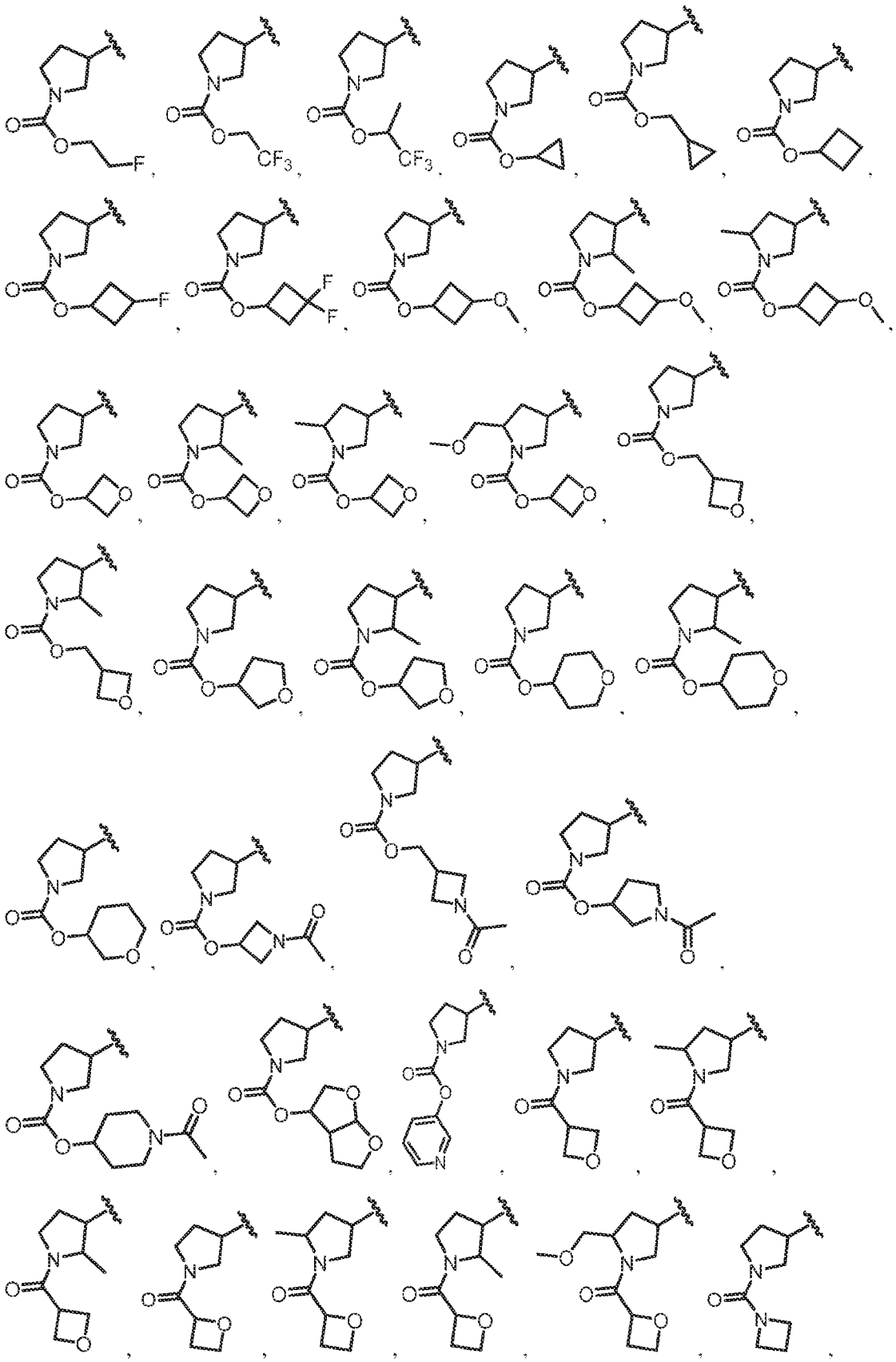
169. The compound of claim 168, wherein each R^{10} is independently selected from deuterium, $-C(O)N(R^{14})_2$, $-C(O)(C_{1-6}$alkyl), $-C(O)O(C_{1-6}$alkyl), -C(O)(3-6 membered carbocycle), -C(O)(3-8

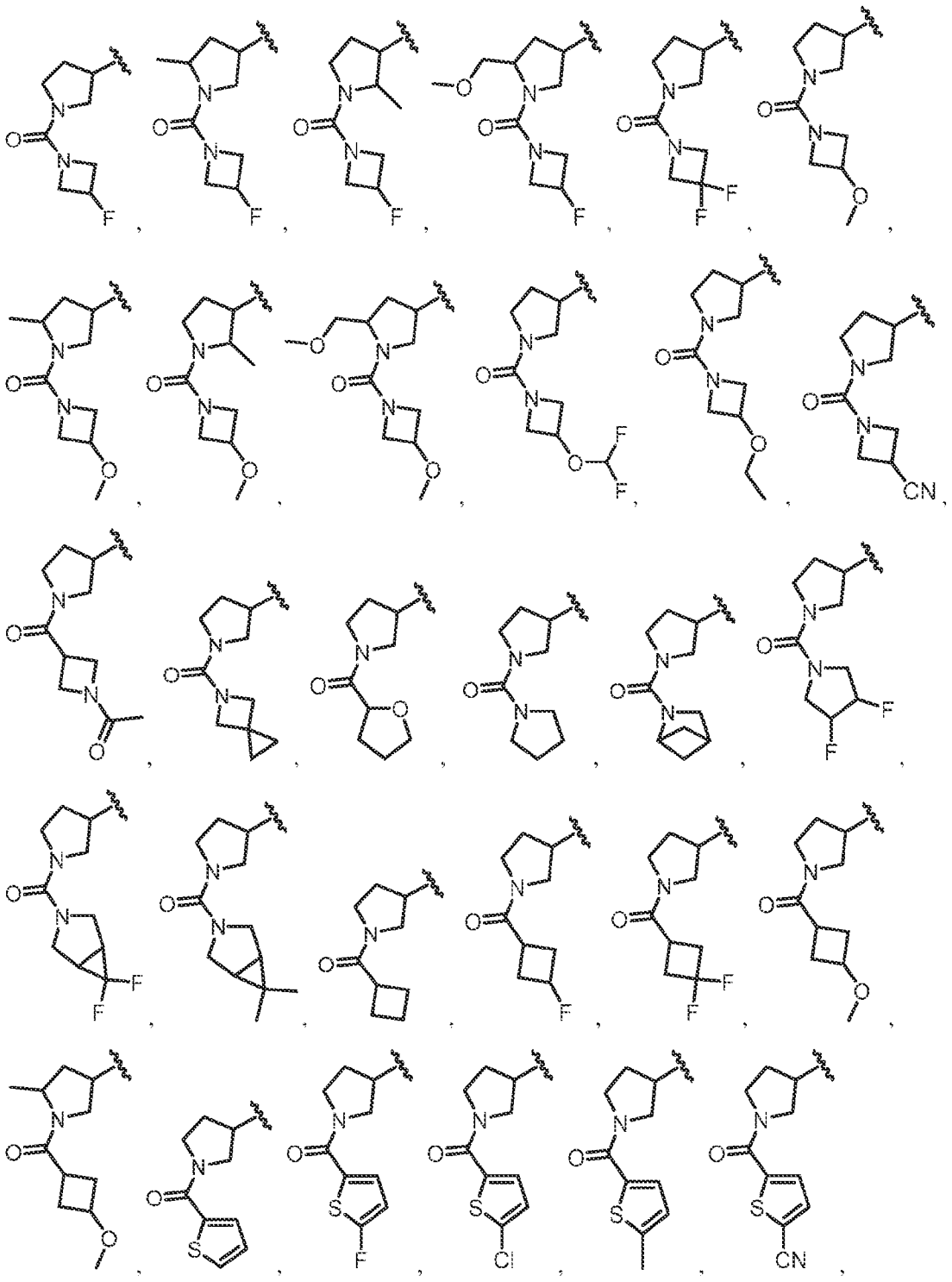
membered heterocycle), a 3-6 membered heterocycle, C_{2-6} alkenyl, a 5-6 membered heteroaryl, halogen, phenyl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and wherein any 3-6 membered carbocycle, 5-6 membered heteroaryl, or 3-6 or 3-8 membered heterocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

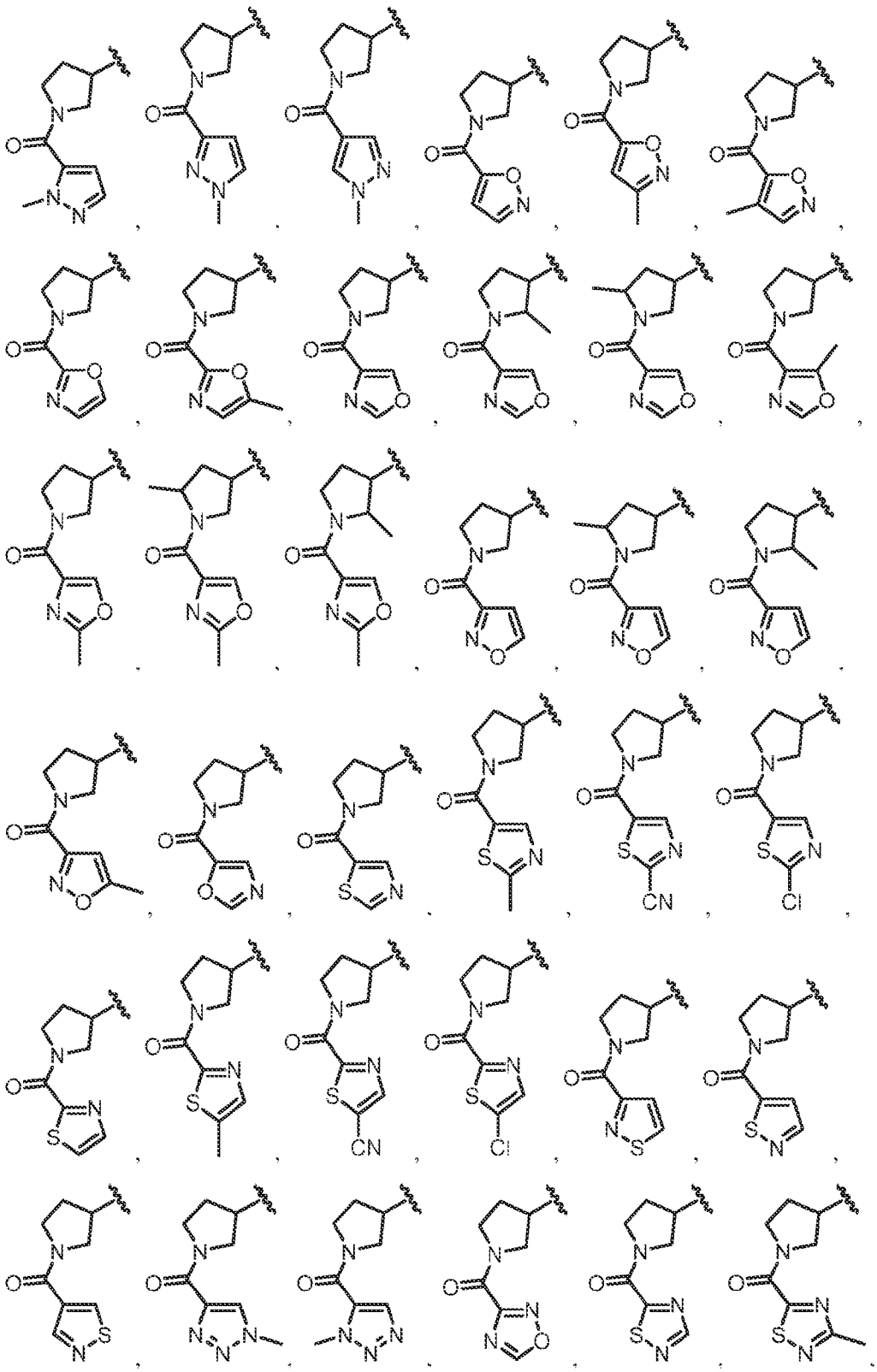
170. The compound of any one of claims 164-169, wherein R^3 is selected from:  , 

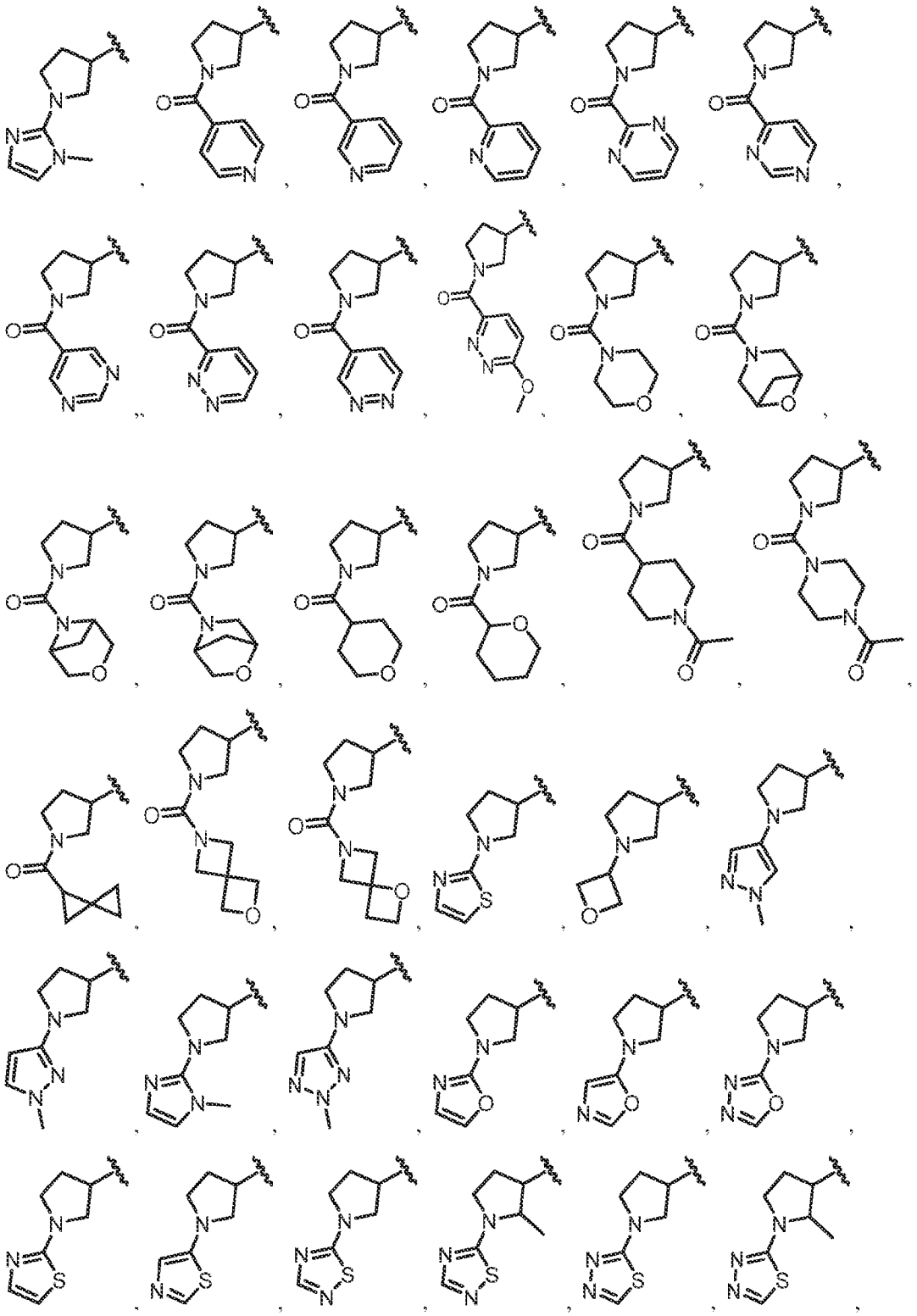


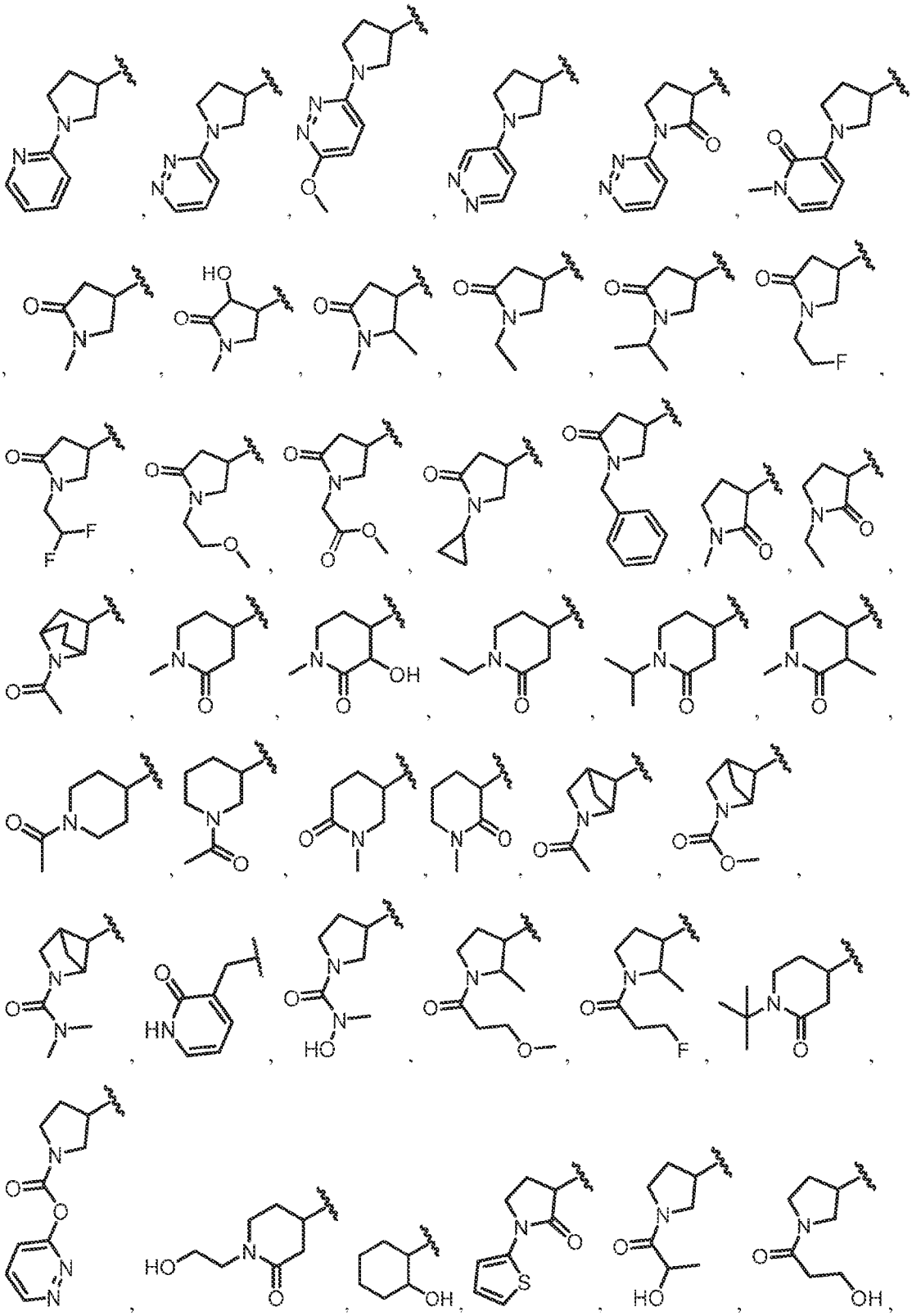


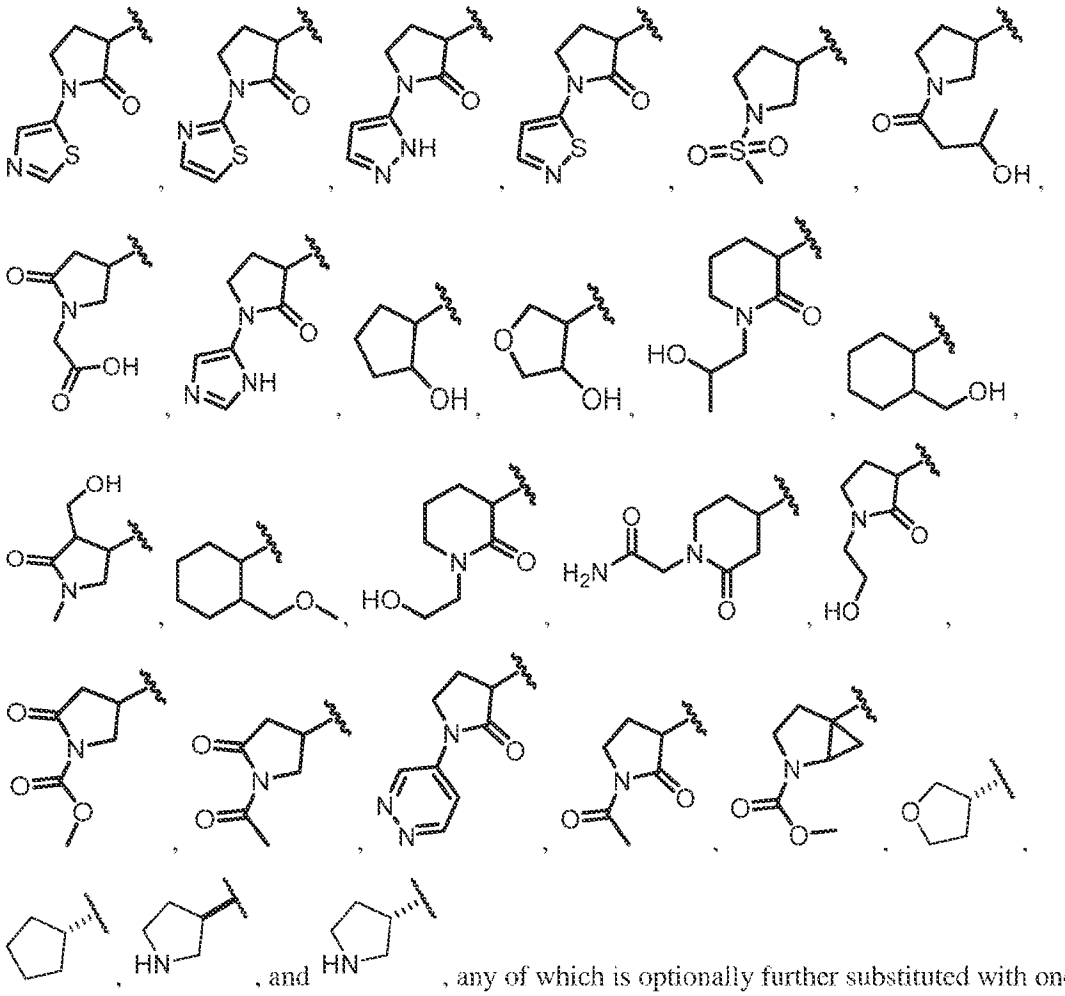






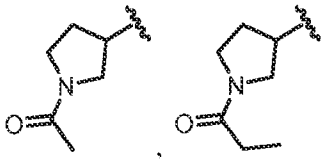


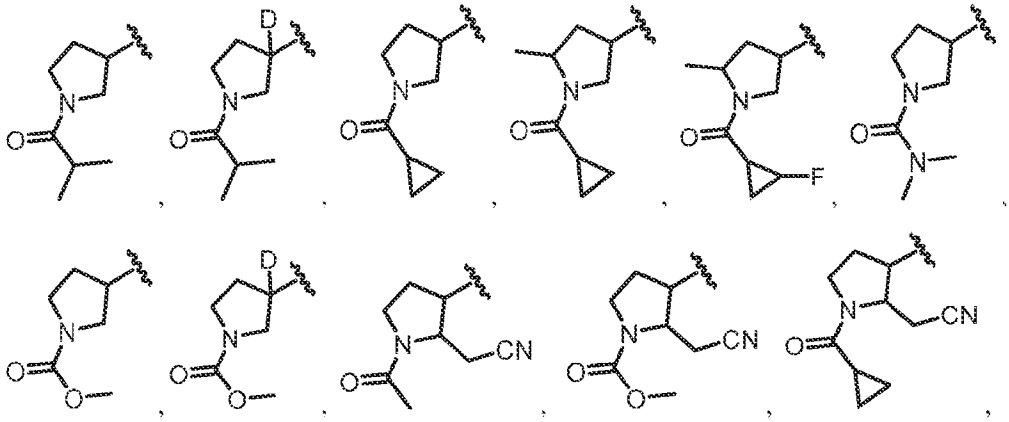


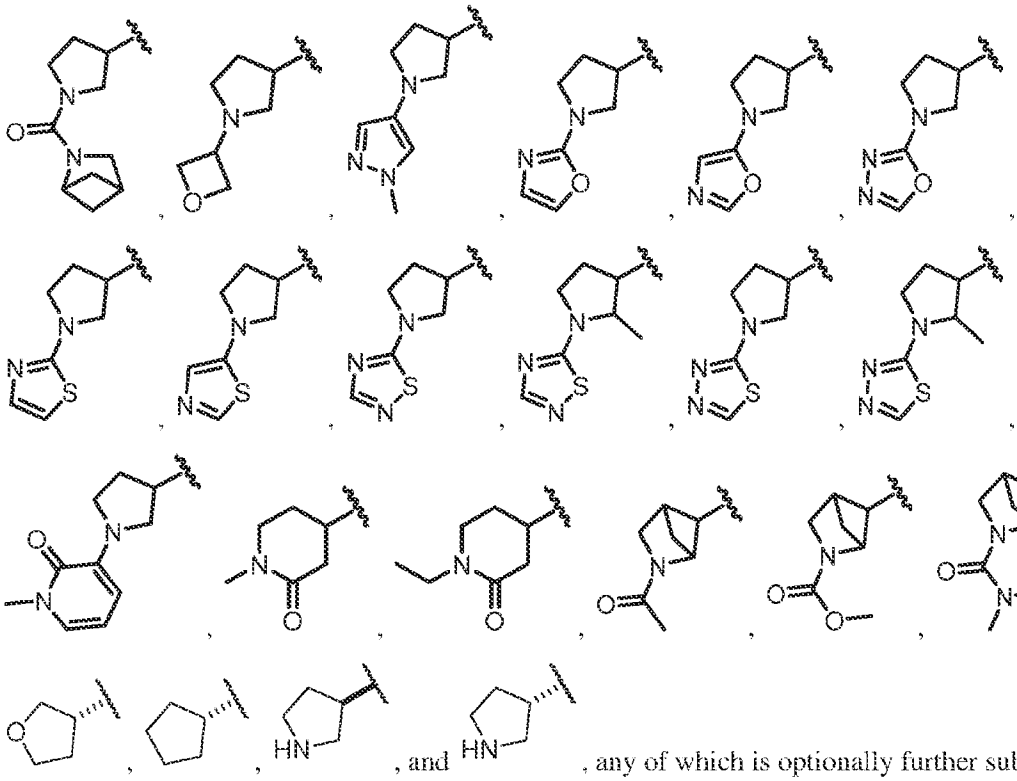


, and , any of which is optionally further substituted with one or more R^{10}.

171. The compound of claim 170, wherein R^3 is selected from:







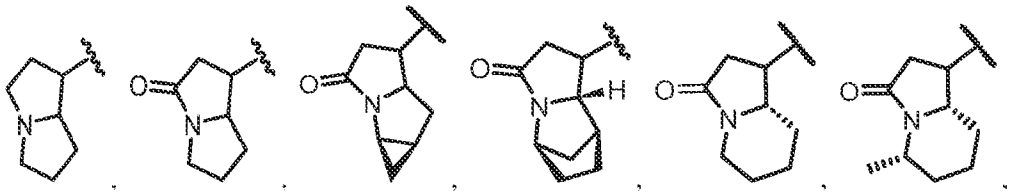
, any of which is optionally further substituted with one or more R^{10}.

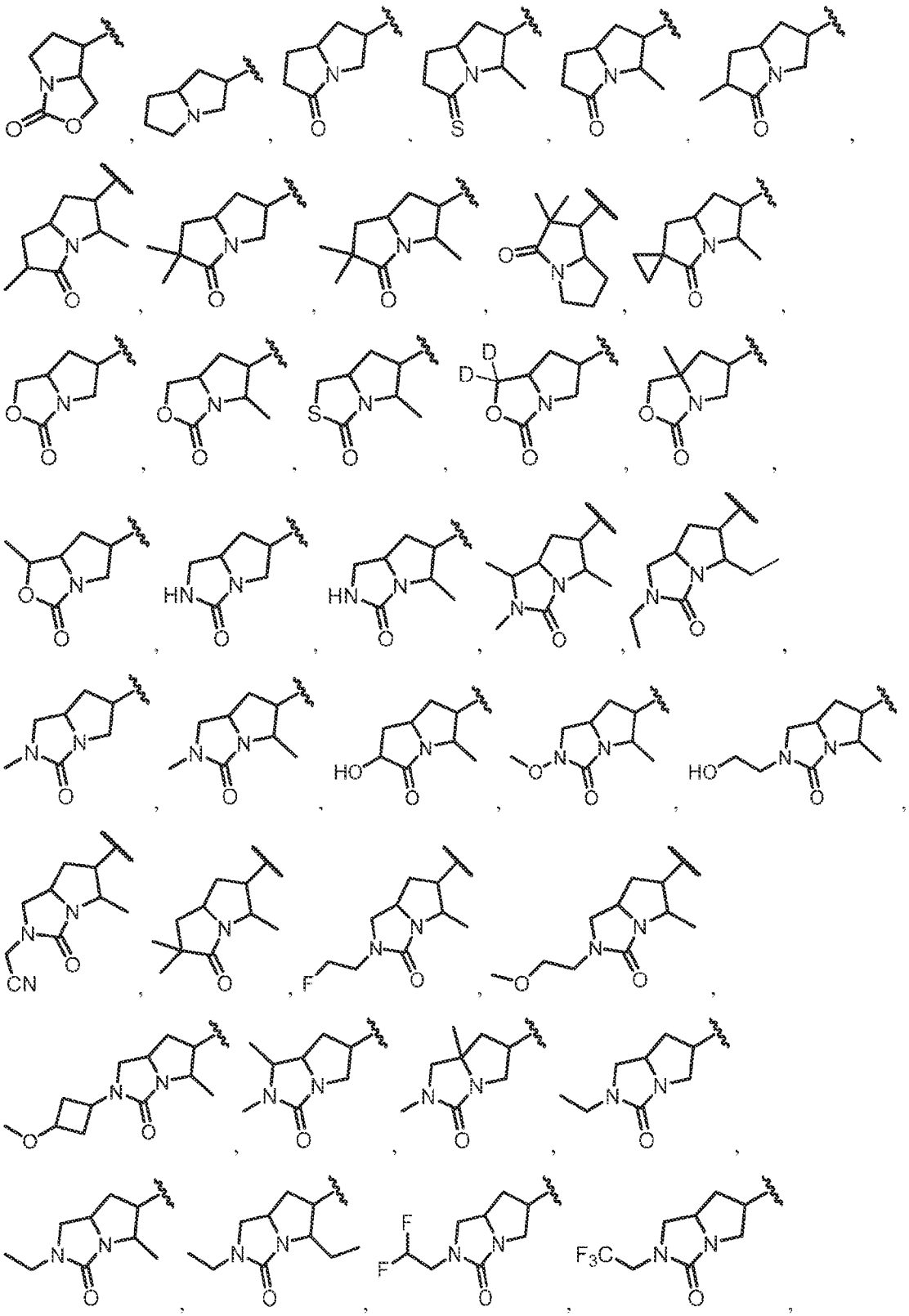
172. The compound of any one of claims 164-165, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

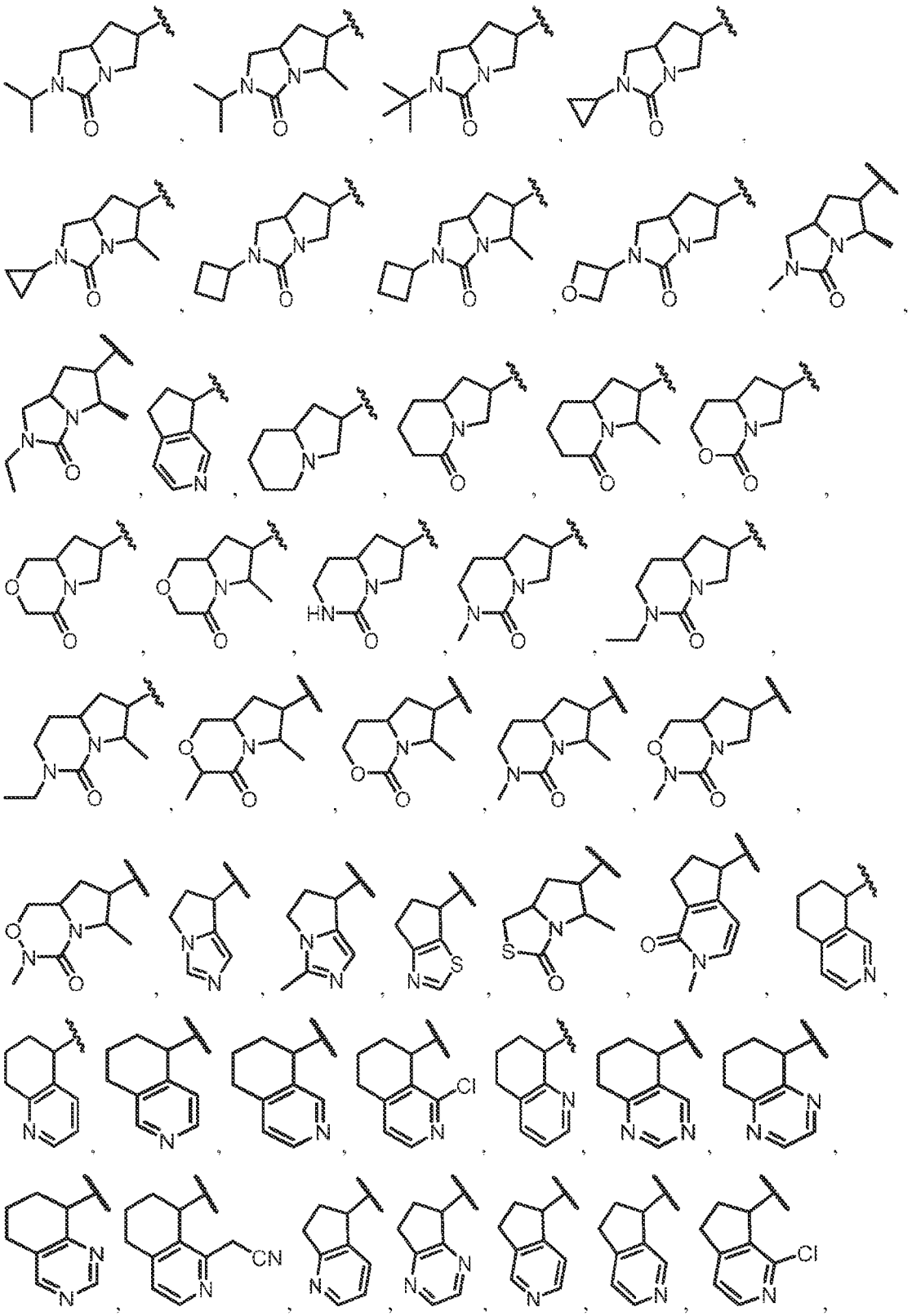
173. The compound of claim 172, wherein R^3 is a 7-10 membered heterocycle that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}, provided that (i) when the heterocycle contains a nitrogen atom, the nitrogen atom is substituted with R^{10} or (ii) the heterocycle does not comprise an –NH- moiety.

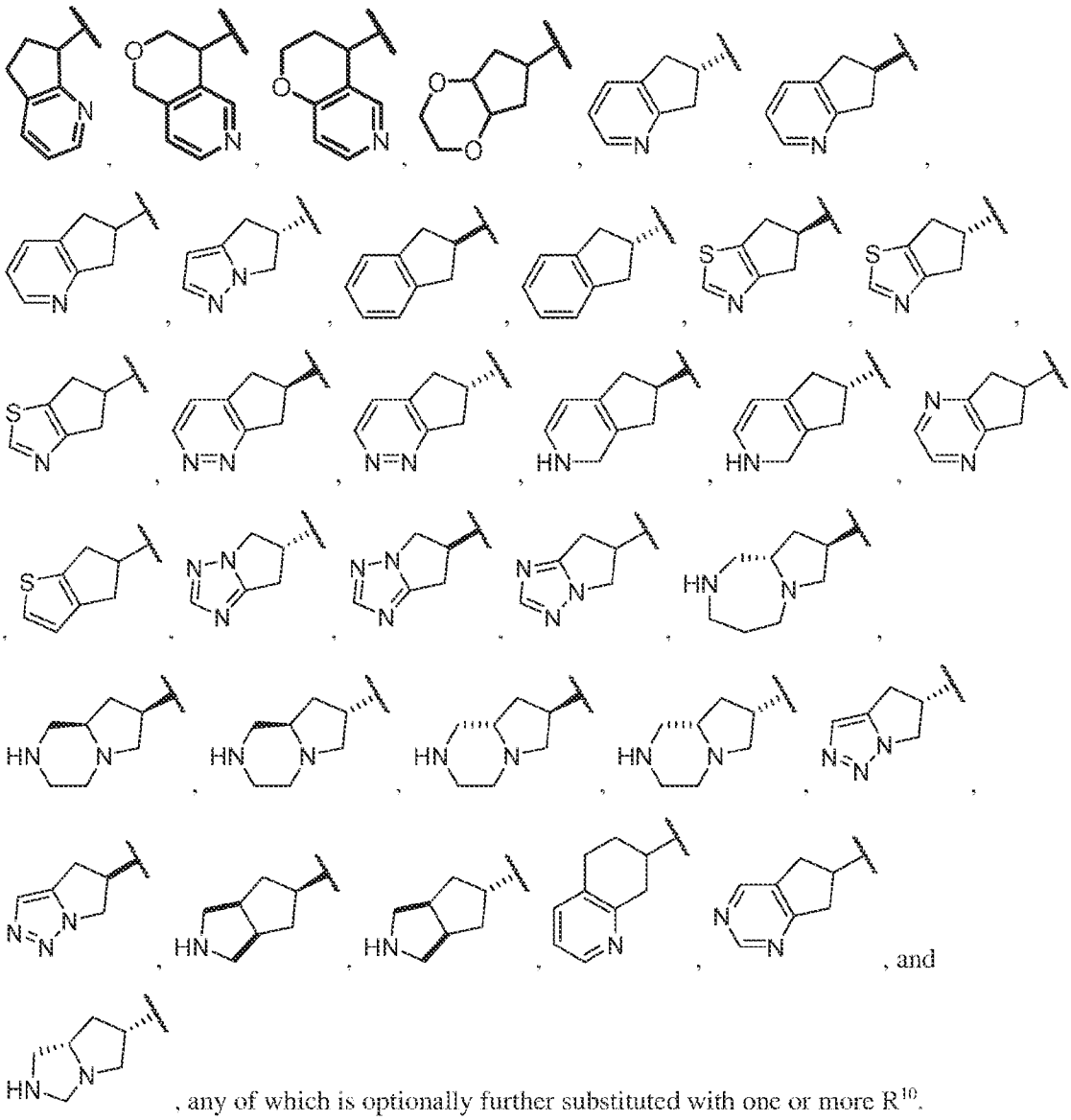
174. The compound of claim 172, wherein R^3 is a 7-10 membered heterocycle comprising a fused ring system that includes one or more heteroatoms selected from O, S, and N, wherein the heterocycle is unsubstituted or is substituted with one or more R^{10}.

175. The compound of any one of claims 164-165 and 172-174, wherein R^3 is selected from:



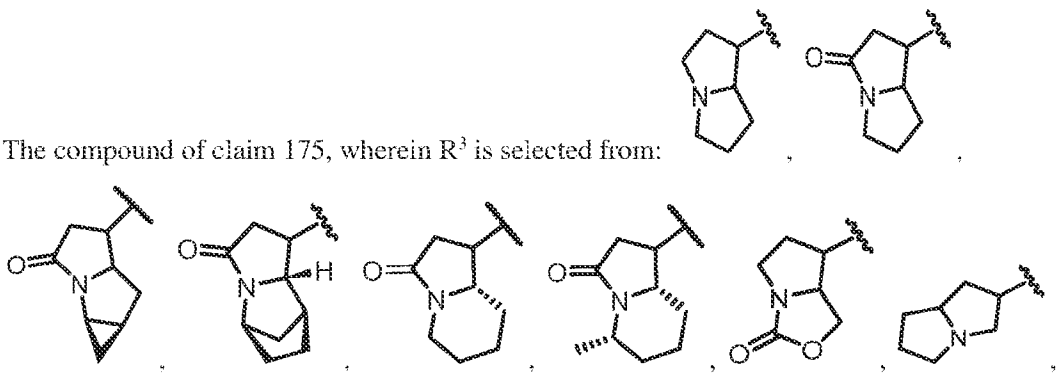


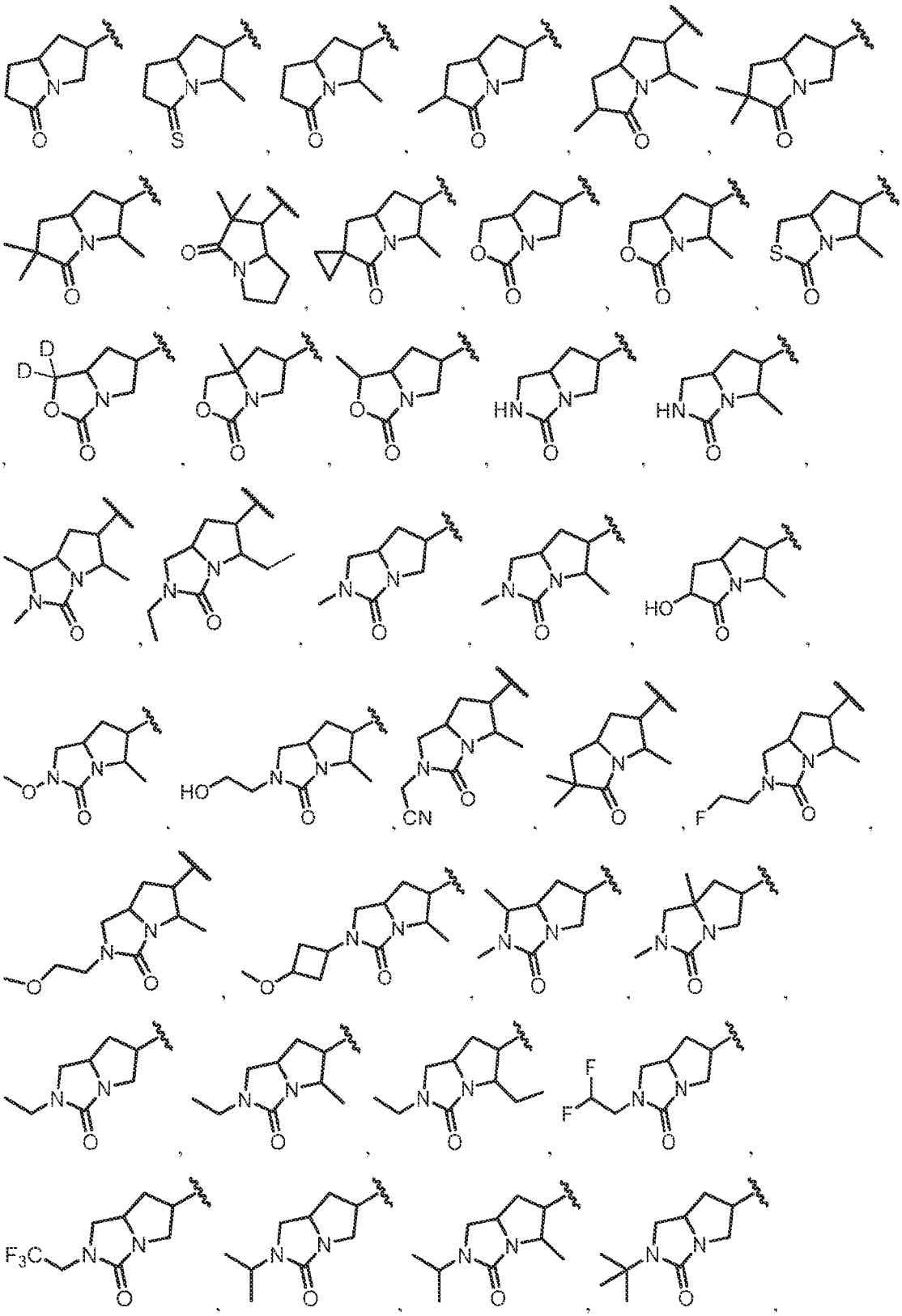


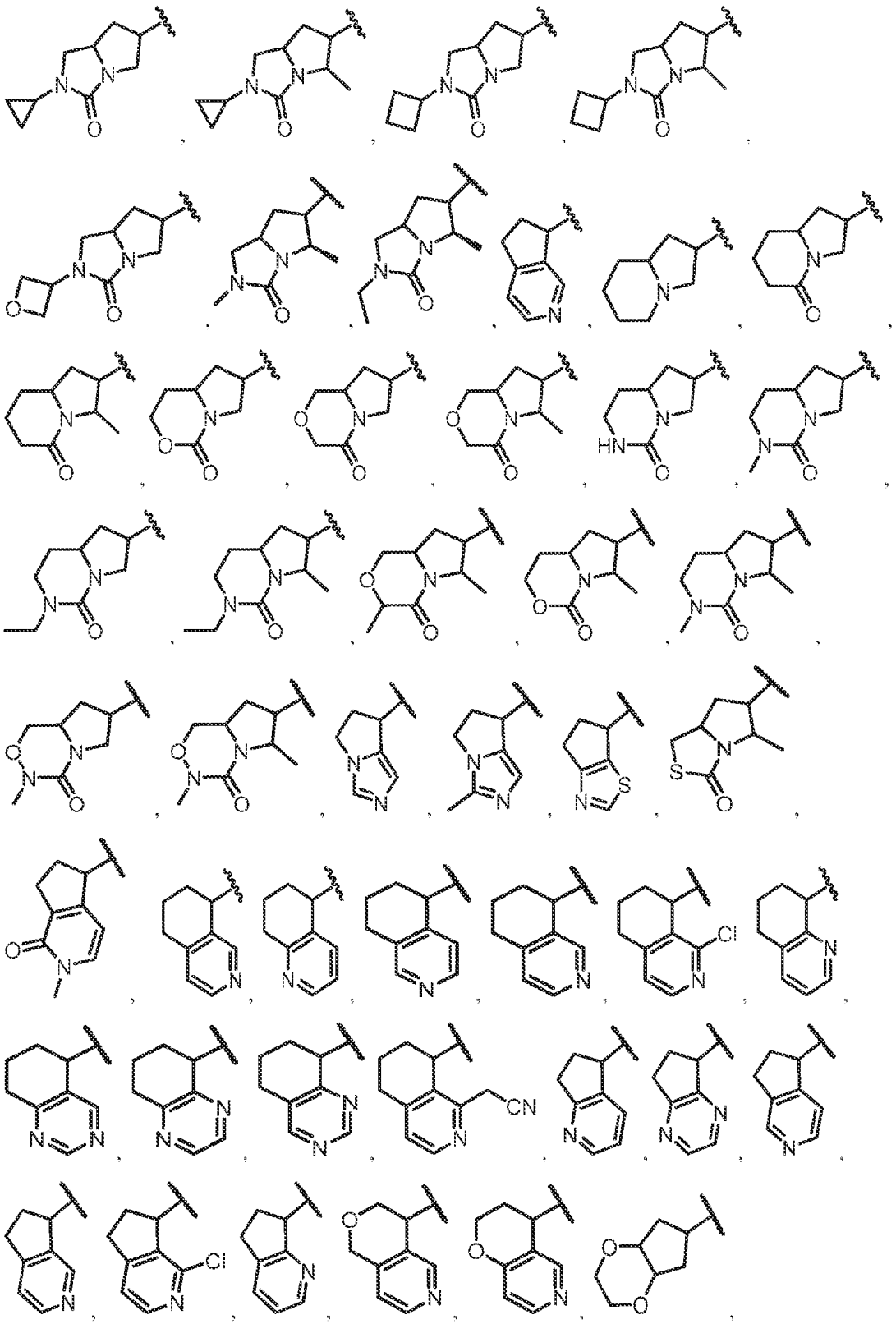


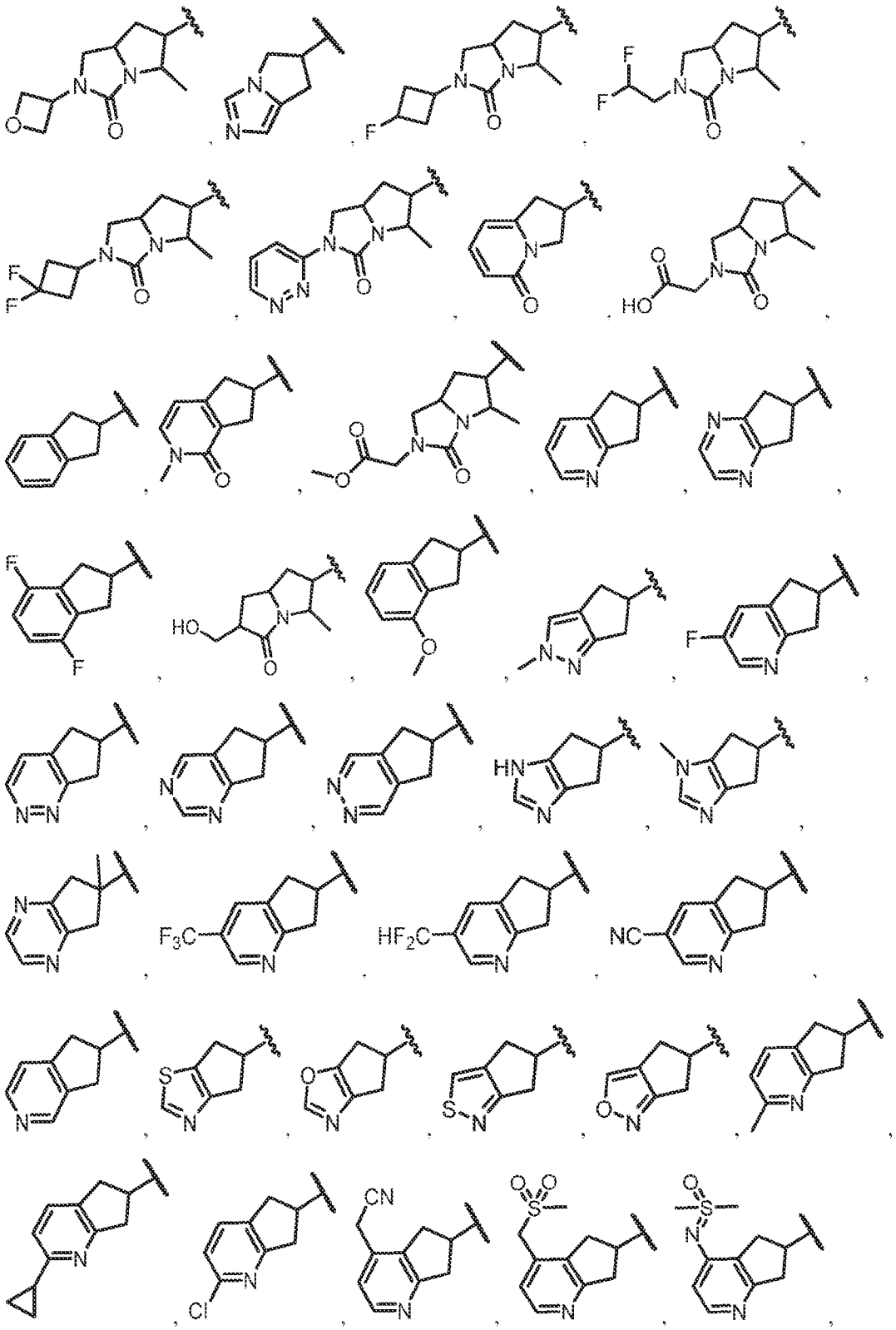
, any of which is optionally further substituted with one or more R^{10}.

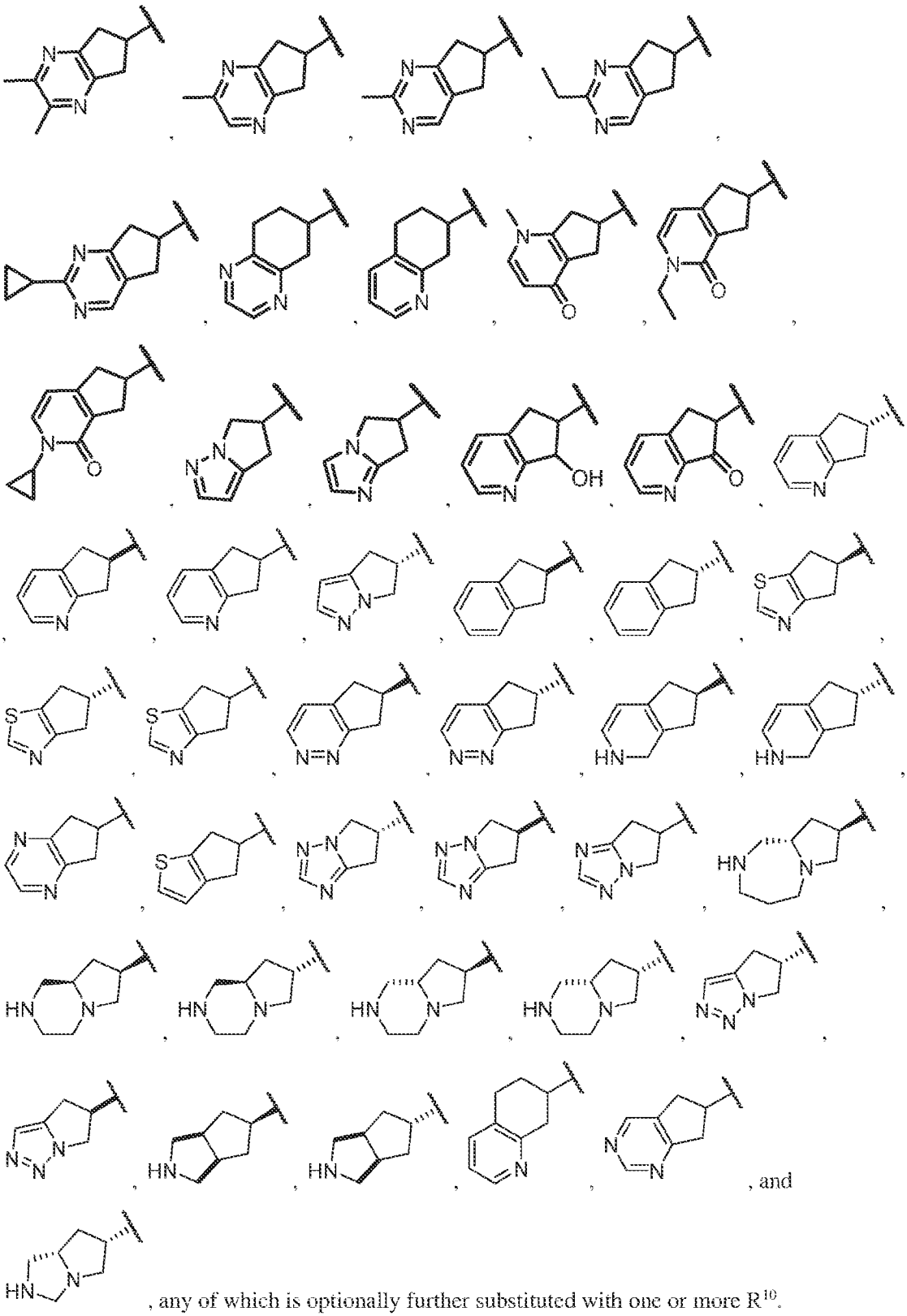
176. The compound of claim 175, wherein R^3 is selected from:



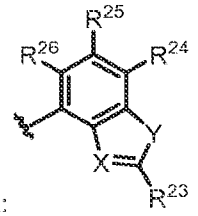


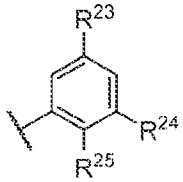
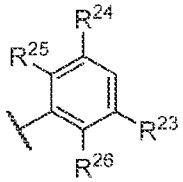
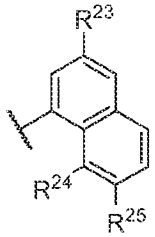
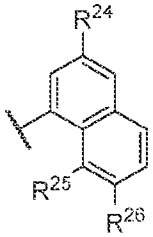






, any of which is optionally further substituted with one or more R^{10}.

177. The compound of any one of claims 164-176, wherein R^6 is selected from:  ,

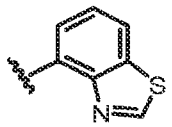
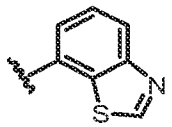
 ,  ,  , or  wherein:

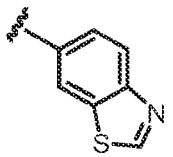
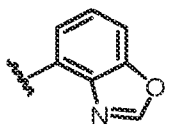
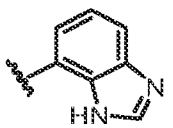
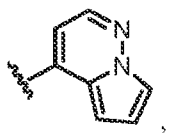
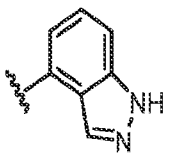
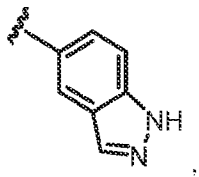
X is selected from N and C-CN;

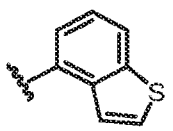
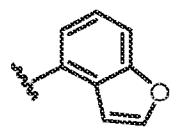
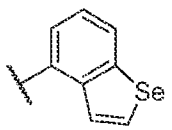
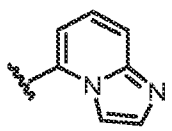
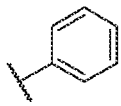
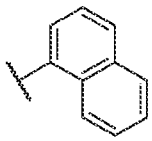
Y is selected from O, S, and Se;

R^{23} is selected from $-N(R^{12})_2$, C_{1-6}alkyl, and C_{1-6}alkyl-$N(R^{14})_2$, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}; and

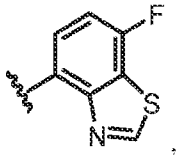
R^{24}, R^{25}, and R^{26} are independently selected from H, deuterium, -OH, halogen, C_{2-6} alkynyl, and C_{1-6}alkyl, wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{13}.

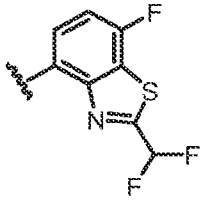
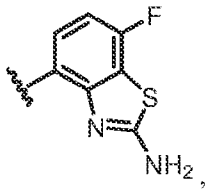
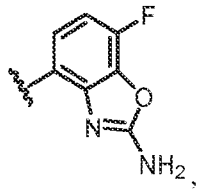
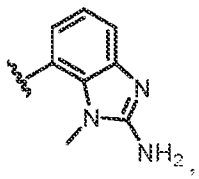
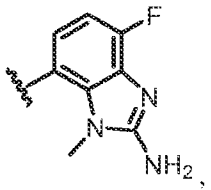
178. The compound of claim 177, wherein R^6 is selected from:  ,  ,

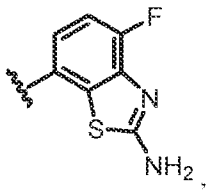
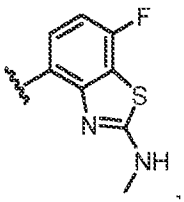
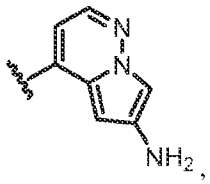
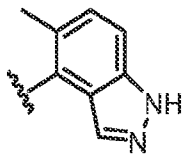
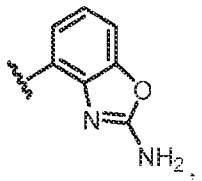
 ,  ,  ,  ,  ,  ,

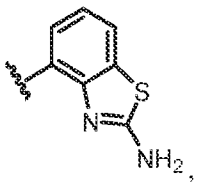
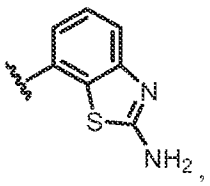
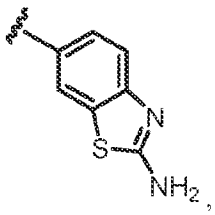
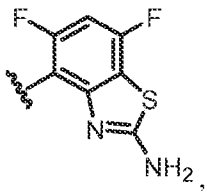
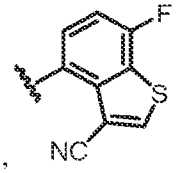
 ,  ,  ,  ,  , and 

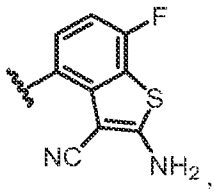
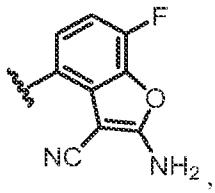
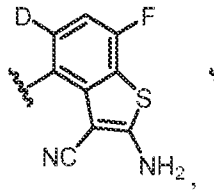
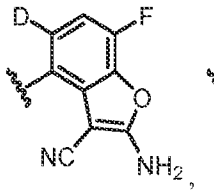
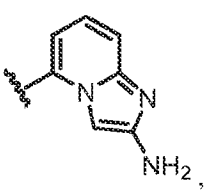
any of which is substituted with one or more R^{15}.

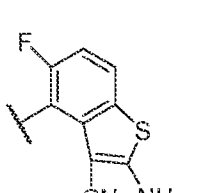
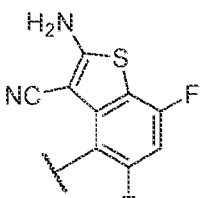
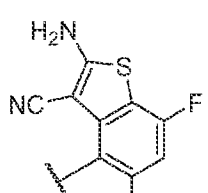
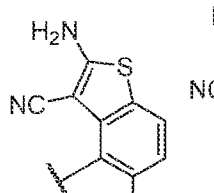
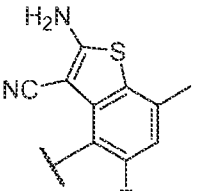
179. The compound of claim 177 or 178, wherein R^6 is selected from:  ,

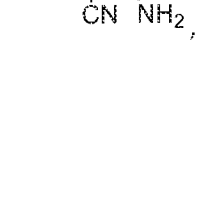
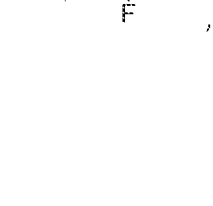
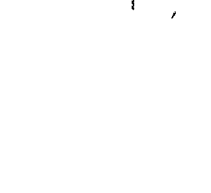
 ,  ,  ,  ,  ,

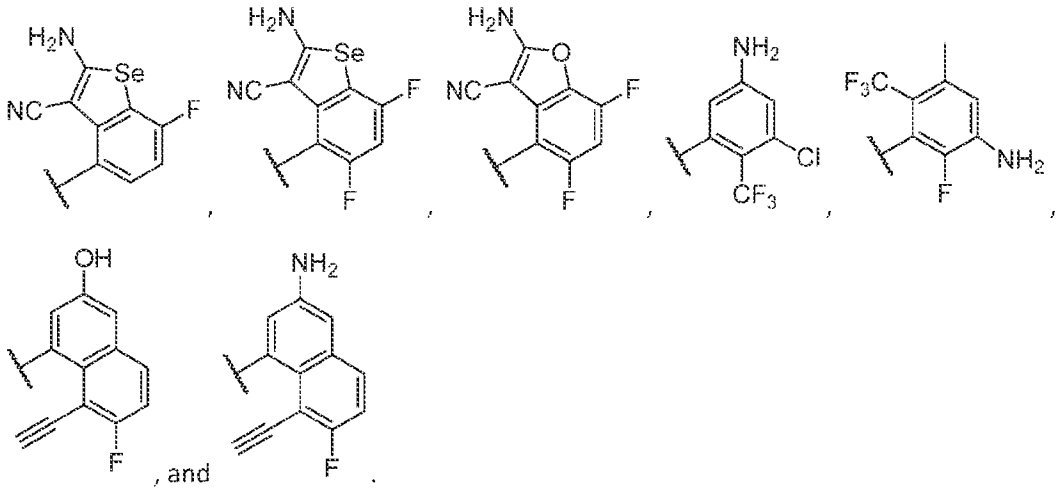
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

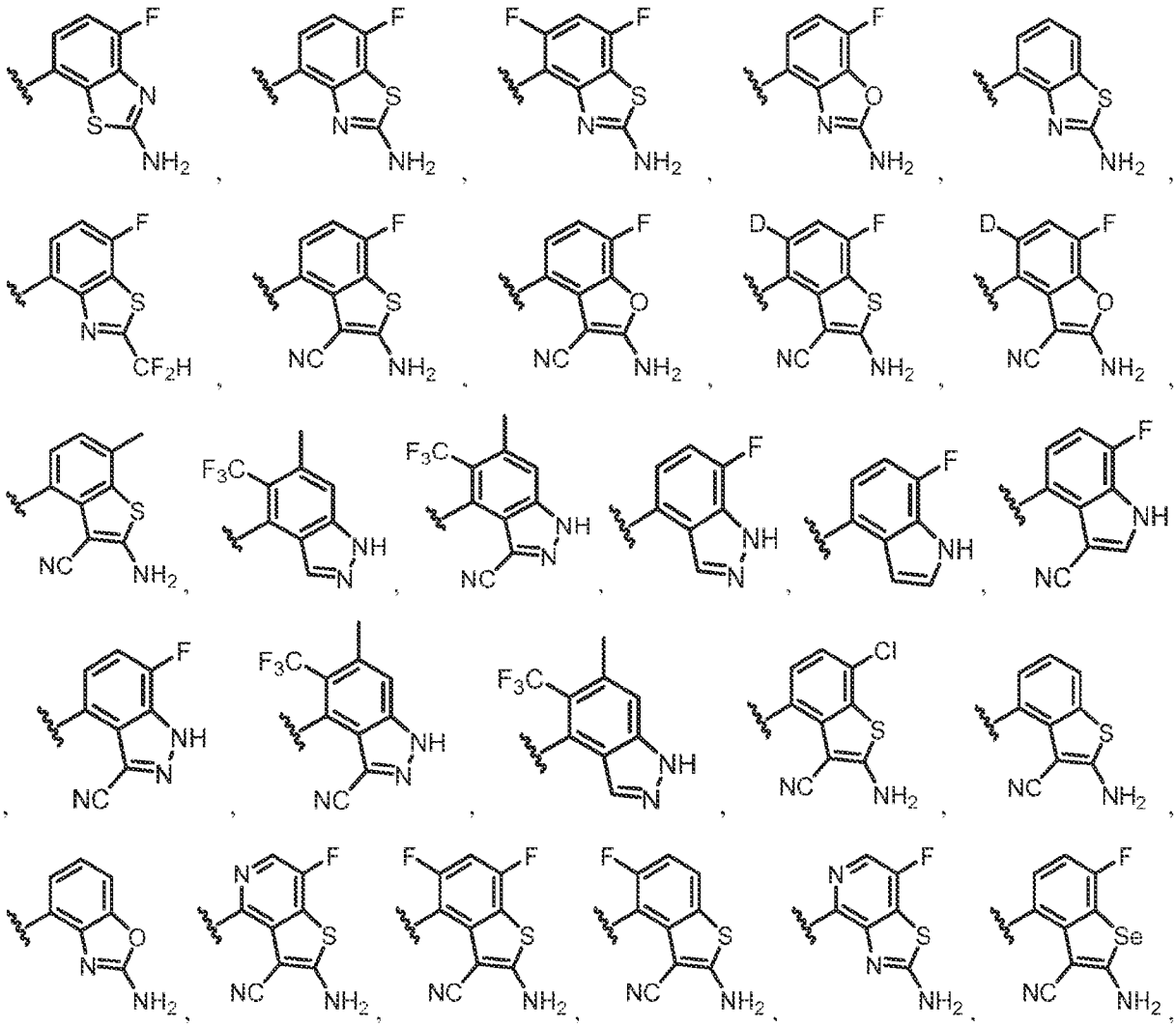
 ,  ,  ,  ,  ,

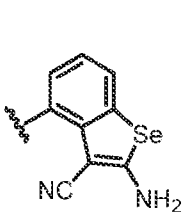
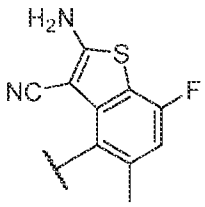
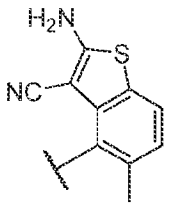
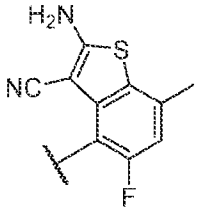
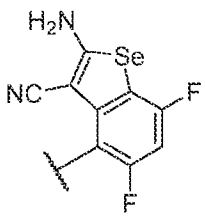
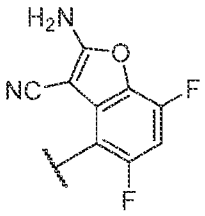
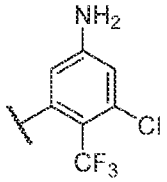
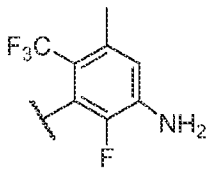
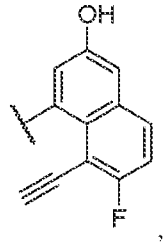
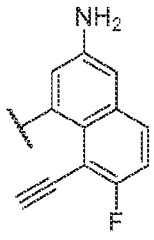
 ,  , ,  , ,



, and .

180. The compound of any one of claims 177-179, wherein R^6 is selected from:



181. The compound of any one of claims 177-180, wherein R^e is C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{20}.

182. The compound of any one of claims 177-180, wherein R^e is -C(O)(3-6 membered carbocycle).

183. The compound of any one of claims 177-180, wherein R^e is selected from -C(O)(C_{1-6}alkyl), -C(O)(3-6 membered carbocycle), and -C(O)O(C_{1-6}alkyl), wherein any C_{1-6}alkyl is unsubstituted or substituted with one or more R^{20}, and any 3-6 membered carbocycle is unsubstituted or substituted with one or more R^{12} or R^{20}.

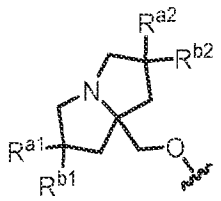
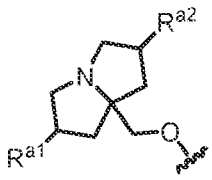
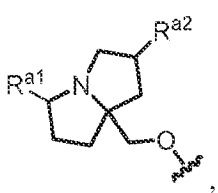
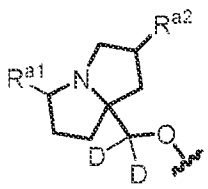
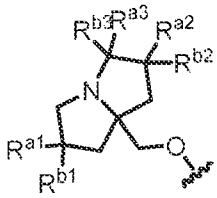
184. The compound of any one of claims 177-183, wherein each R^d is H.

185. The compound of any one of claims 164-184, wherein R^2 is H.

186. The compound of any one of claims 164-185, wherein R^2 is selected from C_{1-6}alkyl that is unsubstituted or is substituted with one or more R^{13} and is optionally deuterated.

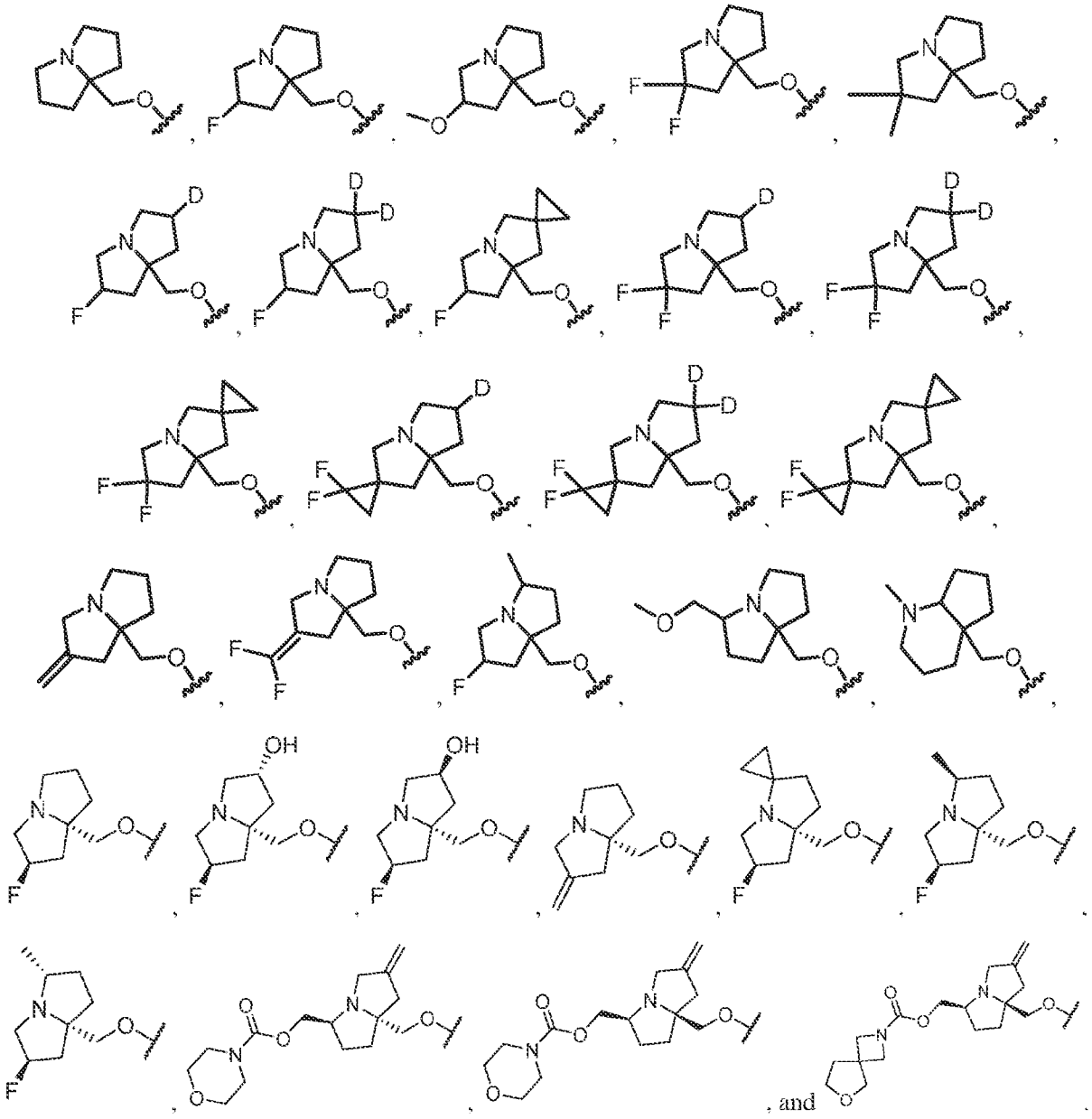
187. The compound of claim 186, wherein R^2 is selected from C_{1-2}alkyl and is optionally deuterated.

188. The compound of any one of claims 164-187, wherein R^1 is selected from -OR^8.

189. The compound of claim 188, wherein R^1 is selected from:  ,  ,  ,  , or  , R^{a1}, R^{a2}, R^{b1}, R^{b2}, R^{a3}, and R^{b3} are each independently selected from deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, , -C_{1-6}

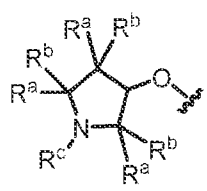
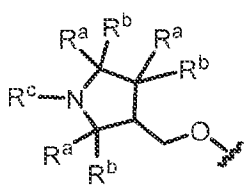
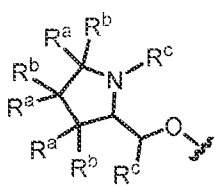
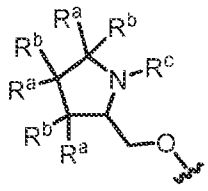
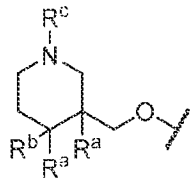
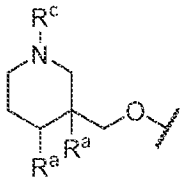
heteroalkyl, -OR^{12}, and H, wherein R^{a2} and R^{b2} or R^{a3} and R^{b3} can optionally join together to form a 3-6 membered carbocycle, and wherein any C_{1-6}alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle is unsubstituted or is substituted with one or more R^{13}.

190. The compound of claim 189, wherein R^1 is selected from:

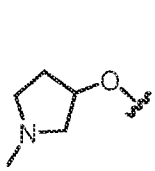
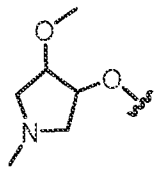


, and .

191. The compound of claim 188, wherein R^1 is selected from:






, or

.

wherein each R^a and R^b is independently selected from halogen, C_{1-6} alkyl, C_{2-6}alkenyl, , -OR^{12}, and H; and each R^c is independently selected from C_{1-6} alkyl and H, wherein an R^a and R^b or R^c optionally join together to form a 3-6 membered carbocycle or heterocycle, and wherein any C_{1-6} alkyl, C_{2-6}alkenyl, or 3-6 membered carbocycle or heterocycle is unsubstituted or is substituted with one or more R^{13}.

192. The compound of claim 191, wherein R^1 is selected from: 

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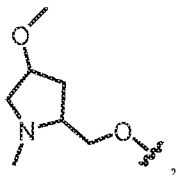
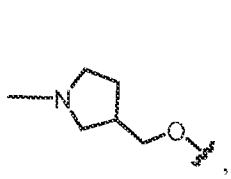
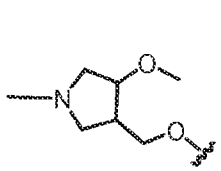
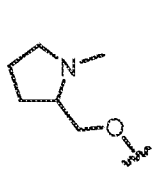
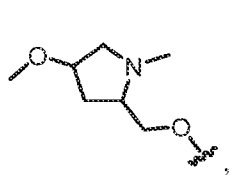
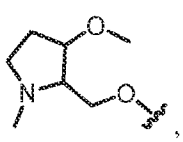
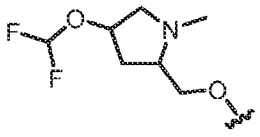
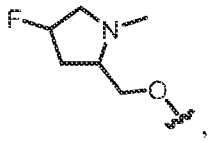
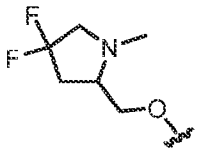
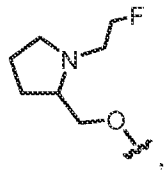
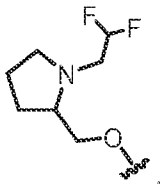
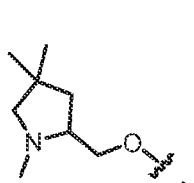
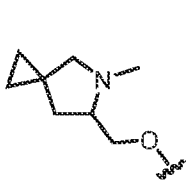
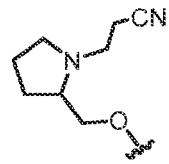
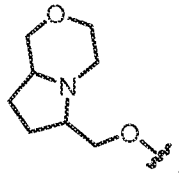
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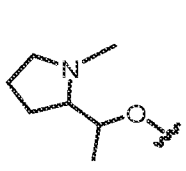
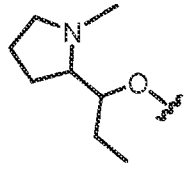
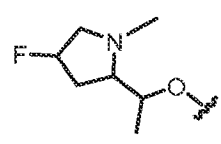
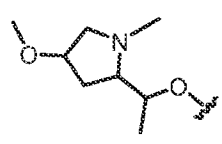
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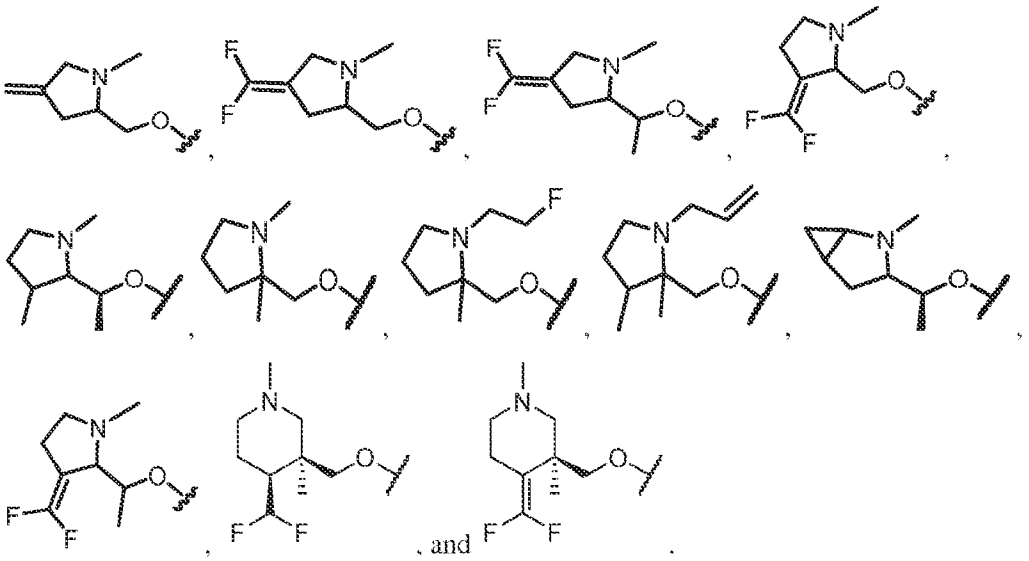
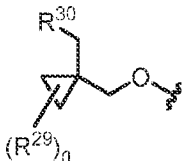


193. The compound of any one of claims 164-187, wherein R^1 is selected from



, wherein:

each R^{28} is independently selected from C_{1-6}alkyl and halogen; and

each R^{29} is independently selected from halogen and C_{1-6}alkyl;

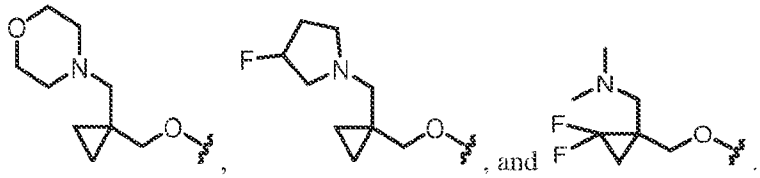
R^{30} is $N(R^{14})_2$ or a 3-6 membered heterocycle including one or more heteroatoms selected from N, O, and S, wherein the heterocycle is unsubstituted or substituted with one or more R^{28}; and

n is 0-2.

194. The compound of claim 193, wherein R^{30} is $N(R^{14})_2$.

195. The compound of claim 193 or 194, wherein at least one R^{29} is a halogen such as F.

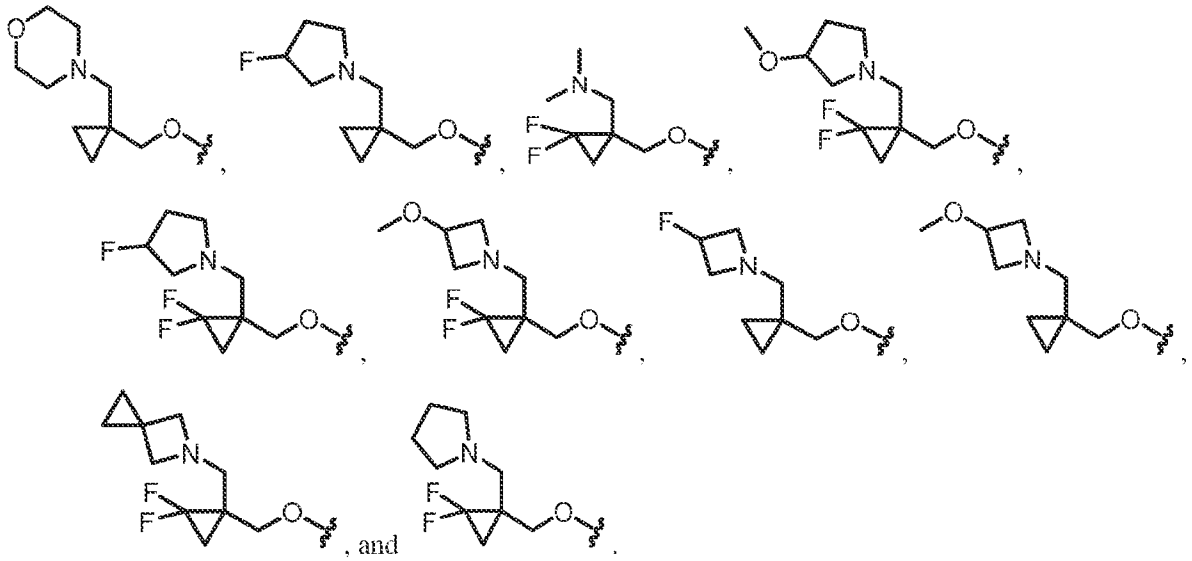
196. The compound of any one of claims 193-195, wherein R^1 is selected from:



197. The compound of any one of claims 164-187, wherein R^1 is a heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

198. The compound of claim 197, wherein R^1 is a 6-10 membered heterocycle comprising one or more N atoms, wherein the heterocycle is unsubstituted or substituted with one or more R^{31}, wherein each R^{31} is selected from C_{1-6} alkyl.

199. The compound of claim 197 or 198, wherein R^1 is selected from:



, and

200. The compound of any one of claims 164-187, wherein R^1 is H.

201. The compound of any one of claims 164-200, wherein R^5 is a halogen (e.g., F or Cl).

202. The compound of any one of claims 164-200, wherein R^5 is selected from C_{1-6}alkyl that is unsubstituted or substituted with one or more R^{13}.

203. The compound of claim 202, wherein R^5 is selected from - CH_3, -CF_2H, -CF_3, -CH_2CN, and -CH_2CH_3.

204. The compound of claim 203, wherein R^5 is -CF_3.

205. The compound of any one of claims 164-204, wherein the compound is a compound included in Table 1.

206. A compound shown in Table 3, Table 3a, Table 3b, or Table 3b, or a salt (e.g., pharmaceutically acceptable salt) thereof.

207. A pharmaceutical composition comprising a compound of any one of claims 1-206, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable excipient.

208. A compound of any one of claims 1-206, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use as a medicament.

209. The compound of claim 208, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D,

G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

210. The compound of claim 209, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

211. The compound of claim 209, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

212. The compound of any one of claims 208-211, wherein the medicament is useful in the prevention or treatment of a cancer.

213. The compound of claim 212, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

214. A compound of any one of claims 1-205, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the treatment of a disease, disorder, or condition.

215. The compound of claim 214, wherein the disease, disorder, or condition is a cancer.

216. The compound of claim 215, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

217. The compound of any one of claims 214-216, wherein the compound is used in the treatment of a disease, disorder, or condition in a subject in need thereof.

218. A compound of any one of claims 1-205, or a salt (e.g., pharmaceutically acceptable salt) thereof, for use in the manufacture of a medicament.

219. The compound of claim 218, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

220. The compound of claim 219, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

221. The compound of claim 219 or 220, wherein the medicament is useful in the prevention or treatment of a disease, disorder, or condition ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

222. The compound of any one of claims 218-221, wherein the medicament is useful in the treatment of a cancer.

223. The compound of claim 222, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

224. A method, comprising administering a therapeutically effective amount of a compound of any one of claims 1-205, or a salt (e.g., pharmaceutically acceptable salt) thereof, to a subject in need thereof.

225. The method of claim 224, wherein the subject has a disease, disorder, or condition ameliorated by the inhibition of KRAS having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, or wild-type KRAS, including wild-type amplified KRAS.

226. The method of claim 225, wherein the disease, disorder, or condition is ameliorated by the inhibition of wild-type KRAS, including wild-type amplified KRAS.

227. The method of claim 225 or 226, wherein the disease, disorder, or condition is ameliorated by the inhibition of KRAS having a G12D, G12R, or G12V mutation.

228. The method of any one of claims 224-227, wherein the subject has a cancer.

229. The method of claim 228, wherein the subject was previously diagnosed with the cancer.

230. The method of claim 228 or 229, wherein the subject has previously undergone a treatment regimen for the cancer.

231. The method of any one of claims 228-230, wherein the subject has previously entered remission from the cancer.

232. The method of any one of claims 228-231, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

233. The method of any one of claims 224-232, wherein the compound, or the salt thereof, is administered in combination with an additional therapeutic agent.

234. The use of a compound of any one of claims 1-205, or a salt (e.g., pharmaceutically acceptable salt) thereof, for the manufacture of a medicament for the treatment of a cancer.

235. The use of claim 234, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

236. A method, comprising contacting a KRAS protein with a compound of any one of claims 1-205, or a salt (e.g., pharmaceutically acceptable salt) thereof.

237. The method of claim 236, wherein contacting the KRAS protein with the compound modulates KRAS.

238. The method of claim 236 or 237, wherein the KRAS protein has a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation.

239. The method of claim 236 or 237, wherein the KRAS protein is a wild-type KRAS protein, including wild-type amplified KRAS.

240. The method of any one of claims 236-239, wherein the KRAS protein is in an active (GTP-bound) state.

241. The method of any one of claims 236-239, wherein the KRAS protein is in an inactive (GDP-bound) state.

242. The method of any one of claims 236-241, wherein the KRAS protein is located within a cell.

243. The method of claim 242, wherein the cell is located within a subject.

244. The method of claim 243, wherein the subject is a human.

245. The method of claim 243 or 244, wherein the subject has a cancer.

246. The method of claim 245, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, and lung cancer.

247. A method of inhibiting the function of a wild-type KRAS protein, including wild-type amplified KRAS, or a KRAS protein having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation, comprising contacting the KRAS protein with a compound of any one of claims 1-205, or a salt (e.g., pharmaceutically acceptable salt) thereof.

248. The method of claim 247, wherein the KRAS protein is a wild-type KRAS protein, including wild-type amplified KRAS.

249. The method of claim 247, wherein the KRAS protein has a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation.

250. The method of claim 247, wherein the KRAS protein has a G12D, G12V, or G12R mutation.

251. The method of any one of claims 247-250, wherein the KRAS protein is in an active (GTP-bound) state.

252. The method of any one of claims 247-250, wherein the KRAS protein is in an inactive (GDP-bound) state.

253. The method of any one of claims 247-252, wherein the KRAS protein is located within a cell.

254. The method of claim 253, wherein the cell is located within a subject.

255. The method of claim 254, wherein the subject is a human.

256. The method of claim 254 or 255, wherein the subject has a cancer.

257. The method of claim 256, wherein the cancer is selected from the group consisting of pancreatic cancer, colorectal cancer, esophageal adenocarcinoma, gastroesophageal junction cancer, invasive ductal carcinoma, and lung cancer.

258. A compound capable of inhibiting a wild-type KRAS protein, including wild-type amplified KRAS, or a KRAS protein having a Q61H, G13D, G12D, G12V, G12C, G12S, G12A, or G12R mutation in both its active (GTP-bound) and inactive (GDP-bound) state.

259. The compound of claim 258, wherein the compound:

(i) has $IC_{50} \leq 0.1$ μM, 0.1 μM< $IC_{50} \leq 1$ μM, 1 μM< $IC_{50} \leq 10$ μM, or 10 μM< IC_{50} in the assay of Biological Example 1 (e.g., a protein:protein interaction (PPI) Homogenous Time Resolved Fluorescence (HTRF) analysis of 50 nM Avi-KRAS G12D (amino acids

2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12C (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12V (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS WT (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), and/or 75 nM 3xFLAG-RAF1 RBD (51-131)-Avi; and/or

(ii) has IC_{50} ≤0.1 μM, or IC_{50}>0.1 μM in the assay of Biological Example 2 or 4 (e.g., cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iii) has IC_{50} ≤0.1 μM, 0.1 μM< IC_{50} ≤1 μM, or IC_{50} >1 μM in the assay of Biological Example 3 (cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iv) has IC_{50} ≤0.1 μM, 0.1 μM< IC_{50} ≤1 μM, or IC_{50} >1 μM in the assay of Biological Example 4 (cell-based pERK HTRF assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080); and/or

(v) has IC_{50} ≤0.1 μM, 0.1 μM< IC_{50} ≤1 μM, or IC_{50} >1 μM in the assay of Biological Example 5 (3D Cell viability assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080).

260. The compound of claim 259, wherein the compound:

(i) has IC_{50} ≤0.1 μM, 0.1 μM< IC_{50} ≤1 μM, or 1 μM< IC_{50} ≤10 μM in the assay of Biological Example 1 (e.g., a protein:protein interaction (PPI) Homogenous Time Resolved Fluorescence (HTRF) analysis of 50 nM Avi-KRAS G12D (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12C (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS G12V (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), 50 nM Avi-KRAS WT (amino acids 2-169) GTP/ RAF1 RBD-3xFLAG (51-131), and/or 75 nM 3xFLAG-RAF1 RBD (51-131)-Avi; and/or

(ii) has IC_{50} ≤0.1 μM in the assay of Biological Example 2 or 4 (e.g., cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iii) has IC_{50} ≤0.1 μM or 0.1 μM< IC_{50} ≤1 μM in the assay of Biological Example 3 (cell-based pERK HTRF assay in GP2d (G12D) cell); and/or

(iv) has IC_{50} ≤0.1 μM or 0.1 μM< IC_{50} ≤1 μM in the assay of Biological Example 4 (cell-based pERK HTRF assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080); and/or

(v) has IC_{50} ≤0.1 μM or 0.1 μM< IC_{50} ≤1 μM in the assay of Biological Example 5 (3D Cell viability assay in AsPC-1, SW1900, HPAC, Capan-2, RKN, H358, HCT116, KP-2, H1573, A549, MKN1, and HT1080).

261. The compound of any one of claims 258-260, wherein the compound is capable of irreversibly binding the KRAS protein.

262. The compound of any one of claims 258-260, wherein the compound is capable of reversibly binding the KRAS protein.

263. The compound of any one of claims 258-262, wherein the compound is a compound according to any one of claims 1-205.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/057867

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D409/04 C07D409/14 C07D413/14 C07D487/04 C07D487/10
C07D489/04 C07D519/00 A61P35/00 A61K31/517 A61K31/5377
A61K31/5517 A61K31/519 A61K31/5386 A61K31/55 A61K31/5395

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/177917 A2 (THERAS INC [US]; LEIDOS BIOMEDICAL RES INC [US] ET AL.) 25 August 2022 (2022-08-25) claims 1, 54, 89, 94, 97 compounds 115, 230, 251, 326, 364, 365, 382, 533, etc. ----- -/--	1-135, 164-263

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

[x] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2025	05/03/2025

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/057867

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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