FUSED PYRIDINES FOR THE TREATMENT OF CANCER AND OTHER INDICATIONS

GOVERNMENT SUPPORT

[0001] This invention was made with government support under 75N91019D00024 awarded by the National Institutes of Health and under 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 and benefit of U.S. Application No. 63/518,242, filed August 8, 2023, and U.S. Application No. 63/666,479, filed July 1, 2024, the entire contents of each of which are hereby incorporated by reference.

BACKGROUND

[0003] An estimated over 600,000 Americans will have died from cancer in 2021, corresponding to more than 1600 deaths per day (Cancer Facts and Figures 2021). The greatest number of deaths are from cancers of the lung, prostate, and colorectum in men, and cancers of the lung, breast, and colorectum in women. Almost one-quarter of all cancer deaths are due to lung cancer, 82% of which is directly caused by cigarette smoking. The 5-year survival rate for lung cancer patients is only about 20%.

[0004] The aberrant activation of the phosphoinositide 3-kinase (PI3K) is one of the most frequent oncogenic events across human cancers, and its inhibition is an attractive therapeutic approach in treating cancers. PI3Ks signal downstream of receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs), and RAS proteins to regulate a large number of cellular activities, including metabolism, proliferation, and migration.

[0005] The frequency of PI3K oncogenic events has fueled the development and testing of PI3K inhibitors. Most PI3K inhibitors that have entered clinical development thus far are reversible, ATP-competitive kinase inhibitors. Despite considerable efforts, the clinical outcome of PI3K inhibitor-based treatments for solid tumors has been disappointing, mainly due to intolerable toxicity and drug resistance.

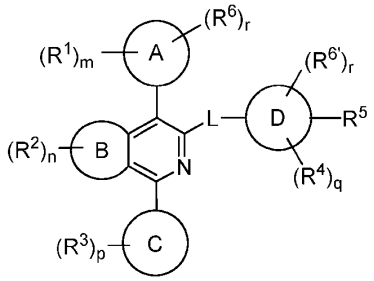
SUMMARY

[0006] The present disclosure provides new therapeutic modalities for treating cancers and other indications (e.g., cancers and other indications associated with and/or characterized by aberrant activation of PI3K). The present disclosure encompasses the recognition that a therapeutic agent (e.g., a therapeutic agent comprising a small molecule, e.g., a compound provided herein) that disrupts, inhibits, and/or prevents an interaction between a PI3K protein (e.g., PI3Kα) and a small GTPase (e.g., Rac1, CDC42, or a

RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) may be particularly useful for treating, ameliorating, delaying the progress of, ameliorating or eliminating a symptom of, and/or inhibiting a cancer and/or other indication (e.g., an indication associated with and/or characterized by aberrant activation of PI3K). Without wishing to be bound by theory, therapeutic agents provided herein (e.g., therapeutic agents comprising small molecules, e.g., compounds provided herein) may be capable of binding to a PI3K protein (e.g., PI3Kα) while displaying (i) no or minimal binding to a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and/or (ii) no substantial effect on the kinase activity of the PI3K protein (e.g., PI3Kα). In some embodiments, such therapeutic agents may provide advantages such as improved efficacy or reduced side effects as compared to, e.g., ATP-competitive PI3K kinase inhibitors, as described herein. For example, in some embodiments, such therapeutic agents may provide reduced instances of hyperglycemia and/or hyperinsulinemia relative to PI3K kinase inhibitors.

[0007] The present disclosure provides compounds (including in any available form, such as salt forms) useful in disrupting, inhibiting, and/or preventing an interaction between a PI3K protein (e.g., PI3Kα) and a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1). In some embodiments, the present disclosure provides compounds capable of binding a PI3Kα protein, such that (i) the interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and the PI3Kα protein is disrupted, inhibited, and/or prevented; and/or (ii) the kinase activity of the PI3Kα protein is not inhibited. In some embodiments, such compounds are useful for treating a cancer or other indication, as described herein.

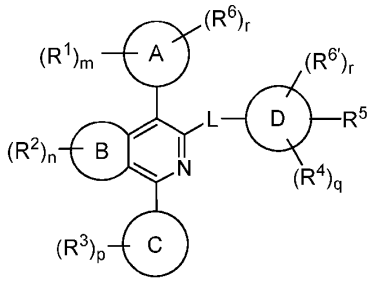
[0008] In some embodiments, the present disclosure provides a compound of Formula I'':



I''

or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein each of Ring A, Ring B, Ring C, Ring D, L, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, q, and r is as defined herein.

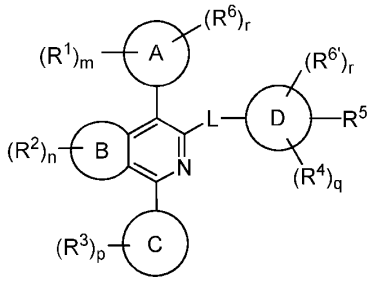
[0009] In some embodiments, the present disclosure provides a compound of Formula I':



I'

or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein each of Ring A, Ring B, Ring C, Ring D, L, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, q, and r is as defined herein.

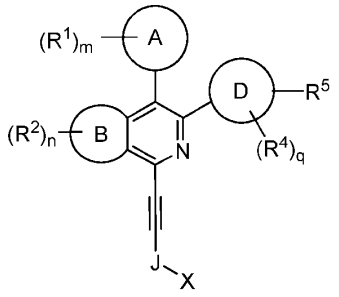
[00010] In some embodiments, the present disclosure provides a compound of Formula I:



I

or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein each of Ring A, Ring B, Ring C, Ring D, L, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, q, and r is as defined herein.

[00011] In some embodiments, the present disclosure provides a compound of Formula II:



II

or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein each of Ring A, Ring B, Ring D, J, R^1, R^2, R^4, R^5, X, m, n, and q is as defined herein.

[00012] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound provided herein (e.g., a compound of Formula I'', I', I, or II), or a salt (e.g., a pharmaceutically acceptable salt) thereof, together with a pharmaceutically acceptable carrier.

[00013] In some embodiments, the present disclosure provides a method of inhibiting, disrupting, and/or preventing an interaction between a PI3Kα protein and a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) such that the kinase activity of the PI3Kα protein is not inhibited. In some embodiments, the PI3Kα protein is in a cell, such as in a cell of a human or animal subject (e.g., as described herein).

[00014] In some embodiments, the present disclosure provides a method of treating, ameliorating, delaying the progress of, ameliorating or eliminating a symptom of, and/or inhibiting a cancer and/or other indication (e.g., an indication associated with and/or characterized by aberrant activation of PI3K) comprising administering a compound provided herein (e.g., a compound of Formula I'', I', I, or II), or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00015] In some embodiments, the present disclosure provides a use of a compound provided herein (e.g., a compound of Formula I'', I', I, or II), or a salt (e.g., a pharmaceutically acceptable salt) thereof, in the manufacture of a medicament for the treatment, amelioration, or inhibition of a cancer or other indication (e.g., an indication associated with and/or characterized by aberrant activation of PI3K). The present disclosure also provides a compound (e.g., a compound of Formula I'', I', I, or II), or a salt (e.g., a pharmaceutically acceptable salt) thereof, for use as a medicament, which medicament may be used in the treatment, amelioration, or inhibition of a cancer or other indication (e.g., an indication associated with and/or characterized by aberrant activation of PI3K).

DETAILED DESCRIPTION

Compounds and Definitions

[00016] Compounds of this disclosure include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

[00017] Unless otherwise stated, structures depicted herein are meant to include all stereoisomeric (e.g., enantiomeric, diastereomeric, atropisomeric, or epimeric) forms of the structure, as well as all geometric or conformational isomeric forms of the structure. For example, the R and S configurations of each

stereocenter are contemplated as part of the disclosure; and the D- and L-isomers of each compound are contemplated as part of the disclosure. Therefore, single stereochemical isomers, as well as enantiomeric, diastereomeric, atropisomeric, and geometric (or conformational) mixtures of provided compounds are within the scope of the disclosure. For example, in some cases, Table 1, Table 2, or Table 3 shows one or more stereoisomers of a compound, and unless otherwise indicated, represents each stereoisomer alone and/or as a mixture. The present disclosure includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers, as well as mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials that 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 via, e.g., recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method. Starting compounds of a particular stereochemistry are either commercially available or can be made and resolved by various techniques. Unless otherwise stated, all tautomeric forms (e.g., rapidly interconverting forms) of provided compounds are within the scope of the disclosure.

[00018] Unless otherwise indicated, structures depicted herein are meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including replacement of hydrogen by deuterium or tritium, or replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

[00019] ***Aliphatic:*** The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation (e.g., multiple bonds, such as double or triple bonds). Unless otherwise specified, aliphatic groups contain 1-12 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms.

[00020] ***Alkyl:*** The term "alkyl", used alone or as part of a larger moiety, refers to a saturated, optionally substituted straight or branched hydrocarbon group having (unless otherwise specified) 1-12, 1-10, 1-8, 1-6, 1-4, 1-3, or 1-2 carbon atoms (e.g., C_{1-12}, C_{1-10}, C_{1-8}, C_{1-6}, C_{1-4}, C_{1-3}, or C_{1-2}). Examples of alkyl groups include methyl, ethyl, propyl (e.g., n-propyl), isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, pentyl, isoamyl, hexyl, heptyl, octyl, and nonyl. The term "alkylene," as used herein, alone or in combination, refers to a bivalent, saturated, optionally substituted straight or branched hydrocarbon, such as methylene ($-CH_2-$).

[00021] ***Alkenyl:*** The term "alkenyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched hydrocarbon chain having at least one double bond and having (unless otherwise specified) 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms (e.g., C_{2-12}, C_{2-10}, C_{2-8}, C_{2-6}, C_{2-4}, or C_{2-3}). Examples of alkenyl groups include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl, butenyl, pentenyl, hexenyl, and heptenyl.

[00022] ***Alkynyl:*** The term "alkynyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one triple bond and having (unless otherwise specified) 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms (e.g., C_{2-12}, C_{2-10}, C_{2-8}, C_{2-6}, C_{2-4}, or C_{2-3}). Examples of alkynyl groups include ethynyl, 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.

[00023] ***Aryl***: The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of six to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring(s)." Examples of aryl groups include phenyl, naphthyl, anthracyl and the like, which may bear one or more substituents as defined herein. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl or tetrahydronaphthyl, and the like. Unless otherwise specified, "aryl" groups are hydrocarbons.

[00024] ***Carbocyclyl:*** The terms "carbocyclyl," "carbocycle," and "carbocyclic ring" as used herein, refer to saturated or partially unsaturated cyclic aliphatic monocyclic, bicyclic, or polycyclic ring systems, as described herein, having from 3 to 14 members, wherein the aliphatic ring system is optionally substituted as described herein. A carbocycle may comprise fused ring systems, bridged ring systems, and/or spiro ring systems (e.g., a system including two rings sharing a single carbon atom). Carbocyclic groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, norbornyl, adamantyl, and cyclooctadienyl. In some embodiments, "carbocyclyl" (or "cycloaliphatic") refers to an optionally substituted monocyclic C_3-C_8 hydrocarbon, or an optionally substituted C_5-C_{10} bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic. The term "cycloalkyl" refers to an optionally substituted saturated ring system of 3 to 10 ring carbon atoms. In some embodiments, cycloalkyl groups have 3–6 carbons. Examples of monocyclic cycloalkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" refers to an optionally substituted non-aromatic monocyclic or multicyclic ring system containing at least one carbon-

carbon double bond and having 3 to 10 carbon atoms. Examples of monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[00025] ***Composition***: As used herein, the term "composition" refers to a discrete physical entity that comprises one or more specified components (e.g., a product comprising one or more specified ingredients (e.g., in specified amounts) or a product that results, directly or indirectly, from combination of specified ingredients in specified amounts). Unless otherwise specified, a composition may be of any form – e.g., gas, gel, liquid, solid, etc. A composition may comprise one or more pharmaceutically acceptable components, such as a carrier, diluent, or excipient. By "pharmaceutically acceptable" it is generally meant the carrier, diluent, or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. For example, a "pharmaceutically acceptable excipient" refers to a substance that aids the administration of an active agent to and absorption by a subject.

[00026] ***Halogen***: The term "halogen" or "halo" means F, Cl, Br, or I.

[00027] ***Heteroaryl***: The terms "heteroaryl", "heteroaromatic", and "heteroar–," used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to optionally substituted groups having 5 to 14 ring atoms (e.g., 5- to 6-membered monocyclic heteroaryl or 9- to 10-membered bicyclic heteroaryl); having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. Examples of heteroaryl groups include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. "Heteroaryl", as used herein, also includes groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclic rings. Examples of bicyclic heteroaromatic groups include indolyl, isoindolyl, benzothienyl, benzofuranyl, indazolyl, indolizinyl, benzimidazolyl, benzthiazolyl, benzotriazolyl, benzoxazolyl, benzoxadiazolyl, benzothiadiazolyl, tetrazolopyridazinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl, chromonyl, coumarinyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, and 4*H*–quinolizinyl. Examples of tricyclic heterocyclic groups include carbazolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenazinyl, phenanthridinyl, phenothiazinyl, phenoxazinyl, and xanthenyl. It will be appreciated that certain tautomeric forms of a heteroaryl ring can exist and are encompassed by the term "heteroaryl." Such tautomeric forms include, for example, pyridin-2(1*H*)-one.

[00028] ***Heteroatom***: The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon); the quaternized form of any basic nitrogen or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)). In some embodiments, a heteroatom is selected from oxygen, sulfur, and nitrogen.

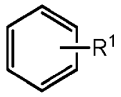
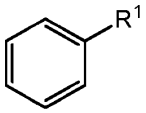
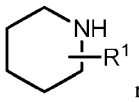
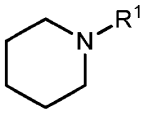
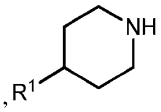
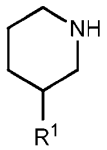
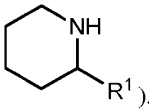
[00029] ***Heterocycle***: As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a 3- to 8-membered monocyclic or 5- to 10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to one or more carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. A heterocycle may comprise fused ring systems, bridged ring systems, and/or spiro ring systems (e.g., a system including two rings sharing a single carbon atom). A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be unsubstituted or substituted with one or more substituents (e.g., as described herein). Examples of such saturated or partially unsaturated heterocyclic radicals include tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. "Heterocycle," as used herein, also includes groups in which a heterocyclic ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl.

[00030] ***Partially Unsaturated***: As used herein, the term "partially unsaturated", when referring to a ring moiety, means a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[00031] ***Patient or Subject:*** As used herein, the term "patient" or "subject" refers to any organism to which a provided compound or composition is or may be administered, e.g., for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients or subjects include animals (e.g., mammals such as mice, rats, rabbits, hamsters, guinea pigs, cats, dogs, goats, pigs, sheep, cows, deer, horses, non-human primates, and/or humans). In some embodiments, a patient or subject is a human. In some embodiments, a patient or a subject is suffering from or susceptible to one or more disorders or conditions. In some embodiments, a patient or subject displays one or more symptoms of a disorder or condition. In some embodiments, a patient or subject has been diagnosed with one or more disorders or conditions. In some embodiments, a patient or a subject is receiving or has received certain therapy to diagnose and/or to treat a disease, disorder, or condition.

[00032] ***Prevent or prevention:*** As used herein, when used in connection with the occurrence of a disease, disorder, and/or condition, "prevent" or "prevention" refers to reducing the risk of developing the disease, disorder, or condition; delaying onset of one or more characteristics or symptoms of the disease, disorder, or condition; and/or preventing 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. Prevention may be considered complete when onset of a disease, disorder or condition has been delayed for a predefined period of time.

[00033] ***Substituted or Optionally Substituted:*** As described herein, compounds of this disclosure may contain "optionally substituted" moieties (e.g., moieties bearing one or more substituents). In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. "Substituted" applies to one or more hydrogens that are either explicit or implicit from the structure (e.g.,  refers to at least ; and  refers to at least , , , or ). Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes provided herein. Groups described as being "substituted" preferably have between 1 and 4 substituents, more preferably 1 or 2 substituents. Groups described as being "optionally substituted" may be unsubstituted or be "substituted" as described above.

[00034] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R°$; $-(CH_2)_{0-4}OR°$; $-O(CH_2)_{0-4}R°$, $-O-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}CH(OR°)_2$; $-(CH_2)_{0-4}SR°$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; –CN; $-N_3$; $-(CH_2)_{0-4}N(R°)_2$; $-(CH_2)_{0-4}N(R°)C(O)R°$; $-N(R°)C(S)R°$; $-(CH_2)_{0-4}N(R°)C(O)NR°_2$; $-N(R°)C(S)NR°_2$; $-(CH_2)_{0-4}N(R°)C(O)OR°$; -

$N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $-(CH_2)_{0-4}C(O)R°$; $-C(S)R°$; $-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}C(O)SR°$; $-(CH_2)_{0-4}C(O)OSiR°_3$; $-(CH_2)_{0-4}OC(O)R°$; $-OC(O)(CH_2)_{0-4}SR°$; $-(CH_2)_{0-4}SC(O)R°$; $-(CH_2)_{0-4}C(O)NR°_2$; $-C(S)NR°_2$; $-C(S)SR°$; $-SC(S)SR°$, $-(CH_2)_{0-4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $-C(O)C(O)R°$; $-C(O)CH_2C(O)R°$; $-C(NOR°)R°$; $-(CH_2)_{0-4}SSR°$; $-(CH_2)_{0-4}S(O)_2R°$; $-(CH_2)_{0-4}S(O)_2OR°$; $-(CH_2)_{0-4}OS(O)_2R°$; $-S(O)_2NR°_2$; $-(CH_2)_{0-4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $-N(R°)S(O)_2R°$; $-N(OR°)R°$; $-C(NH)NR°_2$; $-P(O)_2R°$; $-P(O)R°_2$; $-OP(O)R°_2$; $-OP(O)(OR°)_2$; $-SiR°_3$; $-(C_{1-4}$ straight or branched alkylene$)O-N(R°)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R°)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2-$(5- to 6-membered heteroaryl ring), or a 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3- to 12-membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[00035] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^•$, $-(haloR^•)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^•$, $-(CH_2)_{0-2}CH(OR^•)_2$, $-O(haloR^•)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^•$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^•$, $-(CH_2)_{0-2}SR^•$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^•$, $-(CH_2)_{0-2}NR^•_2$, $-NO_2$, $-SiR^•_3$, $-OSiR^•_3$, $-C(O)SR^•$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^•$, or $-SSR^•$ wherein each $R^•$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[00036] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O ("oxo"), =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, $C_{1\ 6}$ aliphatic which may be substituted as defined below, or an unsubstituted 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00037] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, -(halo$R^\bullet$), -OH, $-OR^\bullet$, -O(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00038] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3- to 12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00039] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^\bullet$, -(halo$R^\bullet$), –OH, $-OR^\bullet$, -O(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00040] ***Treat:*** As used herein, the term "treat" (also "treatment" or "treating") refers to any administration of a therapy (e.g., therapeutic agent) that partially or completely alleviates, ameliorates, relives, inhibits, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms, features, and/or causes of a particular disease, disorder, and/or condition. Treatment may also refer to any other 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. In some embodiments, such treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. Alternatively or additionally, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, and/or condition.

PI3K and Small GTPase Proteins

[00041] The aberrant activation of the phosphoinositide 3-kinase (PI3K) is one of the most frequent oncogenic events across human cancers, and its inhibition is an attractive therapeutic approach in treating cancers. PI3Ks signal downstream of receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs), and RAS proteins to regulate a large number of cellular activities, including metabolism, proliferation, and migration. Upon activation, PI3K catalyzes the synthesis of the second messenger phosphatidylinositol (3,4,5)-trisphosphate (PIP3) by phosphorylating phosphatidylinositol 4,5-bisphosphate (PIP2). Signaling proteins such as Ser/Thr kinase AKT (e.g., Protein Kinase B (PKB)) can bind to PIP3 and thereby localize to the cell membrane. Phosphorylated AKT activates or inhibits several signaling proteins through direct phosphorylation including the mammalian target of rapamycin complex 1 (mTORC1), which acts as a regulator of cell growth and survival pathways, cyclin D1, GSK3(B), BAD, MDM2, FOXO, TSC1/2, and PRAS40. Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) regulates this pathway by dephosphorylating PIP3 to PIP2 and thus prevents activation of downstream kinases.

[00042] Based on the sequence homology and substrate preference, PI3Ks have been grouped into three separate classes (e.g., classes I, II, and III). Class I PI3Ks are further divided into two subclasses, IA and IB depending on their modes of regulation. Class IA PI3Ks are heterodimers comprising p110 catalytic and p85 regulatory subunits, and are most clearly implicated in human cancer. Class IA PI3K contains p110α, p110β, and p110δ catalytic subunits produced from different genes (PIK3CA, PIK3CB, and PIK3CD, respectively), while p110γ produced by PIK3CG represents the only catalytic subunit in class IB PI3K. The expression of PI3K isoforms (e.g., PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ) is specific to cell types. The p110α and β isoforms are expressed in all cell types, whereas p110δ expression is mainly confined to leukocytes. The p110γ isoform is expressed primarily in the myeloid cell lineage.

[00043] PIK3CA gene encodes the 1068 amino acid p110α protein that contains five domains: an N-terminal adaptor binding domain (ABD) that binds to regulatory subunit p85α, a RAS-binding domain (RBD), a C2 domain, a helical domain, and a kinase catalytic domain. RAS contributes directly to the activation of the PI3K pathway through direct binding of RAS proteins (e.g., HRAS, NRAS, and KRAS) to a RAS-binding domain (RBD) in the p110α catalytic subunit of PI3Kα. Activating mutations in the KRAS and PIK3CA genes are frequently detected in cancer, making these two proteins important targets for drug discovery. Somatic missense mutations in the PIK3CA gene have been reported in many human cancer types including breast, colon, liver, stomach, endometrial, bladder, and lung cancers. The most frequent hotspot mutations in PIK3CA are E542K, E545K, H1047R, and H1047L, and they account for 80–90% of all PIK3CA mutations detected in human malignancies. These *PIK3CA* mutations lead to

increased catalytic activity of p110α, which causes downstream effects such as unregulated cell growth, proliferation, and survival.

[00044] Mutations in RAS proteins are found in over 20% of all human cancers. RAS proteins function as molecular switches that cycle between an active, GTP-bound state and an inactive, GDP-bound state. In the active state, RAS proteins interact with various effector proteins including PI3K, RAF kinase, and RalGDS, leading to activation of multiple downstream signaling pathways. Oncogenic RAS mutations are predominantly found at amino acid positions G12, G13, and Q61, and these mutations impair GTPase activities leading to the accumulation of active RAS proteins. The most common oncogenic RAS mutations are G12C, G12D, G12S, G12V, G12R, G13D, and Q61H.

[00045] RAS signaling through PI3K is necessary for normal lymphatic development and RAS-induced transformation, especially in lung cancer, where the interaction between mutant RAS and p110a-RBD is essential for tumor initiation and maintenance. RAS interactions with p110α-RBD have been shown to be crucial for epidermal growth factor (EGF) signaling to PI3K. Recent studies have shown that disrupting the RAS-PI3K interaction inhibits AKT and RAC1 activation in EGFR-mutant lung cancer cells, leading to reduced growth and survival and inhibiting EGFR-mutant-induced tumor onset. These results suggest that the binding of p110α to endogenous RAS proteins in EGFR-driven lung adenocarcinoma is critical in tumors driven by upstream activators of the RAS pathways and not just those in which RAS is mutationally activated.

[00046] Small GTPases (e.g., other than RAS) are also expected to bind the RBD of PI3Kα resulting in activation of signaling. The small GTPases Rac1 and CDC42 have been shown to bind the RBD of PI3Kβ and are hypothesized to also be capable of binding the RBD of PI3Kα. Accordingly, in some embodiments, the present disclosure encompasses the recognition that disrupting an interaction between PI3Kα and any small GTPase that binds the RBD of PI3Kα may be a useful therapeutic strategy for treating cancers and other indications. In some embodiments, a small GTPase is selected from Rac1, CDC42, and RAS proteins (including HRAS, NRAS, KRAS, RRAS, RRAS2, MRAS, and RIT1).

[00047] The frequency of oncogenic PIK3CA hotspot mutations across cancers has fueled the development and testing of numerous PI3K (e.g., PI3Kα) inhibitors. Most PI3K inhibitors that have entered clinical development thus far are reversible, ATP-competitive kinase inhibitors. Despite considerable efforts, the clinical outcome of PI3K inhibitor-based treatments for solid tumors has been disappointing, mainly due to intolerable toxicity and drug resistance. In 2019, the U.S. Food and Drug Administration (FDA) approved alpelisib (BYL719; Novartis Pharma AG), an inhibitor specific to the PI3Kα isoform, combined with fulvestrant for the treatment of patients diagnosed with HR+/HER2- PIK3CA-mutation. The therapeutic window of PI3K inhibitors is mainly limited by isoform selectivity and off-tumor toxicity. Moreover, hyperglycemia and hyperinsulinemia have been observed as major dose-limiting toxicities for

p110α inhibitors, which prevent the use of sufficiently high doses to fully suppress PI3Kα signaling in the tumor. Hyperglycemia and hyperinsulinemia are considered on-target effects of PI3Kα inhibition, as inhibition of the PI3K/AKT pathway reduces glucose uptake, which in turn leads to increased secretion of insulin and subsequent activation of insulin/insulin-like growth factor I receptor in tumor cells, providing a survival mechanism for tumor cells and limiting the therapeutic efficacy of the PI3Kα inhibitor. Indeed, hyperglycemia was observed in 65% of patients in a Phase III clinical trial of alpelisib, leading to significant dose interruptions.

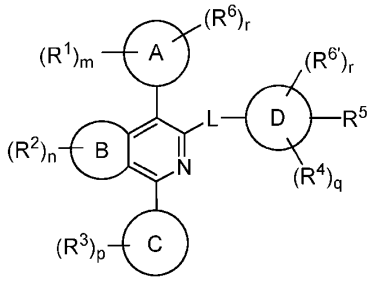
[00048] To overcome the limitations of current PI3Kα inhibitors, novel strategies to target PI3Kα need to be explored. Previous studies have suggested that inhibiting the RAS-p110α(RBD) interaction has minimal toxicity in adult animals while effectively causing tumor regression. The present disclosure encompasses the recognition that this therapeutic approach may be effective in various cancers including RAS-mutant-driven cancers and/or those driven by mutations or amplification of receptor tyrosine kinases (RTKs). The present disclosure also appreciates that this therapeutic modality may provide certain advantages over known PI3Kα inhibitors (e.g., those that target the ATP binding pocket of PI3Kα). For example, provided technologies may avoid hyperglycemia and insulin-driven resistance common to PI3Kα inhibitors, e.g., because such technologies target activation of PI3Kα by RAS, which is mostly present in transformed cells.

Provided Compounds

[00049] In some embodiments, the present disclosure provides compounds useful for disrupting, inhibiting, and/or preventing the interaction between small GTPases (e.g., RAS proteins, as described herein) and PI3Kα proteins. In some embodiments, the present disclosure provides compounds capable of binding PI3Kα, such that (i) the interaction between the small GTPase (e.g., RAS protein, as described herein) and PI3Kα is disrupted, inhibited, or prevented; and/or (ii) the kinase activity of PI3Kα is not significantly inhibited. In some embodiments, such compounds bind PI3Kα reversibly. As used herein, a compound that binds "reversibly" refers to a compound that is able to bind to and become dissociated from a target protein kinase (e.g., PI3Kα). Often, but not always, reversible inhibitors are not able to form a covalent bond with a target protein kinase. In some embodiments, such compounds bind PI3Kα irreversibly. As used herein, a compound that binds "irreversibly" refers to a compound that is able to interact (e.g., to form a covalent bond) with a target protein kinase (e.g., PI3Kα) in a substantially non-reversible manner. In some embodiments, a reversible or irreversible inhibitor may be capable of interacting covalently with PI3Kα. For example, in some embodiments the present disclosure provides compounds comprising an electrophilic moiety (e.g., a Michael acceptor or the like) capable of binding (e.g., reversibly or irreversibly) to, e.g., a cysteine residue in the catalytic subunit of PI3Kα (e.g., C242).

In some embodiments, provided compounds that interact with PI3Kα covalently are compounds of Formula I or II wherein $-R^5$ comprises an electrophilic moiety (e.g., a Michael acceptor or the like) capable of binding (e.g., reversibly or irreversibly) to, e.g., a cysteine residue of PI3Kα (e.g., C242).

[00050] In some embodiments, the present disclosure provides a compound of Formula I'':



I''

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

Ring A is phenyl, pyridinyl, or a 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered carbocyclic ring; and phenyl;

Ring C is selected from phenyl; 9- to 10-membered bicyclic aryl ring, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is absent or selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; 5- to 10-membered bicyclic or polycyclic carbocyclic ring; 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen,

and sulfur; and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is a covalent bond or a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-;

and when Ring D is absent, then L is also absent;

each R^1 is independently selected from halogen, optionally substituted C_{1-6} alkyl, cycloalkyl, –CN, –C(O)OR, –C(O)NR_2, –CH_2NR_2, –$N(R^7)_2$, -N=S$(R^7)_2$, –SR^7, –(C_{1-4} alkylene)OR, and –OR^7, wherein a sulfur atom in R^1 can be oxidized;

each R^7 is independently selected from hydrogen, optionally substituted C_{1-6} aliphatic, –(C_{1-4} alkylene)OR, –(C_{1-4} alkylene)NR_2, optionally substituted 3- to 6-membered carbocyclic ring, optionally substituted 4- to 7-membered heteroaryl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

or two R^7 groups, together with the atom(s) to which they are attached, form a 4- to 6-membered heterocyclic ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently selected from halogen and optionally substituted C_{1-6} aliphatic, and -OR;

each R^3 is independently selected from oxo, halogen, -CN, -OR, -C(O)R, -C(O)$N(R)_2$, -$(CH_2)_x$C(O)OR, -$(CH_2)_x$C(O)$N(R)_2$, -$(CH_2)_x$N(R)C(O)R, -$(CH_2)_x$Cy, -O$(CH_2)_x$Cy, -C(O)Cy, optionally substituted carbocyclic ring, and optionally substituted C_{1-6} aliphatic;

each R^4 is independently optionally substituted C_{1-6} aliphatic;

R^5 is absent, optionally substituted C_{1-6} aliphatic, -C(O)R^9, -$(CH_2)_x$N(R)C(O)R^9, or -CN;

R^9 is optionally substituted C_{2-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or a 4-membered bicyclic carbocyclic ring;

R^6 and $R^{6'}$ are connected with an optionally substituted C_{4-8} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2;

r is 0 or 1;

each x is independently 0, 1, or 2;

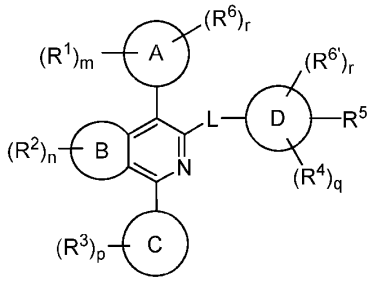
each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

each Cy is independently selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8; and

each R^8 is independently selected from oxo, halogen, and optionally substituted C_{1-6} aliphatic.

[00051] In some embodiments, the present disclosure provides a compound of Formula I'' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00052] In some embodiments, the present disclosure provides a compound of Formula I':



I'

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

Ring A is phenyl, pyridinyl, or a 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered carbocyclic ring; and phenyl;

Ring C is selected from phenyl; 9- to 10-membered bicyclic aryl ring, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; 5- to 10-membered bicyclic or polycyclic carbocyclic ring; 4- to 7-

membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

and when L is C_{2-5} alkynyl, then Ring D may be absent;

L is a covalent bond or a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-;

each R^1 is independently selected from halogen, optionally substituted C_{1-6} alkyl, cycloalkyl, –CN, –C(O)OR, –C(O)NR_2, –CH_2NR_2, –SR^7, –(C_{1-4} alkylene)OR, and –OR^7;

each R^7 is independently selected from optionally substituted C_{1-6} aliphatic, –(C_{1-4} alkylene)OR, –(C_{1-4} alkylene)NR_2, optionally substituted 3- to 6-membered carbocyclic ring, optionally substituted 4- to 7-membered heteroaryl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently selected from halogen and optionally substituted C_{1-6} aliphatic;

each R^3 is independently selected from oxo, halogen, -CN, -OR, -C(O)R, -C(O)$N(R)_2$, -$(CH_2)_xC(O)OR$, -$(CH_2)_xC(O)N(R)_2$, -$(CH_2)_xN(R)C(O)R$, -$(CH_2)_xCy$, -$O(CH_2)_xCy$, -C(O)Cy, optionally substituted carbocyclic ring, and optionally substituted C_{1-6} aliphatic;

each R^4 is independently optionally substituted C_{1-6} aliphatic;

R^5 is -$C(O)R^9$, -$(CH_2)_xN(R)C(O)R^9$, or -CN;

R^9 is optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or a 4-membered bicyclic carbocyclic ring;

R^6 and $R^{6'}$ are connected with an optionally substituted C_{4-8} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2;

r is 0 or 1;

each x is independently 0, 1, or 2;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

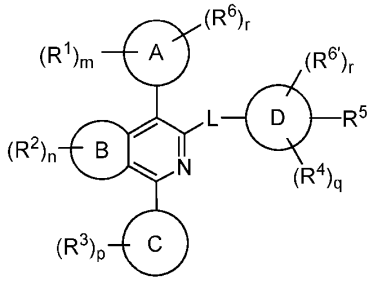
each Cy is independently selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to

7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8; and

each R^8 is independently selected from oxo, halogen, and optionally substituted C_{1-6} aliphatic.

[00053] In some embodiments, the present disclosure provides a compound of Formula I' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00054] In some embodiments, the present disclosure provides a compound of Formula I:



I

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

Ring A is phenyl;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5- to 6-membered carbocyclic ring, and phenyl;

Ring C is selected from phenyl, 9- to 10-membered bicyclic aryl ring, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

and when L is C_{2-5} alkynyl, then Ring D may be absent;

L is a covalent bond or a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-;

each R^1 is independently selected from halogen and $-OR^7$;

each R^7 is independently selected from optionally substituted C_{1-6} aliphatic and $-(C_{1-4}$ alkylene)OR;

each R^2 is independently selected from halogen and optionally substituted C_{1-6} aliphatic;

each R^3 is independently selected from oxo, halogen, -CN, -OR, -C(O)R, $-(CH_2)_xC(O)OR$, $-(CH_2)_xC(O)N(R)_2$, $-(CH_2)_xN(R)C(O)R$, $-(CH_2)_xCy$, $-O(CH_2)_xCy$, -C(O)Cy, and optionally substituted C_{1-6} aliphatic;

each R^4 is independently optionally substituted C_{1-6} aliphatic;

R^5 is $-C(O)R^9$, $-(CH_2)_xN(R)C(O)R^9$, or -CN;

R^9 is optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or a 4-membered bicyclic carbocyclic ring;

R^6 and $R^{6'}$ are connected with an optionally substituted C_{4-8} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2;

r is 0 or 1;

each x is independently 0, 1, or 2;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

each Cy is independently selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8; and

each R^8 is independently selected from oxo, halogen, and optionally substituted C_{1-6} aliphatic.

[00055] In some embodiments, the present disclosure provides a compound of Formula I or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00056] In some embodiments, the present disclosure provides a compound of Formula I, I', or I'', wherein:

Ring A is phenyl;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5- to 6-membered carbocyclic ring, and phenyl;

Ring C is selected from phenyl, 9- to 10-membered bicyclic aryl ring, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

and when L is C_{2-5} alkynyl, then Ring D may be absent;

L is a covalent bond or a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-;

each R^1 is independently selected from halogen and $-OR^7$;

each R^7 is independently selected from C_{1-6} aliphatic and $-(C_{1-4}$ alkylene)OR;

each R^2 is independently selected from halogen and C_{1-6} aliphatic;

each R^3 is independently selected from oxo, halogen, -CN, -OR, -C(O)R, $-(CH_2)_xC(O)OR$, $-(CH_2)_xC(O)N(R)_2$, $-(CH_2)_xN(R)C(O)R$, $-(CH_2)_xCy$, $-O(CH_2)_xCy$, -C(O)Cy, and C_{1-6} aliphatic optionally substituted with one or more R^{10};

each R^4 is independently selected from C_{1-6} aliphatic optionally substituted with one or more R^{10};

R^5 is $-C(O)R^9$, $-(CH_2)_xN(R)C(O)R^9$, or -CN;

R^9 is C_{2-6} alkenyl optionally substituted with one or more R^{10}, C_{2-6} alkynyl optionally substituted with one or more R^{10}, or a 4-membered bicyclic carbocyclic ring;

R^6 and $R^{6'}$ are connected with a C_{4-8} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2;

r is 0 or 1;

each x is independently 0, 1, or 2;

each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with one or more R^{10};

each Cy is independently selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8;

each R^8 is independently selected from oxo, halogen, and C_{1-6} aliphatic; and

each R^{10} is independently selected from halogen, -CN, -OH, -O(C_{1-6} alkyl), -NH_2, -NH(C_{1-6} alkyl), and -N(C_{1-6} alkyl)$_2$.

[00057] In some embodiments, the present disclosure provides a compound of Formula I', wherein:

Ring A is phenyl;

Ring B is a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring C is selected from phenyl, 9- to 10-membered bicyclic aryl ring, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is a covalent bond;

each R^1 is independently selected from halogen and –OR^7;

each R^7 is independently selected from optionally substituted C_{1-6} aliphatic, –(C_{1-4} alkylene)OR, and optionally substituted 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently selected from halogen and C_{1-6} aliphatic;

each R^3 is independently selected from oxo, halogen, -CN, -OR, -C(O)R, -C(O)N(R)$_2$, -(CH$_2$)$_x$C(O)OR, -(CH$_2$)$_x$C(O)N(R)$_2$, -(CH$_2$)$_x$N(R)C(O)R, -(CH$_2$)$_x$Cy, -O(CH$_2$)$_x$Cy, -C(O)Cy, a carbocyclic ring, and C_{1-6} aliphatic optionally substituted with one or more R^{10};

each R^4 is independently selected from C_{1-6} aliphatic optionally substituted with one or more R^{10};

R^5 is -C(O)R^9, -(CH$_2$)$_x$N(R)C(O)R^9, or -CN;

R^9 is C_{2-6} alkenyl optionally substituted with one or more R^{10}, C_{2-6} alkynyl optionally substituted with one or more R^{10}, or a 4-membered bicyclic carbocyclic ring;

R^6 and $R^{6'}$ are connected with a C_{4-8} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2;

r is 0;

each x is independently 0, 1, or 2;

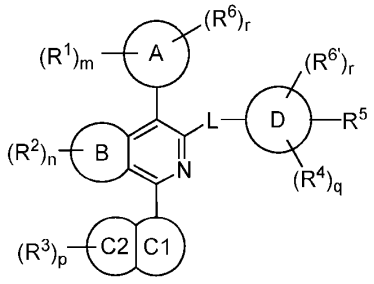
each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with one or more R^{10};

each Cy is independently selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8;

each R^8 is independently selected from oxo, halogen, and C_{1-6} aliphatic; and

each R^{10} is independently selected from halogen, -CN, -OH, -O(C_{1-6} alkyl), -NH_2, -NH(C_{1-6} alkyl), and -N(C_{1-6} alkyl)$_2$.

[00058] In some embodiments, the present disclosure provides a compound of Formula IA:



IA

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring D, L, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, q, and r are

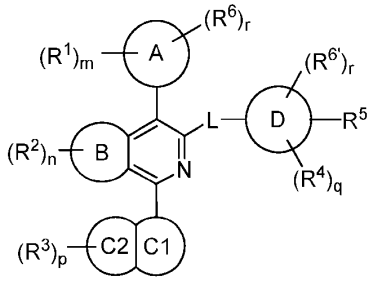
as defined above for Formula I and described in classes and subclasses herein, both singly and in combination, and wherein:

Ring C1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

wherein Ring C1 is fused to Ring C2; and

Ring C2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00059] In some embodiments, the present disclosure provides a compound of Formula IA':



IA'

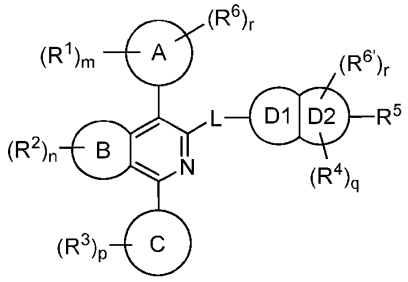
or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring D, L, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, q, and r are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination, and wherein:

Ring C1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

wherein Ring C1 is fused to Ring C2; and

Ring C2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00060] In some embodiments, the present disclosure provides a compound of Formula IB:



IB

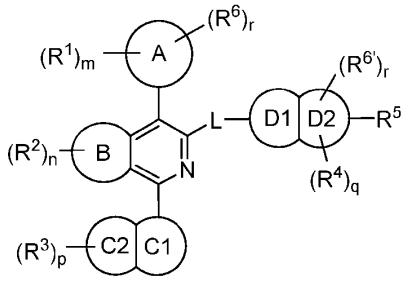
or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, L, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, q, and r are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination, and wherein:

Ring D1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

wherein Ring D1 is fused to Ring D2; and

Ring D2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00061] In some embodiments, the present disclosure provides a compound of Formula IB1:

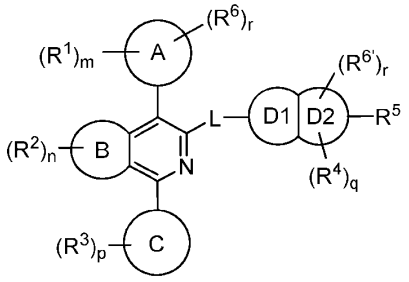


IB1

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, L, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, q, and r are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; Ring C1 and Ring C2 are as defined above for Formula IA and described in classes and subclasses herein, both

singly and in combination; and Ring D1 and Ring D2 are as defined above for Formula IB and described in classes and subclasses herein, both singly and in combination.

[00062] In some embodiments, the present disclosure provides a compound of Formula IB':



IB'

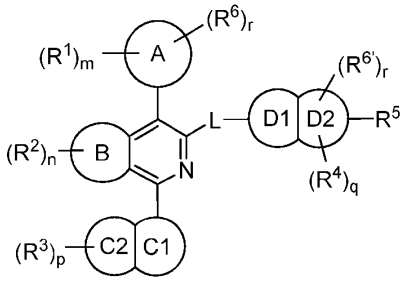
or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, L, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, q, and r are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination, and wherein:

Ring D1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

wherein Ring D1 is fused to Ring D2; and

Ring D2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00063] In some embodiments, the present disclosure provides a compound of Formula IB1':



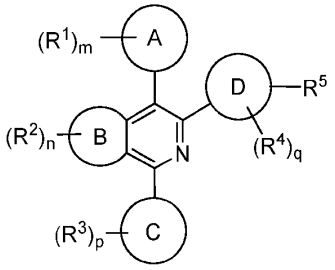
IB1'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, L, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, q, and r are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination; Ring C1 and Ring C2 are as defined above for Formula IA' and described in classes and subclasses herein, both singly and in combination; and Ring D1 and Ring D2 are as defined above for Formula IB' and described in classes and subclasses herein, both singly and in combination.

[00064] It will be appreciated that for a compound of Formula IA, IA', IB1, or IB1', any R^3 group may be attached to either Ring C1 or Ring C2. It will also be appreciated that for a compound of Formula IB, IB', IB1, or IB1', any R^4, R^5, or $R^{6'}$ group may be attached to either Ring D1 or Ring D2.

[00065] In some embodiments, the present disclosure provides a compound of Formula IA or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IA' or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IB or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IB' or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IB1 or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IB1' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

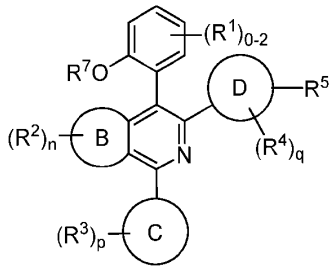
[00066] In some embodiments, the present disclosure provides a compound of Formula IC:



IC

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC or a salt (e.g., a pharmaceutically acceptable salt) thereof.

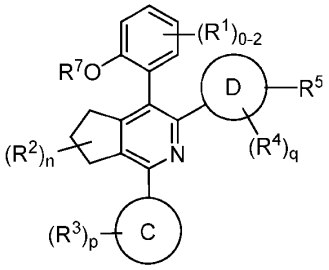
[00067] In some embodiments, the present disclosure provides a compound of Formula IC1:



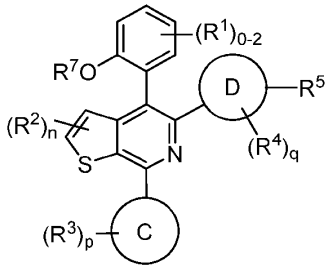
IC1

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, R^7, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC1 or a salt (e.g., a pharmaceutically acceptable salt) thereof.

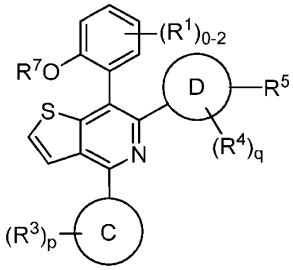
[00068] In some embodiments, the present disclosure provides a compound selected from Formulae IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, and IC1-g:



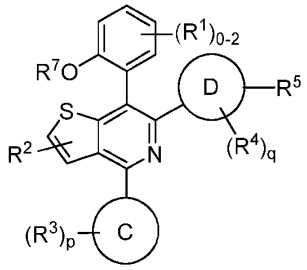
IC1-a



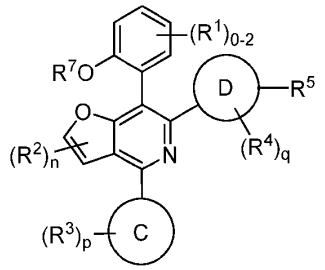
IC1-b



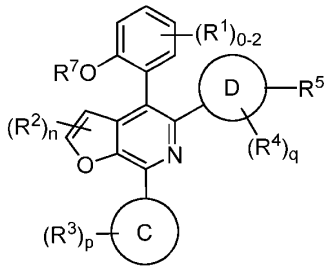
IC1-c



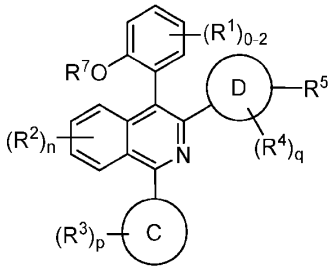
IC1-d



IC1-e



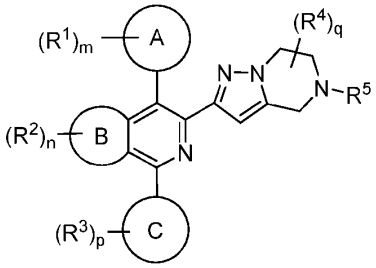
IC1-f



IC1-g

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, R^7, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC1-a, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1-c, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1-d, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1-e, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1-f, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1-g, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

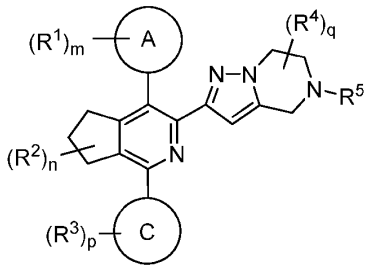
[00069] In some embodiments, the present disclosure provides a compound of Formula IC2:



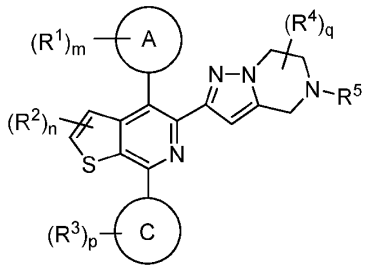
IC2

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC2 or a salt (e.g., a pharmaceutically acceptable salt) thereof.

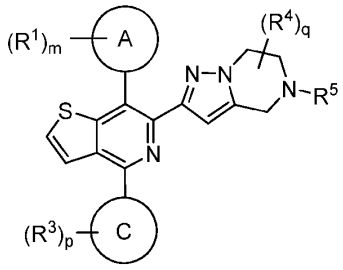
[00070] In some embodiments, the present disclosure provides a compound selected from Formulae IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, and IC2-g:



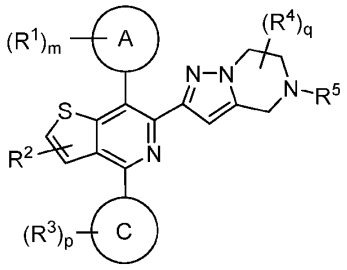
IC2-a



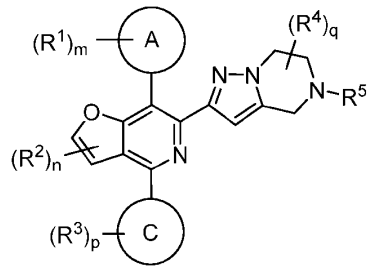
IC2-b



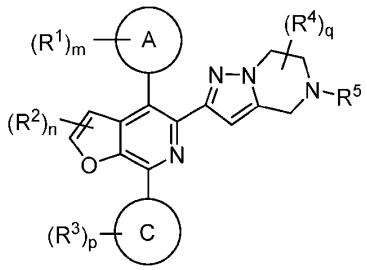
IC2-c



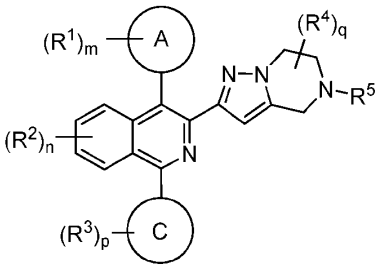
IC2-d



IC2-e



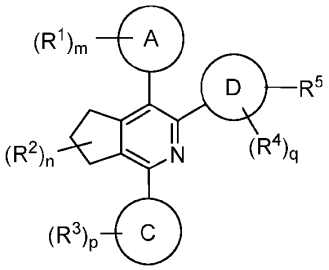
IC2-f



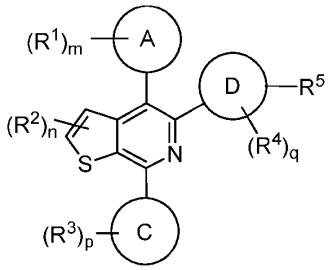
IC2-g

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring C, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC2-a, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2-c, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2-d, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2-e, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2-f, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2-g, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

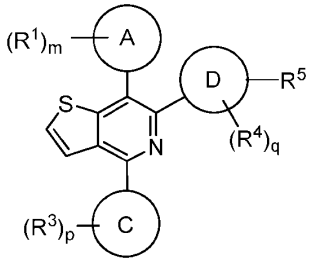
[00071] In some embodiments, the present disclosure provides a compound selected from Formulae IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, or IC3-m:



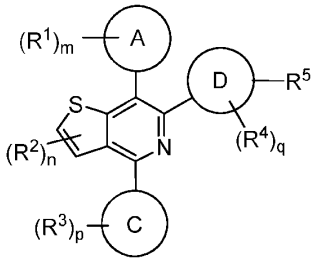
IC3-a



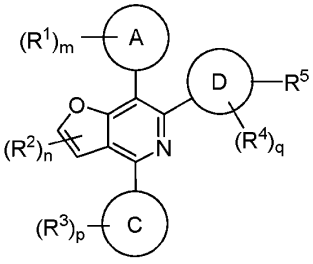
IC3-b



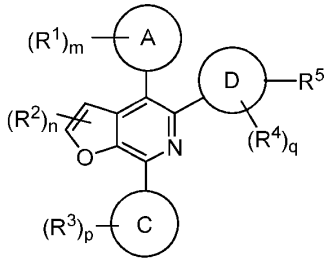
IC3-c



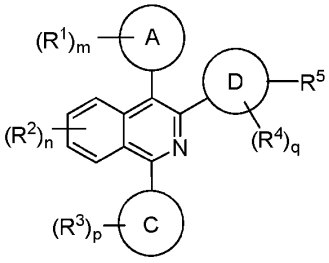
IC3-d



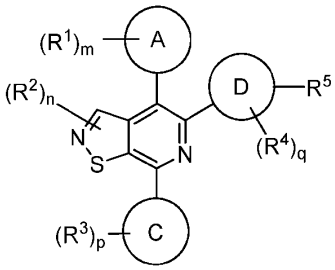
IC3-e



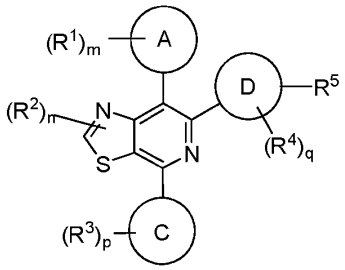
IC3-f



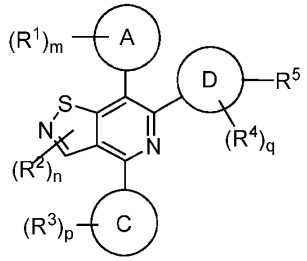
IC3-g



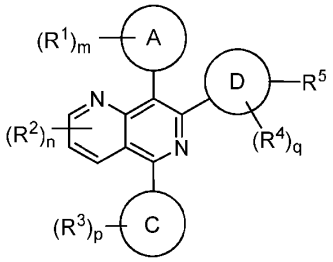
IC3-h



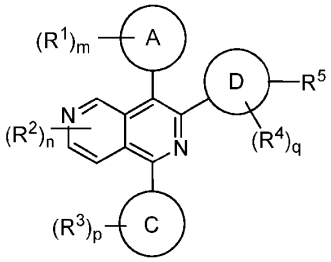
IC3-i



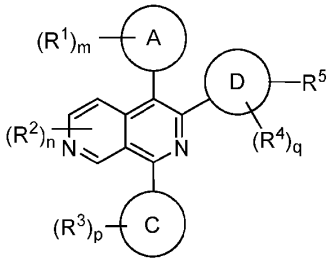
IC3-j



IC3-k



IC3-l

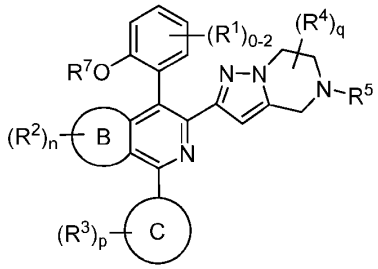


IC3-m

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC3-a, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-c, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-d, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-e, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-f, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some

embodiments, the present disclosure provides a compound of Formula IC3-g, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-h, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-i, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-j, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-k, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-l, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3-m, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

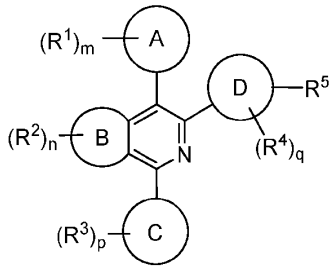
[00072] In some embodiments, the present disclosure provides a compound of Formula IC4:



IC4

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, Ring C, R^1, R^2, R^3, R^4, R^5, R^7, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC4 or a salt (e.g., a pharmaceutically acceptable salt) thereof.

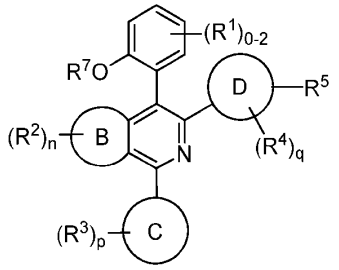
[00073] In some embodiments, the present disclosure provides a compound of Formula IC':



IC'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

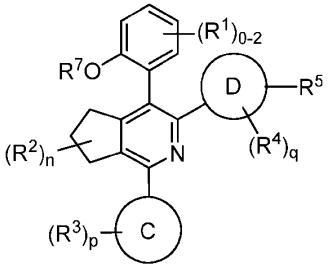
[00074] In some embodiments, the present disclosure provides a compound of Formula IC1':



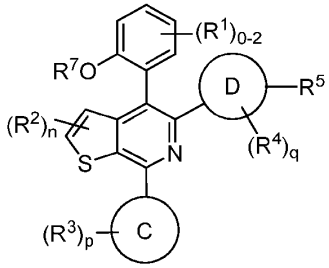
IC1'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, R^7, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC1' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

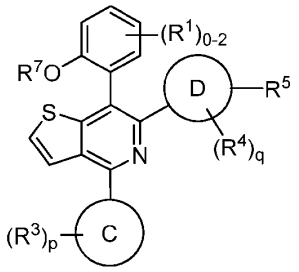
[00075] In some embodiments, the present disclosure provides a compound selected from Formulae IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, and IC1'-g:



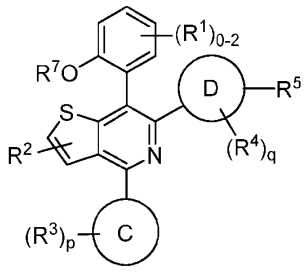
IC1'-a



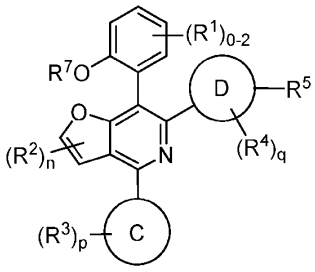
IC1'-b



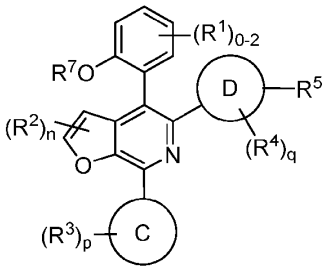
IC1'-c



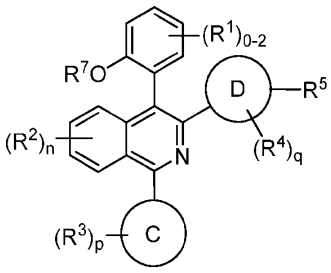
IC1'-d



IC1'-e



IC1'-f

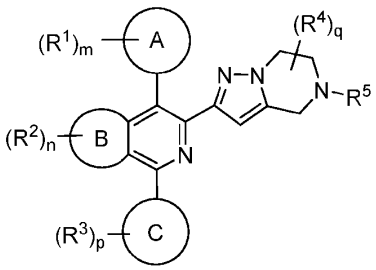


IC1'-g

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, R^7, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC1'-a, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1'-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1'-c, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1'-d, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1'-e, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a

compound of Formula IC1'-f, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC1'-g, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

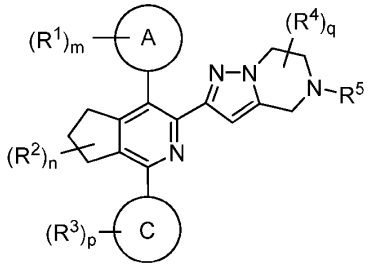
[00076] In some embodiments, the present disclosure provides a compound of Formula IC2':



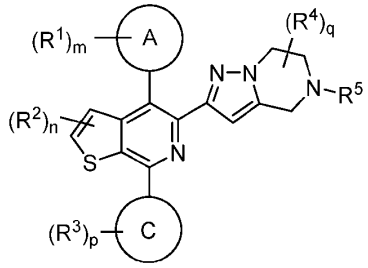
IC2'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC2' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

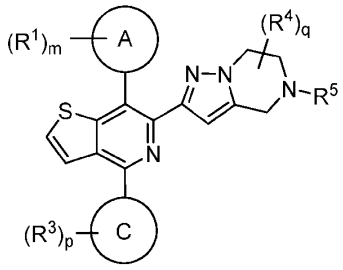
[00077] In some embodiments, the present disclosure provides a compound selected from Formulae IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, and IC2'-g:



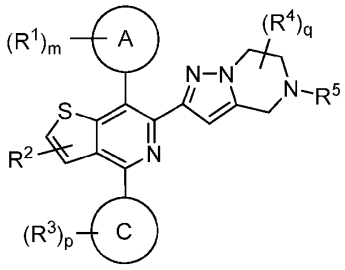
IC2'-a



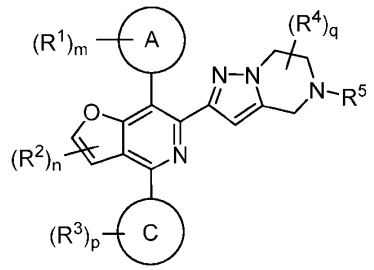
IC2'-b



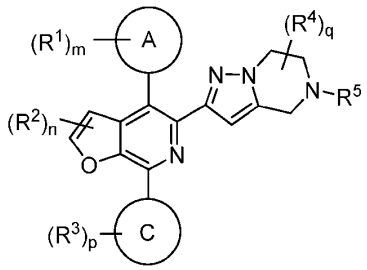
IC2'-c



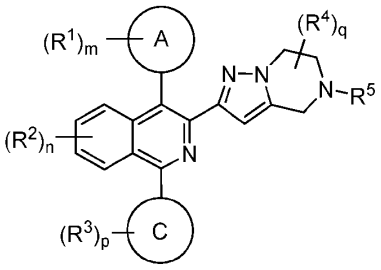
IC2'-d



IC2'-e



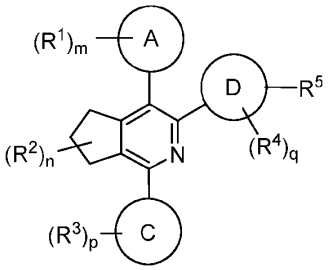
IC2'-f



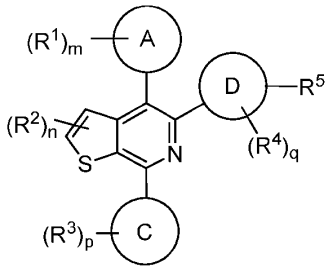
IC2'-g

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring C, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC2'-a, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2'-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2'-c, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2'-d, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2'-e, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2'-f, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC2'-g, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

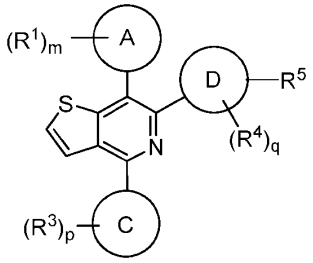
[00078] In some embodiments, the present disclosure provides a compound selected from Formulae IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, or IC3'-m:



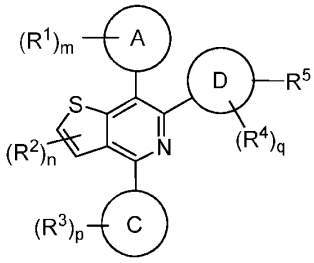
IC3'-a



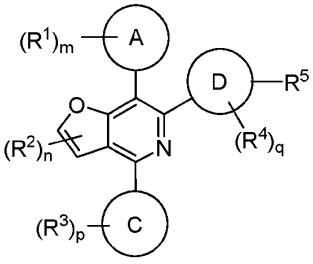
IC3'-b



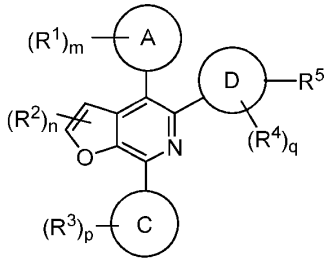
IC3'-c



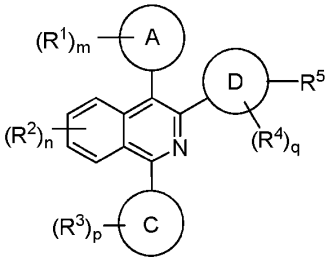
IC3'-d



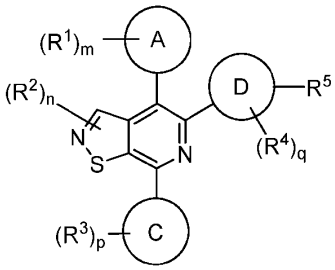
IC3'-e



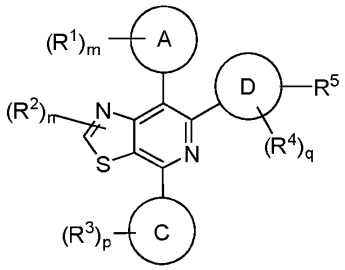
IC3'-f



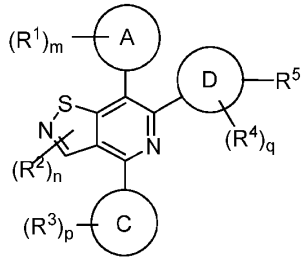
IC3'-g



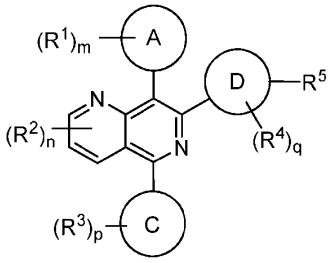
IC3'-h



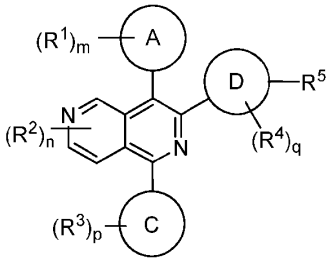
IC3'-i



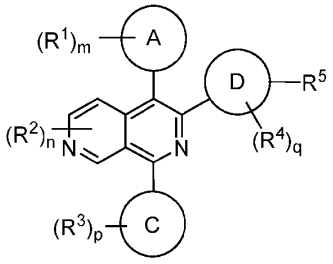
IC3'-j



IC3'-k



IC3'-l

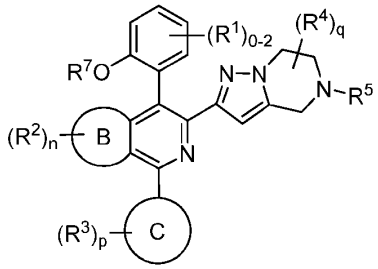


IC3'-m

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC3'-a, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-c, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-d, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-e, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-f, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some

embodiments, the present disclosure provides a compound of Formula IC3'-g, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-h, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-i, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-j, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-k, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-l, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IC3'-m, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

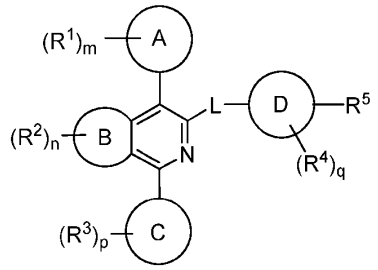
[00079] In some embodiments, the present disclosure provides a compound of Formula IC4':



IC4'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, Ring C, R^1, R^2, R^3, R^4, R^5, R^7, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IC4' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00080] In some embodiments, the present disclosure provides a compound of Formula ID:



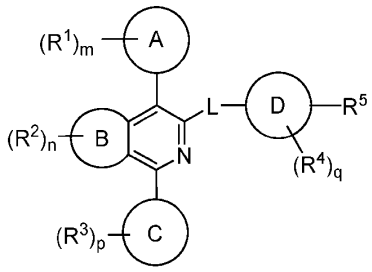
ID

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and wherein:

L is a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-.

[00081] In some embodiments, the present disclosure provides a compound of Formula ID or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00082] In some embodiments, the present disclosure provides a compound of Formula ID':



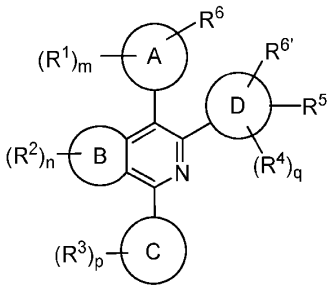
ID'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, m, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination; and wherein:

L is a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-.

[00083] In some embodiments, the present disclosure provides a compound of Formula ID' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

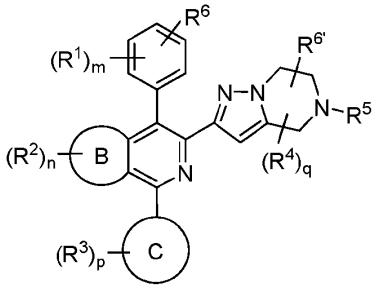
[00084] In some embodiments, the present disclosure provides a compound of Formula IE:



IE

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IE or a salt (e.g., a pharmaceutically acceptable salt) thereof.

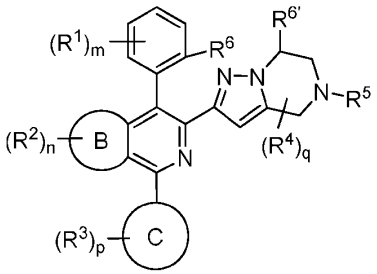
[00085] In some embodiments, the present disclosure provides a compound of Formula IE1:



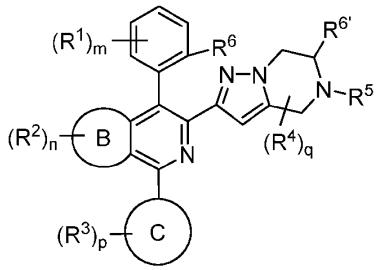
IE1

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, Ring C, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IE1 or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00086] In some embodiments, the present disclosure provides a compound selected from Formulae IE1-a and IE1-b:



IE1-a

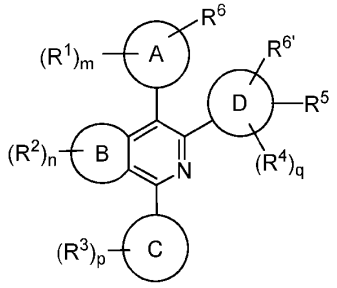


IE1-b

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, Ring C, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, and q are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IE1-a, or a salt (e.g., a

pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IE1-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

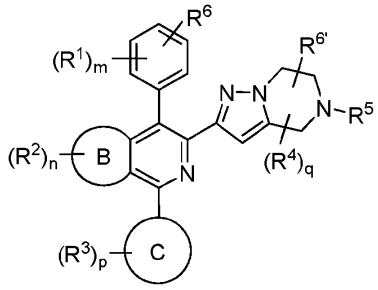
[00087] In some embodiments, the present disclosure provides a compound of Formula IE':



IE'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, Ring C, Ring D, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IE' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

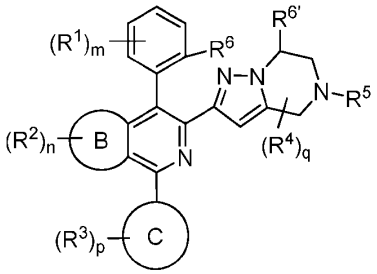
[00088] In some embodiments, the present disclosure provides a compound of Formula IE1':



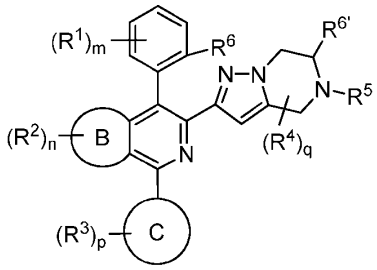
IE1'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, Ring C, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IE1' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00089] In some embodiments, the present disclosure provides a compound selected from Formulae IE1'-a and IE1'-b:



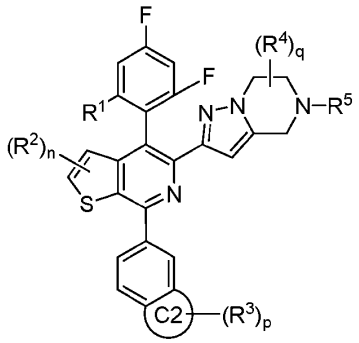
IE1'-a



IE1'-b

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, Ring C, R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, m, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IE1'-a, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IE1'-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

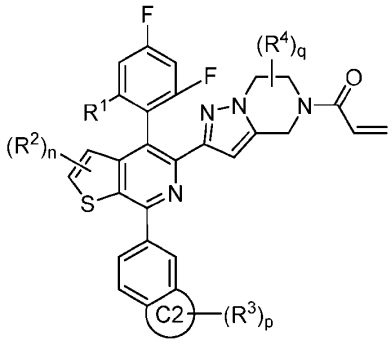
[00090] In some embodiments, the present disclosure provides a compound of Formula IF':



IF'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein R^1, R^2, R^3, R^4, R^5, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination; and Ring C2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the present disclosure provides a compound of Formula IF' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

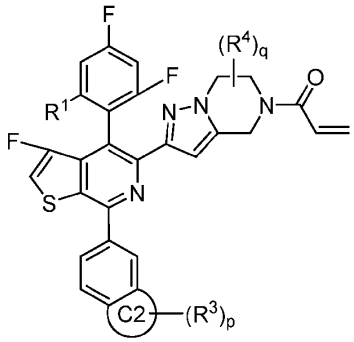
[00091] In some embodiments, the present disclosure provides a compound of Formula IF1':



IF1'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein R^1, R^2, R^3, R^4, n, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination; and Ring C2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the present disclosure provides a compound of Formula IF1' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

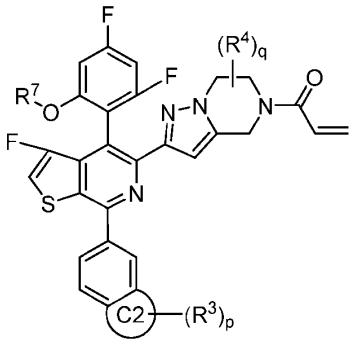
[00092] In some embodiments, the present disclosure provides a compound of Formula IF2':



IF2'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein R^1, R^3, R^4, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination; and Ring C2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the present disclosure provides a compound of Formula IF2' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

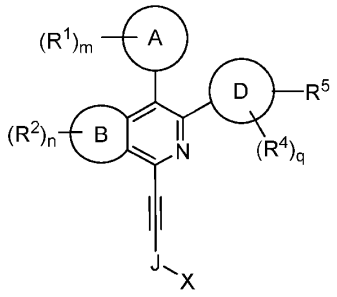
[00093] In some embodiments, the present disclosure provides a compound of Formula IF3':



IF3'

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein R^3, R^4, R^7, p, and q are as defined above for Formula I' and described in classes and subclasses herein, both singly and in combination; and Ring C2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the present disclosure provides a compound of Formula IF3' or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00094] In some embodiments, the present disclosure provides a compound of Formula II:



II

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

Ring A is phenyl and a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5- to 6-membered carbocyclic ring, and phenyl;

Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl

ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

J is a covalent bond or a bivalent straight or branched C_{1-4} hydrocarbon chain;

X is –OR, $-N(R)_2$, $-C(O)N(R)_2$, or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 is independently selected from halogen and $–OR^7$;

each R^7 is independently selected from optionally substituted C_{1-6} aliphatic and $–(C_{1-4}$ alkylene)OR;

each R^2 is independently selected from halogen and optionally substituted C_{1-6} aliphatic;

each R^4 is independently selected from optionally substituted C_{1-6} aliphatic;

R^5 is $-C(O)R^9$, $-(CH_2)_xN(R)C(O)R^9$, or -CN;

R^9 is optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or a 4-membered bicyclic carbocyclic ring;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

q is 0, 1, or 2;

x is 0, 1, or 2;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00095] In some embodiments, the present disclosure provides a compound of Formula II, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00096] In some embodiments, the present disclosure provides a compound of Formula II, wherein:

Ring A is phenyl and a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5- to 6-membered carbocyclic ring, and phenyl;

Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl

ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

J is a covalent bond or a bivalent straight or branched C_{1-4} hydrocarbon chain;

X is –OR, -$N(R)_2$, -$C(O)N(R)_2$, or a group selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein any ring is optionally substituted with C_{1-6} alkyl;

each R^1 is independently selected from halogen and $–OR^7$;

each R^7 is independently selected from C_{1-6} aliphatic and –(C_{1-4} alkylene)OR;

each R^2 is independently selected from halogen and C_{1-6} aliphatic;

each R^4 is independently selected from C_{1-6} aliphatic optionally substituted with one or more R^{10};

R^5 is -$C(O)R^9$, -$(CH_2)_xN(R)C(O)R^9$, or -CN;

R^9 is C_{2-6} alkenyl optionally substituted with one or more R^{10}, C_{2-6} alkynyl optionally substituted with one or more R^{10}, or a 4-membered bicyclic carbocyclic ring;

m is 0, 1, 2, or 3;

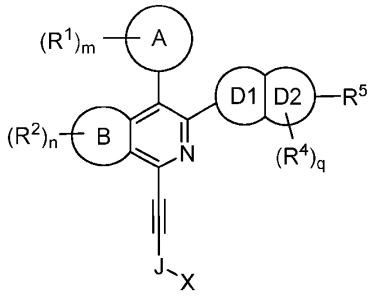
n is 0, 1, or 2;

q is 0, 1, or 2;

x is 0, 1, or 2;

each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with one or more R^{10}; and each R^{10} is independently selected from halogen, -CN, -OH, -$O(C_{1-6}$ alkyl), -NH_2, -$NH(C_{1-6}$ alkyl), and -$N(C_{1-6}$ alkyl$)_2$.

[00097] In some embodiments, the present disclosure provides a compound of Formula IIA:



IIA

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, J, R^1, R^2, R^4, R^5, X, m, n, and q are as defined above for Formula II and described in classes and subclasses herein, both singly and in combination, and wherein:

Ring D1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

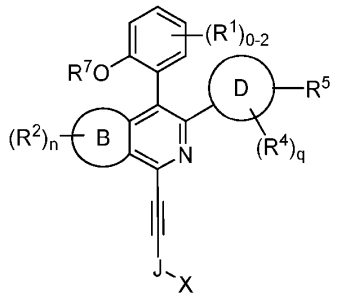
wherein Ring D1 is fused to Ring D2; and

Ring D2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00098] In some embodiments, the present disclosure provides a compound of Formula IIA or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[00099] It will also be appreciated that for a compound of Formula IIA, any R^4 or R^5 group may be attached to either Ring D1 or Ring D2.

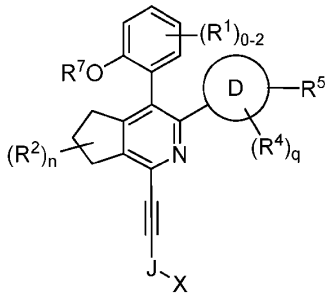
[000100] In some embodiments, the present disclosure provides a compound of Formula IIB:



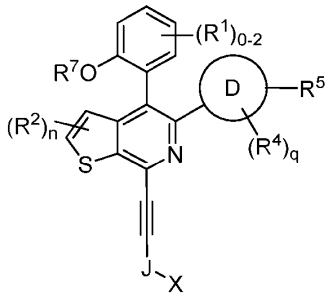
IIB

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, Ring D, J, R^1, R^2, R^4, R^5, R^7, X, n, and q are as defined above for Formula II and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IIB or a salt (e.g., a pharmaceutically acceptable salt) thereof.

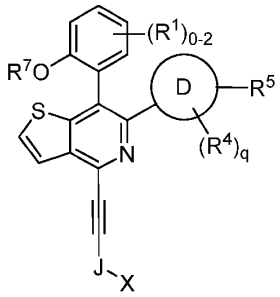
[000101] In some embodiments, the present disclosure provides a compound selected from Formulae IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, or IIB7:



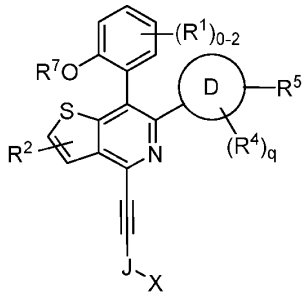
IIB1



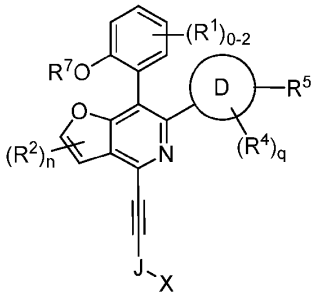
IIB2



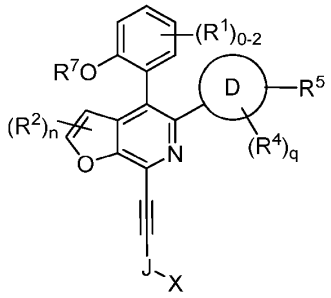
IIB3



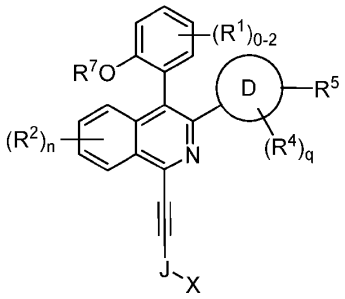
IIB4



IIB5



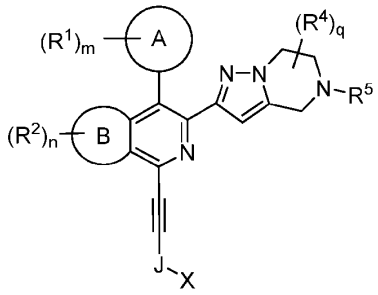
IIB6



IIB7

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring D, J, R^1, R^2, R^4, R^5, R^7, X, n, and q are as defined above for Formula II and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IIB1, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIB2, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIB3, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIB4, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIB5, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIB6, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIB7, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000102] In some embodiments, the present disclosure provides a compound of Formula IIC:

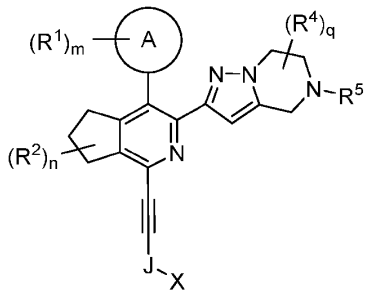


IIC

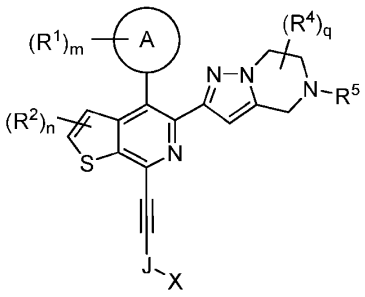
or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring B, J, R^1, R^2, R^4, R^5, X, m, n, and q are as defined above for Formula II and described in classes and subclasses herein, both singly and in combination. In some

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

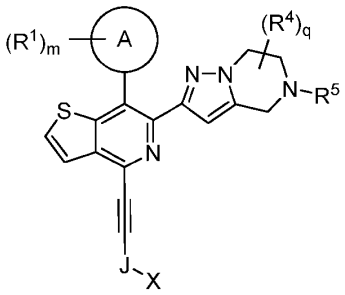
[000103] In some embodiments, the present disclosure provides a compound selected from Formulae IIC1, IIC2, IIC3, IIC4, IIC5, IIC6, and IIC7:



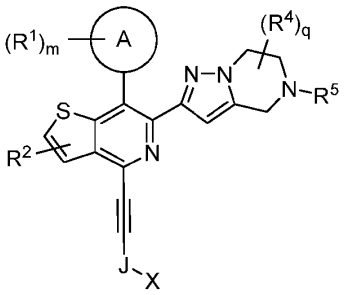
IIC1



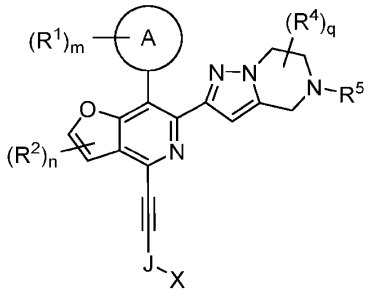
IIC2



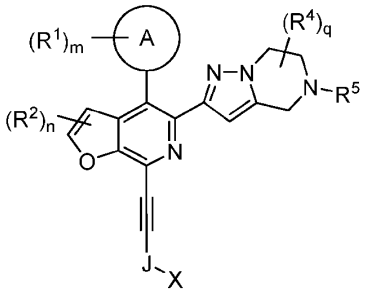
IIC3



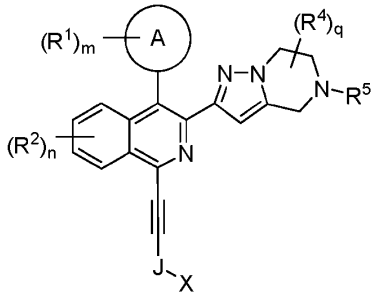
IIC4



IIC5



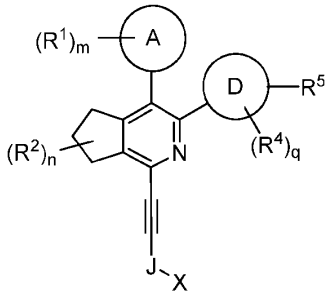
IIC6



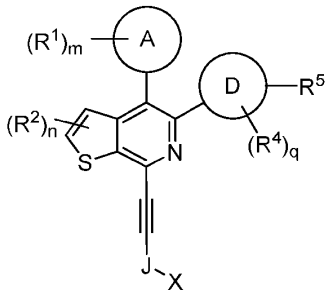
IIC7

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, J, R^1, R^2, R^4, R^5, X, m, n, and q are as defined above for Formula II and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IIC1, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIC2, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIC3, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIC4, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIC5, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIC6, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IIC7, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

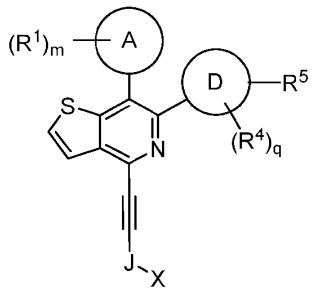
[000104] In some embodiments, the present disclosure provides a compound selected from Formulae IID1, IID2, IID3, IID4, IID5, IID6, and IID7:



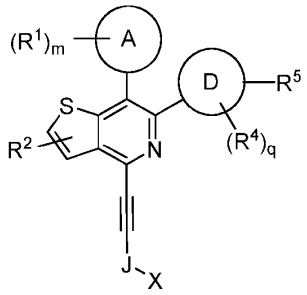
IID1



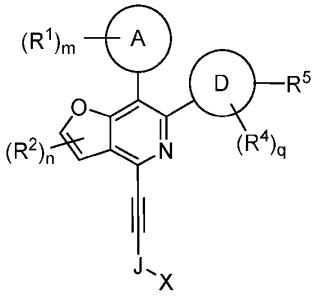
IID2



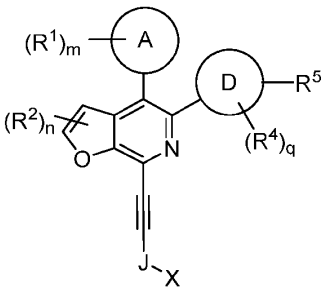
IID3



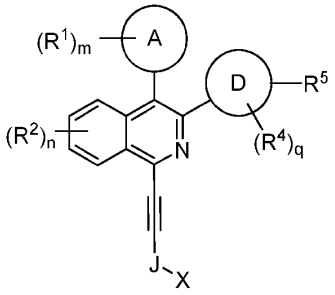
IID4



IID5



IID6

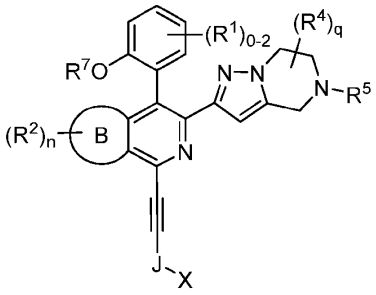


IID7

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring A, Ring D, J, R^1, R^2, R^4, R^5, X, m, n, and q are as defined above for Formula II and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IID1, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IID2, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IID3, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IID4, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IID5, or a salt (e.g., a

pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IID6, or a salt (e.g., a pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound of Formula IID7, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

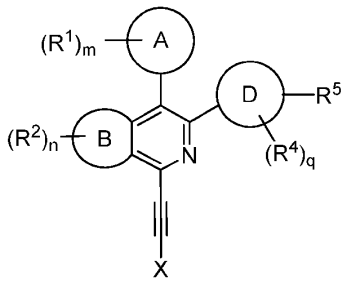
[000105] In some embodiments, the present disclosure provides a compound of Formula IIE:



IIE

or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein Ring B, J, R^1, R^2, R^4, R^5, R^7, X, n, and q are as defined above for Formula II and described in classes and subclasses herein, both singly and in combination. In some embodiments, the present disclosure provides a compound of Formula IIE or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000106] In some embodiments, the present disclosure provides a compound of Formula IIF:



IIF

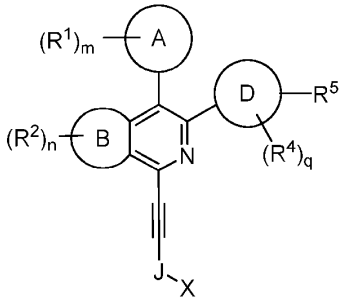
or a salt (e.g., a pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof, wherein:

X is $-C(O)N(R)_2$ or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently

selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000107] In some embodiments, the present disclosure provides a compound of Formula IIF or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000108] In some embodiments, the present disclosure provides a compound of Formula IIG:



IIG

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

J is a bivalent straight or branched C_{1-4} hydrocarbon chain; and

X is –OR or -$N(R)_2$.

[000109] In some embodiments, the present disclosure provides a compound of Formula IIG or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000110] In some embodiments of any one of Formulae I, I', I'', IA, IA', IB, IB', IC, IC', IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', IE, and IE', Ring A is phenyl. In some embodiments, Ring A is pyridinyl. In some embodiments, Ring A is a 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

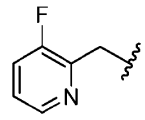
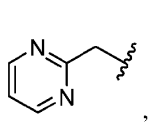
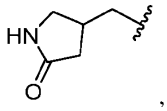
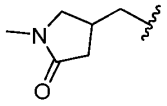
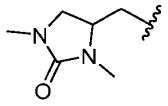
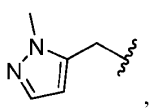
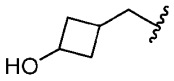
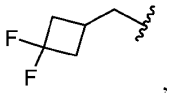
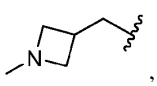
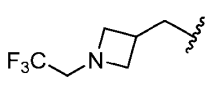
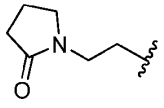
[000111] In some embodiments of Formulae II, IIA, IIC, IIC1, IIC2, IIC3, IIC4, IIC5, IIC6, IIC7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, Ring A is phenyl. In some embodiments, Ring A is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is a 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is a 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

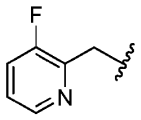
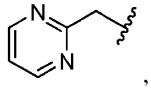
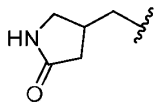
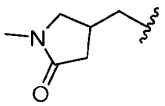
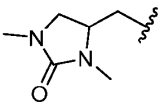
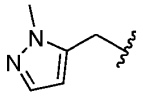
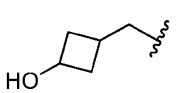
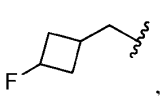
[000112] In some embodiments of any Formulae described herein, a R^1 is halogen (e.g., fluoro). In some embodiments, R^1 is selected from optionally substituted C_{1-6} alkyl, cycloalkyl (e.g., 3-6 membered

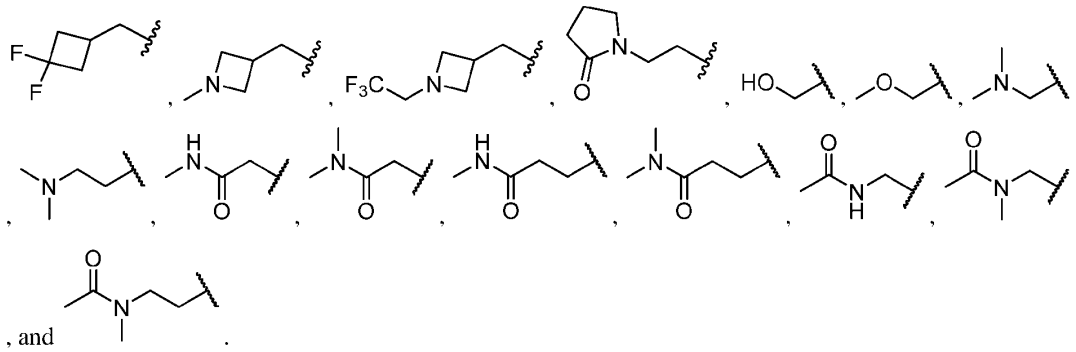
cycloalkyl, such as cyclopropyl), –CN, –C(O)OR, –C(O)NR_2, –CH_2NR_2, –SR^7, and –(C_{1-4} alkylene)OR. In some embodiments, R^1 is optionally substituted C_{1-6} alkyl. In some such embodiments, R^1 is optionally substituted C_{1-2} alkyl. In some embodiments, R^1 is -CH_3. In some embodiments, R^1 is cycloalkyl (e.g., 3-6 membered cycloalkyl, such as cyclopropyl). In some embodiments, R^1 is cyclopropyl. In some embodiments, R^1 is –CN. In some embodiments, R^1 is –C(O)OR. In some such embodiments, R^1 is –C(O)OH. In some embodiments, R^1 is –C(O)NR_2. In some embodiments, R^1 is –C(O)$N(CH_3)_2$. In some embodiments, R^1 is –CH_2NR_2. In some embodiments, R^1 is –$CH_2N(CH_3)_2$. In some embodiments, R^1 is –SR^7. In some embodiments, R^1 is –SCH_3. In some embodiments, R^1 is –(C_{1-4} alkylene)OR. In some embodiments, R^1 is –CH_2OR. In some embodiments, R^1 is –CH_2OH. In some embodiments, R^1 is –CH_2OCH_3. In some embodiments, a R^1 is –OR^7. In some embodiments, at least one R^1 is –OR^7. In some embodiments, one R^1 is –OR^7 and any other R^1 groups are halogen (e.g., fluoro). In some embodiments, one R^1 is –OR^7 and one other R^1 group is halogen (e.g., fluoro). In some embodiments, one R^1 is –OR^7 and two other R^1 groups are halogen (e.g., fluoro).

[000113] In some embodiments of any Formulae described herein, each R^7 is independently selected from C_{1-6} aliphatic and –(C_{1-4} alkylene)OR. In some embodiments, each R^7 is independently selected from C_{1-6} alkyl and –(C_{1-4} alkylene)OR. In some embodiments, each R^7 is optionally substituted C_{1-6} aliphatic. In some embodiments, each R^7 is C_{1-6} aliphatic. In some embodiments, each R^7 is C_{1-6} aliphatic substituted with a group selected from –$(CH_2)_{0-4}R°$, –$(CH_2)_{0-4}OR°$, –$(CH_2)_{0-4}N(R°)_2$, -$(CH_2)_{0-4}N(R°)C(O)R°$, -$(CH_2)_{0-4}NHC(O)R°$, –$(CH_2)_{0-4}C(O)NHR°$, and –$(CH_2)_{0-4}C(O)N(R°)_2$. In some embodiments, each R^7 is C_{1-6} aliphatic substituted with –R°, –OR°, –$N(R°)_2$, -$N(R°)C(O)R°$, -NHC(O)R°, –C(O)NHR°, and –$C(O)N(R°)_2$. In some such embodiments, R° is an optionally substituted group selected from C_{1-6} aliphatic, a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4- to 6-membered carbocyclic ring. In some embodiments, R° is substituted with halogen, oxo,–$(CH_2)_{0-2}R^•$, –(halo$R^•$), –$(CH_2)_{0-2}OH$, and –$(CH_2)_{0-2}OR^•$. In some embodiments, R° is substituted with halogen, oxo,–$R^•$, –(halo$R^•$), –OH, and –$OR^•$. In some embodiments, $R^•$ is C_{1-4} aliphatic. In some embodiments, $R^•$ is -CH_3 or -CH_2CH_3. In some embodiments, R° is substituted with halogen, oxo, -CH_3, -CH_2CF_3, -OH, and -OCH_3.

[000114] In some embodiments, each R^7 is optionally substituted C_{1-6} alkyl. In some embodiments, each R^7 is C_{1-6} alkyl substituted with a group selected from –$(CH_2)_{0-4}R°$, –$(CH_2)_{0-4}OR°$,–$(CH_2)_{0-4}N(R°)_2$, -$(CH_2)_{0-4}N(R°)C(O)R°$, -$(CH_2)_{0-4}NHC(O)R°$, –$(CH_2)_{0-4}C(O)NHR°$, –$(CH_2)_{0-4}C(O)N(R°)_2$, . In some embodiments, each R^7 is C_{1-6} alkyl substituted with –R°, –OR°, –$N(R°)_2$, -$N(R°)C(O)R°$, -NHC(O)R°, –C(O)NHR°, and –$C(O)N(R°)_2$. In some embodiments, each R^7 is C_{1-2} alkyl substituted with –R°, –OR°, –$N(R°)_2$, -$N(R°)C(O)R°$, -NHC(O)R°, –C(O)NHR°, and –$C(O)N(R°)_2$. In some embodiments, R° is an optionally

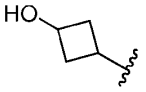
substituted group selected from C_{1-6} aliphatic, a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4- to 6-membered carbocyclic ring. In some embodiments, each R^7 is C_{1-6} alkyl. In some embodiments, each R^7 is $-(C_{1-4}$ alkylene)OR. In some embodiments, each R^7 is $-(C_{1-4}$ alkylene)NR_2. In some embodiments, each R^7 is independently selected from C_{1-6} aliphatic substituted with an optionally substituted 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; C_{1-6} aliphatic substituted with an optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and C_{1-6} aliphatic substituted with an optionally substituted 3-7 membered carbocyclic ring. In some embodiments, each R^7 is independently selected from C_{1-6} aliphatic substituted with an optionally substituted 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each R^7 is independently selected from C_{1-6} aliphatic substituted with an optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^7 is an optionally substituted 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each R^7 is independently selected from C_{1-6} aliphatic substituted with an optionally substituted 3-7 membered carbocyclic ring. In some embodiments, each R^7 is independently selected from , , , , , , , , , , and .

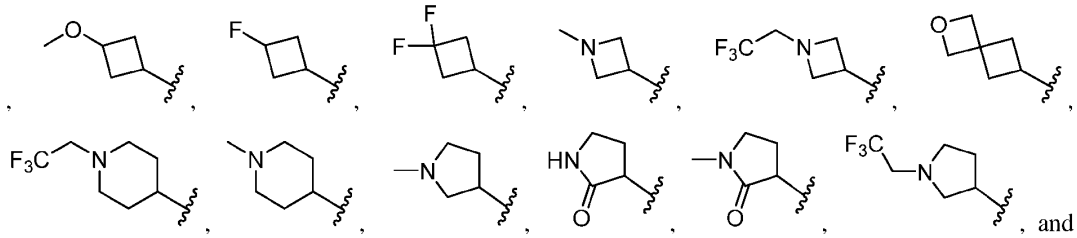
[000115] In some embodiments, each R^7 is independently selected from , , , , , , , .



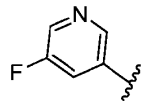
, and .

[000116] In some embodiments, each R^7 is independently selected from optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; optionally substituted 4- to 7-membered heteroaryl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and optionally substituted 3- to 6-membered carbocyclic ring. In some embodiments, each R^7 is independently selected from optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each R^7 is independently selected from optionally substituted pyrrolidinyl and piperidinyl. In some embodiments, each R^7 is independently selected from optionally substituted 4- to 7-membered heteroaryl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each R^7 is independently selected from optionally substituted 3- to 6-membered carbocyclic ring. In some embodiments, each R^7 is independently selected from

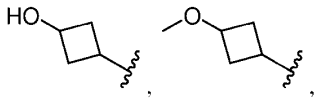
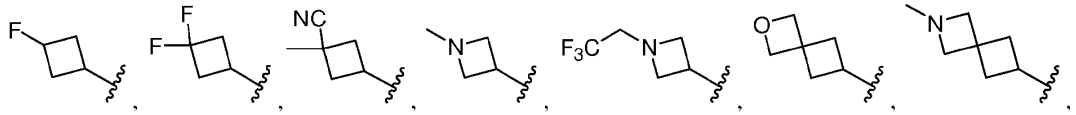
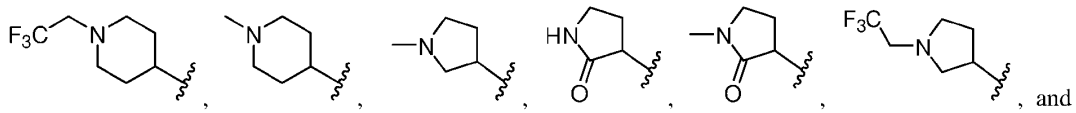
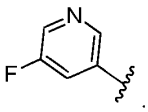




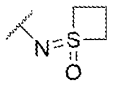
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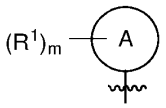
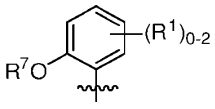
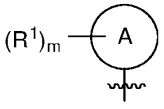
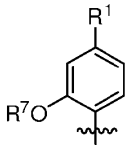
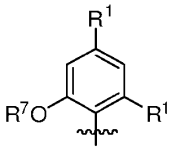
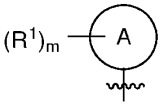
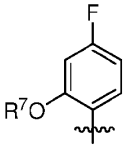
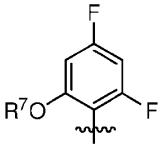
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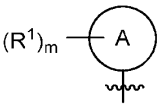
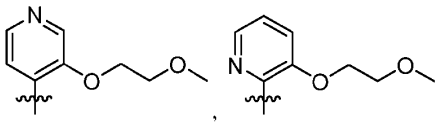
[000117] In some embodiments, each R^7 is independently selected from , , , and .

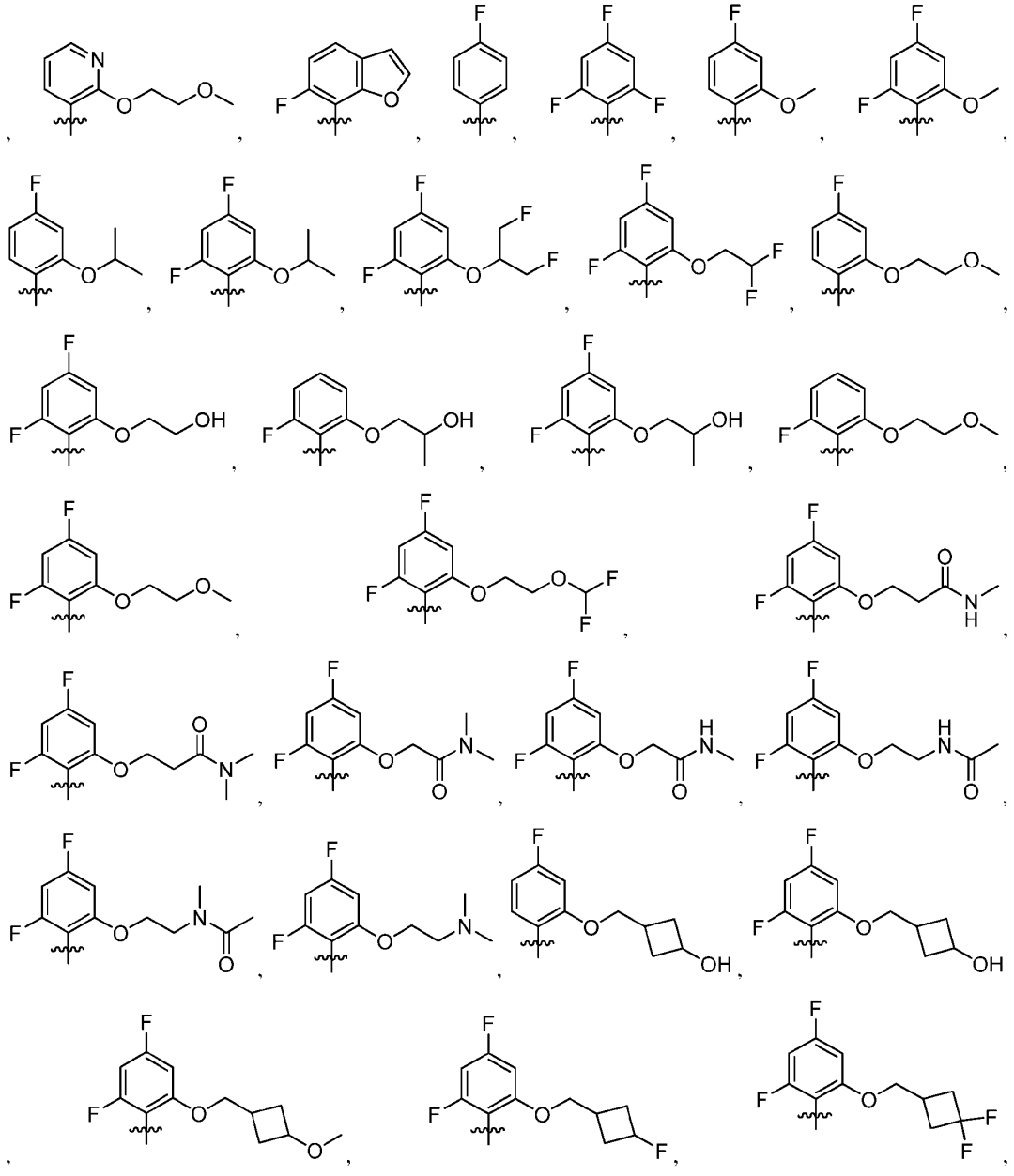
[000118] In some embodiments of any Formulae described herein, at least one R^1 is $-OR^7$, and $-OR^7$ is selected from: $-OCH_3$, $-OCH(CH_3)_2$, $-O(CH_2)_2OH$, $-O(CH_2)CH(CH_3)OH$, $-O(CH_2)_2OCH_3$, and $-O(CH_2)_2OCHF_2$.

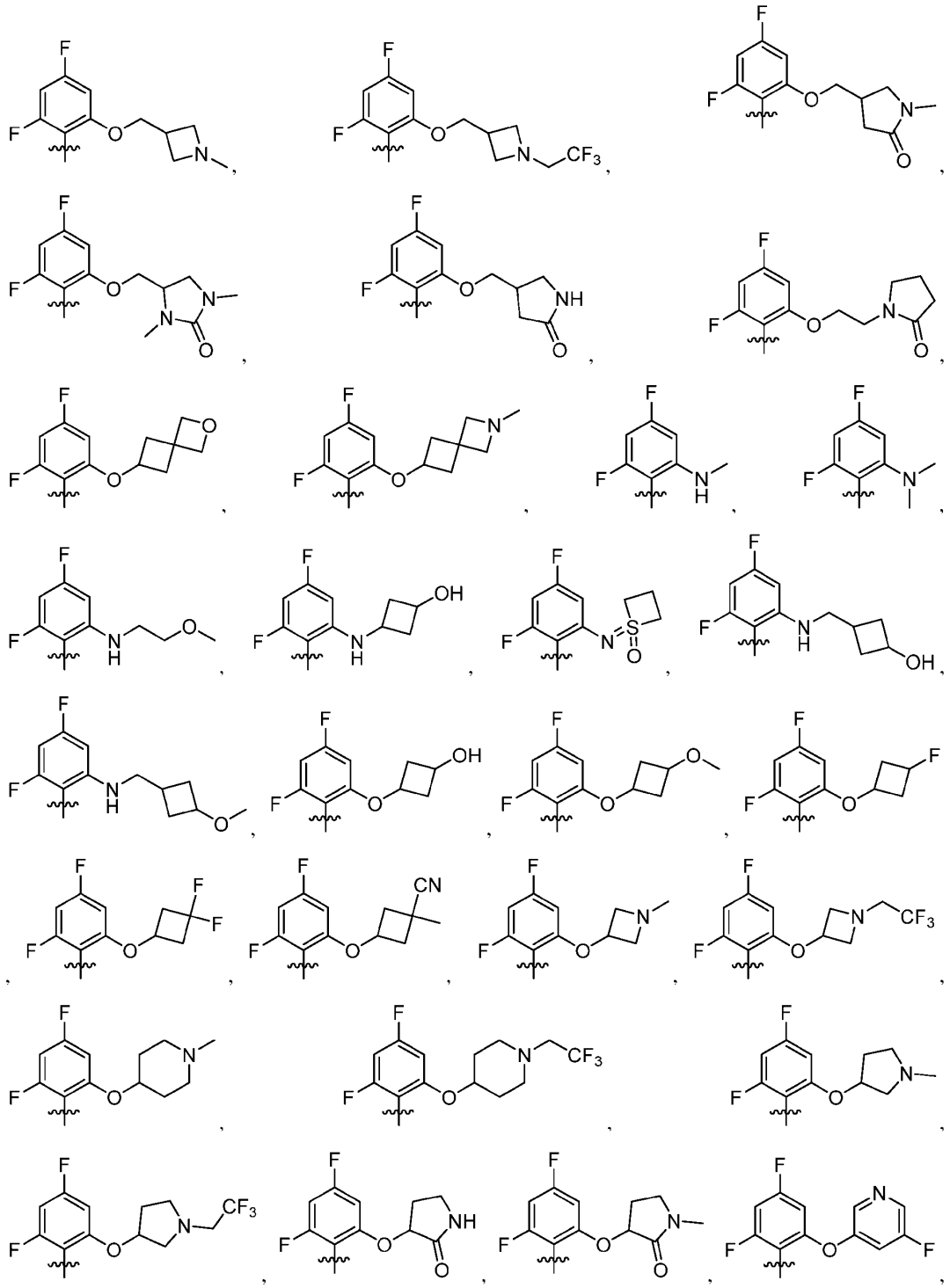
[000119] In some embodiments, R^1 is $-N=S(R^7)_2$, wherein the two R^7 groups, together with the atom(s) to which they are attached, form a 4- to 6-membered heterocyclic ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some such embodiments, R^1 is .

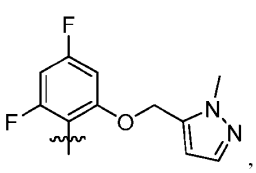
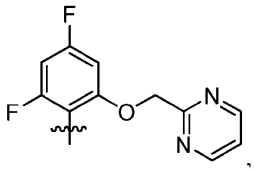
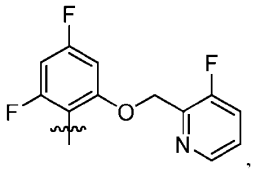
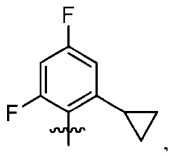
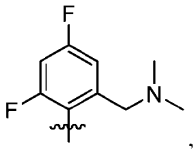
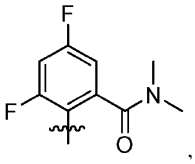
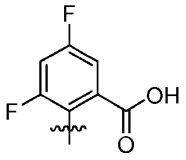
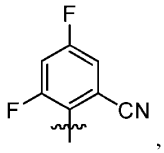
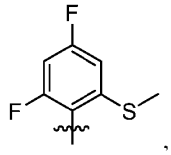
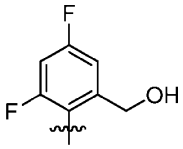
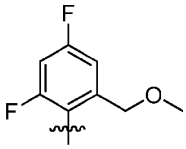
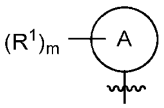
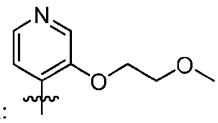
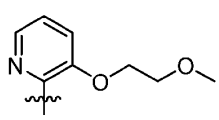
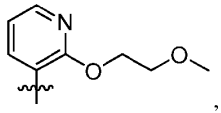
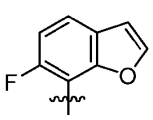
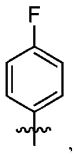
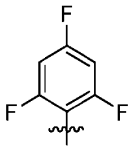
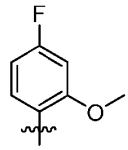
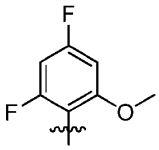
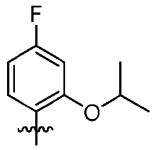
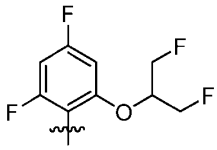
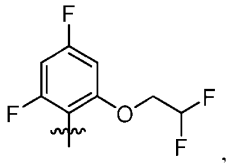
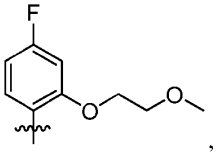
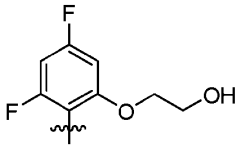
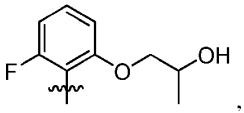
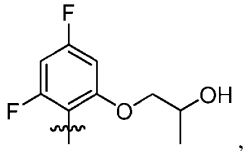
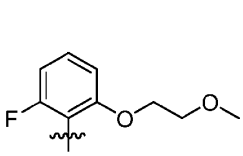
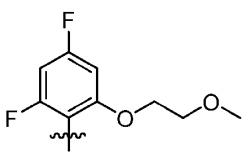
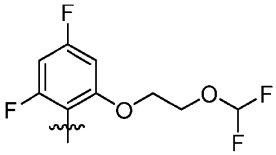
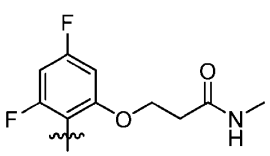
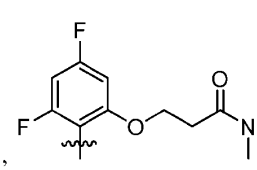
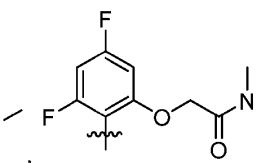
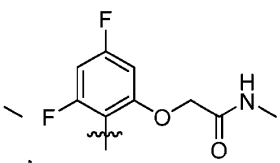
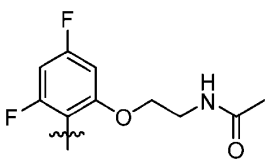
[000120] In some embodiments of any Formulae described herein, m is 0, 1, or 2. In some embodiments, m is 1, 2, or 3. In some embodiments, m is 0 or 1. In some embodiments, m is 1 or 2. In some embodiments, m is 2 or 3. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

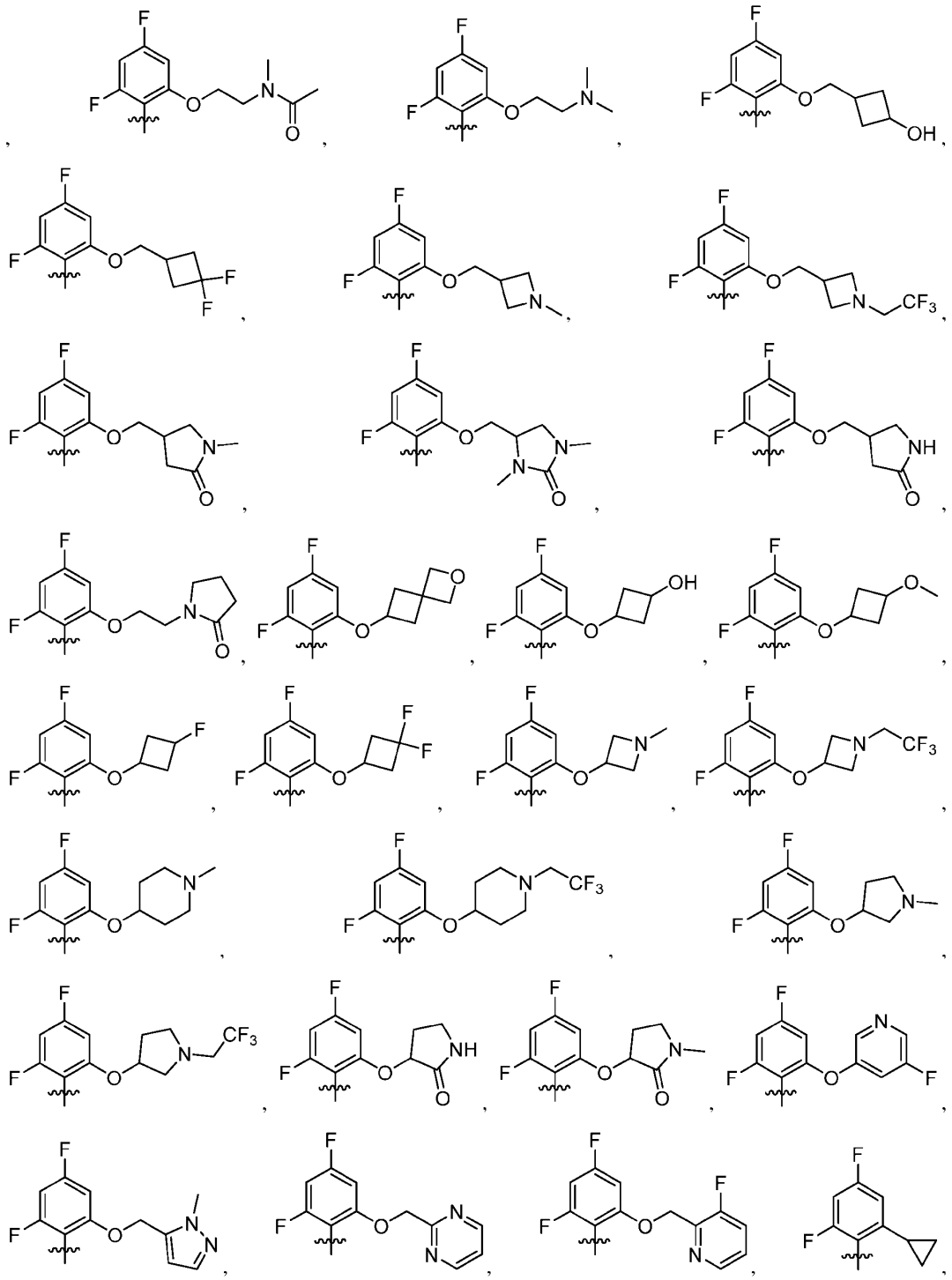
[000121] In some embodiments of any Formulae described herein, a moiety  is . In some embodiments, a moiety  is  or . In some embodiments, a moiety  is  or . In

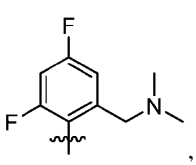
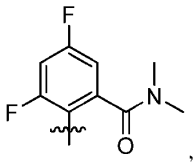
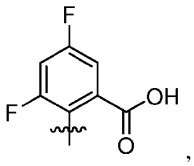
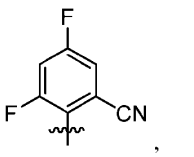
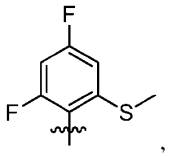
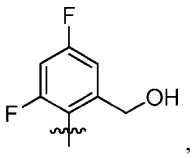
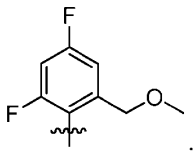
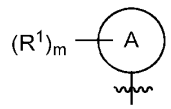
some embodiments, a moiety  is selected from: 

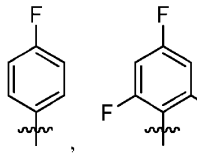
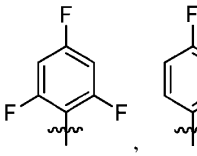
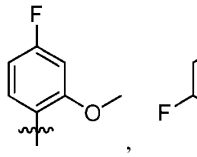
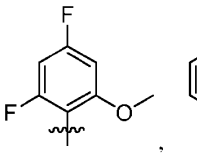
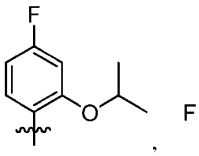
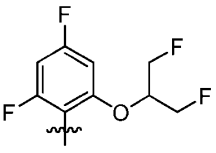
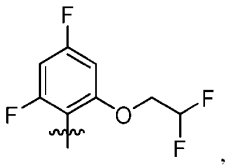
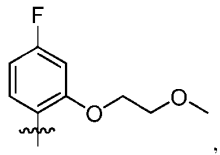
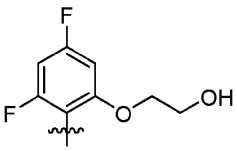
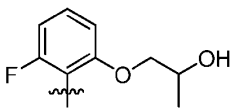
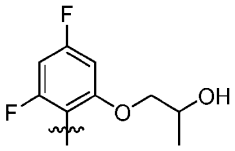
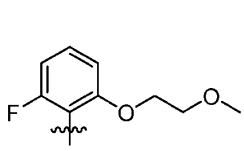
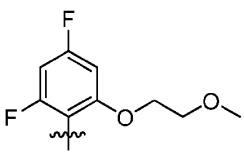
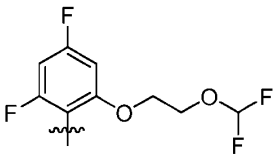
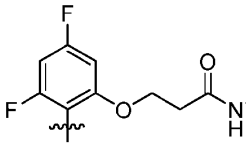
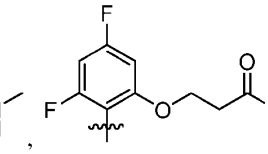
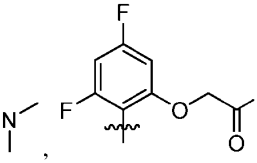


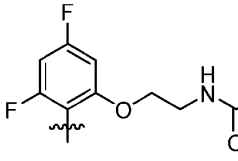
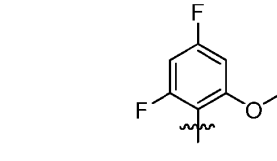
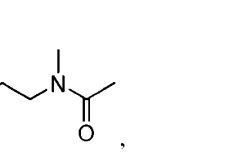
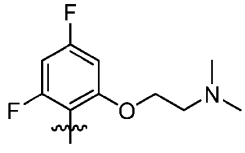
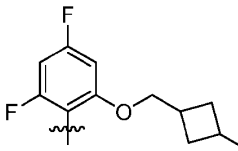
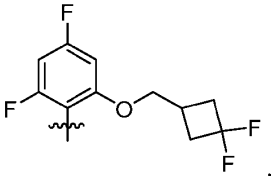
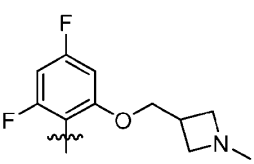


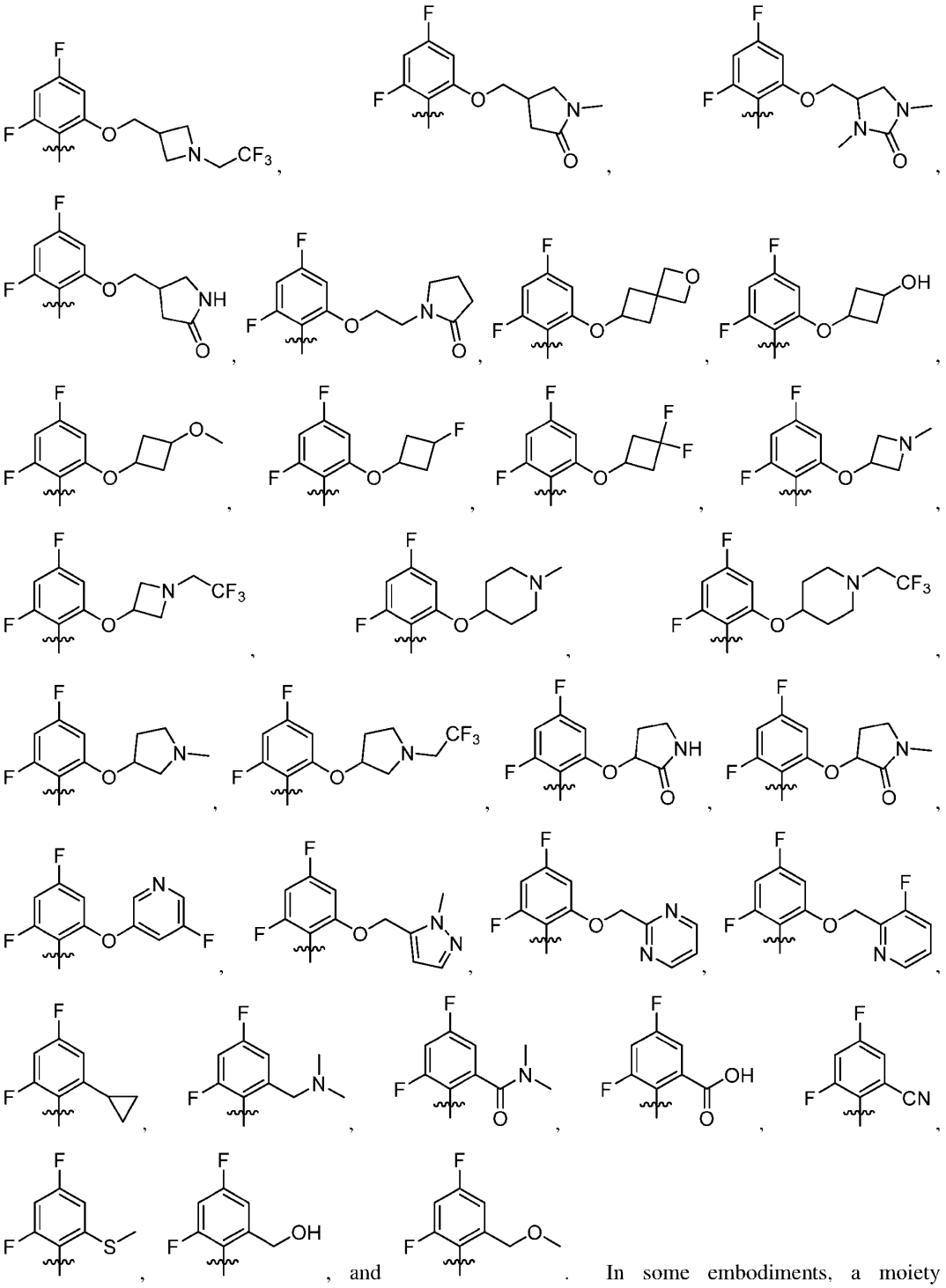











, and . In some embodiments, a moiety is selected from:


























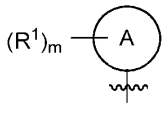
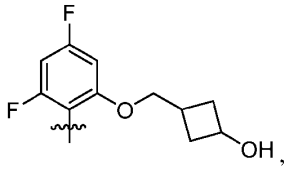
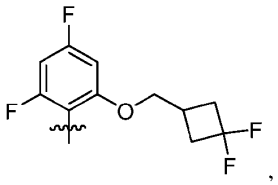
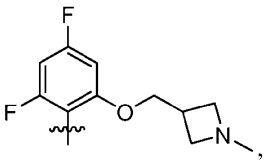
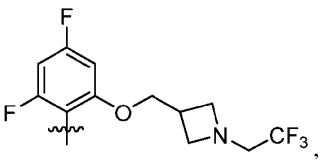
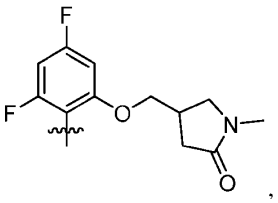
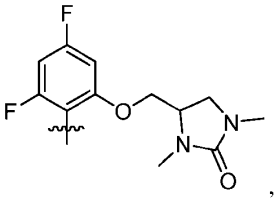
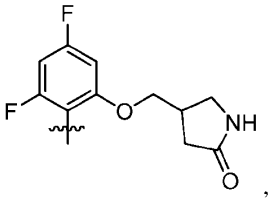
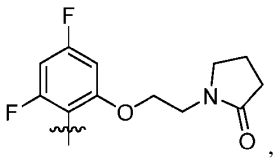
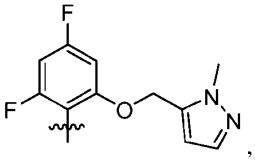
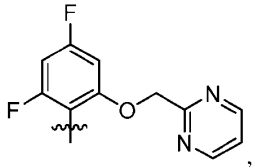
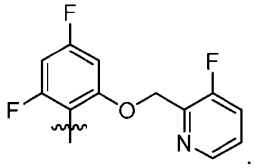
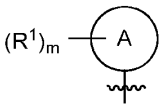
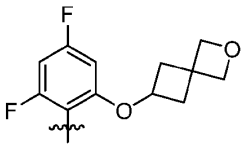
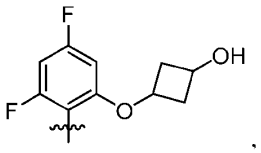
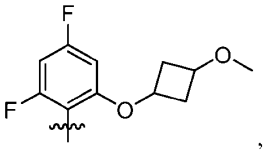
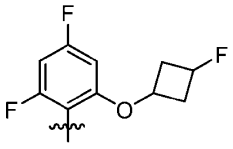
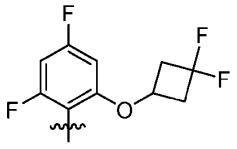
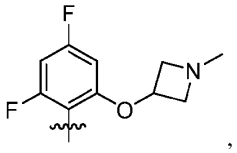
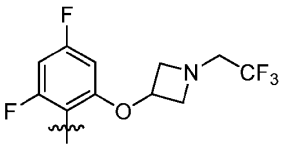
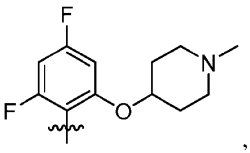
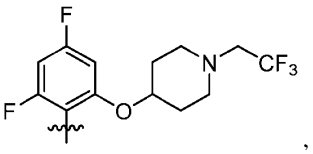
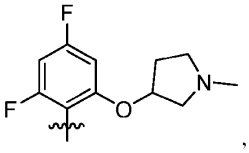
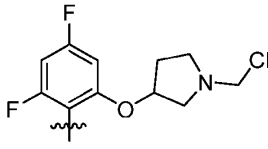
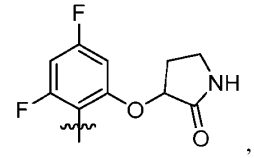
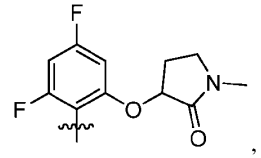







, and

. In some embodiments, a moiety

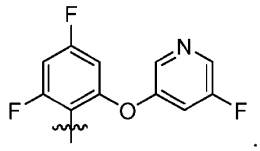
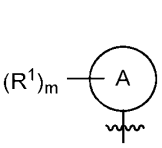
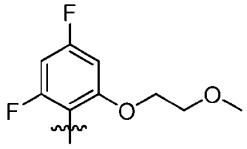
is selected from:




















In some embodiments, a moiety

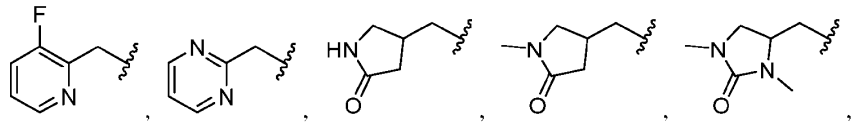
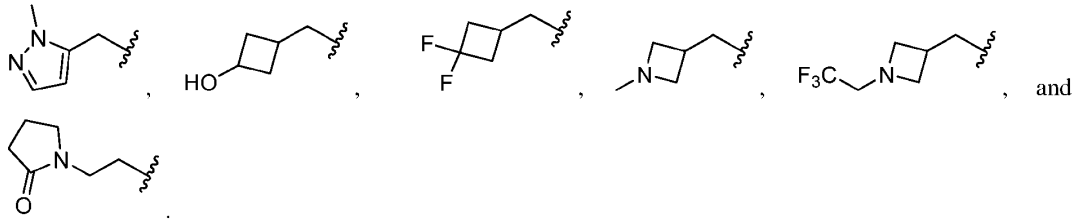

is selected from: , , , , , , , , , , and . In some embodiments, a moiety  is selected from: , , , , , , , , , , , , 

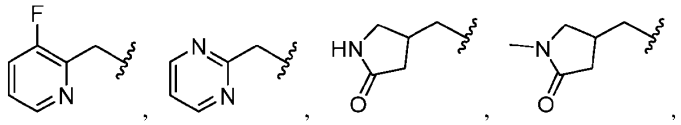
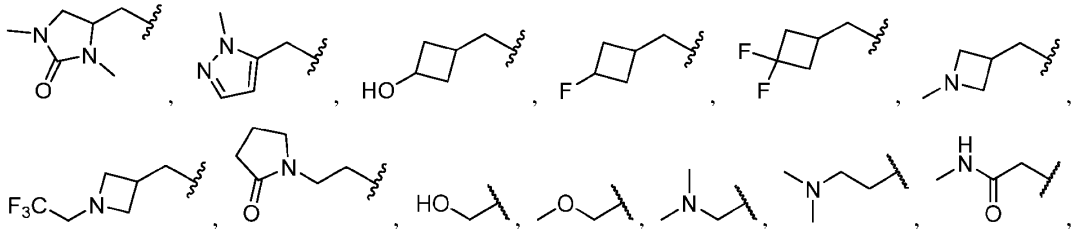
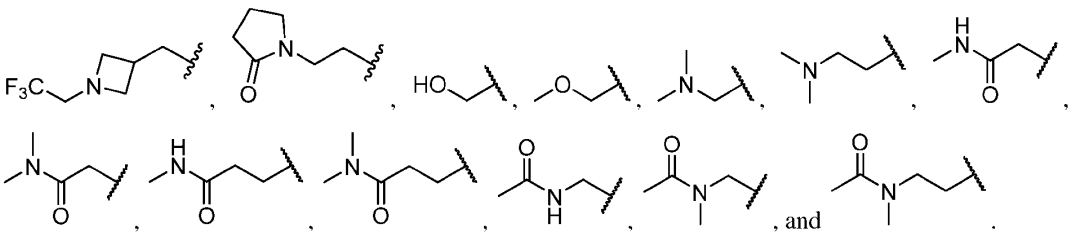
and . In some embodiments, a moiety  is .

[000122] In some embodiments, for a compound of any one of Formulae IF', IF1', and IF2', R^1 is $-OR^7$.

[000123] In some embodiments, for a compound of any one of Formulae IF', IF1', IF2', and IF3', R^7 is selected from optionally substituted C_{1-6} aliphatic and $-(C_{1-4}$ alkylene)OR. In some embodiments, R^7 is selected from C_{1-6} alkyl and $-(C_{1-4}$ alkylene)OR. In some embodiments, R^7 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^7 is C_{1-6} aliphatic. In some embodiments, R^7 is optionally substituted C_{1-6} alkyl. In some embodiments, each R^7 is C_{1-6} aliphatic substituted with a group selected from $-(CH_2)_{0-4}R°$, $-(CH_2)_{0-4}OR°$, $-(CH_2)_{0-4}N(R°)_2$, $-(CH_2)_{0-4}N(R°)C(O)R°$, $-(CH_2)_{0-4}NHC(O)R°$, $-(CH_2)_{0-4}C(O)NHR°$, and $-(CH_2)_{0-4}C(O)N(R°)_2$. In some embodiments, each R^7 is C_{1-6} aliphatic substituted with $-R°$, $-OR°$, $-N(R°)_2$, $-N(R°)C(O)R°$, $-NHC(O)R°$, $-C(O)NHR°$, and $-C(O)N(R°)_2$. In some such embodiments, R° is an optionally substituted group selected from C_{1-6} aliphatic, a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4- to 6-membered carbocyclic ring. In some embodiments, R° is substituted with halogen, oxo,$-(CH_2)_{0-2}R^•$, $-$(haloR•), $-(CH_2)_{0-2}OH$, and $-(CH_2)_{0-2}OR^•$. In some embodiments, R° is substituted with halogen, oxo,$-R^•$, $-$(haloR•), $-OH$, and $-OR^•$. In some embodiments, R• is C_{1-4} aliphatic. In some embodiments, R• is $-CH_3$ or $-CH_2CH_3$. In some embodiments, R° is substituted with halogen, oxo, $-CH_3$, $-CH_2CF_3$, -OH, and $-OCH_3$.

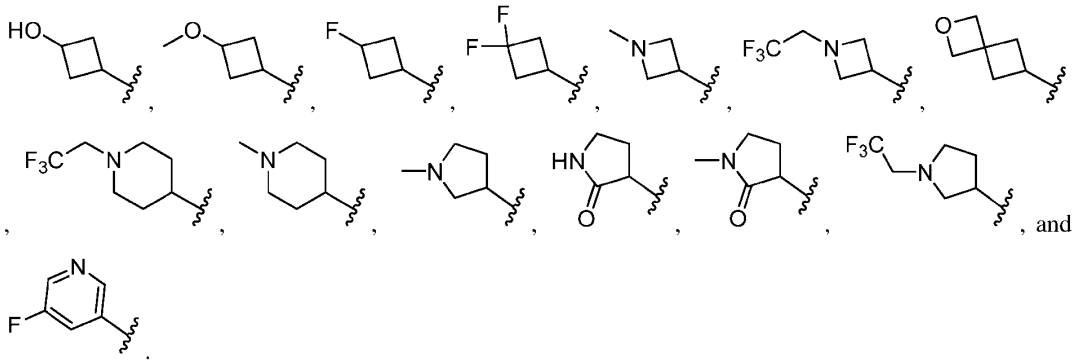
[000124] In some embodiments, for a compound of any one of Formulae IF', IF1', IF2', and IF3', each R^7 is optionally substituted C_{1-6} alkyl. In some embodiments, each R^7 is C_{1-6} alkyl substituted with a group selected from $-(CH_2)_{0-4}R°$, $-(CH_2)_{0-4}OR°$,$-(CH_2)_{0-4}N(R°)_2$, $-(CH_2)_{0-4}N(R°)C(O)R°$, $-(CH_2)_{0-4}NHC(O)R°$, $-(CH_2)_{0-4}C(O)NHR°$, $-(CH_2)_{0-4}C(O)N(R°)_2$, . In some embodiments, each R^7 is C_{1-6} alkyl substituted with $-R°$, $-OR°$, $-N(R°)_2$, $-N(R°)C(O)R°$, $-NHC(O)R°$, $-C(O)NHR°$, and $-C(O)N(R°)_2$. In some embodiments, each R^7 is C_{1-2} alkyl substituted with $-R°$, $-OR°$, $-N(R°)_2$, $-N(R°)C(O)R°$, $-NHC(O)R°$, $-C(O)NHR°$, and $-C(O)N(R°)_2$. In some embodiments, R° is an optionally substituted group selected from C_{1-6} aliphatic, a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 4- to 6-membered carbocyclic ring. In some embodiments, R^7 is C_{1-6} alkyl. In some embodiments, R^7 is $-(C_{1-4}$ alkylene)OR. In some embodiments, R^7 is $-(C_{1-4}$ alkylene)NR_2. In some embodiments, R^7 is independently selected from C_{1-6} aliphatic substituted with an optionally

substituted 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; C_{1-6} aliphatic substituted with an optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and C_{1-6} aliphatic substituted with an optionally substituted 3-7 membered carbocyclic ring. In some embodiments, R^7 is selected from C_{1-6} aliphatic substituted with an optionally substituted 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^7 is selected from C_{1-6} aliphatic substituted with an optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^7 is an optionally substituted 4- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^7 is selected from C_{1-6} aliphatic substituted with an optionally substituted 3-7 membered carbocyclic ring. In some embodiments, R^7 is selected from , , and .

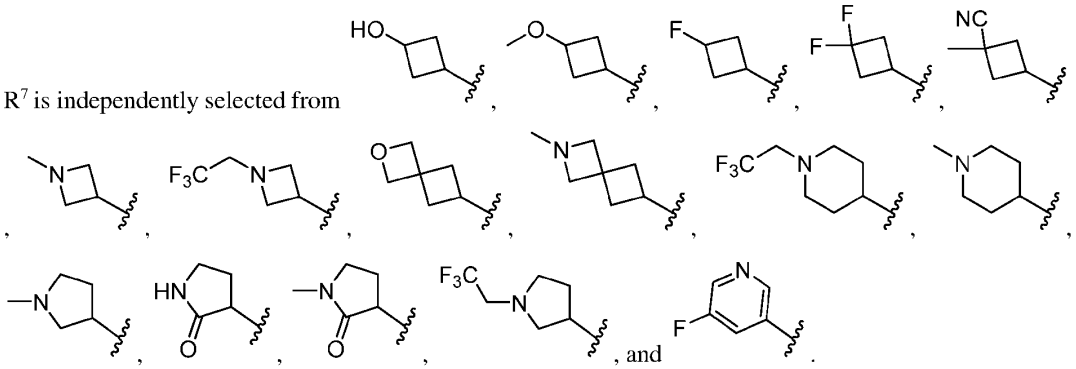
[000125] In some embodiments, for a compound of any one of Formulae IF', IF1', IF2', and IF3', each R^7 is independently selected from , , , , and .

[000126] In some embodiments, for a compound of any one of Formulae IF', IF1', IF2', and IF3', R^7 is selected from optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms

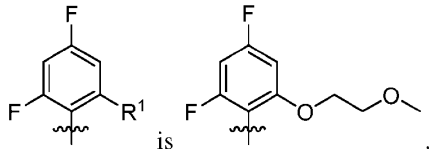
independently selected from nitrogen, oxygen, and sulfur, and optionally substituted 3- to 6-membered carbocyclic ring. In some embodiments, R^7 is selected from optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^7 is selected from optionally substituted pyrrolidinyl and piperidinyl. In some embodiments, R^7 is selected from optionally substituted 3- to 6-membered carbocyclic ring. In some embodiments, for a compound of any one of Formulae IF', IF1', IF2', and IF3', R^7 is selected from


, and

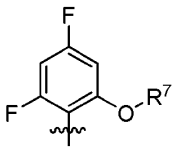
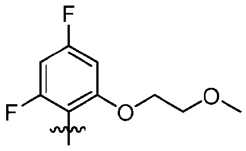
[000127] In some embodiments, for a compound of any one of Formulae IF', IF1', IF2', and IF3', each R^7 is independently selected from


, and

[000128] In some embodiments, for a compound of any one of Formulae IF', IF1', and IF2', a moiety


is

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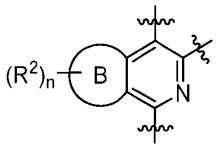
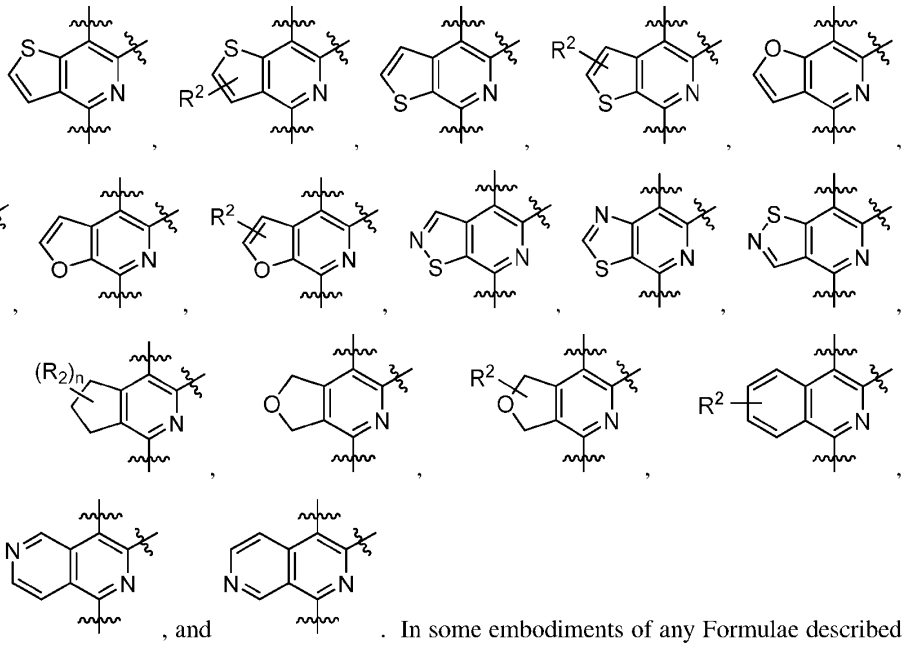
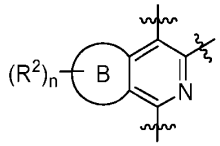
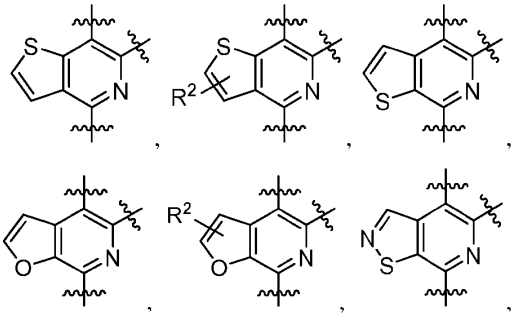
[000129] In some embodiments, for a compound of Formula IF3', a moiety  is .

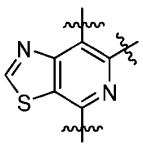
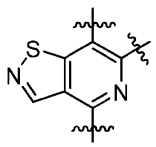
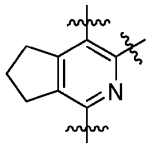
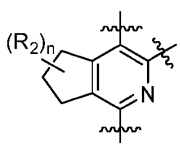
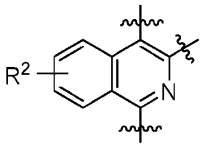
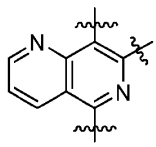
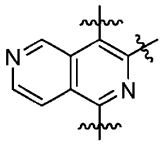
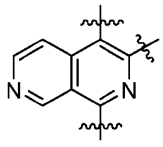
[000130] In some embodiments of any Formulae described herein, Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered carbocyclic ring; and phenyl. In some embodiments of any Formulae described herein, Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur and a 5- to 6-membered carbocyclic ring. In some embodiments, Ring B is selected from a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-membered carbocyclic ring, and a phenyl ring. In some embodiments, Ring B is selected from a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur and a 5-membered carbocyclic ring. In some embodiments, Ring B is a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring B is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring B is selected from a thiophene, a furan, or an isothiazole. In some embodiments, Ring B is a thiophene. In some embodiments, Ring B is a furan. In some embodiments, Ring B is an isothiazole. In some embodiments, Ring B is 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring B is a 5- to 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring B is a 5-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring B is a 5- to 6-membered carbocyclic ring. In some embodiments, Ring B is a 5- to 6-membered cycloalkyl ring. In some embodiments, Ring B is a 5-membered carbocyclic ring (e.g., cyclopentyl). In some embodiments, Ring B is a 6-membered carbocyclic ring. In some embodiments, Ring B is a phenyl ring.

[000131] In some embodiments of any Formulae described herein, each R^2 is independently selected from halogen and optionally substituted C_{1-6} alkyl. In some embodiments, each R^2 is independently selected from halogen and C_{1-6} aliphatic. In some embodiments, each R^2 is independently selected from halogen and

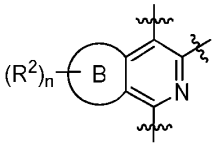
C_{1-6} alkyl. In some embodiments, R^2 is halogen (e.g., fluoro or chloro). In some embodiments, R^2 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^2 is C_{1-6} aliphatic. In some embodiments, R^2 is optionally substituted C_{1-6} alkyl. In some embodiments, R^2 is C_{1-6} alkyl (e.g., methyl).

[000132] In some embodiments of any Formulae described herein, n is 0 or 1. In some embodiments, n is 1 or 2. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

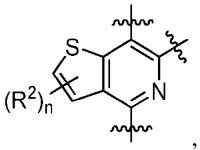
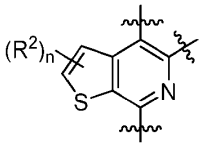
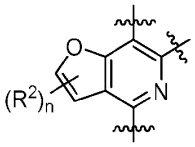
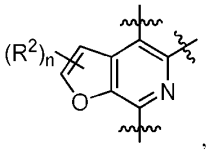
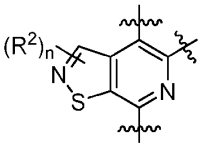
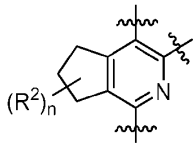
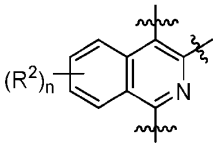
[000133] In some embodiments of any Formulae described herein, a moiety  is selected from: , and . In some embodiments of any Formulae described herein, a moiety  is selected from: .

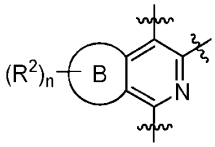
, and . In some embodiments of any Formulae described herein, a moiety



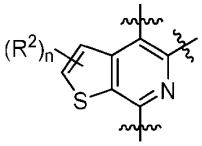
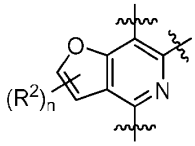
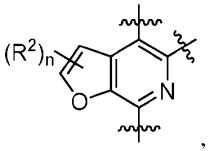
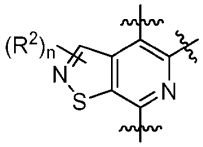
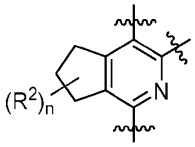
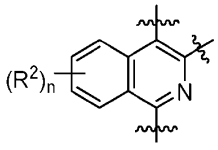
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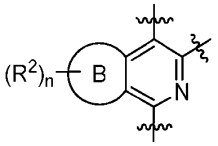
, , , and . In some embodiments of any Formulae described herein, a moiety



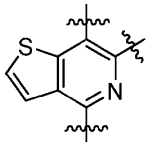
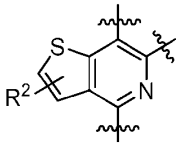
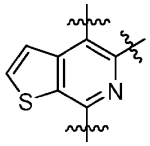
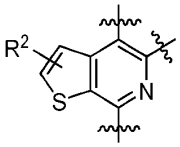
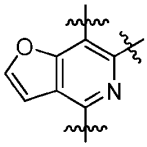
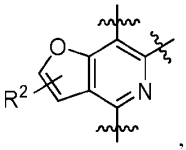
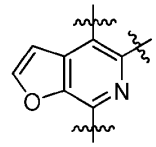
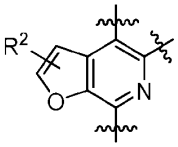
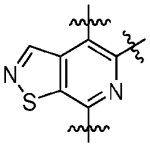
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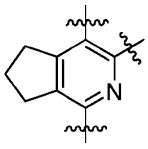
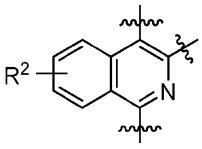
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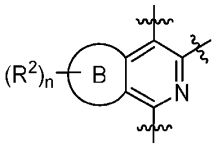
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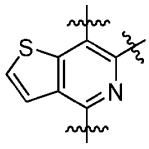
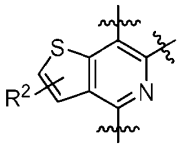
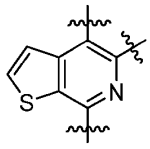










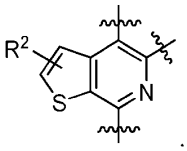
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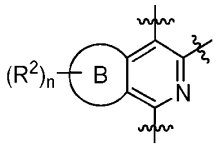
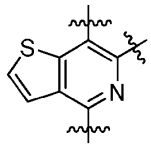



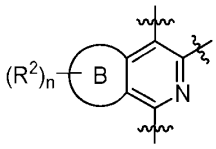
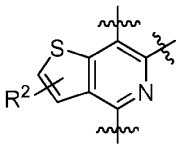
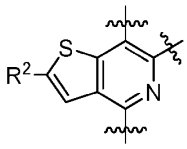
, and . In some embodiments of any Formulae described herein, a moiety



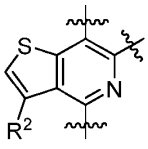
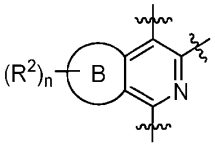
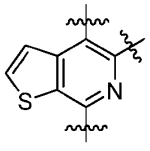
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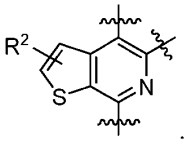
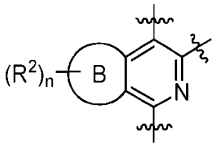
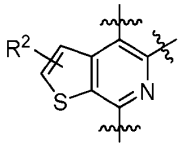
. In some embodiments, a moiety  is . In some

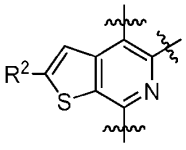
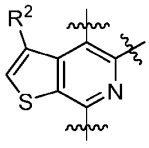
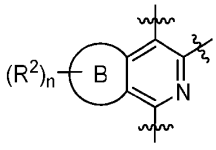
embodiments, a moiety is (e.g., or

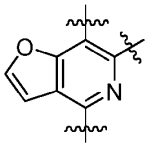
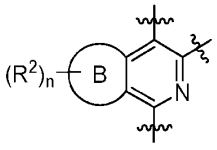
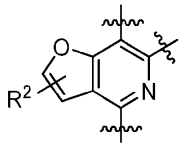
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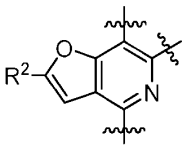
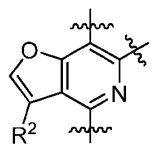
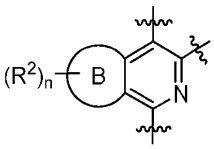
. In some embodiments, a moiety is (e.g.,

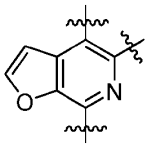
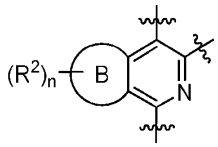
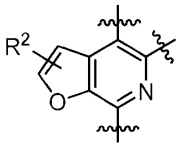
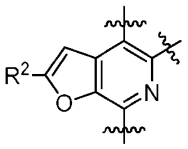
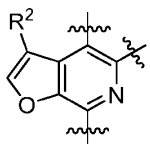
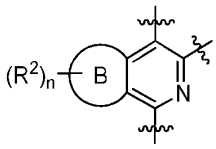
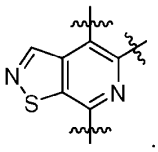
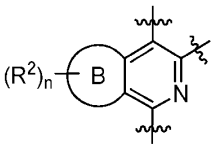
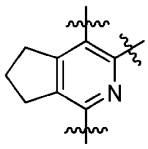
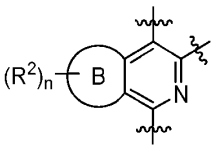
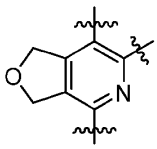
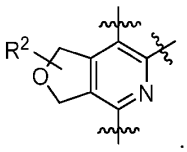
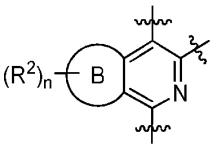
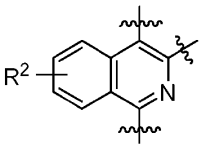
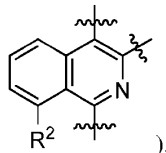
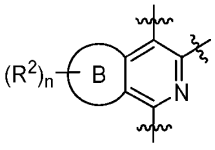
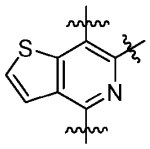
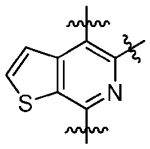
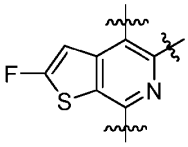
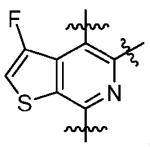
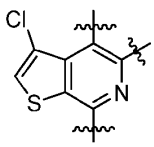
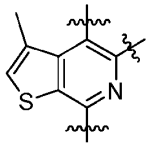
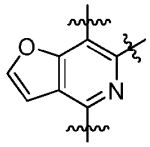
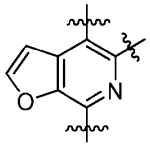
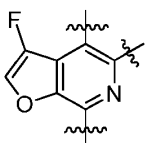
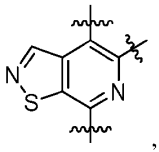
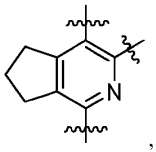
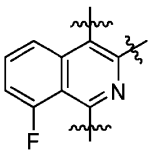
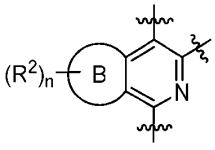
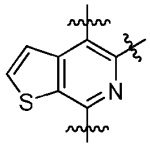
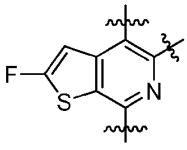
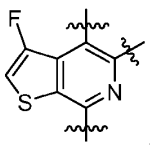
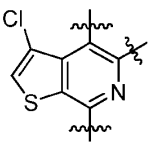
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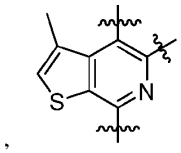
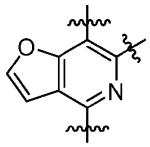
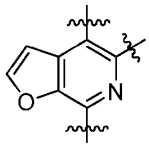
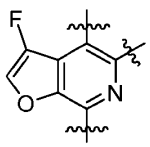
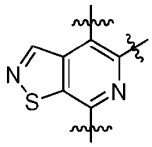
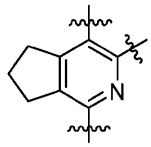
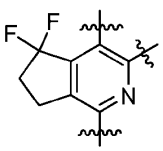
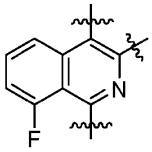
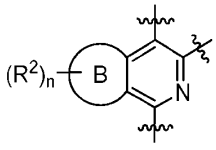
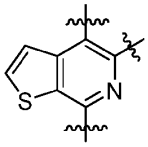
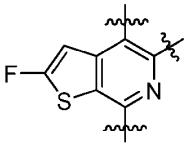
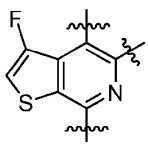
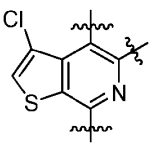
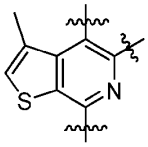
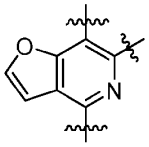
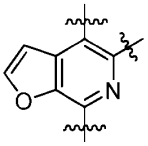
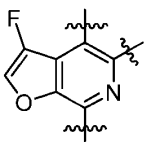
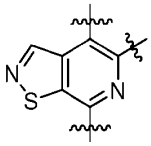
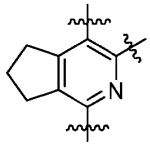
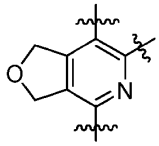
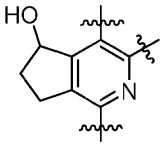
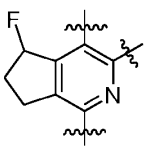
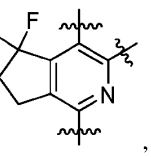
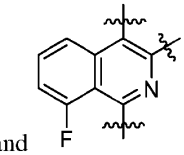




. In some embodiments, a moiety is (e.g.,

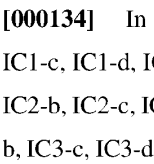
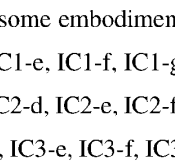
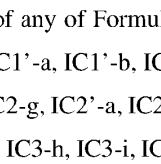
or). In some embodiments, a moiety is


. In some embodiments, a moiety  is  (e.g.,  or ). In some embodiments, a moiety  is . In some embodiments, a moiety  is . In some embodiments, a moiety  is selected from  and . In some embodiments, a moiety  is  (e.g., ). In some embodiments, a moiety  is selected from: , , , , , , , , , , , and . In some embodiments, a moiety  is selected from: , , , .


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[000134] In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is selected from 9- to 10-membered bicyclic aryl ring, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is selected from phenyl, 9- to 10-membered bicyclic aryl ring, and 3- to 7-membered carbocyclic ring. In some embodiments, Ring C is selected from 5- to 6-membered heteroaryl

ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000135] In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C is phenyl.

[000136] In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C is a 9- to 10-membered bicyclic aryl ring. In some embodiments, Ring C is a 9-membered bicyclic aryl ring (e.g., an indane). In some embodiments, Ring C is a 10-membered bicyclic aryl ring.

[000137] In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 5- to 6-membered heteroaryl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a pyrazolyl.

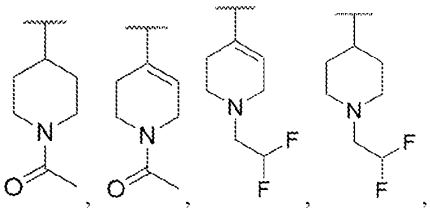
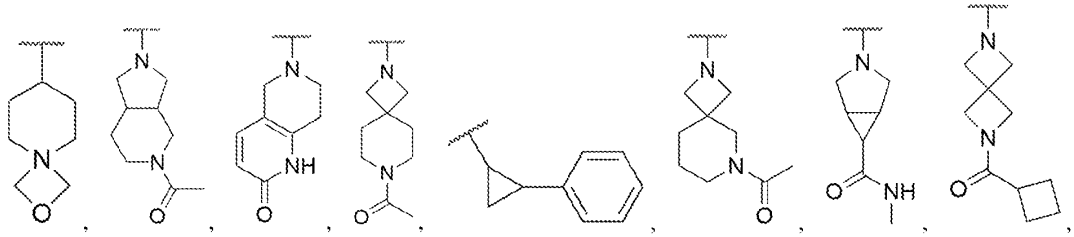
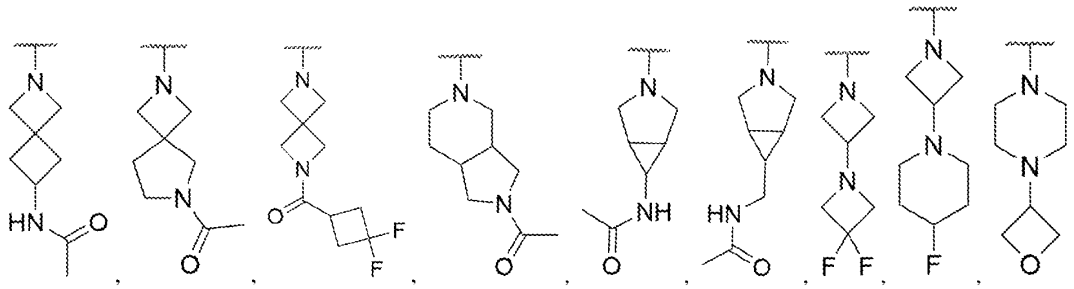
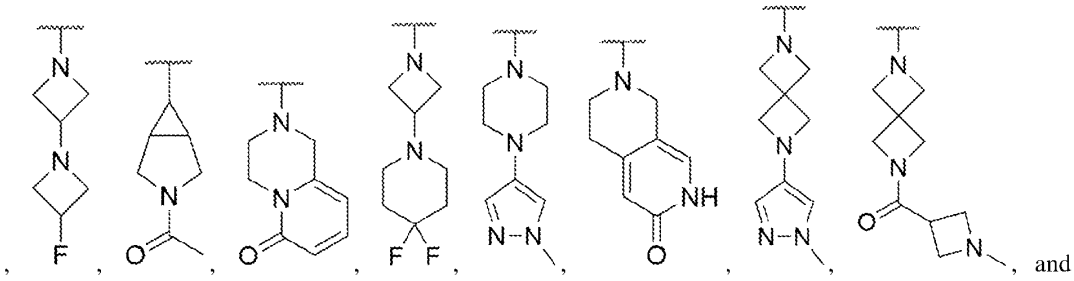
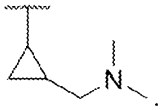
In some embodiments, Ring C is a 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a pyridinyl.

[000138] In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C is a 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 9-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is an indolyl, indazolyl, benzimidazolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[3,2-b]pyridinyl, pyrrolo[3,2-c]pyridinyl, imidazo[1,2-a]pyridinyl, or imidazo[4,5-b]pyridinyl. In some embodiments, Ring C is a 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000139] In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C is a 3- to 7-membered carbocyclic ring. In some embodiments, Ring C is a 3- to 7-membered cycloalkyl ring. In some embodiments, Ring C is a 3- to 5-membered carbocyclic ring. In some embodiments, Ring C is a 3- to 5-membered cycloalkyl ring. In some embodiments, Ring C is a cyclopropyl.

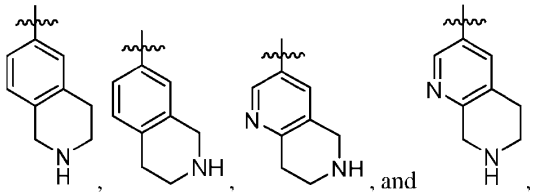
[000140] In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 4-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is an azetidinyl ring. In some embodiments, Ring C is a 5-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 6-membered heterocyclic ring having 1-2 heteroatoms independently selected

from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a piperazinyl ring. In some embodiments, Ring C is a 1,2,3,6-tetrahydropyridinyl ring. In some embodiments, Ring C is a 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000141] In some embodiments, Ring C is selected from , , , , and .

[000142] In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-

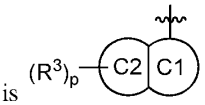
d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C is a 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a fused 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a heterocyclic ring fused to an aryl, heteroaryl, cycloalkyl, or heterocyclic ring, wherein the point of attachment to the rest of the molecule is on either ring). In some embodiments, Ring C is a spirocyclic 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a heterocyclic ring spirofused to a cycloalkyl or heterocyclic ring, wherein the point of attachment to the result of the molecule is on either ring). In some embodiments, Ring C is a 6-membered bicyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 7-membered bicyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is an 8-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 9-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 10-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is selected from:



, any of which is substituted with p R^3 groups. In some embodiments, Ring C is an 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C is a 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, comprising two or more fused and/or bridged rings. In some embodiments, Ring C is a 12-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from

nitrogen, oxygen, and sulfur. In some embodiments, Ring C is a 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000143] In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, and IE1'-b, Ring C substituted with p R^3 groups is 

, wherein:

Ring C1 is fused to Ring C2;

Ring C1 is selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

Ring C2 is selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000144] In some such embodiments, Ring C1 is a phenyl, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, or 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000145] In some embodiments of any of Formulae IA, IA', IB1, and IB1', Ring C1 is selected from phenyl and 3- to 7-membered carbocyclic ring. In some embodiments, Ring C1 is selected from 5- to 6-

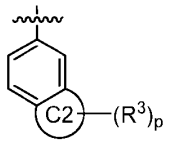
membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is selected from phenyl and 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is selected from 3- to 7-membered carbocyclic ring and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is phenyl. In some embodiments, Ring C1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is a 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrrolyl or imidazolyl). In some embodiments, Ring C1 is a 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a pyridinyl). In some embodiments, Ring C1 is a 3- to 7-membered carbocyclic ring. In some embodiments, Ring C1 is a 3- to 7-membered cycloalkyl ring. In some embodiments, Ring C1 is a 3- to 5-membered carbocyclic ring. In some embodiments, Ring C1 is a 3- to 5-membered cycloalkyl ring (e.g., a cyclopropyl). In some embodiments, Ring C1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is a 5- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is a 5-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrrolidinyl). In some embodiments, Ring C1 is a 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a piperidinyl or a piperazinyl).

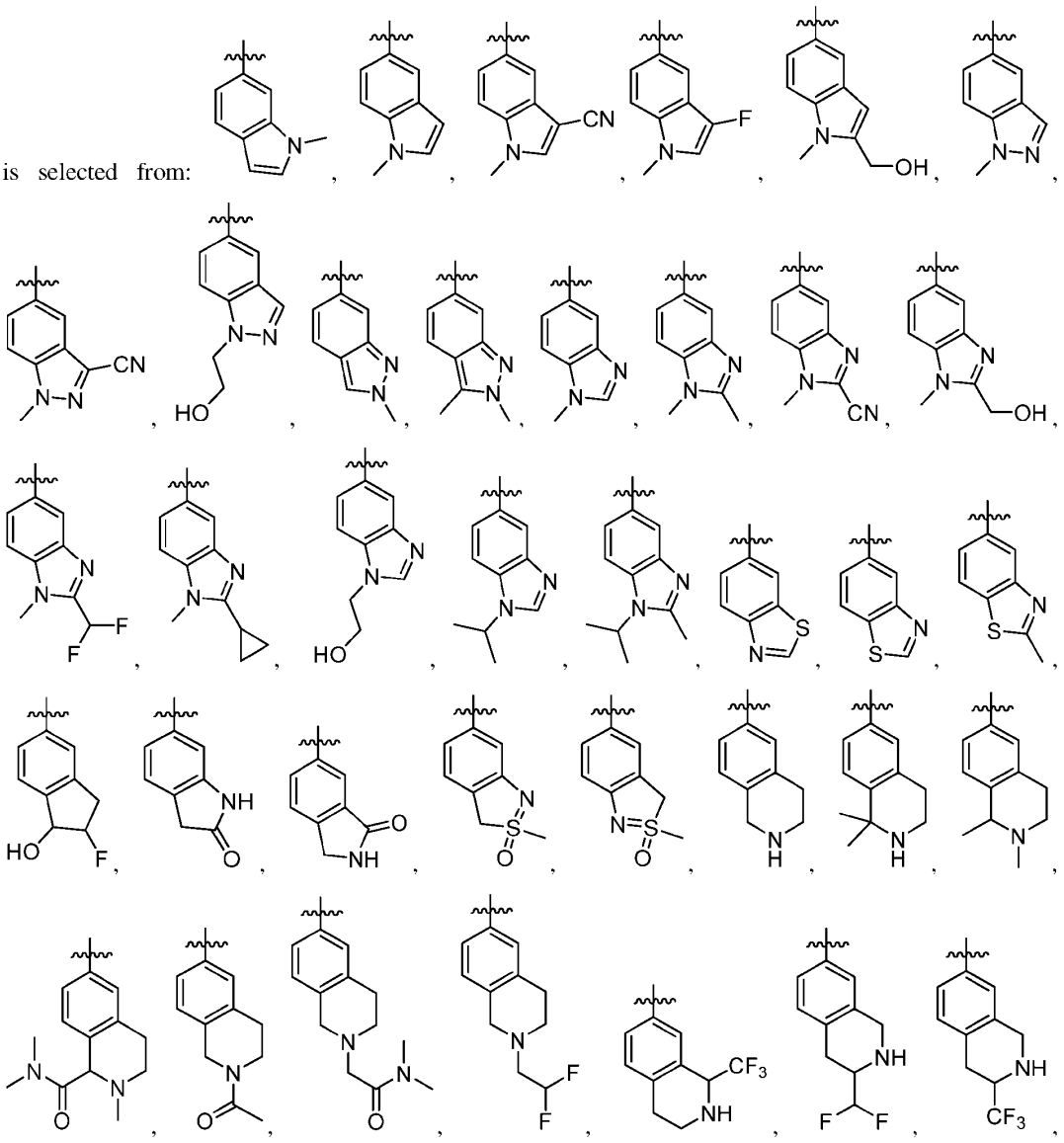
[000146] In some embodiments of any of Formulae IA, IA', IB1, IB1', IF', IF1', IF2', and IF3', Ring C2 is selected from phenyl and 3- to 7-membered carbocyclic ring. In some embodiments, Ring C2 is selected from 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C2 is selected from phenyl and 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C2 is selected from 3- to 7-membered carbocyclic ring and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C2 is phenyl. In some embodiments, Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C2 is a 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrrolyl, pyrazolyl, or imidazolyl). In some embodiments, Ring C2 is a 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen,

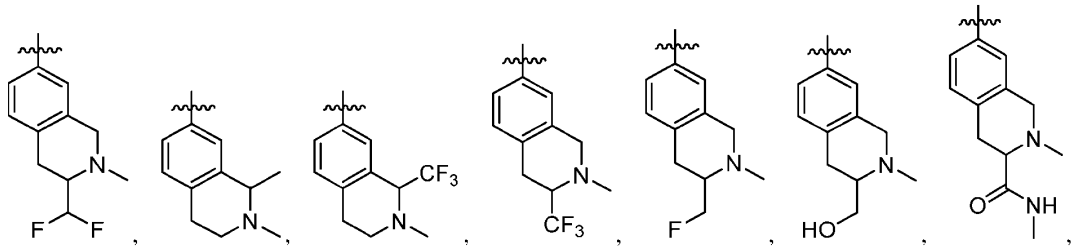
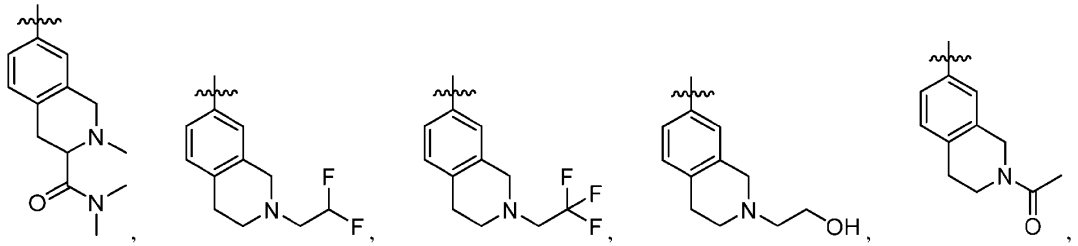
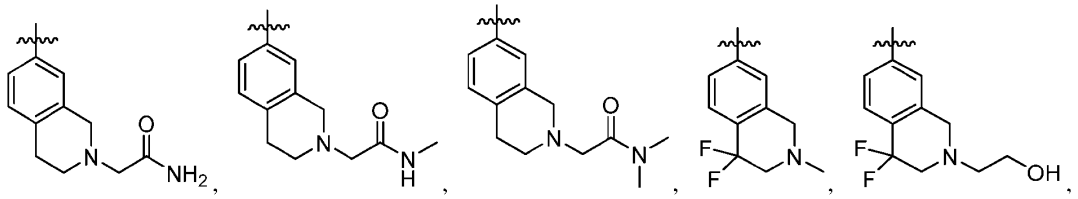
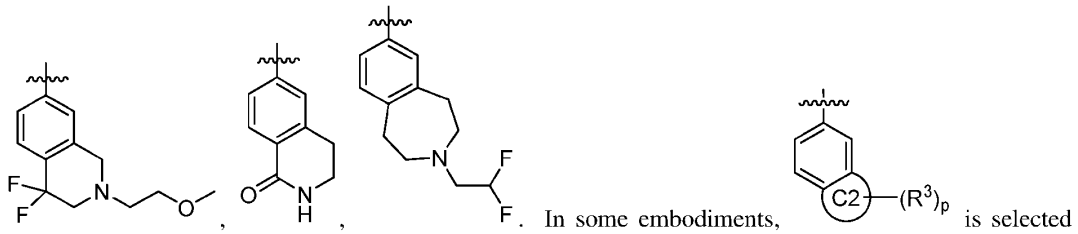
and sulfur (e.g., a pyridinyl, or pyridonyl). In some embodiments, Ring C2 is a 3- to 7-membered carbocyclic ring. In some embodiments, Ring C2 is a 3- to 7-membered cycloalkyl ring. In some embodiments, Ring C2 is a 3- to 5-membered carbocyclic ring. In some embodiments, Ring C2 is a 3- to 5-membered cycloalkyl ring (e.g., a cyclopropyl or cyclopentyl). In some embodiments, Ring C2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C2 is a 5- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C2 is a 5-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrrolidinyl). In some embodiments, Ring C2 is a 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a piperidinyl or a piperazinyl). In some embodiments, Ring C2 is a 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., an azepanyl).

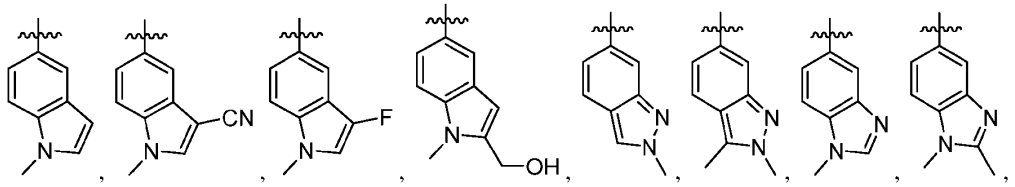
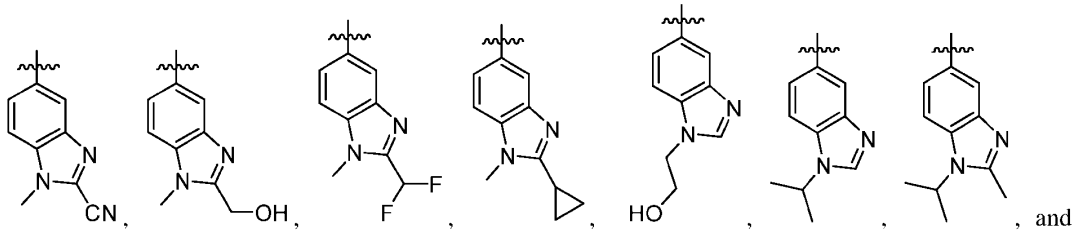
[000147] In some embodiments of any of Formulae IA, IA', IB1, and IB1', Ring C1 is a phenyl, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 3- to 7-membered carbocyclic ring, or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

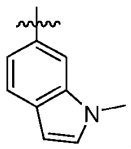
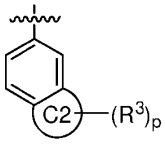
[000148] In some embodiments of any of Formulae IF', IF1', IF2', and IF3', Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring C2 is a 3- to 7-membered carbocyclic ring.

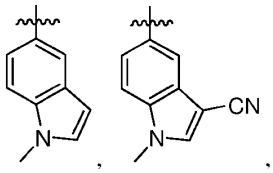
[000149] In some embodiments of any of Formulae IF', IF1', IF2', and IF3', a moiety 

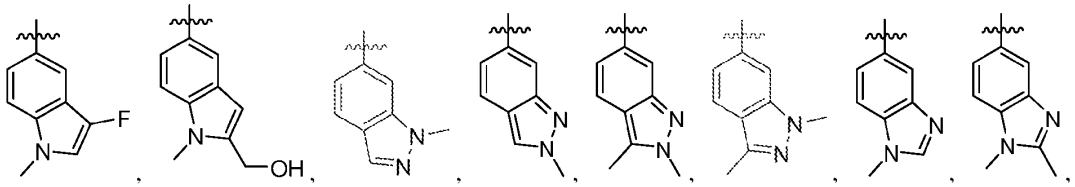
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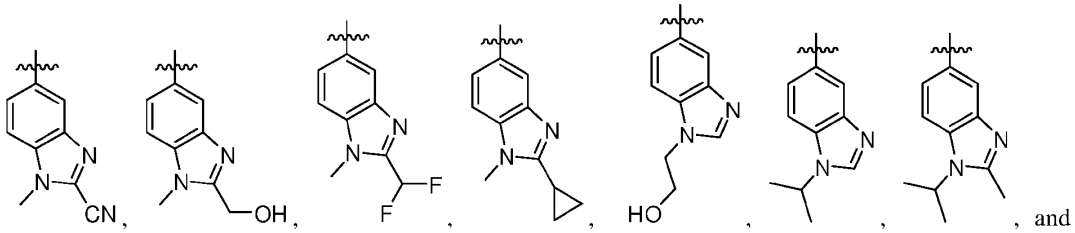





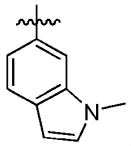
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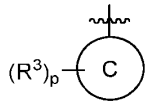
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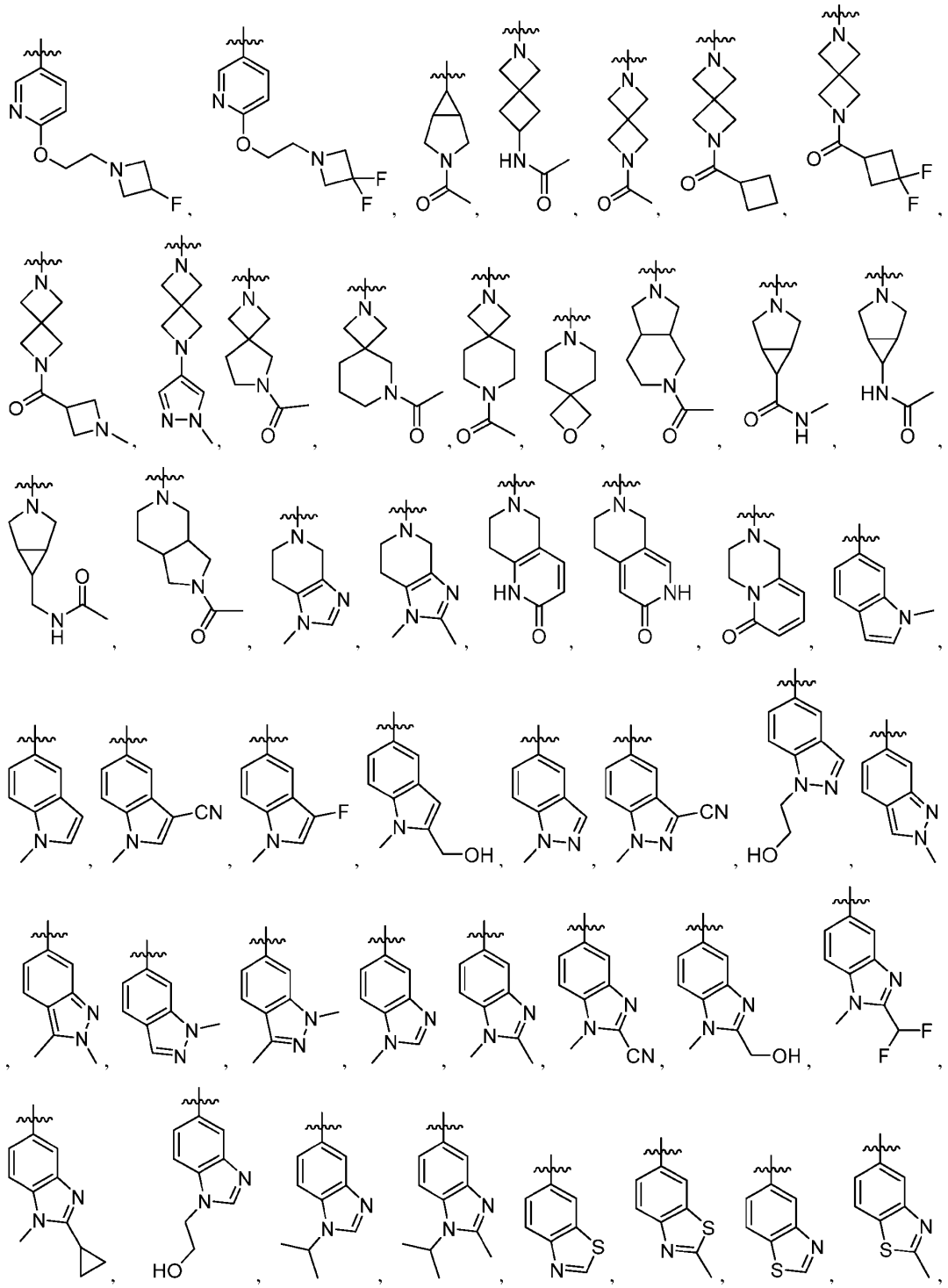
[000150] In some embodiments of any of Formulae I, I', I'', IA, IA', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, IE1'-b, IF', IF1', IF2', and IF3', each R^3 is independently selected from oxo, halogen, -CN, -OR, -C(O)R, -C(O)N(R)$_2$, -(CH$_2$)$_x$C(O)OR, -(CH$_2$)$_x$C(O)N(R)$_2$, -(CH$_2$)$_x$N(R)C(O)R, -(CH$_2$)$_x$Cy, -O(CH$_2$)$_x$Cy, -C(O)Cy, optionally substituted carbocyclic ring, and optionally substituted C_{1-6} alkyl. In some embodiments, each R^3 is independently selected from halogen, -CN, -OR, -C(O)R, -(CH$_2$)$_x$C(O)OR, -(CH$_2$)$_x$C(O)N(R)$_2$, -(CH$_2$)$_x$N(R)C(O)R, -(CH$_2$)$_x$Cy, -O(CH$_2$)$_x$Cy, -C(O)Cy, and optionally substituted C_{1-6} aliphatic. In some embodiments, each R^3 is independently selected from oxo, halogen, -CN, -OR, -C(O)R, -(CH$_2$)$_x$C(O)OR, -(CH$_2$)$_x$C(O)N(R)$_2$, -(CH$_2$)$_x$N(R)C(O)R, -(CH$_2$)$_x$Cy, -O(CH$_2$)$_x$Cy, -C(O)Cy, and C_{1-6} aliphatic optionally substituted with one or more R^{10}. In some embodiments, each R^3 is independently selected from halogen, -C(O)N(R)$_2$, and optionally substituted C_{1-6} alkyl (e.g., C_{1-6} alkyl optionally substituted with one or more R^{10}). In some embodiments, each R^3 is independently selected from halogen, -C(O)N(R)$_2$, and C_{1-6} alkyl. In some embodiments, an R^3 is oxo. In some embodiments, an R^3 is

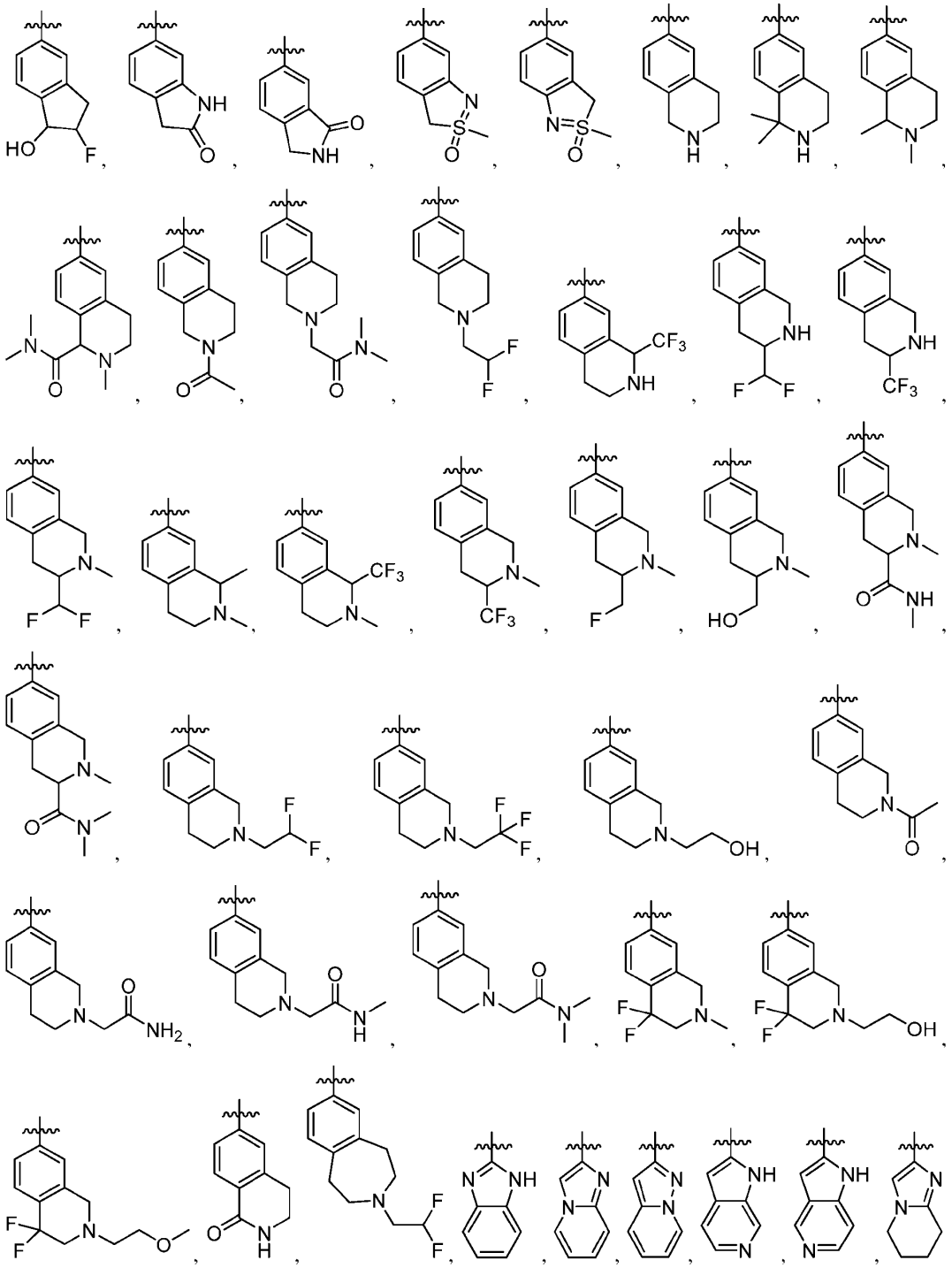
halogen (e.g., fluoro). In some embodiments, an R^3 is –CN. In some embodiments, an R^3 is –OR (e.g., -OH). In some embodiments, an R^3 is -C(O)R. In some embodiments, an R^3 is –C(O)(C_{1-6} alkyl) (e.g., -$C(O)CH_3$). In some embodiments, an R^3 is -$(CH_2)_xC(O)OR$, such as –$CH_2C(O)OR$. In some embodiments, an R^3 is -$(CH_2)_xC(O)OH$ (e.g., -$CH_2C(O)OH$). In some embodiments, an R^3 is -$(CH_2)_xC(O)N(R)_2$ (e.g., -$CH_2C(O)N(R)_2$ or –$C(O)N(R)_2$). In some embodiments, an R^3 is –$(CH_2)_xC(O)NH(C_{1-6}$ alkyl) (e.g., -$CH_2C(O)NHCH_3$ or –$C(O)NHCH_3$). In some embodiments, an R^3 is –$(CH_2)_xC(O)N(C_{1-6}$ alkyl)$_2$ (e.g., –$CH_2C(O)N(CH_3)_2$ or –$C(O)N(CH_3)_2$). In some embodiments, an R^3 is -$(CH_2)_xN(R)C(O)R$, such as -$CH_2N(R)C(O)R$. In some embodiments, an R^3 is -$(CH_2)_xN(H)C(O)(C_{1-6}$ alkyl) (e.g., -$N(H)C(O)CH_3$ or -$CH_2N(H)C(O)CH_3$). In some embodiments, an R^3 is –$(CH_2)_xCy$ (e.g., phenyl, -$(CH_2)_x$azetidinyl, -$(CH_2)_x$pyrolidinyl, -$(CH_2)_x$piperidinyl, oxetanyl, or pyrazolyl, any of which are substituted with 0-3 instances of R^8). In some embodiments, an R^3 is -$O(CH_2)_xCy$, such as –$O(CH_2)_2Cy$. In some embodiments, an R^3 is –$O(CH_2)_2Cy$, wherein Cy is an azetidinyl substituted with 0-3 instances of R^8. In some embodiments, an R^3 is -C(O)Cy (e.g., -C(O)Cy, wherein Cy is a cyclobutyl or azetidinyl, either of which is substituted with 0-3 instances of R^8). In some embodiments, an R^3 is optionally substituted C_{1-6} aliphatic (e.g., C_{1-6} aliphatic optionally substituted with one or more R^{10}). In some embodiments, an R^3 is optionally substituted C_{1-6} alkyl (e.g., C_{1-6} alkyl optionally substituted with one or more R^{10}). In some embodiments, an R^3 is C_{1-6} alkyl optionally substituted with one or more halogen (e.g., fluoro), -OH, -O(C_{1-6} alkyl) (e.g., -OCH_3), or -N(C_{1-6} alkyl)$_2$ (e.g., -$N(CH_3)_2$). In some embodiments, an R^3 is selected from –CH_3, -CH_2F, -CF_3, -CH_2OH, –$CH_2N(CH_3)_2$, -CH_2CHF_2, -CH_2CF_3, -CH_2CH_2OH, -$CH_2CH_2OCH_3$, -$CH(CH_3)_2$, –$CH_2CH(OH)CH_2OH$, and –$CH_2CH(OH)CH_2OCH_3$.

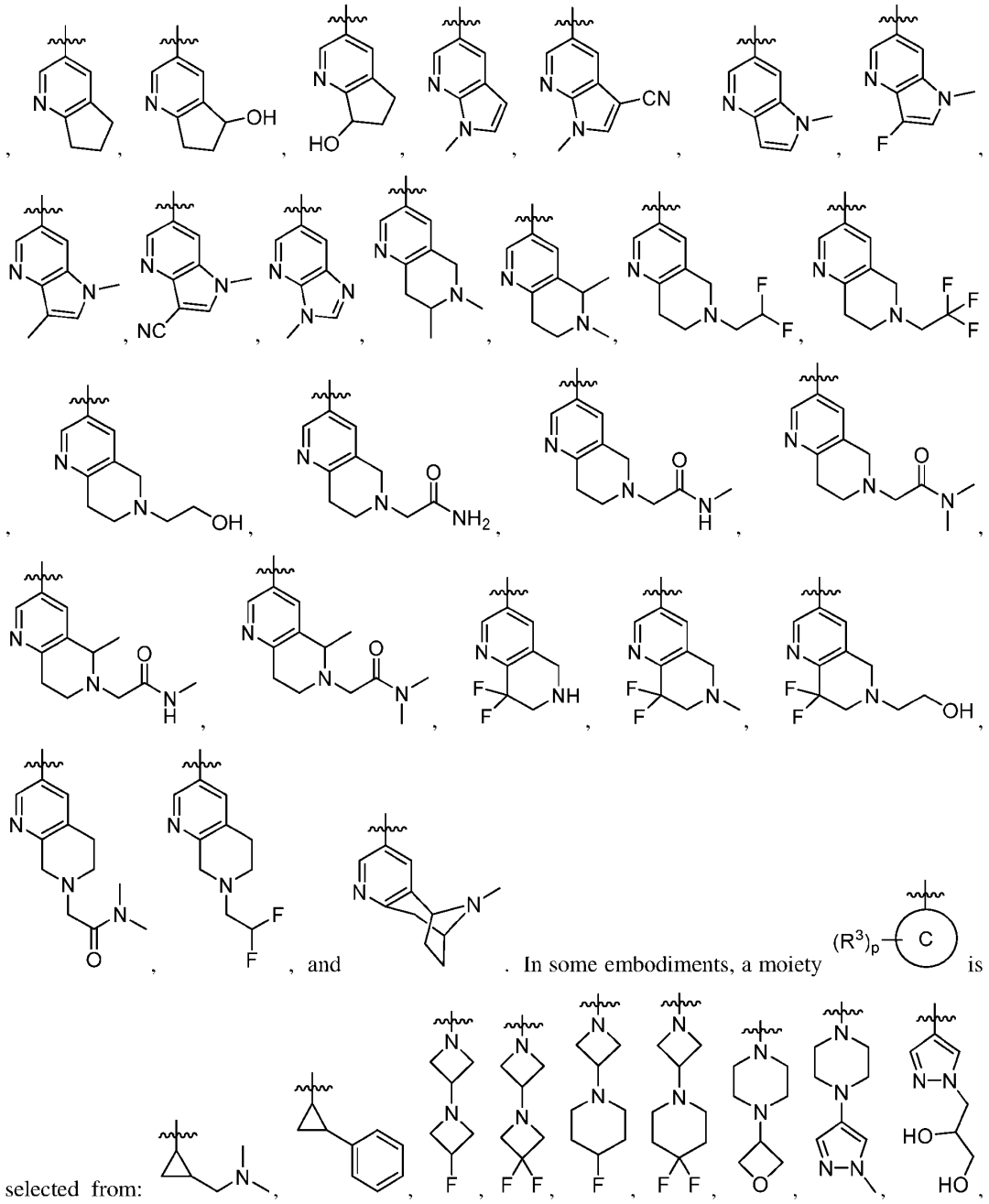
[000151] In some embodiments of any of Formulae I, I', I'', IA, IA', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a, IE1-b, IE1'-a, IE1'-b, IF', IF1', IF2', and IF3', p is 0, 1, or 2. In some embodiments, p is 1, 2, or 3. In some embodiments, p is 0 or 1. In some embodiments, p is 1 or 2. In some embodiments, p is 2 or 3. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3.

In some embodiments of any of Formulae I, I', I'', IB, IB', IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC2, IC2', IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC2'-a, IC2'-b, IC2'-c, IC2'-d, IC2'-e, IC2'-f, IC2'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-c, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-c, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, IC4, IC4', ID, ID', IE, IE', IE1, IE1', IE1-a,

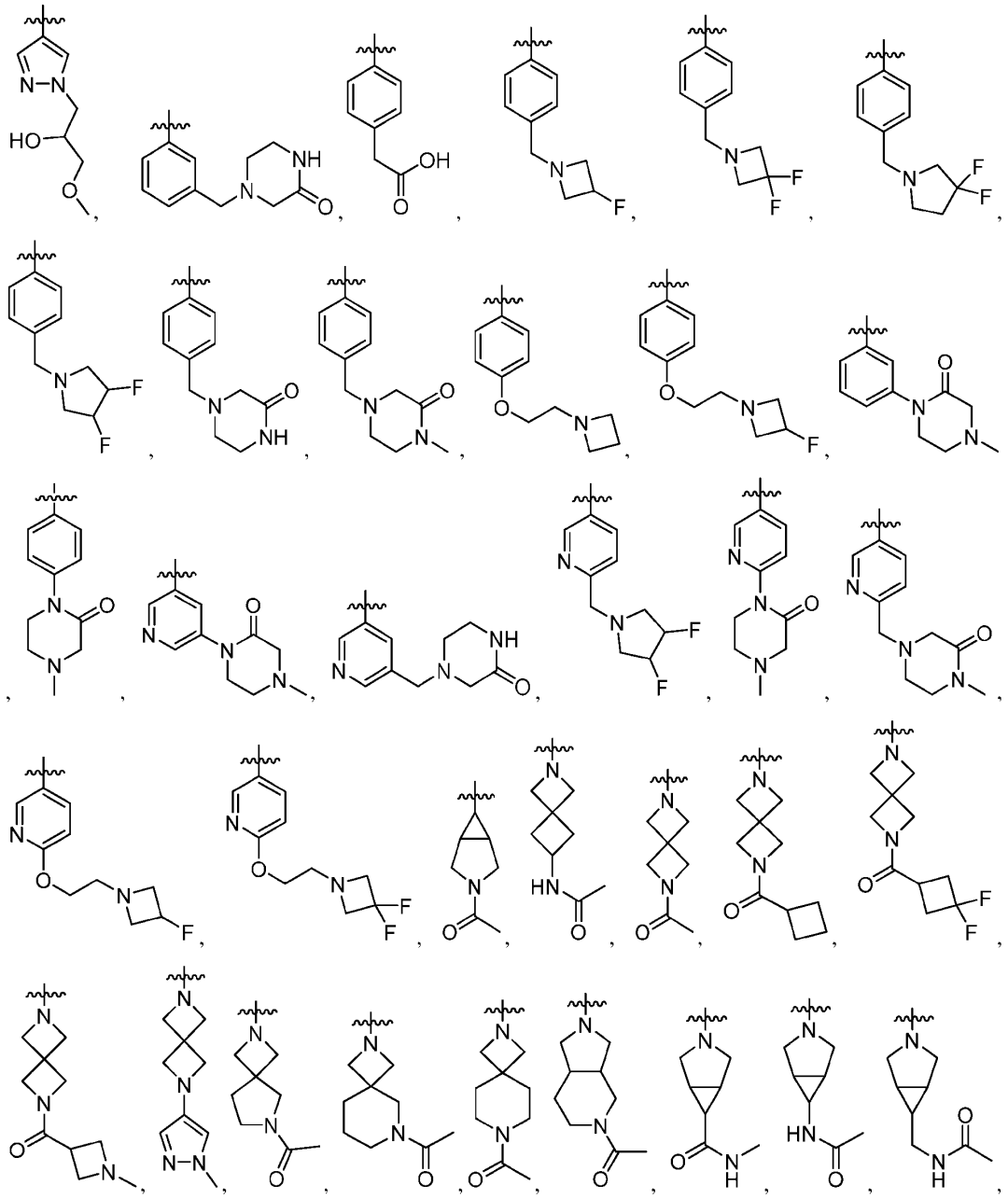
IE1-b, IE1'-a, and IE1'-b, a moiety  is selected from:

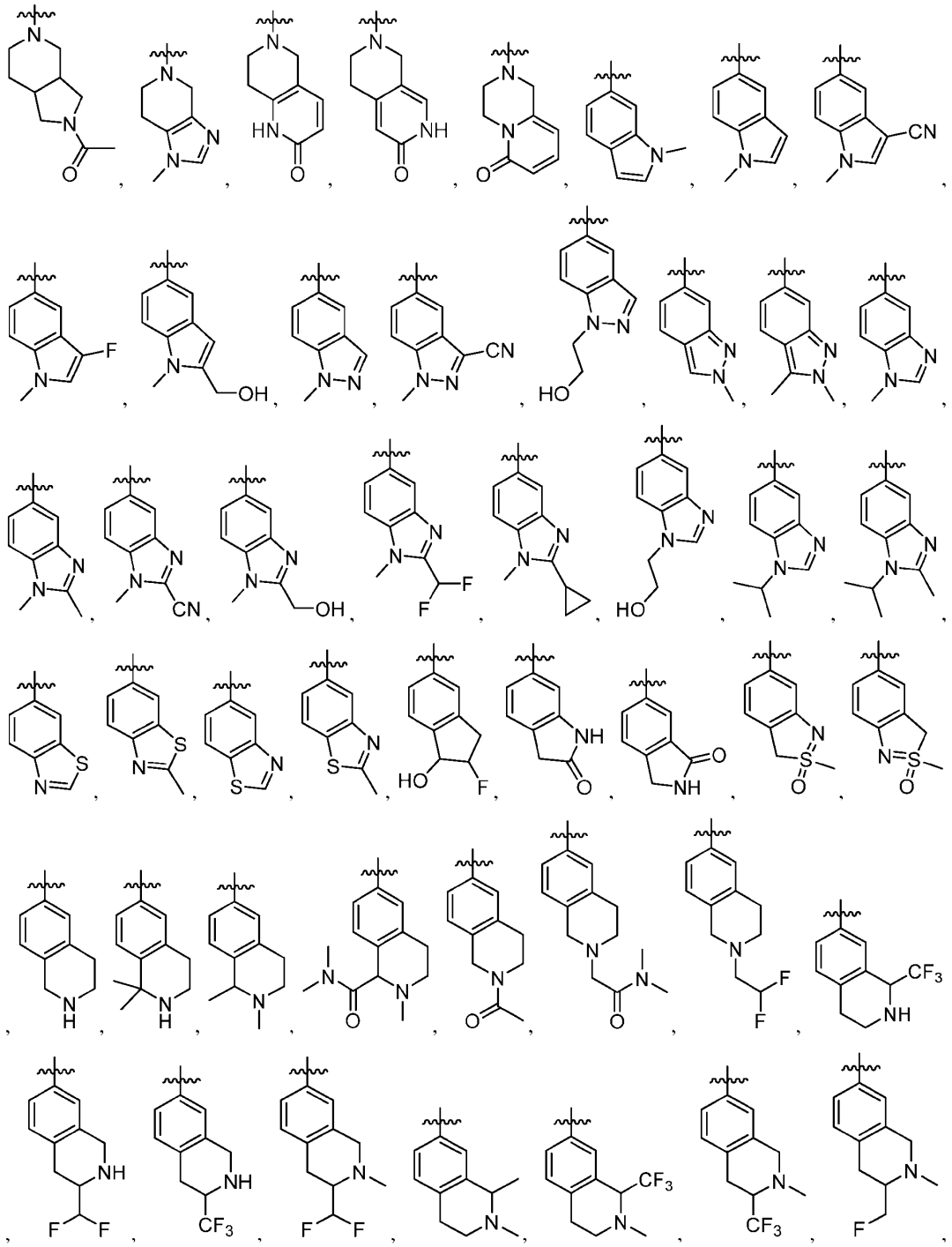


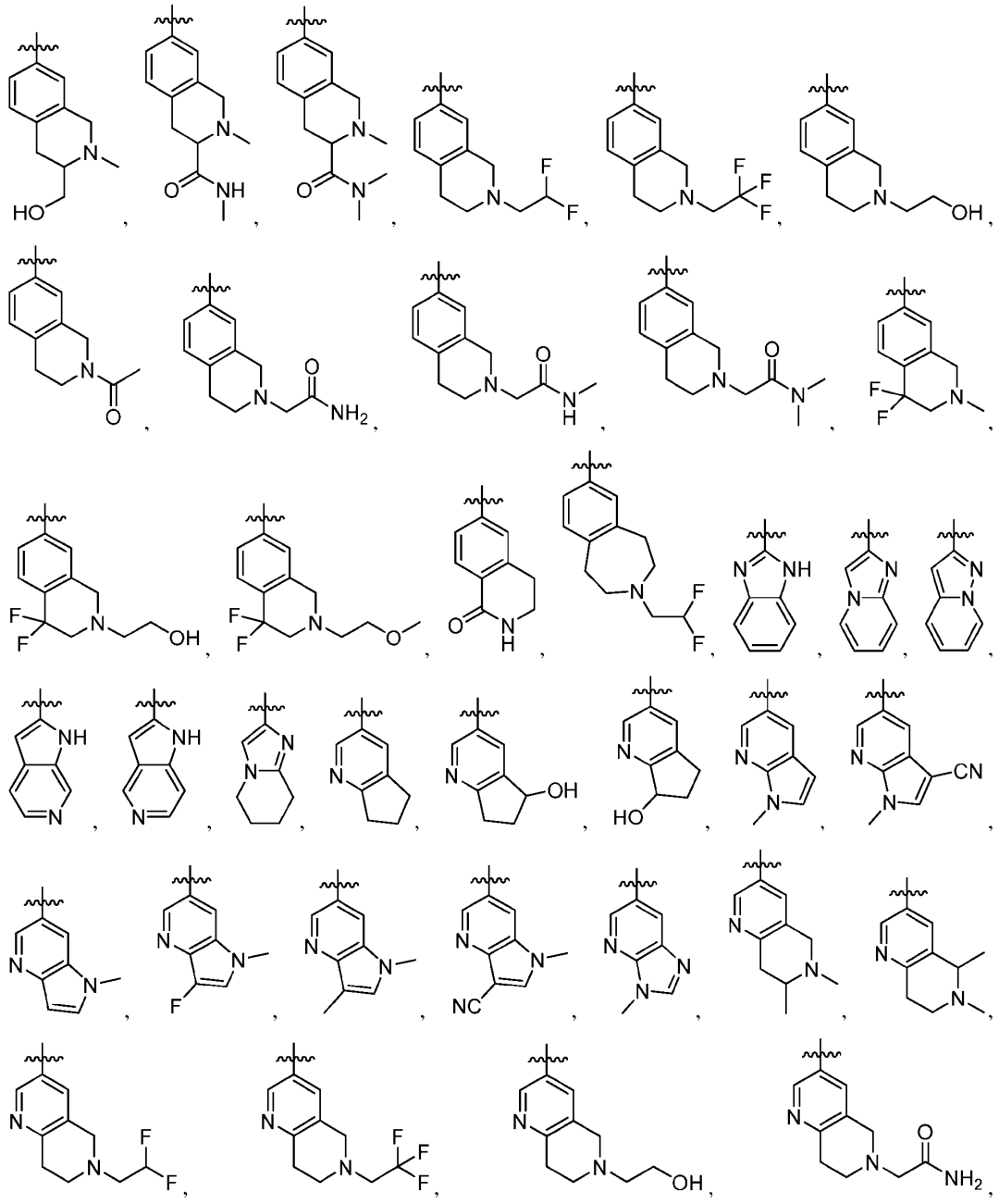


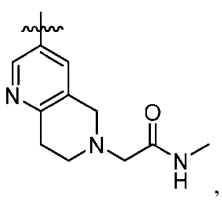
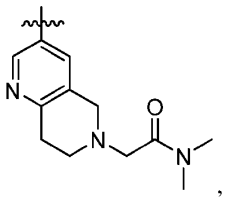
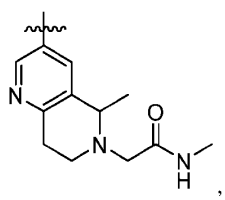
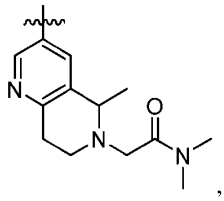
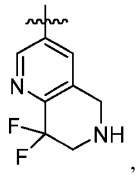
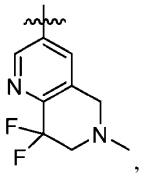
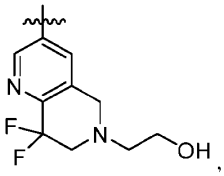
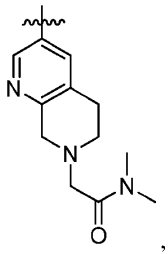
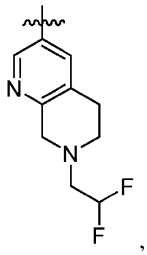
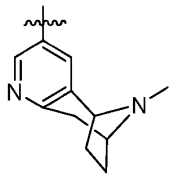


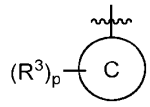
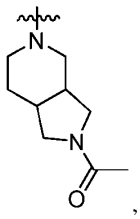
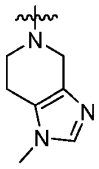
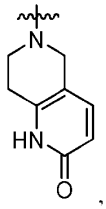
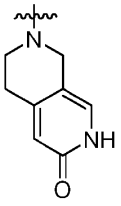
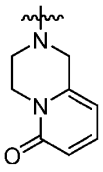
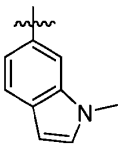
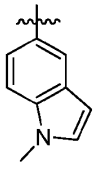
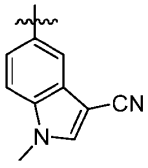
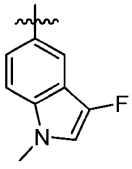
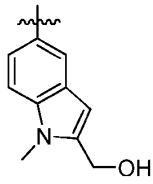
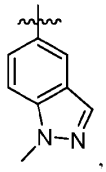
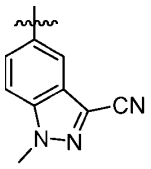
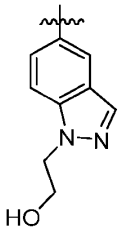
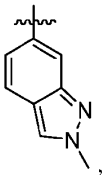
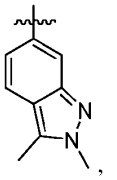
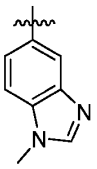
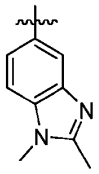
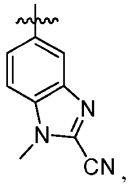
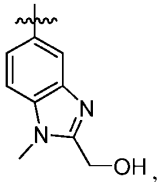
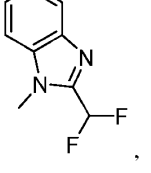
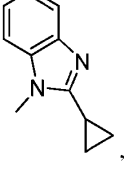
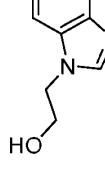
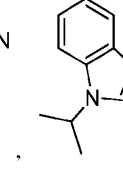
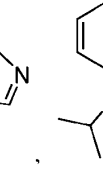
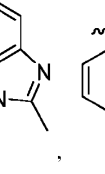
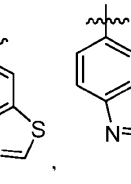
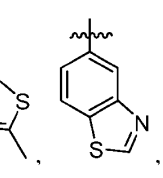
. In some embodiments, a moiety is selected from: .

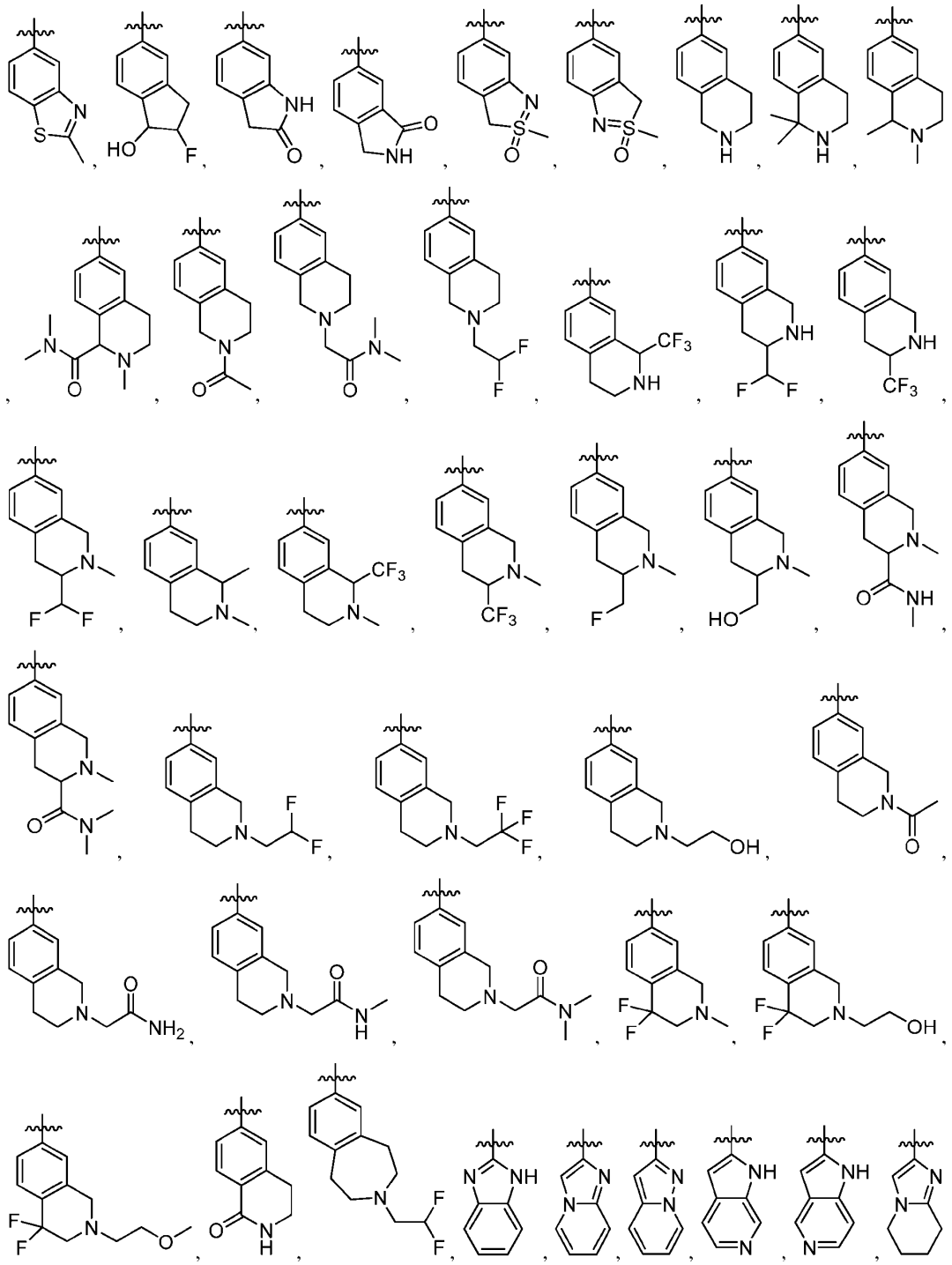


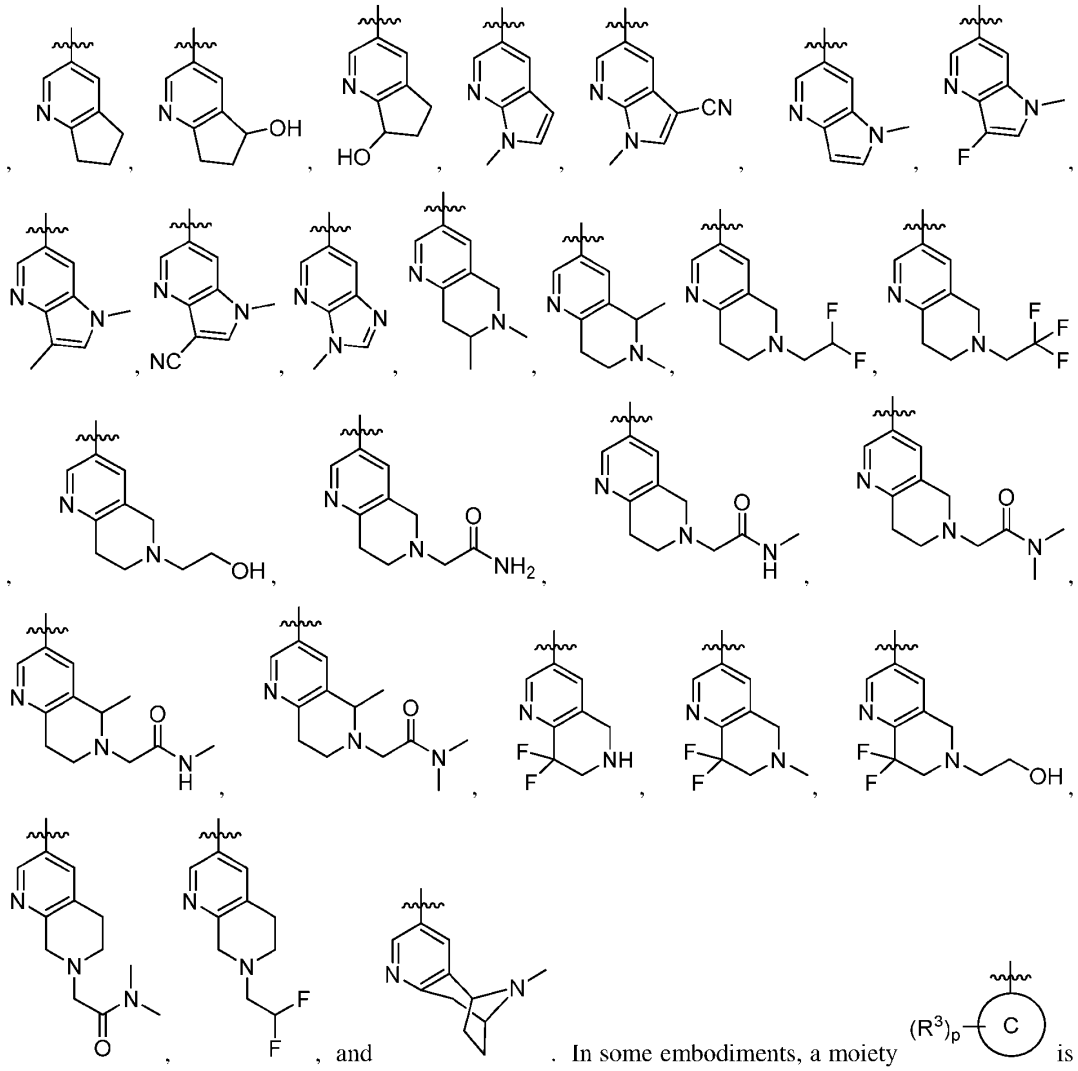


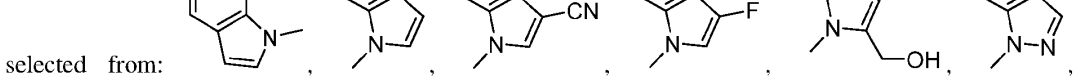


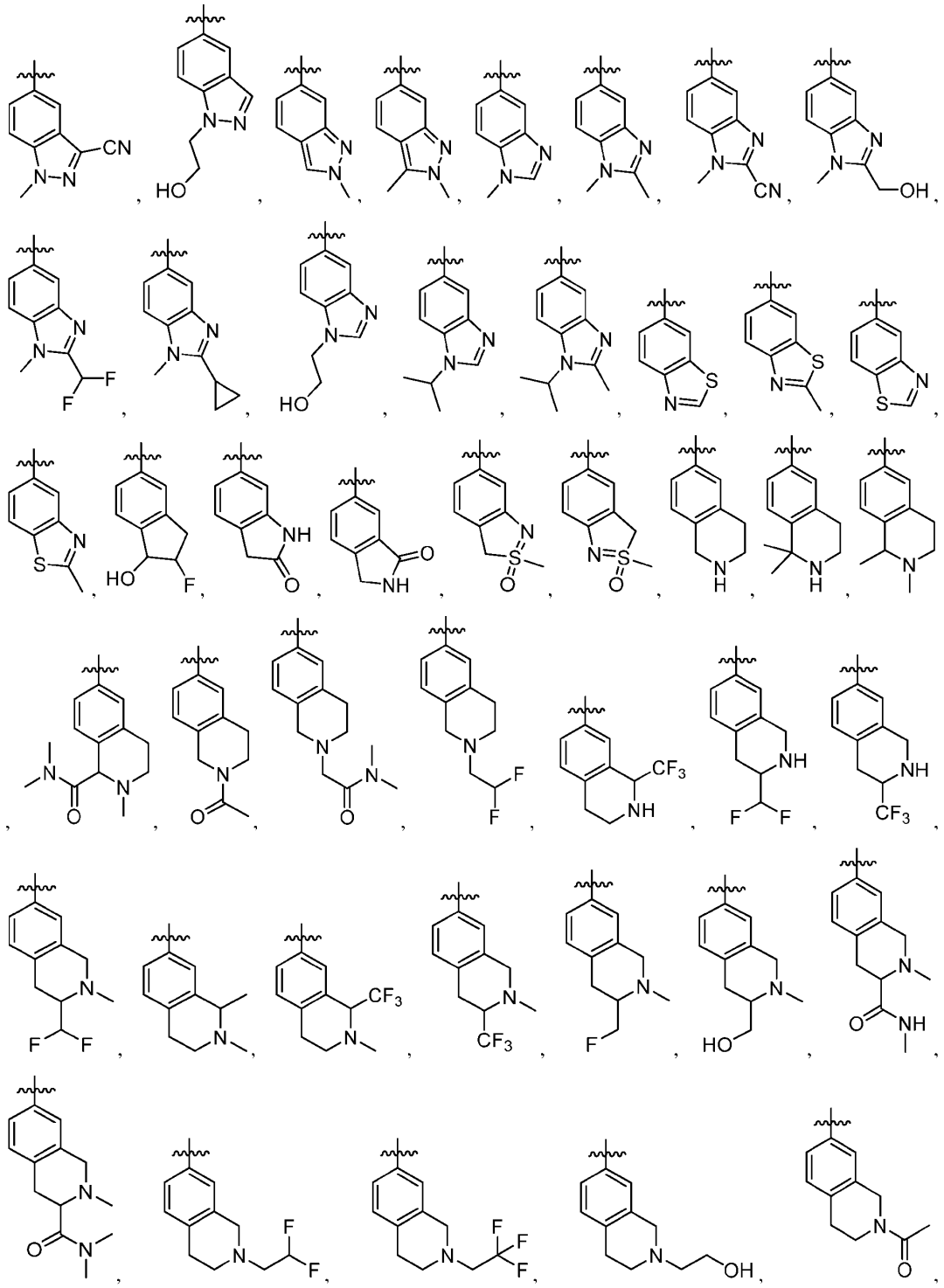










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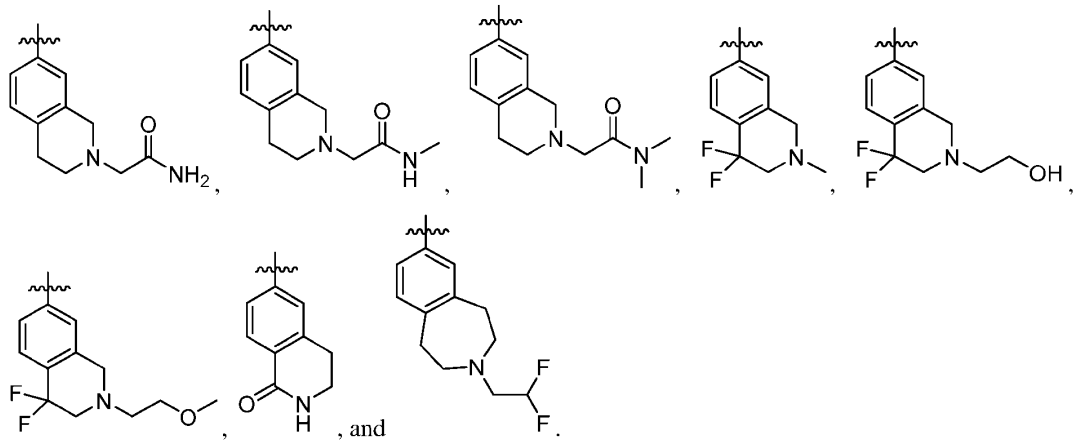
. In some embodiments, a moiety  is selected from: 





































[000152] In some embodiments of any of Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', IE, IE', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is selected from phenyl, 3- to 7-membered carbocyclic ring, and 5- to 10-membered bicyclic or polycyclic carbocyclic ring. In some embodiments, Ring D is selected from 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000153] In some embodiments of any of Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-

e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', IE, IE', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, Ring D is phenyl.

[000154] In some embodiments of any of Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', IE, IE', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, Ring D is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a 5- to 6-membered heteroaryl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000155] In some embodiments of any of Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', IE, IE', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, Ring D is a 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a 9-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a pyrazolo[1,5-a]pyrimidinyl. In some embodiments, Ring D is a 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000156] In some embodiments of any of Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', IE, IE', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, Ring D is a 3- to 7-membered carbocyclic ring. In some embodiments, Ring D is a 3- to 7-membered cycloalkyl ring. In some embodiments, Ring D is a 3- to 5-membered carbocyclic ring. In some embodiments, Ring D is a 3- to 5-membered cycloalkyl ring.

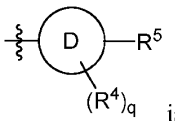
[000157] In some embodiments of any of Formulae Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c,

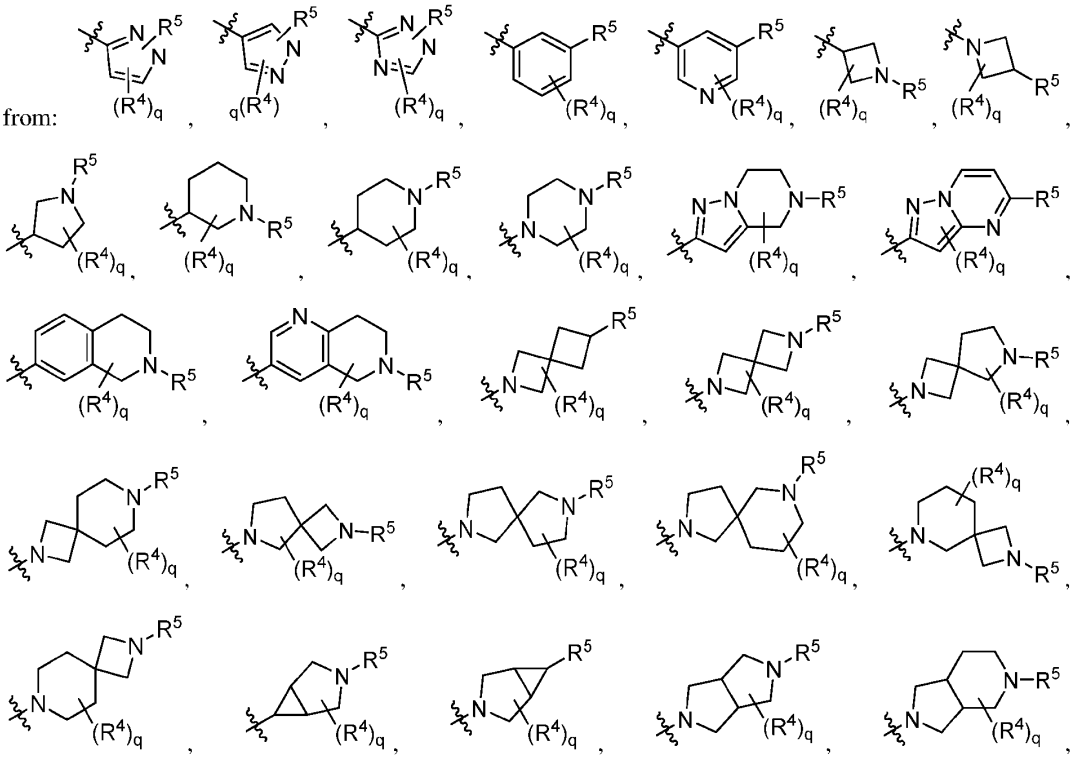
IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', IE, IE', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, Ring D is a 5- to 10-membered bicyclic or polycyclic carbocyclic ring. In some embodiments, Ring D is a 5- to 10-membered bicyclic carbocyclic ring. In some embodiments, Ring D is a bridged 5- to 10-membered bicyclic carbocyclic ring. In some embodiments, Ring D is a bridged 5- to 7-membered bicyclic carbocyclic ring (e.g., a bicyclo[1.1.1]pentane). In some embodiments, Ring D is a 8- to 10-membered polycyclic carbocyclic ring (e.g., a cubane).

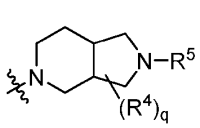
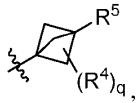
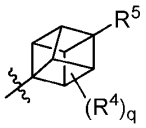
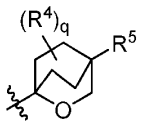
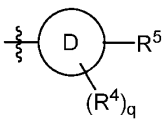
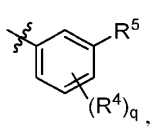
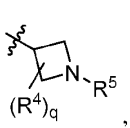
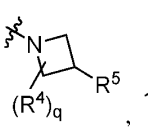
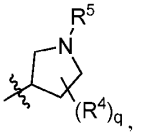
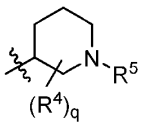
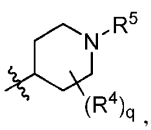
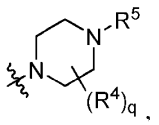
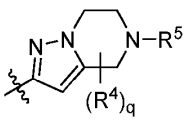
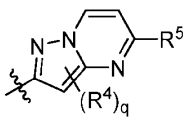
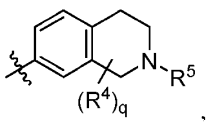
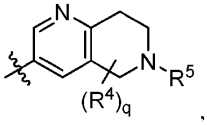
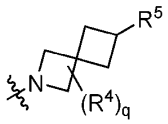
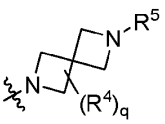
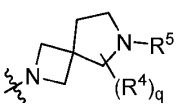
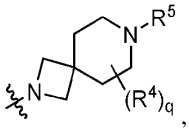
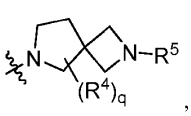
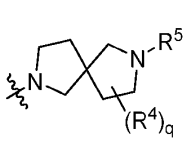
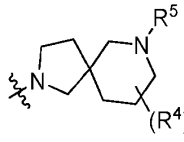
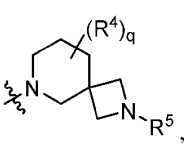
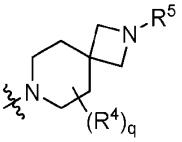
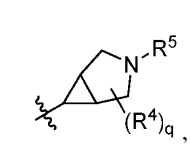
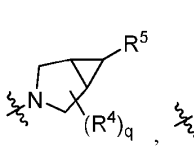
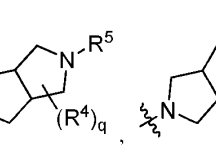
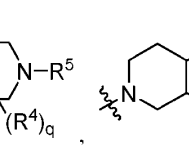
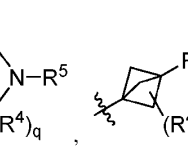
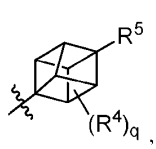
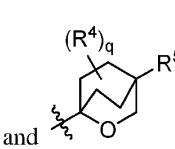
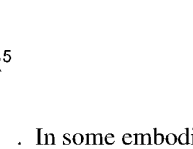
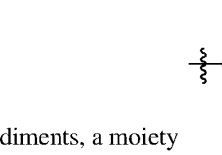
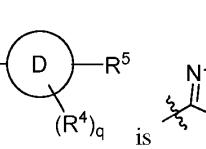
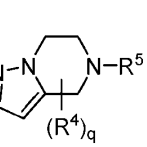
[000158] In some embodiments of any of Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', IE, IE', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, Ring D is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a 4-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is an azetidinyl. In some embodiments, Ring D is a 5-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a pyrrolidinyl. In some embodiments, Ring D is a 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a piperidinyl or piperazinyl. In some embodiments, Ring D is a 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000159] In some embodiments of any of Formulae Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', IE, IE', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, Ring D is a 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a fused 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a heterocyclic ring fused to an aryl, heteroaryl, cycloalkyl, or heterocyclic ring, wherein the point of attachment to the rest of the molecule is on either ring). In some embodiments, Ring D is a spirocyclic 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a heterocyclic ring spirofused to a cycloalkyl or heterocyclic ring, wherein the point of attachment to the result of the molecule is on either ring). In some embodiments, Ring D is a 6-membered bicyclic

heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a 7-membered bicyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is an 8-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a 9-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is a 10-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is an 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D is absent.

[000160] In some embodiments of any of Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, a moiety  is selected from:



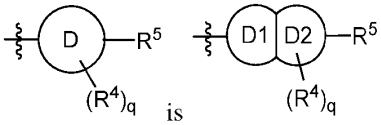



and 
. In some embodiments, a moiety is 
































and
. In some embodiments, a moiety is

.

[000161] In some embodiments of any of Formulae Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, L is $C_{2\text{-}5}$ alkynyl, and Ring D is absent.

[000162] In some embodiments of any of Formulae Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', II, IIB, IIB1, IIB2,

IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, a moiety  is , wherein:

Ring D1 is fused to Ring D2;

Ring D1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;and

Ring D2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

In some such embodiments, Ring D1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

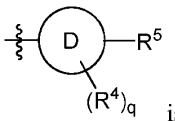
[000163] In some embodiments of any of Formulae IB, IB', IB1, and IB1', Ring D1 is selected from phenyl and 3- to 7-membered carbocyclic ring. In some embodiments, Ring D1 is selected from 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D1 is selected from phenyl and 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D1 is selected from 3- to 7-membered carbocyclic ring and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D1 is phenyl. In some embodiments, Ring D1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D1 is a 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrazolyl). In some embodiments, Ring D1 is a 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a pyridinyl). In some embodiments, Ring D1 is a 3- to 7-membered carbocyclic ring. In some embodiments, Ring D1 is a 3- to 7-membered cycloalkyl ring. In some embodiments, Ring D1 is a 3- to 5-membered

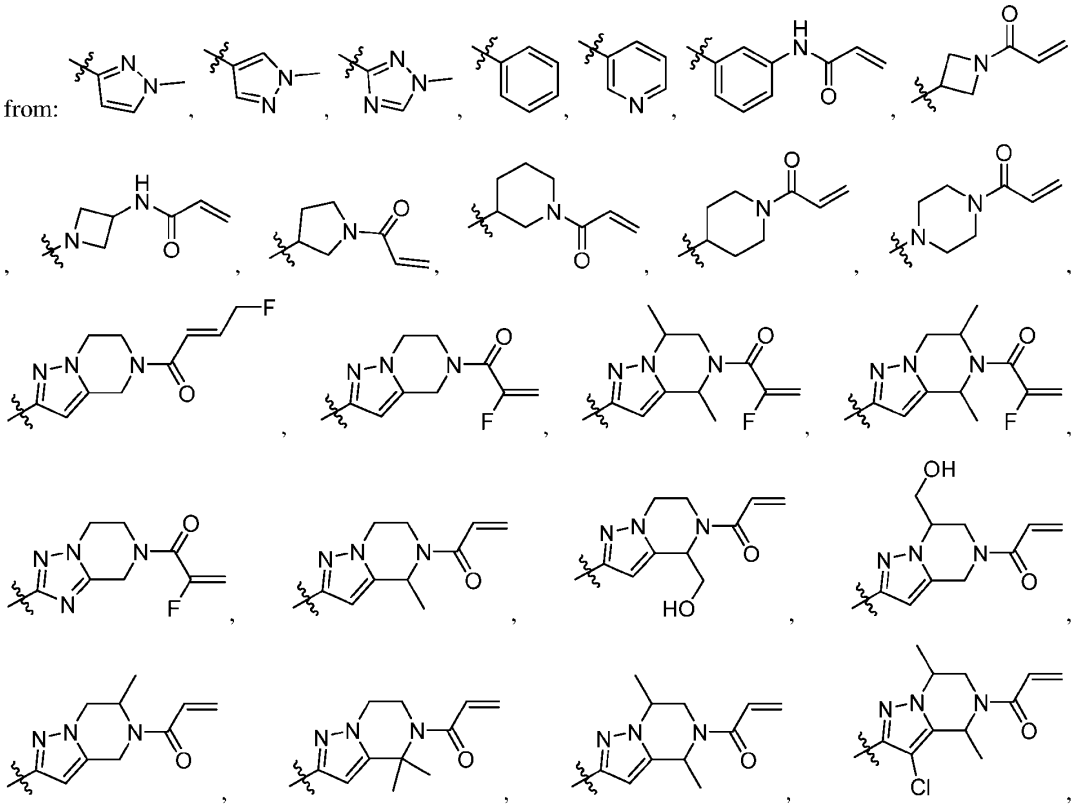
carbocyclic ring. In some embodiments, Ring D1 is a 3- to 5-membered cycloalkyl ring (e.g., a cyclopropyl). In some embodiments, Ring D1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D1 is a 5- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D1 is a 5-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrrolidinyl). In some embodiments, Ring D1 is a 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a piperidinyl).

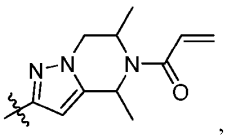
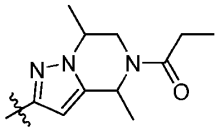
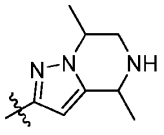
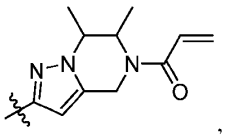
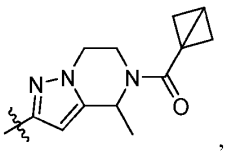
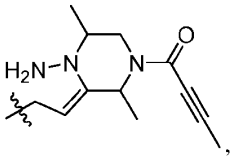
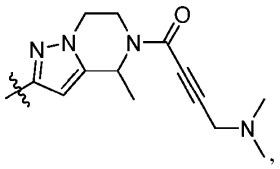
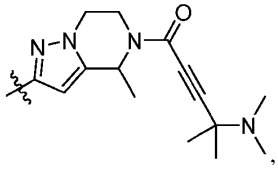
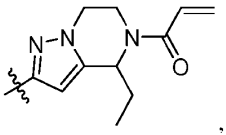
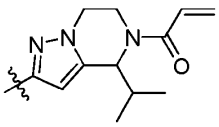
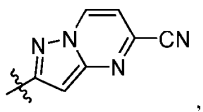
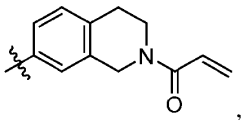
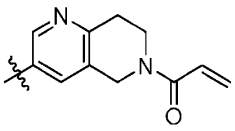
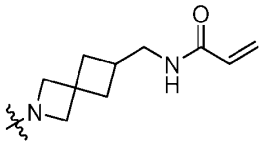
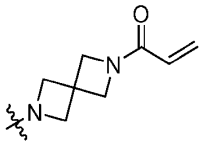
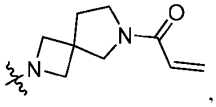
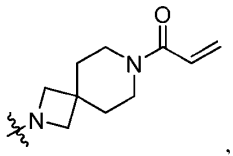
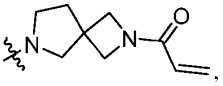
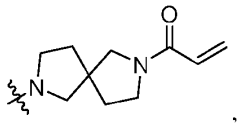
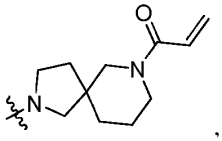
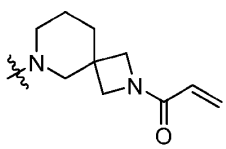
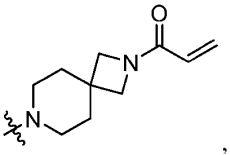
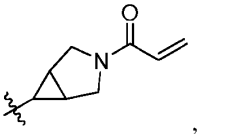
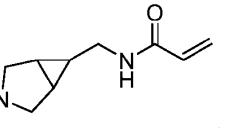
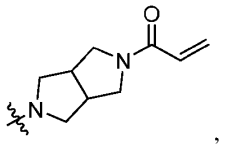
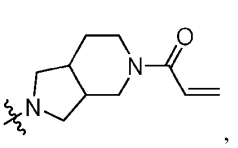
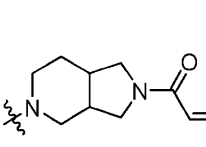
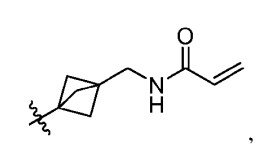
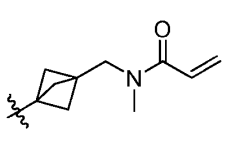
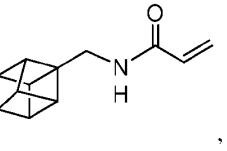
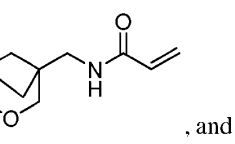
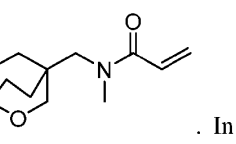
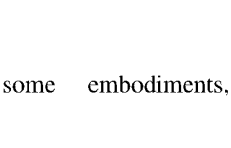
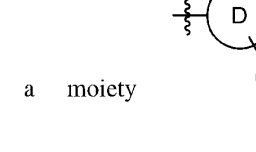
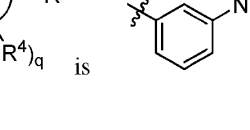
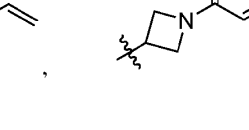
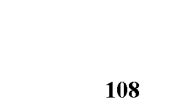
[000164] In some embodiments of any of Formulae IB, IB', IB1, and IB1', Ring D2 is selected from phenyl and 3- to 7-membered carbocyclic ring. In some embodiments, Ring D2 is selected from 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D2 is selected from phenyl and 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D2 is selected from 3- to 7-membered carbocyclic ring and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D2 is phenyl. In some embodiments, Ring D2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D2 is a 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D2 is a 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrimidinyl). In some embodiments, Ring D2 is a 3- to 7-membered carbocyclic ring. In some embodiments, Ring D2 is a 3- to 7-membered cycloalkyl ring. In some embodiments, Ring D2 is a 3- to 5-membered carbocyclic ring. In some embodiments, Ring D2 is a 3- to 5-membered cycloalkyl ring (e.g., a cyclopropyl). In some embodiments, Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D2 is a 5- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D2 is a 5-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrrolidinyl). In some embodiments, Ring D2 is a 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a piperidinyl or a piperazinyl). In some embodiments, Ring D2 is a 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000165] In some embodiments of any of Formulae IB, IB', IB1, and IB1', Ring D1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and

sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring D1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

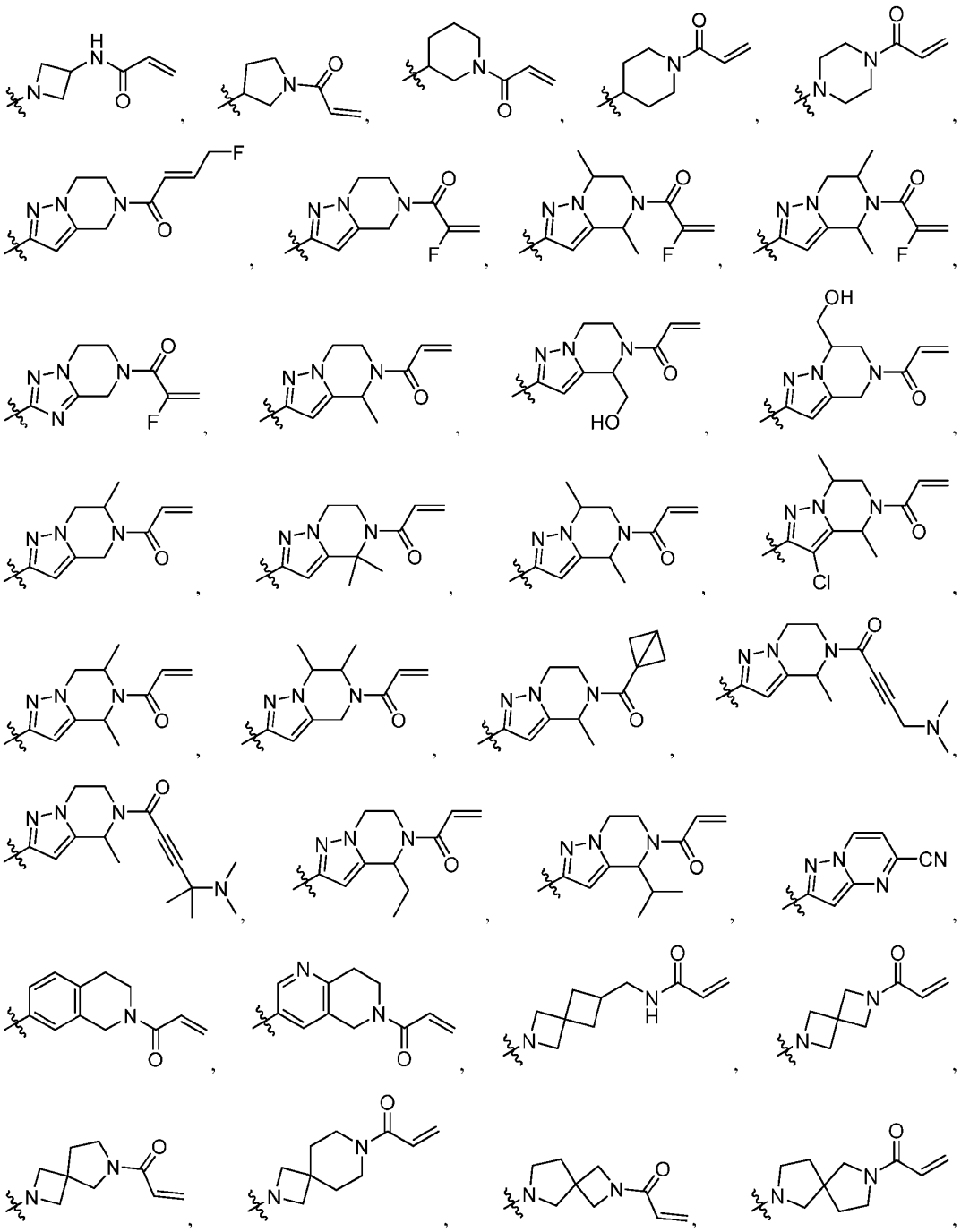
[000166] In some embodiments of any of Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, a moiety  is selected from:

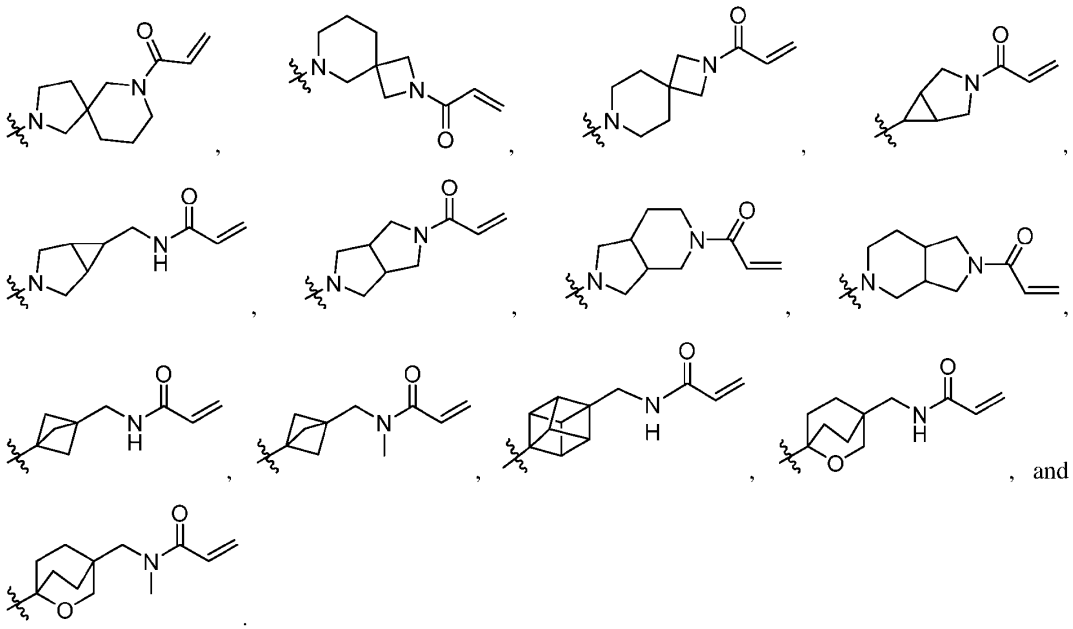


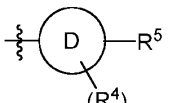
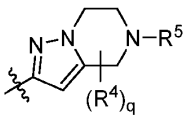
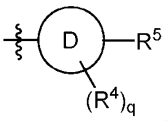
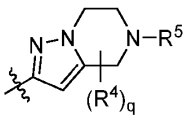
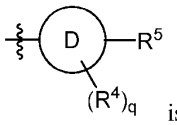

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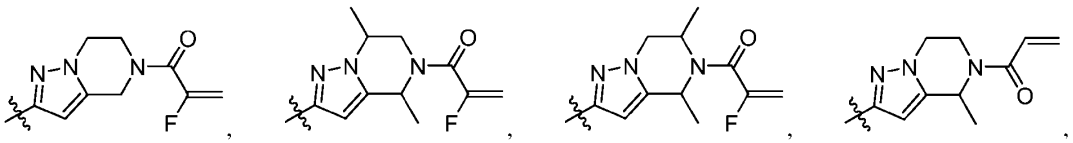
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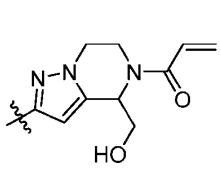
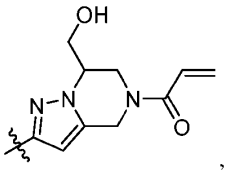
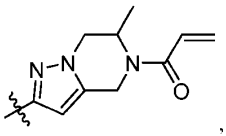
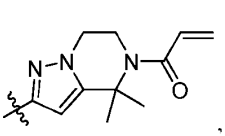
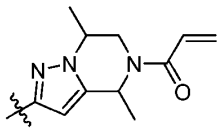
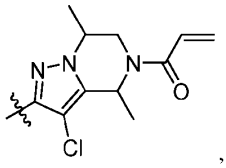
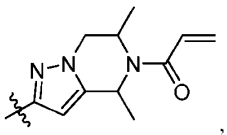
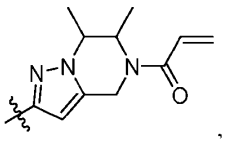
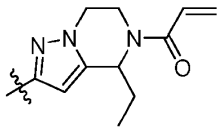
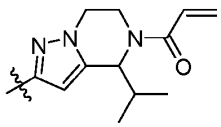
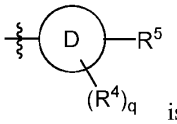
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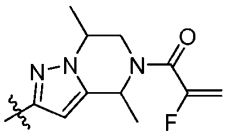
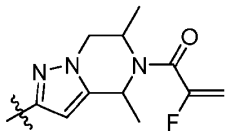
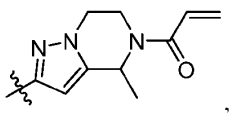
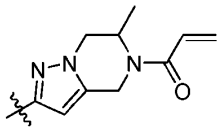
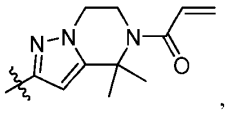
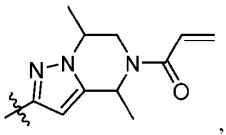
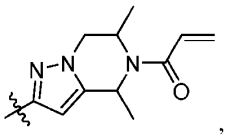


[000167] In some embodiments of any of Formulae I, I', I'', IA, IA' IC, IC', IC1, IC1', IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC1'-a, IC1'-b, IC1'-c, IC1'-d, IC1'-e, IC1'-f, IC1'-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, IC3'-m, ID, ID', II, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIF, and IIG, a moiety  is . In some embodiments, a moiety  is , wherein each R^4 is independently methyl. In some embodiments, a moiety  is selected from:

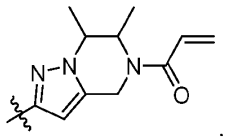


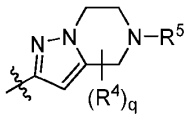
, and . In some embodiments, a moiety is selected from:

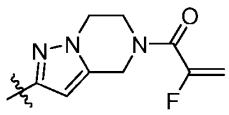
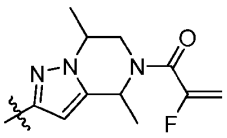
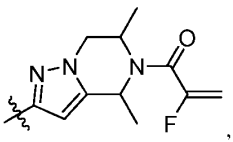
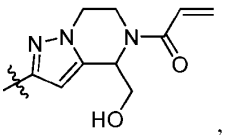








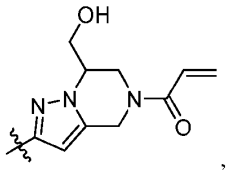
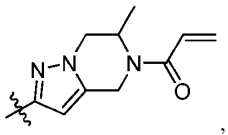
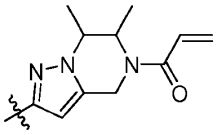
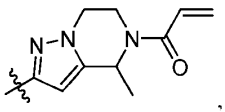
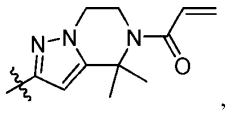
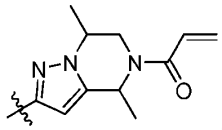
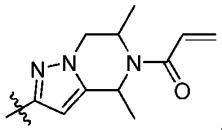
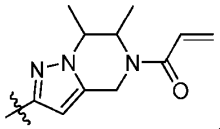
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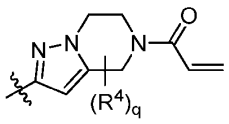
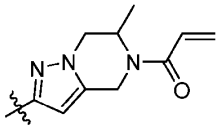
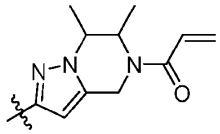
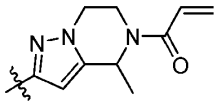
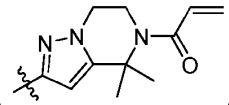
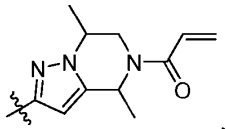
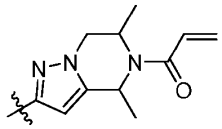
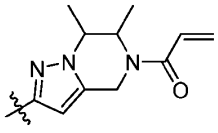


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[000168] In some embodiments of Formulae IF',  is selected from:

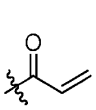
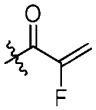
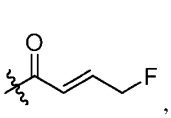





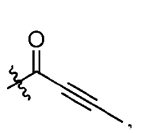
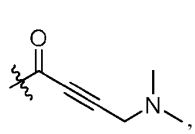
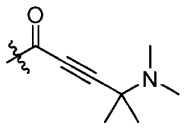
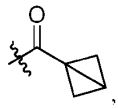
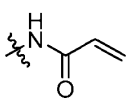
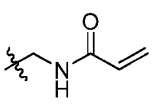
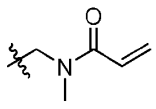
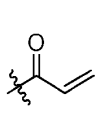
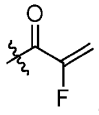
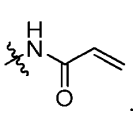
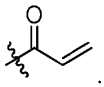







, and .

[000169] In some embodiments of any of Formulae IF1', IF2', and IF3',  is selected from: 





, and .

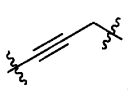
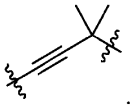
[000170] In some embodiments of any Formulae described herein, each R^4 is independently optionally substituted C_{1-6} alkyl. In some embodiments, each R^4 is independently selected from C_{1-6} aliphatic optionally substituted with one or more R^{10}. In some embodiments, each R^4 is independently selected from C_{1-6} alkyl optionally substituted with one or more R^{10}. In some embodiments, each R^4 is independently C_{1-6} aliphatic (e.g., C_{1-6} alkyl). In some embodiments, each R^4 is independently C_{1-6} alkyl optionally substituted with one or more –OH. In some embodiments, each R^4 is independently selected from $–CH_3$, $-CH_2OH$, $-CH_2CH_3$, and $-CH(CH_3)_2$.

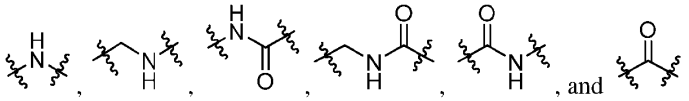
[000171] In some embodiments of any Formulae described herein, q is 0 or 1. In some embodiments, q is 1 or 2. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2.

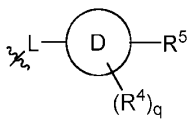
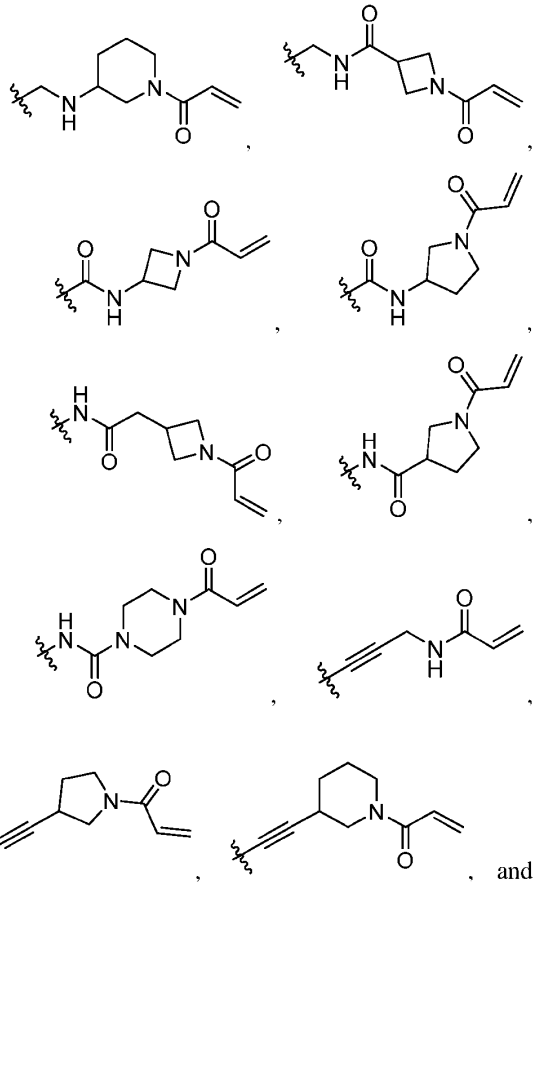
[000172] In some embodiments of any Formulae described herein, R^5 is $-C(O)R^9$ or $-(CH_2)_xN(R)C(O)R^9$. In some embodiments, R^5 is $-C(O)R^9$ or $-N(R)C(O)R^9$. In some embodiments, R^5 is $-C(O)R^9$. In some embodiments, R^5 is $-(CH_2)_xN(R)C(O)R^9$ (e.g., $-CH_2N(R)C(O)R^9$ or $-N(R)C(O)R^9$). In some embodiments, R^5 is –CN. In some embodiments, R^5 is selected from: -CN, 

,

, , , , , , and . In some embodiments, R^5 is , , or . In some embodiments, R^5 is .

[000173] In some embodiments of any Formulae described herein, R^9 is optionally substituted C_{2-6} alkenyl or optionally substituted C_{2-6} alkynyl. In some embodiments, R^9 is optionally substituted C_{2-4} alkenyl or optionally substituted C_{2-4} alkynyl. In some embodiments, R^9 is C_{2-6} alkenyl optionally substituted with one or more R^{10}, C_{2-6} alkynyl optionally substituted with one or more R^{10}, or a 4-membered bicyclic carbocyclic ring. In some embodiments, R^9 is C_{2-6} alkenyl optionally substituted with one or more R^{10} or C_{2-6} alkynyl optionally substituted with one or more R^{10}. In some embodiments, R^9 is optionally substituted C_{2-6} alkenyl. In some embodiments, R^9 is optionally substituted C_{2-4} alkenyl. In some embodiments, R^9 is C_{2-6} alkenyl optionally substituted with one or more R^{10} (e.g., one or more halogen). In some embodiments, R^9 is optionally substituted C_{2-6} alkynyl. In some embodiments, R^9 is optionally substituted C_{2-4} alkynyl. In some embodiments, R^9 is C_{2-6} alkynyl optionally substituted with one or more R^{10} (e.g., one or more $-N(C_{1-6}$ alkyl$)_2$). In some embodiments, R^9 is a 4-membered bicyclic carbocyclic ring.

[000174] In some embodiments of any of Formulae I, I', I'', IA, IA', IB, IB', IB1, IB1', ID, and ID', L is a covalent bond. In some embodiments, L is a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-. In some embodiments, L is a bivalent straight or branched C_{2-6} hydrocarbon chain having at least one triple bond, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-. In some embodiments, L is a bivalent straight or branched C_{2-6} hydrocarbon chain having at least one triple bond (e.g., a C_{2-6} alkynylene). In some embodiments, L is selected from: , , and . In some embodiments, L is a bivalent straight or branched C_{1-4} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-. In some embodiments, L is a bivalent straight or branched C_{1-2} hydrocarbon chain, wherein one or more methylene units are optionally

and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-. In some embodiments, L is selected from: , and .

[000175] In some embodiments of any of Formulae I, I', I'', IA, IA', IB, IB', IB1, IB1', ID, and ID', a moiety  is selected from: .

[000176] In some embodiments of any of Formulae I, I', I'', IA, IA', IB, IB', IB1, IB1', IE, IE', IE1, IE1', IE1-a, IE1-a', IE1-b, and IE1-b', R^6 and $R^{6'}$ are connected with an optionally substituted C_{4-8} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-. In some embodiments, R^6 and $R^{6'}$ are connected with a C_{4-8} hydrocarbon chain, wherein one

or more methylene units are optionally and independently replaced with –O- or –N(R)-. In some embodiments, R^6 and $R^{6'}$ are connected with an optionally substituted C_{5-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-. In some embodiments, R^6 and $R^{6'}$ are connected with an optionally substituted C_{4-8} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O-. In some embodiments, R^6 and $R^{6'}$ are connected with an optionally substituted C_{5-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O-. In some embodiments, R^6 and $R^{6'}$ are connected with: $-O(CH_2)_5-$, $-O(CH_2)_4-$, $–O(CH_2)_2OCH_2-$, or $–O(CH_2)_3OCH_2-$.

[000177] In some embodiments of any of Formulae Formulae I, I', I'', IA, IA', IB, IB', IB1, IB1', IE, IE', IE1, IE1', IE1-a, IE1-a', IE1-b, and IE1-b', r is 0. In some embodiments, r is 1. It will be appreciated that r has the same value for both R^6 and $R^{6'}$, such that either both R^6 and $R^{6'}$ are present or both R^6 and $R^{6'}$ are absent.

[000178] In some embodiments of any Formulae described herein, each x is independently 1 or 2. In some embodiments, each x is independently 0 or 1. In some embodiments, each x is 0. In some embodiments, each x is 1. In some embodiments, each x is 2.

[000179] In some embodiments of any Formulae described herein, each R is independently hydrogen or optionally substituted C_{1-6} alkyl. In some embodiments, each R is independently hydrogen or optionally substituted C_{1-4} alkyl. In some embodiments, each R is independently hydrogen or C_{1-6} aliphatic optionally substituted with one or more R^{10}. In some embodiments, each R is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^{10}. In some embodiments, each R is hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen (e.g., fluoro). In some embodiments, an R is hydrogen. In some embodiments, an R is optionally substituted C_{1-6} aliphatic (e.g., optionally substituted C_{1-6} alkyl). In some embodiments, an R is C_{1-6} aliphatic optionally substituted with one or more R^{10} (e.g., C_{1-6} alkyl optionally substituted with one or more R^{10}). In some embodiments, an R is C_{1-6} aliphatic (e.g., C_{1-6} alkyl).

[000180] In some embodiments of any Formulae described herein, each Cy is independently selected from phenyl and 3- to 7-membered carbocyclic ring, wherein each Cy is substituted with 0-3 instances of R^8. In some embodiments, each Cy is independently selected from 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8. In some embodiments, each Cy is independently selected from phenyl and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8. In some embodiments, each Cy is independently selected from 3- to 7-membered carbocyclic ring and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is

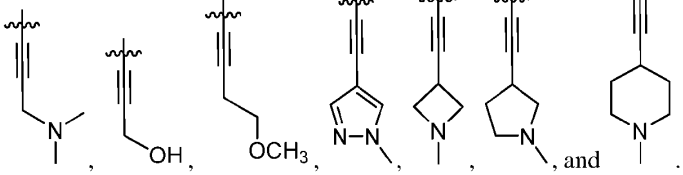
substituted with 0-3 instances of R^8. In some embodiments, a Cy is phenyl substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrazolyl), wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 3- to 7-membered carbocyclic ring, wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 3- to 5-membered carbocyclic ring, wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 5- to 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 4-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur (e.g., an azetidinyl or an oxetanyl), wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 5-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur (e.g., a pyrrolidinyl), wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, a Cy is a 6-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., a piperidinyl or piperazinyl), wherein Cy is substituted with 0-3 instances of R^8. In some embodiments, each Cy is independently substituted with 0-2 instances of R^8.

[000181] In some embodiments of any Formulae described herein, each R^8 is independently selected from oxo, halogen, and optionally substituted C_{1-6} alkyl. In some embodiments, each R^8 is independently selected from oxo, halogen, and C_{1-6} aliphatic. In some embodiments, each R^8 is independently selected from oxo, halogen, and C_{1-6} alkyl. In some embodiments, each R^8 is independently selected from halogen and optionally substituted C_{1-6} aliphatic. In some embodiments, a R^8 is oxo. In some embodiments, a R^8 is halogen (e.g., fluoro). In some embodiments, a R^8 is optionally substituted C_{1-6} aliphatic (e.g., optionally substituted C_{1-6} alkyl). In some embodiments, a R^8 is C_{1-6} aliphatic (e.g., C_{1-6} alkyl). In some embodiments, each R^8 is independently fluoro or methyl.

[000182] In some embodiments of any of Formulae II, IIA, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IIC, IIC1, IIC2, IIC3, IIC4, IIC5, IIC6, IIC7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIE, IIF, and IIG, J is a covalent bond. In some embodiments, J is a bivalent straight or branched C_{1-4} hydrocarbon chain. In some embodiments, J is a bivalent straight or branched C_{1-2} hydrocarbon chain. In some embodiments, when J is a covalent bond, X is not –OR or $-N(R)_2$.

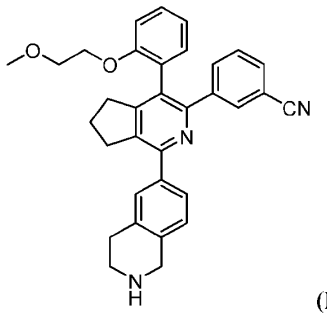
[000183] In some embodiments of any of Formulae II, IIA, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7 IIC, IIC1, IIC2, IIC3, IIC4, IIC5, IIC6, IIC7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIE, IIF, and IIG, X is –OR or $–N(R)_2$. In some embodiments, X is an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, X is a group selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein any ring is optionally substituted with C_{1-6} alkyl. In some embodiments, X is a group selected from 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein any ring is optionally substituted with C_{1-6} alkyl. In some embodiments, X is –OR (e.g., -OH or $–OCH_3$). In some embodiments, X is $–N(R)_2$ (e.g., $-N(CH_3)_2$). In some embodiments, X is $-C(O)N(R)_2$. In some embodiments, X is optionally substituted phenyl. In some embodiments, X is optionally substituted 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, X is optionally substituted 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (e.g., pyrazolyl optionally substituted with one or more C_{1-6} alkyl). In some embodiments, X is optionally substituted 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, X is optionally substituted 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, X is optionally substituted 3- to 7-membered carbocyclic ring. In some embodiments, X is optionally substituted 5- to 10-membered bicyclic carbocyclic ring. In some embodiments, X is optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, X is optionally substituted 4-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur (e.g., azetidinyl optionally substituted with one or more C_{1-6} alkyl). In some embodiments, X is optionally substituted 5-membered heterocyclic ring having 1 heteroatom independently

selected from nitrogen, oxygen, and sulfur (e.g., pyrrolidine optionally substituted with one or more C_{1-6} alkyl). In some embodiments, X is optionally substituted 6-membered heterocyclic ring having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur (e.g., piperidinyl optionally substituted with one or more C_{1-6} alkyl). In some embodiments, X is optionally substituted 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

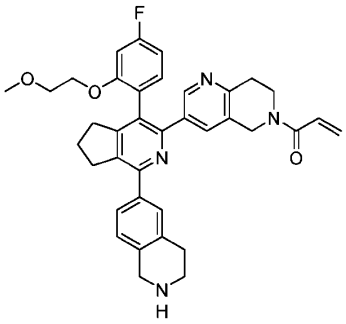
[000184] In some embodiments of any of Formulae II, IIA, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IIC, IIC1, IIC2, IIC3, IIC4, IIC5, IIC6, IIC7, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIE, IIF, and IIG, a moiety  is selected from: .

[000185] In some embodiments of any Formulae described herein, the compound is not a compound selected from Table P1.

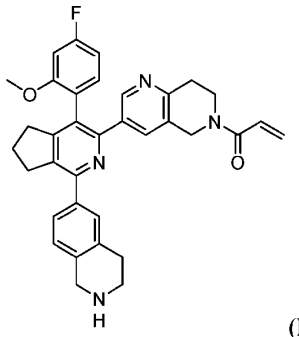
Table P1



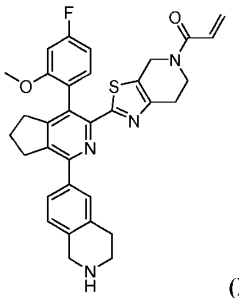
(P-2)



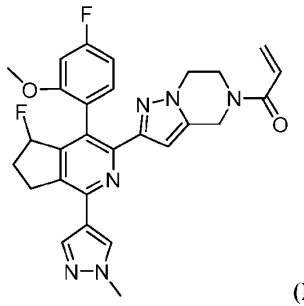
(P-88)



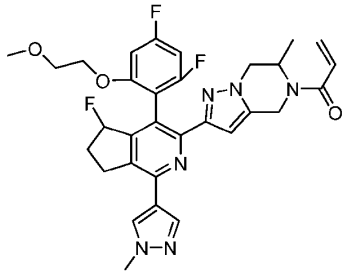
(P-89)



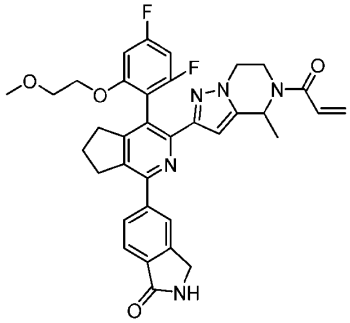
(P-96)



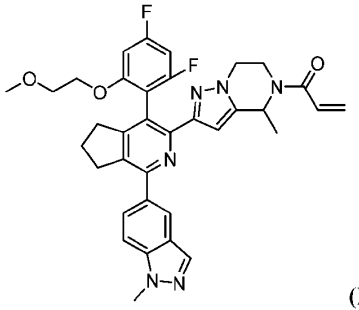
(P-574)



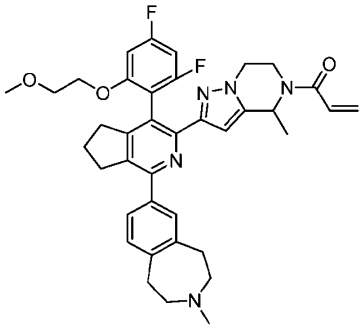
(P-667a)



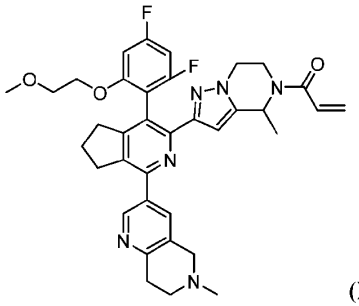
(P-1174a)



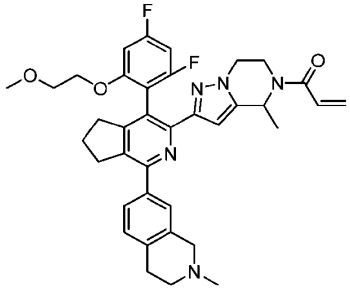
(P-1222a)



(P-1223a)



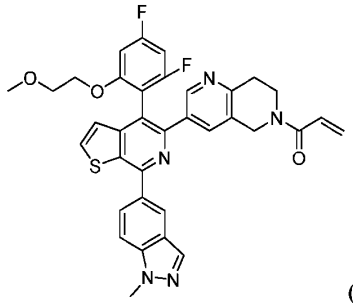
(P-1243a)



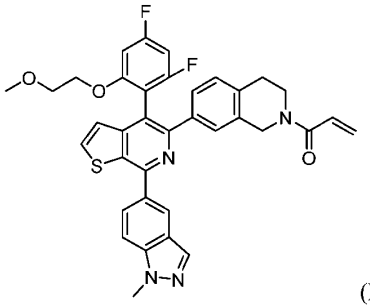
(P-1244a)

[000186] In some embodiments of any Formulae described herein, the compound is not a compound selected from Table P2.

Table P2



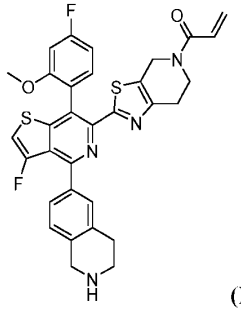
(P-1261)



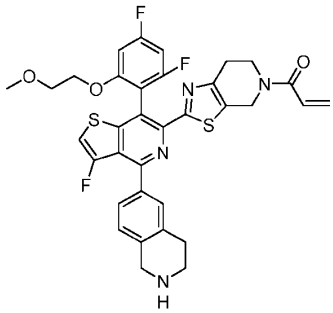
(P-1262)

[000187] In some embodiments of any Formulae described herein, the compound is not a compound selected from Table P3.

Table P3



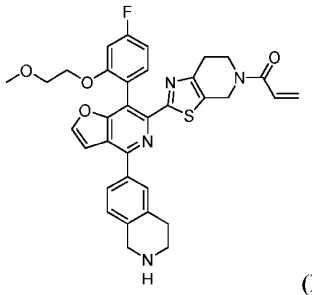
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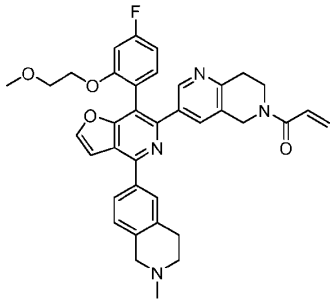
(P-434)

[000188] In some embodiments of any Formulae described herein, the compound is not a compound selected from Table P4.

Table P4



(P-417)



(P-442)

[000189] 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 combined 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.

[000190] In some embodiments, the present disclosure provides a compound selected from Table 1, Table 2, or any of the Examples provided herein, or a salt (e.g., pharmaceutically acceptable salt), ester, tautomer, prodrug, zwitterionic form, or stereoisomer thereof. In some embodiments, the present disclosure provides a compound selected from Table 1, Table 2, or any of the Examples provided herein, or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound selected from Table 1 or a salt (e.g., pharmaceutically acceptable salt) thereof. In some embodiments, the present disclosure provides a compound selected from Table 2 or a salt (e.g., pharmaceutically acceptable salt) thereof.

[000191] In some embodiments, provided compounds are provided and/or utilized in a salt form (e.g., a pharmaceutically acceptable salt form). Reference to a compound provided herein is understood to include reference to salts thereof, unless otherwise indicated. Pharmaceutically acceptable salt forms are known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66:1-19(1977). Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further

pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[000192] It will be appreciated that compounds described herein may be provided and/or utilized in any available form (e.g., a salt form) and that all such forms are contemplated by the present disclosure. The present disclosure also contemplates forms such as esters, tautomers, prodrugs, zwitterionic forms, and stereoisomers of the compounds provided herein.

[000193] It will be appreciated that throughout the present disclosure, unless otherwise indicated, reference to a compound of Formula I is intended to also include Formulae IA, IB, IB1, IC, IC1, IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC2, IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC4, ID, IE, IE1, IE1-a, and IE1-b, and compound species of such formulae disclosed herein; reference to a compound of Formula I' is intended to also include Formulae IA', IB', IB1', IC', IC1', IC1-a', IC1-b', IC1-c', IC1-d', IC1-e','IC1-f', IC1-g', IC2', IC2-a', IC2-b', IC2-c', IC2-d', IC2-e', IC2-f', IC2-g', IC3-a', IC3-b', IC3-c', IC3-d', IC3-e', IC3-f', IC3-g', IC3-h', IC3-I', IC3-j', IC3-k', IC3-l', IC3-m', IC4', ID', IE', IE1', IE1-a', IE1-b', IF', IF1', IF2', and IF3' and compound species of such formulae disclosed herein; and reference to a compound of Formula II is intended to also include Formulae IIA, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IIC1, IIC2, IIC3, IIC4, IIC5, IIC6, IIC7, IID, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIE, IIF, and IIG, and compound species of such formulae disclosed herein.

Compositions

[000194] The present disclosure also provides compositions comprising a compound provided herein with one or more other components. In some embodiments, provided compositions comprise and/or deliver a compound described herein (e.g., compounds of Formulae I'', I, IA, IB, IB1, IC, IC1, IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC2, IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC4, ID, IE, IE1, IE1-a, IE1-b, I', IA', IB', IB1', IC', IC1', IC1-a', IC1-b', IC1-c', IC1-d', IC1-e','IC1-f', IC1-g', IC2', IC2-a', IC2-b', IC2-c', IC2-d', IC2-e', IC2-f', IC2-g', IC3-a', IC3-b', IC3-c', IC3-d', IC3-e', IC3-f', IC3-g', IC3-h', IC3-I', IC3-j', IC3-k', IC3-l', IC3-m', IC4', ID', IE', IE1', IE1-a', IE1-b', IF', IF1', IF2', IF3', II, IIA, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IIC1, IIC2, IIC3, IIC4, IIC5, IIC6, IIC7, IID, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIE, IIF, and IIG).

[000195] In some embodiments, a provided composition is a pharmaceutical composition that comprises and/or delivers a compound provided herein (e.g., compounds of Formulae I'', I, IA, IB, IB1, IC, IC1, IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC2, IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC3-a,

IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC4, ID, IE, IE1, IE1-a, IE1-b, I', IA', IB', IB1', IC', IC1', IC1-a', IC1-b', IC1-c', IC1-d', IC1-e','IC1-f', IC1-g', IC2', IC2-a', IC2-b', IC2-c', IC2-d', IC2-e', IC2-f', IC2-g', IC3-a', IC3-b', IC3-c', IC3-d', IC3-e', IC3-f', IC3-g', IC3-h', IC3-I', IC3-j', IC3-k', IC3-l', IC3-m', IC4', ID', IE', IE1', IE1-a', IE1-b', IF', IF1', IF2', IF3', II, IIA, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IIC1, IIC2, IIC3, IIC4, IIC5, IIC6, IIC7, IID, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIE, IIF, and IIG) and further comprises a pharmaceutically acceptable carrier. Pharmaceutical compositions typically contain an active agent (e.g., a compound described herein) in an amount effective to achieve a desired therapeutic effect while avoiding or minimizing adverse side effects. In some embodiments, provided pharmaceutical compositions comprise a compound described herein and one or more fillers, disintegrants, lubricants, glidants, anti-adherents, and/or anti-statics, etc. Provided pharmaceutical compositions can be in a variety of forms including oral dosage forms, topical creams, topical patches, iontophoresis forms, suppository, nasal spray and/or inhaler, eye drops, intraocular injection forms, depot forms, as well as injectable and infusible solutions. Methods of preparing pharmaceutical compositions are well known in the art.

[000196] In some embodiments, provided compounds are formulated in a unit dosage form for ease of administration and uniformity of dosage. The expression "unit dosage form" as used herein refers to a physically discrete unit of an active agent (e.g., a compound described herein) for administration to a subject. Typically, each such unit contains a predetermined quantity of active agent. In some embodiments, a unit dosage form contains an entire single dose of the agent. In some embodiments, more than one unit dosage form is administered to achieve a total single dose. In some embodiments, administration of multiple unit dosage forms is required, or expected to be required, in order to achieve an intended effect. A unit dosage form may be, for example, a liquid pharmaceutical composition containing a predetermined quantity of one or more active agents, a solid pharmaceutical composition (e.g., a tablet, a capsule, or the like) containing a predetermined amount of one or more active agents, a sustained release formulation containing a predetermined quantity of one or more active agents, or a drug delivery device containing a predetermined amount of one or more active agents, etc.

[000197] Provided compositions may be administered using any amount and any route of administration effective for treating or lessening the severity of any disease or disorder described herein.

Uses

[000198] The present disclosure provides uses for compounds and compositions described herein (e.g., compounds of Formulae I'', I, IA, IB, IB1, IC, IC1, IC1-a, IC1-b, IC1-c, IC1-d, IC1-e, IC1-f, IC1-g, IC2, IC2-a, IC2-b, IC2-c, IC2-d, IC2-e, IC2-f, IC2-g, IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, IC3-g, IC3-h, IC3-i, IC3-j, IC3-k, IC3-l, IC3-m, IC4, ID, IE, IE1, IE1-a, IE1-b, I', IA', IB', IB1', IC', IC1', IC1-a', IC1-

b', IC1-c', IC1-d', IC1-e','IC1-f', IC1-g', IC2', IC2-a', IC2-b', IC2-c', IC2-d', IC2-e', IC2-f', IC2-g', IC3-a', IC3-b', IC3-c', IC3-d', IC3-e', IC3-f', IC3-g', IC3-h', IC3-I', IC3-j', IC3-k', IC3-l', IC3-m', IC4', ID', IE', IE1', IE1-a', IE1-b', IF', IF1', IF2', IF3', II, IIA, IIB, IIB1, IIB2, IIB3, IIB4, IIB5, IIB6, IIB7, IIC1, IIC2, IIC3, IIC4, IIC5, IIC6, IIC7, IID, IID1, IID2, IID3, IID4, IID5, IID6, IID7, IIE, IIF, and IIG). In some embodiments, provided compounds and compositions are useful in medicine (e.g., as therapeutic agents for use in the treatment, amelioration, delaying progress of, amelioration or elimination of a symptom of, and/or inhibition of a disease or disorder, as described herein). In some embodiments, provided compounds and compositions are useful as medicaments. In some embodiments, provided compounds and compositions are useful in research as, for example, analytical tools and/or control compounds in biological assays.

[000199] In some embodiments, provided compounds are useful for disrupting (e.g., inhibiting and/or preventing and/or modulating) an interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and a PI3Kα protein. In some embodiments, the present disclosure provides methods of disrupting, interrupting, and/or preventing an interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and a PI3Kα protein in a subject, comprising administering a provided compound or composition. In some embodiments, the present disclosure provides methods of disrupting, interrupting, and/or preventing an interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and a PI3Kα protein in a biological sample, comprising administering a provided compound or composition. In some embodiments, the present disclosure provides methods comprising contacting a cell containing a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and a PI3Kα protein with a provided compound or composition. In some such embodiments, a small GTPase is capable of binding a RAS-binding domain (RBD) of a PI3Kα protein. In some embodiments, a small GTPase is selected from Rac1, CDC42, and RAS proteins. In some embodiments, a RAS protein is selected from HRAS, NRAS, KRAS, RRAS, RRAS2, MRAS, and RIT1. In some embodiments, a RAS protein is a wild-type RAS protein. In some embodiments, a RAS protein is a mutant RAS protein. In some embodiments, a RAS protein (e.g., HRAS, NRAS, or KRAS) comprises a mutation in codon 12 (e.g., G12), codon 13 (e.g., G13), or codon 61 (e.g., Q61). In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G13D, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12D, G12V, G13D, and/or Q61R mutation. In some embodiments, an HRAS protein comprises a G12C, G12D, G12S, G12V, G12R,

G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an HRAS protein comprises a G12V, G13R, and/or Q61R mutation. In some embodiments, a PI3Kα protein is a wild-type PI3Kα protein. In some embodiments, a PI3Kα protein is a mutant PI3Kα protein. In some embodiments, a PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, a PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation.

[000200] In some embodiments, the present disclosure provides methods comprising administering a provided compound or composition to a subject in need thereof. In some such embodiments, a subject has a disease, disorder, or condition associated with an interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and a PI3Kα protein. In some embodiments, a subject has a disease, disorder, or condition ameliorated by disruption of an interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and a PI3Kα protein. In some embodiments, a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) is capable of binding a RAS-binding domain (RBD) of a PI3Kα protein. In some embodiments, a small GTPase is selected from Rac1, CDC42, and RAS proteins. In some embodiments, a RAS protein is selected from HRAS, NRAS, KRAS, RRAS, RRAS2, MRAS, and RIT1. In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G13D, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12D, G12V, G13D, and/or Q61R mutation. In some embodiments, an HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an HRAS protein comprises a G12V, G13R, and/or Q61R mutation. In some embodiments, a RAS protein is a wild-type RAS protein. In some embodiments, a PI3Kα protein is a wild-type PI3Kα protein. In some embodiments, a PI3Kα protein is a mutant PI3Kα protein. In some embodiments, a PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, a PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, a subject has a cancer or other indication described herein. In some embodiments, a subject has previously undergone a treatment regimen for a cancer. In some embodiments, a subject has previously entered remission from a cancer.

[000201] In some embodiments, provided methods comprise administering a provided compound or composition to a subject in need thereof, according to a regimen such that the subject does not experience hyperglycemia or insulin-driven resistance.

[000202] In some embodiments, the present disclosure provides methods of treating a cancer, comprising administering to a subject a provided compound or composition. In some embodiments, a cancer is associated with and/or characterized by aberrant activation of PI3Kα. In some embodiments, a cancer is characterized by a mutation in a RAS protein (e.g., HRAS, NRAS, KRAS, RRAS, RRAS2, MRAS, and RIT1). In some embodiments, a cancer is characterized by a mutation in a KRAS protein. In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G13D, and/or Q61H mutation. In some embodiments, a cancer is characterized by a mutation in an NRAS protein. In some embodiments, an NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12D, G12V, G13D, and/or Q61R mutation. In some embodiments, a cancer is characterized by a mutation in an HRAS protein. In some embodiments, an HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an HRAS protein comprises a G12V, G13R, and/or Q61R mutation. In some embodiments, a cancer is characterized by a mutation in a PI3Kα protein. In some embodiments, a PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, a PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation.

[000203] As used herein, "cancer" (and also, "malignancy", "neoplasm", "tumor", and "carcinoma"), refer to cells that exhibit relatively abnormal, uncontrolled, and/or autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. In some embodiments, a tumor may be or comprise cells that are precancerous (e.g., benign), malignant, pre-metastatic, metastatic, and/or non-metastatic. In some embodiments, a cancer may be characterized by a solid tumor. In some embodiments, a cancer may be characterized by a hematologic tumor. Numerous different types of cancers are known.

[000204] In some embodiments, a cancer is selected from pancreatic cancer; colon cancer; rectal cancer; colorectal cancer; breast cancer; ovarian cancer; endometrial cancer; lung cancer; prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, liver and biliary passages, 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; cancers of the thyroid and other endocrine glands; 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 exemplary types of cancer include, but are not limited to, adenocarcinoma, angiosarcoma, astrocytoma, acoustic neuroma, anaplastic astrocytoma, basal cell carcinoma, blastoglioma, chondrosarcoma, choriocarcinoma, chordoma, cranioph'ryngioma, 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. In some embodiments, a cancer is selected from breast cancer, lung cancer (e.g., non-small cell lung cancer), endometrial cancer, esophageal cancer, ovarian cancer, colorectal cancer, gastric cancer, squamous cell carcinoma, prostate cancer, and pancreatic cancer.

[000205] In some embodiments, a cancer is characterized by one or more mutations. In some such embodiments, a subject may be diagnosed with cancer and/or selected for therapy based on the detection of one or more mutations in a biological sample obtained from the subject. In some embodiments, a cancer is characterized by a mutation in a RAS protein (e.g., KRAS, HRAS, or NRAS). In some embodiments, a cancer is characterized by a mutation in a KRAS protein. In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G13D, and/or Q61H mutation. In some embodiments, a cancer is characterized by a mutation in an NRAS protein. In some embodiments, an NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12D, G12V, G13D, and/or

Q61R mutation. In some embodiments, a cancer is characterized by a mutation in an HRAS protein. In some embodiments, an HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an HRAS protein comprises a G12V, G13R, and/or Q61R mutation. In some embodiments, a cancer is characterized by a mutation in a PI3Kα protein. In some embodiments, the PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, a PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, a cancer is characterized by mutated, overexpressed, and/or amplified receptor tyrosine kinases (e.g., HER family (e.g., HER2 and/or HER3), Met, FGFR, Alk, PDGF, EGFR, or ROS kinases). In some embodiments, a cancer is characterized by a mutation in or a deletion of a PTEN protein. In some embodiments, a cancer has demonstrable sensitivity to Avastin. For example, a cancer may be non-small cell lung cancer (NSCLC) or colorectal cancer. In some embodiments, a cancer is ER positive (e.g., having estrogen receptors). In some embodiments, a cancer is PR positive (e.g., having progesterone receptors).

[000206] In some embodiments, the present disclosure provides methods of treating a metabolic syndrome, comprising administering to a subject a provided compound or composition. In some embodiments, a metabolic syndrome is selected from hyperinsulinemia and type 2 diabetes.

[000207] In some embodiments, the present disclosure provides methods of treating a RASopathy (e.g., a genetic syndrome caused by a germline mutation in a gene that encodes a component or regulator of the RAS/MAPK pathway), comprising administering to a subject a provided compound or composition. In some embodiments, a RASopathy is selected from the group consisting of capillary malformation-arteriovenous malformation syndrome and Legius syndrome. In some embodiments, a RASopathy is neurofibromatosis type 1 (NF1).

[000208] In some embodiments, the present disclosure provides methods of treating a vascular disorder, comprising administering to a subject a provided compound or composition. In some embodiments, a vascular disorder is selected from *PIK3CA*-related overgrowth syndrome (PROS) and vascular malformations (e.g., venous malformations; lymphatic malformations; congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies syndrome (CLOVES); Klippel-Trenaunay Syndrome; PTEN hamartoma tumor syndrome (PHTS); and fibro-adipose vascular anomaly (FAVA)).

[000209] In some embodiments, the present disclosure provides methods of treating pulmonary hypertension, such as pulmonary arterial hypertension, comprising administering to a subject a provided compound or composition.

[000210] In some embodiments, the present disclosure provides methods of treating age-related macular degeneration or diabetic macular edema, comprising administering to a subject a provided compound or composition.

[000211] In some embodiments, the present disclosure provides compounds or compositions for use in the manufacture of a medicament. In some embodiments, provided compounds or compositions are useful in the manufacture of a medicament for treating a disease, disorder, or condition associated with or ameliorated by an interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and a PI3Kα protein. In some embodiments, a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) is capable of binding a RAS-binding domain (RBD) of a PI3Kα protein. In some embodiments, a small GTPase is selected from Rac1, CDC42, and RAS proteins. In some embodiments, a RAS protein is selected from HRAS, NRAS, KRAS, RRAS, RRAS2, MRAS, and RIT1. In some embodiments, a RAS protein is a wild-type RAS protein. In some embodiments, a RAS protein is a mutant RAS protein. In some embodiments, a RAS protein (e.g., HRAS, NRAS, or KRAS) comprises a mutation in codon 12 (e.g., G12), codon 13 (e.g., G13), or codon 61 (e.g., Q61). In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G13D, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12D, G12V, G13D, and/or Q61R mutation. In some embodiments, an HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an HRAS protein comprises a G12V, G13R, and/or Q61R mutation. In some embodiments, a PI3Kα protein is a wild-type PI3Kα protein. In some embodiments, a PI3Kα protein is a mutant PI3Kα protein. In some embodiments, a PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, a PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, provided compounds or compositions are useful in the manufacture of a medicament for treating a disease, disorder, or condition described herein. In some embodiments, provided compounds or compositions are useful in the manufacture of a medicament for treating a cancer or other indication described herein.

[000212] In some embodiments, the present disclosure provides compounds or compositions for use in treating a disease, disorder, or condition in a subject in need thereof. In some embodiments, provided compounds or compositions are useful in treating a disease, disorder, or condition associated with or

ameliorated by an interaction between a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) and a PI3Kα protein. In some embodiments, a small GTPase (e.g., Rac1, CDC42, or a RAS protein such as KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1) is capable of binding a RAS-binding domain (RBD) of a PI3Kα protein. In some embodiments, a small GTPase is selected from Rac1, CDC42, and RAS proteins. In some embodiments, a RAS protein is selected from HRAS, NRAS, KRAS, RRAS, RRAS2, MRAS, and RIT1. In some embodiments, a RAS protein is a wild-type RAS protein. In some embodiments, a RAS protein is a mutant RAS protein. In some embodiments, a RAS protein (e.g., HRAS, NRAS, or KRAS) comprises a mutation in codon 12 (e.g., G12), codon 13 (e.g., G13), or codon 61 (e.g., Q61). In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, a KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G13D, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an NRAS protein comprises a G12D, G12V, G13D, and/or Q61R mutation. In some embodiments, an HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation. In some embodiments, an HRAS protein comprises a G12V, G13R, and/or Q61R mutation. In some embodiments, a PI3Kα protein is a wild-type PI3Kα protein. In some embodiments, a PI3Kα protein is a mutant PI3Kα protein. In some embodiments, a PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, a PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation. In some embodiments, provided compounds or compositions are useful for treating a disease, disorder, or condition described herein. In some embodiments, provided compounds or compositions are useful for treating a cancer or other indication as described herein.

[000213] In some embodiments, a provided compound or composition is administered as part of a combination therapy. As used herein, the term "combination therapy" refers to those situations in which a subject is simultaneously exposed to two or more therapeutic or prophylactic regimens (e.g., two or more therapeutic or prophylactic agents). In some embodiments, the two or more regimens may be administered simultaneously. In some embodiments, such regimens may be administered sequentially (e.g., all "doses" of a first regimen are administered prior to administration of any doses of a second regimen); in some embodiments, such agents are administered in overlapping dosing regimens. In some embodiments, "administration" of combination therapy may involve administration of one or more agents or modalities to a subject receiving the other agent or modality in the combination. For clarity, combination therapy does

not require that individual agents be administered together in a single composition (or even necessarily at the same time), although, in some embodiments, two or more agents may be administered together in a combination composition.

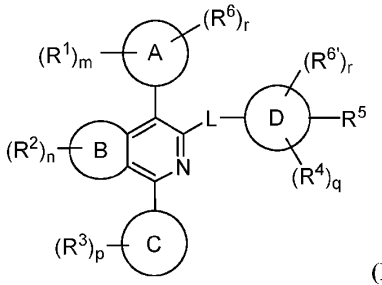
[000214] In some embodiments, a provided compound or composition is administered to a subject who is receiving or has received one or more additional therapeutic agents (e.g., an anti-cancer agent and/or a therapy to address one or more side effects of such anti-cancer therapy, or otherwise to provide palliative care). Exemplary anti-cancer agents include, but are not limited to, 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, a kinase inhibitor, a HIF2α inhibitor, 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 (RIYIZOR), 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). A kinase inhibitor may be, for example, a BRAF inhibitor, MEK inhibitor, or a KRAS inhibitor (e.g., KRAS G12C inhibitor, such as sotorasib, adagrasib, or BBO-8520). Additional examples of agents that may be useful in combination with a compound provided herein 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 (ZO'ADEX); 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.

Exemplary Embodiments

[000215] The following numbered embodiments, while non-limiting, are exemplary of certain aspects of the present disclosure:

[000216] 1. A compound of Formula I:



(I)

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

Ring A is phenyl;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5- to 6-membered carbocyclic ring, and phenyl;

Ring C is selected from phenyl, 9- to 10-membered bicyclic aryl ring, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to 7-membered

heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

and when L is C_{2-5} alkynyl, then Ring D may be absent;

L is a covalent bond or a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-;

each R^1 is independently selected from halogen and $-OR^7$;

each R^7 is independently selected from optionally substituted C_{1-6} aliphatic and $-(C_{1-4}$ alkylene)OR;

each R^2 is independently selected from halogen and optionally substituted C_{1-6} aliphatic;

each R^3 is independently selected from oxo, halogen, -CN, -OR, -C(O)R, $-(CH_2)_xC(O)OR$, $-(CH_2)_xC(O)N(R)_2$, $-(CH_2)_xN(R)C(O)R$, $-(CH_2)_xCy$, $-O(CH_2)_xCy$, -C(O)Cy, and optionally substituted C_{1-6} aliphatic;

each R^4 is independently optionally substituted C_{1-6} aliphatic;

R^5 is $-C(O)R^9$, $-(CH_2)_xN(R)C(O)R^9$, or -CN;

R^9 is optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or a 4-membered bicyclic carbocyclic ring;

R^6 and $R^{6'}$ are connected with an optionally substituted C_{4-8} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2;

r is 0 or 1;

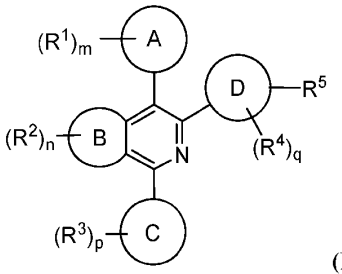
each x is independently 0, 1, or 2;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

each Cy is independently selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8; and

each R^8 is independently selected from oxo, halogen, and optionally substituted C_{1-6} aliphatic.

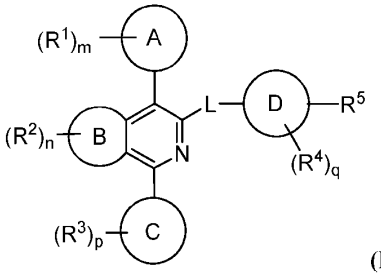
[000217] 2. The compound of embodiment 1, wherein the compound is of Formula IC:



(IC)

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

[000218] 3. The compound of embodiment 1, wherein the compound is of Formula ID:

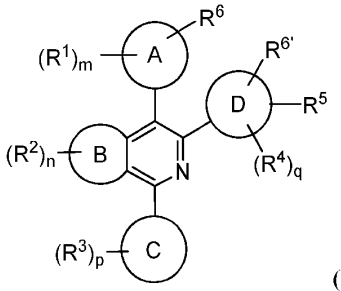


(ID)

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

L is a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-.

[000219] 4. The compound of embodiment 1, wherein the compound is of Formula IE:



(IE)

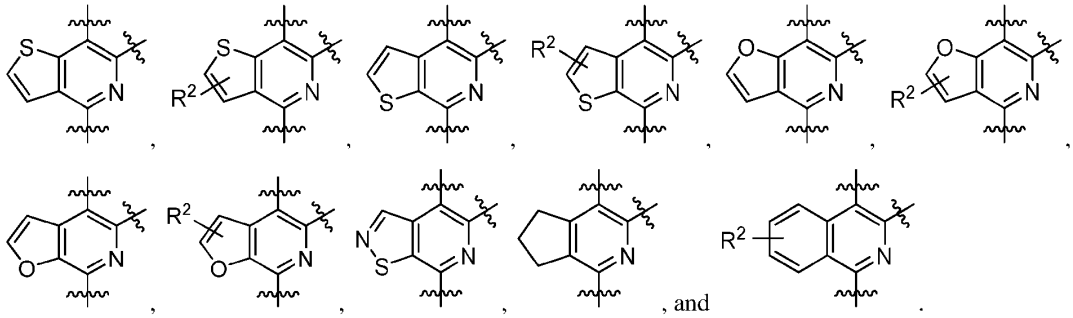
or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000220] 5. The compound of any one of embodiments 1-4, wherein Ring B is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur and a 5-membered carbocyclic ring.

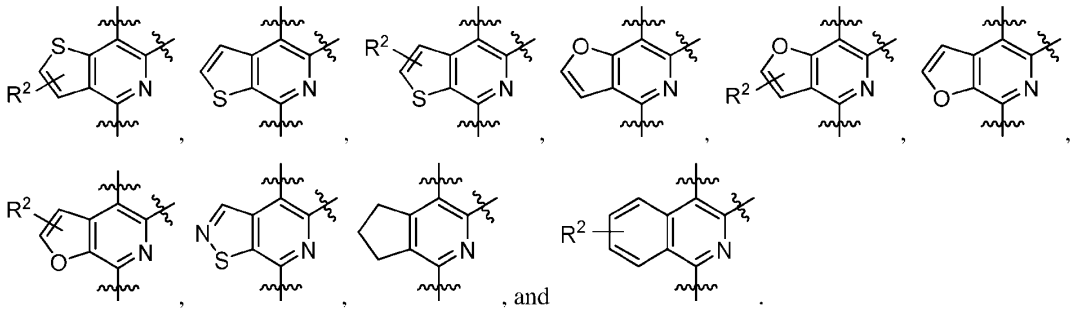
[000221] 6. The compound of embodiment 5, wherein Ring B is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000222] 7. The compound of embodiment 5, wherein Ring B is a 5-membered carbocyclic ring.

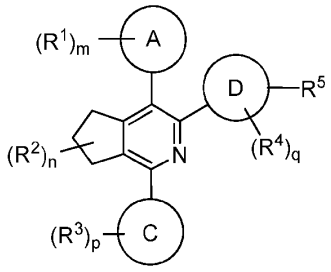
[000223] 8. The compound of any one of embodiments 1-4, wherein Ring B is selected from:



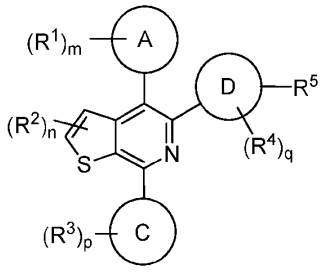
[000224] 9. The compound of embodiment 8, wherein Ring B is selected from:



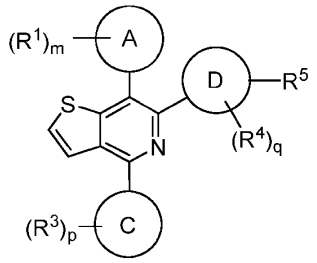
[000225] 10. The compound of embodiment 1 or 2, wherein the compound is of Formula IC3-a, IC3-b, IC3-c, IC3-d, IC3-e, IC3-f, or IC3-g:



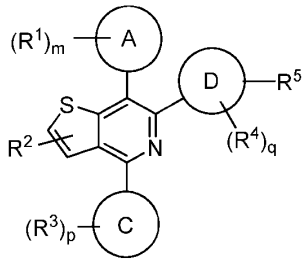
IC3-a



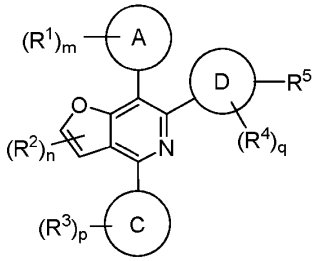
IC3-b



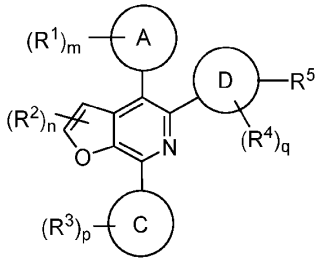
IC3-c



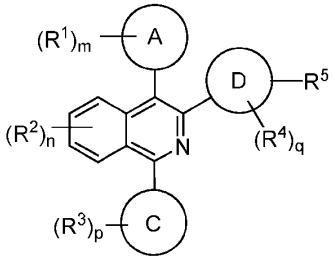
IC3-d



IC3-e



IC3-f



IC3-g

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

[000226] 11. The compound of embodiment 10, wherein the compound is of Formula IC3-a, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000227] 12. The compound of embodiment 11, wherein the compound is not a compound selected from Table P1.

[000228] 13. The compound of embodiment 10, wherein the compound is of Formula IC3-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000229] 14. The compound of embodiment 13, wherein the compound is not a compound selected from Table P2.

[000230] 15. The compound of embodiment 10, wherein the compound is of Formula IC3-c, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000231] 16. The compound of embodiment 10, wherein the compound is of Formula IC3-d, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000232] 17. The compound of embodiment 16, wherein the compound is not a compound selected from Table P3.

[000233] 18. The compound of embodiment 10, wherein the compound is of Formula IC3-e, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000234] 19. The compound of embodiment 18, wherein the compound is not a compound selected from Table P4.

[000235] 20. The compound of embodiment 10, wherein the compound is of Formula IC3-f, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000236] 21. The compound of embodiment 10, wherein the compound is of Formula IC3-g, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

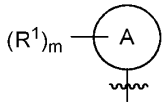
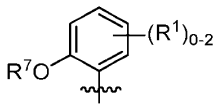
[000237] 22. The compound of any one of embodiments 1-21, wherein each R^2 is independently selected from halogen and C_{1-6} alkyl.

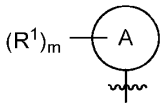
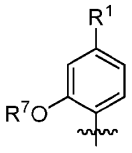
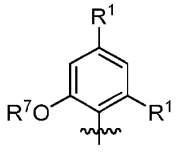
[000238] 23. The compound of any one of embodiments 1-22, wherein n is 0 or 1.

[000239] 24. The compound of embodiment 23, wherein n is 1.

[000240] 25. The compound of any one of embodiments 1-24, wherein at least one R^1 is $-OR^7$.

[000241] 26. The compound of embodiment 25, wherein one R^1 is $-OR^7$ and any other R^1 groups are halogen.

[000242] 27. The compound of any one of embodiments 1-26, wherein a moiety  is .

[000243] 28. The compound of embodiment 27, wherein a moiety  is  or .

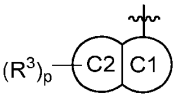
[000244] 29. The compound of any one of embodiments 1-28, wherein each R^7 is independently selected from C_{1-6} alkyl and –(C_{1-4} alkylene)OR.

[000245] 30. The compound of any one of embodiments 1-29, wherein m is 2 or 3.

[000246] 31. The compound of any one of embodiments 1-30, wherein Ring C is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000247] 32. The compound of any one of embodiments 1-30, wherein Ring C is selected from 9- to 10-membered bicyclic aryl ring, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000248] 33. The compound of embodiment 32, wherein Ring C is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000249] 34. The compound of any one of embodiments 1-30, wherein Ring C substituted with p R^3 groups is 

, wherein:

Ring C1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

wherein Ring C1 is fused to Ring C2; and

Ring C2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

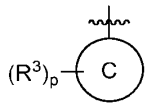
[000250] 35. The compound of embodiment 34, wherein Ring C1 is a phenyl, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

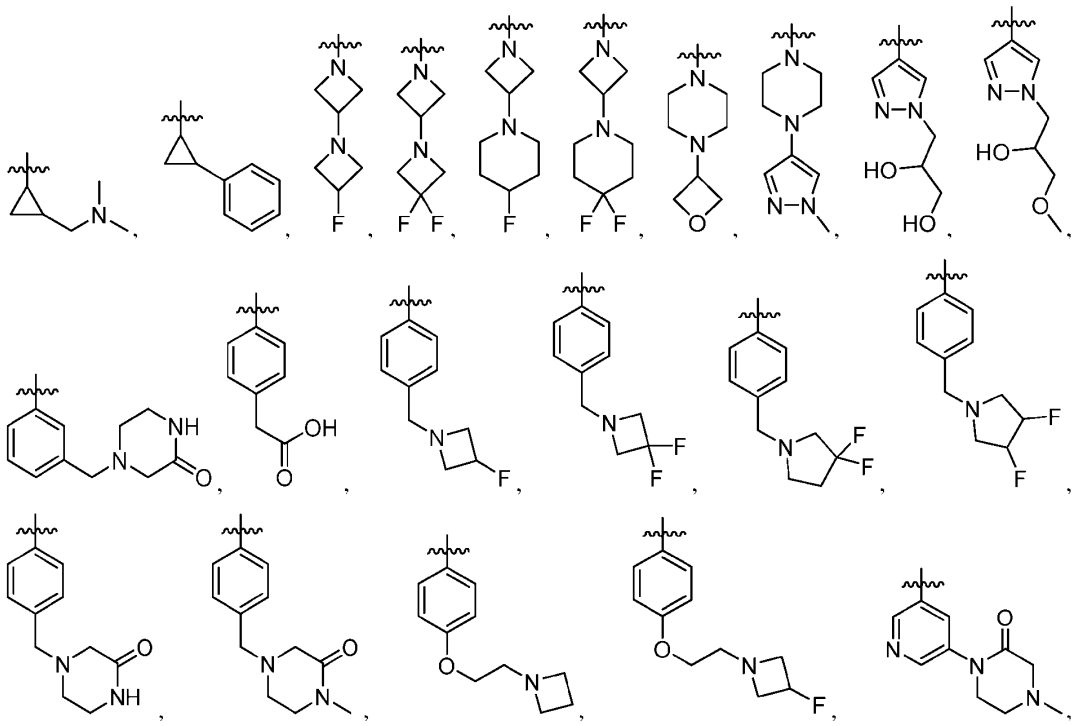
[000251] 36. The compound of embodiment 34, wherein Ring C1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

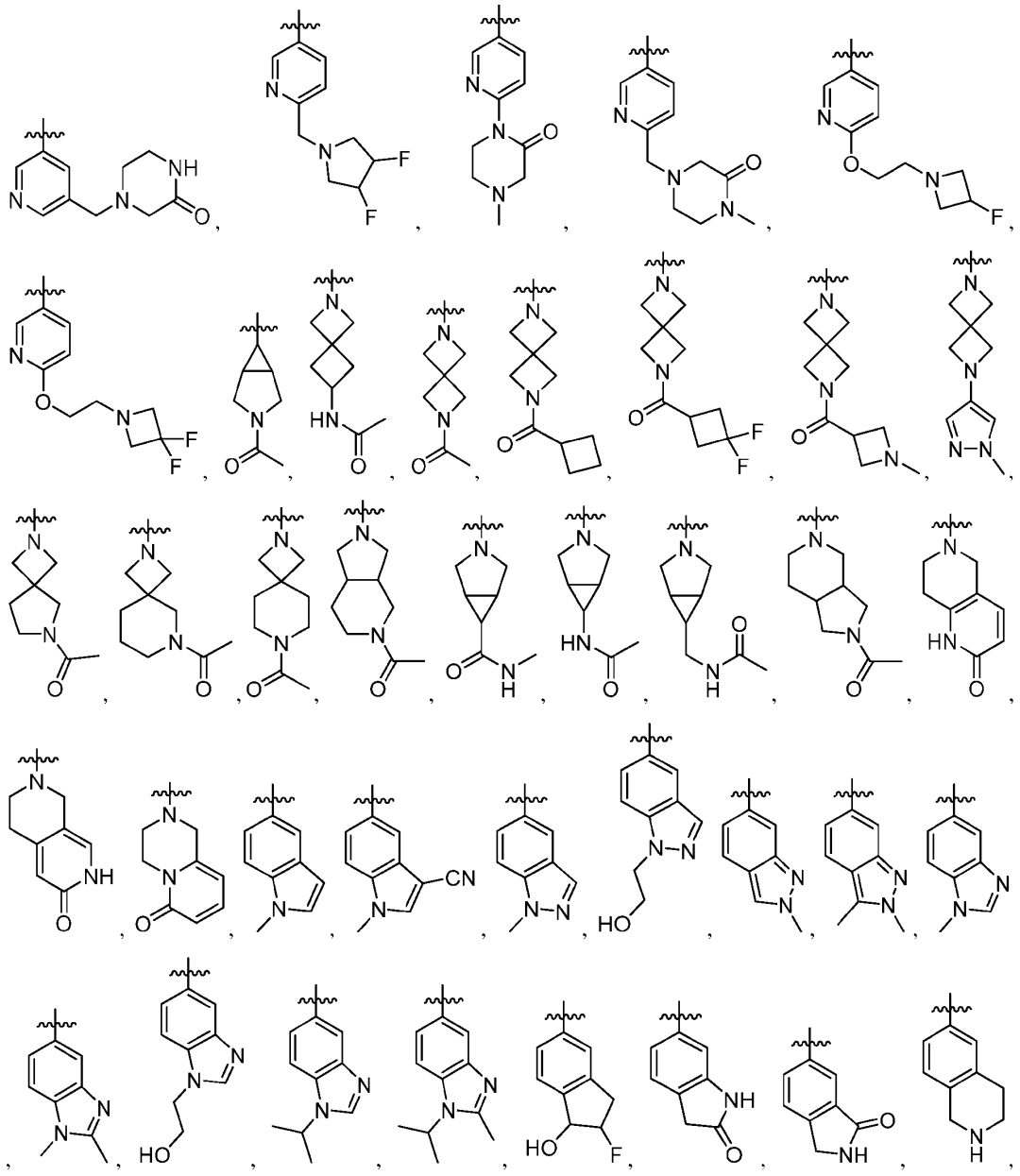
[000252] 37. The compound of embodiment 34, wherein Ring C1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, or 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

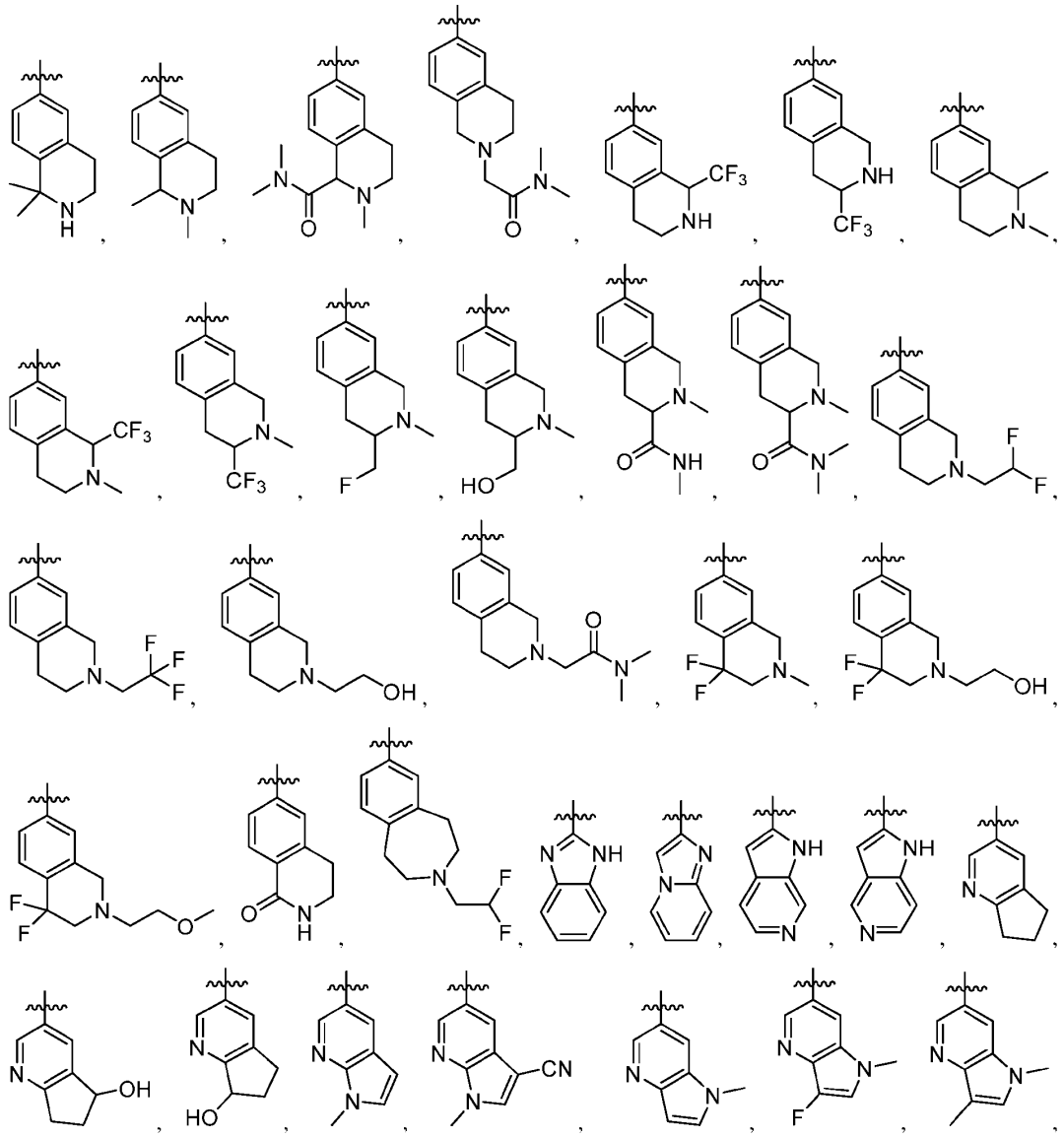
[000253] 38. The compound of any one of embodiments 1-37, wherein each R^3 is independently selected from halogen, -C(O)N(R)$_2$, and optionally substituted C_{1-6} alkyl.

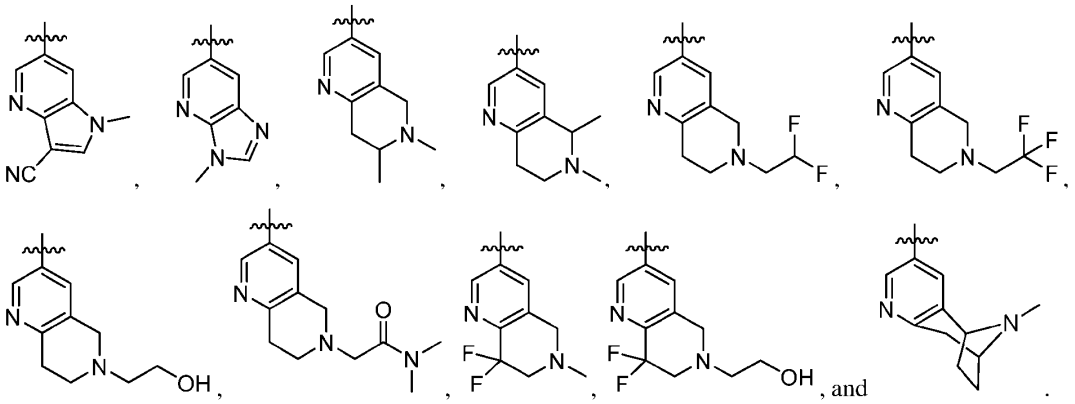
[000254] 39. The compound of any one of embodiments 1-38, wherein p is 1, 2, or 3.

[000255] 40. The compound of any one of embodiments 1-39, wherein a moiety  is selected from:





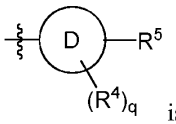
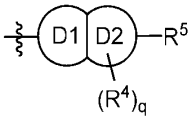




[000256] 41. The compound of any one of embodiments 1-40, wherein Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000257] 42. The compound of any one of embodiments 1-40, wherein Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000258] 43. The compound of embodiment 42, wherein Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000259] 44. The compound of any one of embodiments 1-40, wherein a moiety  is , wherein:

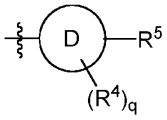
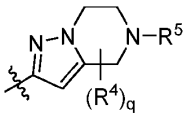
Ring D1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

wherein Ring D1 is fused to Ring D2; and

Ring D2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000260] 45. The compound of embodiment 44, wherein Ring D1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000261] 46. The compound of embodiment 44, wherein Ring D1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

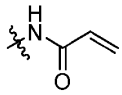
[000262] 47. The compound of any one of embodiments 1-40, wherein a moiety  is .

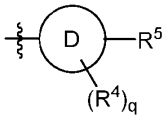
[000263] 48. The compound of any one of embodiments 1-47, wherein each R^4 is independently C_{1-6} alkyl optionally substituted with one or more –OH.

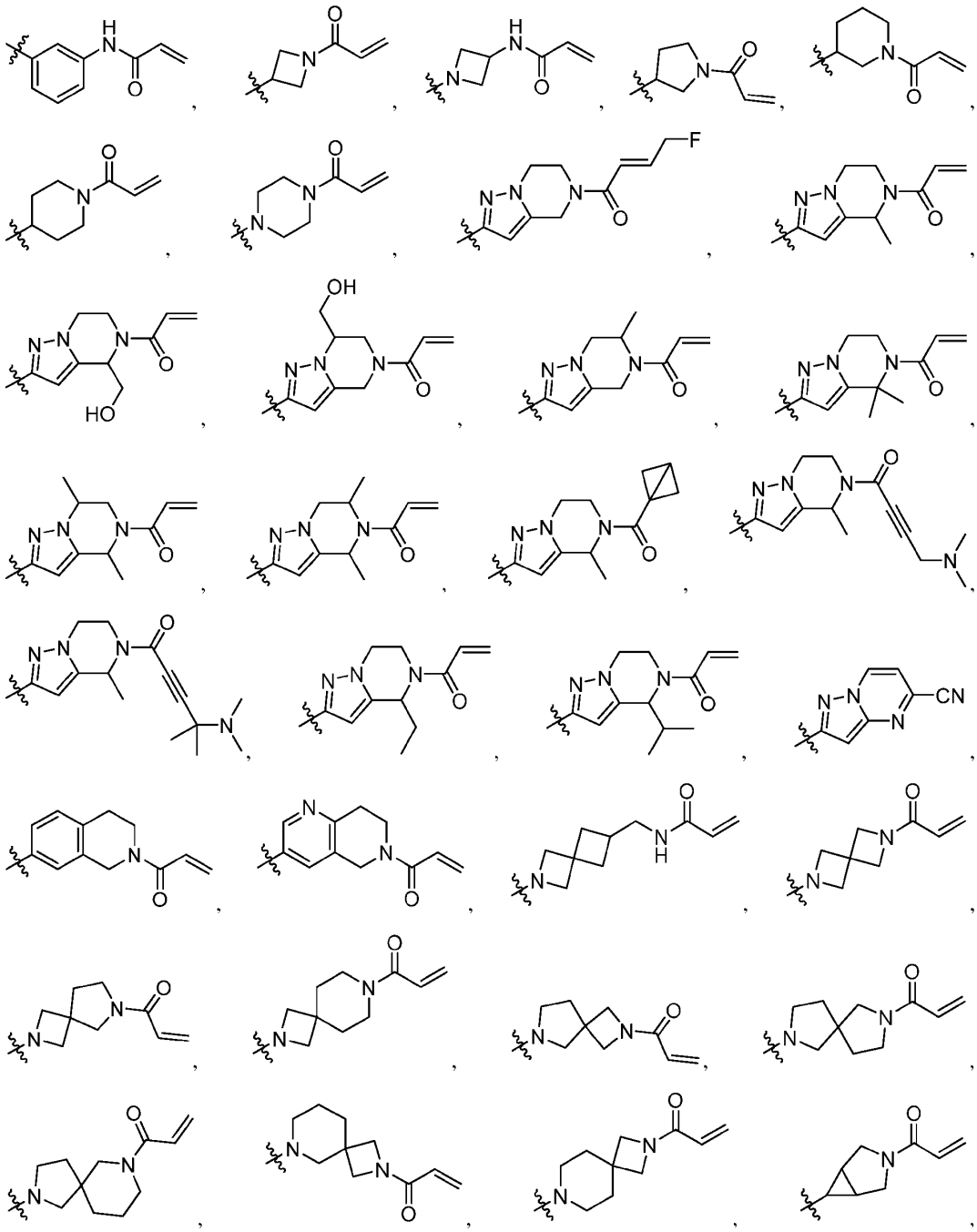
[000264] 49. The compound of any one of embodiments 1-48, wherein q is 0 or 1.

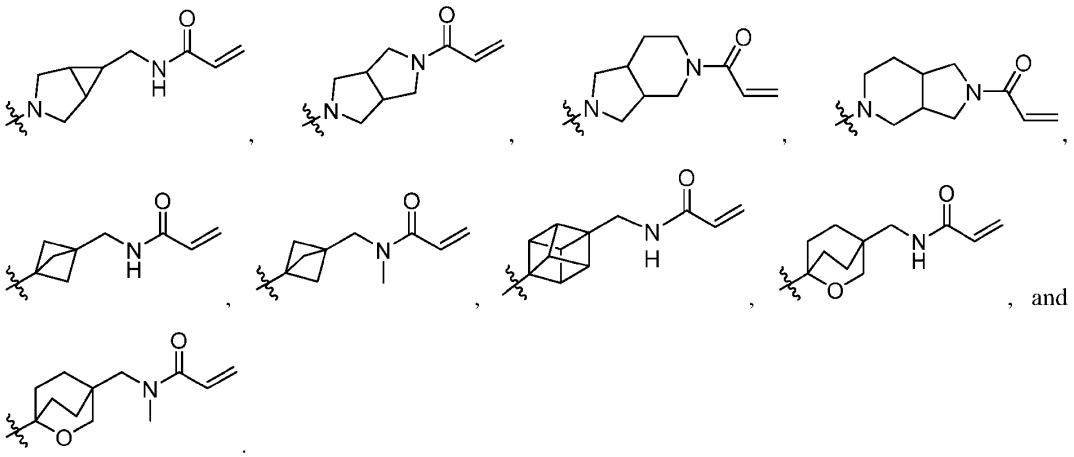
[000265] 50. The compound of any one of embodiments 1-49, wherein R^5 is $-C(O)R^9$ or $-(CH_2)_xN(R)C(O)R^9$.

[000266] 51. The compound of any one of embodiments 1-50, wherein R^9 is optionally substituted C_{2-6} alkenyl or optionally substituted C_{2-6} alkynyl.

[000267] 52. The compound of any one of embodiments 1-51, wherein R^5 is  or .

[000268] 53. The compound of any one of embodiments 1-52, wherein a moiety  is selected from:





[000269] 54. The compound of embodiment 1 or 3, wherein L is a bivalent straight or branched C_{2-6} hydrocarbon chain having at least one triple bond.

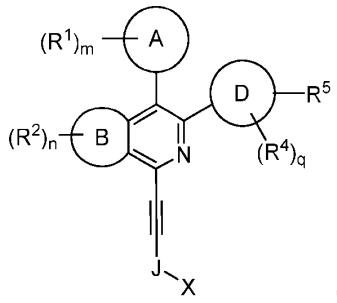
[000270] 55. The compound of embodiment 1 or 3, wherein L is a bivalent straight or branched C_{1-2} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-.

[000271] 56. The compound of embodiment 1 or 4, wherein R^6 and $R^{6'}$ are connected with an optionally substituted C_{5-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-.

[000272] 57. The compound of embodiment 56, wherein R^6 and $R^{6'}$ are connected with: $-O(CH_2)_5-$, $-O(CH_2)_4-$, or $-O(CH_2)_3OCH_2-$.

[000273] 58. The compound of any one of embodiments 1-57, wherein each R is hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen.

[000274] 59. A compound of Formula II:



(II)

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

Ring A is phenyl and a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5- to 6-membered carbocyclic ring, and phenyl;

Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

J is a covalent bond or a bivalent straight or branched C_{1-4} hydrocarbon chain;

X is –OR, $-N(R)_2$, $-C(O)N(R)_2$, or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 is independently selected from halogen and $–OR^7$;

each R^7 is independently selected from optionally substituted C_{1-6} aliphatic and $–(C_{1-4}$ alkylene)OR;

each R^2 is independently selected from halogen and optionally substituted C_{1-6} aliphatic;

each R^4 is independently selected from optionally substituted C_{1-6} aliphatic;

R^5 is $-C(O)R^9$, $-(CH_2)_xN(R)C(O)R^9$, or -CN;

R^9 is optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or a 4-membered bicyclic carbocyclic ring;

m is 0, 1, 2, or 3;

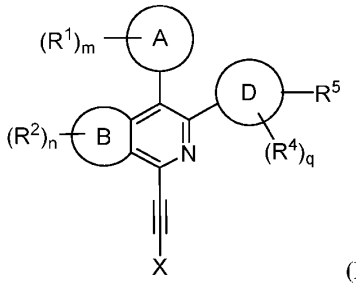
n is 0, 1, or 2;

q is 0, 1, or 2;

x is 0, 1, or 2;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[000275] 60. The compound of embodiment 63, wherein the compound is of Formula IIF:

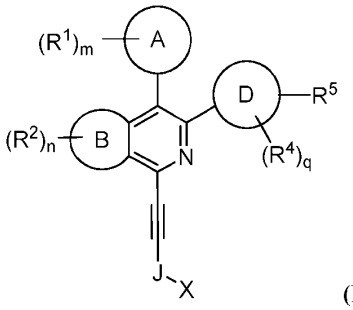


(IIF)

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

X is -C(O)N(R)$_2$ or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000276] 61. The compound of embodiment 59, wherein the compound is of Formula IIG:



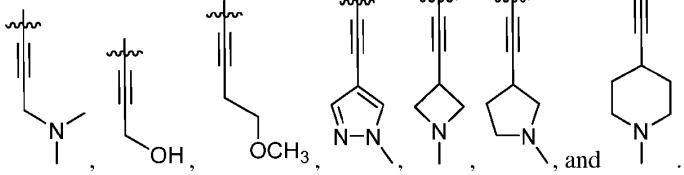
(IIG)

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

J is a bivalent straight or branched C_{1-4} hydrocarbon chain; and

X is –OR or -N(R)$_2$.

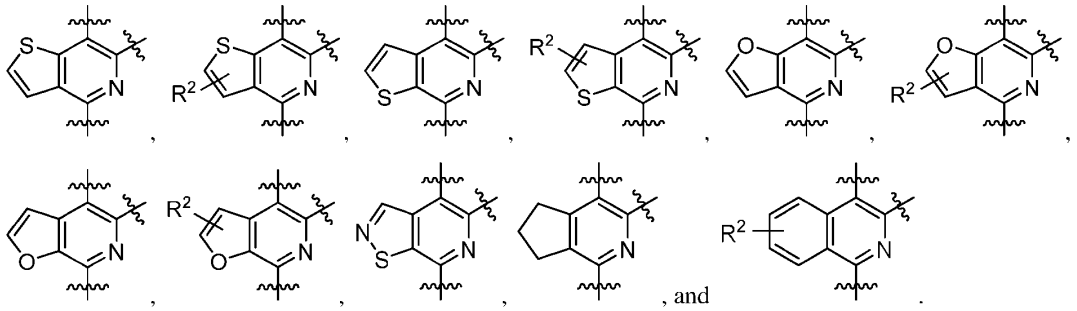
[000277] 62. The compound of embodiment 59 or 60, wherein X is a group selected from 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein any ring is optionally substituted with C_{1-6} alkyl.

[000278] 63. The compound of any one of embodiments 59-62, wherein a moiety  is selected from: .

[000279] 64. The compound of any one of embodiments 59-63, wherein Ring B is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur and a 5-membered carbocyclic ring.

[000280] 65. The compound of embodiment 64, wherein Ring B is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000281] 66. The compound of embodiment 64, wherein Ring B is a 5-membered carbocyclic ring.

[000282] 67. The compound of any one of embodiments 59-66, wherein Ring B is selected from: .

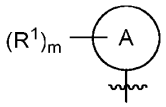
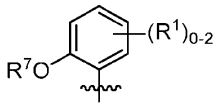
[000283] 68. The compound of any one of embodiments 59-67, wherein each R^2 is independently selected from halogen and C_{1-6} alkyl.

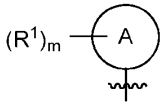
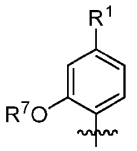
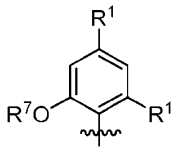
[000284] 69. The compound of any one of embodiments 59-68, wherein n is 0 or 1.

[000285] 70. The compound of any one of embodiments 59-69, wherein Ring A is phenyl.

[000286] 71. The compound of any one of embodiments 59-70, wherein at least one R^1 is $-OR^7$.

[000287] 72. The compound of embodiment 71, wherein one R^1 is $-OR^7$ and any other R^1 groups are halogen.

[000288] 73. The compound of any one of embodiments 59-72, wherein a moiety  is .

[000289] 74. The compound of embodiment 73, wherein a moiety  is  or .

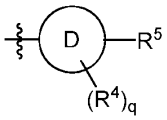
[000290] 75. The compound of any one of embodiments 59-74, wherein each R^7 is independently selected from C_{1-6} alkyl and –(C_{1-4} alkylene)OR.

[000291] 76. The compound of any one of embodiments 59-75, wherein m is 2 or 3.

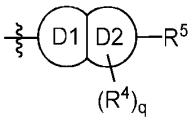
[000292] 77. The compound of any one of embodiments 59-76, wherein Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000293] 78. The compound of any one of embodiments 59-76, wherein Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000294] 79. The compound of embodiment 78, wherein Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.



[000295] 80. The compound of any one of embodiments 59-76, wherein a moiety is



, wherein:

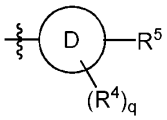
Ring D1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

wherein Ring D1 is fused to Ring D2; and

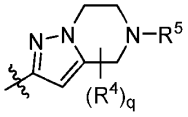
Ring D2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000296] 81. The compound of embodiment 80, wherein Ring D1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[000297] 82. The compound of embodiment 80, wherein Ring D1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.



[000298] 83. The compound of any one of embodiments 59-82, wherein a moiety is



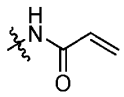
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[000299] 84. The compound of any one of embodiments 59-83, wherein each R^4 is independently C_{1-6} alkyl optionally substituted with one or more –OH.

[000300] 85. The compound of any one of embodiments 59-84, wherein q is 0 or 1.

[000301] 86. The compound of any one of embodiments 59-85, wherein R^5 is $-C(O)R^9$ or $-(CH_2)_xN(R)C(O)R^9$.

[000302] 87. The compound of any one of embodiments 59-86, wherein R^9 is optionally substituted C_{2-6} alkenyl or optionally substituted C_{2-6} alkynyl.

[000303] 88. The compound of any one of embodiments 59-87, wherein R^5 is  or .

[000304] 89. The compound of any one of embodiments 59-88, wherein each R is hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen.

[000305] 90. A compound selected from Table 1, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

[000306] 91. A pharmaceutical composition comprising a compound according to any one of embodiments 1-90, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable carrier or excipient.

[000307] 92. A method comprising administering a therapeutically effective amount of a compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof to a subject in need thereof.

[000308] 93. The method of embodiment 92, wherein the subject has a disease, disorder, or condition ameliorated by disruption, inhibition, and/or prevention of an interaction between a small GTPase and a PI3Kα protein.

[000309] 94. The method of embodiment 93, wherein the small GTPase is Rac1, CDC42, or a RAS protein.

[000310] 95. The method of embodiment 94, wherein the small GTPase is a RAS protein.

[000311] 96. The method of embodiment 95, wherein the RAS protein is KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1.

[000312] 97. The method of any one of embodiments 92-96, wherein the subject has a cancer.

[000313] 98. A method of treating a cancer, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof.

[000314] 99. The method of embodiment 97 or 98, wherein the cancer is associated with and/or characterized by aberrant activation of PI3Kα and/or a mutation in PI3Kα.

[000315] 100. The method of embodiment 99, wherein the PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation.

[000316] 101. The method of embodiment 100, wherein the PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation.

[000317] 102. The method of any one of embodiments 97-101, wherein the cancer is characterized by a mutation in a RAS protein.

[000318] 103. The method of embodiment 102, wherein the RAS protein comprises a mutation in codon 12, 13, or 61.

[000319] 104. The method of embodiment 102 or 103, wherein the RAS protein is KRAS.

[000320] 105. The method of embodiment 104, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000321] 106. The method of embodiment 105, wherein the KRAS protein comprises a G12C or G12D mutation.

[000322] 107. The method according to embodiment 102 or 103, wherein the RAS protein is HRAS.

[000323] 108. The method according to embodiment 107, wherein the HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000324] 109. The method according to embodiment 102 or 103, wherein the RAS protein is NRAS.

[000325] 110. The method according to embodiment 109, wherein the NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000326] 111. The method according to any one of embodiments 97-110, wherein the cancer is selected from pancreatic cancer; colon cancer; rectal cancer; colorectal cancer; bowel cancer; breast cancer; ovarian cancer; endometrial cancer; lung cancer; prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, liver and biliary passages, 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; cancers of the thyroid and other endocrine glands; 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.

[000327] 112. The method according to embodiment 111, wherein the cancer is selected from breast cancer, lung cancer (e.g., non-small cell lung cancer), endometrial cancer, esophageal cancer, ovarian cancer, colorectal cancer, gastric cancer, squamous cell carcinoma, prostate cancer, and pancreatic cancer.

[000328] 113. The method according to any one of embodiments 97-112, wherein the cancer is characterized by mutated, overexpressed, and/or amplified receptor tyrosine kinases (e.g., HER family, Met, FGFR, Alk, PDGF, EGFR, or ROS kinases).

[000329] 114. The method according to any one of embodiments 97-113, wherein the cancer is characterized by a mutation in or a deletion of a PTEN protein.

[000330] 115. The method according to any one of embodiments 92-114, wherein the subject has previously undergone a treatment regimen for cancer.

[000331] 116. The method according to any one of embodiments 92-115, wherein the subject has previously entered remission from cancer.

[000332] 117. A method of treating a metabolic disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof.

[000333] 118. The method according to embodiment 117, wherein the metabolic disorder is selected from hyperinsulinemia and type 2 diabetes.

[000334] 119. A method of treating a RASopathy, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof.

[000335] 120. The method according to embodiment 119, wherein the RASopathy is selected from neurofibromatosis type 1 (NF1), capillary malformation-arteriovenous malformation syndrome, and Legius syndrome.

[000336] 121. A method of treating a vascular disorder or condition, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof.

[000337] 122. The method according to embodiment 121, wherein the vascular disorder or condition is selected from PIK3CA-related overgrowth syndrome (PROS) and vascular malformations (e.g., venous malformations; lymphatic malformations; congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies syndrome (CLOVES); Klippel-Trenaunay Syndrome; PTEN hamartoma tumor syndrome (PHTS); and fibro-adipose vascular anomaly (FAVA)).

[000338] 123. A method of disrupting, inhibiting, and/or preventing an interaction between a small GTPase and a PI3Kα protein in a subject, comprising administering to the subject a compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof.

[000339] 124. A method of disrupting, inhibiting, and/or preventing an interaction between a small GTPase and a PI3Kα protein, comprising contacting a cell containing the small GTPase and the PI3Kα protein with a compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof.

[000340] 125. A method comprising contacting a cell containing a small GTPase and a PI3Kα protein with a compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof.

[000341] 126. The method of embodiment 124 or 125, wherein the cell is included in a subject.

[000342] 127. The method of any one of embodiments 123-126, wherein the small GTPase is selected from Rac1, CDC42, and a RAS protein.

[000343] 128. The method of embodiment 127, wherein the small GTPase is a RAS protein.

[000344] 129. The method of embodiment 128, wherein the RAS protein is selected from HRAS, NRAS, KRAS, RRAS, RRAS2, MRAS, and RIT1.

[000345] 130. The method of embodiment 129, wherein the RAS protein is KRAS.

[000346] 131. The method of embodiment 130, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000347] 132. The method of embodiment 131, wherein the KRAS protein comprises a G12C or G12D mutation.

[000348] 133. The method according to embodiment 129, wherein the RAS protein is HRAS.

[000349] 134. The method according to embodiment 133, wherein the HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000350] 135. The method according to embodiment 129, wherein the RAS protein is NRAS.

[000351] 136. The method according to embodiment 135, wherein the NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000352] 137. A compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof for use as a medicament.

[000353] 138. Use of a compound according to any one of embodiments 1-90 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament.

[000354] 139. The compound or use according to embodiment 137 or 138, wherein the medicament is for treating a cancer.

[000355] 140. The compound or use according to embodiment 139, wherein the cancer is associated with and/or characterized by aberrant activation of PI3Kα and/or a mutation in PI3Kα.

[000356] 141. The compound or use according to embodiment 140, wherein the PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation.

[000357] 142. The compound or use according to embodiment 141, wherein the PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation.

[000358] 143. The compound or use according to any one of embodiments 139-142, wherein the cancer is characterized by a mutation in a RAS protein.

[000359] 144. The compound or use according to embodiment 143, wherein the RAS protein comprises a mutation in codon 12, 13, or 61.

[000360] 145. The compound or use according to embodiment 143 or 144, wherein the RAS protein is KRAS.

[000361] 146. The compound or use according to embodiment 145, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000362] 147. The compound or use according to embodiment 146, wherein the KRAS protein comprises a G12C or G12D mutation.

[000363] 148. The compound or use according to embodiment 143 or 144, wherein the RAS protein is HRAS.

[000364] 149. The compound according to embodiment 148, wherein the HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000365] 150. The compound or use according to embodiment 143 or 144, wherein the RAS protein is NRAS.

[000366] 151. The compound or use according to embodiment 150, wherein the NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000367] 152. The compound or use according to any one of embodiments 139-151, wherein the cancer is selected from pancreatic cancer; colon cancer; rectal cancer; colorectal cancer; bowel cancer; breast cancer; ovarian cancer; endometrial cancer; lung cancer; prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine,

liver and biliary passages, 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; cancers of the thyroid and other endocrine glands; 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.

[000368] 153. The compound or use according to embodiment 152, wherein the cancer is selected from breast cancer, lung cancer (e.g., non-small cell lung cancer), endometrial cancer, esophageal cancer, ovarian cancer, colorectal cancer, gastric cancer, squamous cell carcinoma, prostate cancer, and pancreatic cancer.

[000369] 154. The compound or use according to any one of embodiments 139-151, wherein the cancer is characterized by mutated, overexpressed, and/or amplified receptor tyrosine kinases (e.g., HER family, Met, FGFR, Alk, PDGF, EGFR, or ROS kinases).

[000370] 155. The compound or use according to any one of embodiments 139-151, wherein the cancer is characterized by a mutation in or a deletion of a PTEN protein.

[000371] 156. The compound or use according to embodiment 137 or 138, wherein the medicament is for treating a metabolic disorder, a RASopathy, or a vascular disorder.

[000372] 157. The compound or use according to embodiment 156, wherein: (i) the metabolic disorder is selected from hyperinsulinemia and type 2 diabetes; (ii) the RASopathy is selected from neurofibromatosis type 1 (NF1), capillary malformation-arteriovenous malformation syndrome, and Legius syndrome; and/or (iii) the vascular disorder or condition is selected from PIK3CA-related overgrowth syndrome (PROS) and vascular malformations (e.g., venous malformations; lymphatic malformations; congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies syndrome (CLOVES); Klippel-Trenaunay Syndrome; PTEN hamartoma tumor syndrome (PHTS); or fibro-adipose vascular anomaly (FAVA)).

[000373] 158. A compound according to any one of embodiment 1-90 or a pharmaceutically acceptable salt thereof for use in treating a disease, disorder, or condition.

[000374] 159. The compound for use according to embodiment 158 for use in treating a cancer.

[000375] 160. The compound for use according to embodiment 159, wherein the cancer is associated with and/or characterized by aberrant activation of PI3Kα and/or a mutation in PI3Kα.

[000376] 161. The compound for use according to embodiment 160, wherein the PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation.

[000377] 162. The compound for use according to embodiment 161, wherein the PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation.

[000378] 163. The compound for use according to any one of embodiments 159-162, wherein the cancer is characterized by a mutation in a RAS protein.

[000379] 164. The compound for use according to embodiment 163, wherein the RAS protein comprises a mutation in codon 12, 13, or 61.

[000380] 165. The compound for use according to embodiment 163 or 164, wherein the RAS protein is KRAS.

[000381] 166. The compound for use according to embodiment 165, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000382] 167. The compound for use according to embodiment 166, wherein the KRAS protein comprises a G12C or G12D mutation.

[000383] 168. The compound for use according to embodiment 163 or 164, wherein the RAS protein is HRAS.

[000384] 169. The compound for use according to embodiment 168, wherein the HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000385] 170. The compound for use according to embodiment 163 or 164, wherein the RAS protein is NRAS.

[000386] 171. The compound for use according to embodiment 170, wherein the NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

[000387] 172. The compound for use according to any one of embodiments 159-171, wherein the cancer is selected from pancreatic cancer; colon cancer; rectal cancer; colorectal cancer; bowel cancer; breast cancer; ovarian cancer; endometrial cancer; lung cancer; prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, liver and biliary passages, 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; cancers of the thyroid and other endocrine glands; 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.

[000388] 173. The compound for use according to embodiment 172, wherein the cancer is selected from breast cancer, lung cancer (e.g., non-small cell lung cancer), endometrial cancer, esophageal cancer, ovarian cancer, colorectal cancer, gastric cancer, squamous cell carcinoma, prostate cancer, and pancreatic cancer.

[000389] 174. The compound for use according to any one of embodiments 159-173, wherein the cancer is characterized by mutated, overexpressed, and/or amplified receptor tyrosine kinases (e.g., HER family, Met, FGFR, Alk, PDGF, EGFR, or ROS kinases).

[000390] 175. The compound for use according to any one of embodiments 159-174, wherein the cancer is characterized by a mutation in or a deletion of a PTEN protein.

[000391] 176. The compound for use according to embodiment 158 for use in treating a metabolic disorder, a RASopathy, or a vascular disorder.

[000392] 177. The compound for use according to embodiment 176, wherein: (i) the metabolic disorder is selected from hyperinsulinemia and type 2 diabetes; (ii) the RASopathy is selected from neurofibromatosis type 1 (NF1), capillary malformation-arteriovenous malformation syndrome, and Legius syndrome; and/or (iii) the vascular disorder or condition is selected from PIK3CA-related overgrowth syndrome (PROS) and vascular malformations (e.g., venous malformations; lymphatic malformations; congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies syndrome (CLOVES); Klippel-Trenaunay Syndrome; PTEN hamartoma tumor syndrome (PHTS); and fibro-adipose vascular anomaly (FAVA)).

EXAMPLES

[000393] As described in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present disclosure, the following general methods and other methods known to one of ordinary skill in the art can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[000394] Selected abbreviations used in the preceding sections and the Examples are summarized in the following table:

Abbreviation	Term
MeCN	acetonitrile
cm	centimeter
°C	degrees Celsius
°K	degrees Kelvin
BINAP	[1,1'-Binaphthalene]-2,2'-diyl)bis(diphenylphosphane)
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIEA	N,N-diisopropylethylamine (Hünig's base)
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ESI	electrospray ion-mass spectrometry
EtOH	ethanol
EtOAc, EA	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
µg	microgram
µL	microliter
µM	micromolar

Abbreviation	Term
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
Prep-HPLC	preparative HPLC
Prep-TLC	preparative thin layer chromatography
^{1}HNMR	proton nuclear magnetic resonance
RBD	Ras binding domain
RP	reverse phase
rpm	revolutions per minute
SPR	surface plasmon resonance
THF	tetrahydrofuran
TMS	tetramethylsilane
TLC	thin layer chromatography
TEA	triethylamine
TFA	trifluoroacetic acid
TCEP	tris(2-carboxyethyl)phosphine
UV	ultraviolet
UV/Vis	ultraviolet/visible

Materials & Methods

[000395] Preparative thin layer chromatography (Prep-TLC) separations described herein were typically performed on 20 x 20 cm plates (500-μm thick silica gel).

[000396] 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.

[000397] ^{1}H NMR analyses of intermediates and exemplified compounds were typically performed on a Bruker Ascend TM 400 spectrometer (operating at 400 MHz), Bruker Ascend 500 MHz Avance Neo Spectrometer (Bruker-Biospin) or Bruker Avance Neo Nanobay (operating at 400 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.

[000398] LCMS analyses were typically performed using one of the following conditions:

[000399] (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.

[000400] (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).

[000401] (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 x150 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.

[000402] (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).

[000403] (5) LCMS spectra were taken on Waters Micromass-ZQ 2000 Quadrupole spectrometer. The mobile phase for the LC was (A) 0.1% formic acid in water; (B) acetonitrile 100% and the eluent gradient was from 10-90% B in 10.0 min, 90% up to 12 min B, 12-13 min 90-10% B, 13-15 min 90-10% B using Phenomenex Gemini-C18 (50 mm x 4.6 mm x 5 μm); Flow Rate: 0.5 mL/min. Mass spectra (MS) were measured by Electrospray Ion-Mass spectroscopy (ESI).

[000404] Typically, analytical HPLC spectrometry conditions were as follows:

[000405] 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.

[000406] LC2: Shimadzu 2010 CHT, Column Waters X-select CSH C18 (150 x 4.6) mm x 3.5 μm, Temperature: 30 °C; MP-A 10 mM ammonium acetate Buffer, MP-B: acetonitrile (100%), Flow Rate: 1.0 mL/min; Detection: VWD, 270 nm. Gradient elevation: time/B con: 0/5,2/5,20/50,25/50,30/90,35/90,37/05,40/05.

[000407] Preparative HPLC were carried out with one of the following conditions:

[000408] Condition 1: GILSON Preparative HPLC System; Column: Ultimate XB-C18, 21.2mm x 250mm, 5 μm; 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.

[000409] 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 5uM

OBD™ 19 x 250 mm column with a mobile phase of water / MeCN or water (0.1% TFA) / MeCN (0.1% TFA).

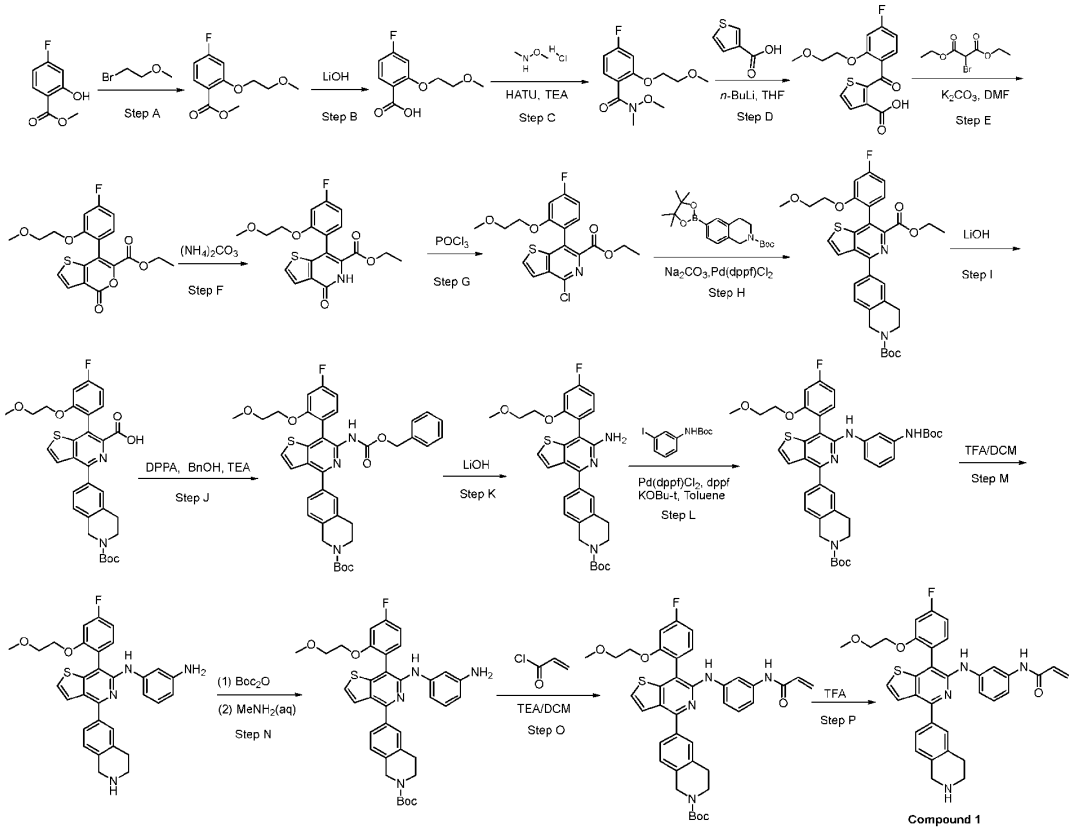
[000410] Condition 3: Shimadzu Preparative HPLC System; Column: Phenomenex Luna C18, 21.1 mm × 250 mm, 10 μm; Mobile phase; MP-A 10 mM ammonium acetate buffer, MP-B: methanol (100%), 35 minutes gradient elution UV: 254; Flow: 10 mL/min. Gradient elevation: time/B con:0/50,25/90,30/90,32/50,35/50.

[000411] Compound names were generated with ChemDraw Professional.

Synthesis of Provided Compounds

[000412] 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.

Synthetic Example 1: Synthesis of *N*-[3-[[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1,2,3,4-tetrahydroisoquinolin-6-yl)thieno[3,2-c]pyridin-6-yl]amino]phenyl]prop-2-enamide (**Compound 1**)



[000413] **Step A:** Preparation of methyl 4-fluoro-2-(2-methoxyethoxy)benzoate: To a solution of methyl 4-fluoro-2-hydroxy-benzoate (25.0 g, 147 mmol) in MeCN (500 mL) was added 1-bromo-2-methoxy-ethane (24.5 g, 176 mmol) and cesium carbonate (97.4 g, 220 mmol). The mixture was stirred at 70 °C for 16 h under Ar. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was diluted with water (200 mL) and extracted with ethyl acetate (100 mL × 3). The organic layers were washed with saturated brine (100 mL), dried over Na_2SO_4 and concentrated in vacuum to give methyl 4-fluoro-2-(2-methoxyethoxy)benzoate (32.6 g, 97 % yield) as a yellow oil. LCMS ESI (+) m/z 229.2 (M+H).

[000414] **Step B:** Preparation of 4-fluoro-2-(2-methoxyethoxy)benzoic acid: To a solution of methyl 4-fluoro-2-(2-methoxyethoxy)benzoate (16.3 g, 71.4 mmol) in THF (82 mL), methanol (27 mL) and water (27 mL) was added lithium hydroxide monohydrate (8.55 g, 357 mmol). The mixture was stirred at 25 °C for 6 h. The reaction was concentrated to remove THF and methanol, and then diluted with water (150 mL). Aqueous HCl (3 N) was added to adjust the pH to 2. The mixture was extracted with ethyl acetate (70 mL × 3). The combined organic layers were washed with saturated brine (70 ml), dried over Na_2SO_4 and concentrated in vacuum to give 4-fluoro-2-(2-methoxyethoxy)benzoic acid (14.8 g, 97% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 8.8, 6.8 Hz, 1H), 6.80-6.91 (m, 1H), 6.76 (dd, J = 10.0, 2.3 Hz, 1H), 4.34 (t, J = 4.6 Hz, 2H), 3.82 (t, J = 4.6 Hz, 2H), 3.46 (s, 3H), 2.10 (s, 1H).

[000415] **Step C:** Preparation of 4-fluoro-N-methoxy-2-(2-methoxyethoxy)-N-methyl-benzamide: To a solution of 4-fluoro-2-(2-methoxyethoxy)benzoic acid (10.0 g, 46.7 mmol), *N,O*-dimethylhydroxylamine hydrochloride (5.47 g, 56.0 mmol) and triethylamine (20.0 mL, 140 mmol) in DCM (150 mL) was added HATU (23.1 g, 60.7 mmol). The mixture was stirred at 25 °C for 6 h. The mixture was poured into water and the product was extracted with DCM. The organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc) to give 4-fluoro-N-methoxy-2-(2-methoxyethoxy)-N-methyl-benzamide (10.8 g, 89.9% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.34 (m, 1H), 6.61 – 6.76 (m, 2H), 4.13 (t, J = 4.8 Hz, 2H), 3.73 (t, J = 4.8 Hz, 2H), 3.41 (s, 3H), 2.80 (s, 6H).

[000416] **Step D:** Preparation of 2-[4-fluoro-2-(2-methoxyethoxy)benzoyl]thiophene-3-carboxylic acid: To a solution of thiophene-3-carboxylic acid (5.92 g, 46.2 mmol) in THF (130 mL) was added n-butyllithium (37.0 mL, 2.5 M solution in hexanes, 92.4 mmol) dropwise at -60 °C under Ar. The mixture was stirred at -60 °C for 0.5 h under Ar, then 4-fluoro-N-methoxy-2-(2-methoxyethoxy)-N-methyl-benzamide (10.8 g, 42.0 mmol) was added at -60 °C. The temperature was allowed to warm to 0 °C, and the resulting mixture was stirred at 0 °C for an additional 1 h. The mixture was poured into water. 1 N aqueous HCl was added to adjust the pH to 5. The mixture was concentrated to remove THF and diluted with water. The solid was filtered, washed with water and dried in vacuo to give crude 2-[4-fluoro-2-(2-

methoxyethoxy)benzoyl] thiophene-3-carboxylic acid (13.0 g, 57% yield). LCMS ESI (+) m/z 325.1 (M+H).

[000417] **Step E:** Preparation of ethyl 7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-oxo-thieno[3,2-c]pyran-6-carboxylate: To a solution of 2-[4-fluoro-2-(2-methoxyethoxy)benzoyl]thiophene-3-carboxylic acid (2.15 g, 6.63 mmol) and diethyl 2-bromopropanedioate (1.90 g, 7.96 mmol) in DMF (25 mL) was added potassium carbonate (2.29 g, 16.6 mmol). The mixture was stirred at 25 °C for 76 h. The mixture was poured into water and the product was extracted with EtOAc. The organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography on silica gel (EtOAc/petroleum ether=1/3) to give ethyl 7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-oxo-thieno[3,2-c]pyran-6-carboxylate (2.10 g, 81% yield). LCMS ESI (+) m/z 393.1 (M+H).

[000418] **Step F:** Preparation of ethyl 7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-oxo-5H-thieno[3,2-c]pyridine-6-carboxylate: To a mixture of ethyl 7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-oxo-thieno[3,2-c]pyran-6- carboxylate (1.80 g, 4.59 mmol) and AcOH (50 mL) under argon was added $(NH_4)_2CO_3$ (6.61 g, 68.8 mmol) by portions. The mixture was stirred at 95 °C for 14 h. The mixture was allowed to cool to ambient temperature, and the precipitate was collected by filtration. The filter-cake was washed with water and MeOH, and dried in vacuo to give ethyl 7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-oxo-5H-thieno[3,2-c]pyridine-6-carboxylate (1.26 g, 70% yield). LCMS ESI (+) m/z 392.1 (M+H).

[000419] **Step G:** Preparation of ethyl 4-chloro-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridine-6-carboxylate: A suspension of ethyl 7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-oxo-5H-thieno[3,2-c]pyridine-6-carboxylate (3.00 g, 5.37 mmol) in phosphorus oxychloride (10.0 mL, 107 mmol) was stirred at 95 °C for 3 h. The mixture was concentrated in vacuum and diluted with DCM. The mixture was poured into aqueous $NaHCO_3$ solution, and the product was extracted with EtOAc. The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash chromatography on silica gel (EtOAc / petroleum ether=1/6) to give ethyl 4-chloro-7-[4-fluoro-2-(2-methoxyethoxy) phenyl]thieno[3,2-c]pyridine-6-carboxylate (1.09 g, 49% yield). LCMS ESI (+) m/z 410.1 (M+H).

[000420] **Step H:** Preparation of ethyl 4-(2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinolin-6-yl)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridine-6-carboxylate: To a solution of tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (1.48 g, 4.12 mmol), ethyl 4-chloro-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridine-6-carboxylate (1.30 g, 3.17 mmol), and Na_2CO_3 (0.841 g, 7.93 mmol) in 1,4-dioxane (20 mL) and water (2 mL) was added $Pd(dppf)Cl_2$ (220 mg, 0.300 mmol). The mixture was stirred at 95 °C for 16 h under Ar. The mixture was poured into water and the product was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by chromatography on silica gel (EtOAc/petroleum

ether=1/3) to give ethyl-4-(2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinolin-6-yl)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridine-6-carboxylate (1.20 g, 62% yield). LCMS ESI (+) m/z 607.3 (M+H).

[000421] **Step I:** Preparation of 4-(2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinolin-6-yl)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridine-6-carboxylic acid: To a solution of ethyl 4-(2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinolin-6-yl)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridine-6-carboxylate (800 mg, 1.32 mmol) in 3:1:1 mixture of tetrahydrofuran, water and methanol (20.0 mL) was added $LiOH.H_2O$ (554 mg, 13.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours and then concentrated. The residue was dissolved in water. The pH was adjusted to 3 with 1 N HCl. The mixture was extracted with dichloromethane. The combined organic layers were washed water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 4-(2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinolin-6-yl)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridine-6-carboxylic acid (605 mg, 79% yield). LCMS ESI (+) m/z 579.2 (M+H).

[000422] **Step J:** Preparation of tert-butyl 6-[6-(benzyloxycarbonylamino)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate: A solution of 4-(2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinolin-6-yl)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridine-6-carboxylic acid (40 mg, 0.069 mmol), benzyl alcohol (0.036 mL, 0.35 mmol), triethylamine (0.096 mL, 0.69 mmol) and [azido(phenoxy)phosphoryl]oxybenzene (96 mg, 0.35 mmol) in dry toluene (3 mL) was stirred at 25 °C for 30 min. The mixture was stirred at 90 °C for 4 h. The mixture was poured into water and the product was extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (EtOAc/Petroleum ether:1/3) to give tert-butyl 6-[6-(benzyloxycarbonylamino)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (38 mg, 80% yield).

[000423] **Step K:** Preparation of tert-butyl 6-[6-amino-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate: To a solution of tert-butyl 6-[6-(benzyloxycarbonylamino)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (30 mg, 0.044 mmol) in 1,4-dioxane (1 mL) and water (1 mL) was added lithium hydroxide monohydrate (61 mg, 1.4 mmol). The mixture was stirred at 100 °C for 6 h. The mixture was diluted with water and extracted with EtOAc. The organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by Prep-TLC (EtOAc/hexane=1/2) to give tert-butyl 6-[6-amino-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (21 mg, 87% yield). LCMS ESI (+) m/z 550.2 (M+H).

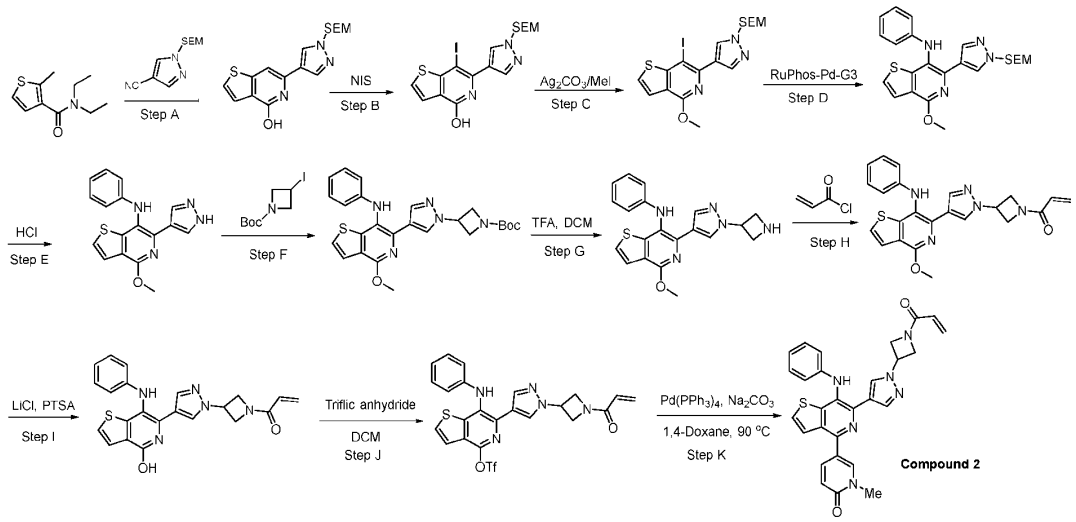
[000424] **Step L:** Preparation of tert-butyl 6-[6-[3-(tert-butoxycarbonylamino)anilino]-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate: To a suspension of tert-butyl 6-[6-amino-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (40 mg, 0.073 mmol), tert-butoxypotassium (16 mg, 0.15 mmol) and tert-butyl N-(3-iodophenyl)carbamate (35 mg, 0.11 mmol) in toluene (2 mL) was added 1,1'-bis(diphenylphosphino)ferrocene (8.1 mg, 0.015 mmol). The mixture was stirred at 100 °C for 10 h under Ar. The mixture was poured into water and extracted with EtOAc. The organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (EtOAc/petroleum ether:1/2) to give tert-butyl 6-[6-[3-(tert-butoxycarbonylamino)anilino]-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (24 mg, 45% yield). LCMS ESI (+) m/z 741.3 (M+H).

[000425] **Step M to Step N:** Preparation of tert-butyl 6-[6-(3-aminoanilino)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate: To a solution of tert-butyl 6-[6-[3-(tert-butoxycarbonylamino)anilino]-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (24 mg, 0.032 mmol) in DCM (2 mL) was added trifluoroacetic acid (0.50 mL, 6.5 mmol). The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated to dryness to give N1-(7-(4-fluoro-2-(2-methoxyethoxy)phenyl)-4-(1,2,3,4-tetrahydroisoquinolin-6-yl)thieno[3,2-c]pyridin-6-yl)benzene-1,3-diamine (30 mg). The crude product was dissolved in THF (2 mL). Aqueous Na_2CO_3 solution (2 mL) and di-tert-butyl dicarbonate (7.1 mg, 0.032 mmol) in THF (1 mL) was added at 0 °C. The mixture was stirred at 0 °C for an additional 1 h. Aqueous $MeNH_2$ (1 mL) was added to quench the reaction. The product was extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by Prep-TLC (EtOAc/petroleum ether:1/2) to give tert-butyl 6-[6-(3-aminoanilino)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (18 mg, 87% yield).

[000426] **Step O:** Preparation of tert-butyl 6-[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-6-[3-(prop-2-enoylamino)anilino]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate: To a solution of tert-butyl 6-[6-(3-aminoanilino)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (12 mg, 0.019 mmol) and triethylamine (0.013 mL, 0.094 mmol) in DCM (2 mL) was added acryloyl chloride (1.9 mg, 0.020 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was poured into water and the product was extracted with EtOAc. The organic fractions were dried over anhydrous Na_2SO_4, concentrated and purified by Prep-TLC (EtOAc/petroleum ether:1/2) to give tert-butyl 6-[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-6-[3-(prop-2-enoylamino)anilino]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (9.6 mg, 74% yield). LCMS ESI (+) m/z 695.2 (M+H).

[000427] Step P: Preparation of N-[3-[[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1,2,3,4-tetrahydroisoquinolin-6-yl)thieno[3,2-c]pyridin-6-yl]amino]phenyl]prop-2-enamide: To a solution of tert-butyl 6-[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-6-[3-(prop-2-enoylamino)anilino]thieno[3,2-c]pyridin-4-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (9.6 mg, 0.014 mmol) in DCM (2 mL) was added trifluoroacetic acid (0.50 mL, 6.5 mmol). The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated and purified by Prep-HPLC to give N-[3-[[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1,2,3,4-tetrahydroisoquinolin-6-yl)thieno[3,2-c]pyridin-6-yl]amino]phenyl]prop-2-enamide (6.6 mg, 81% yield) as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.99 (s, 1H), 7.88 (d, J = 5.4 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 5.6 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 10.7 Hz, 1H), 6.86 - 6.75 (m, 1H), 6.65 - 6.33 (m, 1H), 6.25 - 6.05 (m, 2H), 5.71 - 5.52 (m, 1H), 4.34 - 4.10 (m, 3H), 4.10 - 3.86 (m, 6H), 3.85 - 3.72 (m, 1H), 3.69 - 3.60 (m, 1H), 3.12 - 2.95 (m, 2H), 1.55 - 1.32 (m, 2H). LCMS ESI (+) m/z 595.2 (M+H).

Synthetic Example 2: Synthesis of 5-(6-(1-(1-Acryloylazetidin-3-yl)-1H-pyrazol-4-yl)-7-(phenylamino)thieno[3,2-c] pyridin-4-yl)-1-methylpyridin-2(1H)-one (**Compound 2**)



[000428] Step A: Preparation of 6-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-4-ol: A solution of N,N-diethyl-2-methyl-thiophene-3-carboxamide (1.4 g, 7.1 mmol) in THF (15 mL) was cooled to -78 °C. n-BuLi (2.5 M) (0.68 g, 10.6 mmol) was slowly added at -78 °C and the stirring was continued for 2.0 h. Neat 1-(2-trimethylsilylethoxy methyl)pyrazole-4-carbonitrile (1.9 g, 8.51 mmol) was added into the reaction mixture at -78 °C. The temperature was slowly allowed to rise to room temperature, and it was stirred at room temperature for 5 h. After completion of the reaction, the reaction mixture was cooled to 0 °C and pH was adjusted to 5 with 1.0 N HCl solution. The mixture was stirred at room temperature for 30 min. The reaction mixture was then diluted with EtOAc (100 mL) and the organic

layer was washed with water (2 x 50 mL), followed by saturated brine solution (50 mL). The organic layer was separated and dried over Na_2SO_4. The crude compound was purified by column chromatography eluting with 30% EtOAc in hexanes. The desired fractions were concentrated to dryness in vacuum to get 6-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-4-ol (1.1 g, 44.7%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 1H), 8.53 (s, 1H), 8.02 (s, 1H), 7.66-7.64 (m, 1H), 7.26-7.25 (m, 1H), 6.97 (s, 1H), 5.52 (s, 2H), 3.64 (t, J = 8.4 Hz, 2H), 0.95 (t, J = 8.4 Hz, 2H), -0.00 to -0.02 (m, 9H).

[000429] Step B: Preparation of 7-Iodo-6-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-4-ol: To a stirred solution of 6-[1-(2-Trimethylsilylethoxymethyl)pyrazol-4-yl]thieno[3,2-c]pyridin-4-ol (1.70 g, 4.89 mmol) in DMF (17 mL) at 10 °C. N-Iodosuccinimide (1.32 g, 5.87 mmol) was added at 10 °C. The reaction mixture was slowly warmed to room temperature and continued stirring for 12 h. The reaction mixture was slowly poured into ice cold water (50 mL) and stirred for 10 min. The solid was filtered and dried under vacuum to afford 7-iodo-6-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-4-ol (1.2 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 7.91 (d, J = 5.6 Hz, 1H), 7.37 (d, J = 5.2 Hz, 1H), 5.52 (s, 2H), 3.66 (t, J = 8.4 Hz, 2H), 0.98-0.94 (m, 2H), -0.011 to -0.014 (m, 9H).

[000430] Step C: Preparation of 7-Iodo-4-methoxy-6-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridine: To a stirred solution of 7-iodo-6-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]thieno[3,2-c]pyridin-4-ol (100 mg, 0.211 mmol) in toluene (2 mL) at room temperature were added Ag_2CO_3 (90 mg, 0.33 mmol), and MeI (62 mg, 0.44 mmol). The reaction mixture was heated to 90 °C and stirred for 3 h. The reaction was diluted with EtOAc (10 mL), filtered through a Celite® bed and solvent was removed under reduced pressure. The crude product was purified by column purification to give 7-iodo-4-methoxy-6-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridine (67 mg, 65%) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 0.4 Hz, 1H), 8.33 (d, J = 0.4 Hz, 1H), 7.72 (d, J = 5.2 Hz, 1H), 7.39 (d, J = 5.6 Hz, 1H), 5.50 (s, 2H), 4.12 (s, 3H), 3.68-3.63 (m, 2H), 0.97-0.92 (m, 2H), -0.003 (m, 9H).

[000431] Step D: Preparation of 4-Methoxy-N-phenyl-6-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-7-amine: To a stirred solution of 2-[[4-(7-iodo-4-methoxy-thieno[3,2-c]pyridin-6-yl)pyrazol-1-yl] methoxy]ethyl-trimethyl-silane (2.5 g, 5.1 mmol) in THF (20 mL) at room temperature with N_2-purging, aniline (0.94 mL, 10.3 mmol), Ruphos-Pd-G3 (0.086 g, 0.10 mmol) and t-BuOK (0.69 g, 6.2 mmol) were added. Then the reaction mixture purged with N_2-gas for 10 min. The contents were heated to 100 °C and stirred for 12 h. The reaction mixture was diluted with EtOAc (50 mL) and stirred for 10 min. The solids were filtered and the organic layer was evaporated under reduced pressure. The crude product was purified by column chromatography to afford 4-methoxy-N-phenyl-6-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-7-amine (1.3 g, 53%) as a solid. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.03 (s, 1H), 7.87 (s, 1H), 7.66 (d, J = 5.6 Hz, 1H), 7.46 (d, J = 5.6 Hz, 1H), 7.08-7.04 (m, 2H), 6.61 (t, J = 7.2 Hz, 1H), 6.50-6.47 (m, 2H), 5.38 (s, 2H), 4.12 (s, 3H), 3.46 (t, J = 7.6 Hz, 2H), 0.78 (t, J = 8.4 Hz, 2H), -0.07 (m, 9H).

[000432] **Step E:** Preparation of 4-methoxy-N-phenyl-6-(1H-pyrazol-4-yl)thieno[3,2-c]pyridin-7-amine: To a stirred solution of 6.0 M HCl in isopropanol (1.0 mL) at 0 °C, 4-methoxy-N-phenyl-6-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]thieno[3,2-c]pyridin-7-amine (300 mg, 0.0442 mmol) was added and warmed to room temperature. After 1 h, volatiles were removed under reduced pressure to give 208 mg of 4-methoxy-N-phenyl-6-(1H-pyrazol-4-yl)thieno[3,2-c]pyridin-7-amine which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (bs, 1H), 8.06 (s, 2H), 7.87 (s, 1H), 7.64 (d, J = 5.2 Hz, 1H), 7.46 (d, J = 5.6 Hz, 1H), 7.07 (t, J = 8.0 Hz, 2H), 6.61 (t, J = 7.2 Hz, 1H), 6.48 (d, J = 7.6 Hz, 2H), 4.11 (s, 3H).

[000433] **Step F:** Preparation of tert-butyl 3-(4-(4-methoxy-7-(phenylamino)thieno[3,2-c]pyridin-6-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate: To a stirred solution of 4-methoxy-N-phenyl-6-(1H-pyrazol-4-yl)thieno[3,2-c]pyridin-7-amine (20 mg, 0.062 mmol) in DMF (2 mL) at room temperature were added Cs_2CO_3 (30 mg, 0.092 mmol) and tert-butyl 3-iodoazetidine-1-carboxylate (22 mg, 0.078 mmol). The temperature was increased to 80 °C and stirred at same temperature for 12 h. The contents were poured into ice cold water (5 mL). The product was extracted into EtOAc (10 mL), washed with brine (5 mL) and the solvent was removed under reduced pressure followed by a preparative TLC purification to get tert-butyl 3-(4-(4-methoxy-7-(phenylamino)thieno[3,2-c]pyridin-6-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate (10 mg, 35%) as a solid. LCMS ESI (+) m/z 378.4 (M-Boc+H).

[000434] **Step G:** Preparation of 6-(1-(azetidin-3-yl)-1H-pyrazol-4-yl)-4-methoxy-N-phenylthieno[3,2-c]pyridin-7-amine: To a stirred solution of tert-butyl 3-[4-(7-anilino-4-methoxy-thieno[3,2-c]pyridin-6-yl)pyrazol-1-yl]azetidine-1-carboxylate (20 mg, 0.042 mmol) in dichloromethane (1 mL) at 0 °C was added trifluoroacetic acid (0.016 mL, 0.21 mmol). It was allowed to warm to room temperature and stirred at same temperature for 12 h. The volatiles were removed, co-evaporated with dichloromethane (5 mL). The crude 6-(1-(azetidin-3-yl)-1H-pyrazol-4-yl)-4-methoxy-N-phenylthieno[3,2-c]pyridin-7-amine (15 mg) was used as such in the next step without any further purification.

[000435] **Step H:** Preparation of 1-(3-(4-(4-methoxy-7-(phenylamino)thieno[3,2-c]pyridin-6-yl)-1H-pyrazol-1-yl)azetidin-1-yl)prop-2-en-1-one: To a stirred solution of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-4-methoxy-N-phenyl-thieno[3,2-c]pyridin-7-amine (15 mg, 0.040 mmol) in dichloromethane (1 mL) at 0 °C was added N,N-diisopropylethylamine (0.021 mL, 0.12 mmol) followed by acryloyl chloride (0.0032 mL, 0.040 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. The solvents were removed and the crude product was purified by preparative TLC to give 1-(3-(4-(4-methoxy-7-(phenylamino)thieno[3,2-c]pyridin-6-yl)-1H-pyrazol-1-yl)azetidin-1-yl)prop-2-en-1-one (5 mg, 30%) as a

solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.07 (s, 1H), 7.86 (s, 1H), 7.66 (d, J = 5.6 Hz, 1H), 7.46 (d, J = 5.2 Hz, 1H), 7.09-7.05 (m, 2H), 6.62 (t, J = 7.2 Hz, 1H), 6.50-6.47 (m, 2H), 6.37-6.31 (m, 1H), 6.16-6.11 (m, 1H), 5.72-5.61 (m, 1H), 5.36-5.29 (m, 1H), 4.66 (t, J = 8.8 Hz, 1H), 4.44-4.34 (m, 2H), 4.18-4.14 (m, 1H), 4.11 (s, 3H); LCMS ESI (+) m/z 432.4 (M+H).

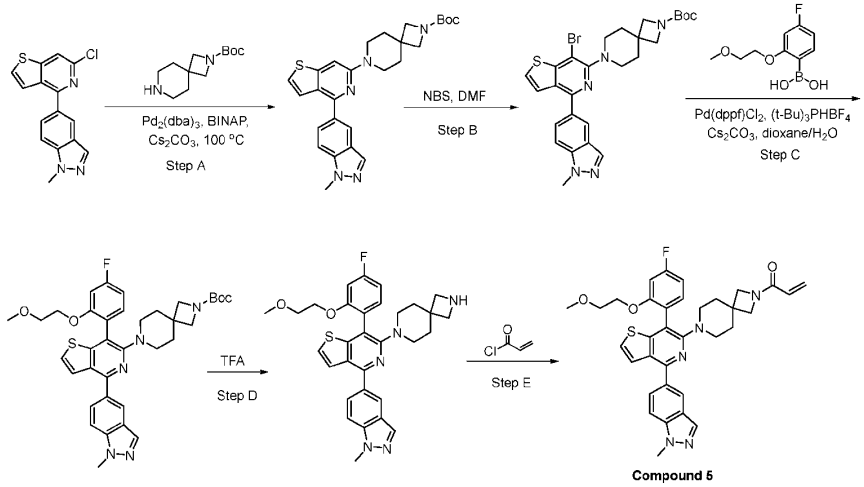
[000436] Step I: Preparation of 1-(3-(4-(4-hydroxy-7-(phenylamino)thieno[3,2-c]pyridin-6-yl)-1H-pyrazol-1-yl)azetidin-1-yl)prop-2-en-1-one: To a stirred solution of 1-[3-[4-(7-anilino-4-methoxy-thieno[3,2-c]pyridine-6-yl)pyrazol-1-yl]azetidin-1-yl]prop-2-en-1-one (150 mg, 0.348 mmol) in DMF (15 mL) were added lithium chloride (74 mg, 1.7 mmol) and *para*-toluenesulfonic acid (299 mg, 1.74 mmol) at room temperature. The contents were heated to 120 °C and stirred for 12 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The organic layer was washed with brine solution (5 mL) and solvent was removed under reduced pressure. A preparative TLC purification afforded 1-(3-(4-(4-hydroxy-7-(phenylamino)thieno[3,2-c]pyridin-6-yl)-1H-pyrazol-1-yl)azetidin-1-yl)prop-2-en-1-one (15 mg, 10%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.44 (d, J = 0.4 Hz, 1H), 8.03 (s, 1H), 7.61 (s, 1H), 7.51 (d, J = 5.2 Hz, 1H), 7.47 (d, J = 5.2 Hz, 1H), 7.09-7.05 (m, 2H), 6.63-6.59 (m, 1H), 6.53-6.51 (m, 2H), 6.37-6.30 (m, 1H), 6.16-6.11 (m, 1H), 5.70 (dd, J = 10.0, 2.0 Hz, 1H), 5.29-5.22 (m, 1H), 4.66 (t, J = 8.8 Hz, 1H), 4.40-4.35 (m, 2H), 4.14-4.10 (m, 1H).

[000437] Step J: Preparation of 6-(1-(1-acryloylazetidin-3-yl)-1H-pyrazol-4-yl)-7-(phenylamino)thieno[3,2-c]pyridin-4-yl trifluoromethanesulfonate: A solution of 1-(3-(4-(4-hydroxy-7-(phenylamino)thieno[3,2-c]pyridin-6-yl)-1H-pyrazol-1-yl)azetidin-1-yl)prop-2-en-1-one (30 mg, 0.072 mmol) in dichloromethane (1 mL) was cooled to 0 °C and triethylamine (15 mg, 0.14 mmol) and trifluoromethanesulfonic anhydride (40 mg, 0.14 mmol) were added. The reaction mixture was stirred at same temperature for 5 h. The volatiles were removed under reduced pressure and the crude product was purified by preparative TLC to get 6-(1-(1-acryloylazetidin-3-yl)-1H-pyrazol-4-yl)-7-(phenylamino)thieno[3,2-c]pyridin-4-yl trifluoromethanesulfonate (8 mg, 20%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 7.6 Hz, 2H), 8.02 (s, 1H), 7.98 (d, J = 5.6 Hz, 1H), 7.54 (d, J = 5.6 Hz, 1H), 7.17-7.13 (m, 2H), 6.77-6.73 (m, 1H), 6.61 (dd, J = 8.4, 0.8 Hz, 2H), 6.37-6.31 (m, 1H), 6.16-6.11 (m, 1H), 5.70 (dd, J = 10.4, 2.4 Hz, 1H), 5.42-5.35 (m, 1H), 4.65 (t, J = 8.8 Hz, 1H), 4.43-4.34 (m, 2H), 4.16-4.13 (m, 1H).

[000438] Step K: Preparation of 5-(6-(1-(1-acryloylazetidin-3-yl)-1H-pyrazol-4-yl)-7-(phenylamino) thieno[3,2-c] pyridin-4-yl)-1-methylpyridin-2(1H)-one: A solution of [7-anilino-6-[1-(1-prop-2-enoylazetidin-3-yl)pyrazol-4-yl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate (8.0 mg, 0.015 mmol) in 1,4-dioxane (1 mL) was purged with N_2 for 5 min. Sodium carbonate (4.6 mg, 0.044 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (4.4 mg, 0.019 mmol)

and tetrakis(triphenylphosphine)palladium (2.5 mg, 0.0022 mmol) were added at room temperature. The reaction mixture was heated to 90 °C and stirred for 3 h. The reaction mixture was diluted with 1,4-dioxane (15 mL), filtered through Celite® bed and solvent was removed under reduced pressure. The crude product was purified by preparative TLC with 10% DCM in ethyl acetate as the eluent to give 5-(6-(1-(1-acryloylazetidin-3-yl)-1H-pyrazol-4-yl)-7-(phenylamino)thieno[3,2-c]pyridin-4-yl)-1-methylpyridin-2(1H)-one (2.85 mg, 38%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.04 (s, 1H), 7.99-7.79 (m, 2H), 7.54-7.47 (m, 2H), 7.24-7.20 (m, 2H), 6.89 (t, J =7.4 Hz, 1H), 6.76-6.73 (m, 1H), 6.70-6.68 (m, 2H), 6.40-6.35 (m, 1H), 6.23-6.16 (m, 1H), 5.72 (dd, J = 10.2 Hz, 1H), 5.59 (s, 1H), 5.16-5.09 (m, 1H), 4.65-4.51 (m, 3H), 4.45-4.41 (m, 1H), 3.70 (s, 3H). LCMS ESI (+) m/z 509.4 (M+H).

Synthetic Example 3: Synthesis of 1-[7-[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonan-2-yl]prop-2-en-1-one (**Compound 5**)



[000439] **Step A:** Preparation of tert-butyl 7-[4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate: 4-fluoro-2-hydroxybenzoic acid (25.0 g, 392 mmol) was dissolved in acetone (500 mL). A mixture of 6-chloro-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine (200 mg, 0.667 mmol), tert-butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate (166 mg, 0.734 mmol), $Pd_2(dba)_3$ (61 mg, 0.067 mmol), BINAP (83 mg, 0.13 mmol) and cesium carbonate (435 mg, 1.33 mmol) in toluene (6 mL) was stirred at 100 °C for 18 hours under N_2. The mixture was concentrated and purified by column chromatography on silica gel (DCM:MeOH=50:1 to 20:1) to give tert-butyl 7-[4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (180 mg, 55% yield). LCMS ESI (+) m/z 490.3 (M+H).

[000440] **Step B:** Preparation of product tert-butyl 7-[7-bromo-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate: To a stirred solution of tert-butyl 7-[4-(1-

methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (130 mg, 0.266 mmol) in DMF (2 mL) was added NBS (47 mg, 0.27 mmol) at 0 °C. After that the mixture was stirred at 0 °C for 30 min. The mixture was quenched with water (4 mL) and extracted with EtOAc. The combined organic fractions were washed with saturated brine solution, dried (Na_2SO_4) and concentrated to dryness to give crude product tert-butyl 7-[7-bromo-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (200 mg), which was used in the next step without further purification. LCMS ESI (+) m/z 568.2/570.2 (M+H).

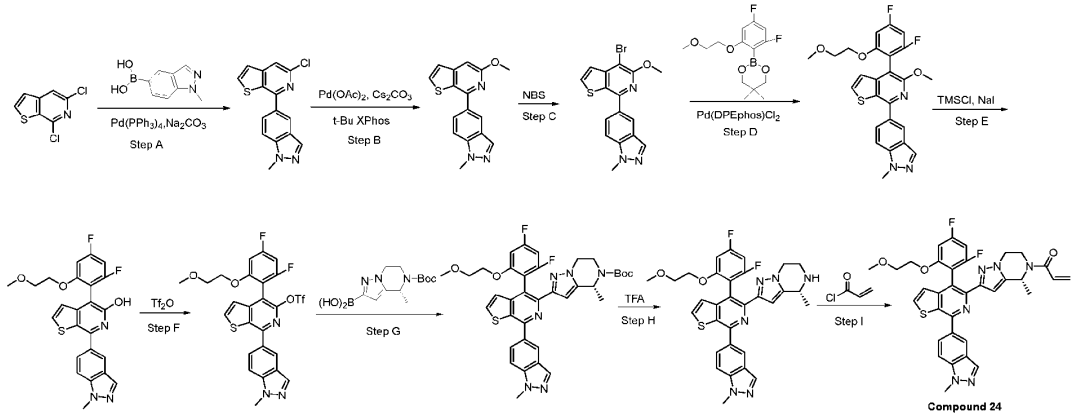
[000441] Step C: Preparation of tert-butyl 7-[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate: To a stirred solution of tert-butyl 7-[7-bromo-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (20 mg, 0.035 mmol) in 1,4-dioxane (2 mL)/water (0.2 mL) were added [4-fluoro-2-(2-methoxyethoxy)phenyl]boronic acid (15 mg, 0.070 mmol), 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane complex (2.6 mg, 0.0035 mmol), tri-tert-butylphosphine tetrafluoroborate (2.0 mg, 0.0070 mmol) and cesium carbonate (23 mg, 0.070 mmol). The mixture was heated to 90 °C and stirred for 12 hours under N_2. The mixture was concentrated and the residue was purified by Prep-TLC (petroleum ether:EtOAc=1:1) to give tert-butyl 7-[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (15 mg, 65% yield). LCMS ESI (+) m/z 658.4 (M+H).

[000442] Step D: Preparation of 6-(2,7-diazaspiro[3.5]nonan-7-yl)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine: To a solution of tert-butyl 7-[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonane-2-carboxylate (15 mg, 0.023 mmol) in DCM (2 mL) was added TFA (0.50 mL, 6.5 mmol). The mixture was stirred at 10 °C for 30 min. The mixture was concentrated to dryness to give crude 6-(2,7-diazaspiro[3.5]nonan-7-yl)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine (15 mg) which was used without further purification. LCMS ESI (+) m/z 558.3 (M+H).

[000443] Step E: Preparation of 1-[7-[7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonan-2-yl]prop-2-en-1-one: To a stirred solution of 6-(2,7-diazaspiro[3.5]nonan-7-yl)-7-[4-fluoro-2-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine (15 mg, 0.027 mmol) in ethyl acetate (2 mL)/water (2 mL) was added sodium carbonate to adjust the pH to 8. Additional sodium carbonate (5.7 mg, 0.054 mmol) was added followed by a solution of acryloyl chloride (0.0026 mL, 0.032 mmol) in DCM (0.2 mL) dropwise at 0 °C. The mixture was stirred at 10 °C for 30 min. The mixture was extracted with EtOAc, dried over Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to give 1-[7-[7-[4-fluoro-2-(2-

methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-2,7-diazaspiro[3.5]nonan-2-yl]prop-2-en-1-one (8.7 mg, 52% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR(400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.22 (s, 1H), 7.94 (dd, J = 8.8, 1.6 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 5.6 Hz, 1H), 7.60 (d, J = 5.6 Hz, 1H), 7.45 (dd, J = 8.4, 6.6 Hz, 1H), 7.12 (dd, J = 11.0, 2.2 Hz, 1H), 6.94 (td, J = 8.2, 2.4 Hz, 1H), 6.35 - 6.29 (m, 1H), 6.22 (dd, J = 17.0, 2.0 Hz, 1H), 5.71 (dd, J = 10., 2.0 Hz, 1H), 4.29 - 4.24 (m, 1H), 4.17 (s, 3H), 4.16 - 4.13 (m, 1H), 3.98 (s, 2H), 3.74 (s, 2H), 3.58 (t, J = 4.0 Hz, 2H), 3.18 (s, 3H), 1.76 - 1.73 (m, 4H). LCMS ESI (+) m/z 612.2 (M+H).

Synthetic Example 4: Synthesis of 7-[2-(2-methoxyethoxy)phenyl]-4-(1-methylsulfonyl-4-piperidyl)thieno[2,3-d]pyridazine (**Compound 24**)



[000444] **Step A**: Preparation of 5-chloro-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine: A solution of 5,7-dichlorothieno[2,3-c]pyridine (1.00 g, 4.90 mmol), (1-methylindazol-5-yl)boronic acid (1.12 g, 6.37 mmol), tetrakis(triphenylphosphine)palladium(0) (566 mg, 0.490 mmol) and sodium carbonate (1.04 g, 9.80 mmol) in 1,4-dioxane (20 mL)/water (2 mL) was stirred at 95 °C under N_2 for 2 hours. The mixture was diluted with EtOAc, washed with brine solution, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether:EtOAc=5:1 to 2:1) to give 5-chloro-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine (707 mg, 48% yield). LCMS ESI (+) m/z 300.0 (M+H).

[000445] **Step B**: Preparation of 5-methoxy-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine: A solution of 5-chloro-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine (707 mg, 2.36 mmol), palladium(II) acetate (53 mg, 0.24 mmol), t-Bu XPhos (200 mg, 0.472 mmol) and cesium carbonate (1.54 g, 4.72 mmol) in 1,4-dioxane (4 mL)/methanol (8 mL) was stirred at 85 °C under N_2 for 10 hours. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc=2:1) to give 5-methoxy-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine (380 mg, 55% yield). LCMS ESI (+) m/z 296.1 (M+H).

[000446] **Step C**: Preparation of 4-bromo-5-methoxy-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine: To a stirred solution of 5-methoxy-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine (380 mg, 1.29 mmol) in DMF (2 mL) at 0 °C was added NBS (275 mg, 1.54 mmol). The mixture was stirred at 0 °C for 30 min. The reaction was quenched by water and extracted with EtOAc. The combined organics were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc=2:1) to give 4-bromo-5-methoxy-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine (440 mg, 91% yield). LCMS ESI (+) m/z 374.0 (M+H).

[000447] **Step D**: Preparation of 4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5-methoxy-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine: A solution of 4-bromo-5-methoxy-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine (100 mg, 0.267 mmol), 2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5,5-dimethyl-1,3,2-dioxaborinane (241 mg, 0.802 mmol), $Pd(DPEphos)Cl_2$ (19 mg, 0.027 mmol) and Cs_2CO_3 (174 mg, 0.534 mmol) in 1,4-dioxane (6 mL) was stirred at 95 °C under N_2 for 12 hours. The mixture was concentrated and purified by preparative TLC (petroleum ether:EtOAc=2:1) to give 4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5-methoxy-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine (52 mg, 40% yield). LCMS ESI (+) m/z 482.2 (M+H).

[000448] **Step E**: Preparation of 4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridin-5-ol: A solution of 4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5-methoxy-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridine (47 mg, 0.098 mmol), trimethylchlorosilane (0.12 mL, 0.98 mmol) and sodium iodide (44 mg, 0.29 mmol) in acetonitrile (6 mL) was stirred at 80 °C for 1 hour. The mixture was cooled to rt. Aqueous Na_2SO_3 solution was added to quench the reaction. The mixture was extracted with EtOAc, washed by brine, dried over Na_2SO_4 and concentrated to give crude 4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridin-5-ol (53 mg) which was used in the next step without further purification. LCMS ESI (+) m/z 468.2 (M+H).

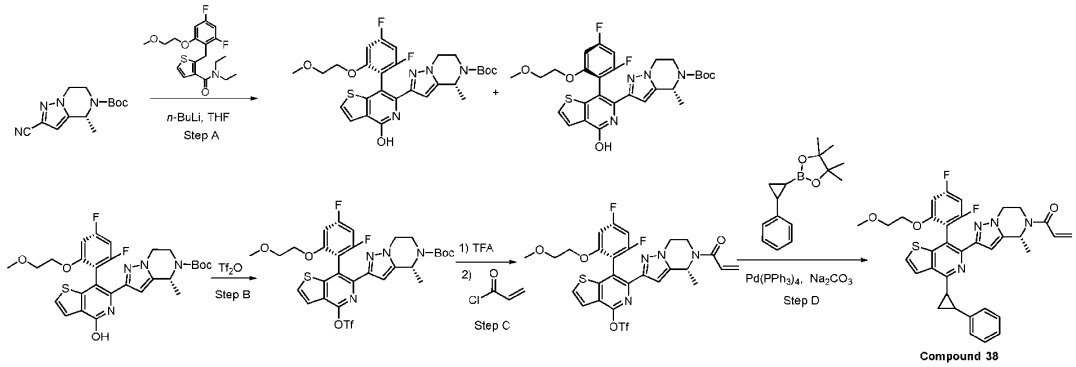
[000449] **Step F**: Preparation of [4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridin-5-yl] trifluoromethanesulfonate: To a stirred solution of 4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridin-5-ol (48 mg, 0.10 mmol) and triethylamine (0.057 mL, 0.41 mmol) in DCM (2 mL) was added trifluoromethanesulfonic anhydride (0.035 mL, 0.21 mmol) at 0 °C. The mixture was stirred at 5 °C for 30 min. Saturated aqueous $NaHCO_3$ solution was added and the reaction was stirred for additional 5 min. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (petroleum ether/EtOAc=1/1) to give [4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridin-5-yl] trifluoromethanesulfonate (40 mg, 65% yield). LCMS ESI (+) m/z 600.2 (M+H).

[000450] **Step G**: Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A solution of [4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridin-5-yl] trifluoromethanesulfonate (30 mg, 0.050 mmol), [(4R)-5-tert-butoxycarbonyl-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]boronic acid (28 mg, 0.100 mmol), palladium(II) acetate (1.1 mg, 0.0050 mmol), Xphos (4.8 mg, 0.010 mmol) and potassium carbonate (21 mg, 0.15 mmol) in acetonitrile (2 mL)/water (1 mL) was stirred at 100 °C for 12 hours under N_2. The mixture was concentrated and purified by Prep-TLC (DCM / MeOH = 25/1) to give tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (5.0 mg, 15% yield). LCMS ESI (+) m/z 687.4 (M+H).

[000451] **Step H**: Preparation of 4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)-5-[(4R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl]thieno[2,3-c]pyridine: To a solution of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (5.0 mg, 0.0073 mmol) in DCM (2 mL) was added TFA (1.0 mL, 13 mmol) at 5 °C. The mixture was stirred at this temperature for 1 hour, The mixture was concentrated to dryness to give crude 4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)-5-[(4R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl]thieno[2,3-c]pyridine (5.0 mg). LCMS ESI (+) m/z 587.2 (M+H).

[000452] **Step I**: Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of 4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-(1-methylindazol-5-yl)-5-[(4R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl]thieno[2,3-c]pyridine (5.0 mg, 0.0085 mmol) in ethyl acetate (2 mL)/water (2 mL) was added Na_2CO_3 aqueous solution to adjust the pH to 8. Sodium carbonate (1.8 mg, 0.017 mmol) was added, followed by acryloyl chloride (0.00083 mL, 0.010 mmol) in DCM (1 mL) dropwise at 0 °C. The mixture was stirred at 10 °C for 30 min. The mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-HPLC to give tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (1.9 mg, 34% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR(400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.33 (dd, J = 5.6, 1.6 Hz, 1H), 8.25 (s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 5.4 Hz, 1H), 6.95-6.74 (m, 3H), 6.29 (d, J = 15.2 Hz, 1H), 6.04 (d, J = 5.9 Hz, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.70-5.48 (m, 1H), 4.33-4.29 (m, 1H), 4.18 (s, 3H), 4.14-3.98 (m, 3H), 3.44 (t, J = 4.2 Hz, 2H), 3.09 (d, J = 6.6 Hz, 3H), 1.44-1.43 (m, 3H). LCMS ESI (+) m/z 641.3 (M+H).

Synthetic Example 5: Synthesis of 1-((4R)-2-((7S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(2-phenylcyclopropyl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 38**)



[000453] **Step A:** Preparation of (tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-hydroxythieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo [1,5-a]pyrazine-5(4H)-carboxylate: To a solution of 2-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]-N,N-diethyl-thiophene-3-carboxamide (155 g, 404 mmol) in THF (1000 mL) was added n-butyllithium (157 mL, 2.5 M in hexanes, 393 mmol) at -60 °C. The mixture was stirred at this temperature for 30 min, and then tert-butyl (R)-2-cyano-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (97.80 g, 373.0 mmol) in THF (200 mL) was added below -50 °C. The resulting mixture was stirred at 0 °C for 3 h. Water (1.5 L) was added to quench the reaction. 1 N HCl aqueous solution was added to adjust the pH to 5-6. The product was extracted with EtOAc (1.2 L x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether:5/2) three times to give the less polar isomer tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-hydroxythieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (72.0 g, 34% yield) and the more polar isomer tert-butyl (R)-2-((R)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-hydroxythieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (58.0 g, 27% yield). LCMS ESI (+) m/z 573.2 (M+H).

[000454] **Step B**: Preparation of tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(((trifluoromethyl) sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-hydroxythieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (20.00 g, 34.90 mmol) and pyridine (13.80 g, 174.5 mmol) in DCM (150 mL) was added trifluoromethanesulfonic anhydride (12.0 mL, 69.9 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was poured into water. The product was extracted with DCM, dried over anhydrous Na_2SO_4,

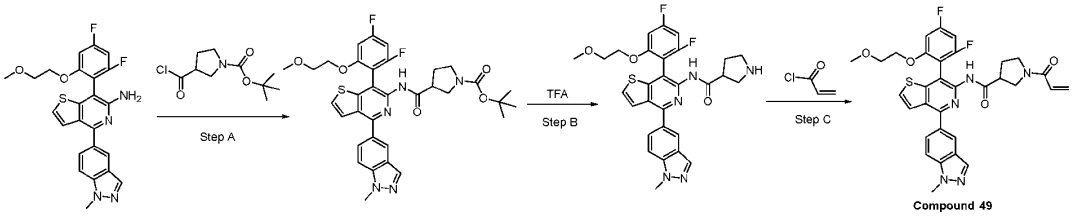
filtered and concentrated. The residue was purified by silica gel column chromatography eluting with 20% EtOAc in petroleum ether to give tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (22.0 g, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 5.6 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 6.54-6.60 (m, 2H), 6.41-6.50 (m, 1H), 5.21-5.40 (m, 1H), 4.25-4.48 (m, 1H), 3.82-4.05 (m, 4H), 3.32-3.39 (m, 2H), 3.15-3.30 (m ,1H), 3.10 (s, 1H), 1.49 (s, 9H), 1.42 (d, J = 6.6 Hz, 3H). LCMS ESI (+) m/z 705.2 (M+H).

[000455] **Step C**: Preparation of tert-butyl (4S,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy) phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (1.04 g, 1.48 mmol) in DCM (6 mL) was added trifluoroacetic acid (2.0 mL). The mixture was stirred at 24 °C for 30 minutes. The mixture was concentrated to dryness. The residue was taken up in ethyl acetate (10 mL) and water (10 mL). $NaHCO_3$ (1.29 g, 15.3 mmol) was added, followed by a solution of acryloyl chloride (0.160 g, 1.78 mmol) in DCM (2 mL) dropwise at 0 °C. The mixture was stirred for 0.5 hour at 0 °C. The reaction mixture was diluted with DCM, washed with water and brine and dried (Na_2SO_4) before concentration to dryness. The crude was purified by column chromatography on silica gel eluting with 20% EtOAc in petroleum ether to give tert-butyl (4S,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (0.750 g, 77% yield over two steps). LCMS ESI (+) m/z 659.1 (M+H).

[000456] **Step D**: Preparation of 1-((4R)-2-((7S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(2-phenylcyclopropyl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: A mixture of 4,4,5,5-tetramethyl-2-(2-phenylcyclopropyl)-1,3,2-dioxaborolane (18 mg, 0.073 mmol), tert-butyl (4S,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (40 mg, 0.061 mmol), Na_2CO_3 (19 mg, 0.18 mmol) and $Pd(PPh_3)_4$ (11 mg, 0.0091 mmol) were stirred in 1,4-dioxane (5 mL) and water (0.5 mL) at 100 °C under N_2 for 1 h. The reaction was concentrated to dryness. The residue was then purified by flash column chromatography eluting 5% MeOH in DCM followed by prep-HPLC to give 1-((4R)-2-((7S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(2-phenylcyclopropyl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one trifluoroacetate (4.8 mg, 13% yield) as a mixture of two diastereomers. ^{1}H NMR (400 MHz, CD_3OD) δ 7.88 – 7.71 (m, 2H), 7.44 – 7.17 (m, 5H), 6.96 – 6.80 (m, 2H), 6.78 – 6.67 (m, 1H), 6.31 (d, J = 16.2 Hz, 1H), 6.12 (d, J = 13.6 Hz, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.62 (d, J = 84.7 Hz, 1H), 4.42

(s, 1H), 4.24 (d, J = 12.4 Hz, 1H), 4.17 – 3.94 (m, 3H), 3.76 (s, 1H), 3.43 (dd, J = 9.1, 4.6 Hz, 2H), 3.05 (s, 3H), 3.00 – 2.88 (m, 2H), 2.25 – 2.10 (m, 1H), 1.80 – 1.70 (m, 1H), 1.43 (s, 3H). LCMS ESI (+) m/z 627.3 (M+H).

Synthetic Example 6: Synthesis of tert-butyl 3-((7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)carbamoyl)pyrrolidine-1-carboxylate (**Compound 49**)



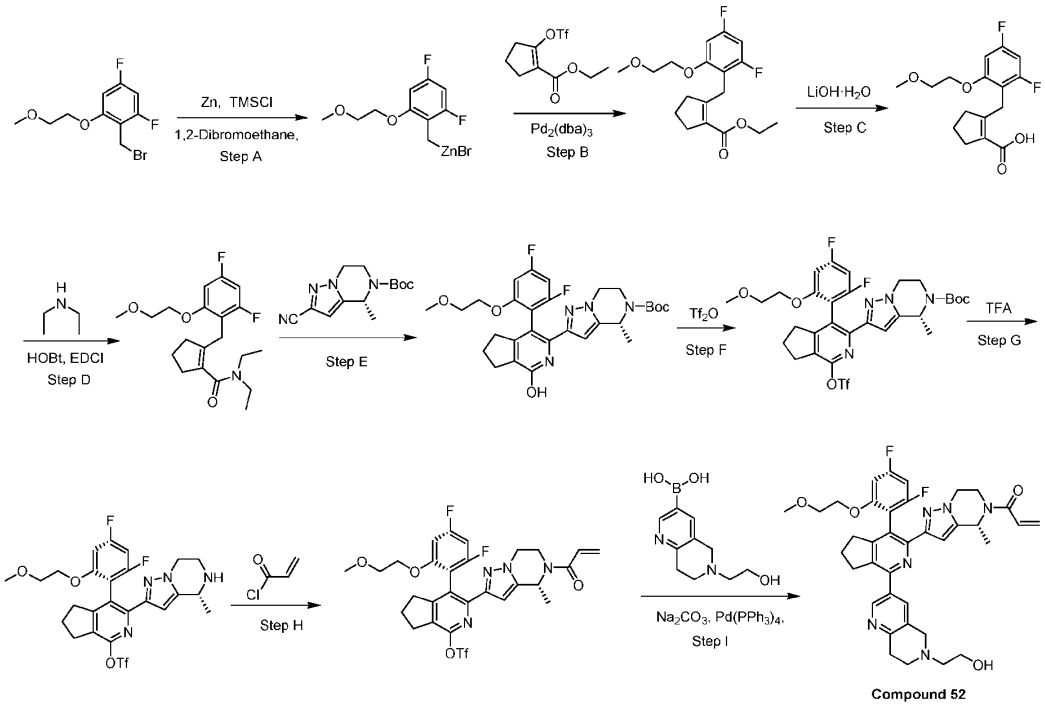
[000457] Step A: Preparation of tert-butyl 3-((7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)carbamoyl)pyrrolidine-1-carboxylate: To a stirring solution of 7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-amine (100 mg, 0.214 mmol) and Et_3N (65 mg, 0.64 mmol) in DCM (5 mL) was added tert-butyl-3-chlorocarbonylpyrrolidine-1-carboxylate (75 mg, 0.32 mmol), and the mixture was stirred at rt for 12 h. Upon completion of the reaction, the mixture was diluted with H_2O and extracted with DCM. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (MeOH/DCM = 0 to 10%) to give tert-butyl 3-((7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)carbamoyl)pyrrolidine-1-carboxylate (80 mg, 53% yield) as a brown oil. LCMS ESI (+) m/z = 664.3 (M+H).

[000458] Step B: Preparation of N-(7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)pyrrolidine-3-carboxamide: A mixture of tert-butyl 3-[[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]carbamoyl]pyrrolidine-1-carboxylate (80 mg, 0.12 mmol) and TFA (785 mg, 2.41 mmol) in DCM (5 mL) was stirred at rt for 3 h. Upon completion of the reaction, the reaction mixture was concentrated in vacuo. The mixture was diluted with H_2O, then made basic with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give N-(7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)pyrrolidine-3-carboxamide (65 mg, 90% yield). LCMS ESI (+) m/z = 564.0 (M+H).

[000459] Step C: Preparation of tert-butyl 3-((7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)carbamoyl)pyrrolidine-1-carboxylate: To a stirring solution of N-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-

6-yl]pyrrolidine-3-carboxamide (80 mg, 0.14 mmol) and DIPEA (0.076 mL, 0.43 mmol) in DCM (10 mL) was added acryloyl chloride (0.017 mL, 0.21 mmol) at 0 °C. The resulting mixture was stirred at rt for 1 h. The mixture was concentrated and diluted with H_2O. The mixture was made basic by saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (MeOH/DCM = 0 to 10%) to give tert-butyl 3-((7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)carbamoyl)pyrrolidine-1-carboxylate (19.3 mg, 21% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.16 (s, 1H), 7.97 (dd, J = 8.8, 1.4 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.68 (d, J = 5.6 Hz, 1H), 6.94 – 6.72 (m, 2H), 6.61 – 6.44 (m, 1H), 6.25 (ddd, J = 16.8, 5.5, 1.9 Hz, 1H), 5.72 (dd, J = 10.5, 1.9 Hz, 1H), 4.26 – 4.05 (m, 5H), 3.78 – 3.41 (m, 6H), 3.25 – 3.10(m, 4H), 2.20 – 1.95 (m, 2H). LCMS ESI (+) m/z 618.1 (M+H).

Synthetic Example 7: Synthesis of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(6-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 52**)



[000460] **Step A**: Preparation of (2,4-difluoro-6-(2-methoxyethoxy)benzyl)zinc(II) bromide: A mixture of Zn (11.9 g, 184 mmol) and 1,2-dibromoethane (1.72 g, 9.18 mmol) in DMF (80 mL) was stirred at 80 °C for 20 min. TMSCl (166 mg, 1.53 mmol) was added at rt. The resulting mixture was stirred at rt for 30

min. A solution of 2-(bromomethyl)-1,5-difluoro-3-(2-methoxyethoxy)benzene (4.30 g, 15.3 mmol) in DMF was added. The mixture was stirred at rt for 1 h and then used in next step directly.

[000461] **Step B**: Preparation of ethyl 2-(2,4-difluoro-6-(2-methoxyethoxy)benzyl)cyclopent-1-ene-1-carboxylate: A mixture of bromo-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]zinc (7.95 g, 22.9 mmol), ethyl 2-(trifluoromethylsulfonyloxy)cyclopentene-1-carboxylate (4.41 g, 15.3 mmol), tri(o-tolyl)phosphine (465 mg, 1.53 mmol) and $Pd_2(dba)_3$ (1.40 g, 1.53 mmol) in DMF (80 mL) was stirred at rt for 12 h. Water (100 mL) was added. The resulting mixture was filtered. The filtrate was poured into water and extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether = 0 to 20%) to give ethyl 2-(2,4-difluoro-6-(2-methoxyethoxy)benzyl)cyclopent-1-ene-1-carboxylate (4.10 g, 75% yield). LCMS ESI (+) m/z 363.1 (M+H).

[000462] **Step C**: Preparation of tert-butyl (6R)-2-(7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(3-((dimethylamino)methyl)bicyclo[1.1.1]pentan-1-yl)thieno[3,2-c]pyridin-6-yl)-6-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A mixture of ethyl 2-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]cyclopentene-1-carboxylate (4.00 g, 11.8 mmol) and $LiOH•H_2O$ (4.93 g, 118 mmol) in 1,4-dioxane (32 mL) and water (8 mL) was stirred at rt for 12 h. The pH was adjusted to 2 by adding 1 N HCl solution, The aqueous layer was extracted with EtOAc to give crude 2-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]cyclopentene-1-carboxylic acid (3.00 g, 78% yield). LCMS ESI (+) m/z 335.0 (M+Na).

[000463] **Step D**: Preparation of 2-(2,4-difluoro-6-(2-methoxyethoxy)benzyl)-N,N-diethylcyclopent-1-ene-1-carboxamide: A solution of diethylamine (3.00 mL, 28.8 mmol), 2-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]cyclopentene-1-carboxylic acid (6.00 g, 19.2 mmol), EDCI (7.37 g, 38.4 mmol), HOBT (5.18 g, 38.4 mmol) and TEA (13.0 mL, 96.1 mmol) in DMF (150 mL) was stirred at 25 °C for 16 h. The resulting mixture was concentrated and partitioned between EtOAc and water. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on silica gel (EtOAc/petroleum ether= 0 to 50%) to give 2-(2,4-difluoro-6-(2-methoxyethoxy)benzyl)-N,N-diethylcyclopent-1-ene-1-carboxamide (4.80 g, 65% yield). LCMS ESI (+) m/z 368.1 (M+H).

[000464] **Step E**: Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a stirred solution of 2-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]-N,N-diethyl-cyclopentene-1-carboxamide (924 mg, 2.52 mmol) in THF (6 mL) was added n-BuLi (2.5 M in hexanes, 1.10 mL, 2.74 mmol) at -60 °C. The mixture was stirred at -60 °C for 20 min, and then a solution of tert-butyl (4R)-2-cyano-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (600 mg, 2.29 mmol)

in THF (0.5 mL) was added. The resulting mixture was stirred at rt for 3 h. Upon completion of the reaction, the resulting mixture was poured into water. The reaction was acidified by 1 N HCl solution and extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/DCM = 0 to 10%) to give tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (260 mg, 18% yield). LCMS ESI (+) m/z 557.1 (M+H).

[000465] **Step F**: Preparation of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-1-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (220 mg, 0.395 mmol) and pyridine (0.430 mL, 3.95 mmol) in DCM (5 mL) was added trifluoromethanesulfonic anhydride (0.100 mL, 0.593 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated and diluted with EtOAc. The mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether: 1/8) to separate the two diastereomers. One diastereomer, tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (50 mg), was obtained in 18% yield. LCMS ESI (+) m/z 689.2 (M+H).

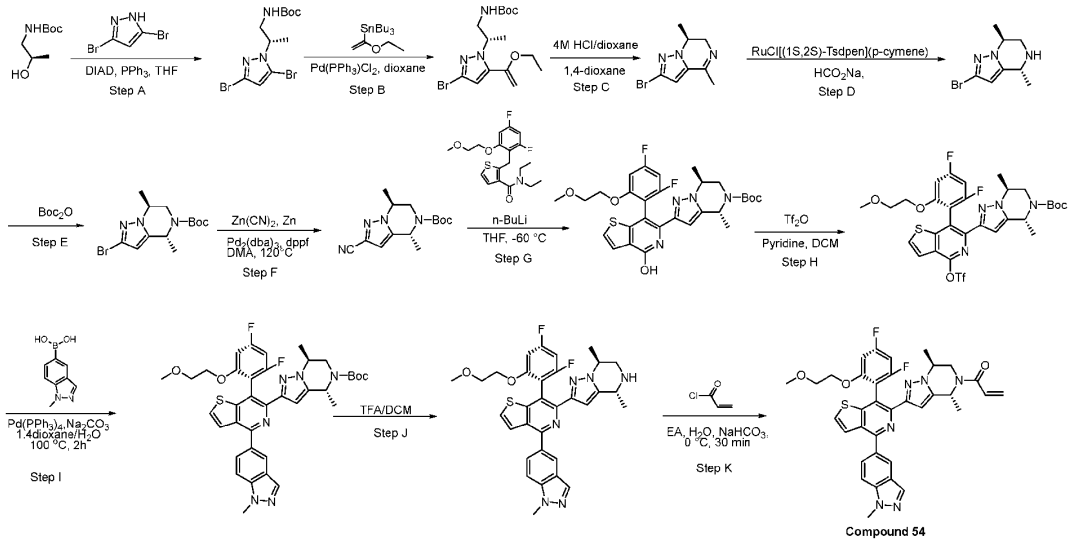
[000466] **Step G**: Preparation of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-yl trifluoromethanesulfonate: A mixture of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (70 mg, 0.10 mmol) and TFA (0.39 mL) was stirred in DCM (2 mL) at 25 °C for 1 h. The reaction was concentrated to give crude (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-yl trifluoromethanesulfonate (70 mg, 94% yield), which was used in the next step without further purification. LCMS ESI (+) m/z 589.1 (M+H).

[000467] **Step H**: Preparation of (R)-3-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-yl trifluoromethanesulfonate: To a solution of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-yl trifluoromethanesulfonate (70 mg, 0.12 mmol) and DIEA (0.050 mL, 0.36 mmol) in DCM (5 mL) was

added acryloyl chloride (0.014 mL, 0.18 mmol). The resulting mixture was stirred at -60 °C for 1 hour. The reaction mixture was poured into saturated $NaHCO_3$ (30 mL). The mixture was extracted with DCM. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by flash column chromatography on silica gel eluting with 50% EtOAc in hexanes to give (R)-3-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-yl trifluoromethane sulfonate (40 mg, 52% yield). LCMS ESI (+) m/z 643.2 (M+H).

[000468] **Step I**: Preparation of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(6-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: A mixture of (R)-3-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[c]pyridin-1-yl trifluoromethane sulfonate (30 mg, 0.047 mmol), [6-(2-hydroxyethyl)-7,8-dihydro-5H-1,6-naphthyridin-3-yl]boronic acid (16 mg, 0.070 mmol), Na_2CO_3 (15 mg, 0.14 mmol) and $Pd(PPh_3)_4$ (8.1 mg, 0.0070 mmol) was stirred in 1,4-dioxane (5 mL) and water (0.5 mL) at 100 °C under N_2 for 1 h. The reaction mixture was concentrated to dryness. The crude was purified by flash column chromatography eluting with 5% MeOH in DCM followed by prep-HPLC to give 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(6-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (4.5 mg, 14% yield). ^1H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.21 (s, 1H), 6.74 (d, J = 10.3 Hz, 2H), 6.55 (t, J = 9.0 Hz, 1H), 6.19 (d, J = 17.0 Hz, 1H), 5.87 (s, 1H), 5.72 (d, J = 10.5 Hz, 1H), 5.48 (d, J = 72.9 Hz, 1H), 4.64 (s, 2H), 4.34 (s, 1H), 4.19 – 3.86 (m, 6H), 3.81 – 3.53 (m, 3H), 3.50 – 3.28 (m, 6H), 3.19 – 3.03 (m, 5H), 2.85 (dd, J = 16.4, 8.4 Hz, 1H), 2.69 (dd, J = 15.8, 8.6 Hz, 1H), 2.16 – 1.99 (m, 2H), 1.29 (s, 3H). LCMS ESI (+) m/z 671.4 (M+H).

Synthetic Example 8: Synthesis of 1-((4R,7S)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 54**)



[000469] **Step A**: Preparation of tert-butyl N-[(2S)-2-(3,5-dibromopyrazol-1-yl)propyl]carbamate: To a solution of 3,5-dibromo-1H-pyrazole (10.0 g, 44.3 mmol), tert-butyl N-[(2R)-2-hydroxypropyl]carbamate (8.53 g, 48.7 mmol), PPh_3 (24.1 g, 66.4 mmol) in THF (100 mL) was added DIAD (18.0 mL, 66.4 mmol) at 0 °C. The mixture was stirred at 25 °C for 3 hours. The mixture was quenched with water and extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether: EtOAc=8:1) to give tert-butyl N-[(2S)-2-(3,5-dibromopyrazol-1-yl) propyl] carbamate (19.6 g, 100 % yield) as a colorless oil. LCMS ESI (+) m/z 328.0 (M+H).

[000470] **Step B**: Preparation of tert-butyl N-[(2S)-2-[3-bromo-5-(1-ethoxyvinyl)pyrazol-1-yl]propyl]carbamate: To a solution of tert-butyl N-[(2S)-2-(3,5-dibromopyrazol-1-yl) propyl] carbamate (10.00 g, 26.1 mmol), 1-ethoxyvinyltri-n-butyltin (9.20 mL, 27.1 mmol) in 1,4-dioxane (50 mL) was added $Pd(PPh_3)_2Cl_2$ (0.92 g, 1.3 mmol). The mixture was stirred at 100 °C for 16 h under argon. The reaction was concentrated to dryness and the residue was taken up with EtOAc (100 mL). Saturated KF solution (100 mL) was added. The mixture was stirred at room temperature for 1 h. The solid was filtered off and washed with EtOAc. The organic phase was separated and washed with 100 mL saturated brine solution, dried ($MgSO_4$) before concentration to dryness. The crude was then purified by column chromatography eluting 10% EtOAc in hexane to give tert-butyl N-[(2S)-2-[3-bromo-5-(1-ethoxyvinyl)pyrazol-1-yl]propyl]carbamate (5.50 g, 56% yield). LCMS ESI (+) m/z 374.1 (M+H).

[000471] **Step C**: Preparation of (7S)-2-bromo-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine: To a solution of tert-butyl N-[(2S)-2-[3-bromo-5-(1-ethoxyvinyl)pyrazol-1-yl] propyl]carbamate (4.20 g, 11.2 mmol) in 1,4-dioxane (5 mL) was added 4 M HCl in dioxane (20.0 mL, 112 mmol) at 0 °C. The mixture

was stirred at 25 °C for 4 h. The reaction was concentrated to dryness and the residue was taken up in DCM (100 mL). To the reaction was added saturated sodium bicarbonate solution to adjust the pH 9. The organic phase was separated and dried ($MgSO_4$) before concentration to dryness. The crude was then purified by column chromatography eluting 50% EtOAc in hexane to give (7S)-2-bromo-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine (850 mg, 33% yield) as a yellow oil. LCMS ESI (+) m/z 228.1 (M+H).

[000472] **Step D**: Preparation of (4R,7S)-2-bromo-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine: To a solution of (7S)-2-bromo-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine (1.00 g, 4.38 mmol) in DMF (5 mL)/water (5 mL) were added RuCl[(1S,2S)-Tsdpen](p-cymene) (55 mg, 0.088 mmol) and HCOONa (1193 mg, 17.5 mmol). The reaction was stirred at 50 °C under argon for 16 h. The reaction was taken up in DCM (100 mL) and the organic layers were washed with saturated brine solution. The organic layers were then separated and dried ($MgSO_4$) before concentration to dryness to give (4R,7S)-2-bromo-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (1.00 g, 99% yield) as a brown oil which was used for next step without further purification. LCMS ESI (+) m/z 230.0 (M+H).

[000473] **Step E**: Preparation of tert-butyl (4R,7S)-2-bromo-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of (4R,7S)-2-bromo-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a] pyrazine (1.00 g, 4.35 mmol) and DIPEA (1680 mg, 13.0 mmol) in DCM (10 mL) was added di-tert-butyl dicarbonate (1420 mg, 6.52 mmol). The mixture was stirred at 25 °C for 2 h. The reaction was concentrated to dryness and the residue was taken up in EtOAc (50 ml). The organic layers were washed with saturated brine solution and dried ($MgSO_4$) before concentrating to dryness. The crude was then purified by column chromatography eluting with 30% EtOAc in hexane. The desired fractions were concentrated to dryness in vacuo to give tert-butyl (4R,7S)-2-bromo-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1100 mg, 77% yield) as a white solid. LCMS ESI (+) m/z 330.1 (M+H).

[000474] **Step F**: Preparation of tert-butyl (4R,7S)-2-cyano-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (4R,7S)-2-bromo-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (600 mg, 1.82 mmol) in DMA (5 mL) were added dicyanozinc (256 mg, 2.18 mmol), Zn (14 mg, 0.22 mmol), dppf (201 mg, 0.363 mmol) and $Pd_2(dba)_3$ (166 mg, 0.182 mmol). The mixture was stirred at 120 °C for 4 h under argon. The reaction was diluted with EtOAc (20 mL) and filtered. The filtrate was washed with saturated brine solution and dried ($MgSO_4$) before concentration to dryness. The crude was purified by column chromatography eluting with 40% EtOAc in hexane. The desired fractions were concentrated to dryness in vacuo to give tert-butyl (4R,7S)-2-cyano-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a] pyrazine-5-carboxylate (400 mg, 80% yield) as a light-yellow solid. LCMS ESI (+) m/z 277.2 (M+H).

[000475] **Step G**: Preparation of tert-butyl (4R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a stirred solution of 2-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]-N,N-diethyl-thiophene-3-carboxamide (214 mg, 0.557 mmol) in THF (2 mL) was added n-BuLi (2.5 M in hexanes, 0.25 mL, 0.61 mmol) dropwise at -60 °C. The mixture was stirred at -60 °C under argon for 30 min. Then, tert-butyl (4R,7S)-2-cyano-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (140 mg, 0.507 mmol) was added at -60 °C. The mixture was warmed to 25 °C and kept at this temperature for 3 h. The reaction was quenched with saturated NH_4Cl solution, and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with 50 mL saturated brine solution, dried over Na_2SO_4 before concentrating to dryness. The residue was purified by column chromatography eluting with 5% MeOH in DCM to give tert-butyl (4R,7S)-2-[7-[2,4- difluoro-6-(2-methoxyethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (200 mg, 67% yield) as a white solid. LCMS ESI (+) m/z 587.2 (M+H).

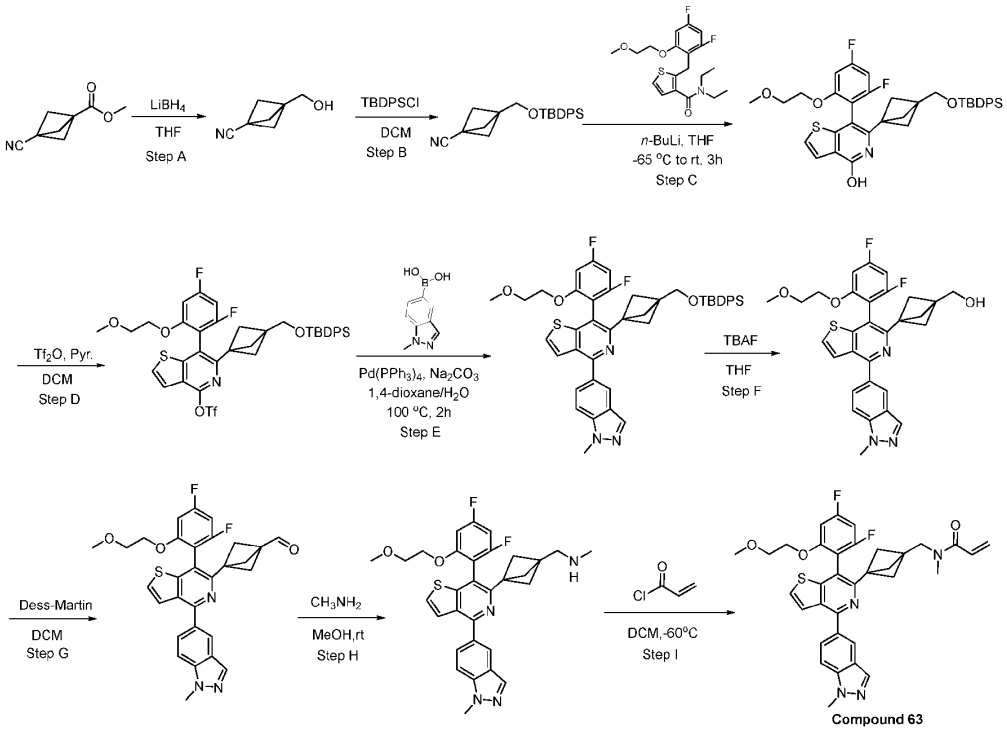
[000476] **Step H**: Preparation of tert-butyl (4R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoromethylsulfonyloxy)thieno[3,2-c] pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (4R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (200 mg, 0.341 mmol) and pyridine (270 mg, 3.41 mmol) in DCM (3 mL) was added trifluoromethanesulfonic anhydride (0.086 mL, 0.51 mmol). The mixture was stirred at 25 °C for 1 h. The reaction was concentrated to dryness and the residue was purified by Prep-TLC (petroleum ether:EtOAc=5:1) to give the more polar isomer, tert-butyl (4R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (120 mg, 49% yield), as a white solid.

[000477] **Step I**: Preparation of tert-butyl (4R,7S)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (40 mg, 0.056 mmol), (1-methylindazol-5-yl)boronic acid (15 mg, 0.084 mmol) and Na_2CO_3 (12 mg, 0.11 mmol) in 1,4-dioxane (1 mL) and water (0.1 mL) was added $Pd(PPh_3)_4$ (6.4 mg, 0.0056 mmol) under nitrogen. The resulting mixture was stirred at 100 °C for 2 hours. The solvent was removed under reduced pressure and the residue was purified by Prep-TLC (DCM : MeOH = 20 : 1) to afford tert-butyl (4R,7S)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (35 mg, 90% yield) as a white solid. LCMS ESI (+) m/z 701.4 (M+H).

[000478] **Step J:** Preparation of (S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-6-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridine: To a solution of tert-butyl (4R,7S)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (32 mg, 0.046 mmol) in DCM (2 mL) was added trifluoroacetic acid (0.70 mL, 9.1 mmol). The resulting solution was stirred at 15 °C for 1 hour. The mixture was concentrated to dryness to give (S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-6-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridine (40 mg, 99% yield). LCMS ESI (+) m/z = 601.2 (M+H).

[000479] **Step K:** Preparation of 1-((4R,7S)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of (S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-6-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridine (40 mg, 0.047 mmol) in ethyl acetate (1 mL)/water (1 mL) was added $NaHCO_3$ (39 mg, 0.47 mmol) to adjust the pH to 8. To the mixture was added acryloyl chloride (0.0057 mL, 0.070 mmol) at 0 °C and the mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried ($MgSO_4$) before concentrating to dryness. The residue was purified by Prep-HPLC to give 1-((4R,7S)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (15 mg, 46% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.16 (d, J = 0.6 Hz, 1H), 8.07 (dd, J = 8.7, 1.4 Hz, 1H), 7.80 - 7.67 (m, 3H), 6.94 - 6.78 (m, 2H), 6.71 - 6.62 (m, 1H), 6.31 (d, J = 16.5 Hz, 1H), 6.27 - 6.18 (m, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.78 - 5.43 (m, 1H), 4.46 - 4.36 (m, 1H), 4.16 (s, 3H), 4.13 - 4.07 (m, 1H), 4.06 - 3.99 (m, 1H), 3.45 (t, J = 4.8 Hz, 2H), 3.05 (s, 3H), 1.54 - 1.37 (m, 3H), 1.34 - 1.21 (m, 3H). LCMS ESI (+) m/z 655.4 (M+H).

Synthetic Example 9: Synthesis of N-[[3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methyl]-N-methyl-prop-2-enamide (**Compound 63**)



[000480] **Step A**: Preparation of 3-(hydroxymethyl)bicyclo[1.1.1]pentane-1-carbonitrile: To a solution of methyl 3-cyanobicyclo[1.1.1]pentane-1-carboxylate (400 mg, 2.65 mmol) in THF (8 mL) was added $LiBH_4$ (1 N solution in THF, 4.00 mL, 4.00 mmol) dropwise at 0 °C. The mixture was stirred at 20 °C for 3 h. MeOH (2 mL) was added, and the mixture was stirred for an additional 0.5 h. Silica gel was added and the reaction was concentrated. The mixture was purified by column chromatography (EtOAc/petroleum ether=1/2 to 100% EtOAc) to give 3-(hydroxymethyl)bicyclo[1.1.1]pentane-1-carbonitrile (190 mg, 58% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (d, J = 4.0 Hz, 2H), 2.19 (s, 6H).

[000481] **Step B**: Preparation of 3-[[tert-butyl(diphenyl)silyl]oxymethyl]bicyclo[1.1.1]pentane-1-carbonitrile: To a solution of 3-(hydroxymethyl)bicyclo[1.1.1]pentane-1-carbonitrile (200 mg, 1.62 mmol) and imidazole (230 mg, 3.38 mmol) in DCM (6 mL) was added tert-butyldiphenylchlorosilane (0.52 mL, 2.04 mmol). The mixture was stirred 10 °C for 2 h. The solid was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether=1/12) to give 3-[[tert-butyl(diphenyl) silyl]oxymethyl]bicyclo[1.1.1]pentane-1-carbonitrile (540 mg, 92% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 -7.60 (m, 4H), 7.45 – 7.30 (m, 6H), 3.60 (s, 2H), 2.11 (s, 6H), 1.05 (s, 9H).

[000482] **Step C**: Preparation of 6-[3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-bicyclo[1.1.1]pentanyl]-7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-ol: To a solution of 2-[[2,4-difluoro-6-

(2-methoxyethoxy)phenyl]methyl]-N,N-diethyl-thiophene- 3-carboxamide (280 mg, 0.730 mmol) in THF (6 mL) was added n-butyllithium (2.5 M in hexanes, 0.28 mL, 0.70 mmol) at -60 °C. The mixture was stirred at this temperature for 30 min. A solution of 3-[[tert-butyl(diphenyl)silyl] oxymethyl]bicyclo[1.1.1]pentane-1-carbonitrile (220 mg, 0.608 mmol) in THF (1 mL) was added, and the resulting mixture was stirred at 0 °C for 3 h. Water was added to the mixture to quench the reaction, and 1 N HCl was added to adjust the pH to 5-6. The product was extracted with EtOAc (10 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (EtOAc/petroleum ether:1/2 to DCM/MeOH: 20/1) to give 6-[3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-bicyclo[1.1.1]pentanyl]-7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-ol (370 mg, 90% yield). LCMS ESI (+) m/z 672.2 (M+H).

[000483] **Step D**: Preparation of [6-[3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-bicyclo[1.1.1]pentanyl]-7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate: To a solution of 6-[3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-bicyclo[1.1.1]pentanyl]-7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-ol (370 mg, 0.551 mmol) and pyridine (0.250 mL, 3.03 mmol) in DCM (5 mL) was added trifluoromethanesulfonic anhydride (0.180 mL, 1.06 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was poured into water (10 mL), and the product was extracted with DCM (10 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc/petroleum ether: 1/2) to give [6-[3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-bicyclo[1.1.1]pentanyl]-7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate (410 mg, 93% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 4H), 7.51 (d, J = 5.5 Hz, 1H), 7.45 (d, J = 5.5 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.38 – 7.32 (m, 4H), 6.65 – 6.58 (m, 2H), 4.01 (t, J = 4.7 Hz, 2H), 3.61 (s, 2H), 3.48 – 3.42 (m, 2H), 3.20 (s, 3H), 1.75 (s, 6H), 1.55(s, 9H), 1.03 (s, 9H).

[000484] **Step E**: Preparation of tert-butyl-[[3-[7-[2,4-difluoro-6- (2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methoxy]-diphenyl-silane: A mixture of Na_2CO_3 (112 mg, 1.06 mmol), [6-[3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1-bicyclo[1.1.1]pentanyl]-7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate (410 mg, 0.510 mmol), (1-methylindazol-5-yl)boronic acid (120 mg, 0.682 mmol) and tetrakis(triphenylphosphine)palladium(0) (42 mg, 0.036 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) was stirred at 100 °C for 2 h under Ar. The mixture was diluted with EtOAc and filtered. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (EtOAc/petroleum ether=1/1) to give tert-butyl-[[3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methoxy]-diphenyl-silane (370 mg, 83% yield) which was used in the next step directly. LCMS ESI (+) m/z 786.3 (M+H).

[000485] **Step F**: Preparation of [3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methanol: To a solution of tert-butyl-[[3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methoxy]-diphenyl-silane (370 mg, 0.424 mmol) in THF (6 mL) was added tetra-n-butylammonium fluoride (1.0 M in THF, 2.73 mL, 2.73 mmol). The mixture was stirred at 10 °C for 5 h. The mixture was diluted with water (20 mL) and the product was extracted with EtOAc (20 mL x 2). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (DCM/MeOH:25/1) to give [3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methanol (228 mg, 98% yield). LCMS ESI (+) m/z 548.2 (M+H).

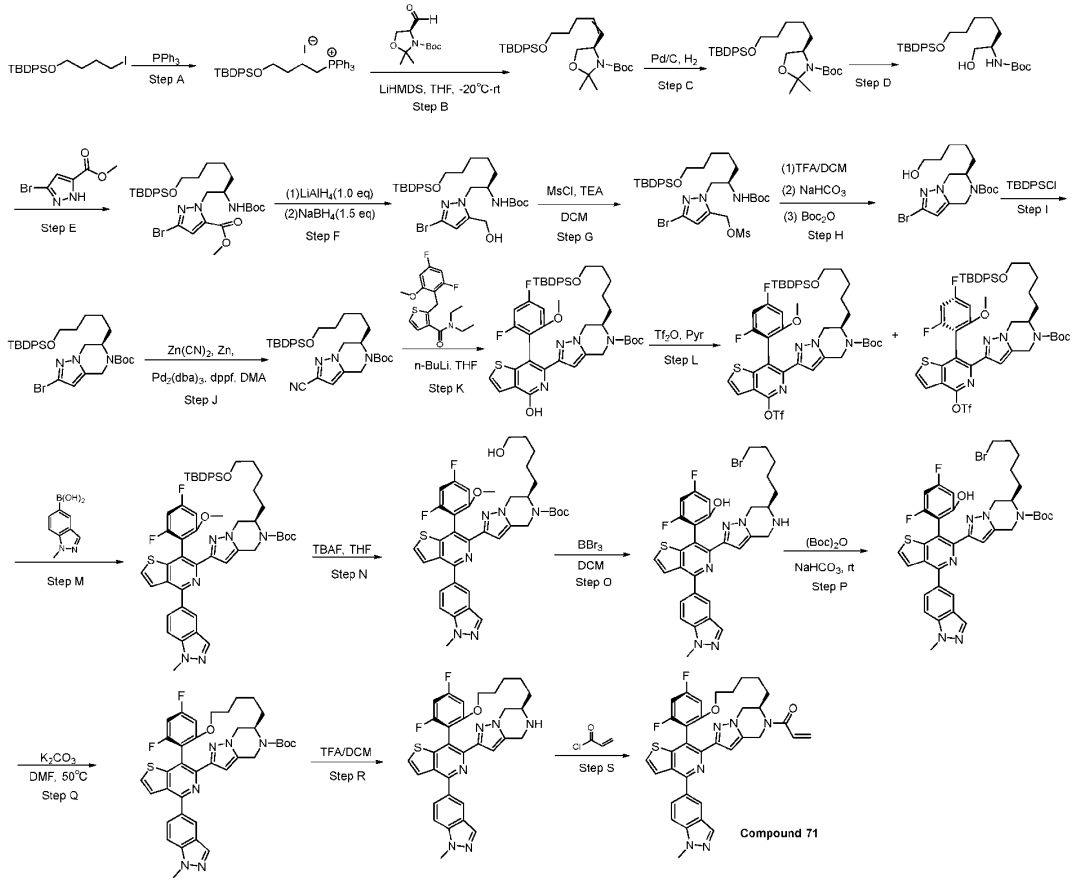
[000486] **Step G**: Preparation of 3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]bicyclo[1.1.1]pentane-1-carbaldehyde: To a solution of [3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methanol (130 mg, 0.237 mmol) in DCM (4 mL) was added Dess-Martin periodinane (151 mg, 0.356 mmol). The mixture was stirred at 25 °C for 2 h. The mixture was poured into water and $NaHCO_3$ was added to adjust the pH to 8. The product was extracted with EtOAc, dried over anhydrous Na_2SO_4, concentrated and purified by Prep-TLC (EtOAc) to give 3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c] pyridin-6-yl]bicyclo[1.1.1]pentane-1-carbaldehyde (30 mg, 23% yield). LCMS ESI (+) m/z 546.2 (M+H).

[000487] **Step H**: Preparation of 1-[3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]-N-methyl-methanamine: To a solution of 3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]bicyclo[1.1.1]pentane-1-carbaldehyde (15 mg, 0.028 mmol) in methanol (2 mL) was added $MeNH_2$ as a THF solution (0.1 mL, 0.2 mmol, 2.0 M in THF). The mixture was stirred at 25 °C for 1 h. Sodium cyanoborohydride (3.5 mg, 0.055 mmol) was then added. The mixture was stirred at 25 °C for an additional 4 h. The mixture was poured into water. The product was extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated to give crude product 1-[3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]-N-methyl-methanamine (20 mg) which was used directly in the next step. LCMS ESI (+) m/z 561.2 (M+H).

[000488] **Step I**: Preparation of N-[[3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methyl]-N-methyl-prop-2-enamide: To a solution of 1-[3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]-N-methyl-methanamine (20 mg, 0.036 mmol) and TEA (0.015 mL, 0.11 mmol) in DCM (2 mL) was added acryloyl chloride (0.0032 mL, 0.039 mmol) at -

60 °C. The mixture was stirred at -60 °C for 1.5 h. The mixture was poured into aqueous $NaHCO_3$ solution. The product was extracted with EtOAc, dried over anhydrous Na_2SO_4, concentrated and purified by Prep-TLC (EtOAc) to give N-[[3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methyl]-N-methyl-prop-2-enamide (2.8 mg, 12% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 8.14 (s, 1H), 7.97 (dd, J = 8.8 Hz, 1.4 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.66 - 7.58 (m, 2H), 6.93 - 6.86 (m, 1H), 6.80 - 6.71 (m, 1H), 6.71 - 6.59 (m, 1H), 6.27 - 6.13 (m, 1H), 5.77 - 5.64 (m, 1H), 4.14 (s, 3H), 4.12 - 4.05 (m, 1H), 3.54 (s, 1H), 3.51 - 3.45 (m, 2H), 3.10 (s, 1H), 3.06 - 3.01 (m, 3H), 2.96 (s, 2H), 1.92 (d, J = 4.8 Hz, 6H), 1.32 - 1.26 (m, 4H), 0.92 - 0.85 (m, 1H). LCMS ESI (+) m/z 615.2 (M+H).

Synthetic Example 10: Synthesis of 1-((1^6*R*,*E*)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-yl)prop-2-en-1-one (**Compound 71**)



[000489] **Step A:** Preparation of (4-((tert-butyldiphenylsilyl)oxy)butyl)triphenylphosphonium: To a solution of tert-butyl-(4-iodobutoxy)-diphenyl-silane (14.50 g, 33.1 mmol) in MeCN (150 mL) was added triphenylphosphine (9.11 g, 34.7 mmol) under Ar. The mixture was heated to 80 °C and stirred for 15 hours. The mixture was concentrated. The residue was diluted with EtOAc and filtered to give (4-((tert-butyldiphenylsilyl)oxy)butyl)triphenylphosphonium (21.40 g, 92% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 – 7.85 (m, 3H), 7.79 – 7.69 (m, 12H), 7.57 – 7.53 (m, 4H), 7.45 – 7.39 (m, 2H), 7.36 – 7.31 (m, 4H), 3.75 (t, J = 5.2 Hz, 2H), 3.43 – 3.33 (m, 2H), 1.85 – 1.69 (m, 4H), 0.95 (s, 9H).

[000490] **Step B:** Preparation of tert-butyl (R)-4-(5-((tert-butyldiphenylsilyl)oxy)pent-1-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate: To a suspension of (4-((tert-butyldiphenylsilyl)oxy) butyl)triphenylphosphonium (17.40 g, 24.8 mmol) in THF (200 mL) being cooled to -20 °C was added LiHMDS (1 N in THF, 29.7 mL, 29.7 mmol) under Ar. The mixture was stirred for 5 minutes and tert-butyl (4S)-4-formyl-2,2-dimethyl-oxazolidine-3-carboxylate (6.82 g, 29.8 mmol) was then added. The reaction was allowed to warm to 24 °C and stirred for 2 hours. The reaction was quenched by the addition of water and extracted with EtOAc (3 x 70 mL). The combined organic phases were washed with saturated brine solution, and dried ($MgSO_4$) before concentrating to dryness. The crude was then purified by column chromatography eluting with 20% EtOAc in petroleum ether to give tert-butyl (R)-4-(5-((tert-butyldiphenylsilyl)oxy)pent-1-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (7.60 g, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 4H), 7.46 – 7.34 (m, 6H), 5.52 – 5.34 (m, 2H), 4.74 – 4.52 (m, 1H), 3.99 (dd, J = 8.6, 6.3 Hz, 1H), 3.70 – 3.56 (m, 1H), 2.36 – 2.04 (m, 2H), 1.62 – 1.38 (m, 17H), 1.05 (s, 9H).

[000491] **Step C:** Preparation of tert-butyl (R)-4-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2,2-dimethyloxazolidine-3-carboxylate: A mixture of tert-butyl (R)-4-(5-((tert-butyldiphenylsilyl)oxy)pent-1-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (7.90 g, 15.1 mmol) and 10% Pd/C (790 mg) in methanol (90 mL) was stirred at 40 °C for 4 hours under H_2. The mixture was filtered and the filtrate was concentrated to dryness to give tert-butyl (R)-4-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2,2-dimethyloxazolidine-3-carboxylate (7.30 g, 92% yield) as an yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 4H), 7.46 – 7.34 (m, 6H), 3.95 – 3.60 (m, 5H), 1.60 – 1.20 (m, 23H), 1.04 (s, 9H).

[000492] **Step D:** Preparation of tert-butyl (R)-(7-((tert-butyldiphenylsilyl)oxy)-1-hydroxyheptan-2-yl)carbamate: To a solution of tert-butyl (R)-4-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2,2-dimethyloxazolidine-3-carboxylate (7.00 g, 13.3 mmol) in MeCN (2 mL) was added $CuCl_2.H_2O$ (4540 mg, 26.6 mmol) under Ar. The mixture was stirred at 24 °C for 30 minutes. The mixture was concentrated and the residue was purified by column chromatography eluting with 25% EtOAc in petroleum ether to give tert-butyl (R)-(7-((tert-butyldiphenylsilyl)oxy)-1-hydroxyheptan-2-yl)carbamate (6.60 g, 102% yield). LCMS ESI (+) m/z 386.3 (M-Boc+H).

[000493] **Step E:** Preparation of methyl (R)-3-bromo-1-(2-((tert-butoxycarbonyl)amino)-7-((tert-butyldiphenylsilyl)oxy)heptyl)-1H-pyrazole-5-carboxylate: To a solution of tert-butyl (R)-(7-((tert-butyldiphenylsilyl)oxy)-1-hydroxyheptan-2-yl)carbamate (1.40 g, 2.88 mmol) in THF (20 mL) were added methyl 3-bromo-1H-pyrazole-5-carboxylate (709 mg, 3.46 mmol) and triphenylphosphine (907 mg, 3.46 mmol) under Ar. The mixture was cooled to 0 °C and stirred for 10 minutes. DIAD (1.60 mL, 5.76 mmol) was then added. The yellow solution was allowed to warm to 18 °C and stirred for 3 hours. The mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 20 mL). The organic fractions were washed with saturated brine solution (30 mL) and dried (Na_2SO_4) before concentration. The residue was purified by column chromatography eluting 10% EtOAc in petroleum etherto give methyl (R)-3-bromo-1-(2-((tert-butoxycarbonyl)amino)-7-((tert-butyldiphenylsilyl)oxy)heptyl)-1H-pyrazole-5-carboxylate (1.60 g, 74% yield) as a light yellow oil. LCMS ESI (+) m/z 572.3 (M-Boc+H).

[000494] **Step F:** Preparation of tert-butyl (R)-(1-(3-bromo-5-(hydroxymethyl)-1H-pyrazol-1-yl)-7-((tert-butyldiphenylsilyl)oxy)heptan-2-yl)carbamate: To a solution of methyl (R)-3-bromo-1-(2-((tert-butoxycarbonyl)amino)-7-((tert-butyldiphenylsilyl)oxy)heptyl)-1H-pyrazole-5-carboxylate (1.60 g, 2.38 mmol) in THF (20 mL) cooled to 0 °C was added $LiAlH_4$ (162 mg, 4.28 mmol) slowly under Ar. The reaction was quenched by the addition of water (5 mL) and dried (Na_2SO_4). The mixture was filtered, and the filtrate was concentrated. The residue was dissolved in ethanol (20 mL) and cooled to 0 °C. $NaBH_4$ (45 mg, 1.2 mmol) was then added. The suspension was stirred at 0 °C for an additional 1 hour. The mixture was filtered and concentrated. The crude was purified by column chromatography on silica gel eluted with petroleum ether:EtOAc=5:1 to give tert-butyl (R)-(1-(3-bromo-5-(hydroxymethyl)-1H-pyrazol-1-yl)-7-((tert-butyldiphenylsilyl)oxy)heptan-2-yl)carbamate (1.10 g, 65% yield) as a colorless oil. LCMS ESI (+) m/z 664.3 (M+H).

[000495] **Step G:** Preparation of (R)-(3-bromo-1-(2-((tert-butoxycarbonyl)amino)-7-((tert-butyldiphenylsilyl)oxy)heptyl)-1H-pyrazol-5-yl)methyl methanesulfonate: To a solution of tert-butyl (R)-(1-(3-bromo-5-(hydroxymethyl)-1H-pyrazol-1-yl)-7-((tert-butyldiphenylsilyl)oxy)heptan-2-yl)carbamate (1.10 g, 1.54 mmol) in DCM (15 mL) were added N,N-diisopropylethylamine (0.800 mL, 4.61 mmol) and methanesulfonyl chloride (0.180 mL, 2.30 mmol) under Ar. The mixture was stirred at 24 °C for 1.5 hours. The mixture was diluted with DCM and washed with saturated brine solution (25 mL). The organic layers were dried (Na_2SO_4) and concentrated to give crude (R)-(3-bromo-1-(2-((tert-butoxycarbonyl)amino)-7-((tert-butyldiphenylsilyl)oxy)heptyl)-1H-pyrazol-5-yl)methyl methanesulfonate (3.2 g) which was used in the next step directly.

[000496] **Step H:** Preparation of tert-butyl (R)-2-bromo-6-(5-hydroxypentyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of (R)-(3-bromo-1-(2-((tert-butoxycarbonyl)amino)-7-((tert-butyldiphenylsilyl)oxy)heptyl)-1H-pyrazol-5-yl)methyl methanesulfonate (2.50 g, 1.73 mmol) in DCM (30

mL) was added trifluoroacetic acid (10 mL, 130 mmol) under Ar. The mixture was stirred at room temperature for 30 minutes. The mixture was concentrated, and the residue was dissolved in ethanol (50 mL). $NaHCO_3$ aqueous solution (50 mL) was added to adjust the pH to 8 and the mixture was stirred at 50 °C for 16 h. di-tert-Butyl dicarbonate (0.800 mL, 3.46 mmol) was added and the mixture was stirred for an additional 2 hours. The mixture was concentrated and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated brine (30 mL) solution and dried (Na_2SO_4) before concentration to dryness to give crude tert-butyl (R)-2-bromo-6-(5-hydroxypentyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (3.2 g) which was used in the next step directly. LCMS ESI (+) m/z 388.1 (M+H).

[000497] **Step I:** Preparation of tert-butyl (R)-2-bromo-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (R)-4-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2,2-dimethyloxazolidine-3-carboxylate (3.20 g crude, 4.12 mmol) in DCM (30 mL) were added imidazole (224 mg, 3.30 mmol) and tert-butyldiphenylchlorosilane (0.64 mL, 2.47 mmol) under Ar. The mixture was stirred at 24 °C for 2 hours. The mixture was diluted with water and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography eluting with petroleum ether:EtOAc=20:1 to give tert-butyl (R)-2-bromo-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (623 mg, 22% yield) as colorless oil. LCMS ESI (+) m/z 623.3 (M+H).

[000498] **Step J:** Preparation of tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-cyano-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (R)-2-bromo-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (638 mg, 1.02 mmol) in DMA (10 mL) were added $Zn(CN)_2$ (179 mg, 1.53 mmol), Zn powder (13 mg, 0.20 mmol), dppf (113 mg, 0.204 mmol) and $Pd_2(dba)_3$ (93 mg, 0.10 mmol) under Ar. The mixture was stirred at 120 °C for 8 hours. The mixture was diluted with EtOAc (20 mL) and filtered. The filtrate was washed with saturated brine solution (20 mL). The organic phase was dried over Na_2SO_4 before concentration to dryness. The residue was purified by the column chromatography eluting with 4-10% EtOAc in petroleum ether to give tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-cyano-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (433 mg, 67% yield) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 4H), 7.46 – 7.34 (m, 6H), 6.48 (s, 1H), 5.17 – 4.90 (m, 1H), 4.85 – 4.50 (m, 1H), 4.24 – 4.05 (m, 3H), 3.63 (t, J = 6.4 Hz, 2H), 1.55 – 1.43 (m, 11H), 1.42 – 1.20 (m, 6H), 1.03 (s, 9H).

[000499] **Step K:** Preparation of tert-butyl (6R)-6-[5-[tert-butyl(diphenyl)silyl]oxypentyl]-2-[7-[2,4-difluoro-6-(2-trimethylsilylethoxymethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of 2-[[2,4-difluoro-6-(2-trimethylsilylethoxymethoxy)phenyl]methyl]-N,N-diethyl-thiophene-3-carboxamide (377 mg, 0.827 mmol) in THF (8 mL) cooled to -60 °C was added n-BuLi (0.33 mL, 2.5 N in THF, 0.83 mmol) under Ar.

The mixture was stirred at -60 °C for 20 minutes. A solution of tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-cyano-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (395 mg, 0.690 mmol) in THF (2 mL) was added. The resulting mixture was then allowed to warm to 24 °C and stirred for an additional 3 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (2 x 7 mL). The organic phase was dried (Na_2SO_4) before concentration to dryness. The crude was purified by column chromatography (DCM:MeOH=20:1) to give tert-butyl (6R)-6-[5-[tert-butyl(diphenyl)silyl]oxypentyl]-2-[7-[2,4-difluoro-6-(2-trimethylsilylethoxymethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (488 mg, 67% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (d, J = 11.5 Hz, 1H), 7.73 – 7.61 (m, 5H), 7.46 – 7.32 (m, 6H), 7.24 (d, J = 5.3 Hz, 1H), 6.68 – 6.60 (m, 2H), 5.26 (d, J = 4.2 Hz, 1H), 5.05 – 4.48 (m, 2H), 4.21 – 3.93 (m, 3H), 3.70 (s, 3H), 3.63 (t, J = 6.3 Hz, 2H), 1.58 – 1.22 (m, 17H), 1.03 (s, 9H).

[000500] **Step L:** Preparation of tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-(7-((S)-2,4-difluoro-6-methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a mixture of tert-butyl (6R)-6-[5-[tert-butyl(diphenyl)silyl]oxypentyl]-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (288 mg, 0.343 mmol) and pyridine (0.110 mL, 1.37 mmol) in DCM (5 mL) cooled to 0 °C was added trifluoromethanesulfonic anhydride (0.087 mL, 0.52 mmol). The mixture was stirred at 0 °C for 30 minutes. The reaction mixture was diluted with DCM and washed with water. The organic phase was dried (Na_2SO_4) before concentration to dryness. The residue was purified by column chromatography eluting with 5-20% EtOAc in petroleum ether to give the more-polar isomer, tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-(7-((S)-2,4-difluoro-6-methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (165 mg, 50% yield), and the less-polar isomer, tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-(7-((R)-2,4-difluoro-6-methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (120 mg, 36% yield).

[000501] **Step M:** Preparation of tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-((S)-7-(2,4-difluoro-6-methoxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-(7-((S)-2,4-difluoro-6-methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (264 mg, 0.272 mmol) in 1,4-dioxane (1 mL) and water (0.10 mL) were added (1-methylindazol-5-yl)boronic acid (57 mg, 0.33 mmol), sodium carbonate (58 mg, 0.54 mmol) and $Pd(PPh_3)_4$ (31 mg, 0.027 mmol) under Ar. The mixture was stirred at 100 °C for 1 hour. The mixture was concentrated

and purified by Prep-TLC (petroleum ether:EtOAc=1:2) to give tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-((S)-7-(2,4-difluoro-6-methoxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (259 mg, 100% yield).

[000502] Step N: Preparation of tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-methoxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6-(5-hydroxypentyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-((S)-7-(2,4-difluoro-6-methoxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (259 mg, 0.272 mmol) in THF (1 mL) cooled to 0 °C was added TBAF (1.0 N in THF, 0.44 mL, 0.44 mmol) under Ar. The mixture was stirred at 18 °C for 3 hours. The mixture was poured into water and extracted with EtOAc. The organic layers were washed with saturated brine solution and dried (Na_2SO_4) before concentrating to dryness. The crude was purified by Prep-TLC (EtOAc) to give tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-methoxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6-(5-hydroxypentyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (180 mg, 93% yield). LCMS ESI (+) m/z 715.3 (M+H).

[000503] Step O to Step P: Preparation of tert-butyl (R)-6-(5-bromopentyl)-2-((S)-7-(2,4-difluoro-6-hydroxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-methoxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6-(5-hydroxypentyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (78 mg, 0.11 mmol) in DCM (1 mL) cooled to 0 °C was added boron tribromide (0.31 mL, 3.3 mmol) under Ar. The mixture was stirred at 0 °C for 12 hours. The mixture was poured into ice-water (5 mL) and $NaHCO_3$ was added to adjust the pH to 8. A solution of di-tert-butyl dicarbonate (35 mg, 0.16 mmol) in MeOH (3 mL) was added at 0 °C. The mixture was stirred at 0 °C for 24 hours. The mixture was diluted with saturated brine solution (20 mL). 1 N HCl was added to adjust the pH to 6-7. The mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (100% DCM, DCM:MeOH=20:1) to give tert-butyl (R)-6-(5-bromopentyl)-2-((S)-7-(2,4-difluoro-6-hydroxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (16 mg, 19% yield). LCMS ESI (+) m/z 663.1 (M+H).

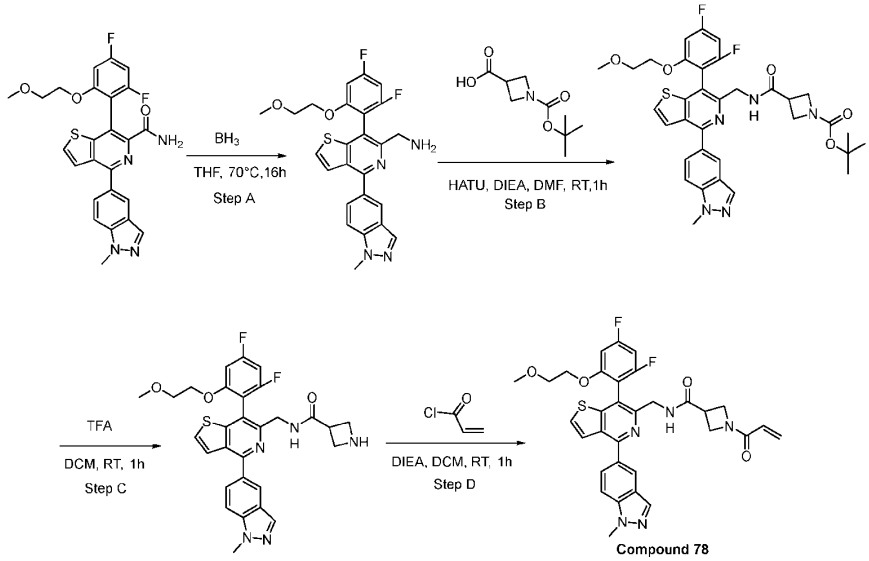
[000504] Step Q: Preparation of tert-butyl ($1^6R,E$)-$3^4,3^6$-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-$1^4,1^5,1^6,1^7$-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-carboxylate: To a solution of tert-butyl (R)-6-(5-bromopentyl)-2-((S)-7-(2,4-difluoro-6-hydroxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (16 mg, 0.021 mmol) in DMF (5 mL) was added K_2CO_3

(22 mg, 0.16 mmol). The mixture was stirred at 50 °C for 4 hours. The mixture was poured into water (30 mL) and extracted with EtOAc (30 mL x 2). The organic layers were washed with saturated brine solution (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (DCM:MeOH=20:1) to give tert-butyl ($1^6R,E$)-$3^4,3^6$-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-$1^4,1^5,1^6,1^7$-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-carboxylate (8 mg, 56% yield). LCMS ESI (+) m/z 683.3 (M+H).

[000505] Step R: Preparation of tert-butyl ($1^6R,E$)-$3^4,3^6$-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-$1^4,1^5,1^6,1^7$-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-15-carboxylate: To a solution of tert-butyl ($1^6R,E$)-$3^4,3^6$-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-$1^4,1^5,1^6,1^7$-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-carboxylate (8.0 mg, 0.012 mmol) in DCM (3 mL) was added trifluoroacetic acid (1.0 mL, 13 mmol). The mixture was stirred at 15 °C for 30 minutes. The mixture was concentrated directly to give tert-butyl ($1^6R,E$)-$3^4,3^6$-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-$1^4,1^5,1^6,1^7$-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-15-carboxylate (15 mg) which was used in the next step without further purification. LCMS ESI (+) m/z 583.2 (M+H).

[000506] Step S: Preparation of 1-(($1^6R,E$)-$3^4,3^6$-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-$1^4,1^5,1^6,1^7$-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-yl)prop-2-en-1-one: To a solution of crude tert-butyl ($1^6R,E$)-$3^4,3^6$-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-$1^4,1^5,1^6,1^7$-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-15-carboxylate (15 mg, 0.012 mmol) in ethyl acetate (2 mL) and water (2 mL) cooled to 0 °C was added $NaHCO_3$ to adjust the pH to 8. A solution of acryloyl chloride (1.6 mg, 0.018 mmol) in DCM (0.1 mL) was added dropwise. The mixture was stirred at 0 °C for 30 minutes. The organic layers were separated, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to give 1-(($1^6R,E$)-$3^4,3^6$-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-$1^4,1^5,1^6,1^7$-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-yl)prop-2-en-1-one (4.2 mg, 54% yield). ^1H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 8.19 – 8.12 (m, 2H), 7.79 – 7.70 (m, 3H), 6.90 – 6.67 (m, 3H), 6.35 – 6.26 (m, 1H), 5.84 – 5.78 (m, 2H), 5.08 – 4.93 (m, 1H), 4.83 – 4.73 (m, 1H), 4.68 – 4.49 (m, 2H), 4.44 – 4.30 (m, 1H), 4.16 (s, 3H), 4.12 – 4.04 (m, 1H), 3.83 – 3.73 (m, 1H), 1.69 – 1.49 (m, 2H), 1.29 – 0.95 (m, 6H). LCMS ESI (+) m/z 637.2 (M+H).

Synthetic Example 11: Synthesis of N-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methyl]-1-prop-2-enoyl-azetidine-3-carboxamide (**Compound 78**)



[000507] **Step A:** Preparation of [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methanamine: A mixture of 7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine-6-carboxamide (43 mg, 0.087 mmol) and BH_3-Me_2S (0.087 mL, 2.0 M, 0.17 mmol) in THF (2 mL) was stirred at 70 °C for 16 h. The reaction mixture was diluted with 2 N HCl solution and stirred for 30 min. The reaction was concentrated in vacuo and basified with saturated $NaHCO_3$ solution. The reaction was extracted with DCM. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give [7-[2,4-difluoro-6-(2-methoxyethoxy) phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methanamine (80 mg, 67% yield). LCMS ESI (+) m/z 481.1 (M+H).

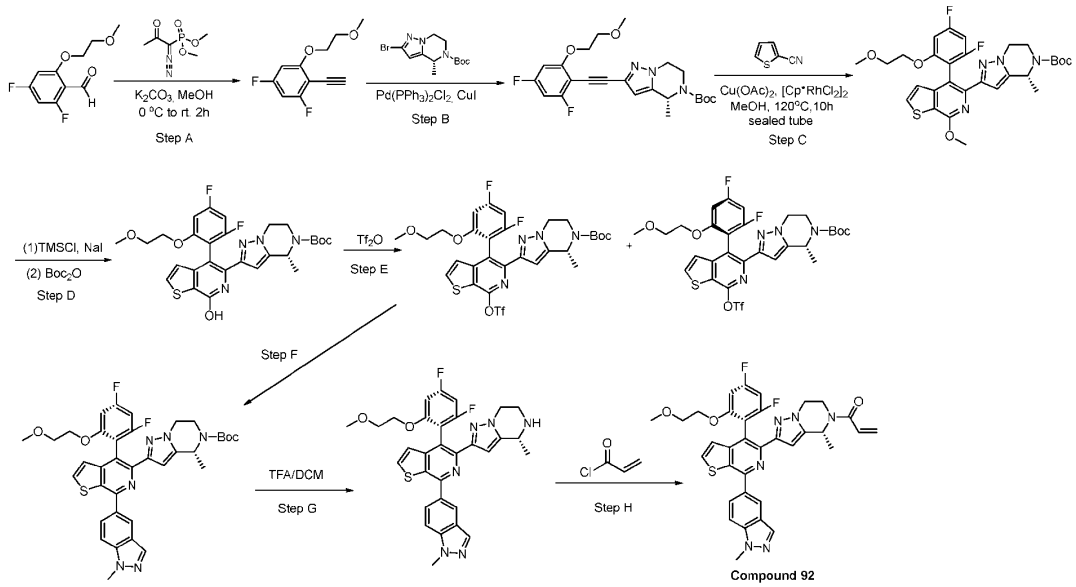
[000508] **Step B:** Preparation of tert-butyl 3-[[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methylcarbamoyl]azetidine-1-carboxylate: A mixture of 7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine-6-carboxylic acid (70 mg, 0.14 mmol), tert-butyl 3-aminoazetidine-1-carboxylate (29 mg, 0.17 mmol), HATU (81 mg, 0.21 mmol) and DIPEA (0.10 mL, 0.56 mmol) in DMF (5 mL) was stirred at rt for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in water (50 mL). The resulting aqueous solution was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The residue was purified by flash chromatography (0-5% MeOH in DCM) to get tert-butyl 3-[[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methylcarbamoyl]azetidine-1-carboxylate (40 mg, 88% yield). LCMS ESI (+) m/z 664.1 (M+H).

[000509] **Step C:** Preparation of N-[[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methyl]azetidine-3-carboxamide: A mixture of tert-butyl 3-[[7-[2,4-

difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methylcarbamoyl]azetidine-1-carboxylate (8.0 mg, 0.012 mmol) in TFA (2 mL) and DCM (10 mL) was stirred at rt for 1 h. Upon completion of the reaction, the mixture was concentrated and diluted with H_2O. The mixture was basified by saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with EtOAc. The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give N-[[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methyl]azetidine-3-carboxamide (5.0 mg, 74% yield). LCMS ESI (+) m/z 564.1 (M+H).

[000510] **Step D:** Preparation of N-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methyl]-1-prop-2-enoyl-azetidine-3-carboxamide: To a stirring solution of N-[[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methyl]azetidine-3-carboxamide (82 mg, 0.15 mmol) and DIEA (0.041 mL, 0.29 mmol) in DCM (10 mL) was added acryloyl chloride (0.012 mL, 0.15 mmol) at 0 °C. The reaction was stirred at 25 °C for 2 h. The mixture was poured into water, then extracted with DCM. The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by CombiFlash ® chromatography eluting with MeOH– DCM (0 to 5%) to give N-[7-[2,4-difluoro-6-(2-methoxyethoxy) phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]methyl]-1-prop-2-enoyl-azetidine-3-carboxamide (25 mg, 23% yield) as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (d, J = 11.2 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.03 (dd, J = 10.6, 3.4 Hz, 2H), 7.89 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.04 (d, J = 10.7 Hz, 1H), 6.90 (t, J = 9.3 Hz, 1H), 6.33 – 6.21 (m, 2H), 5.74 (dd, J = 9.0, 3.2 Hz, 1H), 4.75 – 4.61 (m, 2H), 4.39 (t, J = 8.8 Hz, 1H), 4.29 (td, J = 8.6, 4.3 Hz, 2H), 4.21 (s, 3H), 4.20 – 4.12 (m, 2H), 4.04 (td, J = 9.8, 6.0 Hz, 1H), 3.63 – 3.49 (m, 2H), 3.40 (ddd, J = 8.9, 7.4, 4.5 Hz, 1H), 3.20 – 3.14 (m, 3H). LCMS ESI (+) m/z 618.1 (M+H).

Synthetic Example 12: Synthesis of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 92**)



[000511] **Step A:** Preparation of 2-ethynyl-1,5-difluoro-3-(2-methoxyethoxy)benzene: To a suspension of 2,4-difluoro-6-(2-methoxyethoxy)benzaldehyde (500 mg, 2.31 mmol) and potassium carbonate (639 mg, 4.63 mmol) in methanol (8 mL) was added 1-diazo-1-dimethoxyphosphoryl-propan-2-one (578 mg, 3.01 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h at rt. The mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc = 20/1). The desired fractions were concentrated to give 2-ethynyl-1,5-difluoro-3-(2-methoxyethoxy)benzene (410 mg, 84% yield) as a colorless oil. LCMS ESI (+) m/z 213.1 (M+H).

[000512] **Step B:** Preparation of tert-butyl (R)-2-((2,4-difluoro-6-(2-methoxyethoxy)phenyl)ethynyl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A solution of 2-ethynyl-1,5-difluoro-3-(2-methoxyethoxy)benzene (1.80 g, 8.48 mmol), tert-butyl (R)-2-bromo-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (3.22 g, 10.2 mmol), bis(triphenylphosphine)palladium(II) chloride (298 mg, 0.424 mmol), triethylamine (3.50 mL, 25.4 mmol) and copper(I) iodide (81 mg, 0.42 mmol) in DMF (10 mL) was stirred at 85 °C for 10 h under N_2. The mixture was concentrated and purified by column chromatography (petroleum ether/EtOAc = 4/1) to give tert-butyl (R)-2-((2,4-difluoro-6-(2-methoxyethoxy)phenyl)ethynyl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (1.60 g, 42% yield) as an yellow oil. LCMS ESI (+) m/z 448.2 (M+H).

[000513] **Step C:** Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-methoxythieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A

solution of tert-butyl (4R)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.00 g, 2.23 mmol), thiophene-2-carbonitrile (0.370 g, 3.35 mmol), copper(II) acetate monohydrate (714 mg, 3.58 mmol) and bis[(pentamethylcyclopentadienyl)dichloro-rhodium] (41 mg, 0.067 mmol) in methanol (20 mL) was stirred at 120 °C for 10 h under N_2 in a sealed tube. The mixture was concentrated and purified by column chromatography (petroleum ether/EtOAc = 4/1) to give tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-methoxythieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (283 mg, 22% yield) as a yellow oil. LCMS ESI (+) m/z 587.3 (M+H).

[000514] **Step D:** Preparation of tert-butyl (4S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-methoxythieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (250 mg, 0.514 mmol) and sodium iodide (385 mg, 2.57 mmol) in MeCN (7 mL) was added trimethylchlorosilane (0.330 mL, 2.57 mmol) at 0 °C. The mixture was warmed to rt and stirred for 2 h. Saturated sodium bicarbonate solution was added to adjust the pH to 9 and then di-tert-butyl dicarbonate (0.22 mL, 0.93 mmol) was added. The mixture was stirred at room temperature for an additional 16 h. 1 M HCl aqueous solution was added at 0 °C to adjust the pH to 5, and the mixture was diluted with water (40 mL) and extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with brine solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc = 1/1 to 100% EtOAc) to give tert-butyl (4S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (255 mg, 68% yield) as a light yellow solid. LCMS ESI (+) m/z 573.2 (M+H).

[000515] **Step E:** Preparation of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (250 mg, 0.436 mmol) and pyridine (0.17 mL, 2.1 mmol) in DCM (7 mL) was added trifluoromethanesulfonic anhydride (185 mg, 0.654 mmol) at 0 °C. The mixture was stirred at RT for 1 h. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by Prep-TLC (petroleum ether/EtOAc = 3/1) to give the more polar isomer, tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (95 mg, 31% yield), and the less polar isomer, tert-butyl (R)-2-((S)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-

(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (165 mg, 54% yield). LCMS ESI (+) m/z 705.1 (M+H).

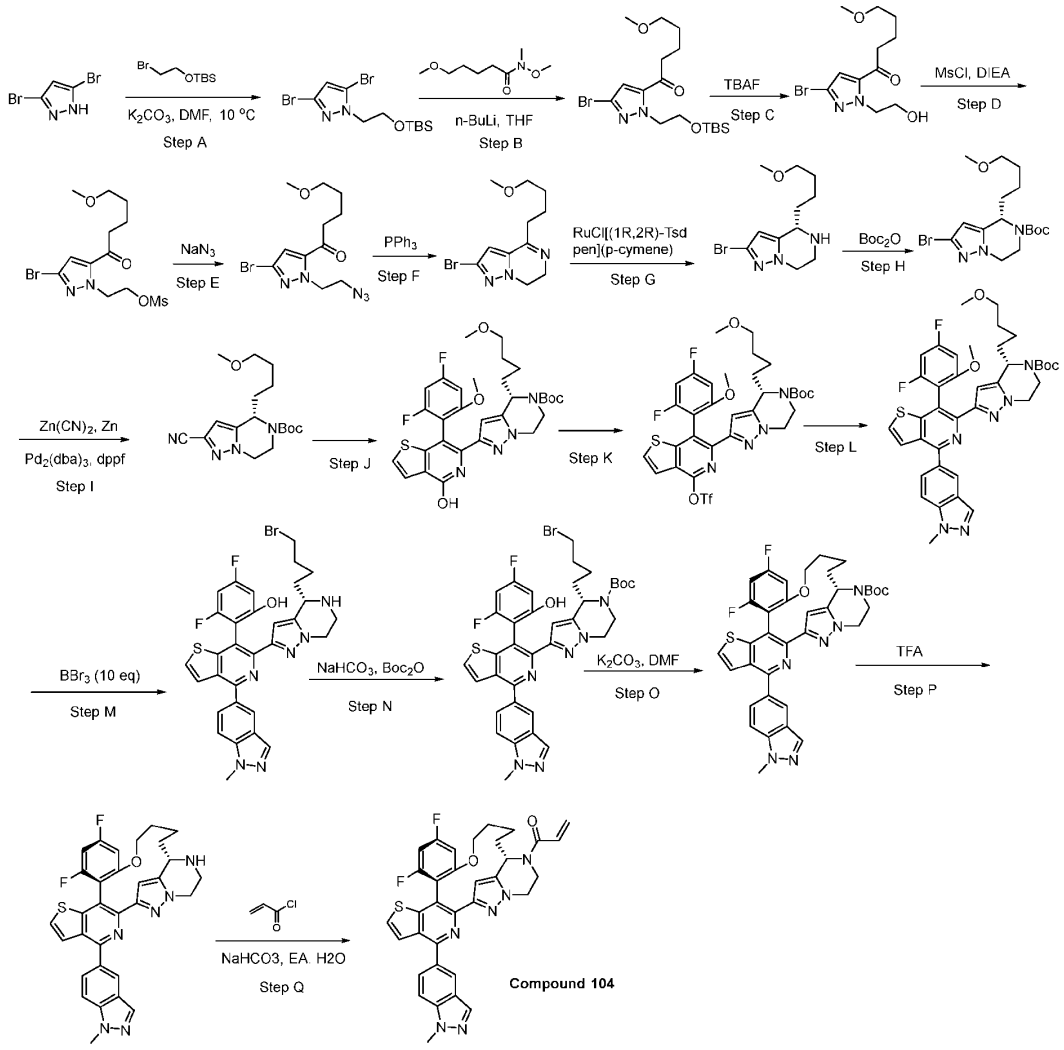
[000516] **Step F:** Preparation of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A solution of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (35 mg, 0.050 mmol), (1-methylindazol-5-yl)boronic acid (11 mg, 0.065 mmol), tetrakis(triphenylphosphine)palladium(0) (5.7 mg, 0.0050 mmol) and sodium carbonate (11 mg, 0.099 mmol) in 1,4-dioxane (1.5 mL) and water (0.3 mL) was stirred at 100 °C for 4 h under N_2. The mixture was concentrated and purified by Prep-TLC (DCM/MeOH = 20/1) to give tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (27 mg, 79% yield). LCMS ESI (+) m/z 687.3 (M+H).

[000517] **Step G:** Preparation of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)-5-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[2,3-c]pyridine: To a solution of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (27 mg, 0.039 mmol) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at rt for 1 h. The reaction was concentrated to dryness under reduced pressure to give crude (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)-5-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[2,3-c]pyridine (35 mg, 100% yield) which was used in the next step without further purification. LCMS ESI (+) m/z 587.2 (M+H).

[000518] **Step H:** Preparation of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: A solution of crude (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)-5-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[2,3-c]pyridine (35 mg, 0.039 mmol) in EtOAc (5 mL) and water (5 mL) was stirred at rt for 5 min, and then the mixture was cooled to 0 °C. Saturated sodium bicarbonate solution was added to adjust the pH to 9. A solution of acryloyl chloride (4.8 mg, 0.053 mmol) in dry DCM (1 mL) was added dropwise. The mixture was stirred at 0 °C for 0.5 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by Prep-HPLC to give 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (20 mg, 81% yield) as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.26 (s, 1H), 8.17 (dd, J = 8.8, 1.6 Hz, 1H), 7.88 (d, J = 8.8 Hz,

1H), 7.32 (d, J = 5.5 Hz, 1H), 7.00 – 6.72 (m, 3H), 6.30 (d, J = 16.9 Hz, 1H), 6.01 (s, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.71-5.42 (m, 1H), 4.19 (s, 3H), 4.17 – 4.03 (m, 3H), 3.44 (t, J = 4.5 Hz, 2H), 3.09 (s, 3H), 1.47-1.35 (m, 3H). LCMS ESI (+) m/z 641.3 (M+H).

Synthetic Example 13: Synthesis of tert-butyl N-[2-[2-[5-fluoro-2-[3-fluoro-4-(1,2,3,4-tetrahydroisoquinolin-6-yl)thieno[2,3-d]pyridazin-7-yl]phenoxy]ethoxy]ethyl]carbamate (**Compound 104**)



[000519] **Step A:** Preparation of tert-butyl-[2-(3,5-dibromopyrazol-1-yl)ethoxy]-dimethyl-silane: To a solution of 3,5-dibromo-1H-pyrazole (20.00 g, 88.5 mmol) in DMF (60 mL) were added K_2CO_3 (18.33 g, 133 mmol) and (2-bromoethoxy)-tert-butyldimethylsilane (23.0 mL, 106 mmol). The mixture was stirred at 25 °C for 6 h. Mixed solvent (petroleum ether/EtOAc 1/1, 0.8 L) was added, and the reaction mixture

was filtered. The filtrate was washed with brine (300 mL x 2) solution. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc 5/1) to give tert-butyl-[2-(3,5-dibromopyrazol-1-yl)ethoxy]-dimethyl-silane (30.00 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.28 (t, J = 5.6 Hz, 2 H), 4.01 (t, J = 5.6 Hz, 2 H), 0.88 (s, 9H), 0.00 (s, 6H).

[000520] **Step B:** Preparation of 1-[5-bromo-2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]pyrazol-3-yl]-5-methoxy-pentan-1-one: To a stirred solution of tert-butyl-[2-(3,5-dibromopyrazol-1-yl)ethoxy]-dimethyl-silane (20.00 g, 52.1 mmol) in THF (200 mL) at -65 °C under argon was added n-BuLi (2.5 M in hexanes, 21.9 mL, 54.7 mmol) via syringe over 15 min. The solution was stirred at -65 °C for 50 min. Then a solution of N,5-dimethoxy-N-methyl-pentanamide (10.03 g, 57.3 mmol) in THF (20 mL) was added. The solution was stirred at -65 °C for 1 h and 20 °C for 16 h. HCl (1 N) aqueous solution was added to adjust the pH to 4. The mixture was extracted with ethyl acetate (200 mL × 2). The combined organic layers were washed with saturated brine (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (petroleum ether/EtOAc 10/1) to give 1-[5-bromo-2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]pyrazol-3-yl]-5-methoxy-pentan-1-one (18.0 g, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 4.72 (t, J = 6.0 Hz, 2 H), 3.97 (t, J = 5.6 Hz, 2 H), 3.47 (t, J = 6.0 Hz, 2 H), 3.39 (s, 3H), 2.89 (t, J = 7.2 Hz, 2 H), 1.90-1.80 (m, 2H), 1.75-1.65 (m, 3H), 0.87 (s, 9H), 0.00 (s, 6H).

[000521] **Step C:** Preparation of 1-[5-bromo-2-(2-hydroxyethyl)pyrazol-3-yl]-5-methoxy-pentan-1-one: To a solution of 1-[5-bromo-2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]pyrazol-3-yl]-5-methoxy-pentan-1-one (18.00 g, 42.9 mmol) in THF (100 mL) was added TBAF (2.0 M in THF, 43.0 mL, 85.8 mmol). The mixture was stirred at 30 °C for 2 h. The mixture was diluted with H_2O and extracted with EtOAc twice. The combined organic phase was dried and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc 1/1) to afford 1-[5-bromo-2-(2-hydroxyethyl)pyrazol-3-yl]-5-methoxy-pentan-1-one (9.00 g, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 4.67 (t, J = 4.8 Hz, 2 H), 3.99 (s, 2 H), 3.40 (t, J = 6.4 Hz, 2 H), 3.32 (s, 3H), 2.85 (t, J = 7.2 Hz, 2 H), 2.70-2.60 (m, 1H), 1.80-1.60 (m, 5H).

[000522] **Step D:** Preparation of 2-[3-bromo-5-(5-methoxypentanoyl)pyrazol-1-yl]ethyl methanesulfonate: To a solution of 1-[5-bromo-2-(2-hydroxyethyl)pyrazol-3-yl]-5-methoxy-pentan-1-one (8.60 g, 28.2 mmol) in DCM (60 mL) was added N,N-diisopropylethylamine (15.0 mL, 84.5 mmol) followed by methanesulfonyl chloride (3.30 mL, 42.3 mmol) at 0 °C. The mixture was stirred for 1 h at 10 °C. The mixture was washed with saturated $NaHCO_3$ solution and brine solution. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford 2-[3-bromo-5-(5-methoxypentanoyl)pyrazol-1-yl]ethyl methanesulfonate (11.00 g, 92% yield). The crude was used in the next step directly. ^{1}H NMR (400

MHz, $CDCl_3$) δ 6.87 (s, 1H), 4.85 (t, J = 5.6 Hz, 2 H), 4.57 (t, J = 5.2 Hz, 2 H), 3.40 (t, J = 6.4 Hz, 2 H), 3.33 (s, 3H), 2.97 (s, 3H), 2.86 (t, J = 7.6 Hz, 2 H), 1.83-1.75 (m, 2H), 1.70-1.60 (m, 3H).

[000523] **Step E:** Preparation of 1-[2-(2-azidoethyl)-5-bromo-pyrazol-3-yl]-5-methoxy-pentan-1-one: To a solution of 2-[3-bromo-5-(5-methoxypentanoyl)pyrazol-1-yl]ethyl methanesulfonate (11.0 g, 25.8 mmol) in DMF (50 mL) was added sodium azide (3.36 g, 51.7 mmol). The reaction was stirred at 65 °C for 4 h. After cooling, the reaction was quenched with H_2O and extracted with EtOAc twice. The combined organic phases were washed with brine, dried and concentrated to afford 1-[2-(2-azidoethyl)-5-bromo-pyrazol-3-yl]-5-methoxy-pentan-1-one (9.60 g, 96% yield).

[000524] **Step F:** Preparation of 2-bromo-4-(4-methoxybutyl)-6,7-dihydropyrazolo[1,5-a]pyrazine: To a solution of 1-[2-(2-azidoethyl)-5-bromo-pyrazol-3-yl]-5-methoxy-pentan-1-one (9.60 g, 23.3 mmol) in THF (100 mL)/water (20 mL) was added triphenylphosphine (7.32 g, 27.9 mmol). The mixture was stirred at 80 °C for 3 h. The mixture was concentrated and purified by column chromatography (petroleum ether/EtOAc 1/1 to neat EtOAc) to afford 2-bromo-4-(4-methoxybutyl)-6,7-dihydropyrazolo[1,5-a]pyrazine (4.80 g, 72% yield). LCMS ESI (+) m/z 286.0 (M+H).

[000525] **Step G:** Preparation of (4S)-2-bromo-4-(4-methoxybutyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine: To a suspension of 2-bromo-4-(4-methoxybutyl)-6,7-dihydropyrazolo[1,5-a]pyrazine (4.60 g, 16.1 mmol) in DMF (40 mL) / water (40 mL) were added HCOONa (4.37 g, 64.3 mmol) and RuCl[(1R,2R)-Tsdpen](p-cymene) (0.51 g, 0.80 mmol). The mixture was stirred at 55 °C for 16 h. After cooling to rt, H_2O was added and the mixture was extracted with DCM twice. After drying and concentration, The residue was purified by column chromatography (DCM/MeOH=20/1) to afford (4S)-2-bromo-4-(4-methoxybutyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (4.10 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H), 4.20-3.90 (m, 3 H), 3.39 (t, *J* = 6.8 Hz, 3 H), 3.33 (s, 3 H), 3.20-3.10 (m, 1H), 1.90-1.80 (m, 1H), 1.75-1.45 (m, 7H).

[000526] **Step H:** Preparation of tert-butyl (4S)-2-bromo-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of (4S)-2-bromo-4-(4-methoxybutyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (3.60 g, 12.5 mmol) in DCM (50 mL) were added triethylamine (5.2 mL, 37.5 mmol) and Boc_2O (3.27 g, 15.0 mmol). The mixture was stirred at 25 °C for 3 h. Water was added and extracted with DCM twice. After drying and concentration, the residue was purified by column chromatography (petroleum ether/EtOAc 5/1) to afford tert-butyl (4S)-2-bromo-4-(4-methoxybutyl)-6,7-dihydro-4H- pyrazolo[1,5-a]pyrazine-5-carboxylate (1.10 g, 23% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.30-5.10 (m, 1H), 4.60-4.20 (m, 1H), 4.20-4.00 (m, 2H), 3.37 (t, *J* = 6.0 Hz, 2H), 3.32 (s, 3H), 1.82-1.72 (m, 2H), 1.68-1.58 (m, 2H), 1.46 (s, 11H).

[000527] **Step I:** Preparation of tert-butyl (4S)-2-cyano-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a stirred solution of tert-butyl (4S)-2-bromo-4-(4-

methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.20 g, 3.09 mmol) in DMA (20 mL) were added dicyanozinc (544 mg, 4.64 mmol), zinc (40 mg, 0.62 mmol), dppf (345 mg, 0.618 mmol) and $Pd_2(dba)_3$ (283 mg, 0.309 mmol). The solution was stirred at 120 °C for 16 h under Ar atmosphere. The mixture was filtered and the filtrate was concentrated in vacuo. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with saturated brine solution, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc = 4/1) to give tert-butyl (4S)-2-cyano-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (800 mg, 77% yield) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 1H), 5.40-5.10 (m, 1H), 4.65-4.35 (m, 1H), 4.28-4.20 (m, 1H), 4.18-4.05 (m, 1H), 3.38 (t, J = 6.0 Hz, 2H), 3.33 (s, 3H), 1.80-1.70 (m, 2H), 1.68-1.58 (m, 2H), 1.52 (s, 11H).

[000528] Step J: Preparation of tert-butyl (4S)-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of 2-[(2,4-difluoro-6-methoxy-phenyl)methyl]-N,N-diethyl-thiophene-3-carboxamide (244 mg, 0.718 mmol) in THF (5 mL) was added n-BuLi (2.5 M in hexanes, 0.263 mL, 0.658 mmol) dropwise at -65 °C. The mixture was stirred at -65 °C for 40 min under Ar. A solution of tert-butyl (4S)-2-cyano-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (200 mg, 0.598 mmol) in THF (3 mL) was added. The dry ice-bath was removed, and the mixture was stirred at 15 °C for 3 h. The reaction was quenched by saturated NH_4Cl and extracted with EtOAc twice. After drying and concentration, the residue was purified by column chromatography (petroleum ether/EtOAc = 1/1 to DCM/MeOH = 9/1) to afford tert-butyl (4S)-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (210 mg, 58% yield). LCMS ESI (+) m/z 601.2 (M+H).

[000529] Step K: Preparation of tert-butyl (4S)-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (4S)-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (210 mg, 0.350 mmol) and DIPEA (0.310 mL, 1.75 mmol) in DCM (5 mL) was added trifluoromethanesulfonic anhydride (0.089 mL, 0.524 mmol) in DCM (1 mL) dropwise at 0 °C. The mixture was stirred at 15 °C for 1 h. The reaction was quenched with H_2O and extracted with DCM twice. After drying and concentration, the residue was purified by Prep-TLC (petroleum ether/EtOAc: 2/1) to afford tert-butyl (4S)-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (230 mg, 90% yield).

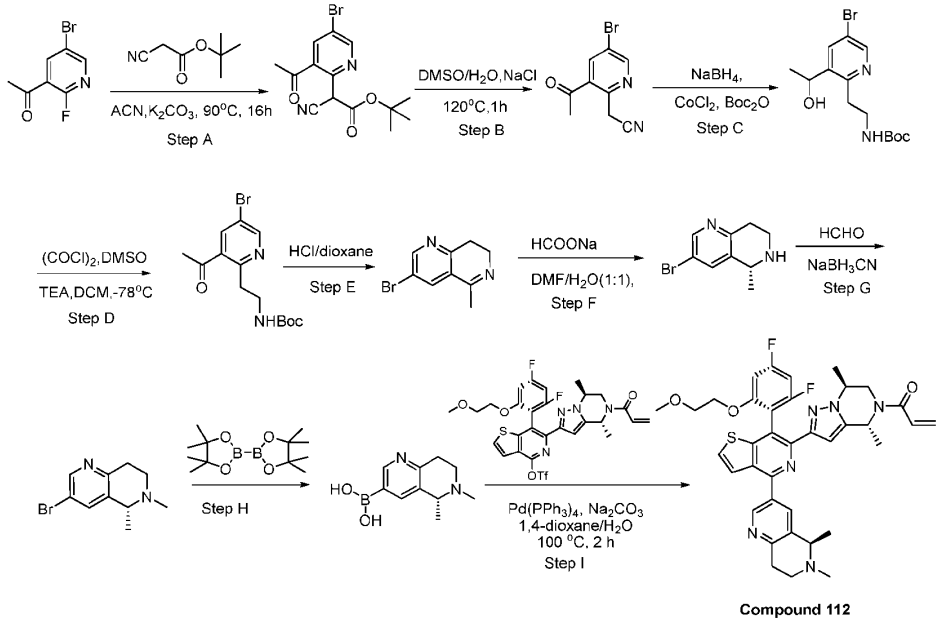
[000530] Step L: Preparation of tert-butyl (4S)-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-

a]pyrazine-5-carboxylate: A mixture of tert-butyl (4S)-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (200 mg, 0.273 mmol), (1-methylindazol-5-yl)boronic acid (96 mg, 0.55 mmol), $Pd(PPh_3)_4$ (32 mg, 0.027 mmol) and Na_2CO_3 (145 mg, 1.36 mmol) in 1,4-dioxane (18 mL) / water (2 mL) was stirred at 100 °C for 3 h under Ar. The mixture was concentrated and purified by column chromatography (DCM/MeOH: 30/1) to afford tert-butyl (4S)-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (230 mg, 94% yield). LCMS ESI (+) m/z 715.4 (M+H).

[000531] Step M: Preparation of tert-butyl (4S)-4-(4-bromobutyl)-2-[7-(2,4-difluoro-6-hydroxy-phenyl)-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (4S)-2-[7-(2,4-difluoro-6-methoxy-phenyl)-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-4-(4-methoxybutyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (30 mg, 0.042 mmol) in DCM (5 mL) was added solution of boron tribromide (0.12 mL, 1.3 mmol) in DCM slowly at -20 °C. The mixture was stirred at 15 °C for 16 h. Water was added to quench the reaction at 0 °C, $NaHCO_3$ was added to adjust pH to 8 and then di-tert-butyl dicarbonate (0.029 mL, 0.13 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 3 h. The mixture was diluted with H_2O and extracted with DCM twice. After drying and concentration, the residue was purified by prep-TLC (DCM/MeOH : 19/1) to afford tert-butyl (4S)-4-(4-bromobutyl)-2-[7-(2,4-difluoro-6-hydroxy- phenyl)-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (16 mg, 51% yield). LCMS ESI (+) m/z 749.2/751.2 (M+H).

[000532] Step N to Step Q: Preparation of (*S,Z*)-1-(3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,4)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclooctaphane-1^5-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 10 Step Q to Step S, substituting tert-butyl (4S)-4-(4-bromobutyl)-2-[7-(2,4-difluoro-6-hydroxy-phenyl)-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate for tert-butyl (R)-6-(5-bromopentyl)-2-((S)-7-(2,4-difluoro-6-hydroxyphenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate in Step Q. The crude was purified by preparative HPLC to afford (*S,Z*)-1-(3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,4)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclooctaphane-1^5-yl)prop-2-en-1-one as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.27 (s, 1H), 8.10-8.03 (m, 2H), 7.89 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.16-7.13 (m, 1H), 6.95-6.80 (m, 2H), 6.35-6.25 (m, 1H), 6.03 (s, 1H), 5.90-5.80 (m, 1H), 5.70-5.40 (m, 1H), 4.70-4.40 (m, 3H), 4.40-4.21 (m, 1H), 4.20 (s, 3H), 3.90-3.75 (m, 2H), 2.50-2.20 (m, 1H), 1.70-1.55 (m, 1H), 1.55-1.15 (m, 5H). LCMS ESI (+) m/z 623.2 (M+H).

Synthetic Example 14: Synthesis of 1-((4R,7S)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 112**)



Compound 112

[000533] **Step A:** Preparation of tert-butyl 2-(3-acetyl-5-bromo-2-pyridyl)-2-cyano-acetate: To a solution of 1-(5-bromo-2-fluoro-3-pyridyl)ethanone (75.0 g, 344 mmol) in acetonitrile (1000 mL) were added K_2CO_3 (190.2 g, 1376 mmol) and tert-butyl 2-cyanoacetate (72.8 g, 516 mmol). The reaction mixture was stirred at 90 °C for 16 h. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc: petroleum ether=0-100%) to give tert-butyl 2-(3-acetyl-5-bromo-2-pyridyl)-2-cyano-acetate (110.0 g, 85% yield). LCMS ESI (+) m/z 339.0/340.9 (M+H).

[000534] **Step B:** Preparation of 2-(3-acetyl-5-bromo-2-pyridyl) acetonitrile: To a solution of tert-butyl 2-(3-acetyl-5-bromo-2-pyridyl)-2-cyano-acetate (110.0 g, 324.0 mmol) in DMSO (345 mL) was added NaCl (37.9 g, 649 mmol) and water (172 mL) and the resulting solution was stirred at 120 °C for 1 hour. The mixture was diluted with water (800 mL) and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (100 x 2 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc: petroleum ether= 0 – 20%) to give 2-(3-acetyl-5-bromo-2-pyridyl) acetonitrile (36.0 g, 46% yield). LCMS ESI (+) m/z 239.1/241.1 (M+H).

[000535] **Step C:** Preparation of tert-butyl N-[2-[5-bromo-3-(1-hydroxyethyl)-2-pyridyl] ethyl] carbamate: To a solution of 2-(3-acetyl-5-bromo-2-pyridyl)acetonitrile (36.0 g, 151 mmol) in methanol

(360 mL) at 0 °C was added $NaBH_4$ (5.70 g, 151 mmol) and the reaction was stirred at 0 °C for 1 hour. After the mixture was cooled to -20 °C, $CoCl_2$•$6H_2O$ (39.1 g, 164 mmol), Boc_2O (45.6 g, 209 mmol) and $NaBH_4$ (5.65 g, 149 mmol) were added. The mixture was stirred at -20 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (700 mL), and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (50% ethyl acetate/pet. ether) to afford tert-butyl N-[2-[5-bromo-3-(1-hydroxyethyl)-2-pyridyl] ethyl]carbamate (24.2 g, 42% yield) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 2.2 Hz, 1H), 7.99 (d, J = 2.2 Hz, 1H), 5.11 (dd, J = 6.1, 3.0 Hz, 2H), 3.67 – 3.57 (m, 1H), 3.53 – 3.44 (m, 1H), 3.10 – 3.00 (m, 1H), 2.98 – 2.84 (m, 2H), 1.48 (d, J = 6.4 Hz, 3H), 1.36 (s, 9H). LCMS ESI (+) m/z 345.0/346.9 (M+H).

[000536] **Step D:** Preparation of tert-butyl N-[2-(3-acetyl-5-bromo-2-pyridyl) ethyl] carbamate: To a solution of $(COCl)_2$ (17.8 g, 140 mmol) in DCM (160 mL) at -78 °C under Ar was added dropwise DMSO (21.9 g, 280 mmol) in DCM (20 mL), and the mixture was stirred at -78 °C for 30 min. tert-Butyl N-[2-[5-bromo-3-(1-hydroxyethyl)-2-pyridyl]ethyl]carbamate (24.2 g, 70.1 mmol) in DCM (120 mL) was added to the reaction mixture at -78 °C and stirring was continued for 1 h. TEA (59.0 mL, 421 mmol) was added at -78 °C and the reaction was allowed to warm to rt. Water was added to the reaction mixture and was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give crude tert-butyl N-[2-(3-acetyl-5-bromo-2-pyridyl)ethyl]carbamate, which was used to the next reaction directly. LCMS ESI (+) m/z 343.1/345.1 (M+H).

[000537] **Step E:** Preparation of 3-bromo-5-methyl-7,8-dihydro-1,6-naphthyridine: To a solution of tert-butyl N-[2-(3-acetyl-5-bromo-2-pyridyl)ethyl]carbamate (35.0 g, 61.2 mmol) in DCM (230 mL) was added 4N HCl/dioxane (122 mL, 489 mmol). The reaction mixture was stirred at 25 °C for 3 h. The solvent was separated out and water (300 mL) was added. The pH was adjusted to ~12 with 20% NaOH. The mixture was extracted with DCM (200 mL x 3). The combined organic layers were washed with brine (100 x 2 mL), dried over Na_2SO_4, and concentrated under vacuum to give 3-bromo-5-methyl-7,8-dihydro-1,6-naphthyridine (17.5 g, 95% yield). LCMS ESI (+) m/z 225.0/227.0 (M+H).

[000538] **Step F:** Preparation of (5R)-3-bromo-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine: A mixture of 3-bromo-5-methyl-7,8-dihydro-1,6-naphthyridine (17.5 g, 77.7 mmol), HCOONa (26.4 g, 389 mmol), and RuCl(p-cymene)[(S,S)-Ts-DPEN] (2.47 g, 3.89 mmol) in DMF (200 mL) and water (200 mL) was stirred at 40 °C under N_2 for 16h. The mixture was diluted with water (500 mL) and extracted with DCM (200 mL x 5). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (MeOH: DCM =1:30) to give the crude product (10.5 g, 88% ee) which was dissolved in EtOAc (735 mL). (+)-Dibenzoyl-D-tartaric acid (18.2 g)

was added and the mixture was stirred at 75 °C for 16 h. The mixture was filtered and washed with EtOAc to give the desired product in 97% ee. The filter cake was added to a flask. DCM (100 mL) and H_2O (100 mL) was added. The mixture was cooled to 0-10 °C and the pH was adjusted to 10-11 with 20% NaOH aqueous solution. After stirring for 10 min, the mixture was extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under vacuum to get (5R)-3-bromo-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (3.00 g, 17% yield) as a pale-yellow oil. LCMS ESI (+) m/z 227.0/229.0 (M+H).

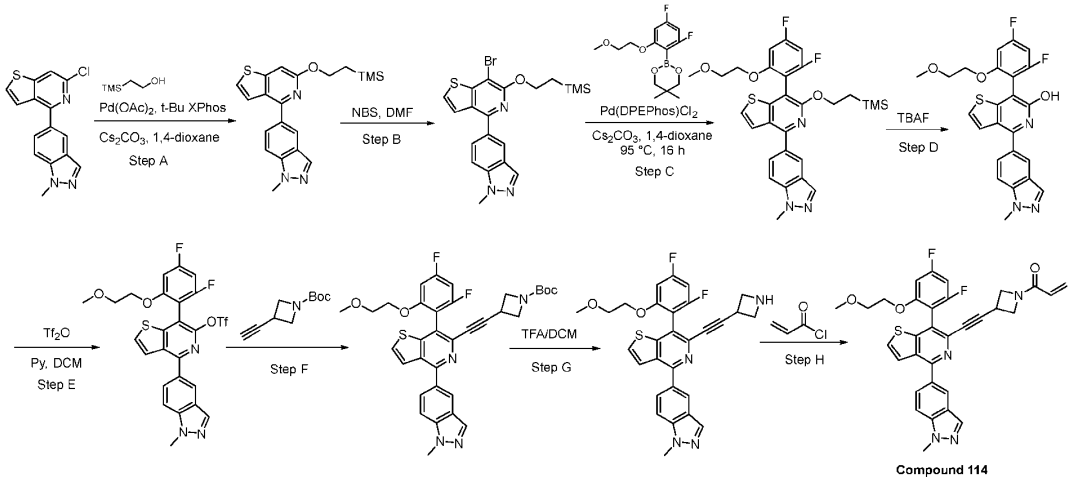
[000539] **Step G:** Preparation of (5R)-3-bromo-5,6-dimethyl-7,8-dihydro-5H-1,6-naphthyridine: To a solution of (5R)-3-bromo-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (3300 mg, 14.53 mmol) and HCHO (40% aqueous solution, 1.77 g, 21.8 mmol) in methanol (50 mL) was added $NaBH_3CN$ (1.37 g, 21.8 mmol). The mixture was stirred at rt for 3 h. The mixture was concentrated to dryness and the residue was purified by flash column chromatography eluting with 3% MeOH in DCM. The desired fractions were concentrated to dryness in vacuo to get (5R)-3-bromo-5,6-dimethyl-7,8-dihydro-5H-1,6-naphthyridine (2.50 g, 71% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 2.1 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 3.63 (d, J = 6.6 Hz, 1H), 3.18 – 3.09 (m, 1H), 2.98 (dt, J = 8.7, 6.3 Hz, 2H), 2.76 (ddd, J = 12.2, 6.9, 5.4 Hz, 1H), 2.49 (s, 3H), 1.40 (d, J = 6.7 Hz, 3H). LCMS ESI (+) m/z 241.0/243.0 (M+H).

[000540] **Step H:** Preparation of (R)-(5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)boronic acid: To a suspension of (5R)-3-bromo-5,6-dimethyl-7,8-dihydro-5H-1,6-naphthyridine (1.50 g, 6.22 mmol), KOAc (1.50 g, 15.3 mmol) and bis(pinacolato)diboron (2.10 g, 8.27 mmol) in 1,4-dioxane (15 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (450 mg, 0.615 mmol). The mixture was stirred at 100 °C for 4 h under Ar. The mixture was filtered and washed with MeCN. The filtrate was concentrated and then dissolved in H_2O (1 mL), MeCN (1 mL) and TFA (1 mL). The residue was purified by reserve-phase column to give (R)-(5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)boronic acid trifluoracetic acid salt (2.70 g, 90% yield) as a white solid. LCMS ESI (+) m/z 207.2 (M+H).

[000541] **Step I:** Preparation of 1-((4R,7S)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of (S)-6-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl trifluoromethanesulfonate (40 mg, 0.047 mmol) in ethyl acetate (1 mL)/water (1 mL) was added $NaHCO_3$ (39 mg, 0.47 mmol) to adjust the pH to 8. To the mixture was added acryloyl chloride (0.0057 mL, 0.070 mmol) at 0 °C and the mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried ($MgSO_4$) before concentrating to dryness. The residue was purified by

Prep-HPLC to give 1-((4R,7S)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (15 mg, 46% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.16 (d, J = 0.6 Hz, 1H), 8.07 (dd, J = 8.7, 1.4 Hz, 1H), 7.80 - 7.67 (m, 3H), 6.94 - 6.78 (m, 2H), 6.71 - 6.62 (m, 1H), 6.31 (d, J = 16.5 Hz, 1H), 6.27 - 6.18 (m, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.78 - 5.43 (m, 1H), 4.46 - 4.36 (m, 1H), 4.16 (s, 3H), 4.13 - 4.07 (m, 1H), 4.06 - 3.99 (m, 1H), 3.45 (t, J = 4.8 Hz, 2H), 3.05 (s, 3H), 1.54 - 1.37 (m, 3H), 1.34 - 1.21 (m, 3H). LCMS ESI (+) m/z 655.4 (M+H).

Synthetic Example 15: Synthesis of 1-(3-((7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-indazol-5-yl)thieno[3,2-c]pyridin-6-yl)ethynyl)azetidin-1-yl)prop-2-en-1-one (**Compound 114**)



[000542] Step A: Preparation of trimethyl-[2-[4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]oxyethyl]silane: To a solution of 6-chloro-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine (800 mg, 2.67 mmol) in 1,4-dioxane (20 mL) were added 2-trimethylsilylethanol (4730 mg, 40.0 mmol), cesium carbonate (2610 mg, 8.01 mmol), palladium(II) acetate (60 mg, 0.27 mmol) and t-Bu XPhos (227 mg, 0.534 mmol). The mixture was stirred at 85 °C for 8 h. The mixture was poured into water (40 mL) and extracted with EtOAc (80 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (petroleum ether:EtOAc 3:1) to give trimethyl-[2-[4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]oxyethyl]silane (0.90 g, 88% yield). LCMS ESI (+) m/z 381.2 (M+H).

[000543] Step B: Preparation of 2-[7-bromo-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]oxyethyl-trimethyl-silane: To a solution of trimethyl-[2-[4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]oxyethyl]silane (1000 mg, 2.62 mmol) in DMF (5 mL) was added N-bromosuccinimide (466 mg, 2.62 mmol). The mixture was stirred at 25 °C for 4 h. The mixture was poured into water (40 mL) and extracted

with EtOAc (40 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (petroleum ether:EtOAc 8:1) to give 2-[7-bromo-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]oxyethyl-trimethyl-silane (710 mg, 59% yield).

[000544] **Step C:** Preparation of 2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]oxyethyl-trimethyl-silane: To a solution of 2-[7-bromo-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]oxyethyl-trimethyl-silane (800 mg, 1.74 mmol) in 1,4-dioxane (5 mL) were added 2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5,5-dimethyl-1,3,2-dioxaborinane (1040 mg, 3.47 mmol), Pd(DPEPhos)Cl_2 (124 mg, 0.174 mmol) and cesium carbonate (1130 mg, 3.47 mmol). The mixture was stirred at 95 °C for 16 h. The mixture was concentrated and purified by column chromatography (petroleum ether:EtOAc 3:1) to give 2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]oxyethyl-trimethyl-silane (490 mg, 50% yield). LCMS ESI (+) m/z 568.2 (M+H).

[000545] **Step D:** Preparation of 7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-ol: To a solution of 2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]oxyethyl-trimethyl-silane (450 mg, 0.793 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 12.0 mL, 11.9 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was poured into water (40 mL) and extracted with EtOAc (40 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (DCM:MeOH 30:1) to give 7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-ol (180 mg, 49% yield). LCMS m/z [M+1]: 468.1.

[000546] **Step E:** Preparation of [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl] trifluoromethanesulfonate: To a solution of 7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-ol (120 mg, 0.257 mmol) in DCM (5 mL) was added pyridine (0.210 mL, 2.57 mmol) followed by trifluoromethanesulfonic anhydride (0.065 mL, 0.38 mmol) under 0 °C. The mixture was stirred at 0 °C for 0.5 h. The mixture was poured into water (40 mL) and extracted with EtOAc (40 mL x 2), and the combined organic layer was washed with brine (40 mL), dried over Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (petroleum ether:EtOAc 1:1) to give [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl] trifluoromethanesulfonate (140 mg, 82% yield) as a white solid. LCMS ESI (+) m/z 600.1 (M+H).

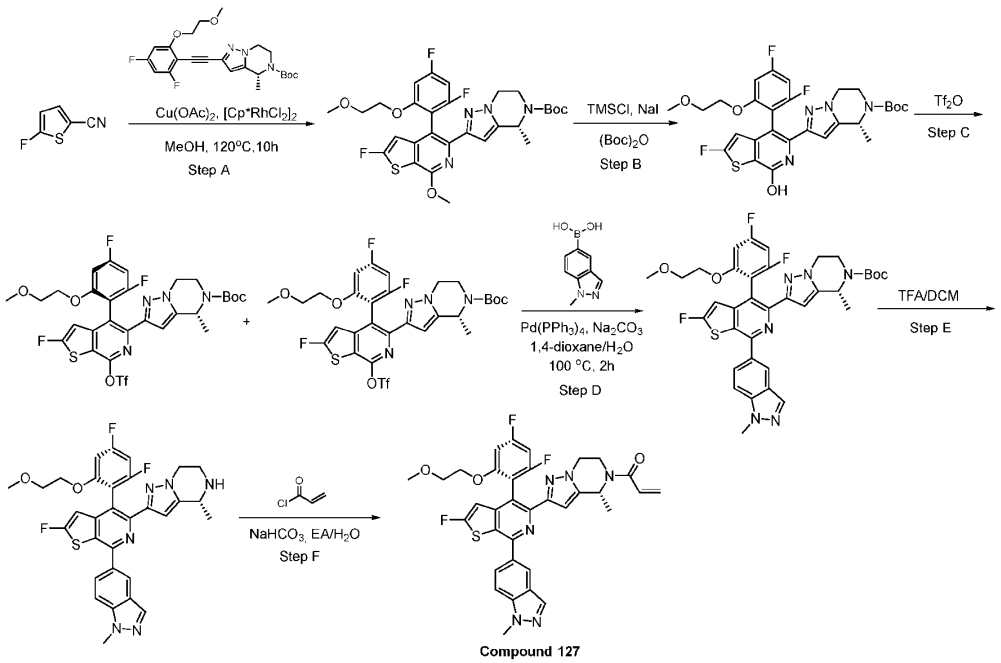
[000547] **Step F:** Preparation of tert-butyl 3-[2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]ethynyl]azetidine-1-carboxylate: A mixture of [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl] trifluoromethanesulfonate (15 mg, 0.025 mmol), tert-butyl 3-ethynylazetidine-1-carboxylate (10 mg, 0.055

mmol), cesium carbonate (25 mg, 0.077 mmol) and bis(triphenylphosphine)palladium(II) chloride (2.4 mg, 0.0034 mmol) in DMSO (2 mL) was stirred at 110 °C for 16 h under Ar atmosphere. The mixture was diluted with brine solution and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (EtOAc/petroleum ether=1/1) to give tert-butyl 3-[2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]ethynyl]azetidine-1-carboxylate (5.6 mg, 28% yield). LCMS ESI (+) m/z 631.3 (M+H).

[000548] Step G: Preparation of 6-[2-(azetidin-3-yl)ethynyl]-7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine: To a solution of tert-butyl 3-[2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]ethynyl]azetidine-1-carboxylate (5.6 mg, 0.0071 mmol) in DCM (1 mL) was added trifluoroacetic acid (0.50 mL, 6.5 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated to dryness to give 6-[2-(azetidin-3-yl)ethynyl]-7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine trifluoroacetic acid salt (8.0 mg, 100% yield) which was used for next step directly. LCMS ESI (+) m/z 531.2 (M+H).

[000549] Step H: Preparation of 1-[3-[2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]ethynyl]azetidin-1-yl]prop-2-en-1-one: To a solution of crude 6-[2-(azetidin-3-yl)ethynyl]-7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridine trifluoroacetic acid salt (8.0 mg, 0.0071 mmol) in water (2 mL) and ethyl acetate (2 mL) was added Na_2CO_3 to adjust the pH to 8. Sodium bicarbonate (4.6 mg, 0.055 mmol) was added. The temperature of the mixture was cooled to 0 °C, and then acryloyl chloride (0.00090 mL, 0.011 mmol) in DCM (0.1 mL) was added dropwise. The mixture was stirred at this temperature for 20 min. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (DCM/MeOH: 30/1) to give 1-[3-[2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]ethynyl]azetidin-1-yl]prop-2-en-1-one (1.8 mg, 42% yield) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.17 (s, 1H), 7.94 – 7.89 (m, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.67 (d, J = 5.5 Hz, 1H), 6.97 – 6.87 (m, 1H), 6.83 - 6.73 (m, 1H), 6.30 – 6.25 (m, 2H), 5.80 – 5.72 (m, 1H), 4.60 – 4.49 (m, 1H), 4.32 - 4.24 (m, 1H), 4.11 - 4.00 (m, 5H), 3.90 – 3.79 (m, 1H), 3.55 - 3.45 (m, 3H), 3.16 - 3.11 (m, 1H), 3.10 (s, 3H). LCMS m/z [M+1]: 585.2

Synthetic Example 16: Synthesis of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 127**)



Compound 127

[000550] **Step A:** Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-methoxythieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A solution of tert-butyl (4R)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (100 mg, 0.223 mmol), 5-fluorothiophene-2-carbonitrile (37 mg, 0.34 mmol), copper(II) acetate monohydrate (71 mg, 0.36 mmol) and bis[(pentamethyl cyclopentadienyl)dichloro-rhodium] (4.1 mg, 0.0067 mmol) in MeOH (3 mL) was stirred at 120 °C overnight. The mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc = 1/1) to give tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-methoxythieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (45 mg, 33% yield). LCMS ESI (+) m/z 605.2 (M+H).

[000551] **Step B:** Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-2-fluoro-7-methoxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (45 mg, 0.074 mmol) and sodium iodide (45 mg, 0.30 mmol) in MeCN (7 mL) was added trimethylchlorosilane (0.038 mL, 0.30 mmol) at 0 °C. The mixture was warmed to rt and stirred for 3 h. Saturated sodium

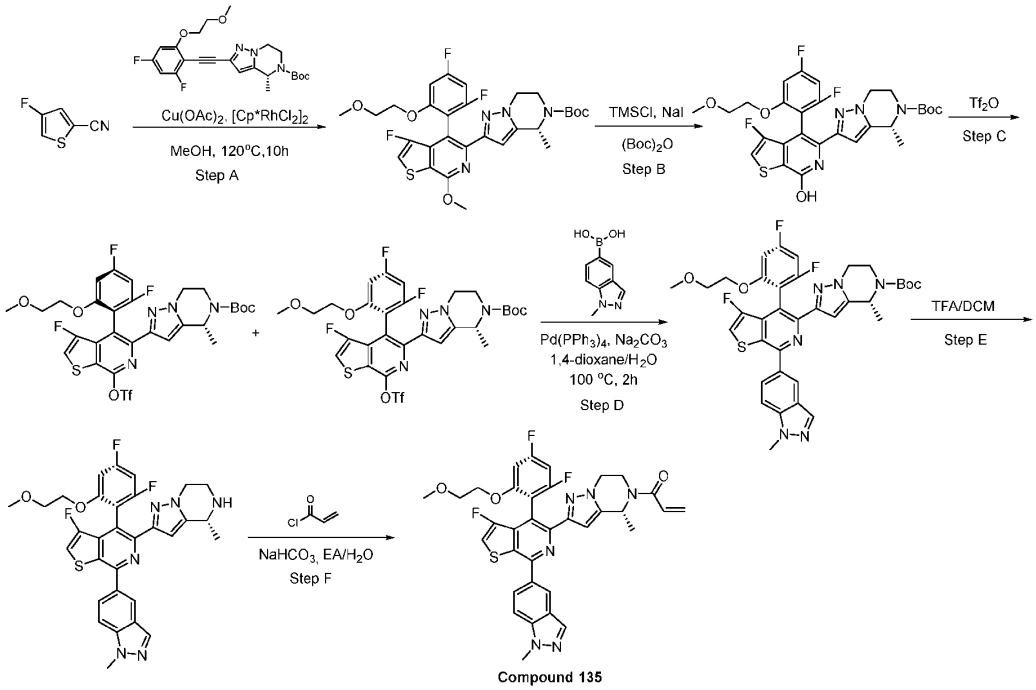
bicarbonate solution was added to adjust the pH to 8, and then di-tert-butyl dicarbonate (0.240 mL, 1.02 mmol) in THF (2 mL) was added. The mixture was stirred at room temperature for an additional 16 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic phases were washed with brine solution, dried over Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (Petroleum Ether/EtOAc = 1/1) to give tert-butyl (4S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-2-fluoro-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (39 mg, 89% yield) as a light yellow solid. LCMS ESI (+) m/z 591.2 (M+H).

[000552] **Step C:** Preparation of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-2-fluoro-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (39 mg, 0.066 mmol) and pyridine (0.0320 mL, 0.396 mmol) in DCM (3 mL) was added trifluoromethanesulfonic anhydride (0.017 mL, 0.099 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (20 mL) and extracted with DCM (15 mL × 3). The combined organic layers were washed with saturated brine (20 mL) solution, dried over Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (petroleum ether/EtOAc = 3/1) to give the less polar isomer, tert-butyl (R)-2-((S)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (23 mg, 48% yield), and the more polar isomer, tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (24 mg, 50% yield) as a white solid. LCMS ESI (+) m/z 723.2 (M+H).

[000553] **Step D to Step F:** Preparation of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 8 Step I to Step K, substituting tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate for tert-butyl(4R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate in Step I. The crude was purified by preparative HPLC to afford 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2-fluoro-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.21 (s, 1H), 8.07 (dd, J = 8.8, 1.6 Hz, 1H), 7.84 (d, J = 8.8

Hz, 1H), 6.98 – 6.71 (m, 4H), 6.29 (d, J = 16.6 Hz, 1H), 5.98 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.74 – 5.42 (m, 1H), 4.29 (dd, J = 12.8, 2.9 Hz, 1H), 4.23 – 3.99 (m, 6H), 3.48 (t, J = 4.5 Hz, 2H), 3.14 (s, 3H), 1.47 – 1.35 (m, 3H). LCMS ESI (+) m/z 659.2 (M+H).

Synthetic Example 17: Synthesis of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 135**)



Compound 135

[000554] **Step A:** Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-methoxythieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A solution of tert-butyl (4R)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (300 mg, 0.670 mmol), 4-fluorothiophene-2-carbonitrile (102 mg, 0.805 mmol), $Cu(OAc)_2$ (195 mg, 1.07 mmol) and $[Cp^*RhCl_2]_2$ (12 mg, 0.020 mmol) in MeOH (6 mL) was stirred at 120 °C under argon for 10 h. The reaction mixture was filtered. The filtrate was concentrated and purified by Prep-TLC (petroleum ether:EtOAc=1:1, Rf=0.6) to give tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (255 mg, 63% yield) as a light-yellow oil. LCMS ESI (+) m/z 605.2 (M+H).

[000555] **Step B:** Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-

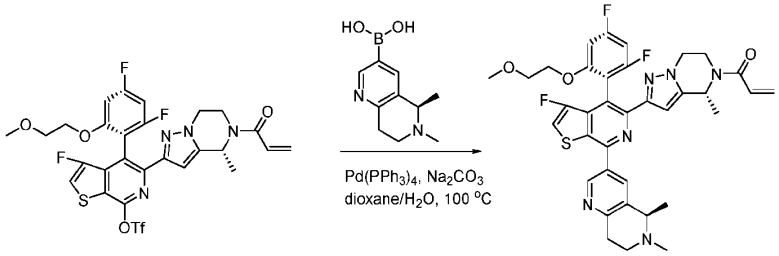
carboxylate: To a solution of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (287 mg, 0.475 mmol) and sodium iodide (285 mg, 1.90 mmol) in MeCN (5 mL) was added trimethylchlorosilane (0.240 mL, 1.90 mmol) at 0 °C. The mixture was warmed to rt and stirred for 4 h. Saturated sodium bicarbonate solution was added to adjust the pH to 8, and then di-tert-butyl dicarbonate (0.170 mL, 0.712 mmol) was added. The mixture was stirred at room temperature for an additional 2 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic phases were washed with brine solution, dried over Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (DCM:MeOH=20:1) to give tert-butyl (4S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (225 mg, 76% yield) as a white solid. LCMS ESI (+) m/z 591.2 (M+H).

[000556] Step C: Preparation of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (225 mg, 0.381 mmol) and pyridine (0.310 mL, 3.81 mmol) in DCM (5 mL) was added trifluoromethanesulfonic anhydride (0.097 mL, 0.57 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (20 mL) and extracted with DCM (15 mL × 3). The combined organic layers were washed with saturated brine solution (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (petroleum ether/EtOAc = 4/1) to give the less polar isomer tert-butyl (R)-2-((S)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (95 mg, 34% yield) and the more polar isomer tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (93 mg, 33% yield) as a white solid. LCMS ESI (+) m/z 723.1 (M+H).

[000557] Step D to Step F: Preparation of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 8 Step I to Step K, substituting tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate for tert-butyl(4R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoro methylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-

a]pyrazine-5-carboxylate in Step I. The crude was purified by preparative HPLC to afford 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(1-methyl-1H-indazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.55 - 7.50 (m, 1H), 6.89 - 6.75 (m, 2H), 6.66 - 6.57 (m, 1H), 6.37 - 6.21 (m, 1H), 6.08 (s, 1H), 5.85 - 5.78 (m, 1H), 5.75 - 5.37 (m, 1H), 4.51 - 4.30 (m, 1H), 4.24 - 4.17 (m, 1H), 4.16 (s, 3H), 4.12 - 3.96 (m, 3H), 3.85 - 3.64 (m, 1H), 3.46 (t, J = 4.7 Hz, 2H), 3.08 (s, 3H), 1.55 - 1.35 (m, 3H). LCMS ESI (+) m/z 659.3 (M+H).

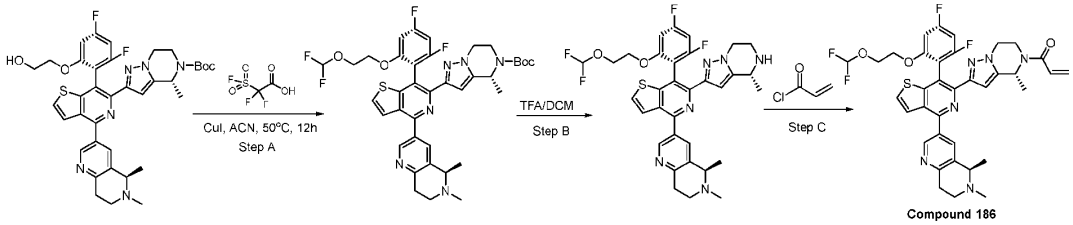
Synthetic Example 18: Synthesis of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 162**)



Compound 162

[000558] A suspension of (R)-5-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (20 mg, 0.029 mmol), Na_2CO_3 (6.3 mg, 0.059 mmol), [(5R)-5,6-dimethyl-7,8-dihydro-5H-1,6-naphthyridin-3-yl]boronic acid (6.0 mg, 0.029 mmol) and $Pd(PPh_3)_4$ (3.4 mg, 0.0029 mmol) in 1,4-dioxane (1 mL) and water (0.1 mL) was stirred at 100 °C for 2 h under Ar. The mixture was filtered, and the filtrate was concentrated. The residue was purified by Prep-TLC (EtOAc/petroleum ether=1/1) to give 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (2.3 mg, 11% yield) as a white solid. ^{1}H NMR (700 MHz, CD_3OD) δ 9.13 (s, 1H), 8.35 (s, 1H), 7.57 (d, J = 2.3 Hz, 1H), 6.90 - 6.76 (m, 2H), 6.67 - 6.58 (m, 1H), 6.37 - 6.21 (m, 1H), 6.06 (s, 1H), 5.86-5.79 (m, 1H), 5.74 - 5.40 (m, 1H), 4.27 - 4.17 (m, 1H), 4.15 - 3.96 (m, 4H), 3.92 - 3.80 (m, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.25 - 3.10 (m, 2H), 3.06 (s, 3H), 2.96 - 2.86 (m, 1H), 2.59 - 2.52 (m, 3H), 1.60 (d, J = 6.6 Hz, 3H), 1.53 - 1.37 (m, 3H). LCMS ESI (+) m/z 689.3 (M+H).

Synthetic Example 19: Synthesis of 1-((R)-2-((S)-7-(2-(2-(difluoromethoxy)ethoxy)-4,6-difluorophenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 186**)



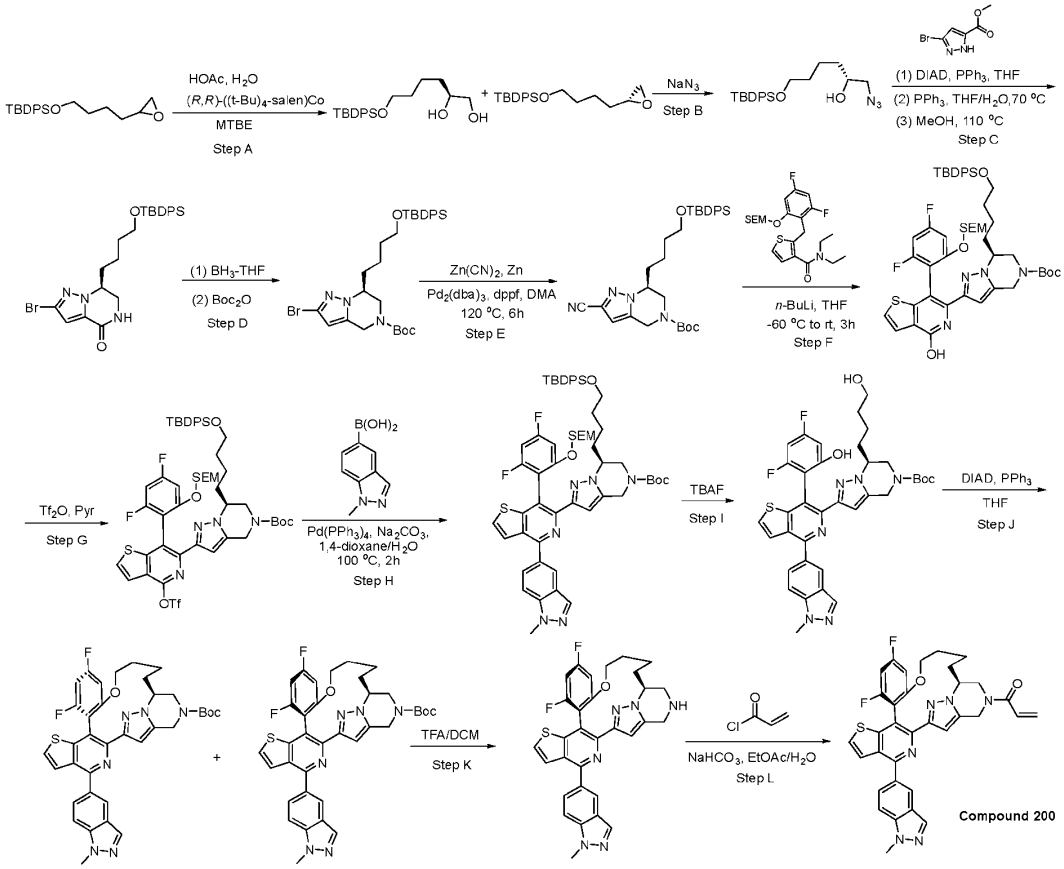
[000559] **Step A:** Preparation of tert-butyl (R)-2-((S)-7-(2-(2-(difluoromethoxy)ethoxy)-4,6-difluorophenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-(2-hydroxyethoxy)phenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (63.0 mg, 0.0896 mmol) in MeCN (1 mL) was added CuI (3.4 mg, 0.018 mmol) under Ar. The mixture was heated to 50 °C and 2,2-difluoro-2-fluorosulfonyl-acetic acid (32 mg, 0.18 mmol) was added. The mixture was stirred at 50 °C for 12 hours. The mixture was filtered, and the filtrate was concentrated. The residue was purified by Prep-TLC (MeOH:DCM=1:10, Rf=0.5) to give crude tert-butyl (R)-2-((S)-7-(2-(2-(difluoromethoxy)ethoxy)-4,6-difluorophenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (30 mg, 31% yield). LCMS ESI (+) m/z 753.2 (M+H).

[000560] **Step B:** Preparation of (S)-7-(2-(2-(difluoromethoxy)ethoxy)-4,6-difluorophenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-6-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[3,2-c]pyridine: To a solution of tert-butyl (R)-2-((S)-7-(2-(2-(difluoromethoxy)ethoxy)-4,6-difluorophenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (30 mg, 0.028 mmol) in DCM (3 mL) was added trifluoroacetic acid (1.0 mL, 13 mmol) dropwise under Ar. The mixture was stirred at 18 °C for 30 minutes. The mixture was concentrated to dryness to give (S)-7-(2-(2-(difluoromethoxy)ethoxy)-4,6-difluorophenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-6-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[3,2-c]pyridine (36 mg) which was used in the next step without further purification.

[000561] **Step C:** Preparation of 1-((R)-2-((S)-7-(2-(2-(difluoromethoxy)ethoxy)-4,6-difluorophenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a mixture of crude (S)-7-(2-(2-(difluoromethoxy)ethoxy)-4,6-difluorophenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-6-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[3,2-c]pyridine (36 mg, 0.028 mmol) and $NaHCO_3$ (35.7 mg, 0.337 mmol) in ethyl acetate (1 mL) and water (1 mL) cooled to 0 °C was

added acryloyl chloride (3.0 mg, 0.034 mmol) under Ar. The mixture was stirred at 0 °C for 30 minutes. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (DCM:MeOH=15:1) to give 1-((R)-2-((S)-7-(2-(2-(difluoromethoxy)ethoxy)-4,6-difluorophenyl)-4-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (4.9 mg, 19% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.41 (d, J = 1.3 Hz, 1H), 7.84 (d, J = 5.5 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 6.95 – 6.73 (m, 3H), 6.35 – 6.23 (m, 1H), 6.17 – 5.77 (m, 3H), 5.75 – 5.42 (m, 1H), 4.50 – 4.35 (m, 1H), 4.25 – 4.00 (m, 4H), 3.97 – 3.80 (m, 3H), 3.77 – 3.67 (m, 1H), 3.44 (t, J = 6.4 Hz, 2H), 3.10 (s, 3H), 1.84 (d, J = 6.7 Hz, 3H), 1.52 – 1.37 (m, 3H); LCMS ESI (+) m/z 707.2 (M+H).

Synthetic Example 20: Synthesis of 1-((1^{7}S,E)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,7)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclooctaphane-1^5-yl)prop-2-en-1-one (**Compound 200**)



[000562] **Step A:** Preparation of tert-butyl-[4-[(2R)-oxiran-2-yl]butyl]-diphenyl-silane: A solution of tert-butyl-[4-(oxiran-2-yl)butyl]-diphenyl-silane (6.76 g, 20.0 mmol) and (R,R)-((t-Bu)$_4$-salen)Co (121 mg, 0.200 mmol) in THF (5 mL) was stirred at 0 °C for 5 min and then distilled water (200 mg, 11.1 mmol) was added. The mixture was stirred at 20 °C for 48 h. The mixture was concentrated and purified by column chromatography (EtOAc/ petroleum ether = 1/15 to 1/1) to give tert-butyl-[4-[(2R)-oxiran-2-yl]butyl]-diphenyl-silane (2.80 g, 41% yield) and (2S)-6-[tert-butyl(diphenyl)silyl]hexane-1,2-diol (3.61 g, 51% yield).

[000563] **Step B:** Preparation of (2R)-1-azido-6-[tert-butyl(diphenyl)silyl]oxy-hexan-2-ol: To a solution of tert-butyl-[4-[(2R)-oxiran-2-yl]butoxy]-diphenyl-silane (1.20 g, 3.38 mmol) in methanol (24 mL) and water (3 mL) were added NaN_3 (440 mg, 6.77 mmol) and NH_4Cl (272 mg, 5.09 mmol). The mixture was stirred at 70 °C for 16 h. The mixture was diluted with saturated brine solution (100 mL) and extracted with EtOAc (100 mL x 2). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (EtOAc/petroleum ether=1/6) to give (2R)-1-azido-6-[tert-butyl(diphenyl)silyl]oxy-hexan-2-ol (1.02 g, 76% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 - 7.62 (m, 4H), 7.46 – 7.34 (m, 6H), 3.76 – 3.70 (m, 1H), 3.67 (t, J = 6.0 Hz, 2H), 3.38 – 3.30 (m, 1H), 3.27 – 3.16 (m, 1H), 1.88 (d, J = 4.6 Hz, 1H), 1.66 - 1.48 (m, 6H), 1.05 (s, 9H).

[000564] **Step C:** Preparation of (7S)-2-bromo-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one: To a solution of (2R)-1-azido-6-[tert-butyl(diphenyl)silyl]oxy-hexan-2-ol (1.02 g, 2.57 mmol) and triphenylphosphine (1.70 g, 6.48 mmol) in THF (16 mL) was added diisopropyl azodicarboxylate (0.630 mL, 3.21 mmol) dropwise at 0 °C. The mixture was stirred at 20 °C for 1 h. To the mixture was added water (2 mL) and the mixture was stirred at 70 °C for 2 h. The mixture was concentrated to dryness and dissolved in MeOH (20 mL). The resulting mixture was stirred at 110 °C for 16 h. The mixture was concentrated and purified by column chromatography (EtOAc/petroleum ether: 1/1) to give (7S)-2-bromo-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (820 mg, 61% yield). ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.60 - 7.52 (m, 4H), 7.38 - 7.28 (m, 6H), 6.90 (s, 1H), 6.76 (s, 1H), 4.29 - 4.21 (m, 1H), 3.76 - 3.70 (m, 1H), 3.64 - 3.55 (m, 2H), 3.42 - 3.35 (m, 1H), 1.72 - 1.60 (m, 2H), 1.56 - 1.48 (m, 2H), 1.45 - 1.35 (m, 2H), 0.97 (s, 9H).

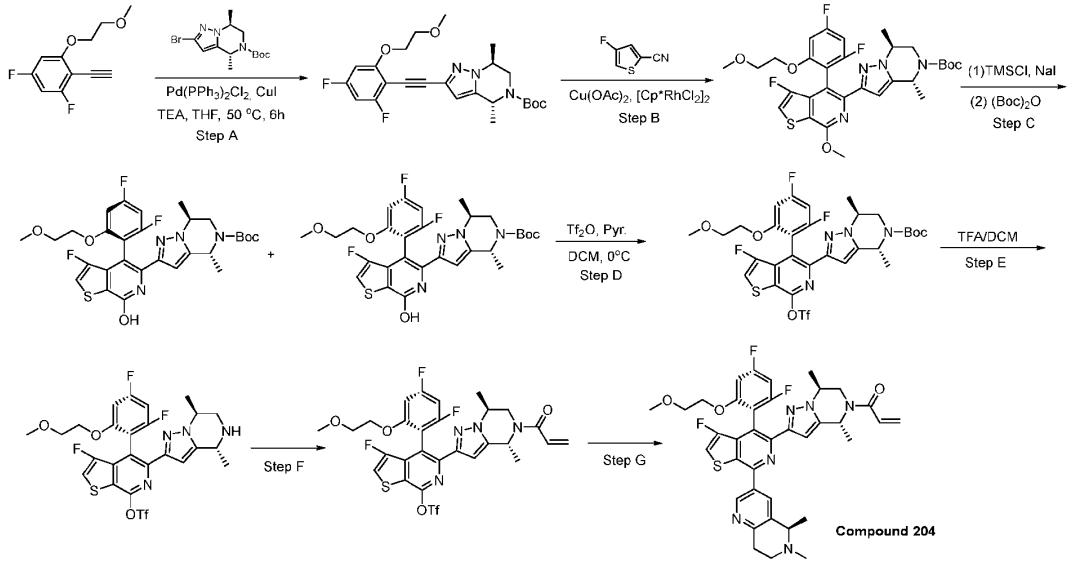
[000565] **Step D:** Preparation of tert-butyl (7S)-2-bromo-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of (7S)-2-bromo-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (900 mg, 1.71 mmol) in THF (15 mL) was added borane-methyl sulfide complex (0.900 mL, 9.00 mmol, 10 M in THF). The mixture was stirred at 50 °C for 16 h. The mixture was allowed to cool to 0 °C and MeOH (20 mL) was added dropwise. The mixture was stirred at 70 °C for 2 h, and then the mixture was concentrated to dryness. The mixture was dissolved in MeOH (5 mL) and $NaHCO_3$ aqueous solution (5 mL). Di-tert-butyl dicarbonate (0.790

mL, 3.38 mmol) was added. The resulting mixture was stirred at 25 °C for 3 h. The mixture was concentrated to remove MeOH, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (EtOAc/petroleum ether: 1/8) to give tert-butyl (7S)-2-bromo-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (410 mg, 39% yield) as a light-yellow oil. LCMS ESI (+) m/z 612.2/614.2 (M+H).

[000566] Step E: Preparation of tert-butyl (7S)-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-2-cyan - dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: A suspension of 1,1'-bis(diphenylphosphino)ferrocene (86 mg, 0.16 mmol), tris(dibenzylideneacetone)dipalladium(0) (72 mg, 0.079 mmol), tert-butyl (7S)-2-bromo-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (482 mg, 0.787 mmol), zinc (20 mg, 0.31 mmol) and dicyanozinc (184 mg, 1.57 mmol) in DMA (5 mL) was stirred at 120 °C for 6 h under N_2. The mixture was filtered, and the filtrate was poured into water and the product was extracted with EtOAc. The organic phase was washed with saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc/petroleum ether: 1/6) to give tert-butyl (7S)-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-2-cyan - dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (380 mg, 86% yield) as a light-yellow oil. ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.66 - 7.62 (m, 4H), 7.45 - 7.35 (m, 6H), 6.44 (s, 1H), 4.95 - 4.40 (m, 2H), 4.30 - 4.16 (m, 1H), 4.05 - 3.80 (m, 1H), 3.69 - 3.60 (m, 3H), 1.87 - 1.83 (m, 4H), 1.56 - 1.45 (m, 11H), 1.04 (s, 9H).

[000567] Step F to Step L: Preparation of 1-((1^{7}S,E)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,7)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclooctaphane-1^5-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 10 Step K to Step S, substituting tert-butyl (7S)-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-2-cyano-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate for tert-butyl (R)-6-(5-((tert-butyldiphenylsilyl)oxy)pentyl)-2-cyano-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate, and substituting 2-(2,4-difluoro-6-((2-(trimethylsilyl)ethoxy)methoxy)benzyl)-N,N-diethylthiophene-3-carboxamide for 2-[[2,4-difluoro-6-(2-trimethylsilylethoxymethoxy)phenyl]methyl]-N,N-diethyl-thiophene-3-carboxamide in Step K. The crude was purified by Prep-TLC(DCM/MeOH: 30/1) to afford 1-((1^{7}S,E)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4-oxa-2(6,7)-thieno[3,2-c]pyridina-1(2,7)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclooctaphane-1^5-yl)prop-2-en-1-one as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (1H, s), 8.25 (s, 1H), 8.10 (d, J = 5.6 Hz. 1H), 8.04 (dd, J =8.7, 1.3 Hz, 1H), 7.94 -7.83 (m, 2H), 6.95 - 6.76 (m, 2H), 6.70 (d, J = 11.2 Hz, 1H), 6.37 - 6.25 (m, 1H), 6.02 (s, 1H), 5.90 - 5.81 (m, 1H), 5.20 - 5.05 (m, 1H), 4.74 - 4.55 (m, 2H), 4.48 - 4.22 (m, 1H), 4.19 (s, 3H), 4.15 - 3.90 (m, 1H), 3.80 - 3.71 (m, 1H), 2.13 - 1.95 (m, 1H), 1.92 - 1.65 (m, 2H), 1.61 - 1.45 (m, 1H), 1.20 - 1.05 (m, 1H), 0.61 - 0.48 (m, 1H). LCMS ESI (+) m/z 623.2 (M+H).

Synthetic Example 21: Synthesis of 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 204**)



[000568] Step A: Preparation of tert-butyl (4R,7S)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of 2-ethynyl-1,5-difluoro-3-(2-methoxyethoxy)benzene (1.54 g, 7.27 mmol) in DMF (20 mL) was added tert-butyl (4R,7S)-2-bromo-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (2.00 g, 6.06 mmol), $PdCl_2(PPh_3)_2$ (213 mg, 0.303 mmol), CuI (58 mg, 0.30 mmol) and TEA (2.50 mL, 18.2 mmol). The reaction mixture was stirred at 85 °C for 10 h under Ar. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether: EtOAc=6:1) to get tert-butyl (4R,7S)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.20 g, 43% yield) as a yellow oil.

[000569] Step B: Preparation of tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a mixture of 4-fluorothiophene-2-carbonitrile (143 mg, 1.13 mmol) and tert-butyl (4R,7S)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (400 mg, 0.867 mmol) in methanol (8 mL) were added $Cu(OAc)_2$ (280 mg, 1.54 mmol) and $[Cp^*RhCl_2]_2$ (60 mg, 0.096 mmol) under Ar. The sealed vial was heated to 120 °C and left standing overnight. The mixture was filtered, and the filtrate was concentrated. The crude was purified by

Prep-TLC(petroleum ether:EtOAc=1:1) to give tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (265 mg, 49% yield) as an yellow oil. LCMS ESI (+) m/z 619.3 (M+H).

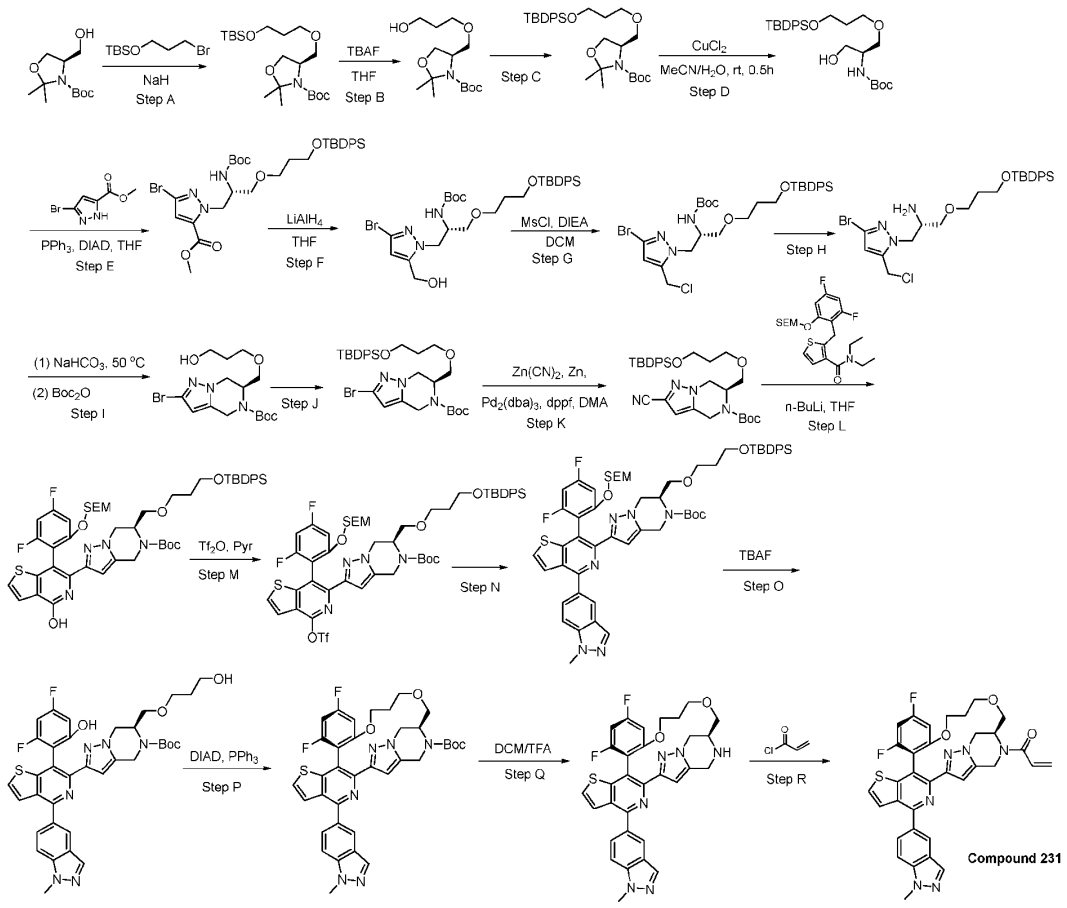
[000570] **Step C:** Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (50 mg, 0.081 mmol) in acetonitrile (2vmL) was added trimethylchlorosilane (0.052 mL, 0.40 mmol) and NaI (61 mg, 0.40 mmol). Water (5 mL) was added. The pH of aqueous layer was adjusted to around 8 by the addition of $NaHCO_3$. Di-tert-butyl dicarbonate (0.038 mL, 0.16 mmol) was then added. The mixture was stirred at 20 °C for another 4 hours. The organic layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3x 15 mL) and brine (20 mL). The organic layers were dried before concentration. The crude was purified by Prep-TLC (EtOAc) to give the less polar isomer tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (25 mg, 51% yield) and the more polar isomer tert-butyl (4R,7S)-2-((S)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (20 mg, 41% yield). LCMS ESI (+) m/z 505.2 (M-Boc+H).

[000571] **Step D:** Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a mixture of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (110 mg, 0.182 mmol) and pyridine (0.150 mL, 1.82 mmol) in DCM (2 mL) cooled to 0 °C was added trifluoromethanesulfonic anhydride (0.061 mL, 0.36 mmol) dropwise slowly under Ar. The mixture was stirred at 0 °C for 30 minutes. The mixture was diluted with EtOAc (10 mL) and then washed with water (3 x 20 mL) and brine (20 mL). The organic layers were separated, dried and concentrated. The crude was purified by Prep-TLC (petroleum ether:EtOAc=3:1) to give tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (100 mg, 75% yield) as a colorless oil.

[000572] **Step E to Step G:** Preparation of 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-3-

fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 5 Step C to Step D, substituting tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate for tert-butyl (R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate in Step C, and substituting [(5R)-5,6-dimethyl-7,8-dihydro-5H-1,6-naphthyridin-3-yl]boronic acid for 4,4,5,5-tetramethyl-2-(2-phenylcyclopropyl)-1,3,2-dioxaborolane in Step D. The crude was purified by Pre-TLC (DCM/MeOH:12/1) and followed by preparative HPLC to afford 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 9.23 (d, J = 1.7 Hz, 1H), 8.48 (s, 1H), 7.53 (d, J = 2.2 Hz, 1H),6.48 –6.86 (m, 2H), 6.26 (d, J = 16.3 Hz, 1H), 6.04 (s, 1H), 5.74–5.81(m, 1H), 5.53 (d, J = 91.8 Hz, 1H), 4.39 (s, 1H), 4.16 (s, 1H), 3.99 (dtd, J = 15.3, 10.8, 4.3 Hz, 3H), 3.85 (s, 3H), 3.38 (dd, J = 10.5, 5.8 Hz, 4H), 3.03 (d, J = 10.4 Hz, 6H), 1.78 (d, J = 6.5 Hz, 2H), 1.30 (d, J = 40.6 Hz, 6H). LCMS ESI (+) m/z 703.2 (M+H).

Synthetic Example 22: Synthesis of 1-((1^{6}S,E)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4,8-dioxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-yl)prop-2-en-1-one (**Compound 231**)



[000573] **Step A:** Preparation of tert-butyl (4R)-4-[3-[tert-butyl(dimethyl)silyl]oxypropoxymethyl]-2,2-dimethyl-oxazolidine-3-carboxylate: Sodium hydride (3.46 g, 86.5 mmol, 60% dispersion in mineral oil) was added to a solution of tert-butyl (4R)-4-(hydroxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylate (8.00 g, 34.6 mmol) in DMF (80 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. (3-Bromopropoxy)-tert-butyldimethylsilane (9.60 mL, 41.5 mmol) was added and the resulting mixture was stirred at 25 °C for 18 h. The mixture was partitioned between brine (300 mL) and EtOAc (300 mL). The organic phase was separated, washed with brine (3 x 100 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica (0% to 10% EtOAc in petroleum ether) to give tert-butyl (4R)-4-[3-[tert-butyl(dimethyl)silyl]oxypropoxymethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (11.3 g, 81% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 – 3.83 (m, 3H), 3.63 (t, J = 5.7 Hz, 2H), 3.58 – 3.40 (m, 3H), 3.27 (t, J = 9.2 Hz, 1H), 1.79 – 1.65 (m, 2H), 1.55 – 1.39 (m, 15H), 0.85 (s, 9H), 0.00 (s, 6H).

[000574] **Step B:** Preparation of tert-butyl (4R)-4-(3-hydroxypropoxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylate: To a solution of tert-butyl (4R)-4-[3-[tert-butyl(dimethyl)silyl]oxypropoxymethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (10.0 g, 24.8 mmol) in THF (100 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 49.6 mL, 49.6 mmol). The mixture was stirred at 25 °C for 2 h. The mixture was concentrated and diluted with water (200 mL). The mixture was extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness to give crude tert-butyl (4R)-4-(3-hydroxypropoxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylate (7.10 g, 99% yield) as a colorless oil.

[000575] **Step C:** Preparation of tert-butyl (4R)-4-[3-[tert-butyl(diphenyl)silyl]oxypropoxymethyl]-2,2-dimethyl-oxazolidine-3-carboxylate: To a solution of tert-butyl (4R)-4-(3-hydroxypropoxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylate (7.10 g, 24.5 mmol) and imidazole (2.51 g, 36.8 mmol) in DCM (70 mL) was added tert-butyldiphenylchlorosilane (8.20 mL, 31.9 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was poured into water and the product was extracted with DCM (100 mL x 2). The organic layers were washed with saturated brine solution (100 mL x 2), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting with 10:1 hexane/ethyl acetate to give tert-butyl (4R)-4-[3-[tert-butyl(diphenyl)silyl]oxypropoxymethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (8.80 g, 68% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 4.05 – 3.88 (m, 3H), 3.66 – 3.49 (m, 5H), 3.36 (t, J = 8.9 Hz, 1H), 3.32 – 3.27 (m, 2H), 1.82 – 1.72 (m, 2H), 1.55 – 1.43 (m, 15H).

[000576] **Step D:** Preparation of tert-butyl N-[(1S)-1-[3-[tert-butyl(diphenyl)silyl]oxypropoxymethyl]-2-hydroxy-ethyl]carbamate: To a solution of tert-butyl (4R)-4-[3-[tert-butyl(diphenyl)silyl]oxypropoxymethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (8.80 g, 16.7 mmol) in acetonitrile (80 mL) was added copper(II) chloride dihydrate (5.62 g, 33.3 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated and purified by silica gel column chromatography (0-50% EtOAc in hexane) to afford tert-butyl N-[(1S)-1-[3-[tert-butyl(diphenyl)silyl]oxypropoxymethyl]-2-hydroxy-ethyl]carbamate (6.20 g, 76% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (dd, J = 7.5, 1.6 Hz, 4H), 7.46 – 7.36 (m, 6H), 3.76 (t, J = 6.2 Hz, 2H), 3.71 – 3.63 (m, 1H), 3.58 (t, J = 6.2 Hz, 2H), 3.53 (d, J = 5.5 Hz, 2H), 3.43 (d, J = 5.6 Hz, 2H), 3.35 – 3.27 (m, 2H), 1.81 (p, J = 6.2 Hz, 2H), 1.42 (s, 9h), 1.03 (s, 9H).

[000577] **Step E:** Preparation of methyl 5-bromo-2-[(2S)-2-(tert-butoxycarbonylamino)-3-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]propyl]pyrazole-3-carboxylate: To a solution of tert-butyl N-[(1S)-1-[3-[tert-butyl(diphenyl)silyl]oxypropoxymethyl]-2-hydroxy-ethyl]carbamate (6.20 g, 12.7 mmol), triphenylphosphine (4.33 g, 16.5 mmol) and methyl 3-bromo-1H-pyrazole-5-carboxylate (3.39 g, 16.5 mmol) in THF (60 mL) was added diisopropyl azodicarboxylate (7.40 mL, 38.1 mmol) dropwise at 0 °C.

The mixture was stirred at rt for 1 h. The reaction was quenched by addition of water (2 mL) and concentrated. The residue was purified by column chromatography on silica gel (0% to 10% EtOAc in DCM) to give methyl 5-bromo-2-[(2S)-2-(tert-butoxycarbonylamino)-3-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]propyl]pyrazole-3-carboxylate (6.40 g, 75% yield) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 – 7.50 (m, 4H), 7.37 – 7.23 (m, 6H), 6.75 (s, 1H), 4.59 (dd, J = 13.6, 4.0 Hz, 1H), 4.29 (dd, J = 13.5, 9.7 Hz, 1H), 4.11 – 4.01 (m, 1H), 3.76 (s, 1H), 3.69 (t, J = 6.2 Hz, 2H), 3.57 – 3.43 (m, 2H), 3.42 – 3.28 (m, 1H), 1.80 – 1.65 (m, 2H), 1.22 (s, 9H), 0.94 (s, 9H).

[000578] Step F: Preparation of tert-butyl N-[(1S)-1-[[3-bromo-5-(hydroxymethyl)pyrazol-1-yl]methyl]-2-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]ethyl]carbamate: To a solution of methyl 5-bromo-2-[(2S)-2-(tert-butoxycarbonylamino)-3-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]propyl]pyrazole-3-carboxylate (3.50 g, 5.19 mmol) in THF (35 mL) cooled to 0 °C was added $LiAlH_4$ (354 mg, 9.34 mmol) slowly under Ar. The reaction was quenched by the addition of water (0.5 mL). The reaction mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried and concentrated to give crude tert-butyl N-[(1S)-1-[[3-bromo-5-(hydroxymethyl)pyrazol-1-yl]methyl]-2-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]ethyl]carbamate (3.30 g, 98% yield) which was used in the next step directly. LCMS ESI (+) m/z 703.2 (M+H).

[000579] Step G: Preparation of tert-butyl N-[(1S)-1-[[3-bromo-5-(chloromethyl)pyrazol-1-yl]methyl]-2-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]ethyl]carbamate: To a solution of tert-butyl N-[(1S)-1-[[3-bromo-5-(hydroxymethyl)pyrazol-1-yl]methyl]-2-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]ethyl]carbamate (3.80 g, 5.88 mmol) and N,N-diisopropylethylamine (5.10 mL, 29.4 mmol) in DCM (35 mL) was added methanesulfonyl chloride (0.920 mL, 11.8 mmol). The mixture was stirred at 25 °C for 3 h. The mixture was poured into water and the product was extracted with DCM (2 x 30 mL). The organic extracts were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated to give crude tert-butyl N-[(1S)-1-[[3-bromo-5-(chloromethyl)pyrazol-1-yl]methyl]-2-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]ethyl]carbamate (3.50 g, 90% yield) which was used in the next step directly.

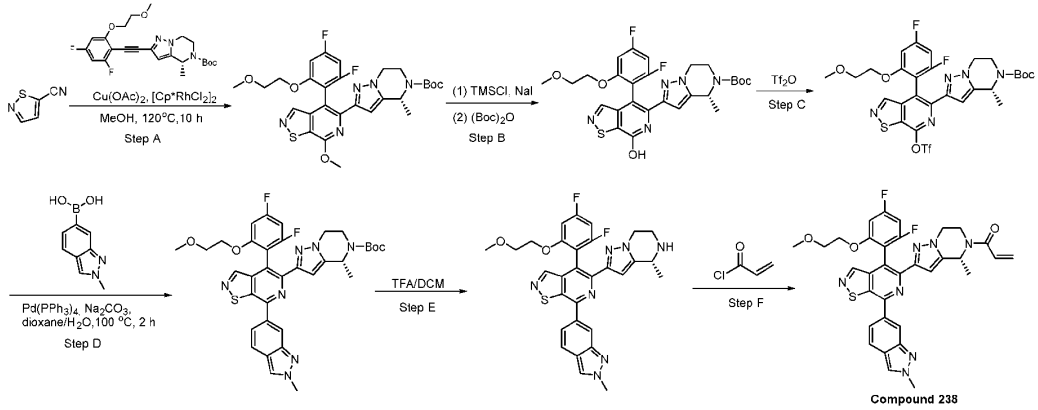
[000580] Step H: Preparation of (2S)-1-[3-bromo-5-(chloromethyl)pyrazol-1-yl]-3-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]propan-2-amine: To a solution of tert-butyl N-[(1S)-1-[[3-bromo-5-(chloromethyl)pyrazol-1-yl]methyl]-2-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]ethyl]carbamate (3.50 g, 5.26 mmol) in DCM (30 mL) was added trifluoroacetic acid (10 mL, 130 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to afford crude (2S)-1-[3-bromo-5-(chloromethyl)pyrazol-1-yl]-3-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]propan-2-amine (4.10 g) which was used in the next step without further purification. LCMS ESI (+) m/z 564.0 (M+H).

[000581] **Step I:** Preparation of tert-butyl (6S)-2-bromo-6-(3-hydroxypropoxymethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of (2S)-1-[3-bromo-5-(chloromethyl)pyrazol-1-yl]-3-[3-[tert-butyl(diphenyl)silyl]oxypropoxy]propan-2-amine (4.10 g, 5.26 mmol) in ethanol/H_2O (100 mL, 1/1) was added sodium bicarbonate (3.66 g, 43.5 mmol) to adjust the pH to 8. The mixture was stirred at 40 °C overnight. Di-tert-butyl dicarbonate (2.00 mL, 8.71 mmol) was added and stirred for 2 hours. The mixture was concentrated in vacuo and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4) before concentration to dryness to give crude tert-butyl (6S)-2-bromo-6-(3-hydroxypropoxymethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (3.90 g) which was used in the next step without further purification. LCMS ESI (+) m/z 390.1 (M+H).

[000582] **Step J:** Preparation of tert-butyl (6S)-2-bromo-6-[3-[tert-butyl(diphenyl)silyl]oxypropoxymethyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of crude tert-butyl (6S)-2-bromo-6-(3-hydroxypropoxymethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (3.90 g, 5.26 mmol) in DCM (60 mL) were added imidazole (654 mg, 9.60 mmol) and tert-butyldiphenylchlorosilane (1.84 mL, 7.20 mmol). The mixture was stirred at 24 °C for 2 hours. The mixture was washed with water (60 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether:EtOAc=20:1) to give tert-butyl (6S)-2-bromo-6-[3-[tert-butyl(diphenyl)silyl]oxypropoxymethyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.80 g, 54% yield for 3 steps). LCMS ESI (+) m/z 628.1 (M+H).

[000583] **Step K to Step R:** Preparation of 1-((1^{6}S,E)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4,8-dioxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 20 Step E to Step L, substituting tert-butyl (6S)-2-bromo-6-[3-[tert-butyl(diphenyl)silyl]oxypropoxymethyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate for tert-butyl (7S)-2-bromo-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate in Step E. The crude was purified by Prep-HPLC to afford 1-((1^{6}S,E)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4,8-dioxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-yl)prop-2-en-1-one as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.28 (s, 1H), 8.14 – 8.05 (m, 2H), 7.92 (d, J = 8.9 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.00 (t, J = 9.0 Hz, 1H), 6.91 (d, J = 10.7 Hz, 1H), 6.86 – 6.75 (m, 1H), 6.43 – 6.27 (m, 1H), 5.89 – 5.81 (m, 1H), 5.77 – 5.68 (m, 1H), 5.17 – 4.92 (m, 2H), 4.78 – 4.64 (m, 2H), 4.63 – 4.42 (m, 1H), 4.20 (s, 3H), 4.10 – 3.92 (m, 1H), 3.88 – 3.60 (m, 3H), 2.98-2.93 (m, 1H), 1.82-1.73 (m, 1H), 1.60 – 1.45 (m, 1H). LCMS ESI (+) m/z 639.3 (M+H).

Synthetic Example 23: Synthesis of 1-((4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(2-methyl-2H-indazol-6-yl)isothiazolo[5,4-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 328**)



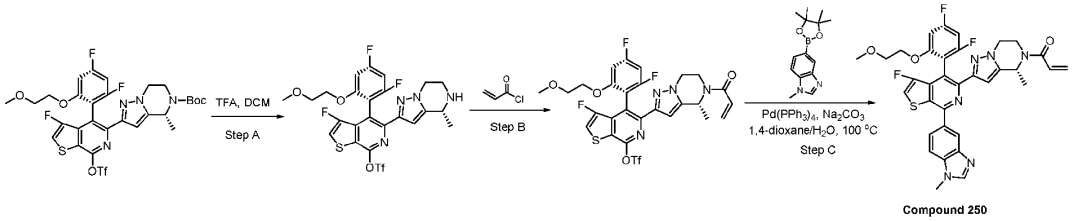
[000584] **Step A:** Preparation of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (4R)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (422 mg, 0.943 mmol) in methanol (2 mL) were added isothiazole-5-carbonitrile (120 mg, 1.09 mmol), $[CP^*RhCl_2]_2$ (58 mg, 0.094 mmol) and $Cu(OAc)_2$ (274 mg, 1.51 mmol) in a sealed tube. The mixture was stirred at 120 °C under argon for 10 h. The mixture was filtered and the filtrate was concentrated. The residue was purified by Prep-TLC (petroleum ether:EtOAc=3:1) to give tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (144 mg, 25% yield) as a light-yellow oil.

[000585] **Step B:** Preparation of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-hydroxy-isothiazolo[5,4-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-methoxy-isothiazolo[5,4-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (116 mg, 0.197 mmol) in acetonitrile (3 mL) were added trimethylchlorosilane (0.130 mL, 0.987 mmol) and NaI (148 mg, 0.987 mmol). The mixture was stirring at 20 °C for 4 h under Ar. Water (5 mL) was added. $NaHCO_3$ aqueous solution was added to adjust the pH to 8, then di-tert-butyl dicarbonate (2.00 eq, 0.092 mL, 0.395 mmol) was added. The resulting mixture was stirred at 20 °C for an additional 4 hours. The mixture was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL) and dried (Na_2SO_4) before concentration. The crude was purified by Prep-TLC (EtOAc) to give tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-hydroxy-

isothiazolo[5,4-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (91 mg, 80% yield) as a light yellow oil. LCMS ESI (+) m/z 574.2 (M+H).

[000586] Step C to Step F: Preparation of 1-((4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(2-methyl-2H-indazol-6-yl)isothiazolo[5,4-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 12 Step E to Step H, substituting tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-hydroxy-isothiazolo[5,4-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate for tert-butyl (4S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate in Step E. The crude was purified by Prep-HPLC to afford 1-((4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(2-methyl-2H-indazol-6-yl)isothiazolo[5,4-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one as a mixture of two diastereomers. ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 - 8.67 (m, 1H), 8.41 (s, 1H), 8.31 (s, 1H), 8.07 - 8.02 (m, 1H), 7.94 (d, J = 9.6 Hz, 1H), 6.91- 6.81 (m, 2H), 6.75 - 6.68 (m, 1H), 6.39 - 6.23 (m, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.76 - 5.41 (m, 1H), 4.59 (s, 1H), 4.29 (s, 3H), 4.21 - 4.10 (m, 2H), 4.02 - 3.95 (m, 1H), 3.43 - 3.38 (m, 2H), 3.03 (s, 1H), 1.55 - 1.42 (m, 3H). LCMS ESI (+) m/z 642.3 (M+H).

Synthetic Example 24: Synthesis of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 250**)



Compound 250

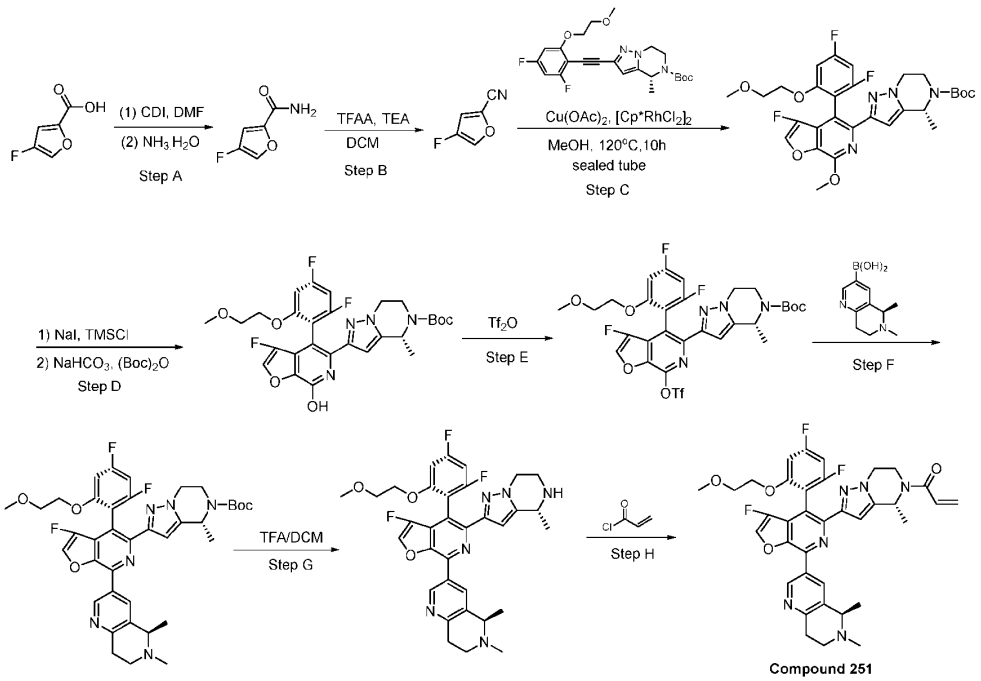
[000587] Step A: Preparation of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-5-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[2,3-c]pyridin-7-yl: To a solution of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (156 mg, 0.216 mmol) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at rt for 1h. The reaction was concentrated to dryness to give (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-5-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[2,3-c]pyridin-7-yl (190 mg) which was used in the next step without further purification. LCMS ESI (+) m/z 623.2 (M+H).

[000588] Step B: Preparation of (R)-5-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl

trifluoromethanesulfonate: A solution of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-5-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[2,3-c]pyridin-7-yl (190 mg, 0.216 mmol) in EtOAc (10 mL) and water (10 mL) was stirred for 5 min. The mixture was cooled to 0 °C and saturated sodium bicarbonate aqueous solution was added to adjust the pH to 8. A solution of acryloyl chloride (0.019 mL, 0.23 mmol) in dry DCM (2 mL) was added dropwise. The mixture was stirred at 0 °C for 0.5 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc/petroleum ether: 1/2) to give (R)-5-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (120 mg, 82% yield) as a light-yellow solid. LCMS ESI (+) m/z 677.2 (M+H).

[000589] **Step C:** Preparation of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: A suspension of (R)-5-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (20 mg, 0.030 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole (9.9 mg, 0.038 mmol), tetrakis(triphenylphosphine)palladium(0) (3.4 mg, 0.0030 mmol) and sodium carbonate (6.3 mg, 0.059 mmol) in 1,4-dioxane (1.2 mL) and water (0.3 mL) was stirred for 1 h at 100 °C under N_2 atmosphere. The mixture was concentrated and purified by Prep-HPLC to give 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (8.7 mg, 43% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 9.45 (s, 1H), 8.60 (s, 1H), 8.46 (dd, J = 8.7, 1.4 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.93 – 6.58 (m, 3H), 6.29 (d, J = 15.4 Hz, 1H), 6.06 (s, 1H), 5.83 (dd, J = 10.6, 1.5 Hz, 1H), 5.71 - 5.42 (m, 1H), 4.26 – 4.20 (m, 4H), 4.13 - 4.01 (m, 3H), 3.46 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 1.47 - 1.31 (m, 3H). LCMS ESI (+) m/z 658.2 (M+H).

Synthetic Example 25: Synthesis of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-3-fluorofuro[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 251**)



[000590] **Step A:** Preparation of 4-fluorofuran-2-carboxamide: To a solution of 4-fluorofuran-2-carboxylic acid (559 mg, 4.30 mmol) in DMF (10 mL) was added CDI (1.05 g, 6.45 mmol) under Ar. The mixture was stirred at 24 °C for 1 hour, then added into aqueous ammonia (10 mL). The mixture was stirred for an additional 1 hour. The product was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography eluted with petroleum ether:EtOAc=1:1 to give 4-fluorofuran-2-carboxamide (523 mg, 94% yield) as a white solid. LCMS ESI (+) m/z 130.1 (M+H).

[000591] **Step B:** Preparation of 4-fluorofuran-2-carbonitrile: To a mixture of 4-fluorofuran-2-carboxamide (487 mg, 3.77 mmol) and triethylamine (5.30 mL, 37.7 mmol) in DCM (10 mL) cooled to 0 °C was added trifluoroacetic anhydride (1.60 mL, 11.3 mmol) dropwise. The mixture was allowed to warm to 24 °C and stirred for 1 hour. The mixture was sequentially washed with saturated aqueous $KHSO_4$ (20 mL), water (20 mL) and saturated brine solution (20 mL). The organic phase was dried and concentrated to give crude 4-fluorofuran-2-carbonitrile (230 mg, 55% yield).

[000592] **Step C:** Preparation of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-furo[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a mixture of 4-fluorofuran-2-carbonitrile (150 mg, 0.945 mmol) and tert-butyl (4R)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (381 mg, 0.851 mmol) in methanol (8 mL) were added $Cu(OAc)_2$ (275 mg, 1.51 mmol) and

$[Cp^*RhCl_2]_2$ (58 mg, 0.095 mmol) under Ar. The mixture was stirred in a sealed vial at 120 °C for 16 h. The mixture was filtered, and the filtrate was concentrated. The residue was purified by Prep-TLC (petroleum ether:EtOAc=1:1) to give tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-furo[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (90 mg, 16% yield) as a mixture of two diastereomers. LCMS ESI (+) m/z 589.3 (M+H).

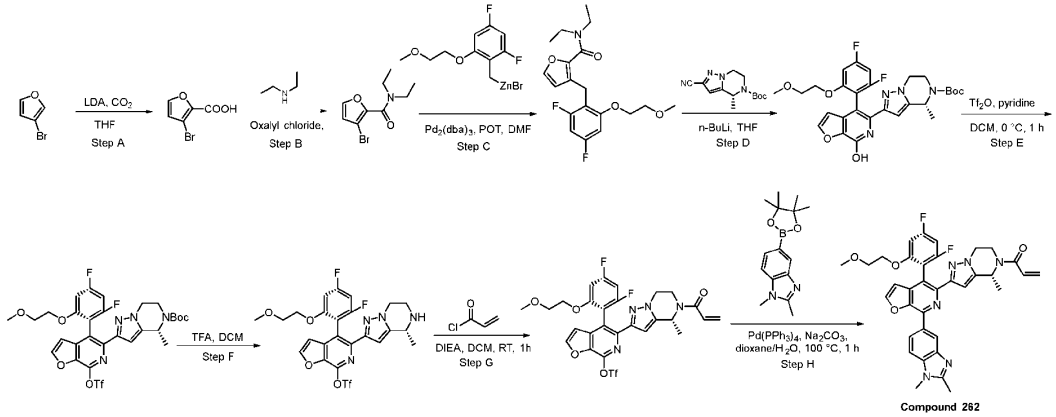
[000593] Step D: Preparation of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxyfuro[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-methoxy-furo[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (131 mg, 0.178 mmol) in acetonitrile (3 mL) was added trimethylchlorosilane (0.11 mL, 0.89 mmol) and NaI (133 mg, 0.890 mmol). The mixture was stirred at 20 °C for 2 hours under Ar. Water (5 mL) was added. $NaHCO_3$ aqueous solution was added to adjust the pH to 8, and then di-tert-butyl dicarbonate (0.083 mL, 0.36 mmol) was added. The mixture was stirred at 20 °C for an additional 2 hours. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4) before concentration. The residue was purified by Prep-TLC (EtOAc) to give one diastereomer tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxyfuro[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (42 mg, 41% yield) and the another diastereomer tert-butyl (R)-2-((S)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxyfuro[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (45 mg, 44% yield). LCMS ESI (+) m/z 575.3 (M+H).

[000594] Step E: Preparation of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxyfuro[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (42 mg, 0.073 mmol) and pyridine (0.059 mL, 0.73 mmol) in DCM (2 mL) cooled to 0 °C was added trifluoromethanesulfonic anhydride (0.025 mL, 0.15 mmol) dropwise. The mixture was stirred at 0 °C for 30 minutes. The mixture was diluted with EtOAc (20 mL) and then washed with water and brine. The combined organic layers were separated, dried (Na_2SO_4) and concentrated. The residue was purified by Prep-TLC (petroleum ether:EtOAc=3:1) to give tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (36 mg, 70% yield).

[000595] Step F to Step H: Preparation of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-3-fluorofuro[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: The title compound was prepared as

described in Synthetic Example 8 Step I to Step K, substituting tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate for tert-butyl (4R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate, and substituting (R)-(5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)boronic acid for (1-methylindazol-5-yl)boronic acid in Step I. The crude was purified by Prep-TLC (DCM:MeOH) to afford 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-3-fluorofuro[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, CD_3OD) δ 9.60 (s, 1H), 8.86 (s, 1H), 8.26 (d, J = 4.4 Hz, 1H), 6.91 – 6.80 (m, 2H), 6.69 – 6.62 (m, 1H), 6.37 – 6.25 (m, 1H), 6.10 (s, 1H), 5.83 (dd, J = 10.6, 1.5 Hz, 1H), 5.78 – 5.42 (m, 1H), 4.51 – 4.35 (m, 0.5H), 4.28 – 4.20 (m, 1H), 4.17 – 3.85 (m, 4H), 3.85 – 3.65 (m, 2H), 3.52 – 3.37 (m, 4H), 3.16 – 3.05 (m, 6H), 1.85 (d, J = 6.0 Hz, 3H), 1.54 – 1.37 (m, 3H). LCMS ESI (+) m/z 673.4 (M+H).

Synthetic Example 26: Synthesis of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 262**)



[000596] **Step A:** Preparation of 3-bromofuran-2-carboxylic acid: To a solution of 3-bromofuran (6.00 mL, 68.0 mmol) in THF (52 mL) under argon was added LDA (2.0 M, 37.0 mL, 73.5 mmol) dropwise at -78 °C, and the mixture was stirred at -78 °C for 30 min. CO_2 was added to the reaction mixture at -78 °C. The mixture was stirred at -78 °C for 1 h. Upon completion of the reaction, the mixture was diluted with water (100 mL), acidified with 1N HCl and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum to give 3-bromofuran-2-carboxylic acid (9.00 g, crude). LCMS ESI (+) m/z 189.0 (M+H).

[000597] **Step B:** Preparation of 3-bromo-N,N-diethylfuran-2-carboxamide: A mixture of 3-bromofuran-2-carboxylic acid (8.00 g, 41.9 mmol), oxalyl chloride (14.0 mL, 168 mmol) and 3 drops of DMF was stirred in DCM (25 mL) at 25 °C for 3 h. The reaction was concentrated to dryness. Then the mixture was dissolved in DCM (25 mL) and added dropwise to a mixture of diethylamine (8.80 mL, 83.8 mmol) in DCM (25 mL) at 0 °C. The mixture was stirred at 25 °C for 2 h. Upon completion of the reaction, the combined organic layers were washed with 1 N HCl, followed by saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated. The crude was then purified by flash column chromatography eluting with 0-15% EtOAc in hexanes to give 3-bromo-N,N-diethylfuran-2-carboxamide (5.90 g, 57% yield). LCMS ESI (+) m/z 246.1 (M+H).

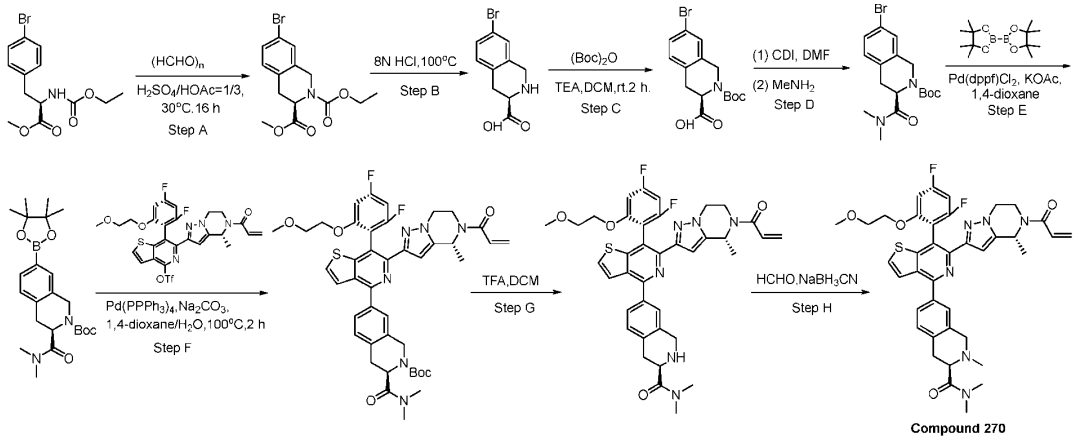
[000598] **Step C:** Preparation of 3-(2,4-difluoro-6-(2-methoxyethoxy)benzyl)-N,N-diethylfuran-2-carboxamide: A mixture of Zn (18.86 g, 290.0 mmol)) and 1,2-dibromoethane (2.73 g, 14.5 mmol) in DMF (20 mL) was stirred at 80 °C for 20 min. TMSCl (263 mg, 2.42 mmol) was added at rt, the resulting mixture was stirred at rt for 30 min. A solution of 2-(bromomethyl)-1,5-difluoro-3-(2-methoxyethoxy)benzene (6.80 g, 24.2 mmol) in DMF (15 mL) was added, and the mixture was stirred at rt for 1 h. To the mixture were added 3-bromo-N,N-diethyl-furan-2-carboxamide (5.00 g, 20.3 mmol), $Pd_2(dba)_3$ (1.86 g, 2.03 mmol) and tri(o-tolyl)phosphine (618 mg, 2.03 mmol). The mixture was stirred at rt under N_2 for 12 h. Upon completion of the reaction, the resulting mixture was poured into water, filtered, and the filtrate was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/petroleum ether= 0 to 20%) to give 3-(2,4-difluoro-6-(2-methoxyethoxy)benzyl)-N,N-diethylfuran-2-carboxamide (6.50 g, 87% yield). LCMS ESI (+) m/z 368.1 (M+H).

[000599] **Step D:** Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-hydroxyfuro[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a stirring solution of 3-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]-N,N-diethyl-furan-2-carboxamide (5.46 g, 14.9 mmol) in THF (15 mL) was added n-BuLi (2.5 M in hexanes, 5.70 mL, 13.7 mmol) at -60 °C. The mixture was stirred at -60 °C for 60 min, and then tert-butyl (4R)-2-cyano-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (3.00 g, 11.4 mmol) in THF (3 mL) was added. The resulting mixture was stirred at rt for 3 h. Upon completion of the reaction, the mixture was diluted with water (100 mL), acidified with 1 N HCl and extracted with EtOAc (100 mL x 3). The organic layers were combined, washed with brine, dried and concentrated. The residue was purified by flash column chromatography (CH_3OH/DCM= 0 to 5%) to give tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-hydroxyfuro[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (3.0 g, 60% purity, 28% yield) as a mixture of two diastereomers. LCMS ESI (+) m/z 557.3 (M+H).

[000600] **Step E:** Preparation of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(((trifluoromethyl)sulfonyl)oxy)furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-7-hydroxy-furo[2,3-c]pyridin-5-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (3.00 g, 5.39 mmol) and pyridine (5.90 mL, 53.9 mmol) in DCM (15 mL) was added trifluoromethanesulfonic anhydride (1.80 mL, 10.8 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was diluted with citric acid (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with water and brine, dried and concentrated. The residue was purified by flash column chromatography (EtOAc/petroleum ether= 0 to 30%) to give one diastereomer tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(((trifluoromethyl)sulfonyl)oxy)furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (500 mg, 14% yield) and another diastereomer tert-butyl (R)-2-((S)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(((trifluoromethyl)sulfonyl)oxy) furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (600 mg, 16% yield). LCMS ESI (+) m/z 689.3 (M+H).

[000601] **Step F to Step H:** Preparation of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 7 Step G to Step I, substituting tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(((trifluoromethyl)sulfonyl)oxy)furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate for tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate in Step G, and substituting 1,2-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole for [6-(2-hydroxyethyl)-7,8-dihydro-5H-1,6-naphthyridin-3-yl]boronic acid in Step I. The crude was purified by column chromatography on silica gel (MeOH/DCM= 0 to 10%) to afford 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)furo[2,3-c]pyridin-5-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (s, 1H), 8.50 (dd, J = 8.6, 1.4 Hz, 1H), 8.09 (d, J = 2.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 6.94 – 6.85 (m, 1H), 6.83 (d, J = 11.4 Hz, 1H), 6.71 – 6.63 (m, 2H), 6.28 (d, J = 33.0 Hz, 2H), 5.84 (d, J = 10.2 Hz, 1H), 5.64 (d, J = 86.8 Hz, 1H), 4.44 (d, J = 15.8 Hz, 1H), 4.20 (dd, J = 12.4, 2.8 Hz, 1H), 4.13 – 3.91 (m, 3H), 3.87 (s, 3H), 3.83 – 3.59 (m, 1H), 3.46 (t, J = 4.6 Hz, 2H), 3.12 (s, 3H), 2.67 (s, 3H), 1.47 (s, 3H). LCMS ESI (+) m/z 639.2 (M+H).

Synthetic Example 27: Synthesis of (R)-7-(6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-N,N,2-trimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**Compound 270**)



[000602] **Step A:** Preparation of 2-ethyl 3-methyl (R)-7-bromo-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate: To a solution of methyl (2R)-3-(4-bromophenyl)-2-(ethoxycarbonylamino)propanoate (1.80 g, 5.45 mmol) in acetic acid (6.00 mL, 105 mmol) and sulfuric acid (2 mL) was added formaldehyde (164 mg, 5.45 mmol). The mixture was stirred at 30 °C overnight. The mixture was diluted with EtOAc (30 mL). Saturated sodium bicarbonate solution was added to adjust the pH to 8. The organic layer was separated and dried over anhydrous Na_2SO_4 before concentrating to dryness. The residue was purified by column chromatography (petroleum ether/EtOAc = 6/1). The desired fractions were concentrated to dryness to give 2-ethyl 3-methyl (R)-7-bromo-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (900 mg, 48% yield) as a light yellow solid. LCMS ESI (+) m/z 342.0 (M+H).

[000603] **Step B:** Preparation of (R)-7-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid: A mixture of 2-ethyl 3-methyl (R)-7-bromo-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (520 mg, 1.40 mmol) in HCl (4.0 mL, 8.0 N, 32 mmol) was stirred at 100 °C for 16 h. The solvent was removed under reduced pressure to give crude (R)-7-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (500 mg) which was used in the next step directly. LCMS ESI (+) m/z 257.9 (M+H).

[000604] **Step C:** Preparation of (3R)-7-bromo-2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinoline-3-carboxylic acid: To a stirred solution of crude (3R)-7-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (500 mg, 1.40 mmol) and TEA (1.40 mL, 9.76 mmol) in DCM (2 mL) was added di-tert-butyl dicarbonate (0.540 mL, 2.34 mmol). The solution was stirred at 25 °C for 1.5 h. The mixture was diluted with H_2O (10 mL), and 1N HCl aqueous solution was added to the mixture to adjust the pH to 2. The mixture was extracted with EtOAc (10 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse-phase column to give (3R)-7-bromo-2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinoline-3-carboxylic acid (300 mg, 60% yield) as a white solid. LCMS ESI (+) m/z 257.9 (M+H).

[000605] **Step D:** Preparation of tert-butyl (3R)-7-bromo-3-(dimethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate: To a stirred solution of (3R)-7-bromo-2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinoline-3-carboxylic acid (150 mg, 0.0.422 mmol) in DMF (3 mL) was added CDI (89 mg, 0.55 mmol) at 0 °C. The solution was stirred at 0 °C for 0.5 h, then dimethylamine (190 mg, 4.20 mmol) was added at 0 °C. The solution was stirred at 25 °C for 0.5 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (15 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-TLC (petroleum ether:EtOAc=1:1) to give tert-butyl (3R)-7-bromo-3-(dimethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (119 mg, 74% yield) as a yellow solid. LCMS ESI (+) m/z 284.9 (M+H).

[000606] **Step E:** Preparation of tert-butyl (3R)-3-(dimethylcarbamoyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylate: A suspension of tert-butyl (3R)-7-bromo-3-(dimethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (119 mg, 0.310 mmol), bis(pinacolato)diboron (102 mg, 0.404 mmol), $Pd(dppf)Cl_2$ (22 mg, 0.031 mmol) and KOAc (60.8 mg, 0.621 mmol) in 1,4-dioxane (3 mL) was stirred at 90 °C for 4 h under Ar. The mixture was concentrated and purified by column chromatography (petroleum ether:EtOAc=1:1) to give tert-butyl (3R)-3-(dimethylcarbamoyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (120 mg, 90% yield). LCMS ESI (+) m/z 331.1 (M+H).

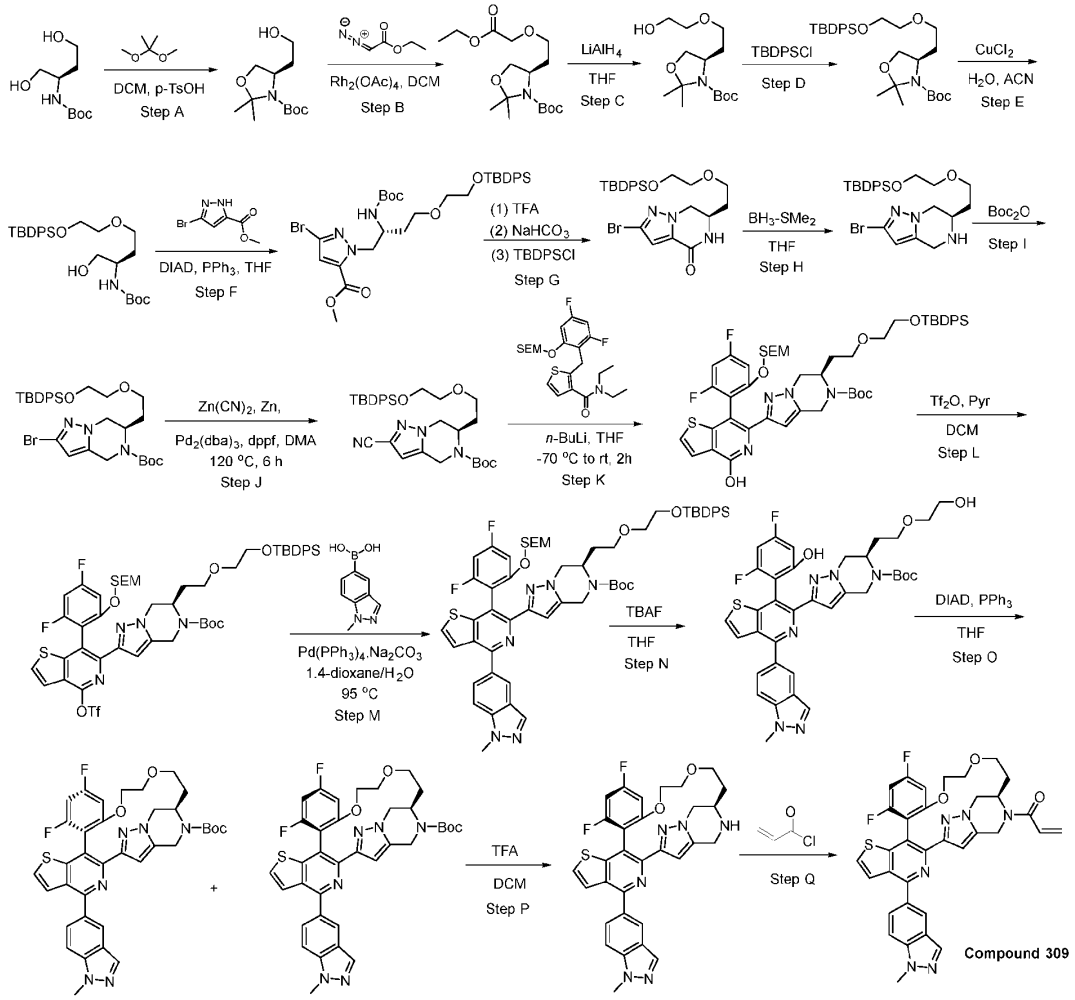
[000607] **Step F:** Preparation of tert-butyl (R)-7-(6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-3-(dimethylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate: A mixture of (S)-6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl trifluoromethanesulfonate (50 mg, 0.076 mmol), tert-butyl (3R)-3-(dimethylcarbamoyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (49 mg, 0.11 mmol), $Pd(PPh_3)_4$ (8.8 mg, 0.0076 mmol) and Na_2CO_3 (16 mg, 0.15 mmol) in 1,4-dioxane (2 mL) and water (0.2 mL) was stirred at 100 °C for 2 h under Ar. The mixture was concentrated and purified by Prep-TLC (DCM:MeOH=20:1) to give tert-butyl (R)-7-(6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-3-(dimethylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (60 mg, 97% yield). LCMS ESI (+) m/z 813.2 (M+H).

[000608] **Step G:** Preparation of (R)-7-(6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-N,N-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide: To a stirred solution of tert-butyl (R)-7-(6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-3-(dimethylcarbamoyl)-3,4-dihydroisoquinoline-

2(1H)-carboxylate (60 mg, 0.074 mmol) in DCM (2 mL) was added TFA (0.50 mL, 6.5 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to dryness to give crude (R)-7-(6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-N,N-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (80 mg, 100% yield) which was used in the next step directly. LCMS ESI (+) m/z 713.1 (M+H).

[000609] **Step H:** Preparation of (R)-7-(6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-N,N,2-trimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide: To a stirred solution of crude (R)-7-(6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-N,N-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (80 mg, 0.074 mmol) in methanol (2 mL) was added sodium formate to adjust the pH to 6. HCHO aqueous solution (40% in H_2O, 0.10 mL, 1.0 mmol) was added. The mixture was stirred at 25 °C for 1 h. $NaBH_3CN$ (11 mg, 0.17 mmol) was added. The resulting mixture was stirred at 25 °C for an additional 1 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to give (R)-7-(6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-N,N,2-trimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (30 mg, 49% yield). ^1H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 8.0 Hz, 1H), 7.71 – 7.69 (m, 2H), 7.65 (d, J = 5.6 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 6.86 – 6.80 (m, 2H), 6.69 – 6.68 (m, 1H), 6.38 – 6.21 (m, 1H), 6.16 (s, 1H), 5.81 (d, J = 12.4 Hz, 1H), 5.75-5.40 (m, 1H), 4.17 – 4.01 (m, 5H), 3.90 – 3.83 (m, 2H), 3.42 (t, J = 4.8 Hz, 2H), 3.33 – 3.20 (m, 4H), 3.13 – 3.02 (m, 7H), 2.44 (s, 3H), 1.52 – 1.38 (m, 3H). LCMS ESI (+) m/z 727.2 (M+H).

Synthetic Example 28: Synthesis of 1-((1^{6}R,E)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4,7-dioxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-yl)prop-2-en-1-one (**Compound 309**)



[000610] **Step A:** Preparation of tert-butyl (4R)-4-(2-hydroxyethyl)-2,2-dimethyl-oxazolidine-3-carboxylate: To a solution of tert-butyl N-[(1R)-3-hydroxy-1-(hydroxymethyl)propyl]carbamate (13.0 g, 63.3 mmol) in DCM (150 mL) were added 2,2-dimethoxypropane (13.2 g, 127 mmol) and p-toluenesulfonic acid monohydrate (1.20 g, 6.33 mmol). The mixture was stirred at 25 °C for 12 h. The mixture was poured into 0.2 N aqueous sodium hydroxide (80 mL) and extracted with DCM (80 mL x 2). The combined organic layers were washed with saturated brine solution (80 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (DCM:MeOH 50:1) to give tert-butyl (4R)-4-(2-hydroxyethyl)-2,2-dimethyl-oxazolidine-3-carboxylate (5.50 g, 35% yield) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 4.48 – 4.40 (m, 1H), 3.92 – 3.75 (m, 3H), 3.43 (dd, J = 12.0, 6.12 Hz, 2H), 1.87 – 1.70 (m, 1H), 1.66 – 1.53 (m, 1H), 1.46 (s, 3H), 1.45 – 1.35 (m, 11H).

[000611] **Step B:** Preparation of tert-butyl (4R)-4-[2-(2-ethoxy-2-oxo-ethoxy)ethyl]-2,2-dimethyl-oxazolidine-3-carboxylate: To a solution of tert-butyl (4R)-4-(2-hydroxyethyl)-2,2-dimethyl-oxazolidine-3-carboxylate (5.00 g, 20.4 mmol) in DCM (50 mL) was added rhodium(II) acetate dimer (450 mg, 1.02 mmol). To the reaction mixture was added a solution of ethyl 2-diazoacetate (4.65 g, 40.8 mmol) in DCM (10 mL) dropwise at 25 °C. The mixture was stirred at 25 °C for 1 h. The mixture was poured into water (40 mL) and extracted with DCM (40 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether:EtOAc 8:1) to give tert-butyl (4R)-4-[2-(2-ethoxy-2-oxo-ethoxy)ethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (4.80 g, 60% yield) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 4.28 – 4.16 (m, 3H), 4.08 – 4.02 (m, 2H), 3.89 – 3.85 (m, 2H), 3.66 – 3.54 (m, 2H), 2.17 – 1.95 (m, 1H), 1.91 – 1.78 (m, 1H), 1.64 – 1.52 (m, 3H), 1.52 – 1.40 (m, 12H), 1.35 – 1.24 (m, 3H).

[000612] **Step C:** Preparation of tert-butyl (4R)-4-[2-(2-hydroxyethoxy)ethyl]-2,2-dimethyl-oxazolidine-3-carboxylate: To a solution of tert-butyl (4R)-4-[2-(2-ethoxy-2-oxo-ethoxy)ethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (4.95 g, 14.9 mmol) in dry THF (5 mL) was added lithium aluminum hydride (0.850 g, 22.4 mmol) under 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was quenched with water (3 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (petroleum ether:EtOAc 8:1) to give tert-butyl (4R)-4-[2-(2-hydroxyethoxy)ethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (4.50 g, 88% yield) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 4.18 – 4.08 (m, 1H), 3.98 – 3.80 (m, 2H), 3.75 – 3.65 (m, 2H), 3.63 – 3.45 (m, 4H), 2.08 – 1.92 (m, 1H), 1.90 – 1.77 (m, 1H), 1.66 – 1.53 (m, 3H), 1.48 (s, 12H).

[000613] **Step D:** Preparation of tert-butyl (4R)-4-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl]-2,2-dimethyl-oxazolidine-3-carboxylate: To a solution of tert-butyl (4R)-4-[2-(2-hydroxyethoxy)ethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (4.50 g, 15.6 mmol) in DCM (40 mL) were added imidazole (5.29 g, 77.8 mmol) and tert-butyldiphenylchlorosilane (4.80 mL, 18.7 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was poured into water (40 mL) and extracted with DCM (40 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether:EtOAc 15:1) to give tert-butyl (4R)-4-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (5.00 g, 55% yield) as a colourless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 – 7.63 (m, 4H), 7.46 – 7.34 (m, 6H), 4.01 – 3.82 (m, 3H), 3.77 (t, J = 5.3 Hz, 2H), 3.57 – 3.46 (m, 4H), 2.12 – 1.90 (m, 1H), 1.85 – 1.71 (m, 1H), 1.64 – 1.43 (m, 15H), 1.08 - 1.03 (m, 9H).

[000614] **Step E:** Preparation of tert-butyl N-[(1R)-3-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]-1-(hydroxymethyl)propyl]carbamate: To a solution of tert-butyl (4R)-4-[2-[2-[tert-

butyl(diphenyl)silyl]oxyethoxy]ethyl]-2,2-dimethyl-oxazolidine-3-carboxylate (4.80 g, 9.09 mmol) in MeCN (50 mL) were added $CuCl_2$ (2.45 g, 18.2 mmol) and water (0.660 g, 36.4 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was poured into water (150 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with saturated brine solution (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether:EtOAc 15:1) to give tert-butyl N-[(1R)-3-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]-1-(hydroxymethyl)propyl]carbamate (3.60 g, 69% yield) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 – 7.63 (m, 4H), 7.46 – 7.34 (m, 6H), 5.18(brs, 1H), 3.80 – 3.45 (m, 9H), 3.21(br.s, 1H), 1.93 – 1.73 (m, 2H), 1.42 (s, 9H), 1.05 (s, 9H).

[000615] Step F: Preparation of methyl 5-bromo-2-[(2R)-2-(tert-butoxycarbonylamino)-4-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]butyl]pyrazole-3-carboxylate: To a solution of tert-butyl N-[(1R)-3-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]-1-(hydroxymethyl)propyl]carbamate (3.80 g, 7.79 mmol), triphenylphosphine (3.07 g, 11.7 mmol) and methyl 3-bromo-1H-pyrazole-5-carboxylate (1.92 g, 9.35 mmol) in dry THF (40 mL) was added the solution of DIAD (3.30 mL, 11.7 mmol) in THF (5 mL) dropwise at 0 °C. The mixture was stirred at rt for 1 h. The mixture was poured into water (100 mL) and extracted with EtOAc (80 mL x 2). The combined organic layers were washed with saturated brine solution (80 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc: 4/1) to give methyl 5-bromo-2-[(2R)-2-(tert-butoxycarbonylamino)-4-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]butyl]pyrazole-3-carboxylate (4.40 g, 71% yield) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 – 7.64 (m, 4H), 7.43 – 7.33 (m, 6H), 6.79 (s, 1H), 4.92 (d, J = 9.2 Hz, 1H), 4.75 – 4.62 (m, 1H), 4.54 – 4.40 (m, 1H), 4.21 – 4.07 (m, 1H), 3.85 (s, 3H), 3.79 (t, J = 5.3 Hz, 2H), 3.61 – 3.48 (m, 4H), 1.88 – 1.75 (m, 1H), 1.73 – 1.62 (m, 1H), 1.33 (s, 9H), 1.03 (s, 9H).

[000616] Step G: Preparation of (6R)-2-bromo-6-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl]-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one: To a solution of methyl 5-bromo-2-[(2R)-2-(tert-butoxycarbonylamino)-4-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]butyl]pyrazole-3-carboxylate (2.50 g, 3.15 mmol) in DCM (18 mL) was added trifluoroacetic acid (7.5 mL, 97 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to dryness to afford crude methyl 1-[(2R)-2-amino-4-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]butyl]-3-bromo-pyrazole-5-carboxylate (2 g), which was dissolved in methanol (18 mL) and water (18 mL). $NaHCO_3$ (2.63 g, 31.3 mmol) was then added slowly at 0 °C to adjust the pH to 8~9. The mixture was stirred at 50 °C for 16 h. The mixture was poured into water (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with saturated brine solution (100 mL), dried over Na_2SO_4 and concentrated to give crude (R)-2-bromo-6-(2-(2-hydroxyethoxy)ethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (1.90 g). To the solution of the crude product in DCM (20 mL) were added imidazole (1.18 g, 17.3 mmol) and tert-butyldiphenylchlorosilane (0.710 mL, 2.76 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was poured into water (40 mL) and extracted with

DCM (40 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc: 2/1) to give (6R)-2-bromo-6-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl]-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (1.80 g, 95% yield) as a colorless oil.

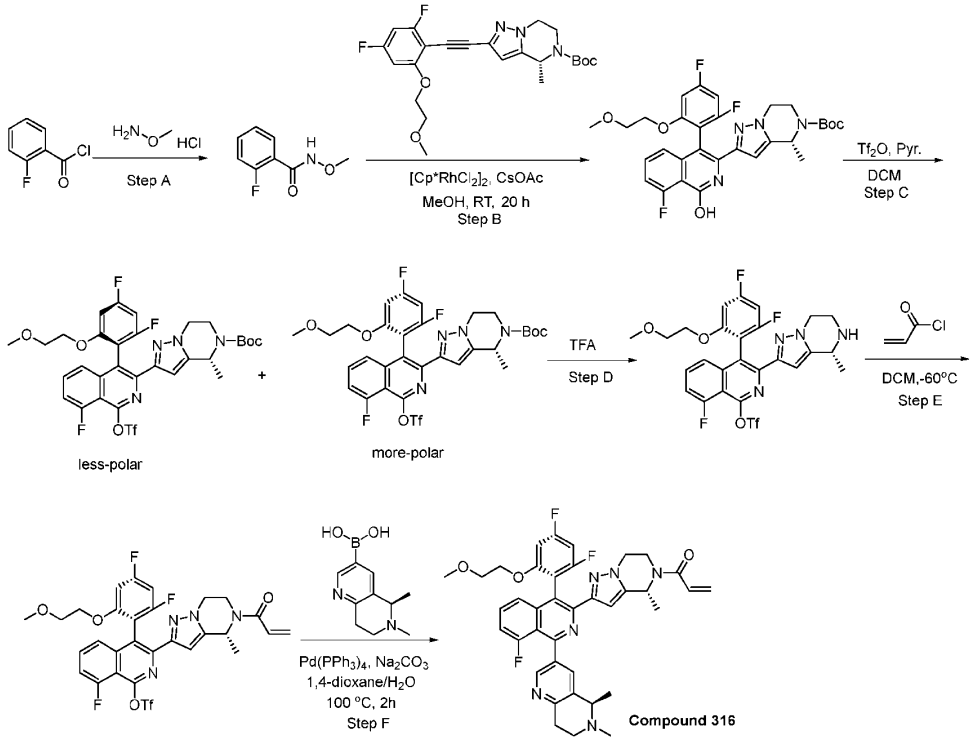
[000617] Step H: Preparation of 2-[2-[(6R)-2-bromo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-6-yl]ethoxy]ethoxy-tert-butyl-diphenyl-silane: To a solution of (6R)-2-bromo-6-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl]-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (2.00 g, 3.69 mmol) in dry THF (30 mL) was added borane-methyl sulfide complex (10 M in THF, 1.50 mL, 15.0 mmol). The mixture was stirred at 60 °C for 12 h under Ar. MeOH (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 1 h, and then heated to 75 °C and kept stirring at this temperature for an additional 3 h. The mixture was concentrated to dryness to give 2-[2-[(6R)-2-bromo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-6-yl]ethoxy]ethoxy-tert-butyl-diphenyl-silane (2.40 g) which was used in the next step directly. LCMS ESI (+) m/z 528.2 (M+H).

[000618] Step I: Preparation of tert-butyl (6R)-2-bromo-6-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of crude 2-[2-[(6R)-2-bromo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-6-yl]ethoxy]ethoxy-tert-butyl-diphenyl-silane (2.40 g, 3.69 mmol) in water (15 mL) and methanol (15 mL) were added sodium bicarbonate (1.44 g, 17.2 mmol) and di-tert-butyl dicarbonate (1.00 mL, 4.29 mmol). The mixture was stirred at 30 °C for 12 h. The mixture was poured into water (40 mL) and extracted with EtOAc (40 mL x 2). The combined organic layers were washed with saturated brine solution (40 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc: 8/1) to give tert-butyl (6R)-2-bromo-6-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.20 g, 52% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, J = 7.2 Hz, 4H), 7.45 - 7.35 (m, 6H), 6.06 (s, 1H), 5.10 - 4.70 (m, 2H), 4.16 – 4.02 (m, 3H), 3.78 (t, J = 5.6 Hz, 2H), 3.60 - 3.40 (m, 4H), 1.80 - 1.60 (m, 2H), 1.46 (s, 9H), 1.04 (s, 9H).

[000619] Step J to Step Q: Preparation of 1-((1^{6}R,E)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4,7-dioxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 20 Step E to Step L, substituting tert-butyl (6R)-2-bromo-6-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate for tert-butyl (7S)-2-bromo-7-[4-[tert-butyl(diphenyl)silyl]oxybutyl]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate in Step E. The crude was purified by Prep-HPLC to afford 1-((1^{6}R,E)-3^4,3^6-difluoro-2^4-(1-methyl-1H-indazol-5-yl)-1^4,1^5,1^6,1^7-tetrahydro-4,7-dioxa-2(6,7)-thieno[3,2-c]pyridina-1(2,6)-pyrazolo[1,5-a]pyrazina-3(1,2)-benzenacyclononaphane-1^5-yl)prop-2-en-1-one as a trifluoroacetic acid

salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.27 (s, 1H), 8.11 - 8.08 (m, 2H), 7.91 - 7.85 (m, 2H), 7.00 - 6.70 (m, 3H), 6.34 - 6.29 (m, 1H), 5.98 - 5.95 (m, 1H), 5.84 - 5.81 (m, 1H), 5.00 - 4.90 (m, 2 H), 4.70 - 4.60 (m, 1H), 4.60 - 4.40 (m, 2H), 4.19 (s, 4H), 3.90 - 3.81 (m, 1H), 3.60 - 3.40 (m, 3H), 2.10 - 1.70 (m, 2H). LCMS ESI (+) m/z 639.1 (M+H).

Synthetic Example 29: Synthesis of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-8-fluoroisoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 316**)



[000620] Step A: Preparation of 2-fluoro-*N*-methoxybenzamide: To a suspension of *O*-methylhydroxylamine hydrochloride (3.16 g, 37.8 mmol) and DIEA (16.8 mL, 94.5 mmol) in DCM (40 mL) was added 2-fluorobenzoyl chloride (5.00 g, 31.5 mmol) dropwise at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was then diluted with aqueous $KHSO_4$ solution and extracted with DCM (40 mL x 2). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude product was recrystallized from EtOAc/petroleum ether to give 2-fluoro-*N*-methoxy-benzamide (4.10 g, 77% yield) as a light yellow solid. LCMS ESI (-) m/z 168.1 (M-H).

[000621] Step B: Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-1-hydroxyisoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A suspension of tert-butyl (4R)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4-methyl-6,7-

dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (300 mg, 0.670 mmol), 2-fluoro-N-methoxy-benzamide (114 mg, 0.674 mmol), cesium acetate (257 mg, 1.34 mmol) and $[Cp^*RhCl_2]_2$ (17 mg, 0.027 mmol) in methanol (2 mL) was stirred at 25 °C for 48 h. The mixture was filtered and washed with DCM/MeOH (1/1, 10 mL). The filtrate was concentrated and purified by Prep-TLC (DCM/MeOH:25/1) to give tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-1-hydroxyisoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (105 mg, 27% yield) as a mixture of two diastereomers. LCMS ESI (+) m/z 585.1 (M+H).

[000622] Step C: Preparation of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-1-(((trifluoromethyl)sulfonyl)oxy)isoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-1-hydroxyisoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (110 mg, 0.188 mmol) and pyridine (0.092 mL, 1.1 mmol) in DCM (10 mL) was added trifluoromethanesulfonic anhydride (0.065 mL, 0.38 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was poured into water and extracted with DCM (10 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and purified by Prep-TLC (EtOAc/petroleum ether:1/5) to give the less-polar isomer (R)-2-((S)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-1-(((trifluoromethyl)sulfonyl)oxy)isoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (58 mg, 43% yield) and the more-polar isomer tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-1-(((trifluoromethyl)sulfonyl)oxy)isoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (60 mg, 44% yield).LCMS ESI (+) m/z 717.0 (M+H).

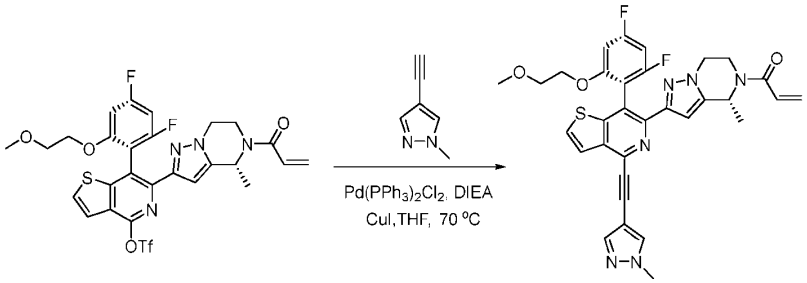
[000623] Step D: Preparation of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-3-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)isoquinolin-1-yl trifluoromethanesulfonate: To a solution of tert-butyl (R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-1-(((trifluoromethyl)sulfonyl)oxy)isoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (58 mg, 0.081 mmol) in DCM (2 mL) was added TFA (0.600 mL, 7.79 mmol). The mixture was stirred at 15 °C for 30 minutes. The mixture was concentrated to give crude (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-3-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)isoquinolin-1-yl trifluoromethanesulfonate (66 mg, 100% yield) which was used in the next step directly. LCMS ESI (+) m/z 617.2 (M+H).

[000624] Step E: Preparation of (R)-3-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoroisoquinolin-1-yl trifluoromethanesulfonate: To a solution of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoro-3-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)isoquinolin-1-yl trifluoromethanesulfonate (66 mg, 0.081 mmol) and TEA (0.037 mL, 0.26 mmol) in DCM (5 mL) was added a solution of acryloyl

chloride (0.0078 mL, 0.096 mmol) in DCM (0.2 mL) at -60 °C. The mixture was stirred at -60 °C for 1 h. The mixture was poured into water (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were washed with water and brine, dried (Na_2SO_4) before concentration. The crude was purified by Prep-TLC (DCM:MeOH=20:1) to give (R)-3-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoroisoquinolin-1-yl trifluoromethanesulfonate (23 mg, 42% yield). LCMS ESI (+) m/z 671.2 (M+H).

[000625] **Step F:** Preparation of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-8-fluoroisoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: A suspension of (R)-3-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-8-fluoroisoquinolin-1-yl trifluoromethanesulfonate (18 mg, 0.027 mmol), sodium carbonate (14 mg, 0.14 mmol), [(5R)-5,6-dimethyl -7,8-dihydro-5H-2, 6-naphthyridin-3-yl]boronic acid (8.0 mg, 0.039 mmol) and tetrakis(triphenylphosphine)palladium(0) (3.1 mg, 0.0027 mmol) in 1,4-dioxane (1 mL) and water (0.1 mL) was stirred at 100 °C for 2 hours. The mixture was filtered and purified by Prep-HPLC to give 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-((R)-5,6-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-8-fluoroisoquinolin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (7.6 mg, 79% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.78 (s, 1H), 8.20 (s, 1H), 7.81 - 7.70 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.44 - 7.33 (m, 1H), 6.94 (d, J = 10.8 Hz, 1H), 6.90 - 6.79 (m, 1H), 6.79 - 6.69 (m, 1H), 6.30 (d, J = 16.2 Hz, 1H), 6.05 (s, 1H), 5.88 - 5.79 (m, 1H), 5.76 - 5.40 (m, 1H), 4.22 (dd, J = 12.6 Hz, 2.6 Hz, 1H), 4.15 - 4.02 (m, 3H), 4.01 - 3.87 (m, 1H), 3.83 - 3.66 (m, 1H), 3.45 (t, J =6.4 Hz, 2H), 3.40 (t, J =4.4 Hz, 2H), 3.12 (s, 3H), 3.02 (s, 3H), 1.83 (d, J = 6.6 Hz, 3H), 1.55-1.34 (m, 3H). LCMS ESI (+) m/z 683.3 (M+H).

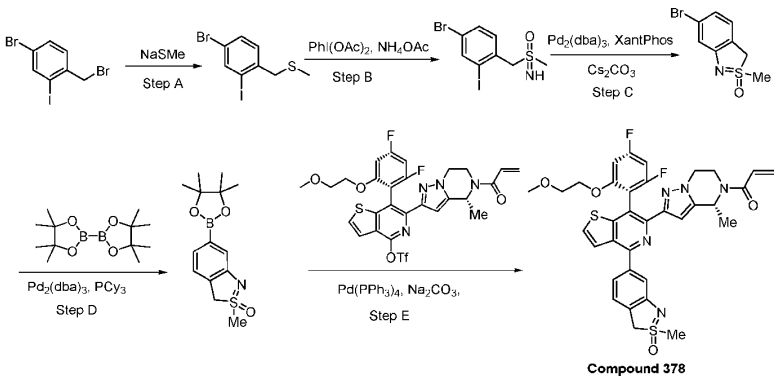
Synthetic Example 30: Synthesis of 1-((R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-((1-methyl-1H-pyrazol-4-yl)ethynyl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 364**)



Compound 364

[000626] To a solution of (S)-6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl trifluoromethanesulfonate (20 mg, 0.030 mmol) and 4-ethynyl-1-methyl-pyrazole (4.8 mg, 0.046 mmol) in THF (2 mL) was added DIEA (6.2 mg, 0.061 mmol), bis(triphenylphosphine)palladium(II) dichloride (4.3 mg, 0.0061 mmol) and CuI (1.2 mg, 0.0061 mmol). The reaction mixture was stirred at 70 °C for 2 h under Ar. The reaction mixture was diluted with water and extracted with EtOAc twice. The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC to give 1-((R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-((1-methyl-1H-pyrazol-4-yl)ethynyl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (8.5 mg, 44% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.81 (s, 1H), 7.78 (d, J = 5.5 Hz, 1H), 7.72 (d, J = 5.5 Hz, 1H), 6.78-6.89 (m, 2H), 6.63-6.71 (m, 1H), 6.28 (d, J = 15.4 Hz, 1H), 6.14 (s, 1H), 5.81 (d, J = 10.6 Hz, 1H), 5.40-5.76 (m, 1H), 4.27-4.50 (m, 1H), 4.11-4.19 (m, 1H), 3.93-4.09 (m, 6H), 3.54-3.89 (m, 1H), 3.40 (t, J = 4.6 Hz, 2H), 3.02 (s, 3H), 1.37-1.54 (m, 3H). LCMS ESI (+) m/z 615.3 (M+H).

Synthetic Example 31: Synthesis of 1-((4R)-2-(7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(2-methyl-2-oxido-3H-2l4-benzo[c]isothiazol-6-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 378**)



[000627] **Step A:** Preparation of 4-bromo-1-iodo-2-(methylsulfanylmethyl)benzene: A mixture of 4-bromo-2-(bromomethyl)-1-iodo-benzene (2.00 g, 5.32 mmol) and methylsulfanylsodium (410 mg, 5.85 mmol) in DMF (20 mL) was stirred at 30 °C for 6 hours. The reaction mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with saturated brine solution, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to afford crude 4-bromo-1-iodo-2-(methylsulfanylmethyl)benzene (1.88 g, 103% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.69 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.08 (dd, J = 8.4, 4.4 Hz, 1H), 3.72 (s, 2H), 2.07 (s, 3H).

[000628] **Step B:** Preparation of (4-bromo-2-iodobenzyl)(imino)(methyl)-λ^6-sulfanone: To a solution of 4-bromo-2-iodo-1-(methylsulfanylmethyl)benzene (500 mg, 1.46 mmol) in ethanol (5 mL) were added iodobenzene diacetate (1409 mg, 4.37 mmol) and NH_4OAc (449 mg, 5.83 mmol). The reaction mixture was stirred at 30 °C for two hours. The reaction mixture was concentrated and purified by column chromatography (EtOAc:petroleum ether=1:2-2:1) to give (4-bromo-2-iodobenzyl)(imino)(methyl)-λ^6-sulfanone (265 mg, 49% yield) as a white solid.

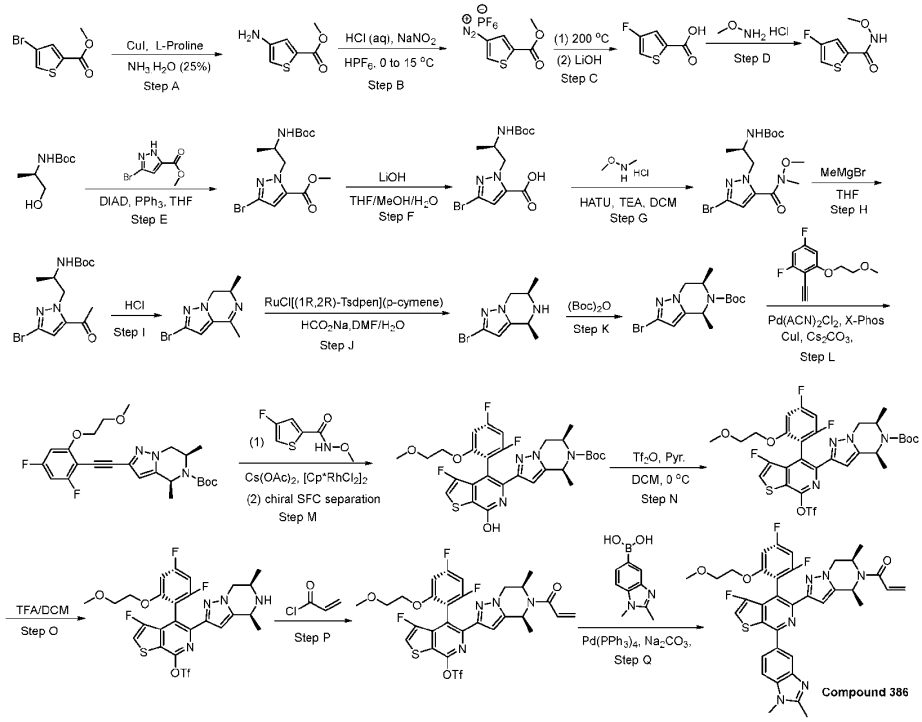
[000629] **Step C:** Preparation of 6-bromo-2-methyl-3H-2,1-benzothiazole 2-oxide: A mixture of (4-bromo-2-iodobenzyl)(imino)(methyl)-λ^6-sulfanone (150 mg, 0.401 mmol), tris(dibenzylideneacetone) dipalladium (0) (18 mg, 0.020 mmol), XantPhos (23 mg, 0.040 mmol) and cesium carbonate (157 mg, 0.481 mmol) in 1,4-dioxane (12 mL) was stirred at 95 °C for 0.5 h. The mixture was poured into water (40 mL) and extracted with EtOAc (30 mLx2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (EtOAc/petroleum ether:2/1) to give 6-bromo-2-methyl-3H-2,1-benzothiazole 2-oxide (75 mg, 76% yield). LCMS ESI (+) m/z 245.9, 247.9 (M+H).

[000630] **Step D:** Preparation of 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-2,1-benzothiazole 2-oxide: A suspension of $Pd(OAc)_2$ (35 mg, 0.36 mmol), 6-bromo-2-methyl-3H-2,1-benzothiazole 2-oxide (44 mg, 0.18 mmol), bis(pinacolato)diboron (68 mg, 0.268 mmol), tris(dibenzylideneacetone)dipalladium (0) (8.1 mg, 0.0089 mmol) and tricyclohexylphosphine (5.0 mg, 0.018 mmol) in 1,4-dioxane (5 mL) was stirred at 100 °C for 0.5 h under Ar. The mixture was cooled to room temperature and poured into saturated brine solution (30 mL), and the product was extracted with EtOAc (30 mLx2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (EtOAc/petroleum ether:2/1) to give crude (~50% purity) 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-2,1-benzothiazole 2-oxide (22 mg, 21% yield). LCMS ESI (+) m/z 294.1 (M+H).

[000631] **Step E:** Preparation of 1-((4R)-2-(7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(2-methyl-2-oxido-3H-2l4-benzo[c]isothiazol-6-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a suspension of 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-2,1-benzothiazole 2-oxide (22 mg, 0.038 mmol), 6-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridin-4-yl trifluoromethanesulfonate (30 mg, 0.046 mmol), and sodium carbonate (14 mg, 0.14 mmol) in 1,4-Dioxane (5 mL) and Water (0.5 mL) was added tetrakis(triphenylphosphine)palladium(0) (5.6 mg, 0.0049 mmol). The mixture was stirred at 100 °C for 25 mins under Ar. The mixture was cooled to rt and poured into water (30 mL). The mixture was extracted with DCM (20 mLx2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and

concentrated. The residue was purified by Prep-HPLC to give 1-((4R)-2-(7-((S)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(2-methyl-2-oxido-3H-2l4-benzo[c] isothiazol-6-yl)thieno[3,2-c]pyridin-6-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (10 mg, 39% yield) as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 5.6 Hz, 1H), 7.80 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.44 - 7.35 (m, 2H), 6.97 (d, J = 10.8 Hz, 1H), 6.90 - 7.76 (m, 2H), 6.38 - 6.21 (m, 1H), 6.06 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.79 - 5.40 (m, 1H), 5.19 - 5.07 (m, 1H), 4.77 - 4.68 (m, 1H), 4.36 - 4.25 (m, 1H), 4.22 - 3.96 (m, 3H), 3.57 (s, 3H), 3.44 (t, J = 4.5 Hz, 2H), 3.07 (s, 3H), 1.54 - 1.35 (m, 1H); LCMS ESI (+) m/z 676.2 (M+H).

Synthetic Example 32: Synthesis of 1-((4S,6R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 386**)



[000632] **Step A:** Preparation of methyl 4-aminothiophene-2-carboxylate: To a suspension of copper (I) iodide (86.15 g, 452 mmol), L-proline (104.16 g, 905 mmol) in DMSO (2500 mL) was added methyl 4-bromothiophene-2-carboxylate (500.00 g, 2262 mmol). The mixture was bubbled with Ar for 5 min, and then ammonia hydroxide (25% aqueous solution, 1000.0 g, 7133 mmol) was added. The mixture was stirred at 70 °C for 16 h. The mixture was diluted with saturated brine solution (500 mL) and extracted with EtOAc (500 mLx3). The combined organic phases were washed with saturated brine solution (1000 mL), dried

over anhydrous Na_2SO_4, filtered and concentrated. The residue was triturated with petroleum ether/EtOAc (1/8) to afford methyl 4-aminothiophene-2-carboxylate (220 g, 62% yield) as a yellow solid.

[000633] **Step B:** Preparation of 5-methoxycarbonylthiophene-3-diazonium hexafluorophosphate: Methyl 4-aminothiophene-2-carboxylate (60.00 g, 382 mmol) was dissolved in 6 N HCl (1800 mL) and stirred at rt for 10 min. The reaction was cooled to 0 °C and $NaNO_2$ (31.56 g, 457 mmol) in water (80 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h and HPF_6 (70% in H_2O, 220 mL, 382 mmol) was added. The solid diazonium salt precipitated out of the mixture was stirred for an additional 10 min. The reaction was allowed to warm up to 15 °C. The solid was filtered, washed with diluted hexafluoro phosphoric acid (80 mL), MeOH (50 mL) and MTBE (300 mL), and then dried in vacuo to give 5-methoxycarbonyl thiophene-3-diazonium hexafluorophosphate (107.50 g, 90% yield).

[000634] **Step C:** Preparation of 4-fluorothiophene-2-carboxylic acid: A mixture of 5-methoxycarbonyl thiophene-3-diazonium hexafluorophosphate (214.00 g, 681 mmol) and sand (1500 g) was warmed to 200 °C under vacuum (0.01 torr) in a Kugelrohr apparatus equipped with a trap at -78 °C. A yellow liquid started to distill and condensed in the trap and it was carefully collected using DCM as solvent. The solvent was evaporated to give crude methyl 4-fluorothiophene-2-carboxylate (90.0 g, 82% yield) which was dissolved in THF (150 mL), methanol (150 mL) and water (150 mL). Lithium hydroxide hydrate (87.10 g, 2076 mmol) was added. The mixture was stirred at 30 °C for 3 h. The mixture was concentrated to remove MeOH and THF, and then aqueous HCl (3 N) was added to adjust the pH to 1. The product was extracted with EtOAc (400 mLx3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The product was recrystallized from hexane to give 4-fluorothiophene-2-carboxylic acid (80.0 g, 98% yield) as an off-white solid. LCMS ESI (-) m/z 145.0 (M-H).

[000635] **Step D:** Preparation of 4-fluoro-*N*-methoxy-thiophene-2-carboxamide: To a solution of 4-fluorothiophene-2-carboxylic acid (80.0 g, 547 mmol) in DCM (1.5 L) were added 1-hydroxybenzotriazole (81.5 g, 603 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (126.0 g, 657 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min, and then O-methylhydroxylamine hydrochloride (54.8 g, 656 mmol) was added followed by *N*,*N*-diisopropylethylamine (320 mL, 1837 mmol). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated and purified by column chromatography on silica gel (EtOAc/Petroleum ether: 1/1) to give 4-fluoro-*N*-methoxy-thiophene-2-carboxamide (72.5 g, 76% yield) as a white solid.

[000636] **Step E:** Preparation of methyl 3-bromo-1-[(2R)-2-(tert-butoxycarbonylamino)propyl]pyrazole-5-carboxylate: To a solution of methyl 3-bromo-1H-pyrazole-5-carboxylate (200.00 g, 976 mmol), tert-butyl N-[(1R)-2-hydroxy-1-methyl-ethyl]carbamate (170.95 g, 976 mmol) and triphenylphosphine (307.06 g, 1171 mmol) in THF (2000 mL) was added diisopropyl azodicarboxylate (247.0 mL, 1268 mmol) in THF (500 mL) dropwise at 0 °C. The mixture was stirred at

25 °C overnight. Water (20 mL) was added and the mixture was concentrated under reduced pressure. To the above solution was added Petroleum ether/EtOAc (1500 mL/300 mL) and stirred for 4 h. The mixture was filtered and the solid was washed with Petroleum ether/EtOAc (5/1, 300 mL). The filtrate was concentrated under reduced pressure to give crude methyl 3-bromo-1-[(2R)-2-(tert-butoxycarbonylamino)propyl]pyrazole-5-carboxylate (340.0 g, 96% yield) as a yellow solid which was used in the next step without further purification. LCMS ESI (+) m/z 306.0, 308.0 (M-Boc+H).

[000637] **Step F:** Preparation of (R)-3-bromo-1-(2-((tert-butoxycarbonyl)amino)propyl)-1H-pyrazole-5-carboxylic acid: To a solution of methyl (R)-3-bromo-1-(2-((tert-butoxycarbonyl)amino)propyl)-1H-pyrazole-5-carboxylate (500 g, 1.38 mol) in THF (3.2 L), Methanol (800 mL) and Water (800 mL) was added lithium hydroxide monohydrate (232 g, 5.52 mol) at 0 °C. The mixture was stirred at 20 °C for 16 h. The mixture was concentrated under reduced pressure to remove MeOH and THF, and then diluted with water (500 mL). The mixture was extracted with MTBE (500 mL×3). HCl (1 M) was added to the aqueous phase to adjust the pH to 2-3 at 0 °C. The mixture was extracted with DCM (1000 mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give crude (R)-3-bromo-1-(2-((tert-butoxycarbonyl)amino)propyl)-1H-pyrazole-5-carboxylic acid (480 g, 100% yield) which was used in the next step directly. LCMS ESI (-) m/z 346.0, 348.0 (M-H).

[000638] **Step G:** Preparation of tert-butyl N-[(1R)-2-[3-bromo-5-[methoxy(methyl)carbamoyl]pyrazol-1-yl]-1-methyl-ethyl]carbamate: A solution of 3-bromo-1-[(2R)-2-(tert-butoxycarbonylamino)propyl]pyrazole-5-carboxylic acid (470.0 g, 1350 mmol), HATU (666.8 g, 1755 mmol) and TEA (470 mL, 3374 mmol) in DCM (4500 mL) was stirred at rt for 0.5 h. N,O-dimethylhydroxylamine (157.99 g, 1620 mmol) was then added. The solution was stirred at 20 °C for 2 h. The mixture was diluted with water (2000 mL) and the residue was extracted with DCM (600 ml x3). The combined organics were washed with saturated brine solution. The organics were then separated and dried over Na_2SO_4 before concentration to dryness. The crude was purified by column chromatography (Petroleum ether/EtOAc = 5/1) to give tert-butyl N-[(1R)-2-[3-bromo-5-[methoxy(methyl)carbamoyl]pyrazol-1-yl]-1-methyl-ethyl]carbamate (353.0 g, 67% yield) as a white solid. LCMS ESI (+) m/z 335.0, 337.0 (M-Boc+H).

[000639] **Step H:** Preparation of tert-butyl N-[(1R)-2-(5-acetyl-3-bromo-pyrazol-1-yl)-1-methyl-ethyl]carbamate: To a solution of tert-butyl N-[(1R)-2-[3-bromo-5-[methoxy(methyl)carbamoyl]pyrazol-1-yl]-1-methyl-ethyl]carbamate (345.0 g, 882 mmol) in THF (1200 mL) at -20 °C under N_2 was added methylmagnesium bromide (1.0 M in THF, 2204 mL, 2204 mmol) dropwise. The mixture was warmed to rt and stirred for 2 h. The reaction was quenched by saturated ammonium chloride solution (100 mL), diluted with water (1000 mL) and extracted with EtOAc (1000 mL × 3). The combined organic extracts were washed with saturated brine solution (1500 mL), dried over Na_2SO_4, filtered and concentrated to give

tert-butyl N-[(1R)-2-(5-acetyl-3-bromo-pyrazol-1-yl)-1-methyl-ethyl]carbamate (290.0 g, 95% yield) as a light yellow solid. LCMS ESI (+) m/z 290.0, 292.0 (M-Boc+H).

[000640] **Step I:** Preparation of (6R)-2-bromo-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine: To a solution of tert-butyl N-[(1R)-2-(5-acetyl-3-bromo-pyrazol-1-yl)-1-methyl-ethyl]carbamate (300.0 g, 867 mmol) in 1,4-dioxane (1500 mL) was added HCl/1,4-dioxane (3000 mL, 4 M). The mixture was stirred at 25 °C for 2 h. The reaction was concentrated under reduced pressure. The residue was diluted with water (1000 mL). Saturated sodium bicarbonate solution was added to adjust the pH to 9. The mixture was extracted with DCM (1500 mLx3), dried over Na_2SO_4 before concentration to dryness to give (6R)-2-bromo-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine (170.0 g, 86% yield) as a brown oil. The crude was used in the next step without further purification. LCMS ESI (+) m/z 228, 230 (M+H).

[000641] **Step J:** Preparation of (4S,6R)-2-bromo-4,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine: A mixture of ((6R)-2-bromo-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine (202.0 g, 886 mmol), (R,R)-N-(p-Toluenesulfonyl)-1,2-diphenylethanediamine(chloro)(p-cymene)ruthenium (II) (16.77 g, 26.6 mmol) and sodium formate (301.15 g, 4428 mmol) in DMF (1500 mL) and Water (1500 mL) was stirred at 55 °C for 20 h. The solution was diluted with more water (1500 mL) and extracted with DCM (1500 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness to remove DCM and DMF. The residue was dissolved in DCM (600 mL). HCl in 1,4-dioxane (4 M, 500 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The precipitated solid was collected by filtration. The filter cake was washed with DCM (500 mL) to give an off-white solid which was dissolved in water (800 mL). Na_2CO_3 was added in portions to adjust the pH to 8. The product was extracted with DCM (800 mLx3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated to give (4S,6R)-2-bromo-4,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (170.0 g, 83% yield).

[000642] **Step K:** Preparation of tert-butyl (4S,6R)-2-bromo-4,6-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: A mixture of (4S,6R)-2-bromo-4,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (170.0 g, 739 mmol) and di-tert-butyl dicarbonate (483.71 g, 2216 mmol) was stirred at 100 °C for 16 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/DCM = 1/3) to give tert-butyl (4S,6R)-2-bromo-4,6-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (230 g, 94% yield) as a brown oil. LCMS ESI (+) m/z 330.1, 332.1 (M+H).

[000643] **Step L:** Preparation of tert-butyl (4S,6R)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4,6-dimethyl-6,7-dihydro-4H-pyrazolo [1,5-a]pyrazine-5-carboxylate: A suspension of tert-butyl (4S,6R)-2-bromo-4,6-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (30.0 g, 90.8 mmol), 2-ethynyl-1,5-difluoro-3-(2-methoxyethoxy)benzene (32.8 g, 154 mmol),

cesium carbonate (60.0 g, 184 mmol), copper(I) iodide (1.73 g, 9.08 mmol), dichlorobis(acetonitrile)palladium(II) (2.34 g, 9.02 mmol) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (4.33 g, 9.08 mmol) in 1,4-dioxane (500 mL) was stirred at 100 °C for 16 h. The mixture was concentrated and diluted with water (500 mL). The mixture was extracted with EtOAc (500 mLx2). The combined organic phases were washed with saturated brine solution (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (EtOAc/Petroleum ether: 1/2) to give tert-butyl (4S,6R)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4,6-dimethyl-6,7-dihydro-4H-pyrazolo [1,5-a]pyrazine-5-carboxylate (42.0 g, 90% yield). LCMS ESI (+) m/z 462.2 (M+H).

[000644] Step M: Preparation of tert-butyl (4S,6R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4S,6R)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4,6-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (42.0 g, 81.9 mmol) in ethanol (400 mL) was added 4-fluoro-N-methoxy-thiophene-2-carboxamide (14.00 g, 79.9 mmol) and $[CP^*RhCl_2]_2$ (1.50 g, 2.43 mmol) and CsOAc (31.0 g, 162 mmol). The mixture was stirred at reflux for 48 h. The mixture was concentrated, diluted with EtOAc (500 mL) and washed with saturated brine solution (500 mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (Petroleum ether:EtOAc=1:1 to 100% EtOAc) to give tert-butyl (4S,6R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4,6-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (35.0 g, 72% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.09 (s, 1H), 6.63 - 6.56 (m, 2H), 5.30 – 5.26 (m, 1H), 5.10 – 4.85 (m, 2H), 4.20 – 3.92 (m, 4H), 3.48 – 3.41 (m, 2H), 3.14 – 3.10 (m, 3H), 1.50 (s, 9H), 1.38 – 1.32 (m, 3H), 1.20 – 1.14 (m, 3H). 58 g of tert-butyl (4S,6R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-3-fluoro-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4,6-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate was separated by chiral SFC (CHIRALPAK® AD-H 250 mm x 20 mm, 5 μm; Mobile phase: 30% EtOH/CO_2 (containing 0.2% NH_4OH) to give tert-butyl (4S,6R)-2-((S)-4-(2,4-difluoro-6-(2-methoxy ethoxy)phenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (29 g) as the first peak, and tert-butyl (4S,6R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (29 g) as the second peak.

[000645] Step N: Preparation of tert-butyl (4S,6R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a stirred solution of tert-butyl (4S,6R)-2-((R)-4-

(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (29.0 g, 48.0 mmol) and pyridine (11.4 g, 144 mmol) in DCM (300 mL) was added trifluoromethanesulfonic anhydride (20.3 g, 71.9 mmol) at 0 °C. The solution was stirred at 0 °C for 1h. The mixture was washed with water (200 mL x 2), dried (Na_2SO_4) and concentrated. The crude was purified by column chromatography (Petroleum ether:EtOAc=5:1-1:1) to give tert-butyl (4S,6R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl) sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (33.5 g, 95% yield) as a light-yellow solid. LCMS ESI (+) m/z 737.1 (M+H).

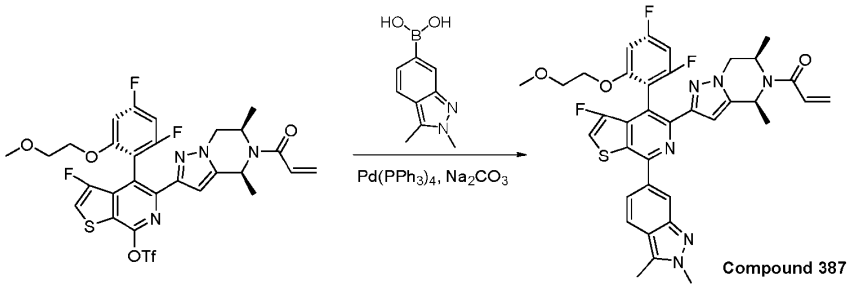
[000646] Step O: Preparation of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5-((4S,6R)-4,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate: To a solution of tert-butyl (4S,6R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(((trifluoromethyl) sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (160 mg, 0.217 mmol) in DCM (3 mL) was added trifluoroacetic acid (1.0 mL, 13 mmol). The mixture was stirred at 24 °C for 30 minutes. The mixture was concentrated to give crude (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5-((4S,6R)-4,6-dimethyl-4,5,6,7-tetrahydro pyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (280 mg) which was used in the next step without further purification. LCMS ESI (+) m/z 637.0 (M+H).

[000647] Step P: Preparation of (R)-5-((4S,6R)-5-acryloyl-4,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate: To a mixture of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5-((4S,6R)-4,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (280 mg, 0.299 mmol) in ethyl acetate (4 mL) and water (2 mL) being cooled to 0 °C was added aqueous Na_2CO_3 solution to adjust the pH to 8. Acryloyl chloride (0.039 mL, 0.48 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 minutes. The mixture was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated, washed with saturated brine solution (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (EtOAc) to give (R)-5-((4S,6R)-5-acryloyl-4,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (120 mg, 50% yield) as a white solid. LCMS ESI (+) m/z 691.0 (M+H).

[000648] Step Q: Preparation of 1-((4S,6R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of (R)-5-((4S,6R)-5-acryloyl-4,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-

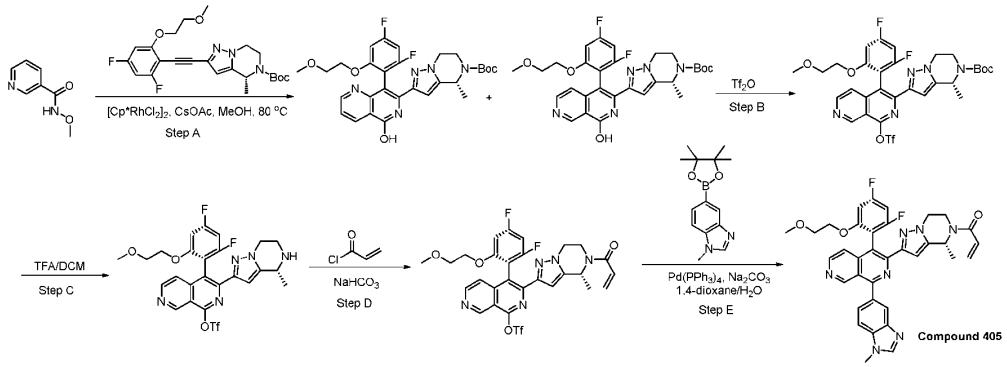
fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (32 mg, 0.046 mmol) in 1,4-dioxane (1 mL) and water (0.1 mL) were added (1,2-dimethylbenzimidazol-5-yl)boronic acid (11 mg, 0.056 mmol), sodium carbonate (9.8 mg, 0.093 mmol) and $Pd(PPh_3)_4$ (5.4 mg, 0.0046 mmol). The mixture was heated to 100 °C and stirred for 1 hour. The mixture was filtered and the filtrate was concentrated. The crude was purified by Prep-HPLC to give 1-((4S,6R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d] imidazole-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (27 mg, 86% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J = 1.1 Hz, 1H), 8.06 (dd, J = 8.4, 1.5 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 6.88 – 6.72 (m, 2H), 6.66 – 6.59 (m, 1H), 6.34 –6.18 (m, 2H), 5.80 (d, J = 10.8 Hz, 1H), 5.52 – 5.40 (m, 1H), 4.20 - 4.03 (m, 3H), 3.98 –3.91 (m, 1H), 3.88 (s, 3H), 3.46 (t, J = 4.7 Hz, 2H), 3.09 (s, 3H), 2.66 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H). LCMS ESI (+) m/z 687.2 (M+H).

Synthetic Example 33: Synthesis of 1-((4S,6R)-2-(4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(2,3-dimethyl-2H-indazol-6-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 387**)



[000649] To a solution of (R)-5-((4S,6R)-5-acryloyl-4,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (15 mg, 0.022 mmol) in 1,4-dioxane (1 mL) and water (0.1 mL) were added (2,3-dimethylindazol-6-yl)boronic acid (5.0 mg, 0.026 mmol), sodium carbonate (4.6 mg, 0.043 mmol) and $Pd(PPh_3)_4$ (2.5 mg, 0.0022 mmol). The mixture was heated to 100 °C for 1 hour. The mixture was filtered and the filtrate was concentrated. The crude was purified by Prep-HPLC to give 1-((4S,6R)-2-(4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-7-(2,3-dimethyl-2H-indazol-6-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (6.5 mg, 41% yield) as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.95 – 7.90 (m, 1H), 7.82 – 7.75 (m, 1H), 7.71 – 7.67 (m, 1H), 6.88 – 6.76 (m, 2H), 6.71 – 6.63 (m, 1H), 6.34 – 6.20 (m, 1H), 6.16 (s, 1H), 5.81 (d, J = 10.1 Hz, 1H), 5.52 – 5.41 (m, 1H), 4.25 – 4.13 (m, 5H), 4.12 – 4.05 (m, 1H), 3.99 – 3.92 (m, 1H), 3.47 (t, J = 4.6 Hz, 2H), 3.10 (s, 3H), 2.74 (s, 3H), 1.51 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H). LCMS ESI (+) m/z 687.2 (M+H).

Synthetic Example 34: 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1-methyl-1H-benzo[d]imidazol-5-yl)-2,7-naphthyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 405**)



[000650] **Step A:** Preparation of tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-hydroxy-2,7-naphthyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A solution of N-methoxypyridine-3-carboxamide (100 mg, 0.657 mmol), tert-butyl (R)-2-((2,4-difluoro-6-(2-methoxyethoxy)phenyl)ethynyl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (294 mg, 0.657 mmol). bis[(pentamethylcyclopentadienyl)dichloro-rhodium] (10 mg, 0.016 mmol) and cesium acetate (252 mg, 1.31 mmol) in MeOH (5 mL) was stirred at 80 °C overnight. The mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/DCM = 1/200) to give tert-butyl (4R)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-hydroxy-2,7-naphthyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (100 mg, 27% yield) and tert-butyl (4R)-2-(8-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5-hydroxy-1,6-naphthyridin-7-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (105 mg, 28% yield). LCMS ESI (+) m/z 568.2 (M+H).

[000651] **Step B:** Preparation of tert-butyl (R)-2-(4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(((trifluoromethyl)sulfonyl)oxy)-2,7-naphthyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-1-hydroxy-2,7-naphthyridin-3-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (90 mg, 0.16 mmol) and pyridine (0.077 mL, 0.95 mmol) in DCM (3 mL) was added trifluoromethanesulfonic anhydride (0.054 mL, 0.32 mmol) at 0 °C. The mixture was stirred at rt for 1 h. The mixture was diluted with water (20 mL) and extracted with DCM (15 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Pre-TLC (petroleum ether/EtOAc = 3/1) to give the desired tert-butyl (R)-2-(4-((R)-2,4-

difluoro-6-(2-methoxyethoxy)phenyl)-1-(((trifluoromethyl)sulfonyl)oxy)-2,7-naphthyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (30 mg, 27% yield) as the more polar diastereomer. LCMS ESI (+) m/z 700.1 (M+H).

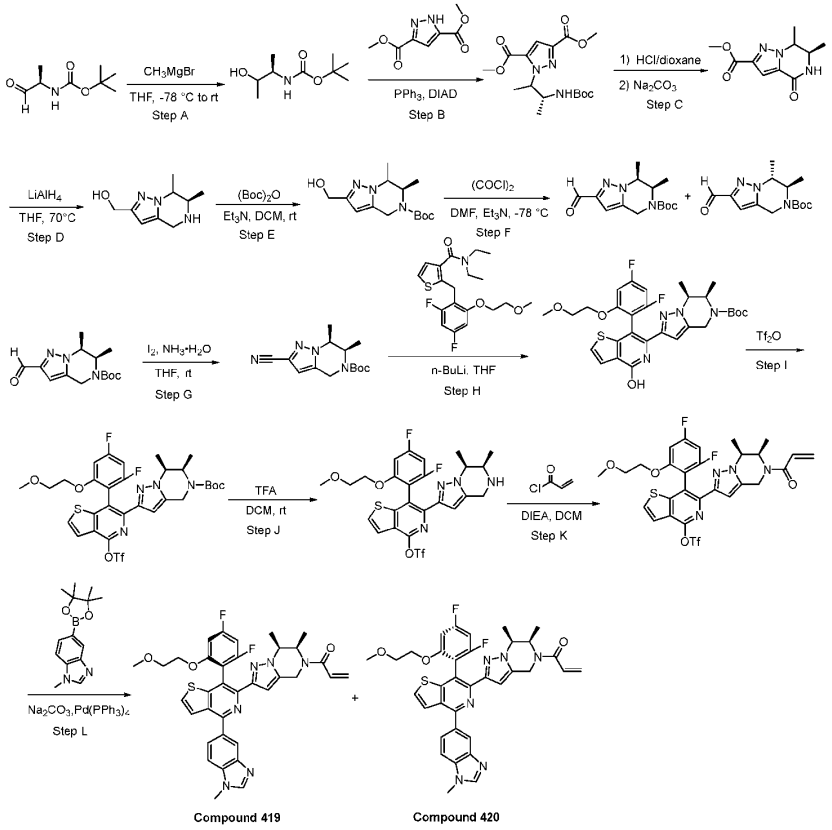
[000652] Step C: Preparation of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-2,7-naphthyridin-1-yl trifluoromethanesulfonate: To a solution of tert-butyl (R)-2-(4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(((trifluoromethyl)sulfonyl)oxy)-2,7-naphthyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (30 mg, 0.043 mmol) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at rt for 1 h. The reaction was concentrated under reduced pressure to give (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-2,7-naphthyridin-1-yl trifluoromethanesulfonate (38 mg, 100% yield) which was used in the next step without further purification. LCMS ESI (+) m/z 600.2 (M+H).

[000653] Step D: Preparation of (R)-3-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2,7-naphthyridin-1-yl trifluoromethanesulfonate: A solution of (R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-((R)-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-2,7-naphthyridin-1-yl trifluoromethanesulfonate (38 mg, 0.043 mmol) in EtOAc (5 mL) and water (5 mL) was stirred at rt for 5 min. The mixture was cooled to 0 °C and saturated sodium bicarbonate solution was added to adjust the pH 8. Acryloyl chloride (0.0027 mL, 0.033 mmol) in DCM (1 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (MeOH/DCM = 1/20) to give (R)-3-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2,7-naphthyridin-1-yl trifluoromethanesulfonate (12 mg, 43% yield). LCMS ESI (+) m/z 654.1 (M+H).

[000654] Step E: Preparation of 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1-methyl-1H-benzo[d]imidazol-5-yl)-2,7-naphthyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: A mixture of (R)-3-((R)-5-acryloyl-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-2,7-naphthyridin-1-yl trifluoromethanesulfonate (11 mg, 0.017 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole (5.6 mg, 0.022 mmol), tetrakis(triphenylphosphine)palladium(0) (1.9 mg, 0.0017 mmol) and sodium carbonate (3.6 mg, 0.034 mmol) in 1,4-dioxane (1.2 mL) and water (0.3 mL) was stirred at 100 °C for 4 h under N_2 atmosphere. The mixture was diluted with water (20 mL) and the residue was taken up in EtOAc. The organics were washed with saturated brine solution, dried over Na_2SO_4 and concentrated. The crude was then purified by Prep-HPLC to give 1-((R)-2-((R)-4-(2,4-difluoro-6-(2-

methoxyethoxy)phenyl)-1-(1-methyl-1H-benzo[d]imidazol-5-yl)-2,7-naphthyridin-3-yl)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (3.5 mg, 33% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR(400 MHz, CD_3OD) δ 9.46 (d, J = 11.8 Hz, 2H), 8.66 (d, J = 6.2 Hz, 1H), 8.38 (s, 1H), 8.23 – 8.12 (m, 2H), 7.61 (d, J = 6.2 Hz, 1H), 6.95 (d, J = 10.7 Hz, 1H), 6.89 – 6.72 (m, 2H), 6.28 (d, J = 10.6 Hz, 2H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.25 (s, 3H), 4.22 – 3.97 (m, 4H), 3.39 (t, J = 4.5 Hz, 2H), 3.01 (s, 3H), 1.52 – 1.35 (m, 3H). LCMS ESI (+) m/z 636.3 (M+H).

Synthetic Example 35: Synthesis of 1-((6R,7S)-2-((R)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 419**) and 1-(6R,7S)-2-(S)-7-(2,4-difluoro-6-(2-methoxyethoxy) phenyl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl) thieno[3,2-c] pyridin-6-yl)-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a] pyrazin-5(4H)-yl) prop-2-en-1-one (**Compound 420**).



[000655] **Step A**: Preparation of *tert*-butyl ((2*R*)-3-hydroxybutan-2-yl) carbamate: To a solution of *tert*-butyl *N*-[(1*R*)-1-methyl-2-oxo-ethyl]carbamate (8.00 g, 46.2 mmol) in THF (100 mL) under N_2 atmosphere at -78 °C was added CH_3MgBr (3.0 M, 46.0 mL, 139 mmol) . The mixture was stirred at rt for 2 h. The reaction was quenched by NH_4Cl (50 mL), diluted with H_2O, then extracted with ethyl acetate (250 mLx3).

The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give *tert*-butyl ((2*R*)-3-hydroxybutan-2-yl) carbamate (8.6 g, 88.5% yield) as a brown oil, which was used in the next step directly. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (s, 1H), 3.89 – 3.52 (m, 2H), 1.45 (d, *J*

[000656] Step B: Preparation of dimethyl 1-[(2*R*)-2-(*tert*-butoxycarbonylamino)-1-methyl-propyl]pyrazole-3,5-dicarboxylate: To a stirred solution of *tert*-butyl *N*-[(1*R*)-2-hydroxy-1-methyl-propyl]carbamate (8.50 g, 44.9 mmol) in THF (120 mL) were added dimethyl 1*H*-pyrazole-3,5-dicarboxylate (8.27 g, 44.9 mmol) and PPh_3 (17.7 g, 67.4 mmol). Then DIAD (19.0 mL, 67.4 mmol) was added dropwise at 0 °C under Ar. The reaction was stirred at 20 °C for 16 h. The mixture was quenched by water (300 mL) and extracted with EtOAc (200 mLx2). The organic phase was concentrated. The residue was purified by silica gel column Chromatography (0 to 10% EtOAc in hexanes) to give dimethyl 1-[(2*R*)-2-(*tert*-butoxycarbonylamino)-1-methyl-propyl]pyrazole-3,5-dicarboxylate (10.0 g, 56% yield) as a colorless oil. LCMS ESI (+) m/z 356.1 (M+H).

[000657] Step C: Preparation of methyl (6*R*)-6,7-dimethyl-4-oxo-6,7-dihydro-5H-pyrazolo[1,5-a] pyrazine-2-carboxylate: A mixture of dimethyl 1-[(2*R*)-2-(tert-butoxycarbonylamino)-1-methyl-propyl] pyrazole-3,5-dicarboxylate (17.0 g, 47.8 mmol) in 1,4-Dioxane (150 mL) was added 4 N HCl in 1,4-Dioxane (96.0 mL, 383 mmol). The mixture was stirred at rt overnight and concentrated. To the residue was added water and the pH was adjusted to 8 with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over sodium sulfate to give methyl (6*R*)-6,7-dimethyl-4-oxo-6,7-dihydro-5H-pyrazolo[1,5-a] pyrazine-2-carboxylate (10.0 g, 94% yield) as a pale brown solid. LCMS ESI (+) m/z 224.1 (M+H).

[000658] Step D: Preparation of ((6*R*)-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-yl)methanol: A mixture of methyl (6*R*)-6,7-dimethyl-4-oxo-6,7-dihydro-5*H*-pyrazolo[1,5-*a*]pyrazine-2-carboxylate (19.0 g, 85.1 mmol) and $LiAlH_4$ (12.9 g, 340 mmol) in THF (300 mL) was stirred at 70 °C for 16 h. Upon completion of the reaction, the reaction was carefully quenched by dropwise addition of 12.9 mL of H_2O followed by 12.9 mL of 15% NaOH and 38.7 ml of H_2O. The mixture was filtrated and the filtrate was concentrated to give ((6*R*)-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-yl)methanol (11.0 g, 64% yield) as a brown oil, which was used directly in the next step. LCMS ESI (+) m/z 182.2 (M+H).

[000659] Step E: Preparation of tert-butyl (6*R*)-2-(hydroxymethyl)-6,7-dimethyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate: A solution of [(6*R*)-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-yl]methanol (7.50 g, 41.4 mmol), Boc_2O (18.1 g, 82.8 mmol) and Et_3N (12.5 g, 124 mmol) was stirred at 25 °C for 16 h. Upon completion of the reaction, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/DCM=0

to 3%) to give tert-butyl (6*R*)-2-(hydroxymethyl)-6,7-dimethyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate (6.80 g, 55% yield) as colorless oil. LCMS ESI (+) m/z 282.3 (M+H).

[000660] **Step F**: Preparation of [*tert*-butyl (6*R*,7*S*)-2-formyl -6,7-dimethyl -6,7-dihydro -4*H*-pyrazolo [1,5-*a*] pyrazine-5-carboxylate and *tert*-butyl (6*R*,7*R*)-2-formyl-6,7-dimethyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate: To a stirring solution of oxalyl chloride (5.41 g, 42.7 mmol) in DCM (150 mL) was added DMSO (6.66 g, 85.3 mmol) at -78 °C under N_2. The mixture was stirred at -78 °C for 30 min, and then tert-butyl (6*R*)-2-(hydroxymethyl)-6,7-dimethyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate (6.00 g, 21.3 mmol) in DCM (2 mL) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 1 h. TEA (18.0 mL, 128 mmol) was added, the mixture was stirred at rt for 1 h. Upon completion of the reaction, the resulting mixture was concentrated, poured into water and extracted with DCM. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (EtOAc/Hexanes = 1/9) to give *tert*-butyl (6*R*,7*S*)-2-formyl -6,7-dimethyl -6,7-dihydro -4*H*-pyrazolo [1,5-*a*] pyrazine-5-carboxylate (2.8 g, 47% yield) and *tert*-butyl (6*R*,7*R*)-2-formyl-6,7-dimethyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate (850 mg, 14% yield). *tert*-butyl (6*R*,7*S*)-2-formyl -6,7-dimethyl -6,7-dihydro -4*H*-pyrazolo [1,5-*a*] pyrazine-5-carboxylate characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 6.61 (s, 1H), 4.98 (d, *J* = 17.2 Hz, 1H), 4.66 (d, J = 13.5 Hz, 1H), 4.43 (s, 1H), 4.35 (d, *J* = 17.3 Hz, 1H), 1.65 (d, *J* = 6.7 Hz, 3H), 1.51 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H); LCMS ESI (+) m/z 280.1 (M+H). *tert*-butyl (6*R*,7*R*)-2-formyl-6,7-dimethyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 6.58 (s, 1H), 5.02 (s, 1H), 4.61 (s, 1H), 4.44-4.20 (m, 2H), 1.51 (s, 9H), 1.48 (d, *J* = 6.7 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H); LCMS ESI (+) m/z 280.1 (M+H).

[000661] **Step G:** Preparation of tert-butyl (6R,7S)-2-cyano-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a] pyrazine-5-carboxylate: A solution of tert-butyl (6R,7S)-2-formyl-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (2.00 g, 7.16 mmol), I_2 (5.45 g, 21.5 mmol) and ammonium hydroxide (10.0 g, 71.6 mmol) in THF (100 mL) was stirred at 25 °C for 16 h. Upon completion of the reaction, the mixture was quenched with aqueous Na_2SO_3 and extracted with EtOAc. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Petroleum Ether = 0 to 30%) to give tert-butyl (6R,7S)-2-cyano-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a] pyrazine-5-carboxylate (1.85 g, 84% yield). LCMS ESI (+) m/z 277.3 (M+H).

[000662] **Step H:** Preparation of tert-butyl (6R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of 2-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]-N,N-diethylthiophene-3-carboxamide (1.20 g, 3.13 mmol) in THF (10 mL) was added n-BuLi (2.4 M in hexanes, 1.30 mL, 3.13

mmol) at - 60 °C under Ar. The mixture was stirred at - 60 °C for 1 h, and then a solution of tert-butyl (6R,7S)-2-cyano-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (720 mg, 2.61 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at rt for 3 h. Upon completion of the reaction, the solution was acidified with 1 *N* HCl and extracted with DCM. The organics were then separated and concentrated. The crude product was purified by flash chromatography (CH_3OH/DCM=0-5%) to give tert-butyl (6R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.80 g, 59% yield). LCMS ESI (+) m/z 587.0 (M+H).

[000663] **Step I:** Preparation of tert-butyl (6R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoromethylsulfonyloxy) thieno [3,2-c]pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (6R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy) phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.80 g, 3.07 mmol) in DCM (5 mL) were added pyridine (3.30 mL, 30.7 mmol) and trifluoromethanesulfonic anhydride (1.00 mL, 6.14 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h and then partitioned between DCM and water. The aqueous layer was acidified with citric acid solution and extracted with DCM. The combined organic layers were washed with water and brine, dried and concentrated. The residue was purified by flash chromatography (EtOAc/Petroleum Ether = 0 to 30%) to give tert-butyl (6R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoromethylsulfonyloxy) thieno [3,2-c]pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (958 mg, 35% yield) as colorless oil. LCMS ESI (+) m/z 719.2 (M+H).

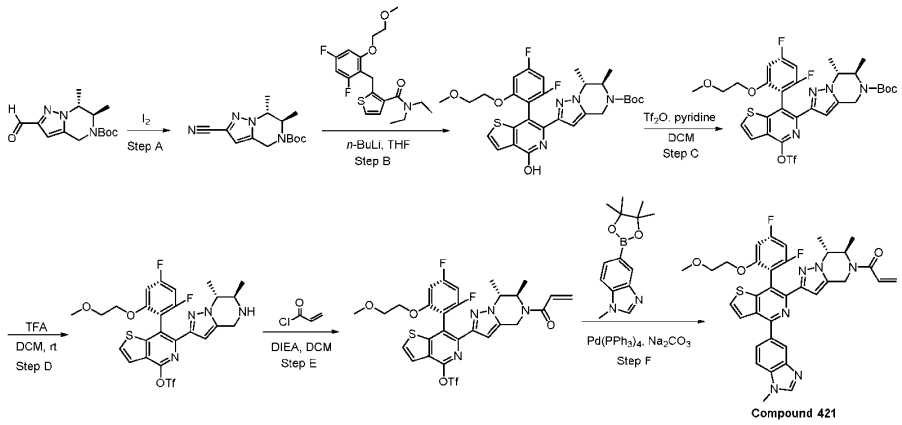
[000664] **Step J:** Preparation of [7-[2,4-difluoro-6-(2-methoxyethoxy) phenyl]-6-[(6R,7S)-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a] pyrazin-2-yl] thieno[3,2-c] pyridin-4-yl] trifluoromethanesulfonate: A solution of tert-butyl (6R,7S)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoromethylsulfonyloxy) thieno[3,2-c]pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (200 mg, 0.278 mmol) in TFA (1.10 mL, 14.1 mmol) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction was concentrated and to the residue was added water. The solution was basified with $NaHCO_3$ solution to pH 8. The aqueous layer was extracted with DCM and concentrated to afford [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-6-[(6R,7S)-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl] thieno[3,2-c] pyridin-4-yl] trifluoromethanesulfonate (157 mg, crude) as a yellow oil. LCMS ESI (+) m/z 618.9 (M+H).

[000665] **Step K:** Preparation of [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-6-[(6R,7S)-6,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate: To a solution of [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-6-[(6R,7S)-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl]thieno[3,2-c]pyridin-4-yl]

trifluoromethanesulfonate (157 mg, 0.254 mmol) in DCM (8 mL) were added DIEA (0.071 mL, 0.51 mmol) and acryloyl chloride (0.031 mL, 0.381 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. The solution was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography (EtOAc/Petroleum Ether = 0 to 70%) to give [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-6-[(6R,7S)-6,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate (172 mg, 81% yield) as a colorless oil. LCMS ESI (+) m/z 672.8 (M+H).

[000666] **Step L:** Preparation of 1-((6R,7S)-2-((R)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 419**) and 1-(6R,7S)-2-(S)-7-(2,4-difluoro-6-(2-methoxyethoxy) phenyl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dimethyl-6,7-dihydropyrazolo [1,5-a] pyrazin-5(4H)-yl) prop-2-en-1-one (**Compound 420**): A mixture of [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-6-[(6R,7S)-6,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate (87 mg, 0.13 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole (43 mg, 0.17 mmol), Na_2CO_3 (41 mg, 0.39 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) were stirred in 1,4-dioxane (10 mL) and water (1 mL) at 100 °C under N_2 for 1 h. The reaction was concentrated to dryness. The crude was purified by flash column chromatography eluting with 4% MeOH in DCM to give the crude product, which was further purified by chiral SFC (column: CHIRALPAK AD-H 250mm x 20 mm, 5 μm, mobile phase: 40% IPA (with 0.2% NH_4OH):60% CO_2, gradient: 40 g/min) to afford 1-((6R,7S)-2-((R)-7-(2,4-difluoro-6-(2-methoxyethoxy) phenyl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dimethyl-6,7-dihydro pyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 419**, Peak 1, 18 mg, 21% yield) and 1-(6R,7S)-2-(S)-7-(2,4-difluoro-6-(2-methoxyethoxy) phenyl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl) thieno[3,2-c] pyridin-6-yl)-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a] pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 420**, Peak 2, 19 mg, 23% yield). **Compound 419**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 – 8.22 (m, 2H), 8.02 – 7.96 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.71 (q, J = 5.6 Hz, 2H), 6.82 (d, J = 10.9 Hz, 2H), 6.73 (td, J = 9.3, 2.3 Hz, 1H), 6.69 (s, 1H), 6.29 (dd, J = 16.7, 1.7 Hz, 1H), 5.85 – 5.78 (m, 1H), 5.16 (t, J = 37.4 Hz, 1H), 4.67 (d, J = 63.1 Hz, 1H), 4.52 – 4.17 (m, 2H), 4.11 – 3.96 (m, 4H), 3.95 – 3.88 (m, 1H), 3.45 – 3.37 (m, 2H), 3.03 (s, 3H), 1.35 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 10.5 Hz, 3H). LCMS ESI (+) m/z 655.1 (M+H). **Compound 420**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 3.6 Hz, 2H), 7.88 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.59 (q, J = 5.6 Hz, 2H), 6.74 (d, J = 10.9 Hz, 2H), 6.58 (dd, J = 9.2, 2.3 Hz, 1H), 6.54 (s, 1H), 6.16 (dd, J = 16.7, 1.7 Hz, 1H), 5.69 (dd, J = 10.6, 1.7 Hz, 1H), 5.00 (d, J = 55.7 Hz, 1H), 4.55 (d, J = 55.8 Hz, 1H), 4.40 – 4.06 (m, 2H), 4.02 – 3.95 (m, 1H), 3.95 – 3.81 (m, 4H), 3.32 (dd, J = 10.6, 5.8 Hz, 2H), 2.91 (s, 3H), 1.25 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 20.2 Hz, 3H). LCMS ESI (+) m/z 655.1 (M+H).

Synthetic Example 36: Synthesis of 1-((6*R*,7*R*)-2-((*S*)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl -1*H*-benzo [d]imidazole -5-yl) thieno [3,2-*c*] pyridin-6-yl) -6,7-dimethyl -6,7-dihydropyrazolo [1,5-*a*]pyrazin-5(4*H*)-yl)prop-2-en-1-one (**Compound 421**)



[000667] **Step A:** Preparation of tert-butyl (6R,7R)-2-cyano-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A solution of tert-butyl (6R,7R)-2-formyl-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (700 mg, 2.51 mmol), I_2 (1.91 g, 7.52 mmol) and ammonium hydroxide (3.51 g, 25.1 mmol) in THF (30 mL) was stirred at 25 °C for 16 h. Upon completion of the reaction, the mixture was quenched with aqueous Na_2SO_3 and extracted with EtOAc. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Petroleum Ether = 0 to 20%) to give tert-butyl (6R,7R)-2-cyano-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (520 mg, 68% yield) as a colorless oil. LCMS ESI (+) m/z 277.1 (M+H).

[000668] **Step B:** Preparation of tert-butyl (6R,7R)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a stirred solution of 2-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]-N,N-diethylthiophene-3-carboxamide (683 mg, 1.78 mmol) in THF (6 mL) was added n-BuLi (2.5 M in hexanes, 0.710 mL, 1.78 mmol) at - 60 °C under Ar. The mixture was stirred at - 60 °C for 30 min, and then a solution of tert-butyl (6R,7R-2-cyano-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (410 mg, 1.48 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at rt for 3 h. Upon completion of the reaction, the solution was acidified with 1 *N* HCl and extracted with EtOAc. The organics were then separated and concentrated. The crude product was purified by flash chromatography (CH_3OH/DCM=0-5%) to give tert-butyl (6R,7R)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (310 mg, 32% yield). LCMS ESI (+) m/z 587.0 (M+H).

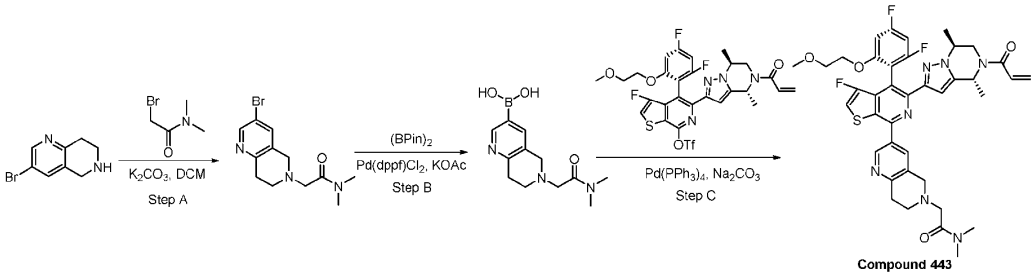
[000669] **Step C:** Preparation of tert-butyl (6R,7R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (6R,7R)-2-[7-[2,4-difluoro-6-(2-methoxyethoxy) phenyl]-4-hydroxy-thieno[3,2-c]pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (300 mg, 0.511 mmol) in DCM (10 mL) were added pyridine (0.410 mL, 5.11 mmol) and trifluoromethanesulfonic anhydride (0.170 mL, 1.02 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h and then partitioned between DCM and water. The aqueous layer was acidified with citric acid solution and extracted with DCM. The combined organic layers were washed with water and brine, dried and concentrated. The residue was purified by flash chromatography (EtOAc/hexanes = 1/8) to give the desired diastereomer tert-butyl (6R,7R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridin-6-yl)-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (110 mg, 35% yield) as a pale yellow solid. LCMS ESI (+) m/z 719.2 (M+H).

[000670] **Step D:** Preparation of (S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-6-((6R,7R)-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)thieno[3,2-c]pyridin-4-yl trifluoromethanesulfonate: A solution of *tert*-butyl (6*R*,7*R*)-2-((*S*)-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4-(trifluoromethylsulfonyloxy) thieno [3,2-*c*] pyridin-6-yl]-6,7-dimethyl-6,7-dihydro-4*H*-pyrazolo [1,5-*a*]pyrazine-5-carboxylate (130 mg, 0.181 mmol) in TFA (0.710 mL, 9.17 mmol) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction was concentrated and to the residue was added water. The solution was basified with $NaHCO_3$ solution to pH 8. The aqueous layer was extracted with DCM and concentrated to afford *(S)*-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-6-[(6*R*,7*R*)-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*] pyrazin-2-yl] thieno [3,2-*c*] pyridine-4-yl] trifluoromethanesulfonate (90 mg,76% yield) as a yellow oil. LCMS ESI (+) m/z 619.2 (M+H).

[000671] **Step E:** Preparation of (S)-6-((6R,7R)-5-acryloyl-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo [1,5-a]pyrazin-2-yl)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)thieno[3,2-c]pyridine-4-yl trifluoromethanesulfonate: To a solution of *(S)*-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-6-[(6*R*,7*R*)-6,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*] pyrazin-2-yl] thieno [3,2-*c*] pyridine-4-yl] trifluoromethanesulfonate (100 mg, 0.162 mmol) in DCM (8 mL) were added DIEA (0.045 mL, 0.32 mmol) and acryloyl chloride (0.020 mL, 0.24 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. The solution was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography (EtOAc/hexanes = 0 to 70%) to give *(S)* -[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-6-[(6*R*,7*R*)-6,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-*a*]pyrazin-2-yl] thieno[3,2-*c*]pyridin-4-yl] trifluoromethanesulfonate (85 mg, 74% yield) as a colorless oil. LCMS ESI (+) m/z 672.7 (M+H).

[000672] **Step F:** Preparation of 1-((6R,7R)-2-((S)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[3,2-c]pyridin-6-yl)-6,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 421**): A mixture of [7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-6-[(6*R*,7*R*)-6,7-dimethyl-5-prop-2-enoyl-6,7-dihydro -4H-pyrazolo [1,5-*a*] pyrazin-2-yl] thieno [3,2-*c*] pyridin-4-yl] trifluoromethanesulfonate (40 mg, 0.060 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole (20 mg, 0.077 mmol), Na_2CO_3 (19 mg, 0.18 mmol) and $Pd(PPh_3)_4$ (6.9 mg, 0.0060 mmol) were stirred in 1,4-dioxane (6 mL) and water (1 mL) at 100 °C under N_2 for 1 h. The reaction was concentrated to dryness. The crude was purified by flash column chromatography eluting with 0-10% MeOH in DCM to give 1-((6*R*,7*R*)-2-((*S*)-7-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-4-(1-methyl -1*H*-benzo [d]imidazole -5-yl) thieno [3,2-*c*] pyridin-6-yl) -6,7-dimethyl -6,7-dihydropyrazolo [1,5-*a*]pyrazin-5(4*H*)-yl)prop-2-en-1-one (23 mg, 59% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 – 8.22 (m, 2H), 8.01 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.82 – 7.66 (m, 3H), 6.93 – 6.75 (m, 2H), 6.70 (t, *J* = 9.2 Hz, 1H), 6.38 – 6.25(m, 2H), 5.84 (dd, *J* = 10.6, 1.8 Hz, 1H), 5.39 – 4.98 (m, 2H), 4.72 – 4.55 (m, 1H), 4.31 – 4.24 (m, 1H), 4.16 – 4.07 (m, 1H), 4.06 – 3.94 (m, 4H), 3.47 (t, *J* = 4.7 Hz, 2H), 3.07 (s, 3H), 1.35 – 1.28 (m, 3H), 1.26 – 1.14 (m, 3H). LCMS ESI (+) m/z 655.3 (M+H).

Synthetic Example 37: Synthesis of 2-(3-((R)-5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-N,N-dimethylacetamide (**Compound 443**)

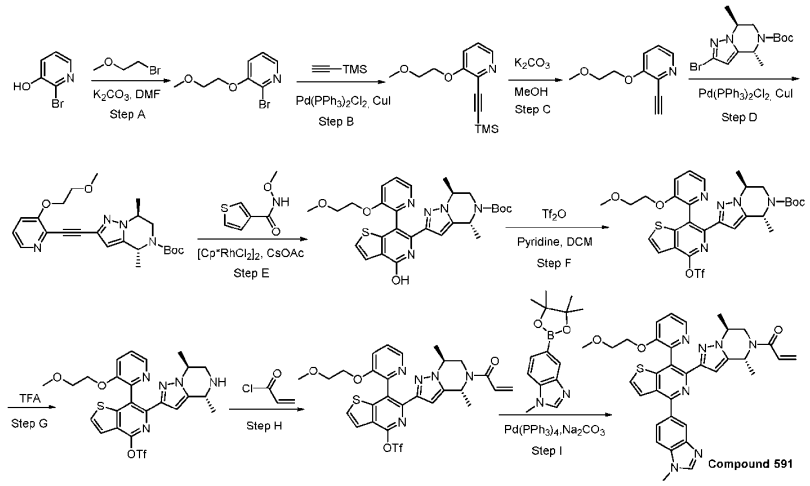


[000673] **Step A:** Preparation of 2-(3-bromo-7,8-dihydro-5H-1,6-naphthyridin-6-yl)-N,N-dimethyl-acetamide: A solution of 3-bromo-5,6,7,8-tetrahydro-1,6-naphthyridine (32 mg, 0.15 mmol), 2-bromo-N,N-dimethyl-acetamide (25 mg, 0.15 mmol) and potassium carbonate (62 mg, 0.45 mmol) in DMF (2 mL) was stirred at rt overnight. The mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (MeOH/DCM = 1/20) to give 2-(3-bromo-7,8-dihydro-5H-1,6-naphthyridin-6-yl)-N,N-dimethyl-acetamide (14 mg, 31% yield) as a white solid. LCMS ESI (+) m/z 298.0 (M+H).

[000674] **Step B:** Preparation of [6-[2-(dimethylamino)-2-oxo-ethyl]-7,8-dihydro-5H-1,6-naphthyridin-3-yl]boronic acid: A suspension of 2-(3-bromo-7,8-dihydro-5H-1,6-naphthyridin-6-yl)-N,N-dimethyl-acetamide (14 mg, 0.047 mmol), bis(pinacolato)diboron (15 mg, 0.061 mmol), 1,1'-bis(diphenylphosphino) ferrocenedichloro palladium(ii) dichloromethane complex (3.4 mg, 0.0047 mmol) and potassium acetate (9.2 mg, 0.094 mmol) in 1,4-dioxane (1.5 mL) was stirred for 2 h at 95 °C under N_2 atmosphere. The mixture was concentrated to dryness. The residue was diluted with EtOAc (10 mL) and filtered. The filtrate was concentration and the residue was purified by Prep-HPLC to give [6-[2-(dimethylamino)-2-oxo-ethyl]-7,8-dihydro-5H-1,6-naphthyridin-3-yl]boronic acid (10 mg, 81% yield). LCMS ESI (+) m/z 264.1 (M+H).

[000675] **Step C:** Preparation of 2-(3-((R)-5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-N,N-dimethylacetamide: A suspension of [4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5-[(4R,7S)-4,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]-3-fluoro-thieno[2,3-c]pyridin-7-yl] trifluoromethanesulfonate (14 mg, 0.020 mmol), [6-[2-(dimethylamino)-2-oxo-ethyl]-7,8-dihydro-5H-1,6-naphthyridin-3-yl]boronic acid (6.9 mg, 0.026 mmol), tetrakis(triphenylphosphine)palladium (0) (2.3 mg, 0.0020 mmol) and sodium carbonate (4.3 mg, 0.040 mmol) in 1,4-Dioxane (3 mL) and water (0.3 mL) was stirred at 100 °C for 2 h under N_2 atmosphere. The mixture was filtered, and the filtrate was concentrated. The residue was purified by Prep-HPLC to give 2-[3-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5-[(4R,7S)-4,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]-3-fluoro-thieno[2,3-c]pyridin-7-yl]-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-N,N-dimethyl-acetamide (6.6 mg, 42% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.4 Hz, 1H), 8.47 (s, 1H), 7.60 (d, J = 2.1 Hz, 1H), 6.92 – 6.77 (m, 2H), 6.61 (td, J = 9.2, 2.0 Hz, 1H), 6.33 (d, J = 16.6 Hz, 1H), 6.13 (s, 1H), 5.84 (dd, J = 10.6, 1.2 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.77 (s, 2H), 4.52 – 4.40 (m, 3H), 4.13 – 4.06 (m, 1H), 4.05 – 3.98 (m, 1H), 3.90 – 3.81 (m, 2H), 3.52 – 3.42 (m, 4H), 3.08 (s, 3H), 3.05 (s, 6H), 1.52 – 1.36 (m, 3H), 1.35 – 1.27 (m, 3H). LCMS ESI (+) m/z 760.2 (M+H).

Synthetic Example 38: Synthesis of 1-[(4R,7S)-2-[7-[3-(2-methoxyethoxy)-2-pyridyl]-4-(1-methylbenzimidazol-5-yl)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl]prop-2-en-1-one (**Compound 591**)



[000676] **Step A**: Preparation of 2-bromo-3-(2-methoxyethoxy)pyridine: To a solution of 2-bromo-3-pyridinol (2.00 g, 11.5 mmol) and 1-bromo-2-methoxy-ethane (3.20 g, 23.0 mmol) in DMF (20 mL) was added K_2CO_3 (4.76 g, 34.5 mmol). The reaction mixture was stirred at 25 °C for 16 h. The mixture was diluted with water (100 mL) and extracted with EtOAc (50 mLx3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc: Petroleum ether = 0-10%) to give 2-bromo-3-(2-methoxyethoxy)pyridine (2.50 g, 94% yield) as a yellow oil. LCMS ESI (+) m/z 232.0 (M+H).

[000677] **Step B**: Preparation of 2-[3-(2-methoxyethoxy)-2-pyridyl]ethynyl-trimethyl-silane: A mixture of 2-bromo-3-(2-methoxyethoxy)pyridine (2.50 g, 10.8 mmol) in 1,4-Dioxane (50 mL) was added TEA (7.50 mL, 53.9 mmol), $Pd(PPh_3)_2Cl_2$ (756 mg, 1.08 mmol), CuI (205 mg, 1.08 mmol) and trimethylsilylacetylene (3.00 mL, 21.5 mmol). The mixture was stirred at 70 °C for 16 h. Upon completion of the reaction, the resulting mixture was concentrated under reduced pressure. The crude was used in the next step directly. LCMS ESI (+) m/z 250.1 (M+H).

[000678] **Step C**: Preparation of 2-ethynyl-3-(2-methoxyethoxy)pyridine: To a stirred solution of 2-[3-(2-methoxyethoxy)-2-pyridyl]ethynyl-trimethyl-silane (2.50 g, 10.0 mmol) in Methanol (30 mL) were added K_2CO_3 (2.77 g, 20.0 mmol). The reaction was stirred at 25°C for 2 h. The mixture was quenched by water (20 mL) and extracted with EtOAc (50 mLx2). The organic phase was concentrated. The residue was purified by silica gel column chromatography (EtOAc: Petroleum ether = 0 – 10%) to give 2-ethynyl-3-(2-methoxyethoxy)pyridine (1.20 g, 61% yield) as a brown oil. LCMS ESI (+) m/z 178.1 (M+H).

[000679] **Step D**: Preparation of tert-butyl (4R,7S)-2-[2-[3-(2-methoxyethoxy)-2-pyridyl]ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: A mixture of tert-butyl (4R,7S)-2-bromo-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.00 g, 3.03 mmol), 2-ethynyl-3-(2-methoxyethoxy)pyridine (805 mg, 4.54 mmol), $Pd(PPh_3)_2Cl_2$ (213 mg, 0.303 mmol), CuI (115

mg, 0.606 mmol) and TEA (1.30 mL, 9.08 mmol) in DMF (75 mL) was stirred at 85 °C under Ar for 10 h. Upon completion of the reaction, the mixture was diluted with H_2O. The aqueous layer was separated and extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Petroleum Ether = 0 to 20%) to give tert-butyl (4R,7S)-2-[2-[3-(2-methoxyethoxy)-2-pyridyl]ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (350 mg, 14% yield). LCMS ESI (+) m/z 427.0 (M+H).

[000680] **Step E**: Preparation of product tert-butyl (4R,7S)-2-[4-hydroxy-7-[3-(2-methoxyethoxy)-2-pyridyl]thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: A mixture of tert-butyl (4R,7S)-2-[2-[3-(2-methoxyethoxy)-2-pyridyl]ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (350 mg, 0.821 mmol), N-methoxythiophene-3-carboxamide (155 mg, 0.985 mmol), cesium acetate (315 mg, 1.64 mmol) and dichloro(pentamethylcyclopentadienyl) rhodium(III) dimer (51 mg, 0.082 mmol) in Methanol (60 mL) was stirred at 60 °C under Ar for 12 h. Upon completion of the reaction, the mixture was concentrated, diluted with H_2O and extracted with EtOAc. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (MeOH/DCM = 0 to 10%) to give tert-butyl (4R,7S)-2-[4-hydroxy-7-[3-(2-methoxyethoxy)-2-pyridyl]thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (60 mg, 12% yield) as a yellow oil. LCMS ESI (+) m/z 552.2 (M+H).

[000681] **Step F**: Preparation of tert-butyl (4R,7S)-2-[7-[3-(2-methoxyethoxy)-2-pyridyl]-4-(trifluoromethylsulfonyloxy) thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: A solution of tert-butyl (4R,7S)-2-[4-hydroxy-7-[3-(2-methoxyethoxy)-2-pyridyl]thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (60 mg, 0.11 mmol) in DCM (3 mL) was added pyridine (0.12 mL, 1.1 mmol) and trifluoromethanesulfonic anhydride (0.037 mL, 0.22 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was diluted with DCM, washed with citric acid solution and brine, dried and concentrated. The crude product was purified by flash chromatography (EtOAc/Petroleum Ether = 0 to 30%) to give tert-butyl (4R,7S)-2-[7-[3-(2-methoxyethoxy)-2-pyridyl]-4-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (40 mg, 48% yield) as a brown oil. LCMS ESI (+) m/z 684.2 (M+H).

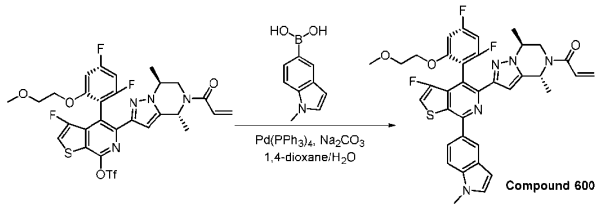
[000682] **Step G**: Preparation of [6-[(4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl]-7-[3-(2-methoxyethoxy)-2-pyridyl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate: A solution of tert-butyl (4R,7S)-2-[7-[3-(2-methoxyethoxy)-2-pyridyl]-4-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (40 mg, 0.058 mmol) in TFA (0.23 mL) and DCM (5 mL) was stirred at 25 °C for 1 h. The solution was concentrated and taken

up in water. The pH was adjusted to 8 with saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM, washed with water and brine, dried and concentrated to afford [6-[(4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl]-7-[3-(2-methoxyethoxy)-2-pyridyl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate (35 mg, crude) as yellow oil. LCMS ESI (+) m/z 584.1 (M+H).

[000683] Step H: Preparation of [6-[(4R,7S)-4,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]-7-[3-(2-methoxyethoxy)-2-pyridyl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate: A solution of [6-[(4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl]-7-[3-(2-methoxyethoxy)-2-pyridyl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate (35 mg, 0.060 mmol) in DCM (4 mL) was added DIEA (0.021 mL, 0.12 mmol) and acryloyl chloride (0.0073 mL, 0.090 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. The solution was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/Petroleum Ether = 0-70%) to give [6-[(4R,7S)-4,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]-7-[3-(2-methoxyethoxy)-2-pyridyl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate (35 mg, 82% yield). LCMS ESI (+) m/z 638.1 (M+H).

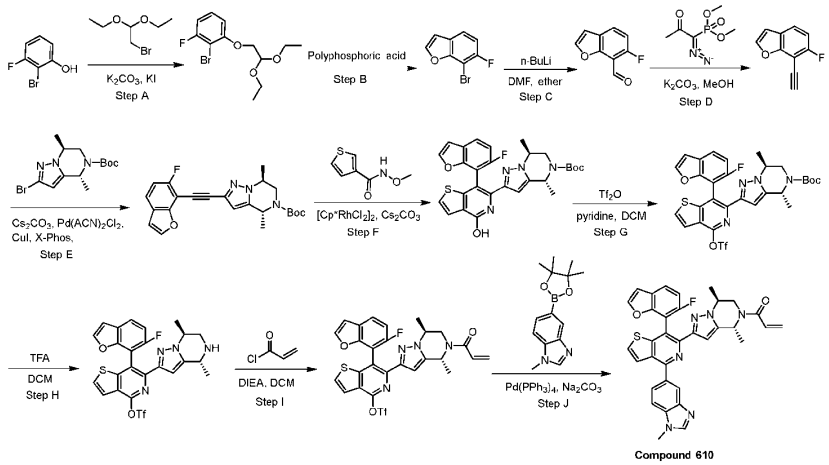
[000684] Step I: Preparation of 1-[(4R,7S)-2-[7-[3-(2-methoxyethoxy)-2-pyridyl]-4-(1-methylbenzimidazol-5-yl)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl]prop-2-en-1-one: A mixture of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole (11 mg, 0.041 mmol), [6-[(4R,7S)-4,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]-7-[3-(2-methoxyethoxy)-2-pyridyl]thieno[3,2-c]pyridin-4-yl] trifluoromethanesulfonate (20 mg, 0.031 mmol) , Na_2CO_3 (10 mg, 0.094 mmol), tetrakis(triphenylphosphine)palladium (3.6 mg, 0.0031 mmol) in 1,4-Dioxane (3 mL) and Water (0.3 mL) was stirred at 100 °C for 1 h under N_2. After cooling, the mixture was filtered, and the filtrate was concentrated. The residue was then purified by flash column chromatography on silica gel eluting with DCM: MeOH = 0~10% to give the crude product, which was further purified by prep-HPLC to give 1-[(4R,7S)-2-[7-[3-(2-methoxyethoxy)-2-pyridyl]-4-(1-methylbenzimidazol-5-yl)thieno[3,2-c]pyridin-6-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl]prop-2-en-1-one (4.7 mg, 24% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (d, J = 6.7 Hz, 3H), 8.01 (d, J = 8.4 Hz, 1H), 7.77 (dd, J = 24.5, 8.3 Hz, 3H), 7.55 (d, J = 9.2 Hz, 2H), 7.02 – 6.73 (m, 1H), 6.39 (s, 2H), 5.86 (d, J = 10.8 Hz, 1H), 5.81 – 5.46 (m, 1H), 4.32 (s, 1H), 4.26 – 4.12 (m, 1H), 4.03 (s, 4H), 3.96 – 3.72 (m, 2H), 3.48 (s, 1H), 3.42 (t, J = 4.6 Hz, 1H), 3.12 (d, J = 2.0 Hz, 3H), 1.49 (d, J = 23.0 Hz, 3H), 1.20 (s, 3H). LCMS ESI (+) m/z 620.0 (M+H).

Synthetic Example 39: Synthesis of 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 600**)



[000685] To a solution of 5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (25 mg, 0.036 mmol) in 1,4-Dioxane (5 mL) and Water (0.5 mL) were added (1-methylindol-5-yl)boronic acid (9.5 mg, 0.054 mmol), sodium carbonate (7.7 mg, 0.072 mmol) and tetrakis(triphenylphosphine)palladium(0) (4.2 mg, 0.0036 mmol). The reaction mixture was stirred at 90 °C for 2 h under N_2. The mixture was poured into water (50 ml) and extracted with EtOAc (50 mLx2). The combined organic layers were washed with saturated brine solution (50 ml), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to give 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (11 mg, 41% yield) as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.95 (s, 1H), 7.92 - 7.89 (m, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 2.9 Hz, 1H), 6.92 - 6.80 (m, 2H), 6.73 - 6.65 (m, 2H), 6.33 (d, J = 16.5 Hz, 1H), 6.05 (s, 1H), 5.88 - 5.80 (m, 1H), 5.79 - 5.40 (m, 1H), 4.15 – 4.10 (m, 1H), 4.06 – 4.01 (m, 1H), 3.96 – 3.80 (m, 3H), 3.47 (t, J = 4.6 Hz, 2H), 3.11 (s, 3H), 1.53 – 1.26 (m, 6H). LCMS ESI (+) m/z 672.3 (M+H).

Synthetic Example 40: Synthesis of 1-((4R,7S)-2-(7-(6-fluorobenzofuran-7-yl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 610**)



[000686] **Step A**: Preparation of 2-bromo-1-(2,2-diethoxyethoxy)-3-fluoro-benzene: A mixture of 2-bromo-3-fluoro-phenol (3.00 g, 15.7 mmol), 2-bromo-1,1-diethoxy-ethane (6.19 g, 31.4 mmol), KI (2.61 g, 15.7 mmol) and K_2CO_3 (3.25 g, 23.6 mmol) in DMF (20 mL) was stirred at 145 °C for 4 h. Upon completion of the reaction, the mixture was diluted with H_2O and extracted with DCM. The organic layers were combined and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/Petroleum Ether = 0 to 20%) to give 2-bromo-1-(2,2-diethoxyethoxy)-3-fluoro-benzene (4.00 g, 58% yield) as colorless oil. LCMS ESI (+) m/z 329.0 (M+Na).

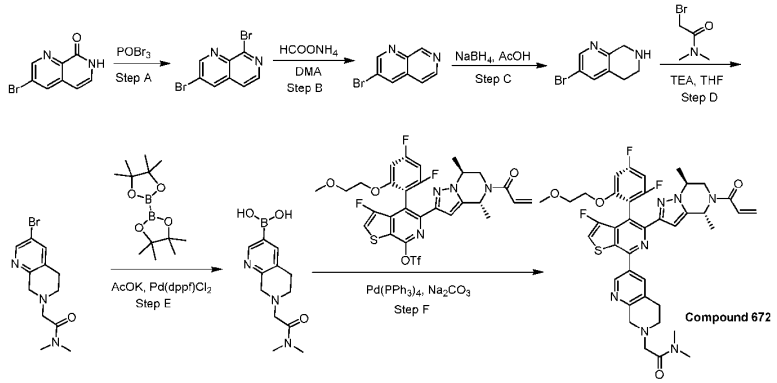
[000687] **Step B**: Preparation of 7-bromo-6-fluoro-benzofuran: A mixture of 2-bromo-1-(2,2-diethoxyethoxy)-3-fluoro-benzene (4.00 g, 13.0 mmol) and polyphosphoric acid (1.97 g, 14.3 mmol) in toluene (10 mL) was stirred at 90 °C for 2 h. Upon completion of the reaction, the organic layers were concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Petroleum Ether =0 to 1%) to give 7-bromo-6-fluoro-benzofuran (2.40 g, 86% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 2.0 Hz, 1H), 7.46 (dd, J = 8.4, 4.8 Hz, 1H), 7.08 (t, J = 8.8 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H).

[000688] **Step C**: Preparation of 6-fluorobenzofuran-7-carbaldehyde: To a stirring solution of 7-bromo-6-fluoro-benzofuran (1.00 g, 4.65 mmol) in ether (10 mL) was added *n*-BuLi (2.5 M in hexanes, 4.70 mL, 11.6 mmol) dropwise at - 60 °C. The mixture was stirred at - 60 °C for 0.5 h. DMF (1.02 g, 14.0 mmol) was added, and the mixture was stirred at - 60 °C for 0.5 h. Upon completion of the reaction, the mixture was quenched with NH_4Cl and extracted with EtOAc. The residue was purified by flash column chromatography (EtOAc/Petroleum Ether = 0 to 5%) to give 6-fluorobenzofuran-7-carbaldehyde (0.400 g, 47% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 7.84 – 7.76 (m, 2H), 7.12 (dd, J = 10.8, 8.6 Hz, 1H), 6.82 (d, J = 2.2 Hz, 1H).

[000689] **Step D**: Preparation of 7-ethynyl-6-fluorobenzofuran: A mixture of 6-fluorobenzofuran-7-carbaldehyde (400 mg, 2.44 mmol), 1-diazo-1-dimethoxyphosphoryl-propan-2-one (562 mg, 2.92 mmol) and K_2CO_3 (673 mg, 4.87 mmol) in Methanol (15 mL) was stirred at 25 °C for 16 h. Upon completion of the reaction, the reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried and concentrated. The residue was purified by flash column chromatography (EtOAc/Petroleum Ether = 0 to 1%) to give 7-ethynyl-6-fluorobenzofuran (300 mg, 69% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 2.0 Hz, 1H), 7.53 (dd, J = 8.6, 5.0 Hz, 1H), 7.05 (t, J = 9.2 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 3.60 (s, 1H).

[000690] **Step E to Step J:** Preparation of 1-((4R,7S)-2-(7-(6-fluorobenzofuran-7-yl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: The title compound was prepared as described in Synthetic Example 37 Step D to Step I, substituting 7-ethynyl-6-fluoro-benzofuran for 2-ethynyl-3-(2-methoxyethoxy)pyridine in Step D. The crude was purified flash column chromatography (MeOH/DCM= 0 to 4%) to afford 1-((4R,7S)-2-(7-(6-fluorobenzofuran-7-yl)-4-(1-methyl-1H-benzo[d]imidazol-5-yl)thieno[3,2-c]pyridin-6-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (d, J = 12.2 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.64 – 7.47 (m, 4H), 7.16 – 7.00 (m, 1H), 6.86 – 6.62 (m, 2H), 6.22 – 5.99 (m, 2H), 5.70 (d, J = 10.4 Hz, 1H), 5.58 – 5.19 (m, 1H), 4.61 – 3.96 (m, 2H), 3.90 (s, 3H), 3.72 – 3.24 (m, 1H), 1.24 (s, 3H), 0.97 (d, J = 59.0 Hz, 3H). LCMS ESI (+) m/z 603.0 (M+H).

Synthetic Example 41: Synthesis of 2-(3-((R)-5-((4R,7S)-5-acryloyl -4,7-dimethyl -4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl)-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)-N,N-dimethylacetamide (**Compound 672**)



[000691] **Step A**: Preparation of 3,8-dibromo-1,7-naphthyridine: A mixture of $POBr_3$ (5.11 g, 17.8 mmol) and 3-bromo-7*H*-1,7-naphthyridin-8-one (4.00 g, 17.8 mmol) was heated at 110 °C for 3 h. After

cooling, the mixture was quenched with aqueous Na_2CO_3 solution and extracted with DCM (50 mLx3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes=0-20%) to give 3,8-dibromo-1,7-naphthyridine (3.00 g, 59% yield) as pale yellow solid. LCMS ESI (+) m/z 286,9, 288.9, 291.0 (M+H).

[000692] **Step B**: Preparation of 3-bromo-1,7-naphthyridine: A mixture of 3,8-dibromo-1,7-naphthyridine (3.00 g, 10.4 mmol), ammonia formate (986 mg, 15.6 mmol), $Pd(PPh_3)_4$ (1.20 g, 1.04 mmol) and DMA (10 mL) was stirred at 80 °C under N_2 for 7 h. The reaction was concentrated to dryness and the residue was purified by flash column chromatography (EtOAc/Hexanes=0-20%) to give 3-bromo-1,7-naphthyridine (1.10 g, 51% yield) as pale yellow solid. LCMS ESI (+) m/z 208.8, 210.8 (M+H).

[000693] **Step C**: Preparation of 3-bromo-5,6,7,8-tetrahydro-1,7-naphthyridine: To a mixture of 3-bromo-1,7-naphthyridine (1.10 g, 5.26 mmol) in AcOH (8 mL) was added $NaBH_4$ (796 mg, 21.0 mmol) portion wise at 25 °C and the mixture was stirred at 25 °C for 4 h. The mixture was quenched with aqueous Na_2CO_3 and extracted with DCM. The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/Hexanes=0-20%) to give 3-bromo-5,6,7,8-tetrahydro-1,7-naphthyridine (550 mg, 49% yield) as a pale-yellow oil. LCMS ESI (+) m/z 213.1, 215.1 (M+H).

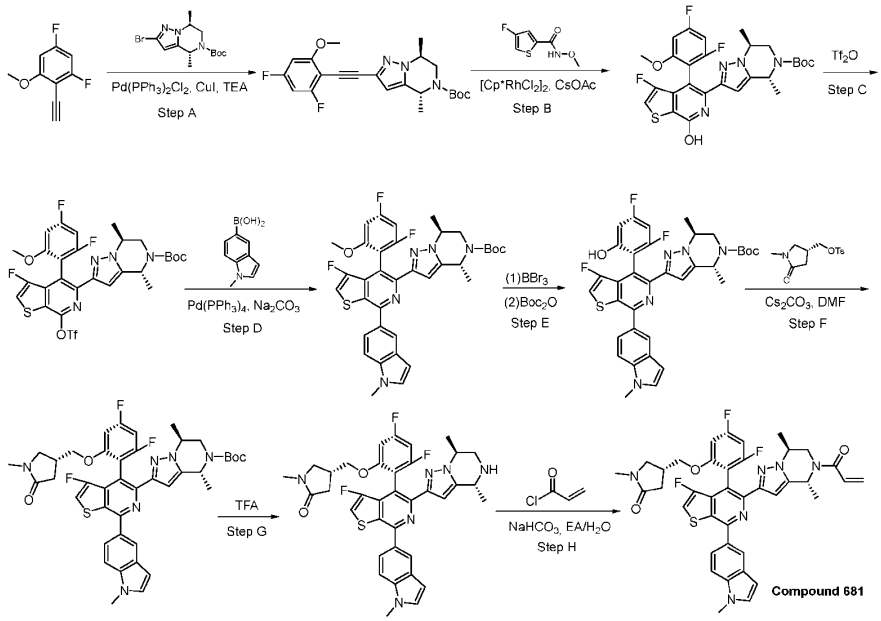
[000694] **Step D**: Preparation of 2-(3-bromo-6,8-dihydro-5*H*-1,7-naphthyridin-7-yl)-*N,N*-dimethyl-acetamide: A mixture of 2-bromo-*N,N*-dimethyl-acetamide (280 mg, 1.69 mmol), 3-bromo-5,6,7,8-tetrahydro-1,7-naphthyridine (300 mg, 1.41 mmol), TEA (0.590 mL, 4.22 mmol) and THF (15 mL) was stirred at 25 °C overnight. The reaction was concentrated to dryness and the crude was then purified by flash column chromatography eluting with 3% MeOH in DCM to afford 2-(3-bromo-6,8-dihydro-5*H*-1,7-naphthyridin-7-yl)-*N,N*-dimethyl-acetamide (280 mg, 67% yield) as a colorless oil. LCMS ESI (+) m/z 298.0, 300.0 (M+H).

[000695] **Step E**: Preparation of [7-[2-(dimethylamino)-2-oxo-ethyl]-6,8-dihydro-5*H*-1,7-naphthyridin-3-yl]boronic acid: To a solution of 2-(3-bromo-6,8-dihydro-5H-1,7-naphthyridin-7-yl)-N,N-dimethyl-acetamide (350 mg, 1.17 mmol) and bis(pinacolato)diboron (358 mg, 1.41 mmol) in 1,4-Dioxane (6 mL) were added $Pd(dppf)Cl_2$ (86 mg, 0.12 mmol) and KOAC (346 mg, 3.52 mmol). The reaction mixture was stirred at 100 °C for 3 h under Ar. The reaction was concentrated. The residue was purified by Prep-HPLC to give [7-[2-(dimethylamino)-2-oxo-ethyl]-6,8-dihydro-5H-1,7-naphthyridin-3-yl]boronic acid (330 mg, 107% yield) as a trifluoroacetate salt. LCMS ESI (+) m/z 264.0 (M+H).

[000696] **Step F**: Preparation of [3-[7-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-4- (1-methylindazol-5-yl)thieno[3,2-c]pyridin-6-yl]-1-bicyclo[1.1.1]pentanyl]methanol: A mixture of [7-[2-(dimethylamino)-2-oxo-ethyl]-6,8-dihydro-5*H*-1,7-naphthyridin-3-yl] boronic acid (20 mg, 0.075 mmol), (R)-5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-

methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl trifluoromethanesulfonate (40 mg, 0.058 mmol), Na_2CO_3 (18 mg, 0.17 mmol), tetrakis (triphenylphosphine) palladium (6.7 mg, 0.0058 mmol) in 1,4-Dioxane (3 mL) and Water (0.3 mL) was stirred at 100 °C for 1 h under N_2. The mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography eluting with 0-10% MeOH/DCM to give 2-(3-((R)-5-((4R,7S) -5-acryloyl -4,7-dimethyl -4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-3-fluorothieno[2,3-c]pyridin-7-yl)-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)-N,N-dimethylacetamide (15 mg, 30% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 9.25 (s, 1H), 8.51 (s, 1H), 7.60 (d, J = 2.0 Hz, 1H), 6.84 (t, J = 12.4 Hz, 2H), 6.62 (dd, J = 10.1, 8.3 Hz, 1H), 6.34 (d, J = 16.5 Hz, 1H), 6.15 (s, 1H), 5.85 (d, J = 11.5 Hz, 1H), 5.62 (d, J = 87.8 Hz, 1H), 4.71 (s, 2H), 4.52 (s, 2H), 4.44 (s, 1H), 4.39 – 4.17 (m, 1H), 4.09 (t, J = 4.9 Hz, 1H), 4.03 (d, J = 4.5 Hz, 1H), 3.79 (d, J = 16.8 Hz, 3H), 3.46 (t, J = 4.6 Hz, 4H), 3.10 – 3.05 (m, 9H), 1.43 (s, 3H), 1.31 (s, 3H). LCMS ESI (+) m/z 760.1 (M+H).

Synthetic Example 42: Synthesis of (R)-4-((2-((R)-5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)methyl)-1-methylpyrrolidin-2-one (**Compound 681**)



[000697] **Step A:** Preparation of tert-butyl (4R,6R)-2-[2-(2,4-difluoro-6-methoxy-phenyl)ethynyl]-4,6-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of 2-ethynyl-1,5-difluoro-3-methoxy-benzene (4.50 g, 26.8 mmol) in DMF (30 mL) were added tert-butyl (4R,6R)-2-bromo-4,6-

dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (8.84 g, 26.8 mmol), $Pd(PPh_3)Cl_2$ (0.940 g, 1.34 mmol), CuI (255 mg, 1.34 mmol) and triethylamine (11.0 mL, 80.3 mmol). The mixture was stirred at 85 °C for 10 h under Ar. The mixture was poured into H_2O (150 mL) and extracted EtOAc (3 x 150 mL). The combined organic layers were washed with saturated brine solution (300 mL), dried (Na_2SO_4) and concentration, the residue was purified by column chromatography (Petroleum Ether:EtOAc=10:1-5:1) to give tert-butyl (4R,6R)-2-[2-(2,4-difluoro-6-methoxy-phenyl)ethynyl]-4,6-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (4.00 g, 36% yield). LCMS ESI (+) m/z 418.2 (M+H).

[000698] **Step B:** Preparation of tert-butyl (4R,7S)-2-(4-(2,4-difluoro-6-methoxyphenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a mixture of tert-butyl (4R,7S)-2-[2-(2,4-difluoro-6-methoxy-phenyl)ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (970 mg, 2.32 mmol) and 4-fluoro-N-methoxy-thiophene-2-carboxamide (448 mg, 2.56 mmol) in Methanol (15 mL) were added CsOAc (892 mg, 4.65 mmol) and $[Cp^*RhCl_2]_2$ (36 mg, 0.058 mmol). The mixture was stirred at 60 °C for 16 h. The mixture was concentrated and purified by column chromatography(petroleum ether:EtOAc=3:1-1:2) to give tert-butyl (4R,7S)-2-(4-(2,4-difluoro-6-methoxyphenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (698 mg, 54% yield).

[000699] **Step C:** Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-methoxyphenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a mixture of tert-butyl (4R,7S)-2-(4-(2,4-difluoro-6-methoxyphenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (698 mg, 1.25 mmol) and pyridine (1.00 mL, 12.5 mmol) in DCM (15 mL) being cooled to 0 °C was added trifluoromethanesulfonic anhydride (0.420 mL, 2.49 mmol) dropwise. The mixture was stirred at 0 °C for 30 minutes. The mixture was diluted with DCM (15 mL), washed with water (20 mL) and saturated brine solution (20 mL), dried and concentrated. The crude was purified by column chromatography (petroleum ether:EtOAc=10:1) to give tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-methoxyphenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (320 mg, 37% yield) as the more-polar diastereomer.

[000700] **Step D:** Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-methoxyphenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A mixture of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-methoxyphenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (160 mg, 0.231 mmol), (1-methylindol-5-yl)boronic acid (53 mg, 0.30 mmol), sodium carbonate (49 mg, 0.46 mmol) and $Pd(PPh_3)_4$ (27 mg, 0.023 mmol) in 1,4-Dioxane (1 mL) and Water (0.1 mL) was stirred at 100 °C for 1 hour. The mixture was filtered and concentrated. The residue

was purified by Prep-TLC (petroleum ether:EtOAc=1:1) to give tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-methoxyphenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (118 mg, 76% yield). LCMS ESI (+) m/z 674.4 (M+H).

[000701] Step E: Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-hydroxyphenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-methoxyphenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (118 mg, 0.174 mmol) was dissolved in BBr_3 (2 N in DCM, 4 mL) at 0 °C. The mixture was stirred at this temperature for 2 hours. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL x 3). The combined organics were washed with brine before concentration to dryness. The crude was dissolved in THF (5 mL) and Water (5 mL), and then $NaHCO_3$ (44 mg, 0.52 mmol) and di-tert-butyl dicarbonate (76 mg, 0.35 mmol) were added. The mixture was stirred at rt for 2 hours. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organics were washed with saturated brine solution (15 mL), dried (Na_2SO_4), and concentrated. The residue was purified by Prep-TLC (petroleum ether:EtOAc=1:1) to give tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-hydroxyphenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (60 mg, 36% yield). LCMS ESI (+) m/z 660.3 (M+H).

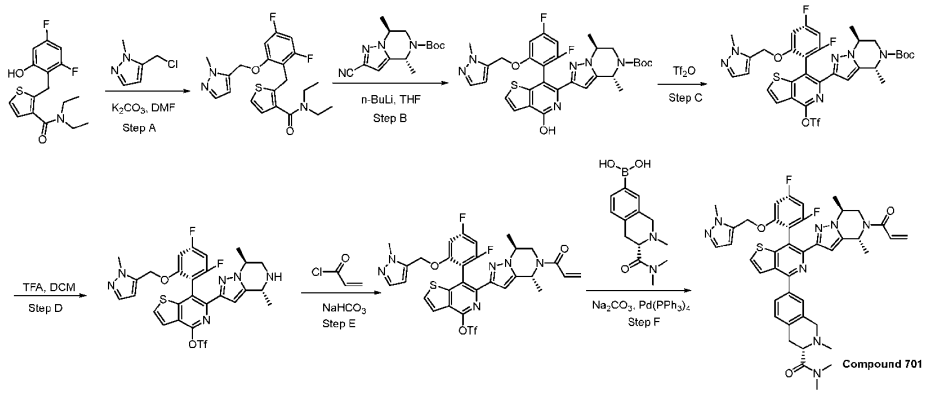
[000702] Step F: Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(((R)-1-methyl-5-oxopyrrolidin-3-yl)methoxy)phenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-hydroxyphenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (30 mg, 0.046 mmol) in DMF (2 mL) were added cesium carbonate (25 mg, 0.077 mmol) and [(3R)-1-methyl-5-oxo-pyrrolidin-3-yl]methyl 4-methylbenzenesulfonate (19 mg, 0.068 mmol). The mixture was stirred at 30 °C for 16 hours. The mixture was diluted with EtOAc (5 mL) and washed with saturated brine solution (15 mL x 2). The organic layer was dried (Na_2SO_4) and concentrated. The crude was purified by Prep-TLC (DCM:MeOH=20:1) to give tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(((R)-1-methyl-5-oxopyrrolidin-3-yl)methoxy)phenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (26 mg, 74% yield) as a white solid. LCMS ESI (+) m/z 771.5 (M+H).

[000703] Step G: Preparation of (R)-4-((2-((R)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)methyl)-1-methylpyrrolidin-2-one: To a solution of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(((R)-1-methyl-5-oxopyrrolidin-3-yl)methoxy)phenyl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (26

mg, 0.034 mmol) in DCM (3 mL) was added trifluoroacetic acid (1.0 mL, 13.0 mmol) dropwise under Ar. The mixture was stirred at rt for 30 mins. The mixture was concentrated to dryness to give crude (R)-4-((2-((R)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)methyl)-1-methylpyrrolidin-2-one (35 mg, 100% yield), which was used in the next step without further purification.

[000704] Step H: Preparation of (R)-4-((2-((R)-5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)methyl)-1-methylpyrrolidin-2-one: To a solution of (R)-4-((2-((R)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluoro-7-(1-methyl-1H-indol-5-yl)thieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)methyl)-1-methylpyrrolidin-2-one (35 mg, 0.034 mmol) in ethyl acetate (3 mL) and Water (3 mL) was added $NaHCO_3$ to adjust the pH to 8. The mixture was cooled to 0 °C and acryloyl chloride (0.0051 mL, 0.063 mmol) in DCM (0.2 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 30 minutes. The mixture was diluted with EtOAc (10 mL) and washed with water (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to give (4R)-4-[[2-[5-[(4R,7S)-4,7-dimethyl-5-prop-2-enoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]-3-fluoro-7-(1-methylindol-5-yl)thieno[2,3-c]pyridin-4-yl]-3,5-difluoro-phenoxy]methyl]-1-methyl-pyrrolidin-2-one (7.5 mg, 20% yield) as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 – 8.35 (m, 1H), 7.97 (dd, J = 8.6, 1.4 Hz, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 6.93 – 6.81 (m, 1H), 6.80 – 6.74 (m, 1H), 6.63 – 6.53 (m, 2H), 6.36 – 6.17 (m, 2H), 5.87 – 5.81 (m, 1H), 5.77 – 5.48 (m, 1H), 4.43 – 4.35 (m, 1H), 4.25 – 4.17 (m, 0.5H), 4.03 – 3.82 (m, 5.5H), 3.27 – 3.20 (m, 1H), 2.98 (dd, J = 10.0, 4.7 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.46 (s, 3H), 2.34 (dd, J = 17.2, 9.6 Hz, 1H), 1.99 (dd, J = 17.1, 5.6 Hz, 1H), 1.54 – 1.39 (m, 3H), 1.31 – 1.20 (m, 3H). LCMS ESI (+) m/z 725.2 (M+H).

Synthetic Example 43: Synthesis of (S)-7-((S)-6-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(2,4-difluoro-6-((1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-N,N,2-trimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**Compound 701**)

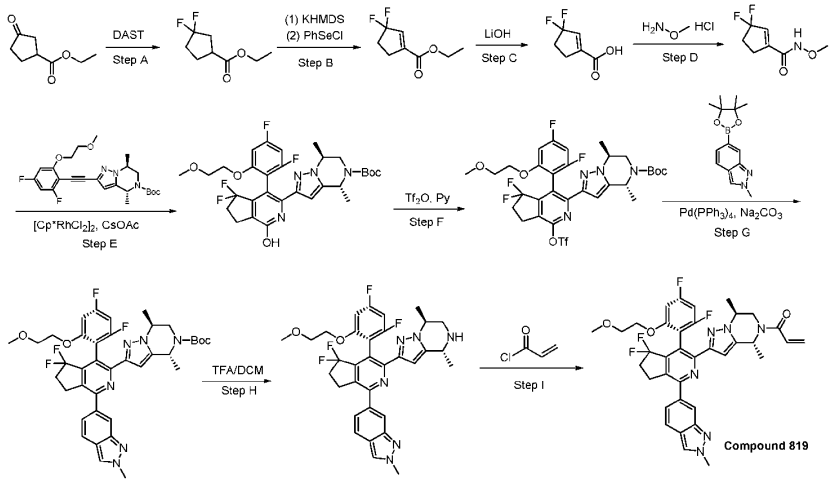


[000705] **Step A:** Preparation of 2-[[2,4-difluoro-6-[(2-methylpyrazol-3-yl)methoxy]phenyl]methyl]-N,N-diethyl-thiophene-3-carboxamide: To a solution of 2-[(2,4-difluoro-6-hydroxy-phenyl)methyl]-N,N-diethyl-thiophene-3-carboxamide (500 mg, 1.54 mmol) and potassium carbonate (0.640 g, 4.61 mmol) in DMF (10 mL) was added 5-(chloromethyl)-1-methyl-pyrazole hydrochloride (334 mg, 2.00 mmol). The mixture was stirred at 50 °C overnight. Then the reaction was quenched with water (80 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine. dried over sodium sulphate and concentrated. The residue was purified by flash column chromatography eluting with 15% EtOAc in hexanes. The desired fractions were concentrated to dryness in *vacuo* to afford 2-[[2,4-difluoro-6-[(2-methylpyrazol-3-yl)methoxy]phenyl]methyl]-N,N-diethyl-thiophene-3-carboxamide (600 mg, 93% yield) as a white solid. LCMS ESI (+) m/z 420.1 (M+H).

[000706] **Step B to Step F:** Preparation of (S)-7-((S)-6-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(2,4-difluoro-6-((1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-N,N,2-trimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide: The title compound was prepared as described in Synthetic Example 8 Step G to Step K, substituting 2-[[2,4-difluoro-6-[(2-methylpyrazol-3-yl)methoxy]phenyl]methyl]-N,N-diethyl-thiophene-3-carboxamide for 2-[[2,4-difluoro-6-(2-methoxyethoxy)phenyl]methyl]-N,N-diethyl-thiophene-3-carboxamide in Step G, and substituting(S)-(3-(dimethylcarbamoyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)boronic acid for (1-methylindazol-5-yl)boronic acid in Step I. The crude was purified flash column chromatography (MeOH/DCM= 0 to 5%) to afford a crude product which was further purified by preparative HPLC to give (S)-7-((S)-6-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(2,4-difluoro-6-((1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)thieno[3,2-c]pyridin-4-yl)-N,N,2-trimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (21 mg, 65% yield) as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.81 (dd, J = 9.0, 4.6 Hz, 1H), 7.70 (dd, J = 5.1, 3.4 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 1.9 Hz, 1H), 7.13 (d, J = 10.8 Hz, 1H), 6.88 (s, 1H), 6.81 – 6.72 (m, 1H), 6.35 (d, J = 16.4

Hz, 1H), 6.28 (d, *J* = 1.9 Hz, 1H), 6.20 (s, 1H), 5.87 (d, *J* = 10.7 Hz, 1H), 5.62 (d, *J* = 94.2 Hz, 1H), 5.28 – 5.10 (m, 2H), 4.98 – 4.91 (m, 1H), 4.81 (d, *J* = 15.5 Hz, 1H), 4.64 (d, *J* = 15.6 Hz, 1H), 4.43 – 4.14 (m, 2H), 3.99 – 3.74 (m, 1H), 3.68 – 3.57 (m, 1H), 3.44 – 3.34 (m, 4H), 3.27 (s, 3H), 3.12 (s, 6H), 1.46 (s, 3H), 1.25 (s, 3H). LCMS ESI (+) m/z 777.4 (M+H).

Synthetic Example 44: Synthesis of 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(2-methyl-2H-indazol-6-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 819**)



[000707] **Step A:** Preparation of ethyl 3,3-difluorocyclopentanecarboxylate: To a solution of ethyl 3-oxocyclopentanecarboxylate (5.00 g, 32.0 mmol) in DCM (50 mL) was added DAST (20.6 g, 128 mmol) at 0 °C. The reaction mixture was stirred at 45 °C for 60 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous phase was extracted with DCM (50 mLx2). The combined organic phases were washed with saturated brine solution, dried over Na_2SO_4, filtered and concentrated in vacuum (20 °C). The residue was purified by column chromatography (100% Petroleum ether to Petroleum ether:DCM=1:1) to give crude ethyl 3,3-difluorocyclopentanecarboxylate (7.3 g) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, J = 7.1 Hz, 2H), 2.97 (tt, J = 8.3, 4.1 Hz, 1H), 2.47 – 2.30 (m, 2H), 2.28 –1.97 (m, 4H), 1.27 (t, J = 7.1 Hz, 4H).

[000708] **Step B:** Preparation of ethyl 3,3-difluorocyclopent-1-ene-1-carboxylate: To a solution of ethyl 3,3-difluorocyclopentanecarboxylate (1.00 g, 5.61 mmol) in THF (130 mL) was added KHMDS (1.0 M in THF, 16.8 mL, 16.8 mmol) at -78 °C . The reaction mixture was stirred at -78 °C for 2 h. A solution of phenyl selenohypochlorite (1.29 g, 6.73 mmol) in THF (30 mL) was added. The reaction mixture was stirred at -20 °C for 10 h. The reaction mixture was quenched with H_2O (100 mL), and the crude solution was used for the next step directly.

[000709] **Step C:** Preparation of 3,3-difluorocyclopentene-1-carboxylic acid: To a solution of crude ethyl 3,3-difluorocyclopentene-1-carboxylate from previous step in THF (160 mL) and Water (100 mL) was added LiOH (200 mg). The reaction mixture was stirred at 10 °C for 2 h. The reaction mixture was concentrated to remove THF, and then extracted with MTBE (50 mLx3). 1 N HCl was added to aqueous solution to adjust the pH to 1. The mixture was extracted with EtOAc (50 mLx3). The combined organics were washed with saturated brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by reverse-phase column chromatography to give 3,3-difluorocyclopentene-1-carboxylic acid (82 mg) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 2.79 – 2.69 (m, 2H), 2.53 – 2.40 (m, 2H).

[000710] **Step D:** Preparation of 3,3-difluoro-N-methoxy-cyclopentene-1-carboxamide: To a solution of 3,3-difluorocyclopentene-1-carboxylic acid (82 mg, 0.55 mmol) in DCM (2 mL) was added EDCI (159 mg, 0.830 mmol) and HOBT (112 mg, 0.830 mmol). The mixture was stirred at rt for 10 min. O-methylhydroxylamine (39 mg, 0.83 mmol) and Et_3N (168 mg, 1.66 mmol) was added. The resulting reaction mixture was stirred at 10 °C for 1 h. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (30 mLx4). The combined organic phases were washed with saturated brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH=20:1) to give 3,3-difluoro-N-methoxy-cyclopentene-1-carboxamide (25 mg, 25% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 3.86 (s, 3H), 2.79 – 2.69 (m, 2H), 2.53 – 2.40 (m, 2H).

[000711] **Step E:** Preparation of tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5,5-difluoro-1-hydroxy-6,7-dihydrocyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (4R,7S)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (65 mg, 0.14 mmol), 3,3-difluoro-N-methoxy-cyclopentene-1-carboxamide (25 mg, 0.14 mmol) and cesium acetate (54 mg, 0.28 mmol) in methanol (10 mL) was added bis[(pentamethylcyclopentadienyl)dichloro-rhodium] (2.2 mg, 0.0035 mmol). The mixture was stirred at 60 °C for 24 h. The mixture was concentrated and purified by prep-TLC (DCM:MeOH=20:1) to give tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5,5-difluoro-1-hydroxy-6,7-dihydrocyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (30 mg, 35% yield) as a yellow oil. LCMS ESI (+) m/z 607.0 (M+H).

[000712] **Step F:** Preparation of tert-butyl (4R,7S)-2-((S)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5,5-difluoro-1-hydroxy-6,7-dihydrocyclopenta[c]pyridin-3-yl]-4,7-

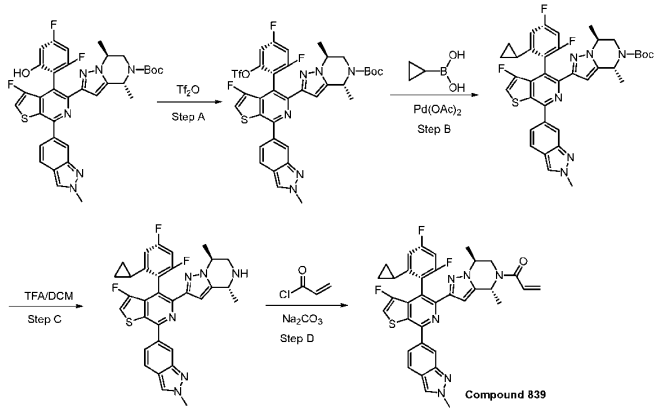
dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (30 mg, 0.050 mmol) and pyridine (0.020 mL, 0.25 mmol) in DCM (5 mL) was added trifluoromethanesulfonic anhydride (0.017 mL, 0.099 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. The reaction mixture was poured into H_2O (10 mL) and extracted with DCM (20 mLx2). The combined organic phases were washed with saturated brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (petroleum ether:EtOAc=5:1) to give tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (10 mg, 27% yield) as the less-polar diastereomer and tert-butyl (4R,7S)-2-((S)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (10 mg, 27% yield) as the more polar diastereomer. LCMS ESI (+) m/z 739.0 (M+H).

[000713] Step G: Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(2-methyl-2H-indazol-6-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of 2-methyl-6-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)indazole (2.1 mg, 0.0081 mmol), tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (5.0 mg, 0.0068 mmol) and Na_2CO_3 (1.4 mg, 0.014 mmol) in 1,4-Dioxane (1 mL) and Water (0.1 mL) was added $Pd(PPh_3)_4$ (0.8 mg, 0.0007 mmol). The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was concentrated and purified by Prep-TLC (DCM:MeOH=20:1) to give tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(2-methyl-2H-indazol-6-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (5.0 mg, 100% yield) as a yellow solid. LCMS ESI (+) m/z 721.0 (M+H).

[000714] Step H: Preparation of (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(2-methyl-2H-indazol-6-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine: To a solution of tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-5,5-difluoro-1-(2-methylindazol-6-yl)-6,7-dihydrocyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (5.0 mg, 0.0069 mmol) in DCM (3 mL) was added TFA (1.0 mL). The reaction mixture was stirred at 10 °C for 1 h. The reaction mixture was concentrated in vacuum to give (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(2-methyl-2H-indazol-6-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (8.0 mg), which was used in the next step without further purification. LCMS ESI (+) m/z 621.3 (M+H).

[000715] Step I: Preparation of (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(2-methyl-2H-indazol-6-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine: To a solution of (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(2-methyl-2H-indazol-6-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (8.0 mg, crude) in ethyl acetate (4 mL) and water (4 mL) was added $NaHCO_3$ to adjust the pH to 8. Acryloyl chloride (0.00052 mL, 0.0064 mmol) in DCM (0.1 mL) was added to the reaction mixture. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mLx2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC to give (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-5,5-difluoro-1-(2-methyl-2H-indazol-6-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (2.6 mg, 60% yield) as a bis trifluoroacetic acid salt. ^1H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.12 (s, 1H), 7.89 (dd, J = 8.7, 0.6 Hz, 1H), 7.72 (dd, J = 8.7, 1.3 Hz, 1H), 6.93 – 6.82 (m, 1H), 6.78 (d, J = 10.9 Hz, 1H), 6.65 – 6.56 (m, 1H), 6.34 (d, J = 16.8 Hz, 1H), 6.22 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.74 – 5.50 (m, 1H), 4.47 – 4.38 (m, 1H), 4.30 (s, 3H), 4.27 – 4.17 (m, 1H), 4.12 – 4.05 (m, 2H), 3.91 – 3.77 (m, 1H), 3.54 (t, J = 4.8 Hz, 2H), 3.39 – 3.35 (m, 2H), 3.19 (s, 3H), 2.72 – 2.59 (m, 2H), 1.54 – 1.40 (m, 3H), 1.34 – 1.28 (m, 3H). LCMS ESI (+) m/z 675.1 (M+H).

Synthetic Example 45: Synthesis of 1-((4R,7S)-2-(4-((R)-2-cyclopropyl-4,6-difluorophenyl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 839**)



[000716] Step A: Preparation of tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-(((trifluoromethyl)sulfonyl)oxy) phenyl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a stirred solution of tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-hydroxyphenyl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl)thieno[2,3-

c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (410 mg, 0.621 mmol) and pyridine (3.00 mL, 37.1 mmol) in DCM (5 mL) was added trifluoromethanesulfonic anhydride (1.00 mL, 5.92 mmol) at 0 °C. The solution was stirred at 0 °C for 2 h. The mixture was diluted with H_2O (20 mL) and extracted with DCM (20.0 mLx3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and purified by Prep-TLC (petroleum ether: EtOAc = 1:1) to get tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-(((trifluoromethyl)sulfonyl)oxy)phenyl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (320 mg, 65% yield) as a white solid. LCMS ESI (+) m/z 793.1 (M+H).

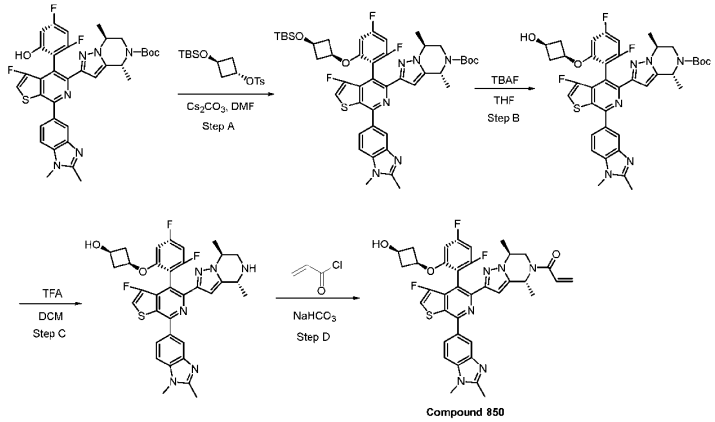
[000717] Step B: Preparation of tert-butyl (4R,7S)-2-(4-((R)-2-cyclopropyl-4,6-difluorophenyl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A mixture of tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-(((trifluoromethyl)sulfonyl)oxy)phenyl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (20 mg, 0.025 mmol), cyclopropylboronic acid (11 mg, 0.13 mmol), $Pd(PPh_3)_4$ (0.3 mg, 0.0003 mmol), K_3PO_4 (16 mg, 0.076 mmol) and LiBr (2.6 mg, 0.030 mmol) in toluene (2 mL) was stirred at 120 °C under Ar in microwave for 4 h. The mixture was concentrated under vacuum and purified by Prep-TLC (petroleum ether: EtOAc = 1:2) to get tert-butyl (4R,7S)-2-(4-((R)-2-cyclopropyl-4,6-difluorophenyl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (10 mg, 58% yield) as a white solid. LCMS ESI (+) m/z 685.3 (M+H).

[000718] Step C: Preparation of (R)-4-(2-cyclopropyl-4,6-difluorophenyl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a] pyrazin-2-yl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl) thieno[2,3-c] pyridine: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2-cyclopropyl-4,6-difluorophenyl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (18 mg, 0.026 mmol) in DCM (1.5 mL) was added trifluoroacetic acid (0.50 mL). The mixture was stirred at 10 °C for 2 h. The reaction was concentrated under vacuum to obtain crude (R)-4-(2-cyclopropyl-4,6-difluorophenyl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a] pyrazin-2-yl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl) thieno[2,3-c] pyridine (28 mg) which was used in the next step without further purification. LCMS ESI (+) m/z 585.3 (M+H).

[000719] Step D: Preparation of 2-[3-bromo-5-(5-methoxypentanoyl)pyrazol-1-yl]ethyl methanesulfonate: To a solution of crude (R)-4-(2-cyclopropyl-4,6-difluorophenyl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a] pyrazin-2-yl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl) thieno[2,3-c] pyridine (28 mg, 0.026 mmol) in ethyl acetate (1 mL)/water (0.5 mL) was added aqueous Na_2CO_3 to adjust the pH to 8. A solution of acryloyl chloride (2.7 mg, 0.030 mmol) in DCM (0.5 mL) was added at 0 °C. The mixture was stirred at 0 °C for 0.5 h. The reaction mixture was diluted with H_2O (10

mL) and extracted with EtOAc (10 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-HPLC to give 1-((4R,7S)-2-(4-((R)-2-cyclopropyl-4,6-difluorophenyl)-3-fluoro-7-(2-methyl-2H-indazol-6-yl)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (5.1 mg, 33% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (d, J = 14.2 Hz, 2H), 7.98 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.77 (s, 1H), 6.87 (t, J = 8.8 Hz, 2H), 6.61 (d, J = 9.9 Hz, 1H), 6.33 (d, J = 16.9 Hz, 1H), 6.00 (s, 1H), 5.84 (d, J = 10.7 Hz, 1H), 5.75 - 5.44 (m, 1H), 4.52 - 4.43 (m, 1H), 4.31 (s, 3H), 1.55 - 1.37 (m, 3H), 1.36 - 1.22 (m, 3H), 0.73 - 0.60 (m, 3H), 0.57 - 0.48 (m, 1H). LCMS ESI (+) m/z 639.3 (M+H).

Synthetic Example 46: Synthesis of 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-((1s,3R)-3-hydroxycyclobutoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 850**)



[000720] **Step A:** Preparation of tert-butyl (4R,7S)-2-(4-((R)-2-((1s,3S)-3-((tert-butyldimethylsilyl)oxy) cyclobutoxy)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-hydroxyphenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (50 mg, 0.074 mmol) in DMF (2 mL) were added (1r,3r)-3-((tert-butyldimethylsilyl)oxy)cyclobutyl 4-methylbenzenesulfonate (79 mg, 0.22 mmol) and Cs_2CO_3 (121 mg, 0.371 mmol). The reaction was stirred at 35 °C for 72 h. The mixture was diluted with EtOAc (20 mL) and washed with saturated brine solution (20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (DCM/MeOH: 20/1) to afford tert-butyl (4R,7S)-2-(4-((R)-2-((1s,3S)-3-((tert-butyldimethylsilyl)oxy) cyclobutoxy)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-

fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (37 mg, 58% yield). LCMS ESI (+) m/z 859.3 (M+H).

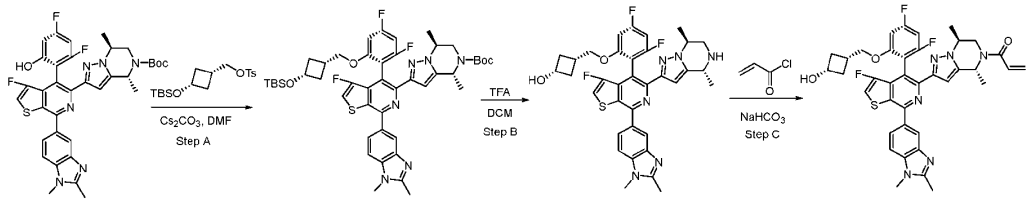
[000721] Step B: Preparation of *tert*-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-((1s,3R)-3-hydroxycyclobutoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2-((1s,3S)-3-((tert-butyldimethylsilyl)oxy) cyclobutoxy)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (57 mg, 0.066 mmol) in THF (3 mL) was added TBAF (1.0 M solution in THF, 0.66 mL, 0.66 mmol). The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc (20 mL) and washed with saturated brine solution (20 mLx2). The organic layer was dried and concentrated. The crude was purified by Prep-TLC (DCM/MeOH: 15/1) to afford *tert*-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-((1s,3R)-3-hydroxycyclobutoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (37 mg, 75% yield). LCMS ESI (+) m/z 745.4 (M+H).

[000722] Step C: Preparation of (1R,3s)-3-(2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)cyclobutan-1-ol: To a solution of *tert*-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-((1s,3R)-3-hydroxycyclobutoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (15 mg, 0.020 mmol) in DCM (3 mL) was added trifluoroacetic acid (1.0 mL). The mixture was stirred at 5 °C for 1 h. The reaction mixture was concentrated to dryness to afford (1R,3s)-3-(2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)cyclobutan-1-ol (23 mg). The crude was used in the next step directly.

[000723] Step D: Preparation of 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-((1s,3R)-3-hydroxycyclobutoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of (1R,3s)-3-(2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)cyclobutan-1-ol (23 mg, 0.020 mmol) in ethyl acetate (4 mL)/ Water (4 mL) was added $NaHCO_3$ to adjust the pH to 8. A solution of acryloyl chloride (0.0020 mL, 0.024 mmol) in DCM (0.1 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h, and then partitioned between ethyl acetate (30 mL) and H_2O (20 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to afford 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-

((1s,3R)-3-hydroxycyclobutoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (5.8 mg, 41% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.51 (s, 1H), 6.92 - 6.80 (m, 1H), 6.60 - 6.50 (m, 2H), 6.40 - 6.10 (m, 2H), 5.86 - 5.50 (m, 2H), 4.75 - 4.50 (m, 1H), 4.45 - 4.35 (m, 1H), 4.30 - 4.20 (m, 1H), 3.90 - 3.80 (m, 5H), 2.85 - 2.70 (m, 2H), 2.66 (s, 3H), 2.90 - 2.65 (m, 2H), 1.55 - 1.35 (m, 3H), 1.35 - 1.20 (m, 3H). LCMS m/z [M+1]: 699.4.

Synthetic Example 47: Synthesis of 1-((4R,7S)-2-(4-((R)-2,4-difluoro-6-(((1s,3S)-3-hydroxycyclobutyl)methoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 884**)



Compound 884

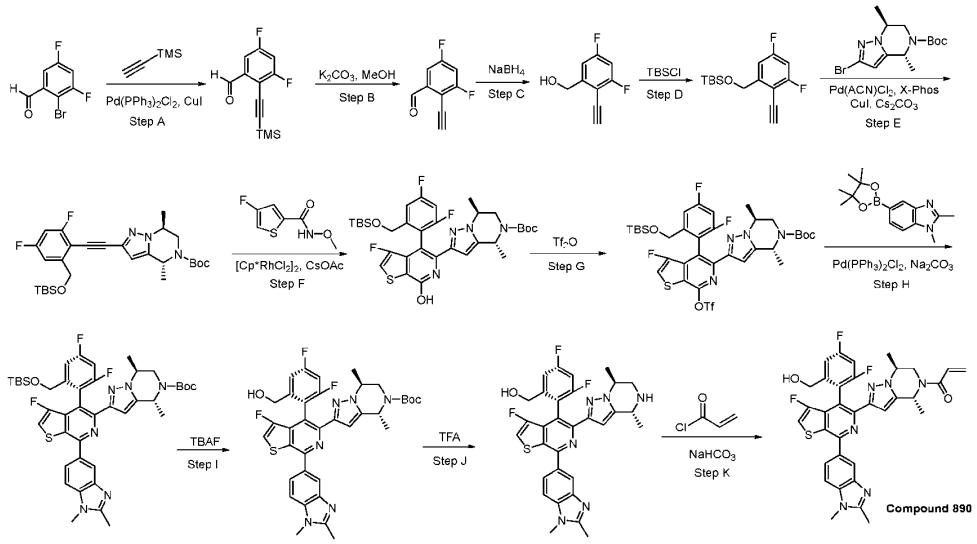
[000724] Step A: Preparation of tert-butyl (4R,7S)-2-(4-((R)-2-(((1s,3S)-3-((tert-butyldimethylsilyl) oxy)cyclobutyl)methoxy)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-hydroxyphenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (30 mg, 0.045 mmol) in DMF (2 mL) was added cesium carbonate (43 mg, 0.13 mmol) and ((1s,3s)-3-((tert-butyldimethylsilyl)oxy)cyclobutyl)methyl 4-methylbenzenesulfonate (25 mg, 0.067 mmol). The mixture was stirred at 30 °C for 24 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL×3). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (DCM:MeOH=20:1) to give tert-butyl (4R,7S)-2-(4-((R)-2-(((1s,3S)-3-((tert-butyldimethylsilyl) oxy)cyclobutyl)methoxy)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (25 mg, 64% yield). LCMS ESI (+) m/z 437.3 (M/2+H).

[000725] Step B: Preparation of (1S,3s)-3-(((R)-2-(7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)methyl)cyclobutan-1-ol: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2-(((1s,3S)-3-((tert-butyldimethylsilyl) oxy)cyclobutyl)methoxy)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-

benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (30 mg, 0.034 mmol) in DCM (1.5 mL) was added trifluoroacetic acid (0.5 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated to dryness to give crude (1S,3s)-3-(((R)-2-(7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)methyl)cyclobutan-1-ol (40 mg) which was used directly in the next step. LCMS ESI (+) m/z 659.2 (M+H).

[000726] Step C: Preparation of 1-((4R,7S)-2-(4-((R)-2,4-difluoro-6-(((1s,3S)-3-hydroxycyclobutyl)methoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of crude (1S,3s)-3-(((R)-2-(7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)methyl)cyclobutan-1-ol (20 mg, 0.030 mmol) in THF (2 ml) and H_2O (2 mL) was added Na_2CO_3 to adjust the pH to 9. The mixture was stirred at rt for 1 h and then concentrated to remove THF. EtOAc (2 mL) was added. A solution of acryloyl chloride (0.0030 mL, 0.036 mmol) in DCM (0.25 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 10 min. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with saturated sodium bicarbonate solution (30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to give 1-((4R,7S)-2-(4-((R)-2,4-difluoro-6-(((1s,3S)-3-hydroxycyclobutyl)methoxy)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (75 mg, 81% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J= 4.8 Hz, 1H), 8.10 – 8.03 (m, 1H), 7.70 – 7.65 (m, 1H), 7.50 (d, J = 2.4Hz, 1H), 6.94 – 6.81 (m, 1H), 6.73 (d, J = 10.8 Hz, 1H), 6.62 – 6.51 (m, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.23 – 6.12 (m, 1H), 5.84 (d, J =11.6 Hz, 1H), 5.78 – 5.53 (m, 1H), 4.60 (s, 1H), 4.45 – 4.38 (m, 1H), 4.00 – 3.75 (m, 7H), 2.67 (s, 3H), 2.11 – 1.91 (m, 3H), 1.55 – 1.37 (m, 5H), 1.34 –1.21 (m, 4H). LCMS ESI (+) m/z 712.2 (M+H).

Synthetic Example 48: Synthesis of 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-(hydroxymethyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 890**)



[000727] **Step A:** Preparation of 3,5-difluoro-2-(2-trimethylsilylethynyl)benzaldehyde: To a solution of 2-bromo-3,5-difluoro-benzaldehyde (25.0 g, 113 mmol) in DMF (250 mL) was added ethynyltrimethylsilane (27.7 g, 283 mmol), Et_3N (34.3 g, 339 mmol), CuI (2.15 g, 11.3 mmol) and $Pd(PPh_3)_2Cl_2$ (3.97 g, 5.66 mmol) under N_2. The mixture was stirred at 30 °C for 2 h. The reaction mixture was filtered, and the filtrate was diluted with 100 mL H_2O. The product was extracted with EtOAc (100 mL). The organic phase was washed with saturated brine solution, dried (Na_2SO_4) and concentrated to dryness to give crude 3,5-difluoro-2-(2-trimethylsilylethynyl)benzaldehyde (22.0 g, 82% yield) which was used directly without further purification. LCMS ESI (+) m/z 239.1 (M+H).

[000728] **Step B:** Preparation of 2-ethynyl-3,5-difluoro-benzaldehyde: To a solution of 3,5-difluoro-2-(2-trimethylsilylethynyl)benzaldehyde (22.0 g, 92.3 mmol) in methanol (250 mL) was added K_2CO_3 (38.3 g, 277 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated, and the residue was diluted with EtOAc (150 ml). The mixture was washed with saturated brine solution (100 mL). The organic phase was dried (Na_2SO_4) before concentration to dryness. The residue was then purified by column chromatography eluting petroleum ether/EtOAc=50:1. The desired fractions were concentrated to dryness in vacuo to afford 2-ethynyl-3,5-difluoro-benzaldehyde (14.5 g, 95% yield) as a yellow oil. LCMS ESI (+) m/z 167.1 (M+H).

[000729] **Step C:** Preparation of (2-ethynyl-3,5-difluoro-phenyl)methanol: To a solution of 2-ethynyl-3,5-difluoro-benzaldehyde (14.5 g, 87.3 mmol) in ethanol (150 mL) was added $NaBH_4$ (3.96 g, 105 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with H_2O (500 mL) and extracted with EtOAc (500 mL). The organic phase was washed with saturated brine solution (300 mL), dried

(Na_2SO_4) and concentrated to dryness to give crude (2-ethynyl-3,5-difluoro-phenyl)methanol (14.3 g, 97% yield) which was used directly without further purification.

[000730] **Step D:** Preparation of tert-butyl-[(2-ethynyl-3,5-difluoro-phenyl)methoxy]-dimethyl-silane: To a solution of (2-ethynyl-3,5-difluoro-phenyl)methanol (14.3 g, 85.0 mmol) in DCM (200 mL) was added imidazole (11.6 g, 170 mmol) and TBSCl (19.2 g, 128 mmol) at 20 °C. The mixture was stirred at 20 °C for 5 h. The reaction was quenched with H_2O (200 mL) and extracted with DCM (200 ml). The organic phase was dried (Na_2SO_4) before concentration to dryness. The residue was then purified by flash column chromatography eluting 1% EtOAc in petroleum ether. The desired fractions were concentrated to dryness in vacuo to afford tert-butyl-[(2-ethynyl-3,5-difluoro-phenyl)methoxy]-dimethyl-silane (22.5 g, 94% yield) as a colorless oil.

[000731] **Step E:** Preparation of tert-butyl (4R,7S)-2-((2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)ethynyl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A mixture of tert-butyl-[(2-ethynyl-3,5-difluoro-phenyl)methoxy]-dimethyl-silane (2.74 g, 9.69 mmol), cesium carbonate (2.33 g, 12.1 mmol), tert-butyl (4R,7S)-2-bromo-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (2.00 g, 6.06 mmol), X-Phos (0289 mg, 0.606 mmol), CuI (115 mg, 0.606 mmol) and bis(acetonitrile)dichloropalladium (II) (157 mg, 0.606 mmol) in 1,4-dioxane (25 mL) was stirred at 100 °C for 12 h. The reaction mixture was concentrated to dryness and diluted with EtOAc. The combined organic phases were washed with saturated brine solution and dried (Na_2SO_4) before concentration to dryness. The residue was purified by column chromatography eluting 10% EtOAc in petroleum ether. The desired fractions were concentrated to dryness in vacuo to afford tert-butyl (4R,7S)-2-((2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)ethynyl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (2.35 g, 73% yield). LCMS ESI (+) m/z 532.3 (M+H).

[000732] **Step F:** Preparation of tert-butyl (4R,7S)-2-(4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-((2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)ethynyl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (1.00 g, 1.88 mmol) in ethanol (10 mL) were added 4-fluoro-N-methoxy-thiophene-2-carboxamide (0.330 g, 1.88 mmol), CsOAc (1.08 g, 5.64 mmol) and bis[(pentamethyl cyclopentadienyl)dichloro-rhodium] (35 mg, 0.056 mmol). The mixture was stirred at 90 °C for 16 h. The reaction was concentrated to dryness. The residue was taken up in EtOAc (30 ml), washed with saturated brine solution (30 mL) and dried (Na_2SO_4) before concentration to dryness. The residue was then purified by flash column chromatography eluting DCM/MeOH =20:1. The desired fractions were concentrated to dryness in vacuo to afford tert-butyl (4R,7S)-2-(4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-

difluorophenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (0.84 g, 66% yield) as a yellow oil. LCMS ESI (+) m/z 675.3 (M+H).

[000733] **Step G:** Preparation of tert-butyl (4R,7S)-2-((S)-4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-(4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)-3-fluoro-7-hydroxythieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (6.50 g, 9.63 mmol) in DCM (80 mL) were added pyridine (3.81 g, 48.2 mmol) and trifluoromethanesulfonic anhydride (5.43 g, 19.3 mmol) at 0 °C . The mixture was stirred at 0 °C for 2 h. The mixture was quenched with H_2O (30 mL) and extracted with DCM (30 mL). The organic phase was then separated and dried (Na_2SO_4) before concentration to dryness. The crude was then purified by flash column chromatography (eluting petroleum ether/EtOAc= 10:1) to afford tert-butyl (4R,7S)-2-((S)-4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (2.30 g, 30% yield). LCMS ESI (+) m/z 807.2 (M+H).

[000734] **Step H:** Preparation of tert-butyl (4R,7S)-2-((R)-4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A mixture of tert-butyl (4R,7S)-2-((S)-4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (780 mg, 0.967 mmol), 1,2-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole (276 mg, 1.01 mmol), Na_2CO_3 (205 mg, 1.93 mmol) and $Pd(PPh_3)_2Cl_2$ (68 mg, 0.097 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was stirred at 100 °C for 6 h under N_2. The reaction was concentrated to dryness and the residue was taken up in EtOAc. The organics were washed with saturated brine solution, dried (Na_2SO_4) and concentrated to give crude tert-butyl (4R,7S)-2-((R)-4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (750 mg, 97% yield) which was used directly without further purification. LCMS ESI (+) m/z 803.4 (M+H).

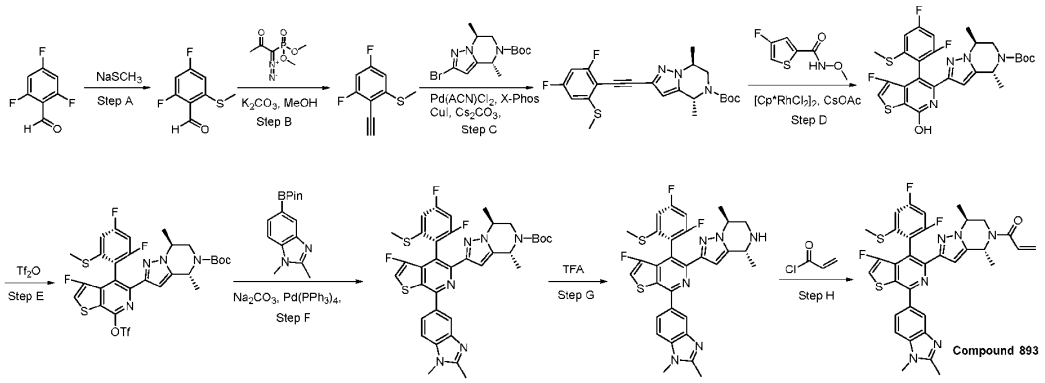
[000735] **Step I:** Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(hydroxymethyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-((R)-4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (740 mg, 0.922 mmol) in THF (10 mL) was added TBAF (1.0 M solution in THF, 4.60 mL, 4.60 mmol).

The mixture was stirred at 20 °C for 1 h. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL). The organic phase was then separated and dried before concentration to dryness. The crude was purified by flash column chromatography (eluting petroleum ether/EtOAc =10:1) to afford tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(hydroxymethyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (570 mg, 90% yield). LCMS ESI (+) m/z 689.2 (M+H).

[000736] **Step J:** Preparation of (2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenyl)methanol: To a solution of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(hydroxymethyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (40 mg, 0.058 mmol) in DCM (2 mL) was added TFA (1.0 mL). The mixture was stirred at 20 °C for 0.5 h. The reaction was concentrated to dryness to give crude (2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenyl)methanol (45 mg) was used directly without further purification. LCMS ESI (+) m/z 589.2 (M+H).

[000737] **Step K:** Preparation of 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-(hydroxymethyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of (2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenyl)methanol (34 mg, 0.058 mmol) in ethyl acetate (2 mL) and water (2 mL) was added $NaHCO_3$ to adjust the pH to 8. Acryloyl chloride (6.2 mg, 0.069 mmol) in DCM (0.1 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 10 min. The reaction was diluted with EtOAc (10 mL) and water (10 mL). The organic phase was then separated, washed with brine, dried ($MgSO_4$) and concentrated. The crude was then purified by Prep-HPLC to afford 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-(hydroxymethyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (19 mg, 51% yield) as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.41 (dd, J = 8.6, 1.2 Hz, 1H), 8.09 (dd, J = 8.5, 1.8 Hz, 1H), 7.63 (s, 1H), 7.23 (d, J = 9.4 Hz, 1H), 6.94 – 6.82 (m, 2H), 6.32 (d, J = 16.4 Hz, 1H), 6.19 (s, 1H), 5.84 (d, J = 10.8 Hz, 1H), 5.71 – 5.49 (m, 1H), 4.39 – 4.21 (m, 4H), 4.09 (s, 3H), 2.94 (s, 3H), 1.50 – 1.40 (m, 3H), 1.25 – 1.20 (m, 3H). LCMS ESI (+) m/z 643.3 (M+H).

Synthetic Example 49: Synthesis of 1-[(4R,7S)-2-[4-(2,4-difluoro-6-methylsulfanyl-phenyl)-7-(1,2-dimethylbenzimidazol-5-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl]prop-2-en-1-one (**Compound 893**)



[000738] **Step A:** Preparation of 2,4-difluoro-6-methylsulfanyl-benzaldehyde: To a solution of 2,4,6-trifluorobenzaldehyde (5.00 g, 31.2 mmol) in DMF (60 mL) was added aqueous NaSMe (11.6 g, 20% in water) dropwise. The mixture was stirred at 60 °C for 12 hours. The mixture was diluted with EtOAc/petroleum ether (1/1, 100 mL) and washed with saturated brine solution (200 mLx2). The organic layer was dried (Na_2SO_4) and concentrated in vaccum. The crude was purified by flash column chromatography (petroleum ether) to give 2,4-difluoro-6-methylsulfanyl-benzaldehyde (1.50 g, 26% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 6.76 – 6.70 (m, 1H), 6.62 – 6.54 (m, 1H), 2.38 (s, 3H).

[000739] **Step B:** Preparation of 2-ethynyl-1,5-difluoro-3-methylsulfanyl-benzene: To a suspension of 2,4-difluoro-6-methylsulfanyl-benzaldehyde (1.50 g, 7.97 mmol) and K_2CO_3 (2.20 g, 15.9 mmol) in methanol (30 mL) being cooled to 0 °C was added 1-diazo-1-dimethoxyphosphoryl-propan-2-one (2.45 g, 12.8 mmol) under Ar. The mixture was stirred at room temperature for 1 hour. The mixture was filtered and the filtrate was concentrated in vaccum. The crude was taken up in EtOAc (20 mL), washed with saturated brine solution (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (petroleum ether) to give 2-ethynyl-1,5-difluoro-3-methylsulfanyl-benzene (1.00 g, 68% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 – 6.57 (m, 2H), 3.67 (s, 1H), 2.49 (s, 3H).

[000740] **Step C:** Preparation of tert-butyl (4R,7S)-2-[2-(2,4-difluoro-6-methylsulfanyl-phenyl)ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of 2-ethynyl-1,5-difluoro-3-methylsulfanyl-benzene (800 mg, 4.34 mmol) in 1,4-Dioxane (15 mL) were added tert-butyl (4R,7S)-2-bromo-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.43 g, 4.34 mmol), bis(acetonitrile)dichloropalladium (II) (113 mg, 0.434 mmol), CsOAc (1.67 g, 8.69 mmol), CuI (83 mg, 0.43 mmol) and X-Phos (207 mg, 0.434 mmol). The mixture was stirred at 100 °C for 12 hours. The mixture was concentrated and purified by column chromatography on silica gel (petroleum ether:EtOAc=5:1 to 1:1) to give tert-butyl (4R,7S)-2-[2-(2,4-difluoro-6-methylsulfanyl-phenyl)ethynyl]-

4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (450 mg, 24% yield). LCMS ESI (+) m/z 434.2 (M+H).

[000741] **Step D:** Preparation of tert-butyl (4R,7S)-2-[4-(2,4-difluoro-6-methylsulfanyl-phenyl)-3-fluoro-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate: To a solution of tert-butyl (4R,7S)-2-[2-(2,4-difluoro-6-methylsulfanyl-phenyl)ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (350 mg, 0.807 mmol) in methanol (60 mL) were added 4-fluoro-N-methoxy-thiophene-2-carboxamide (0.140 g, 0.807 mmol), dichloro(pentamethyl cyclopentadienyl)rhodium(III) dimer (12 mg, 0.020 mmol) and CsOAc (0.150 g, 0.807 mmol). The mixture was stirred at 60 °C for 24 hours. The mixture was concentrated and purified by column chromatography on silica gel (petroleum ether:EtOAc=2:1) to give tert-butyl (4R,7S)-2-[4-(2,4-difluoro-6-methylsulfanyl-phenyl)-3-fluoro-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (325 mg, 70% yield). LCMS ESI (+) m/z 577.2 (M+H).

[000742] **Step E:** Preparation of tert-butyl (4R,7S)-2-(4-((S)-2,4-difluoro-6-(methylthio)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a mixture of tert-butyl (4R,7S)-2-[4-(2,4-difluoro-6-methylsulfanyl-phenyl)-3-fluoro-7-hydroxy-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (400 mg, 0.694 mmol) and pyridine (0.170 mL, 2.08 mmol) in DCM (10 mL) being cooled to 0 °C was added trifluoromethanesulfonic anhydride (0.180 mL, 1.04 mmol) dropwise. The mixture was stirred at 0 °C for 30 minutes. The mixture was diluted with EtOAc (20 mL) and washed with saturated brine solution (20 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by Prep-TLC (petroleum ether:EtOAc=20:1) to give tert-butyl (4R,7S)-2-(4-((S)-2,4-difluoro-6-(methylthio)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (155 mg, 32% yield). LCMS ESI (+) m/z 709.2 (M+H).

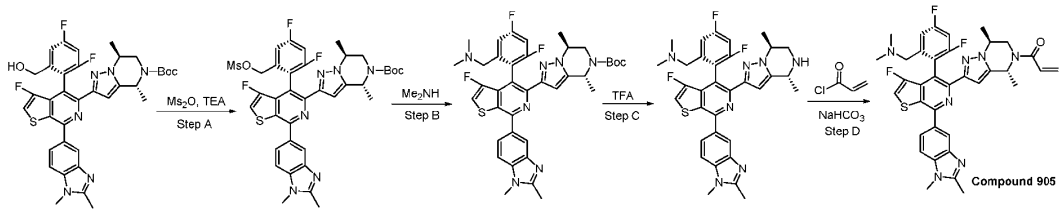
[000743] **Step F:** Preparation of tert-butyl (4R,7S)-2-(4-((S)-2,4-difluoro-6-(methylthio)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-(4-((S)-2,4-difluoro-6-(methylthio)phenyl)-3-fluoro-7-(((trifluoromethyl)sulfonyl)oxy)thieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (35 mg, 0.049 mmol) in 1,4-Dioxane (1 mL) and water (0.10 mL) were added 1,2-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole (19 mg, 0.069 mmol), Na_2CO_3 (10 mg, 0.10 mmol) and tetrakis(triphenylphosphine)palladium (5.7 mg, 0.0049 mmol) under Ar. The mixture was heated to 100 °C and stirred for 2 hours. After cooling, the mixture was filtered and the filtrate was concentrated. The crude was purified by Prep-TLC (DCM:MeOH=15:1) to give tert-butyl (4R,7S)-2-(4-((S)-2,4-difluoro-6-

(methylthio)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (32 mg, 92% yield). LCMS ESI (+) m/z 353.1 (M/2+H).

[000744] Step G: Preparation of 4-((S)-2,4-difluoro-6-(methylthio)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridine: To a solution of tert-butyl (4R,7S)-2-(4-((S)-2,4-difluoro-6-(methylthio)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (32 mg, 0.045 mmol) in DCM (3 mL) was added trifluoroacetic acid (1.0 mL). The mixture was stirred at 24 °C for 2 hours. The mixture was concentrated to dryness to give 4-((S)-2,4-difluoro-6-(methylthio)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridine (55 mg) which was used in the next step directly. LCMS ESI (+) m/z 605.2 (M+H).

[000745] Step H: Preparation of 1-[(4R,7S)-2-[4-(2,4-difluoro-6-methylsulfanyl-phenyl)-7-(1,2-dimethylbenzimidazol-5-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl]prop-2-en-1-one: To a solution of 4-((S)-2,4-difluoro-6-(methylthio)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridine (55 mg, 0.045 mmol) in ethyl acetate (2 mL) and water (1 mL) was added Na_2CO_3 to adjust the pH to 9. Acryloyl chloride (4.5 mg, 0.050 mmol) in DCM (0.2 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The mixture was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was purified by Prep-TLC (DCM:MeOH=10:1) to give 1-[(4R,7S)-2-[4-(2,4-difluoro-6-methylsulfanyl-phenyl)-7-(1,2-dimethylbenzimidazol-5-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl]prop-2-en-1-one (17 mg, 57% yield). LCMS ESI (+) m/z 659.1 (M+H).

Synthetic Example 50: Synthesis of 1-((4R,7S)-2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-4-(2-((dimethylamino)methyl)-4,6-difluorophenyl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 905**)



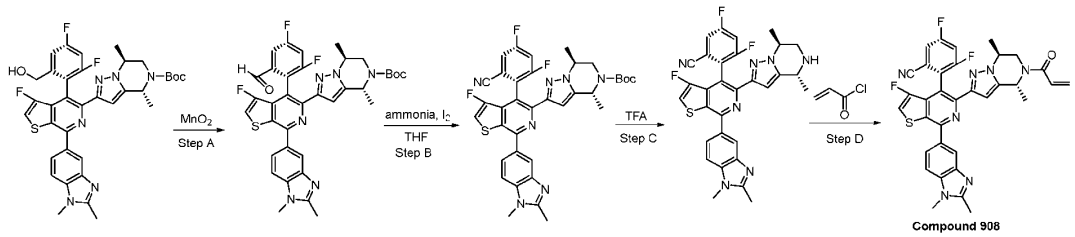
[000746] Step A: Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(((methylsulfonyl)oxy)methyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-(hydroxymethyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (40 mg, 0.058 mmol) in DCM (3 mL) was added Et_3N (29 mg, 0.29 mmol) and methanesulfonic anhydride (20 mg, 0.12 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction was concentrated to dryness to afford crude tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(((methylsulfonyl)oxy)methyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (80 mg) which was used in the next step without further purification.

[000747] Step B: Preparation of tert-butyl (4R,7S)-2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-4-(2-((dimethylamino)methyl)-4,6-difluorophenyl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(((methylsulfonyl)oxy)methyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (80 mg, 0.058 mmol) in THF (2 mL) was added dimethylamine in THF solution (1.5 M, 2.0 mL, 3.0 mmol). The mixture was stirred at 50 °C for 12 h. The reaction was diluted with saturated brine solution (20 mL) and extracted with EtOAc (20 mLx2). The combined organic layers were dried (Na_2SO_4) and filtered before concentration to dryness. The residue was then purified by Prep-TLC (DCM/MeOH: 15/1) to afford tert-butyl (4R,7S)-2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-4-(2-((dimethylamino)methyl)-4,6-difluorophenyl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (16 mg, 36% yield). LCMS ESI (+) m/z 716.3 (M+H).

[000748] Step C: Preparation of 1-(2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenyl)-N,N-dimethylmethanamine: To a solution of tert-butyl (4R,7S)-2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-4-(2-((dimethylamino)methyl)-4,6-difluorophenyl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (16 mg, 0.022 mmol) in DCM (3 mL) was added TFA (1.0 mL). The mixture was stirred at 20 °C for 2 h. The reaction was concentrated to dryness to afford crude 1-(2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenyl)-N,N-dimethylmethanamine (30 mg) which was used in the next step directly. LCMS ESI (+) m/z 616.4 (M+H).

[000749] **Step D:** Preparation of 1-((4R,7S)-2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-4-(2-((dimethylamino)methyl)-4,6-difluorophenyl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of 1-(2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenyl)-N,N-dimethylmethanamine (15 mg, 0.024 mmol) in ethyl acetate (1 mL) and water (1 mL) was added $NaHCO_3$ to adjust the pH to 8. Acryloyl chloride (2.6 mg, 0.029 mmol) in DCM (0.1 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 20 min. The mixture was diluted with H_2O (10 mL) and EtOAc (10 mL). The organic layer was then separated and dried (Na_2SO_4) before concentration to dryness. The residue was then purified Prep-HPLC to afford 1-((4R,7S)-2-((R)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-4-(2-((dimethylamino)methyl)-4,6-difluorophenyl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (7.9 mg, 48% yield) as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.41 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.22 - 7.18 (m, 1H), 6.91-6.75 (m, 1H), 6.67 (s, 1H), 6.33 (d, J = 16.8 Hz, 1H), 5.86 - 5.51 (m, 2H), 4.79 - 4.70 (m, 3H), 4.32 - 4.24 (m, 4H), 4.08 (s, 3H), 3.80 - 3.76 (m, 1H), 2.92 (s, 3H), 2.78 (s, 6H), 1.61 - 1.36 (m, 3H), 1.21 - 1.05 (m, 3H). LCMS ESI (+) m/z 670.4 (M+H).

Synthetic Example 51: Synthesis of 2-((R)-5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorobenzonitrile (**Compound 908**)



[000750] **Step A:** Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-formylphenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-(hydroxymethyl)phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (570 mg, 0.828 mmol) in DCM (20 mL) was added MnO_2 (1439 mg, 16.6 mmol). The mixture was stirred at 40 °C for 18 h. The mixture was filtered and the filtrate was concentrated to dryness to give crude tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-formylphenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-

c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (510 mg, 90% yield) which was used directly in the next step without further purification. LCMS ESI (+) m/z 687.3 (M+H).

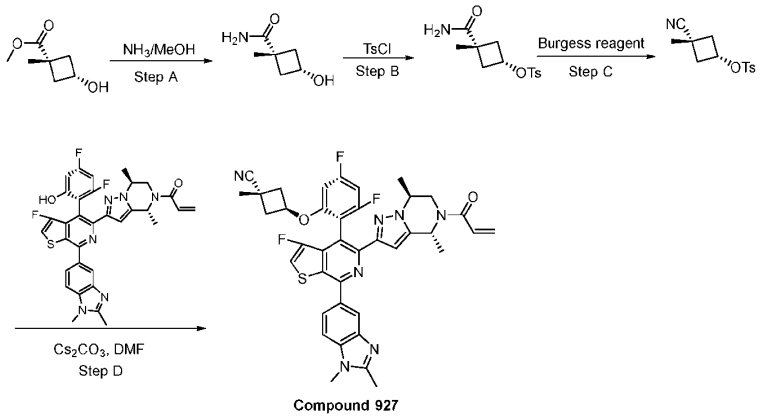
[000751] Step B: Preparation of tert-butyl (4R,7S)-2-(4-((R)-2-cyano-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-formylphenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (40 mg, 0.058 mmol) in THF (5 mL) and ammonia hydroxide (25% in H_2O, 5.0 mL) was added I_2 (29 mg, 0.12 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 h. The reaction was quenched by Na_2SO_3 aqueous solution and extracted with EtOAc (30 mLx2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (DCM:MeOH= 20:1) to give tert-butyl (4R,7S)-2-(4-((R)-2-cyano-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (36 mg, 81% yield) as a yellow solid. LCMS ESI (+) m/z 684.3 (M+H).

[000752] Step C: Preparation of (R)-2-(7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorobenzonitrile: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2-cyano-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (36 mg, 0.053 mmol) in DCM (3 mL) was added trifluoroacetic acid (1.0 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated to dryness to give (R)-2-(7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorobenzonitrile (45 mg, 100% yield) which was used in the next step directly. LCMS ESI (+) m/z 584.3 (M+H).

[000753] Step D: Preparation of 2-((R)-5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorobenzonitrile: To a solution of give (R)-2-(7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorobenzonitrile (45 mg, 0.053 mmol) in water (5 mL) and ethyl acetate (10 mL) was added Na_2CO_3 to adjust the pH to 8. The mixture was cooled to 0 °C, and then acryloyl chloride (5.4 mg, 0.060 mmol) in DCM (0.2 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with H_2O (20 mL). The organic phase was separated, and the aqueous solution was extracted with DCM (20 mLx2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-HPLC to give 2-((R)-5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(1,2-dimethyl-1H-

benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorobenzonitrile (15 mg, 44% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (d, J = 1.7 Hz, 1H), 8.13 (dd, J = 8.5, 1.7 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.44 (td, J = 9.0, 2.6 Hz, 1H), 6.85 (s, 1H), 6.71 (s, 1H), 6.32 (d, J = 16.6 Hz, 1H), 5.83 (d, J = 10.7 Hz, 2H), 4.65 (s, 1H), 4.23-3.83 (m, 5H), 2.68 (s, 3H), 1.55 - 1.47 (m, 3H), 1.18 - 1.12 (m, 3H). LCMS ESI (+) m/z 638.3 (M+H).

[000754] **Synthetic Example 52:** Synthesis of (1R,3r)-3-((R)-2-(5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)-1-methylcyclobutane-1-carbonitrile (**Compound 927**)



Compound 927

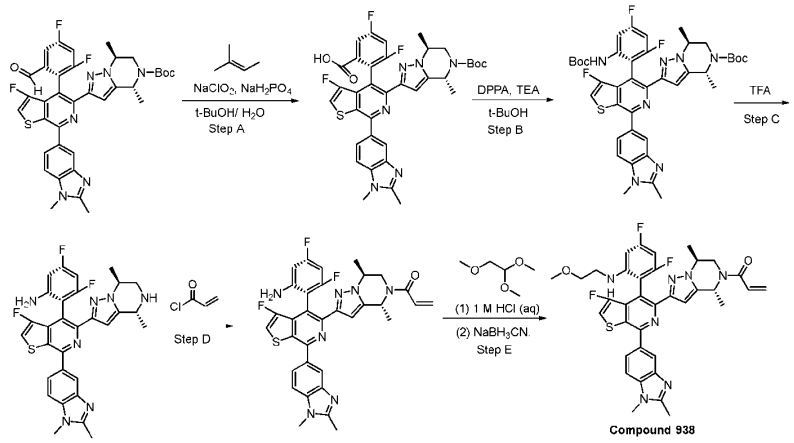
[000755] **Step A:** Preparation of (1s,3s)-3-hydroxy-1-methylcyclobutane-1-carboxamide: A solution of trans-methyl 3-hydroxy-1-methyl-cyclobutanecarboxylate (500 mg, 3.47 mmol) in ammonia/MeOH (8.0 mL, 370 mmol) was stirred at 150 °C for 48 h under Ar. After cooling, the reaction mixture was concentrated and purified by column chromatography on silica gel (DCM/Methanol=5/1) to give (1s,3s)-3-hydroxy-1-methylcyclobutane-1-carboxamide (528 mg, 71% yield) as a white solid. LCMS ESI (+) m/z 130.1 (M+H).

[000756] **Step B:** Preparation of (1s,3s)-3-carbamoyl-3-methylcyclobutyl 4-methylbenzenesulfonate: To a solution of (1s,3s)-3-hydroxy-1-methylcyclobutane-1-carboxamide (500 mg, 2.71 mmol), 4-DMAP (30 mg, 0.27 mmol) and TEA (1.50 mL, 10.8 mmol) in DCM (7 mL) was added p-toluenesulfonyl chloride (775 mg, 4.06 mmol). The mixture was stirred at 25 °C for 16 h. The reaction was diluted with DCM (20 mL) and washed with water. The organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (DCM/Methanol=10/1) to give (1s,3s)-3-carbamoyl-3-methylcyclobutyl 4-methylbenzenesulfonate (512 mg, 60% yield) as a light-yellow solid. LCMS ESI (+) m/z 284.1 (M+H).

[000757] **Step C:** Preparation of (1s,3s)-3-cyano-3-methylcyclobutyl 4-methylbenzenesulfonate: To a solution of (1s,3s)-3-carbamoyl-3-methylcyclobutyl 4-methylbenzenesulfonate (100 mg, 0.353 mmol) in DCM (5 mL) was added Burgess reagent (168 mg, 0.706 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 h. The mixture was poured into water and extracted with EtOAc (50 mLx2). The combined organics were washed with saturated brine solution (50 mL), dried over anhydrous Na_2SO_4, concentrated and purified by Preparative TLC (EtOAc/Petroleum ether=1/6) to give (1s,3s)-3-cyano-3-methylcyclobutyl 4-methylbenzenesulfonate (73 mg, 70% yield) as a yellow solid. LCMS ESI (+) m/z 266.1 (M+H).

[000758] **Step D:** Preparation of (1R,3r)-3-((R)-2-(5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)-1-methylcyclobutane-1-carbonitrile: To a solution of 1-[(4R,7S)-2-[4-(2,4-difluoro-6-hydroxy-phenyl)-7-(1,2-dimethylbenzimidazol-5-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl]prop-2-en-1-one (35 mg, 0.056 mmol) in DMF (5 mL) was added cesium carbonate (54 mg, 0.17 mmol) and (1s,3s)-3-cyano-3-methylcyclobutyl 4-methylbenzenesulfonate (29 mg, 0.11 mmol). The mixture was stirred at 35 °C for 72 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with saturated brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Preparative TLC (DCM:MeOH=20:1) to give (1R,3r)-3-((R)-2-(5-((4R,7S)-5-acryloyl-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenoxy)-1-methylcyclobutane-1-carbonitrile (8.7 mg, 21% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (d, *J* = 1.5 Hz, 1H), 8.42 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 6.87 (s, 1H), 6.77 – 6.59 (m, 2H), 6.33 (d, *J* = 16.7 Hz, 1H), 6.26 (s, 1H), 5.85 (dd, *J* = 10.5, 1.9 Hz, 1H), 5.64 (d, *J* = 87.4 Hz, 1H), 4.86 – 4.65 (m, 2H), 4.39 (s, 1H), 4.23-3.86 (m, 1H), 4.10 (s, 3H), 3.04 – 2.88 (m, 5H), 2.03 (dd, *J* = 12.7, 5.9 Hz, 1H), 1.96 (dd, *J* = 12.4, 5.9 Hz, 1H), 1.44 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H). LCMS ESI (+) m/z 722.3 (M+H).

[000759] **Synthetic Example 53:** Synthesis of 1-((4R,7S)-2-(4-((R)-2,4-difluoro-6-((2-methoxyethyl)amino) phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 938**)



[000760] Step A: Preparation of 2-((R)-5-((4R,7S)-5-(tert-butoxycarbonyl)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorobenzoic acid: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-formylphenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (510 mg, 2.23 mmol) in tert-butanol (6 mL) and water (2 mL) were added NaH_2PO_4 (267 mg, 2.23 mmol), 2-methylbut-2-ene (156 mg, 2.23 mmol) and $NaClO_2$ (201 mg, 2.23 mmol) at 0 °C. The mixture was stirred at 20 °C for 4 h. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 ml). The organics were washed with saturated brine solution. The organics were then separated and dried (Na_2SO_4) before concentrating to dryness. The crude 2-((R)-5-((4R,7S)-5-(tert-butoxycarbonyl)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorobenzoic acid (475 mg, 91% yield) was used directly without further purification. LCMS ESI (+) m/z 703.2 (M+H).

[000761] Step B: Preparation of tert-butyl (4R,7S)-2-(4-((R)-2-((tert-butoxycarbonyl)amino)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of 2-((R)-5-((4R,7S)-5-(tert-butoxycarbonyl)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorobenzoic acid (300 mg, 0.427 mmol) in t-BuOH (4 mL) was added DPPA (176 mg, 0.640 mmol) and TEA (130 mg, 1.28 mmol). The mixture was heated to 110 °C for 2 h. The solvent was removed under vacuum, and the crude product was purified by column chromatography on silica gel eluting with DCM/MeOH (15:1) to give tert-butyl (4R,7S)-2-(4-((R)-2-((tert-butoxycarbonyl)amino)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (105 mg, 32% yield) as a white solid. LCMS ESI (+) m/z 774.2 (M+H).

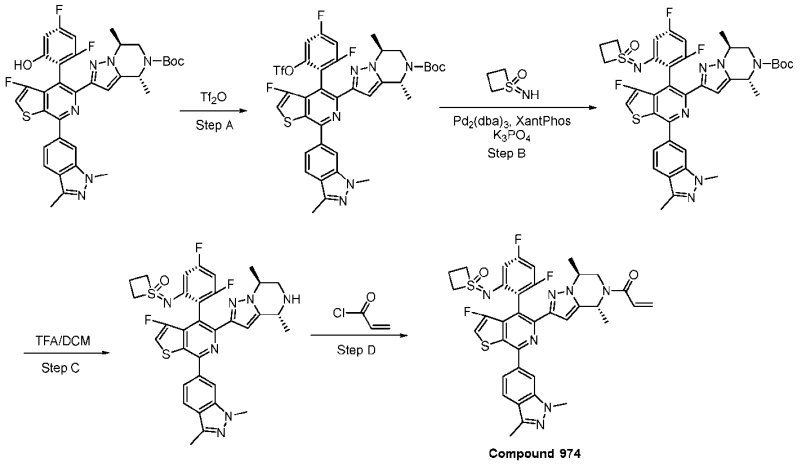
[000762] **Step C:** Preparation of (R)-2-(7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluoroaniline: To a solution of tert-butyl (4R,7S)-2-(4-((R)-2-((tert-butoxycarbonyl)amino)-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (75 mg, 0.097 mmol) in DCM (2 mL) was added TFA (1.0 mL). The mixture was stirred at 28 °C for 2 h. The reaction was concentrated to dryness to give crude (R)-2-(7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo [1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluoroaniline (80 mg, 100% yield) which was used in the next step without further purification. LCMS ESI (+) m/z 574.2 (M+H).

[000763] **Step D:** Preparation of 1-((4R,7S)-2-(4-((R)-2-amino-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of (R)-2-(7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo [1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluoroaniline (80 mg, 0.097 mmol) in ethyl acetate (2 mL) / water (2 mL) was added sodium bicarbonate to adjust the pH to 9. A solution of acryloyl chloride (9.6 mg, 0.11 mmol) in DCM (0.2 mL) was added at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (DCM/MeOH=15:1) to give 1-((4R,7S)-2-(4-((R)-2-amino-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (35 mg, 58% yield) as a light-yellow solid. LCMS ESI (+) m/z 628.2 (M+H).

[000764] **Step E:** Preparation of 1-((4R,7S)-2-(4-((R)-2,4-difluoro-6-((2-methoxyethyl)amino) phenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: A solution of 1,1,2-trimethoxyethane (2.00 g, 16.6 mmol) in 1 M HCl (10 mL) was heated at 50 °C for 2 h. The mixture was allowed to cool to rt. The pH was adjusted to 7.5 with saturated $NaHCO_3$ solution (~10 mL). The solution was used for the next step without further purification. To a solution of 1-((4R,7S)-2-(4-((R)-2-amino-4,6-difluorophenyl)-7-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (15 mg, 0.024 mmol) in Methanol (2 mL) was added the 2-methoxyacetaldehyde solution prepared above (4.0 mL). The solution was stirred at 25 °C for 30 min. Sodium cyanotrihydridoborate (15 mg, 0.24 mmol) was added and the reaction mixture was stirred at 28 °C for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20mLx2). The combined organics were dried (Na_2SO_4), filtered and concentrated. The residue was purified by Prep-HPLC to give 1-((4R,7S)-2-(4-((R)-2,4-difluoro-6-((2-methoxyethyl)amino) phenyl)-7-(1,2-dimethyl-1H-

benzo[d]imidazol-5-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (8.5 mg, 52% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.44 (d, J = 8.7 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.66 - 7.60 (m, 1H), 6.96 - 6.81 (m, 1H), 6.46- 6.30 (m, 2H), 6.29 - 6.21 (m, 1H), 6.11 - 6.05 (m, 1H), 5.90 - 5.82 (m, 1H), 5.78 - 5.42 (m, 1H), 4.11 (s, 3H), 3.44 - 3.36 (m, 3H), 3.29 - 3.22 (m, 2H), 3.20 (s, 3H), 2.96 (s, 3H), 1.56 - 1.30 (m, 6H). LCMS ESI (+) m/z 686.2 (M+H).

[000765] Synthetic Example 54: Synthesis of 1-((4R,7S)-2-(4-((R)-2,4-difluoro-6-((1-oxido-1l6-thietan-1-ylidene)amino)phenyl)-7-(1,3-dimethyl-1H-indazol-6-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 974**)



Compound 974

[000766] Step A: Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(((trifluoromethyl) sulfonyl)oxy)phenyl)-7-(1,3-dimethyl-1H-indazol-6-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-[4-(2,4-difluoro-6-hydroxy-phenyl)-7-(1,3-dimethylindazol-6-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (100 mg, 0.148 mmol) and pyridine (0.060 mL, 0.74 mmol) in DCM (50 mL) was added Tf_2O (0.051 mL, 0.30 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into saturated brine solution (50 mL) and extracted with EtOAc (30 mLx2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH:20/1) to give tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(trifluoromethylsulfonyloxy)phenyl]-7-(1,3-dimethylindazol-6-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (75 mg, 63% yield) as white solid. LCMS ESI (+) m/z 807.2 (M+H).

[000767] Step B: Preparation of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-((1-oxido-1l6-thietan-1-ylidene)amino)phenyl)-7-(1,3-dimethyl-1H-indazol-6-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-

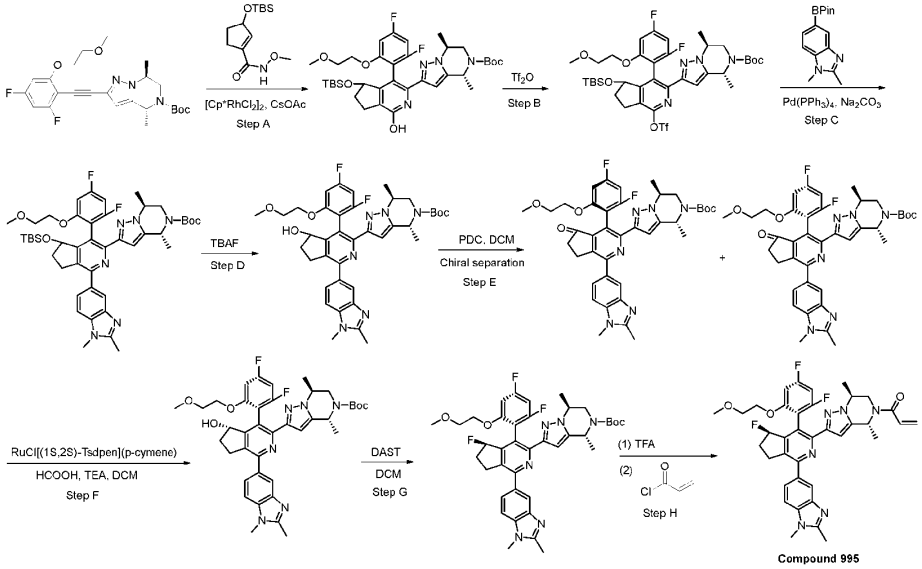
dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A mixture of 1-iminothietane 1-oxide (7.5 mg, 0.071 mmol), cesium carbonate (38 mg, 0.12 mmol), tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(trifluoromethylsulfonyloxy)phenyl]-7-(1,3-dimethylindazol-6-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (30 mg, 0.037 mmol), tris(dibenzylideneacetone)dipalladium(0) (3.7 mg, 0.0041 mmol) and xantphos (4.7 mg, 0.0082 mmol) in toluene (3 mL) was stirred at 110 °C for 16 h. The mixture was concentrated and purified by Prep-TLC (DCM/MeOH:40/1) to give crude tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-[(1-oxothietan-1-ylidene)amino]phenyl]-7-(1,3-dimethylindazol-6-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (7.0 mg, 25% yield). LCMS ESI (+) m/z 762.3 (M+H).

[000768] Step C: Preparation of 1-((2-((R)-7-(1,3-dimethyl-1H-indazol-6-yl)-5-((4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)-3-fluorothieno[2,3-c]pyridin-4-yl)-3,5-difluorophenyl)imino)-1l6-thietane 1-oxide: To a solution of tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-[(1-oxothietan-1-ylidene)amino]phenyl]-7-(1,3-dimethylindazol-6-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (11 mg, 0.014 mmol) in DCM (1.5 mL) was added trifluoroacetic acid (0.50 mL). The mixture was stirred at 30 °C for 1 h. The mixture was concentrated to dryness to give crude 1-[2-[7-(1,3-dimethylindazol-6-yl)-5-[(4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydro pyrazolo[1,5-a]pyrazin-2-yl]-3-fluoro-thieno[2,3-c]pyridin-4-yl]-3,5-difluoro-phenyl]iminothietane 1-oxide (16 mg) which was used in the next step directly. LCMS ESI (+) m/z 662.2 (M+H).

[000769] Step D: Preparation of 1-((4R,7S)-2-((R)-4-(2,4-difluoro-6-((1-oxido-1l6-thietan-1-ylidene)amino)phenyl) -7-(1,3-dimethyl-1H-indazol-6-yl)-3-fluorothieno[2,3-c]pyridin-5-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of crude 1-[2-[7-(1,3-dimethylindazol-6-yl)-5-[(4R,7S)-4,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl]-3-fluoro-thieno[2,3-c]pyridin-4-yl]-3,5-difluoro-phenyl]iminothietane 1-oxide (16 mg, 0.014 mmol) in water (1 mL) and ethyl acetate (2 mL) was added Na_2CO_3 to adjust the pH to 8. The mixture was cooled to 0 °C, and acryloyl chloride (1.5 mg, 0.017 mmol) in DCM (0.1 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 15 min. The mixture was diluted with EtOAc (10 mL) and H_2O (10 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Prep-TLC (DCM/MeOH: 25/1) to give 1-[(4R,7S)-2-[4-[2,4-difluoro-6-[(1-oxothietan-1-ylidene)amino] phenyl]-7-(1,3-dimethylindazol-6-yl)-3-fluoro-thieno[2,3-c]pyridin-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl]prop-2-en-1-one (3.2 mg, 29% yield) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.94 - 7.85 (m, 2H), 7.52 (d, J = 2.5 Hz, 1H), 6.93 - 6.79 (m, 1H), 6.77 (d, J = 10.6 Hz, 1H), 6.61 - 6.52 (m, 1H), 6.31 (d ,J = 16.4 Hz, 1H), 6.14 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.76

- 5.40 (m, 1H), 4.48 - 4.15 (m, 1H), 4.15 - 4.00 (m, 5H), 3.95 - 3.76 (m, 1H), 3.75 - 3.60 (m, 1H), 2.60 (s, 3H), 2.20 - 2.09 (m, 1H), 1.86 - 1.73 (m, 1H), 1.36 - 1.25(m, 6H). LCMS ESI (+) m/z 716.3 (M+H).

[000770] Synthetic Example 55: Synthesis of 1-((4R,7S)-2-((R)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-fluoro-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (**Compound 995**)



[000771] Step A: Preparation of tert-butyl (4R,7S)-2-(5-((tert-butyldimethylsilyl)oxy)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-[2-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]ethynyl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.80 g, 3.90 mmol) in Ethanol (20 mL) were added 3-[tert-butyl(dimethyl)silyl]oxy-N-methoxy-cyclopentene-1-carboxamide (1.58 g, 5.85 mmol), cesium acetate (1.50 g, 7.80 mmol) and bis[(pentamethylcyclopentadienyl)dichloro-rhodium] (0.060 g, 0.098 mmol). The reaction mixture was stirred at 90 °C for 10 h. The mixture was concentrated, diluted with water (100 mL) and extracted with EtOAc (100 mLx2). The combined organic layers were washed with saturated brine solution (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (100% EtOAc) to give tert-butyl (4R,7S)-2-[3-[tert-butyl(dimethyl)silyl]oxy-4-[2,4-difluoro-6-(2-methoxyethoxy) phenyl]-7-hydroxy-indan-5-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.17 g, 36% yield) as a white solid. LCMS ESI (+) m/z 701.4 (M+H).

[000772] Step B: Preparation of tert-butyl (4R,7S)-2-(5-((tert-butyldimethylsilyl)oxy)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-((((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-

yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-[5-[tert-butyl(dimethyl)silyl]oxy-4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-1-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1.10 g, 1.57 mmol) and pyridine (0.640 mL, 7.86 mmol) in DCM (10 mL) was added trifluoromethanesulfonic anhydride (0.400 mL, 2.36 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The mixture was poured into water (50 mL) and extracted with EtOAc (50 mLx2). The combined organic layers were washed with saturated brine solution (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (Petroleum ether/EtOAc: 5/1) to give tert-butyl (4R,7S)-2-[5-[tert-butyl(dimethyl)silyl]oxy-4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-1-(trifluoromethylsulfonyloxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate;hydrofluoride (920 mg, 62% yield) as a white solid. LCMS ESI (+) m/z 833.4 (M+H).

[000773] **Step C:** Preparation of tert-butyl (4R,7S)-2-(5-((tert-butyldimethylsilyl)oxy)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-[5-[tert-butyl(dimethyl)silyl]oxy-4-[2,4-difluoro-6-(2-methoxyethoxy) phenyl]-1-(trifluoromethylsulfonyloxy)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (1000 mg, 1.20 mmol) in 1,4-dioxane (10 mL) and water (1 mL) were added 1,2-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazole (392 mg, 1.44 mmol), Sodium carbonate (254 mg, 2.40 mmol) and bis(triphenylphosphine)palladium(II) dichloride (84 mg, 0.12 mmol). The reaction mixture was stirred at 90 °C for 2 h under N_2. The mixture was poured into water (50 mL) and extracted with EtOAc (50 mLx2). The combined organic layers were washed with saturated brine solution (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc) to give tert-butyl (4R,7S)-2-[5-[tert-butyl(dimethyl)silyl]oxy-4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-1-(1,2-dimethylbenzimidazol-5-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (820 mg, 74% yield) as a white solid. LCMS ESI (+) m/z 829 (M+H).

[000774] **Step D:** Preparation of tert-butyl (4R,7S)-2-(4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: A mixture of tert-butyl (4R,7S)-2-[5-[tert-butyl(dimethyl)silyl]oxy-4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-1-(1,2-dimethylbenzimidazol-5-yl)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (800 mg, 0.965 mmol) in 1.0 M TBAF in THF solution (7.30 mL, 7.30 mmol) was stirred at 25 °C for 12 h. The mixture was poured into water (50 mL) and extracted with EtOAc (50 mLx2). The

combined organic layers were washed with saturated brine solution (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (DCM/MeOH: 15/1) to give tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-1-(1,2-dimethylbenzimidazol-5-yl)-5-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (650 mg, 93% yield) as a light-yellow solid. LCMS ESI (+) m/z 715.4 (M+H).

[000775] Step E: Preparation of tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-1-(1,2-dimethylbenzimidazol-5-yl)-5-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (710 mg, 0.993 mmol) in DCM (3 mL) was added PDC (443 mg, 1.49 mmol). The reaction mixture was stirred at 25 °C for 2 h. The mixture was poured into water (50 mL) and extracted with EtOAc (50 mLx2). The combined organic layers were washed with saturated brine solution (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (DCM/MeOH: 20/1) to give tert-butyl (4R,7S)-2-[4-[2,4-difluoro-6-(2-methoxyethoxy)phenyl]-1-(1,2-dimethylbenzimidazol-5-yl)-5-oxo-6,7-dihydrocyclopenta[c]pyridin-3-yl]-4,7-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate (270 mg, 25% yield) as a mixture of two diastereomers. 366 mg of the mixture was separated by chiral SFC ((R,R)-WHELK-O column, 3cm×25cm, 5 um, CO_2:[MeOH:DCM = 2:1 (0.2% 2 mM NH_3-MeOH)] = 55:45) to give the desired diastereomer tert-butyl (4R,7S)-2-(4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (90 mg) as the second peak. LCMS ESI (+) m/z 713.4 (M+H).

[000776] Step F: Preparation of tert-butyl (4R,7S)-2-((S)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-((R)-4-(2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-oxo-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (40 mg, 0.056 mmol) in DCM (3 mL) were added triethylamine (8.5 mg, 0.084 mmol), formic acid (7.7 mg, 0.17 mmol) and RuCl[(1S,2S)-Tsdpen](p-cymene) (0.35 mg, 0.00056 mmol). The reaction mixture was stirred at 0 °C for 12 h under N_2. The mixture was poured into water (30 mL) and extracted with EtOAC (30 mLx2). The combined organic layers were washed with saturated brine solution (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (DCM/MeOH: 30/1) to give tert-butyl (4R,7S)-2-((S)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d] imidazol-5-yl)-5-hydroxy-6,7-dihydro-5H-

cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (38 mg, 85% yield) as a white solid. LCMS ESI (+) m/z 715.4 (M+H).

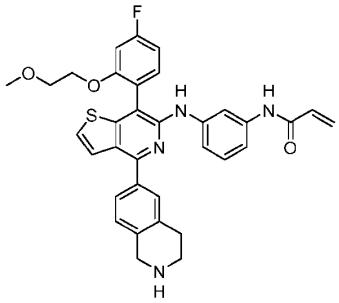
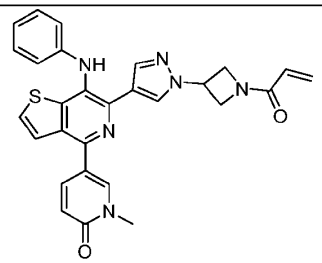
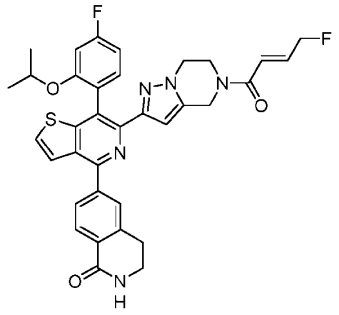
[000777] Step G: Preparation of tert-butyl (4R,7S)-2-((R)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-fluoro-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate: To a solution of tert-butyl (4R,7S)-2-((S)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d] imidazol-5-yl)-5-hydroxy-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (20 mg, 0.028 mmol) in DCM (3 mL) was added DAST (9.0 mg, 0.056 mmol) at -70 °C. The reaction mixture was stirred at -70 °C for 4 h under N_2. The reaction was quenched by the addition of MeOH (1 mL). The mixture was poured into water (30 mL) and extracted with EtOAc (30 mLx2). The combined organic layers were washed with saturated brine solution (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by Prep-TLC (DCM/MeOH: 40/1) to give tert-butyl (4R,7S)-2-((R)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-fluoro-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (18 mg, 81% yield) as a white solid. LCMS ESI (+) m/z 717.4 (M+H).

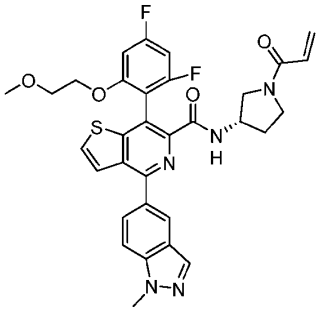
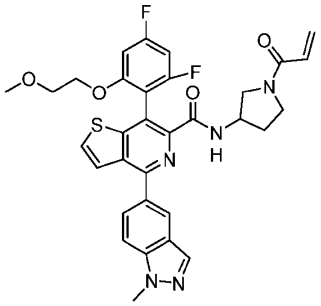
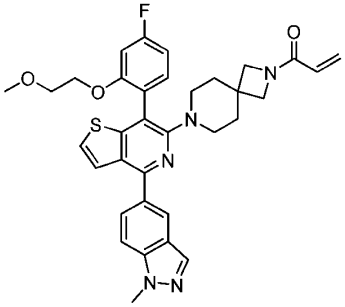
[000778] Step H: Preparation of 1-((4R,7S)-2-((R)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-fluoro-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one: To a solution of tert-butyl (4R,7S)-2-((R)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-fluoro-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (21 mg, 0.029 mmol) in DCM (4 mL) was added trifluoroacetic acid (1.0 mL). The reaction mixture was stirred at 25 °C for 2 h. The mixture was concentrated to dryness and then dissolved in ethyl acetate (5 mL) and water (5 mL). Saturated $NaHCO_3$ solution was added to adjust the pH to 8-9. Acryloyl chloride (2.9 mg, 0.032 mmol) was added at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h. The mixture was poured into water (30 mL) and extracted with EtOAc (30 mLx2). The combined organic layers were washed with saturated brine solution (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to give 1-((4R,7S)-2-((R)-4-((R)-2,4-difluoro-6-(2-methoxyethoxy)phenyl)-1-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-fluoro-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)-4,7-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)prop-2-en-1-one (3.7 mg, 13% yield) as a bis trifluoroacetic acid salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.20 (dd, J = 8.7 Hz, 1.4 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 6.92 – 6.80 (m, 2H), 6.57 – 6.50 (m, 1H), 6.32 (d, J = 15.6 Hz, 1H), 6.15 (s, 1H), 6.00 - 5.80 (m, 2H), 5.78 - 5.45(m, 1H), 4.45 – 4.35 (m, 1H), 4.25 – 4.18 (m, 1H), 4.16 – 4.10 (m, 1H), 4.06 (s, 3H), 3.57 (t, J = 4.7 Hz, 2H), 3.54 – 3.43 (m, 2H), 3.23 (s, 3H), 3.22 – 3.10

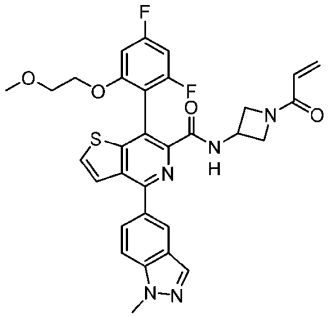
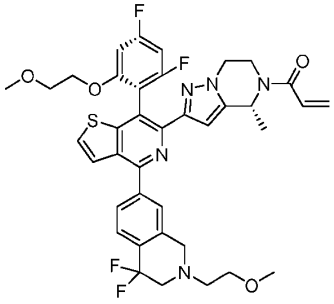
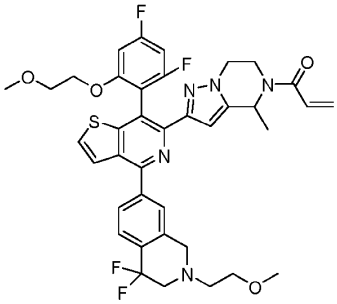
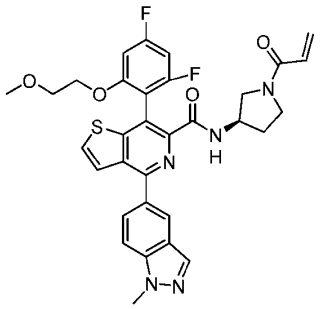
(m, 1H), 2.91 (s, 3H), 2.55 – 2.25 (m, 2H), 1.52 – 1.35 (m, 3H) , 1.35 – 1.20 (m, 4H). LCMS ESI (+) m/z 671.4 (M+H).

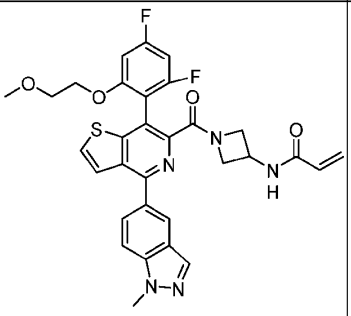
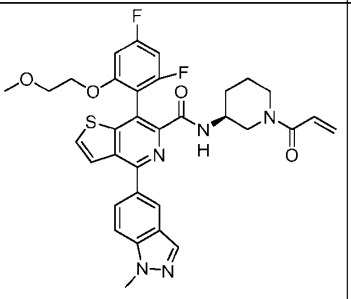
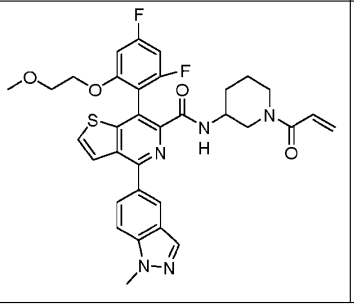
[000779] Table 1 includes selected compounds of the present disclosure.

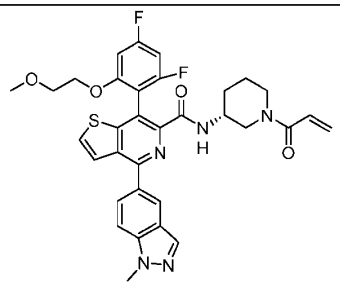
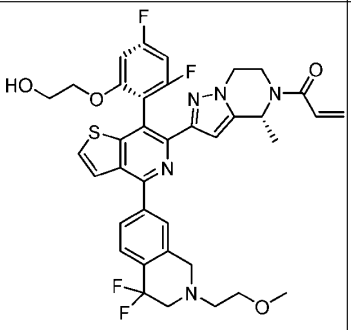
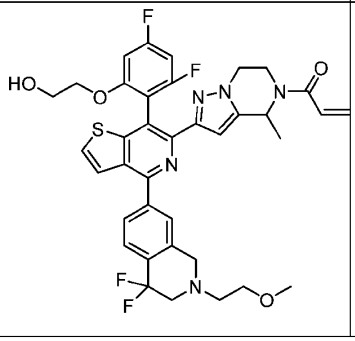
Table 1. Selected compounds of the present disclosure.

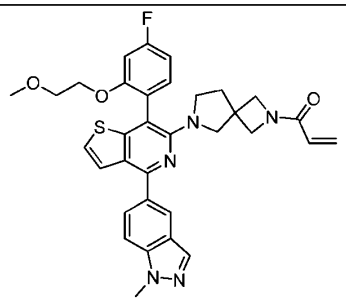
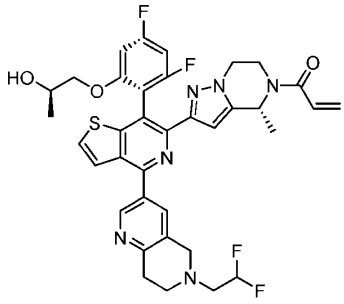
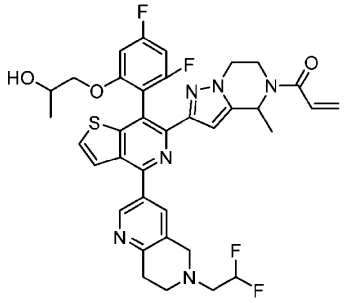
Cmpd. No.	Structure	Analytical data
1		LCMS m/z [M+1]: 595.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.99 (s, 1H), 7.88 (d, J = 5.4 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 5.6 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 10.7 Hz, 1H), 6.86 - 6.75 (m, 1H), 6.65 - 6.33 (m, 1H), 6.25 - 6.05 (m, 2H), 5.71 - 5.52 (m, 1H), 4.34 - 4.10 (m, 3H), 4.10 - 3.86 (m, 6H), 3.85 - 3.72 (m, 1H), 3.69 - 3.60 (m, 1H), 3.12 - 2.95 (m, 2H), 1.55 - 1.32 (m, 2H).
2		LCMS m/z [M+1]: 509.4 ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.04 (s, 1H), 7.99-7.96 (m, 2H), 7.54-7.47 (m, 2H), 7.24-7.20 (m, 2H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.76-6.73 (m, 1H), 6.70-6.68 (m, 2H), 6.40-6.35 (m, 1H), 6.23-6.16 (m, 1H), 5.72 (dd, *J* = 10.2, 2.0 Hz, 1H), 5.59 (s, 1H), 5.16-5.09 (m, 1H), 4.65-4.51 (m, 3H), 4.45-4.41 (m, 1H), 3.70 (s, 3H).
3		LCMS m/z [M+1]: 722.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, J = 8.4 Hz, 1H), 7.98 - 7.90 (m, 2H), 7.82 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 6.91 - 6.80 (m, 2H), 6.74 - 6.66 (m, 1H), 6.34 - 6.23 (m, 1H), 6.18 (s, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.73 - 5.40 (m, 1H), 4.37 (s, 2H), 4.23 - 4.16 (m, 1H), 4.01 (t, J = 4.4 Hz, 3H), 3.86 - 3.69(m, 5H), 3.63 - 3.48 (m, 3H), 3.44 (s, 3H), 3.37 - 3.31 (m, 1H), 1.43 (s, 3H).

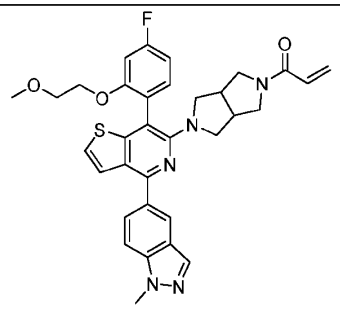
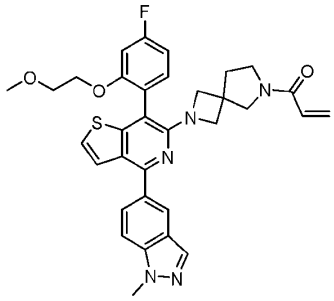
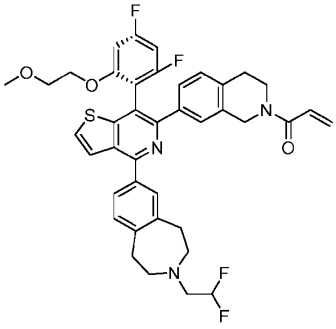
Cmpd. No.	Structure	Analytical data
4		LCMS m/z [M+1]: 618.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.20 (s, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 5.3 Hz, 1H), 7.82 – 7.70 (m, 2H), 6.88 (d, J = 3.5 Hz, 1H), 6.76 (t, J = 9.3 Hz, 1H), 6.66 – 6.50 (m, 1H), 6.36 – 6.25 (m, 1H), 5.81 – 5.71 (m, 1H), 4.51 (dd, J = 17.5, 10.8 Hz, 1H), 4.18 (s, 3H), 4.12 (dd, J = 7.3, 3.7 Hz, 2H), 4.01 – 3.89 (m, 1H), 3.83 – 3.58 (m, 3H), 3.52 – 3.45 (m, 2H), 3.08 (dd, J = 5.5, 1.9 Hz, 3H), 2.31 – 2.08 (m, 2H).
4a		
5		LCMS m/z [M+1]: 612.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.22 (s, 1H), 7.94 (dd, J = 8.8, 1.6 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 5.6 Hz, 1H), 7.60 (d, J = 5.6 Hz, 1H), 7.45 (dd, J = 8.4, 6.6 Hz, 1H), 7.12 (dd, J = 11.0, 2.2 Hz, 1H), 6.94 (td, J = 8.2, 2.4 Hz, 1H), 6.35 - 6.29 (m, 1H), 6.22 (dd, J = 17.0, 2.0 Hz, 1H), 5.71 (dd, J = 10.0, 2.0 Hz, 1H), 4.29 - 4.24 (m, 1H), 4.17 (s, 3H), 4.16 - 4.13 (m, 1H), 3.98 (s, 2H), 3.74 (s, 2H), 3.58 (t, J = 4.0 Hz, 2H), 3.18 (s, 3H), 1.76 - 1.73 (m, 4H).

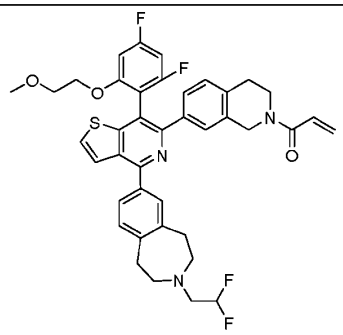
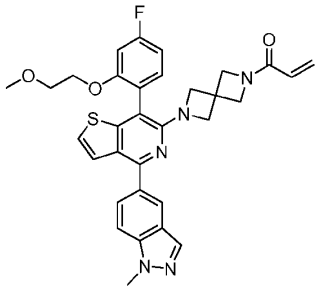
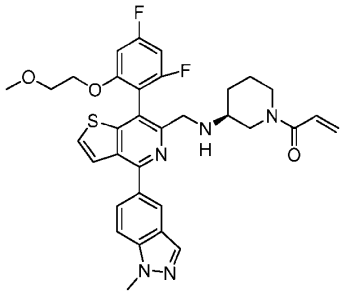
Cmpd. No.	Structure	Analytical data
6		LCMS m/z [M+1]: 604.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (s, 1H), 8.18 (s, 1H), 8.09 (dd, J = 8.7, 1.1 Hz, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.81 – 7.72 (m, 2H), 6.87 (d, J = 10.9 Hz, 1H), 6.80 – 6.69 (m, 1H), 6.40 – 6.21 (m, 2H), 5.74 (dd, J = 10.0, 2.2 Hz, 1H), 4.82 – 4.70 (m, 1H), 4.60 (dd, J = 15.2, 8.5 Hz, 1H), 4.44 – 4.28 (m, 2H), 4.21 – 4.07 (m, 6H), 3.53 – 3.43 (m, 2H), 3.07 (s, 3H).
7		LCMS m/z [M+1]: 736.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 9.6 Hz, 2H), 7.89 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.95 - 6.79 (m, 2H), 6.78 - 6.70 (m, 1H), 6.36 - 6.21 (m, 1H), 6.12 (s, 1H), 5.87 - 5.79 (m, 1H), 5.77 - 5.41 (m, 1H), 4.67 (s, 2H), 4.27 - 4.19 (m, 1H), 4.18 - 4.00 (m, 5H), 3.88 - 3.81 (m, 2H), 3.59 - 3.51 (m, 2H), 3.47 (s, 3H), 3.43 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.52 - 1.30 (m, 3H).
7a		
8		LCMS m/z [M+1]: 618.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 8.05 (s, 1H), 7.91 (dd, J = 8.7, 1.4 Hz, 1H), 7.76 (dd, J = 5.5, 1.5 Hz, 1H), 7.63 (dd, J = 5.8, 2.2 Hz, 2H), 6.83 – 6.71 (m, 1H), 6.63 (dd, J = 12.8, 5.7 Hz, 1H), 6.54 – 6.32 (m, 1H), 6.21 – 6.08 (m, 1H), 5.62 (ddd, J = 9.1, 4.3, 1.7 Hz, 1H), 4.40 (ddd, J = 19.3, 10.2, 5.9 Hz, 1H), 4.04 (s, 3H), 3.99 (dd, J = 7.4, 3.6 Hz, 2H), 3.88 – 3.67 (m, 1H), 3.68

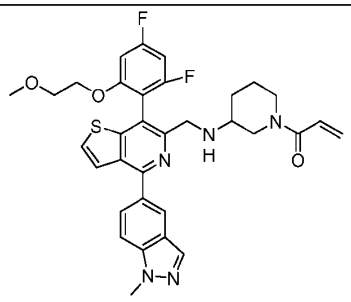
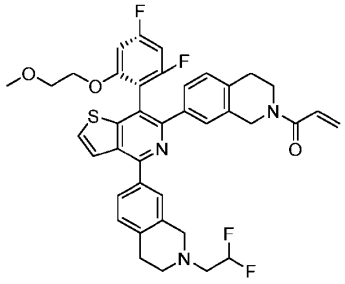
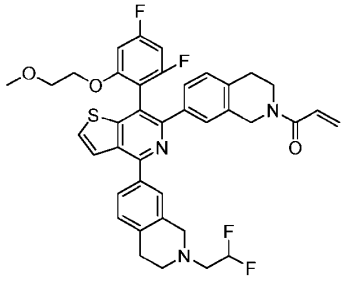
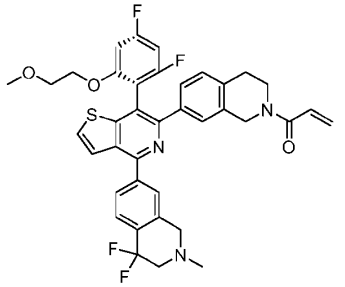
Cmpd. No.	Structure	Analytical data
		– 3.40 (m, 3H), 3.40 – 3.30 (m, 2H), 2.94 (dd, J = 5.4, 2.0 Hz, 3H), 2.23 – 1.91 (m, 2H).
9		LCMS m/z [M+1]: 604.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (d, J = 14.4 Hz, 1H), 8.15 – 8.10 (m, 1H), 7.95 (dd, J = 16.5, 8.4 Hz, 1H), 7.72 (dd, J = 10.2, 5.5 Hz, 1H), 7.66 (t, J = 5.1 Hz, 1H), 7.58 (t, J = 8.2 Hz, 1H), 6.98 (s, 1H), 6.64 (d, J = 9.3 Hz, 2H), 6.30 (d, J = 17.0 Hz, 1H), 6.13 – 6.02 (m, 1H), 5.65 (d, J = 10.2 Hz, 1H), 4.85 (s, 2H), 4.48 – 4.26 (m, 2H), 4.21 – 3.93 (m, 6H), 3.57 (t, J = 4.5 Hz, 1H), 3.54 – 3.44 (m, 1H), 3.16 (d, J = 7.7 Hz, 3H).
10		LCMS m/z [M+1]: 632.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.21 (s, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 5.3 Hz, 1H), 7.80 (dd, J = 15.6, 6.4 Hz, 2H), 6.89 (t, J = 10.0 Hz, 1H), 6.74 (qd, J = 17.0, 10.7 Hz, 2H), 6.11 (t, J = 19.6 Hz, 1H), 5.74 – 5.56 (m, 1H), 4.19 (s, 3H), 4.12 (dd, J = 10.1, 5.7 Hz, 2H), 3.94 (dd, J = 47.3, 23.3 Hz, 2H), 3.70 (dd, J = 46.7, 32.1 Hz, 2H), 3.58 – 3.45 (m, 3H), 3.08 (d, J = 11.1 Hz, 3H), 2.02 (s, 1H), 1.83 (s, 2H), 1.64 (s, 1H).
10a		

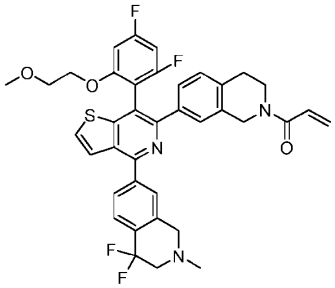
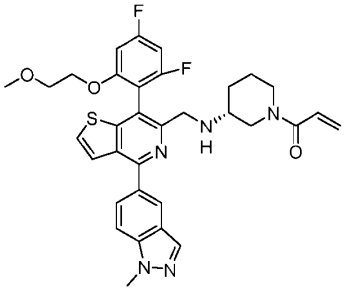
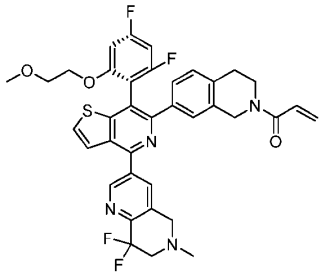
Cmpd. No.	Structure	Analytical data
11		LCMS m/z [M+1]: 632.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.21 (s, 1H), 8.05 (d, J = 7.3 Hz, 1H), 7.91 (t, J = 5.0 Hz, 1H), 7.80 (dd, J = 15.4, 6.6 Hz, 2H), 6.89 (t, J = 10.2 Hz, 1H), 6.74 (qd, J = 17.1, 10.7 Hz, 2H), 6.11 (dd, J = 22.3, 17.2 Hz, 1H), 5.73 – 5.56 (m, 1H), 4.18 (s, 3H), 4.12 (dd, J = 10.2, 5.7 Hz, 2H), 3.94 (dd, J = 48.1, 23.8 Hz, 2H), 3.84 – 3.58 (m, 2H), 3.58 – 3.43 (m, 3H), 3.08 (d, J = 11.3 Hz, 3H), 2.01 (s, 1H), 1.83 (s, 2H), 1.64 (s, 1H).
12		LCMS m/z [M+1]: 722.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, J = 8.4 Hz, 1H), 7.98 - 7.90 (m, 2H), 7.82 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 6.91 - 6.80 (m, 2H), 6.74 - 6.66 (m, 1H), 6.34 - 6.23 (m, 1H), 6.18 (s, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.73 - 5.40 (m, 1H), 4.37 (s, 2H), 4.23 - 4.16 (m, 1H), 4.01 (t, J = 4.4 Hz, 3H), 3.86 - 3.69(m, 5H), 3.63 - 3.48 (m, 3H), 3.44 (s, 3H), 3.37 - 3.31 (m, 1H), 1.43 (s, 3H).
12a		

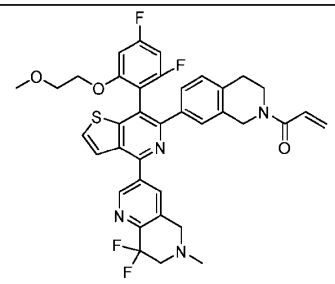
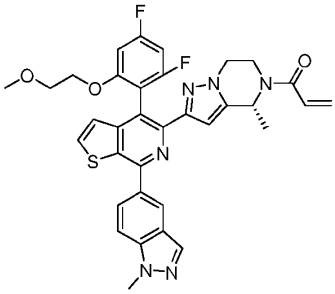
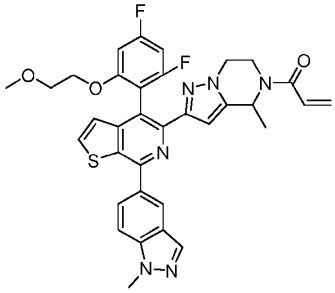
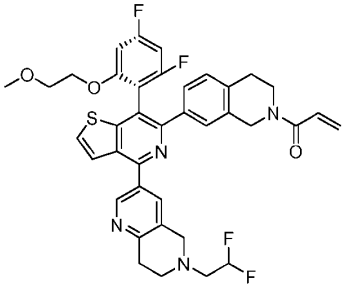
Cmpd. No.	Structure	Analytical data
13		LCMS m/z [M+1]: 626.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J = 5.2 Hz, 1H), 8.22 (d, J = 3.2 Hz, 1H), 7.94 - 7.87 (m, 1H), 7.87 - 7.80 (m, 1H), 7.55 - 7.37 (m, 3H), 7.09 - 7.02 (m, 1H), 6.95 - 6.85 (m, 1H), 6.80 - 6.54 (m, 1H), 6.23 - 6.09 (m, 1H), 5.79 - 5.59 (m, 1H), 4.31 - 4.21 (m, 1H), 4.18 (s, 3H), 4.16 - 4.07 (m, 1H), 3.73 - 3.66 (m, 1H), 3.65 - 3.35 (m, 7H), 3.36 - 3.33 (m, 1H), 3.23 - 3.08 (m, 4H), 1.93 - 1.50 (m, 6H).
14		LCMS m/z [M+1]: 707.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.05 (s, 1H), 8.37 (s, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.90 - 6.77 (m, 2H), 6.75 - 6.66 (m, 1H), 6.35 - 6.23 (m, 1H), 6.20 (s, 1H), 6.17 - 5.98 (m, 1H), 5.86 - 5.77 (m, 1H), 5.75 - 5.37 (m, 1H), 4.24 - 4.15 (m, 1H), 4.12 (s, 2H), 4.08 - 3.93 (m, 1H), 3.90 - 3.82 (m, 1H), 3.80 - 3.64 (m, 2H), 3.22 (s, 4H), 3.20 - 3.07 (m, 3H), 1.56 - 1.34 (m, 3H), 0.88 (d, J = 6.2 Hz, 3H).
14a		

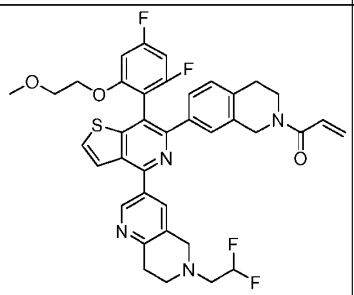
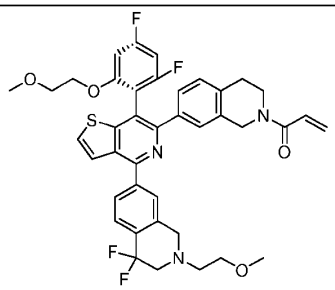
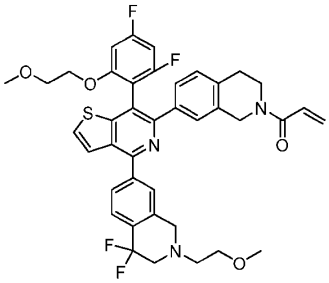
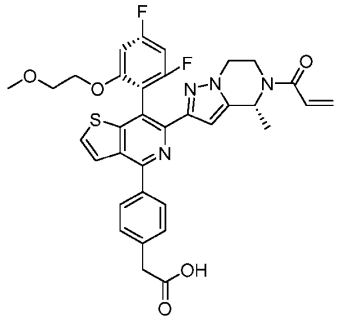
Cmpd. No.	Structure	Analytical data
15		LCMS m/z [M+1]: 598.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.22 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.55 – 7.39 (m, 3H), 7.08 – 7.00 (m, 1H), 6.94 – 6.85 (m, 1H), 6.59 – 6.48 (m, 1H), 6.31 – 6.20 (m, 1H), 5.74 (dd, J = 10.4, 1.7 Hz, 1H), 4.27 – 4.06 (m, 5H), 3.88 – 3.61 (m, 4H), 3.58 (t, J = 4.3 Hz, 2H), 3.54 – 3.49 (m, 1H), 3.46 – 3.33 (m, 2H), 3.21 (d, J = 8.0 Hz, 3H), 3.12 – 2.95 (m, 2H).
16		LCMS m/z [M+1]: 598.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.13 (s, 1H), 7.99 (dd, J = 8.7, 1.3 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.47 (dd, J = 5.6, 0.8 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.24 (dd, J = 5.6, 1.2 Hz, 1H), 6.99 (d, J = 10.2 Hz, 1H), 6.89 – 6.80 (m, 1H), 6.60 – 6.49 (m, 1H), 6.25 (dd, J = 16.8, 1.6 Hz, 1H), 5.77 – 5.67 (m, 1H), 4.26 – 4.19 (m, 1H), 4.17 – 4.10 (m, 4H), 3.80 – 3.54 (m, 9H), 3.48 (t, J = 6.9 Hz, 1H), 3.19 (d, J = 1.0 Hz, 3H), 2.14 (t, J = 6.7 Hz, 1H), 2.06 (t, J = 7.0 Hz, 1H).
17		LCMS m/z [M+1]: 716.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (dd, J = 19.3, 4.0 Hz, 4H), 7.34 – 7.10 (m, 3H), 6.97 (d, J = 4.5 Hz, 1H), 6.80 – 6.65 (m, 2H), 6.57 – 6.46 (m, 1H), 6.13 (dd, J = 16.8, 6.5 Hz, 1H), 5.92 (tt, J = 56.0, 4.1 Hz, 1H), 5.67 (d, J = 10.7 Hz, 1H), 4.61 (d, J = 18.7 Hz, 2H), 4.01 – 3.82 (m, 2H), 3.73 (t, J = 5.6 Hz, 2H), 3.38 (s, 2H), 3.05 – 2.62 (m, 15H).

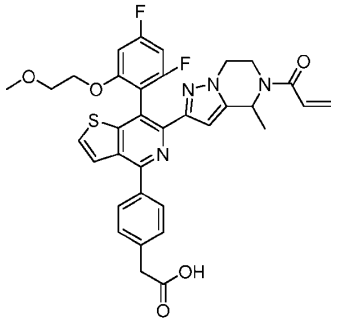
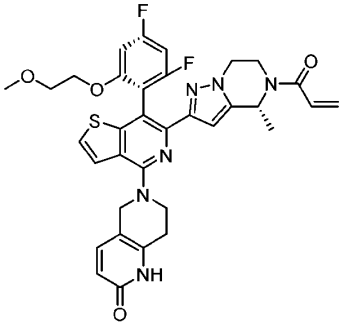
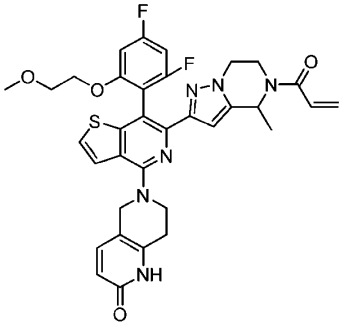
Cmpd. No.	Structure	Analytical data
17a		
18		LCMS m/z [M+1]: 584.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.12 (s, 1H), 7.98 (dd, J = 8.8, 1.4 Hz, 1H), 7.68 (d, J = 8.8 Hz 1H), 7.46 (d, J = 5.64 Hz 1H), 7.32 (dd, J = 8.3, 6.9 Hz, 1H), 7.25 (d, J = 5.64 Hz, 1H), 7.32 (dd, J = 11.1, 2.4 Hz, 1H), 6.86-6.81 (m, 1H), 6.30-6.16 (m, 2H), 5.69 (dd, J = 9.9, 2.4 Hz, 1H), 4.33 (s, 2H), 4.24-4.19 (m, 1H), 4.14-4.09 (m, 6H), 3.95-3.85 (m, 4H), 3.59-3.56 (m, 2H), 3.16 (s, 3H).
19		LCMS m/z [M+1]: 618.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.20 (s, 1H), 8.10 – 8.00 (m, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.72 (s, 2H), 6.99 (d, J = 10.5 Hz, 1H), 6.84 (d, J = 9.3 Hz, 1H), 6.62 (ddd, J = 86.9, 16.8, 10.7 Hz, 1H), 6.11 (dd, J = 38.5, 17.0 Hz, 1H), 5.60 (dd, J = 85.3, 10.6 Hz, 1H), 4.38 – 3.80 (m, 9H), 3.51 (dd, J = 11.3, 6.1 Hz, 2H), 3.31 – 2.94 (m, 5H), 2.81 (dd, J = 48.2, 35.8 Hz, 2H), 2.00 – 1.70 (m, 2H), 1.51 – 1.39 (m, 2H).

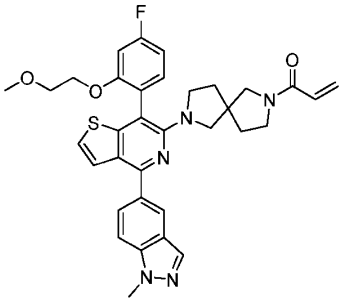
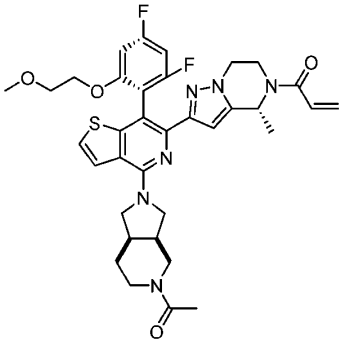
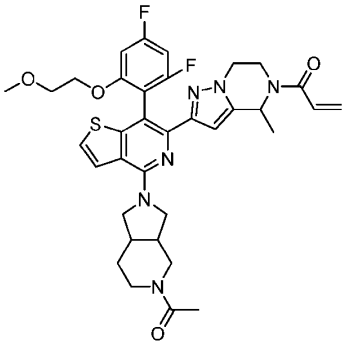
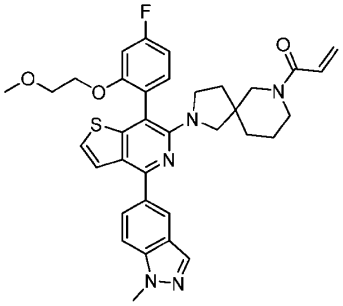
Cmpd. No.	Structure	Analytical data
19a		
20		LCMS m/z [M+1]: 702.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (t, J = 5.8 Hz, 2H), 7.65 (d, J = 5.4 Hz, 1H), 7.62 (s, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.28 (t, J = 8.2 Hz, 1H), 7.09 (dd, J = 7.6, 4.8 Hz, 1H), 6.83 (dd, J = 18.4, 8.0 Hz, 2H), 6.63 (t, J = 9.0 Hz, 1H), 6.25 (dd, J = 16.0, 6.6 Hz, 1H), 6.14 – 5.95 (m, 1H), 5.79 (d, J = 10.6 Hz, 1H), 4.74 (d, J = 20.2 Hz, 2H), 4.04 (d, J = 22.4 Hz, 2H), 3.95 (s, 2H), 3.85 (t, J = 5.8 Hz, 2H), 3.50 (s, 2H), 3.13 (s, 3H), 3.07 – 2.86 (m, 8H).
20a		
21		LCMS m/z [M+1]: 688.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 8.0 Hz, 1H), 8.09 – 7.97 (m, 2H), 7.87 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.4 Hz, 1H), 7.42 (d, J = 14.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.85 (dd, J = 26.3, 15.7 Hz, 2H), 6.67 (t, J = 9.2 Hz, 1H), 6.26 (dd, J = 16.8, 10.2 Hz, 1H), 5.80 (d, J = 10.5 Hz, 1H), 4.75 (d, J = 10.1 Hz, 2H), 4.68 (d, J = 11.8 Hz, 2H), 4.22 – 4.00 (m, 4H),

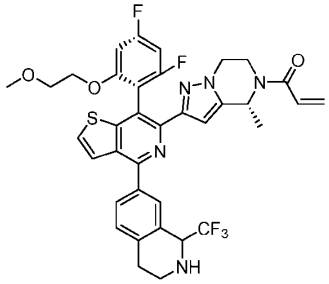
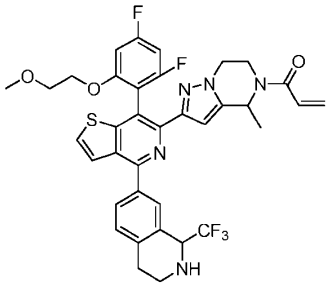
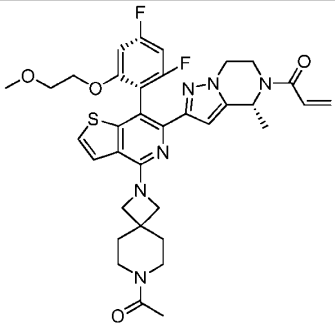
Cmpd. No.	Structure	Analytical data
		3.93 – 3.82 (m, 2H), 3.51 (dd, J = 5.2, 3.5 Hz, 2H), 3.17 (d, J = 8.6 Hz, 6H), 2.93 (d, J = 16.9 Hz, 2H).
21a		
22		LCMS m/z [M+1]: 618.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.88 – 7.66 (m, 3H), 6.99 (d, J = 9.3 Hz, 1H), 6.85 (s, 1H), 6.81 – 6.47 (m, 1H), 6.11 (dd, J = 38.8, 16.8 Hz, 1H), 5.60 (dd, J = 85.5, 10.1 Hz, 1H), 4.44 – 3.71 (m, 9H), 3.52 (s, 2H), 3.28 – 2.96 (m, 5H), 2.93 – 2.59 (m, 2H), 1.95 – 1.69 (m, 2H), 1.50 – 1.35 (m, 2H).
23		LCMS m/z [M+1]: 689.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (d, J = 1.6 Hz, 1H), 8.34 (s, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 7.42 (d, J = 10.8 Hz, 1H), 7.36 – 7.25 (m, 1H), 7.17 – 7.06 (m, 1H), 6.84 (dt, J = 17.8, 9.0 Hz, 2H), 6.66 (td, J = 9.3, 2.2 Hz, 1H), 6.34 – 6.17 (m, 1H), 5.79 (dd, J = 10.6, 1.8 Hz, 1H), 4.74 (d, J = 21.7 Hz, 2H), 4.16 – 3.95 (m, 2H), 3.94 – 3.76 (m, 4H), 3.49 (s, 2H), 3.28 (d, J = 12.0 Hz, 2H), 3.17 – 3.06 (m, 3H), 2.97 – 2.85 (m, 2H), 2.60 (s, 3H).

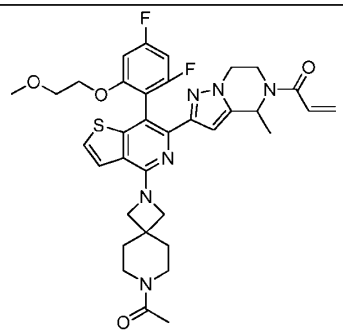
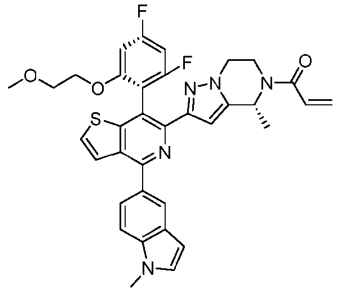
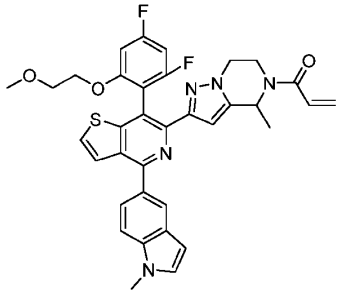
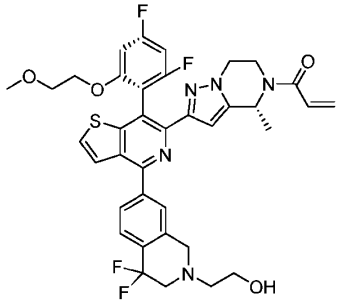
Cmpd. No.	Structure	Analytical data
23a		
24		LCMS m/z [M+1]: 641.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.33 (dd, J = 5.6, 1.6 Hz, 1H), 8.25 (s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 5.4 Hz, 1H), 6.95 - 6.74 (m, 3H), 6.29 (d, J = 15.2 Hz, 1H), 6.04 (d, J = 5.9 Hz, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.70 - 5.48 (m, 1H), 4.33 - 4.29 (m, 1H), 4.18 (s, 3H), 4.14 - 3.98 (m, 3H), 3.44 (t, J = 4.2 Hz, 2H), 3.09 (d, J = 6.6 Hz, 3H), 1.54 - 1.33 (m, 3H).
24a		
25		LCMS m/z [M+1]: 703.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 8.00 (s, 1H), 7.69 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 5.6 Hz, 1H), 7.28 (d, J = 7.1 Hz, 1H), 7.18 (t, J = 8.8 Hz, 1H), 6.99 (dd, J = 7.8, 4.6 Hz, 1H), 6.80 – 6.66 (m, 2H), 6.53 (td, J = 9.2, 2.2 Hz, 1H), 6.17 – 5.85 (m, 2H), 5.68 (dd, J = 10.6, 1.7 Hz, 1H), 4.62 (d, J = 21.2 Hz, 2H), 4.04 – 3.82 (m, 4H), 3.74 (t, J = 5.9 Hz, 2H), 3.37 (s, 2H), 3.12 – 2.66 (m, 11H).

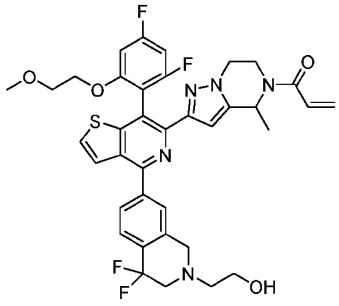
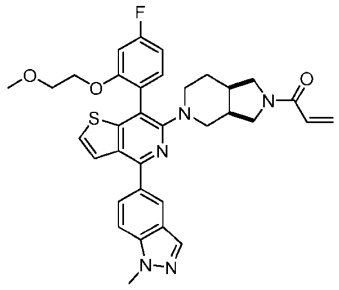
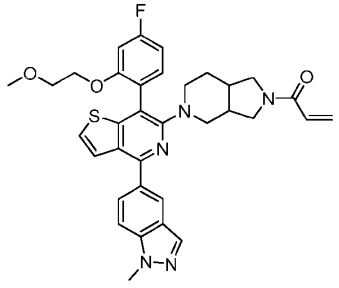
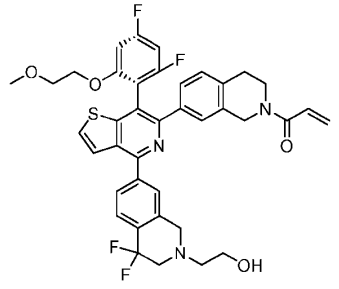
Cmpd. No.	Structure	Analytical data
25a		
26		LCMS m/z [M+1]: 732.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.56 (d, J = 5.6 Hz, 1H), 7.28 (d, J = 7.0 Hz, 1H), 7.17 (t, J = 8.8 Hz, 1H), 7.01 – 6.95 (m, 1H), 6.77 – 6.68 (m, 2H), 6.55 – 6.48 (m, 1H), 6.13 (dd, J = 16.5, 5.6 Hz, 1H), 5.68 (dd, J = 10.6, 1.8 Hz, 1H), 4.63 (d, J = 21.0 Hz, 2H), 3.99 – 3.82 (m, 4H), 3.78 – 3.72 (m, 2H), 3.56 (t, J = 5.3 Hz, 2H), 3.38 (s, 2H), 3.29 (s, 3H), 3.17 (d, J = 12.2 Hz, 2H), 3.02 (d, J = 2.7 Hz, 3H), 2.85 – 2.74 (m, 4H).
26a		
27		LCMS m/z [M+1]: 645.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 5.6 Hz, 1H), 8.00 -7.94 (m, 2H), 7.82 (d, J = 5.6 Hz, 1H), 7.67 - 7.61 (m, 2H), 7.02 - 6.96 (m, 1H), 6.87 - 6.77 (m, 2H), 6.37 - 6.26 (m, 1H), 6.05 (s, 1H), 5.85 - 5.80 (m, 1H), 5.75 - 5.46 (m, 1H), 5.03 - 4.89 (m, 2H), 4.56 - 4.36 (m, 1H), 4.36 – 4.29 (m, 1H), 4.20 - 4.06 (m, 3H), 3.82 (s, 2H),

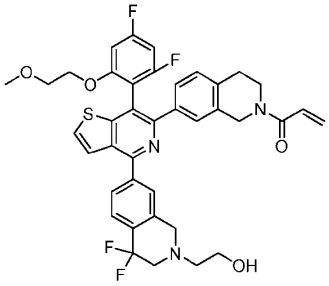
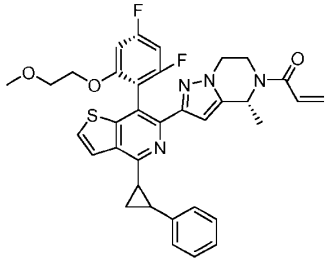
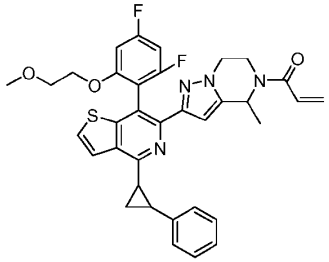
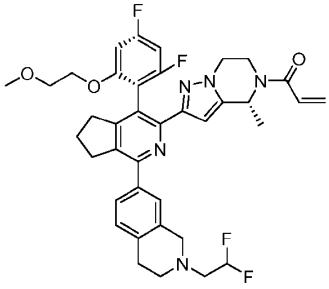
Cmpd. No.	Structure	Analytical data
		3.44 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 1.50 - 1.36 (m, 3H).
27a		
28		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 - 7.75 (m, 2H), 7.56 (d, J = 9.3, 1H), 6.96 - 6.88 (m, 1H), 6.88 - 6.79 (m, 1H), 6.88 - 6.70 (m, 1H), 6.50 (d, J = 9.6, 1H), 6.35 - 6.23 (m, 1H), 5.91 (s, 1H), 5.86 - 5.79 (m, 1H), 5.75 - 5.54 (m, 1H), 5.69 (s, 3H), 4.27 - 4.35 (m, 1H), 4.20 - 4.13 (m, 1H), 4.10 - 4.04 (m, 1H), 3.41 (t, J = 4.4, 2H), 3.14 - 3.07 (m, 2H), 3.04 (s, 3H), 1.50 - 1.34 (m, 3H).
28a		

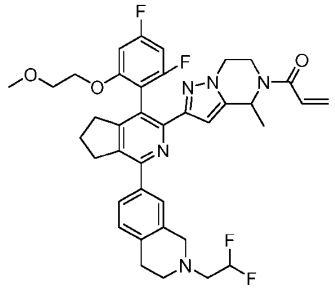
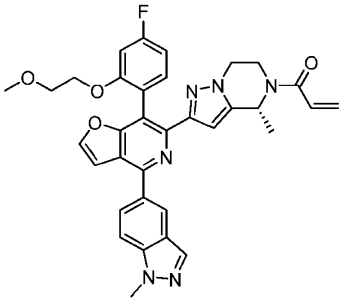
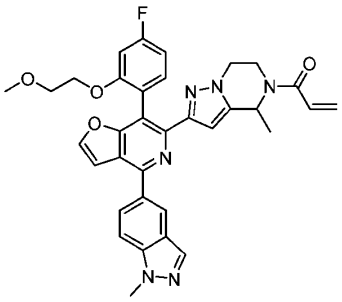
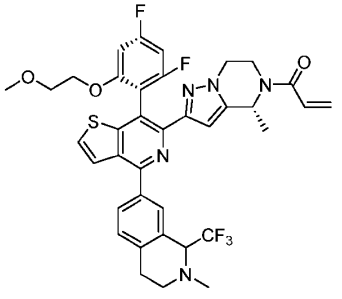
Cmpd. No.	Structure	Analytical data
29		LCMS m/z [M+1]: 612.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.22 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.52 – 7.38 (m, 3H), 7.10 – 7.01 (m, 1H), 6.91 (t, J = 8.2 Hz, 1H), 6.64 – 6.44 (m, 1H), 6.31 – 6.20 (m, 1H), 5.74 (t, J = 11.8 Hz, 1H), 4.31 – 4.05 (m, 5H), 3.67 – 3.35 (m, 10H), 3.20 (d, J = 2.7 Hz, 3H), 2.10 - 1.85 (m, 4H).
30		LCMS m/z [M+1]: 677.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (dd, J = 8.0, 5.8 Hz, 1H), 7.87 (dd, J = 5.7, 3.2 Hz, 1H), 7.04 – 8.02 (m, 3H), 6.29 (d, J = 16.3 Hz, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.77 – 5.41 (m, 2H), 4.45 – 4.35 (m, 1H), 4.27 – 3.96 (m, 7H), 3.88 – 3.75 (m, 3H), 3.47 – 3.38 (m, 4H), 3.06 (d, J = 7.5 Hz, 3H), 2.81 (s, 2H), 2.23-2.15 (m, 3H), 1.47-1.35 (m, 3H).
30a		
31		LCMS m/z [M+1]: 626.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J = 5.2 Hz, 1H), 8.22 (d, J = 3.2 Hz, 1H), 7.94 - 7.87 (m, 1H), 7.87 - 7.80 (m, 1H), 7.55 - 7.37 (m, 3H), 7.09 - 7.02 (m, 1H), 6.95 - 6.85 (m, 1H), 6.80 - 6.54 (m, 1H), 6.23 - 6.09 (m, 1H), 5.79 - 5.59 (m, 1H), 4.31 - 4.21 (m, 1H), 4.18 (s, 3H), 4.16 - 4.07 (m, 1H), 3.73 - 3.66 (m, 1H), 3.65 - 3.35 (m,

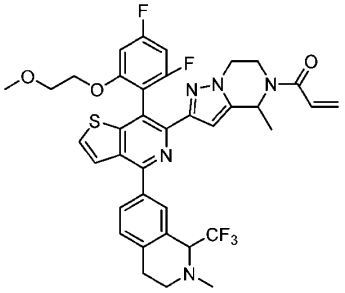
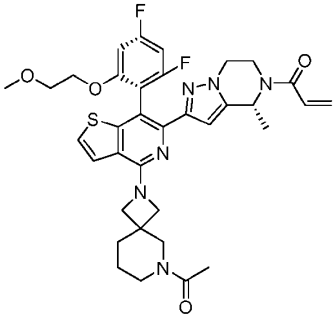
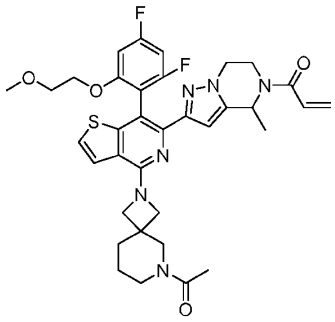
Cmpd. No.	Structure	Analytical data
		7H), 3.36 - 3.33 (m, 1H), 3.23 - 3.08 (m, 4H), 1.93 - 1.50 (m, 6H).
32		LCMS m/z [M+1]: 710.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 - 8.01 (m, 2H), 7.85 (d, J = 5.6 Hz, 1H), 7.67 - 7.63 (m, 1H), 7.61 (d, J = 8.0 Hz, 1H), 6.94 - 6.78 (m, 2H), 6.77 - 6.68 (m, 1H), 6.37 - 6.21 (m, 1H), 6.13 (s, 1H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.76 - 5.42 (m, 2H), 4.59 - 4.28 (m, 1H), 4.26 - 4.17 (m, 1H), 4.16 - 3.94 (m, 3H), 3.70 - 3.60 (m, 1H), 3.60 - 3.50 (m, 1H), 3.43 (dd, J = 8.0, 4.5 Hz, 2H), 3.29 - 3.23 (m, 3H), 3.04 (s, 3H), 1.55 - 1.31 (m, 3H).
32a		
33		LCMS m/z [M+1]: 677.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, J = 5.6 Hz, 1H), 7.44 (d, J = 5.6 Hz, 1H), 6.88 – 6.75 (m, 2H), 6.64 - 6.57 (m 1H), 6.34 – 6.21 (m, 1H), 6.00 (s, 1H), 5.80 (dd, J = 10.6, 1.6 Hz, 1H), 5.72 – 5.36 (m, 1H), 4.26 – 4.13 (m, 5H), 4.10 – 3.93 (m, 3H), 3.66 – 3.52 (m, 4H), 3.41 (t, J = 4.7 Hz, 2H), 3.04 (s, 3H), 2.12 (s, 3H), 1.96 – 1.82 (m, 4H), 1.50 – 1.32 (m, 3H).

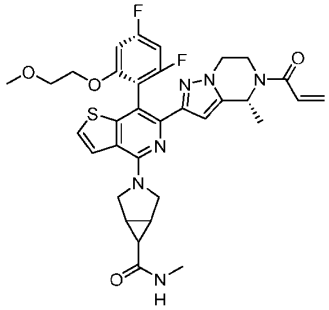
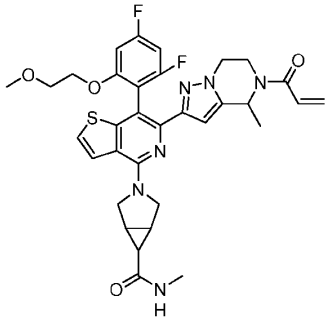
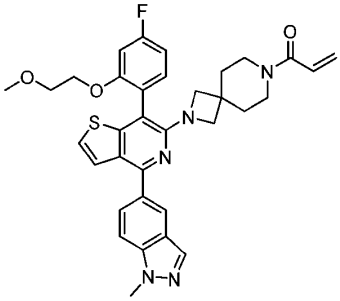
Cmpd. No.	Structure	Analytical data
33a		
34		LCMS m/z [M+1]: 640.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (d, J = 1.2 Hz, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.96 (d, J = 5.6 Hz, 1H), 7.83 – 7.76 (m, 2H), 7.44 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 10.8 Hz, 1H), 6.89 – 6.84 (m, 2H), 6.74 (d, J = 3.1 Hz, 1H), 6.30 (d, J = 15.8 Hz, 1H), 5.99 (s, 1H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.65-5.59 (m, 1H), 4.41 (dd, J = 13.0, 2.9 Hz, 1H), 4.26 – 4.09 (m, 2H), 3.96 (s, 3H), 3.46 (t, J = 4.4 Hz, 2H), 3.36 – 3.30 (m, 5H), 3.11 (d, J = 9.4 Hz, 3H), 1.42 (s, 3H).
34a		
35		LCMS m/z [M+1]: 722.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 8.0 Hz, 1H), 8.02-7.95 (m, 2H), 7.82 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 6.95 - 6.78 (m, 2H), 6.76 - 6.66 (m, 1H), 6.36 - 6.19 (m, 1H), 6.13 (s, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.73 - 5.39(m, 1H), 4.56 (s, 2H), 4.27 - 4.14 (m, 1H), 4.13 - 3.99 (m, 4H), 3.98 - 3.84 (m, 3H), 3.42 (t, J

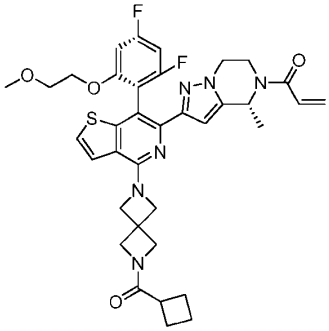
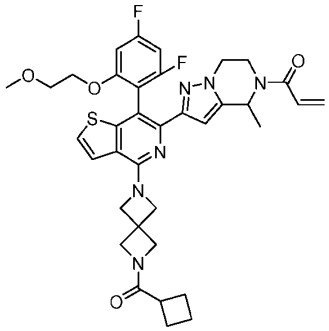
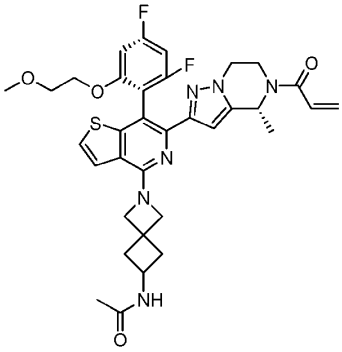
Cmpd. No.	Structure	Analytical data
		= 4.4 Hz, 2H), 3.39 - 3.33 (m, 2H), 3.04 (s, 3H), 1.54 - 1.33 (m, 3H).
35a		
36		LCMS m/z [M+1]: 612.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.12 (s, 1H), 8.01 – 7.95 (m, 1H), 7.71 – 7.65 (m, 1H), 7.59 – 7.52 (m, 1H), 7.43 – 7.23 (m, 2H), 7.08 – 6.95 (m, 1H), 6.91 – 6.77 (m, 1H), 6.60 – 6.36 (m, 1H), 6.32 – 6.19 (m, 1H), 5.81– 5.66 (m, 1H), 4.28 – 4.02 (m, 5H), 3.61 – 3.32 (m, 6H), 3.28 – 3.04 (m, 5H), 3.02 – 2.88 (m, 1H), 2.41 – 2.11 (m, 2H), 1.67 – 1.48 (m, 1H), 1.35 – 1.22 (m, 1H).
36a		
37		LCMS m/z [M+1]: 718.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.55 (d, J = 5.6 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.17 (s, 1H), 7.00 (s, 1H), 6.79 – 6.67 (m, 2H), 6.52 (d, J = 2.1 Hz, 1H), 6.14 (dd, J = 16.7, 7.6 Hz, 1H), 5.68 (dd, J = 10.6, 1.8 Hz, 1H), 4.62 (d, J = 21.1 Hz, 2H), 3.91 (d, J = 34.2

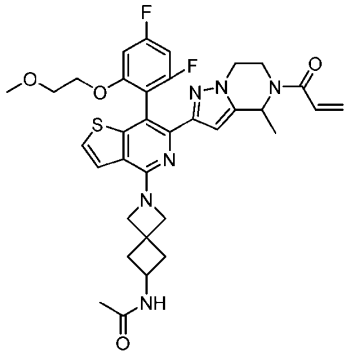
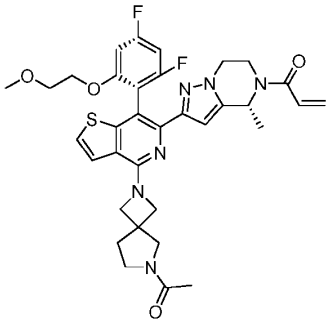
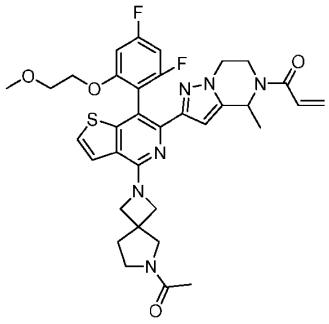
Cmpd. No.	Structure	Analytical data
		Hz, 4H), 3.79 – 3.66 (m, 4H), 3.38 (d, J = 2.7 Hz, 2H), 3.20 – 3.10 (m, 2H), 3.02 (d, J = 2.6 Hz, 3H), 2.83 – 2.72 (m, 4H).
37a		
38		LCMS m/z [M+1]: 627.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.88 – 7.71 (m, 2H), 7.44 – 7.17 (m, 5H), 6.96 – 6.80 (m, 2H), 6.78 – 6.67 (m, 1H), 6.31 (d, J = 16.2 Hz, 1H), 6.12 (d, J = 13.6 Hz, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.62 (d, J = 84.7 Hz, 1H), 4.42 (s, 1H), 4.24 (d, J = 12.4 Hz, 1H), 4.17 – 3.94 (m, 3H), 3.76 (s, 1H), 3.43 (dd, J = 9.1, 4.6 Hz, 2H), 3.05 (s, 3H), 3.00 – 2.88 (m, 2H), 2.25 – 2.10 (m, 1H), 1.80 – 1.70 (m, 1H), 1.43 (s, 3H).
38a		
39		LCMS m/z [M+1]: 690.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.68 (d, J = 7.8 Hz, 1H), 7.62 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 10.8 Hz, 1H), 6.62 (t, J = 8.6 Hz, 1H), 6.33 (s, 1H), 6.21 (s, 1H), 5.82 (s, 1H), 5.73 (d, J = 10.6 Hz, 1H), 4.42 (s, 2H), 4.22 (d, J = 12.8 Hz, 1H), 4.10 – 3.95 (m, 3H), 3.63 – 3.47 (m, 4H), 3.44 (t, J = 4.2 Hz, 2H), 3.19 – 3.15 (m,

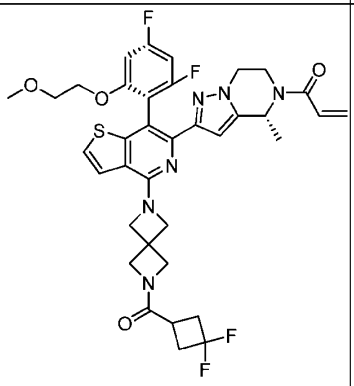
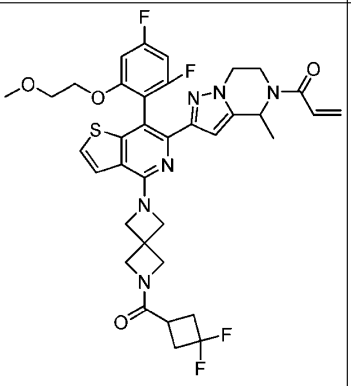
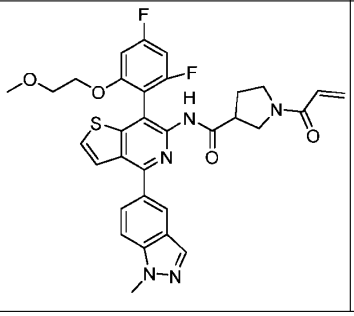
Cmpd. No.	Structure	Analytical data
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39a		
40		LCMS m/z [M+1]: 607.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.29 - 8.23 (m, 1H), 8.16 (s, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.35 - 7.20 (m, 2H), 6.96 - 6.75 (m, 3H), 6.40 - 6.21 (m, 1H), 5.94 (d, J = 12.0 Hz, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.73-5.35 (m, 1H), 4.29 - 4.20 (m, 1H), 4.20 - 3.98 (m, 5H), 3.95 - 3.81 (m, 1H), 3.44 (t, J = 5.0 Hz, 2H), 3.12 (d, J = 7.6 Hz, 3H), 1.55 - 1.37 (m, 3H).
40a		
41		LCMS m/z [M+1]: 724.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 - 7.82 (m, 3H), 7.74 (dd, J = 1.24, 5.6 Hz, 1H), 7.60 - 7.51 (m, 1H), 6.97 (d, J = 10.6 Hz, 1H), 6.91 - 6.74 (m, 2H), 6.36 - 6.23 (m, 1H), 6.11 - 5.92 (m, 1H), 5.89 - 5.79 (m, 1H), 5.78 - 5.35 (m, 1H), 4.81 - 4.61 (m, 1H), 4.59 - 4.35 (m, 1H), 4.33 - 4.20 (m, 1H), 4.19 - 3.95 (m, 3H), 3.89 - 3.61 (m,

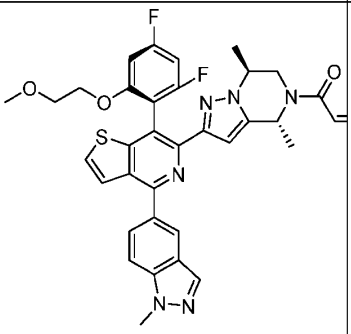
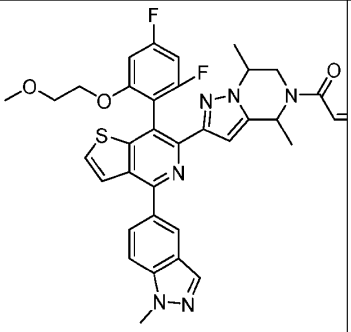
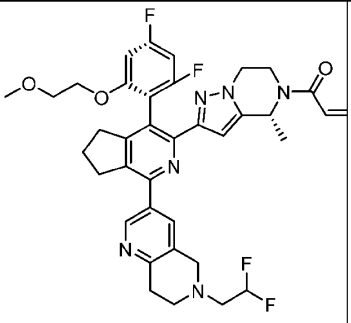
Cmpd. No.	Structure	Analytical data
		1H), 3.49 - 3.36 (m, 3H), 3.15 - 3.00 (m, 5H), 2.94 - 2.81 (m, 1H), 2.78 (s, 2H), 2.74 - 2.65(m, 1H), 1.53 - 1.34 (m, 3H).
41a		
42		LCMS m/z [M+1]: 677.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 - 7.79 (m, 2H), 6.98 (d, J = 10.8 Hz, 1H), 6.87 - 6.73 (m, 2H), 6.29 (d, J = 16.8 Hz, 1H), 5.87 - 5.80 (m, 1H), 5.77 - 5.67 (m, 1H), 4.60 - 4.30 (m, 5H), 4.22 - 4.04 (m, 3H), 3.92 - 3.78 (m, 2H), 3.62 - 3.50 (m, 2H), 3.46 - 3.40 (m, 2H), 3.14 - 3.04 (m, 3H), 2.21 (s, 1H), 2.17 (s, 2H), 2.10 - 2.02 (m, 2H), 1.79 - 1.62 (m, 2H), 1.48 - 1.31 (m, 3H).
42a		

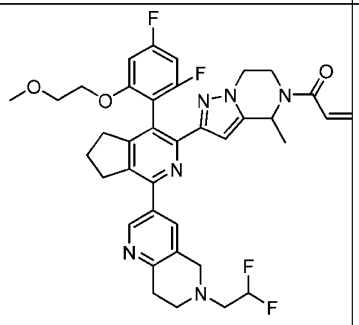
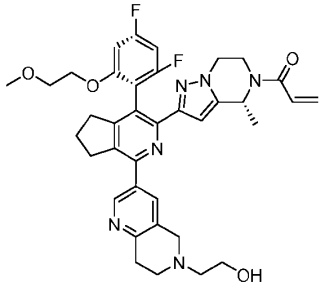
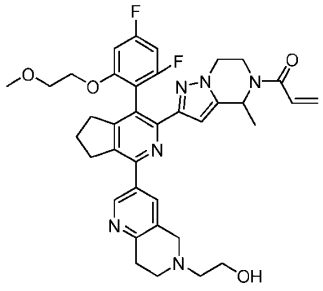
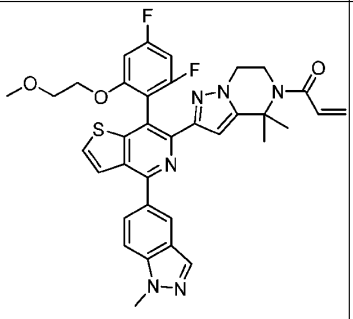
Cmpd. No.	Structure	Analytical data
43		LCMS m/z [M+1]: 649.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 2.4 Hz, 1H), 7.88 (d, J = 2.6 Hz, 1H), 7.02 (d, J = 10.0 Hz, 1H), 6.85 (t, J = 8.8 Hz, 2H), 6.29 (d, J = 16.4 Hz, 1H), 5.83 (d, J = 10.2 Hz, 1H), 5.73 - 5.42 (m, 2H), 5.41 - 5.36 (m, 5H), 4.20 - 4.11 (m, 3H), 3.48 - 3.41 (m, 3H), 3.05 (s, 3H), 2.76 (s, 1H), 2.47 (s, 2H), 1.63 - 1.62 (m, 1H), 1.42 - 1.39 (m, 3H).
43a		
44		LCMS m/z [M+1]: 612.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.11 (s, 1H), 7.98 (dd, J = 8.7, 1.3 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 5.6 Hz, 1H), 7.33 (dd, J = 8.2, 6.9 Hz, 1H), 7.20 (d, J = 5.6 Hz, 1H), 6.97 (dd, J = 11.1, 2.4 Hz, 1H), 6.81 (td, J = 8.3, 2.4 Hz, 1H), 6.72 - 6.68 (m, 1H), 6.14 (dd, J = 16.8, 2.0 Hz, 1H), 5.69 (dd, J = 10.7, 1.9 Hz, 1H), 4.23 – 4.03 (m, 5H), 3.66 – 3.40 (m, 10H), 3.17 (s, 3H), 1.72 - 1.68 (m, 4H).

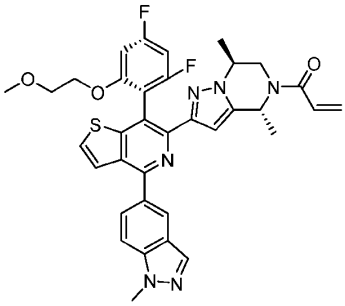
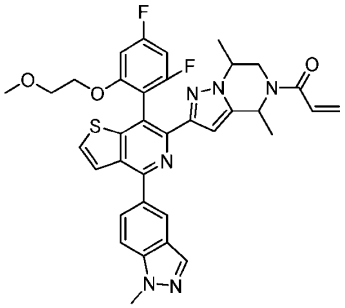
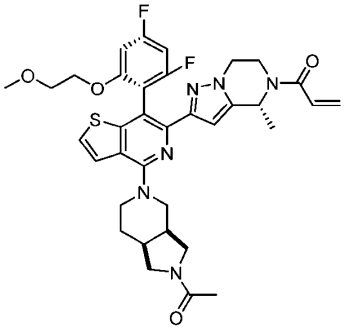
Cmpd. No.	Structure	Analytical data
45		LCMS m/z [M+1]: 689.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 5.6 Hz, 1H), 6.97 (d, J = 10.8 Hz, 1H), 6.87 - 6.71 (m, 2H), 6.78 (d, J = 2.0 Hz, 1H), 5.83 (dd, J = 10.4, 1.6 Hz, 1H), 5.73 (s, 1H), 5.70 -5.41 (m, 1H), 4.95 (s, 5H), 4.51 (s, 2H), 4.36 (dd, J = 13.0, 2.9 Hz, 1H), 4.30 (s, 2H), 4.18 – 4.05 (m, 2H), 3.46 – 3.38 (m, 2H), 3.28 - 3.19 (m, 1H), 3.07 (s, 3H), 2.32 -2.11 (m, 4H), 2.09 - 1.83 (m, 2H), 1.52 - 1.28 (m, 3H).
45a		
46		LCMS m/z [M+1]: 663.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (d, J = 5.6 Hz, 1H), 7.50 (d, J = 5.6 Hz, 1H), 6.91 - 6.75 (m, 2H), 6.68 - 6.56 (m, 1H), 6.35 - 6.17 (m, 1H), 5.95 (s, 1H), 5.81 (dd, J = 10.6, 1.8 Hz, 1H), 5.73 - 5.35 (m, 1H), 4.58 - 4.49 (m, 2H), 4.46 - 4.34 (m, 2H), 4.31 - 4.13 (m, 2H), 4.10 - 3.87 (m, 3H), 3.41 (t, J = 4.8 Hz, 2H), 3.04 (s, 3H), 2.72 - 2.61 (m, 2H), 2.31 - 2.19 (m, 2H), 1.92 (s, 3H), 1.49 - 1.31 (m, 3H).

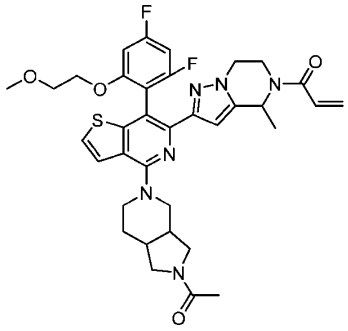
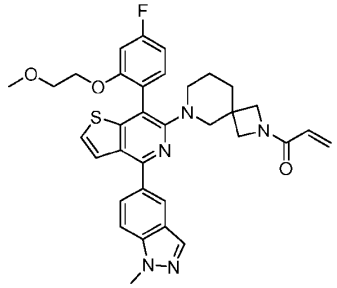
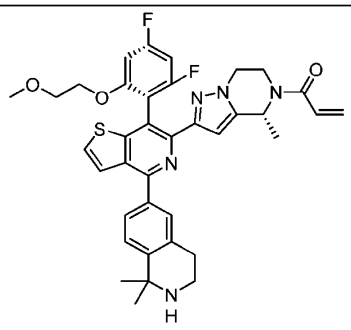
Cmpd. No.	Structure	Analytical data
46a		
47		LCMS m/z [M+1]: 663.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 - 7.86 (m, 1H), 7.85 - 7.78(m, 1H), 6.97 (d, J = 10.8 Hz, 1H), 6.89 - 6.72 (m, 2H), 6.28 (d, J = 16.4 Hz, 1H), 5.82 (dd, J = 10.4, 1.6 Hz, 1H), 5.72 (s, 1H), 5.70-5.41 (m, 1H), 4.82 - 4.64 (m, 4H), 4.39 - 4.31 (m, 1H), 4.15 - 4.02 (m, 2H), 3.89 (s, 1H), 3.79 (s, 1H), 3.68 (t, J = 7.0 Hz, 1H), 3.57 (t, J = 7.0 Hz, 1H), 3.45 - 3.39 (m, 2H), 3.08 (s, 3H), 2.43 (t, J = 6.8 Hz, 1H), 2.34 (t, J = 7.0 Hz, 1H), 2.09 (d, J = 4.0 Hz, 3H), 1.51 - 1.28 (m, 3H).
47a		

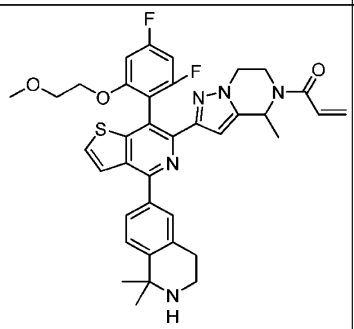
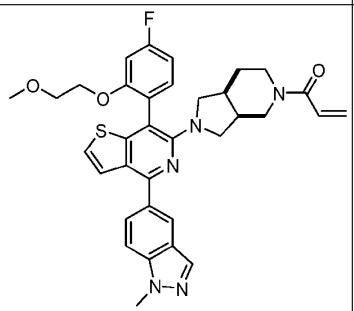
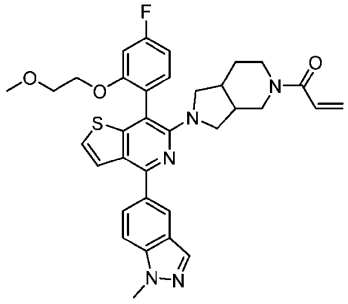
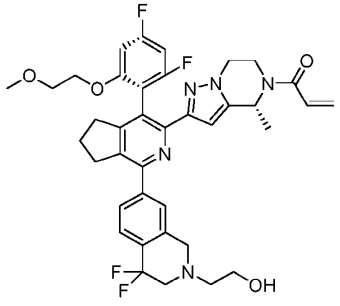
Cmpd. No.	Structure	Analytical data
48		LCMS m/z [M+1]: 725.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 5.6 Hz, 1H), 6.97 (d, J = 10.8 Hz, 1H), 6.79 (t, J = 9.1 Hz, 2H), 6.29 (d, J = 16.6 Hz, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.73 (s, 1H), 5.68 - 5.49 (m, 1H), 4.96 (s, 4H), 4.51 (s, 2H), 4.36 (dd, J = 13.0, 2.9 Hz, 1H), 4.30 (s, 2H), 4.18 – 4.05 (m, 3H), 3.46 – 3.38 (m, 2H), 3.08 (s, 3H), 3.01-2.98 (m, 1H), 2.80 -2.76 (m, 4H), 1.52 - 1.36 (m, 3H).
48a		
49		LCMS m/z [M+1]: 618.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.16 (s, 1H), 7.97 (dd, J = 8.8, 1.4 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.68 (d, J = 5.6 Hz, 1H), 6.94 – 6.72 (m, 2H), 6.61 – 6.44 (m, 1H), 6.25 (ddd, J = 16.8, 5.5, 1.9 Hz, 1H), 5.72 (dd, J = 10.5, 1.9 Hz, 1H), 4.26 – 4.05 (m, 5H), 3.78 – 3.41 (m, 6H), 3.25 – 3.10(m, 4H), 2.20 – 1.95 (m, 2H).

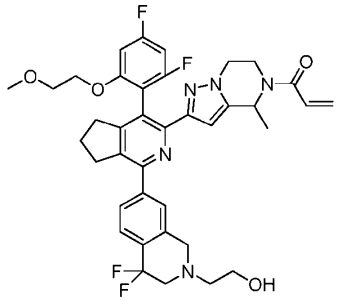
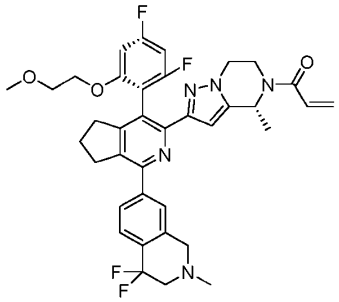
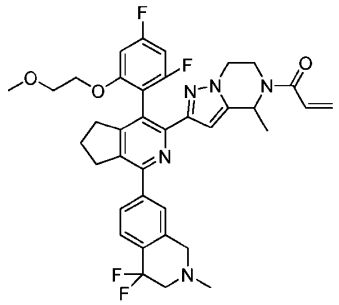
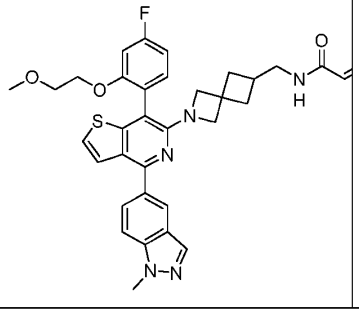
Cmpd. No.	Structure	Analytical data
50		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.27 (s, 1H), 8.08 (d, J = 5.6 Hz, 1H), 8.05 (dd, J = 8.8, 1.6 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 5.6 Hz, 1H), 6.96 (d, J = 10.4 Hz, 1H), 6.81 - 6.91 (m, 2H), 6.34 (d, J = 16.4 Hz, 1H), 6.15 (s, 1H), 5.85 (dd, J = 10.6, 1.6 Hz, 1H), 5.80 - 5.48 (m, 1H), 4.64 - 4.52 (m, 1H), 4.20 (s, 3H), 4.16 - 4.09 (m, 1H), 4.05 - 3.98 (m, 1H), 3.45 (t, J = 4.4 Hz, 2H), 3.10 (s, 3H), 1.54 - 1.39 (m, 3H), 1.34 (d, J = 6.4 Hz, 3H).
50a		
51		LCMS m/z [M+1]: 691.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (d, J = 1.9 Hz, 1H), 8.00 (s, 1H), 6.79 – 6.65 (m, 2H), 6.50 (t, J = 9.2, 2.3 Hz, 1H), 6.23 – 5.82 (m, 3H), 5.76 – 5.68 (m, 1H), 5.46 (d, J = 82.5 Hz, 1H), 4.29 (s, 1H), 4.14 – 3.77 (m, 6H), 3.64 (s, 1H), 3.42 (t, J = 4.5 Hz, 2H), 3.17 – 3.05 (m, 5H), 3.05 – 2.85 (m, 6H), 2.82 – 2.70 (m, 1H), 2.67 – 2.55 (m, 1H), 2.08 – 1.94 (m, 2H), 1.29 (s, 3H).

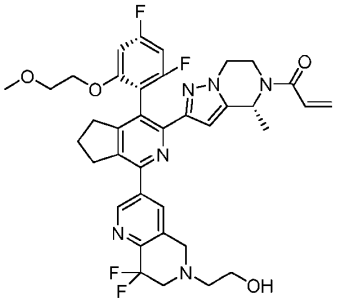
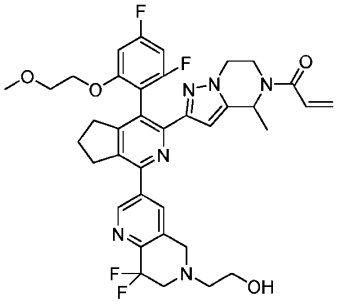
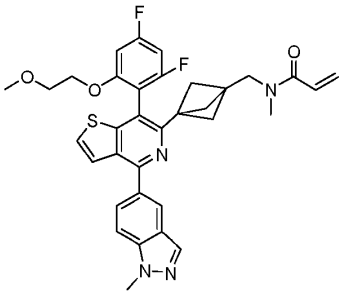
Cmpd. No.	Structure	Analytical data
51a		
52		LCMS m/z [M+1]: 671.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.21 (s, 1H), 6.74 (d, J = 10.3 Hz, 2H), 6.55 (t, J = 9.0 Hz, 1H), 6.19 (d, J = 17.0 Hz, 1H), 5.87 (s, 1H), 5.72 (d, J = 10.5 Hz, 1H), 5.48 (d, J = 72.9 Hz, 1H), 4.64 (s, 2H), 4.34 (s, 1H), 4.19 – 3.86 (m, 6H), 3.81 – 3.53 (m, 3H), 3.50 – 3.28 (m, 6H), 3.19 – 3.03 (m, 5H), 2.85 (dd, J = 16.4, 8.4 Hz, 1H), 2.69 (dd, J = 15.8, 8.6 Hz, 1H), 2.16 – 1.99 (m, 2H), 1.29 (s, 3H).
52a		
53		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.17 (s, 1H), 8.11 - 8.06 (m, 1H), 7.80 - 7.67 (m, 3H), 6.90 - 6.82 (m, 1H), 6.80 - 6.66 (m, 2H), 6.17 (s, 1H), 6.11 (dd, J = 16.6, 1.6 Hz, 1H), 5.71 (dd, J = 10.6, 1.6 Hz, 1H), 4.20 (t, J = 4.8 Hz, 2H), 4.16 (s, 3H), 4.12-4.05 (m, 1H), 4.01 - 3.94 (m, 1H), 3.93 - 3.87 (m, 2H), 3.44 (t, J = 4.8 Hz, 2H), 3.07 (s, 3H), 1.77 (s, 3H), 1.75 (s, 3H).

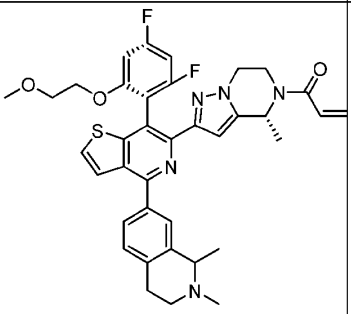
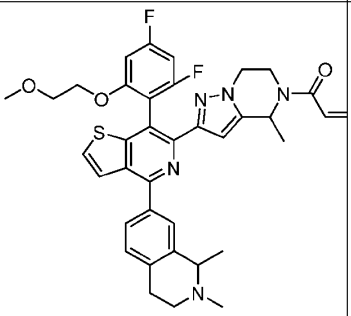
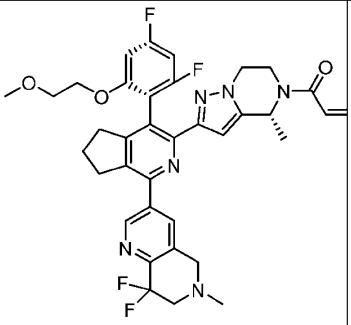
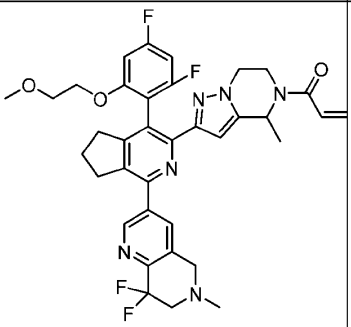
Cmpd. No.	Structure	Analytical data
54		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.16 (d, J = 0.6 Hz, 1H), 8.07 (dd, J = 8.7, 1.4 Hz, 1H), 7.80 - 7.67 (m, 3H), 6.94 - 6.78 (m, 2H), 6.71 - 6.62 (m, 1H), 6.31 (d, J = 16.5 Hz, 1H), 6.27 - 6.18 (m, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.78 - 5.43 (m, 1H), 4.46 - 4.36 (m, 1H), 4.16 (s, 3H), 4.13 - 4.07 (m, 1H), 4.06 - 3.99 (m, 1H), 3.45 (t, J = 4.8 Hz, 2H), 3.05 (s, 3H), 1.54 - 1.37 (m, 3H), 1.34 - 1.21 (m, 3H).
54a		
55		LCMS m/z [M+1]: 677.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.81-7.67 (m, 2H), 6.95 - 6.78 (m, 2H), 6.77 - 6.66 (m, 1H), 6.34 - 6.19 (m, 1H), 5.95 - 5.87 (m, 1H), 5.85 - 5.77 (m, 1H), 5.72 - 5.41 (m, 1H), 4.54 - 4.31 (m, 1H), 4.31 - 4.21 (m, 1H), 4.21 – 3.97 (m, 4H), 3.95 – 3.81 (m, 2H), 3.78 - 3.72 (m, 1H), 3.69 – 3.46 (m, 4H), 3.44 - 3.37 (m, 2H), 3.08 - 3.00 (m, 3H), 2.82 – 2.56 (m, 2H), 2.15 - 2.01 (m, 4H), 1.96 - 1.82 (m, 1H), 1.51 - 1.32 (m, 3H).

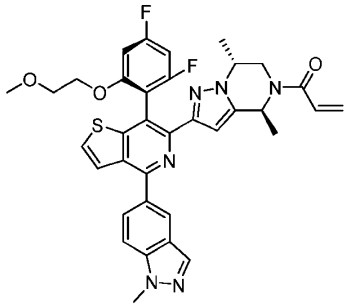
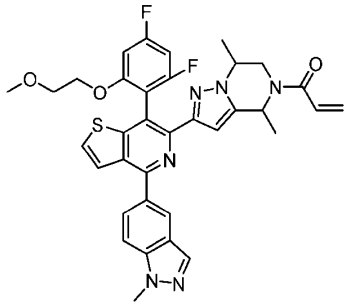
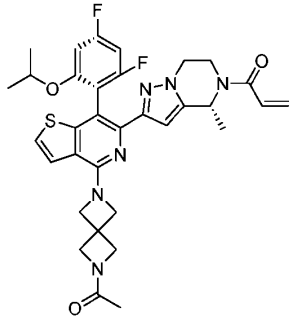
Cmpd. No.	Structure	Analytical data
55a		
56		LCMS m/z [M+1]: 612.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.22 (s, 1H), 7.99-7.90 (m, 1H), 7.85-7.82 (m, 1H), 7.73-7.70 (m, 1H), 7.64-7.62 (m, 1H), 7.44-7.34 (m, 1H), 7.14-7.08 (m, 1H), 6.99-6.92 (m, 1H), 6.26-6.22 (m, 2H), 5.75-5.71 (m, 1H), 4.28-4.11 (m, 5H), 3.87-3.80 (m, 1H), 3.75-3.45 (m, 5H), 3.28-3.10 (m, 6H), 1.85-1.62 (m, 2H), 1.60-1.35 (m, 2H).
57		LCMS m/z [M+1]: 670.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (d, J = 8.0 Hz, 1H), 7.90-7.88 (m, 2H), 7.72-7.66 (m, 2H), 6.92 (d, J = 10.8 Hz, 1H), 6.84-6.77 (m, 1H), 6.74 (t, J = 9.2 Hz, 1H), 6.35-6.25 (m, 1H), 6.11 (s, 1H), 5.82 (dd, J = 10.8 Hz, 1.6 Hz, 1H), 5.80-5.45 (m, 1H), 4.30-4.20 (m, 1H), 4.20-4.00 (m, 3H), 3.64 (t, J = 6.4 Hz, 2H), 3.43 (t, J = 4.4 Hz, 2H), 3.35-3.30 (m, 1H), 3.05 (s, 3H), 1.85 (s, 6H), 1.55-1.35 (m, 3H).

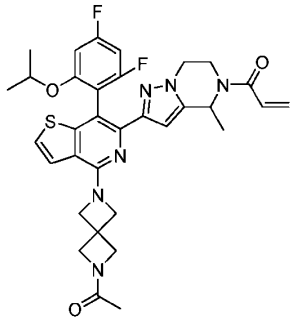
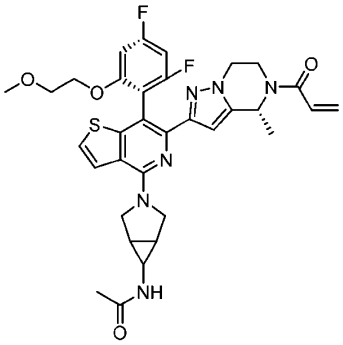
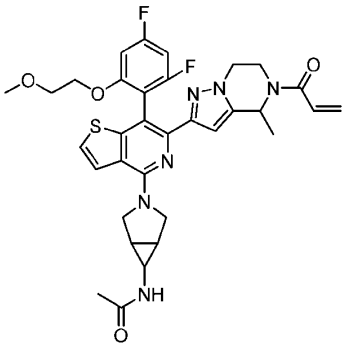
Cmpd. No.	Structure	Analytical data
57a		
58		LCMS m/z [M+1]: 612.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.12 (s, 1H), 8.01 (dd, J = 8.8, 1.5 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.51 – 7.10 (m, 3H), 7.02 – 6.43 (m, 3H), 6.07 – 6. 26 (m, 1H), 5.79 – 5. 65 (m, 1H), 4.35 – 4. 00 (m, 5H), 3.93 – 3. 40 (m, 5H), 3.27 – 2.82 (m, 5H), 2.36 (s, 1H), 1.83 – 1.42 (m, 2H).
58a		
59		LCMS m/z [M+1]: 706.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (q, J = 8.2 Hz, 2H), 7.95 (s, 1H), 6.93 (d, J = 10.8 Hz, 2H), 6.73 (td, J = 9.3, 2.0 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 5.96 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.60 (d, J = 84.3 Hz, 1H), 4.67 (s, 2H), 4.32 (dd, J = 12.8, 2.8 Hz, 2H), 4.24 – 4.15 (m, 2H), 4.14 – 4.05 (m, 3H), 4.04 – 3.97 (m, 2H), 3.79 (s, 1H), 3.57 (t, J = 4.4 Hz, 2H), 3.46 (s, 2H), 3.31 – 3.19 (m, 5H), 3.15 – 3.04 (m, 1H), 2.92 (d, J = 7.5 Hz, 1H), 2.31 – 2.17 (m, 2H), 1.41 (s, 3H).

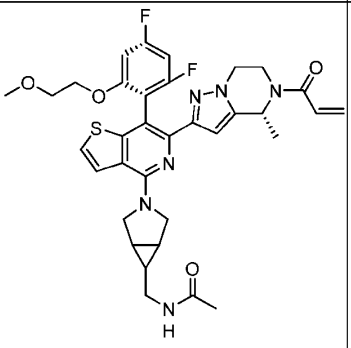
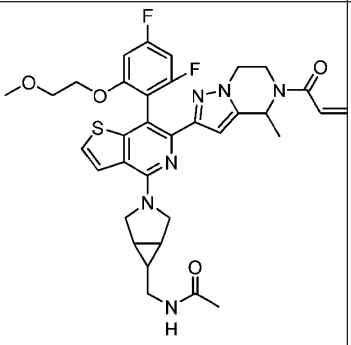
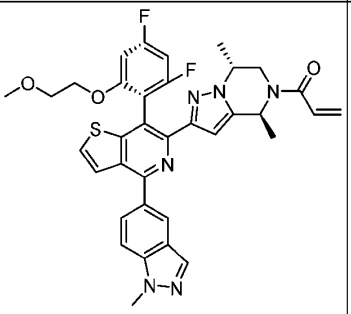
Cmpd. No.	Structure	Analytical data
59a		
60		LCMS m/z [M+1]: 676.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (d, J = 7.6 Hz, 1H), 8.02 – 7.92 (m, 2H), 6.89 (d, J = 10.7 Hz, 2H), 6.69 (td, J = 9.3, 2.1 Hz, 1H), 6.31 (d, J = 15.4 Hz, 1H), 5.97 (s, 1H), 5.85 (dd, J = 10.6, 1.6 Hz, 1H), 5.59 (d, J = 84.8 Hz, 1H), 4.82 – 4.36 (m, 3H), 4.27 (dd, J = 12.7, 2.7 Hz, 1H), 4.22 – 4.08 (m, 2H), 4.07 – 3.89 (m, 3H), 3.79 (s, 1H), 3.56 (t, J = 4.4 Hz, 2H), 3.30 – 3.18 (m, 5H), 3.12 – 2.96 (m, 4H), 2.86 (s, 1H), 2.27 – 2.14 (m, 2H), 1.41 (s, 3H).
60a		
61		LCMS m/z [M+1]: 612.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s , 1H), 8.22 (s, 1 H), 7.89 - 7.80 (m, 2H), 7.50 - 7.42 (m, 2H), 7.34 (d, J = 5.6, 1 H), 7.08 (dd, J = 10.8, 2.4, 1H), 6.95 - 6.87 (m, 1H), 6.21 - 6.13 (m, 2H), 5.67 - 5.61 (m, 1H), 4.35 - 4.24 (m, 1H), 4.15-4.21 (m, 4H), 3.91-4.07 (m, 4H), 3.58-3.64 (m, 2H), 3.23 (s, 3H), 3.17-3.22 (m, 2H),

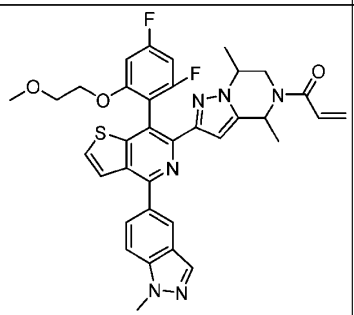
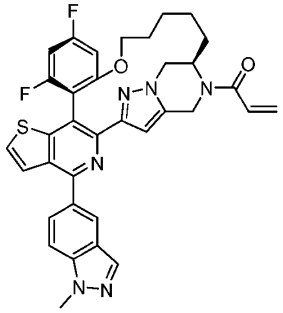
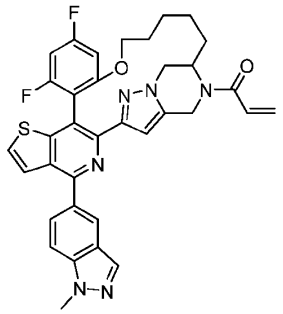
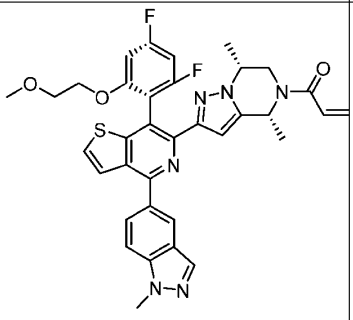
Cmpd. No.	Structure	Analytical data
		2.23-2.36 (m, 3H), 1.87-1.95 (m, 2H), 1.37-1.34 (m, 1H).
62		LCMS m/z [M+1]: 707.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.19 (d, J = 8.0 Hz, 1H), 8.40 (s, 1H), 6.86 (t, J = 12.6 Hz, 2H), 6.68 (td, J = 9.3, 2.2 Hz, 1H), 6.31 (d, J = 16.2 Hz, 1H), 5.98 (d, J = 24.7 Hz, 1H), 5.85 (dd, J = 10.6, 1.6 Hz, 1H), 5.59 (d, J = 89.8 Hz, 1H), 4.93 (s, 3H), 4.47 (s, 2H), 4.24 (d, J = 9.5 Hz, 1H), 4.21 – 4.12 (m, 1H), 4.07 (dd, J = 10.9, 4.2 Hz, 1H), 4.02 – 3.90 (m, 4H), 3.77 (s, 1H), 3.55 (t, J = 4.4 Hz, 2H), 3.29 (t, J = 6.8 Hz, 3H), 3.24 (s, 3H), 3.07 – 2.92 (m, 1H), 2.90 – 2.77 (m, 1H), 2.22 (p, J = 7.3 Hz, 2H), 1.40 (s, 3H).
62a		
63		LCMS m/z [M+1]: 615.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 8.14 (s, 1H), 7.97 (dd, J = 8.8 Hz, 1.4 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.66 - 7.58 (m, 2H), 6.93 - 6.86 (m, 1H), 6.80 - 6.71 (m, 1H), 6.71 - 6.59 (m, 1H), 6.27 - 6.13 (m, 1H), 5.77 - 5.64 (m, 1H), 4.14 (s, 3H), 4.12 - 4.05 (m, 1H), 3.54 (s, 1H), 3.51 - 3.45 (m, 2H), 3.10 (s, 1H), 3.06 - 3.01 (m, 3H), 2.96 (s, 2H), 1.92 (d, J = 4.8 Hz, 6H), 1.32 - 1.26 (m, 4H), 0.92 - 0.85 (m, 1H).

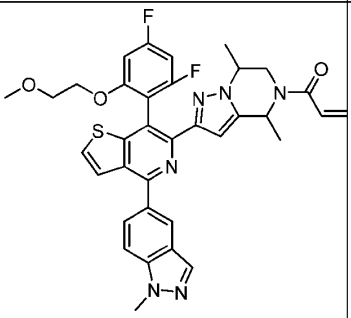
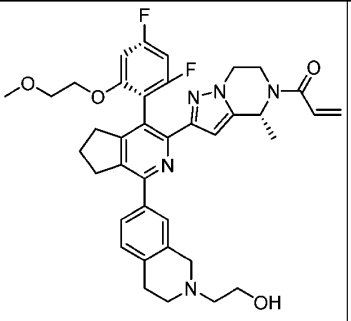
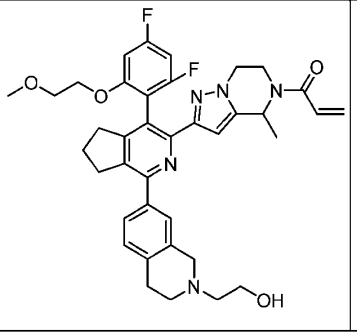
Cmpd. No.	Structure	Analytical data
64		LCMS m/z [M+1]: 670.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99-7.90 (d, J = 7.2 Hz, 2H), 7.83 (d, J = 5.6 Hz, 1H), 7.67 (dd, J = 5.6, 2.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 6.94 - 6.79 (m, 2H), 6.76 - 6.68 (m, 1H), 6.37 - 6.23 (m, 1H), 6.10 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.77 - 5.56 (m, 1H), 4.79 - 4.58 (m, 1H), 4.28 - 4.18 (m, 1H), 4.16 - 3.99 (m, 3H), 3.95 - 3.64 (m, 2H), 3.43 (dd, J = 7.6, 4.8 Hz, 2H), 3.15 - 2.95 (m, 6H), 1.90 - 1.69 (m, 3H), 1.52 - 1.34 (m, 3H).
64a		
65		LCMS m/z [M+1]: 677.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (s, 1H), 8.33 (s, 1H), 8.00 – 7.40 (m, 2H), 6.73 (d, J = 76.8 Hz, 2H), 6.32 (s, 1H), 5.85 – 5.30 (m, 1H), 5.94 – 5.34 (m, 2H), 4.72 – 4.25 (m, 1H), 4.20 – 3.60 (m, 5H), 3.53 (s, 2H), 3.30 – 2.41 (m, 6H), 3.01 – 2.45 (m, 4H), 2.10 (d, J = 55.5 Hz, 2H), 1.60 – 0.95(m, 6H).
65a		

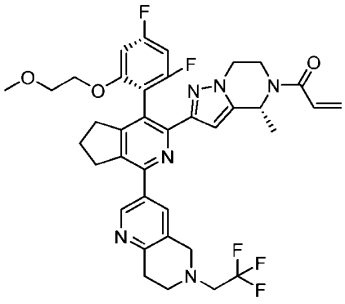
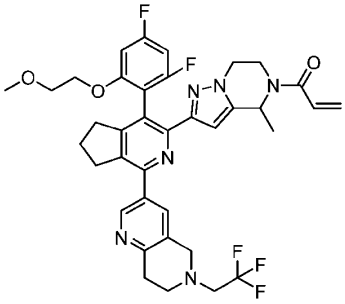
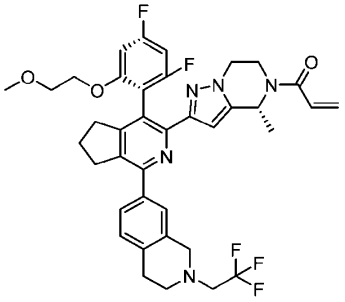
Cmpd. No.	Structure	Analytical data
66		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.16 (s, 1H), 8.09 - 8.05 (m, H), 7.77 - 7.67 (m, 3H), 6.92 - 6.82 (m, 2H), 6.71 - 6.62 (m, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.24 (s, 1H), 5.87 - 5.81(m, 1H), 5.76 - 5.51 (m, 1H), 4.76 - 4.50 (m, 1H), 4.44 - 4.36 (m, 1H), 4.27 - 4.18(m, 1H), 4.15 (s, 3H), 4.13 - 4.07 (m, 1H), 4.06 - 4.00 (m, 1H), 3.45 (t, J = 4.8 Hz, 2H), 3.05 (s, 3H), 1.52 - 1.38 (m, 3H), 1.34 - 1.23 (m, 3H).
66a		
67		LCMS m/z [M+1]: 633.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, J = 5.6 Hz, 1H), 7.46 (d, J = 5.6 Hz, 1H), 6.90 – 6.77 (m, 1H), 6.70 (d, J = 11.1 Hz, 1H), 6.60 – 6.53 (m, 1H), 6.27 (d, J = 17.6 Hz, 1H), 5.94 (s, 1H), 5.81 (dd, J = 10.6, 1.5 Hz, 1H), 5.71 – 5.37 (m, 1H), 4.57 (s, 4H), 4.52 – 4.43 (m, 3H), 4.22 (s, 2H), 4.20 – 4.14 (m, 1H), 4.11 – 3.67 (m, 1H), 1.89 (s, 3H), 1.50 – 1.25 (m, 5H), 1.07 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 6.0 Hz, 3H).

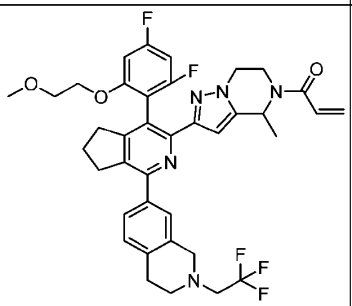
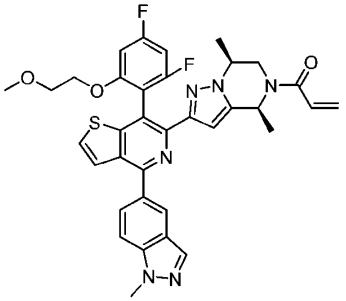
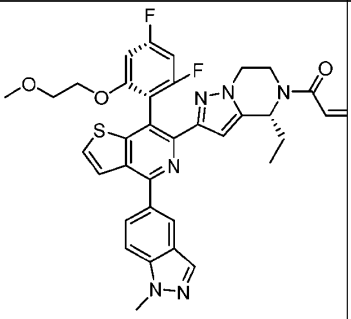
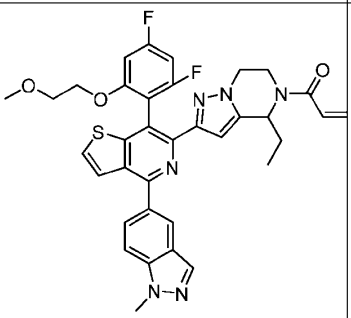
Cmpd. No.	Structure	Analytical data
67a		
68		LCMS m/z [M+1]: 649.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, J = 5.7 Hz, 1H), 7.39 (d, J = 5.7 Hz, 1H), 6.91 – 6.69 (m, 2H), 6.60 (td, J = 9.1, 2.3 Hz, 1H), 6.29 - 6.25 (m, 1H), 6.12 - 6.08 (m, 1H), 5.81 (d, J = 10.7 Hz, 1H), 5.68 - 5.46 (m, 1H), 4.58 (s, 1H), 4.39 (dd, J = 10.6, 5.0 Hz, 2H), 4.13 (dd, J = 12.7, 2.8 Hz, 1H), 4.08-3.82 (m, 5H), 3.40 (t, J = 4.7 Hz, 2H), 3.03 (s, 3H), 2.51 (s, 1H), 1.92-1.82 (m, 5H), 1.42 - 1.36 (m, 3H).
68a		

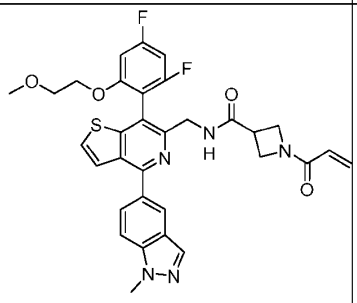
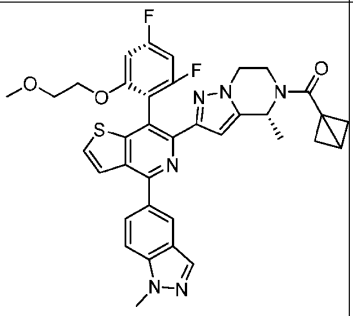
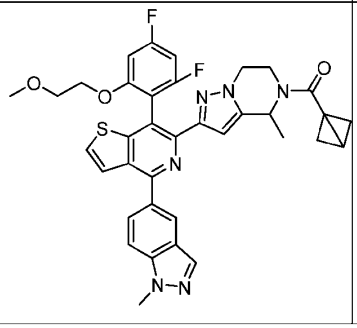
Cmpd. No.	Structure	Analytical data
69		LCMS m/z [M+1]: 663.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, J = 5.8 Hz, 1H), 7.85 (d, J = 5.8 Hz, 1H), 7.01 (d, J = 10.8 Hz, 1H), 6.85 (dd, J = 9.0, 2.0 Hz, 2H), 6.29 (d, J = 16.8 Hz, 1H), 5.82 (dd, J = 10.6, 1.8 Hz, 1H), 5.58 (s, 1H), 5.67 - 5.48 (m, 1H), 4.41-4.37 (m, 1H), 4.27 (s, 4H), 4.10 (t, J = 4.2 Hz, 3H), 3.40 (t, J = 4.4 Hz, 2H), 3.21 (d, J = 6.8 Hz, 2H), 3.04 (s, 3H), 2.03 (s, 2H), 1.96 (s, 3H), 1.38 - 1.33 (m, 3H), 1.09 - 1.06 (m, 1H).
69a		
70		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.15 (s, 1H), 8.05 (dd, J = 8.7, 1.3 Hz, 1H), 7.78 – 7.64 (m, 3H), 6.94 – 6.68 (m, 3H), 6.36 – 6.26 (m, 2H), 5.82 (dd, J = 10.5, 1.2 Hz, 1H), 5.78 – 5.43 (m, 1H), 4.38 (s, 1H), 4.31 – 4.08 (m, 4H), 4.07 – 3.73 (m, 3H), 3.39 (t, J = 1.2 Hz, 2H), 3.02 (s, 3H), 1.55 – 1.39 (m, 3H), 1.27 – 1.18 (m, 3H).

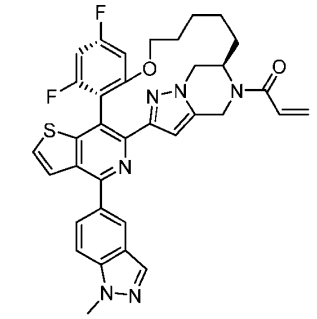
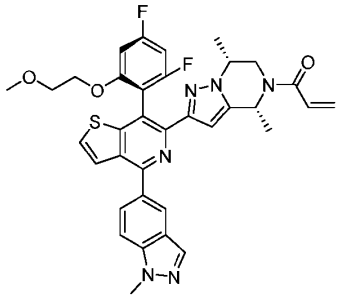
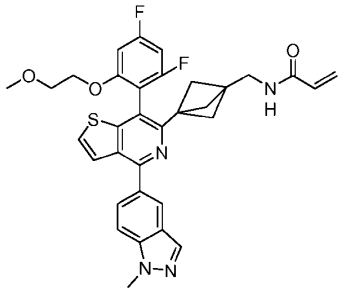
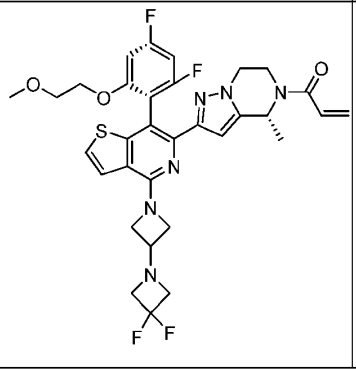
Cmpd. No.	Structure	Analytical data
70a		
71		LCMS m/z [M+1]: 637.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 8.19 – 8.12 (m, 2H), 7.79 – 7.70 (m, 3H), 6.90 – 6.67 (m, 3H), 6.35 – 6.26 (m, 1H), 5.84 – 5.78 (m, 2H), 5.08 – 4.93 (m, 1H), 4.83 – 4.73 (m, 1H), 4.68 – 4.49 (m, 2H), 4.44 – 4.30 (m, 1H), 4.16 (s, 3H), 4.12 – 4.04 (m, 1H), 3.83 – 3.73 (m, 1H), 1.69 – 1.49 (m, 2H), 1.29 – 0.95 (m, 6H).
71a		
72		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.26 (s, 1H), 8.09 (d, J = 5.6 Hz, 1H), 8.03 (dd, J = 8.8, 1.6 Hz, 1H), 7.92 – 7. 83 (m, 2H), 6.98 (d, J = 10.7 Hz, 1H), 6.92 – 6. 74 (m, 2H), 6.36 – 6. 18 (m, 2H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.79 – 5. 45 (m, 1H), 4.51 – 3.96 (m, 6H), 3.45 (t, J = 4.5 Hz, 2H), 3.09 (s, 3H), 1.60 – 1. 39 (m, 6H).

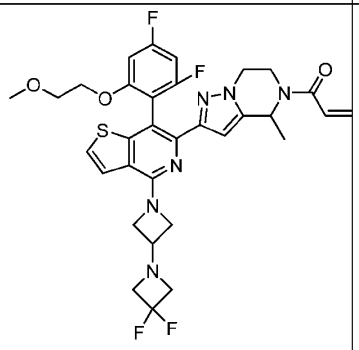
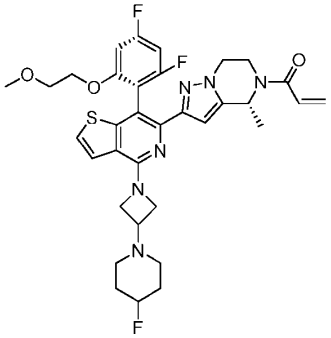
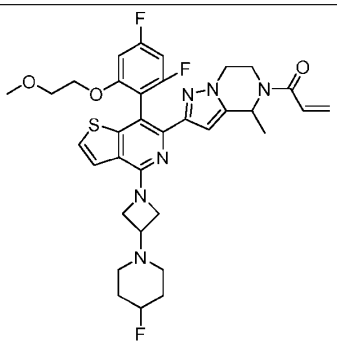
Cmpd. No.	Structure	Analytical data
72a		
73		LCMS m/z [M+1]: 670.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 6.87 – 6.66 (m, 3H), 6.20 (d, J = 15.2 Hz, 1H), 5.84 (s, 1H), 5.74 (d, J = 10.8 Hz, 1H), 5.58 (s, 1H), 4.74 – 4.47 (m, 2H), 4.27 (d, J = 11.6 Hz, 1H), 4.16 – 4.02 (m, 2H), 3.95 – 3.89 (m, 3H), 3.72 – 3.60 (m, 1H), 3.45 (dd, J = 28.0, 14.6 Hz, 4H), 3.28 (dd, J = 14.8, 8.2 Hz, 2H), 3.17 (d, J = 5.4 Hz, 5H), 3.07 – 2.97 (m, 1H), 2.86 (dd, J = 35.8, 24.0 Hz, 2H), 2.24 – 2.11 (m, 2H), 1.97 – 1.95 (m, 1H), 1.92 – 1.89 (m, 1H), 1.29 (s, 3H).
73a		

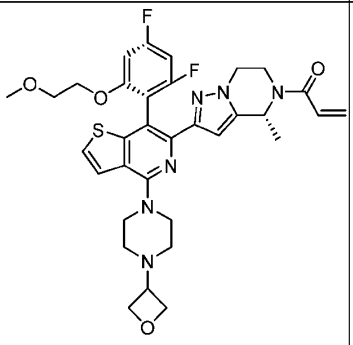
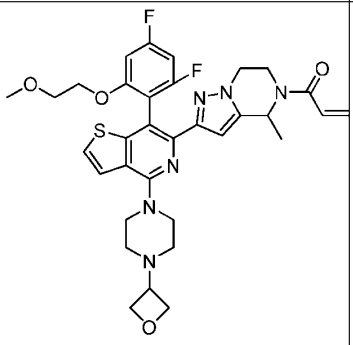
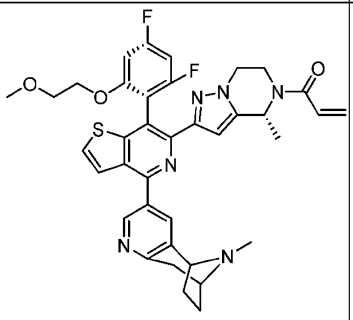
Cmpd. No.	Structure	Analytical data
74		LCMS m/z [M+1]: 709.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.21 (s, 1H), 8.75 (s, 1H), 6.87 (d, J = 10.6 Hz, 2H), 6.67 (td, J = 9.2, 2.0 Hz, 1H), 6.31 (d, J = 14.6 Hz, 1H), 5.95 (s, 1H), 5.85 (dd, J = 10.6, 1.6 Hz, 1H), 5.68 (s, 1H), 4.58 – 4.35 (m, 1H), 4.31 – 4.25 (m, 1H), 4.21 (s, 2H), 4.17 – 4.13 (m, 1H), 4.06 – 4.01 (m, 1H), 3.79 (s, 1H), 3.56 – 3.43 (m, 4H), 3.35 (d, J = 3.4 Hz, 1H), 3.31 – 3.25 (m, 5H), 3.23 (s, 3H), 3.02 – 2.71 (m, 3H), 2.25 – 2.16 (m, 2H), 1.40 (s, 3H).
74a		
75		LCMS m/z [M+1]: 708.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 10.8 Hz, 1H), 6.79 (t, J = 9.2 Hz, 1H), 6.32 (d, J = 16.2 Hz, 1H), 5.92 (s, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.72 (s, 1H), 4.41 (dd, J = 13.2, 2.6 Hz, 1H), 4.27 – 4.17 (m, 1H), 4.15 – 4.10 (m, 1H), 4.08 (s, 2H), 3.58 (t, J = 4.0 Hz, 2H), 3.40 (q, J = 9.6 Hz, 2H), 3.27 (s, 3H), 3.23 – 3.15 (m, 1H), 3.14 – 3.08 (m, 3H), 3.02 (s, 2H), 3.00 – 2.95 (m, 1H), 2.88 (s, 2H), 2.72 (s, 1H), 2.68 (s, 1H), 2.33 – 2.24 (m, 2H), 1.39 (s, 3H).

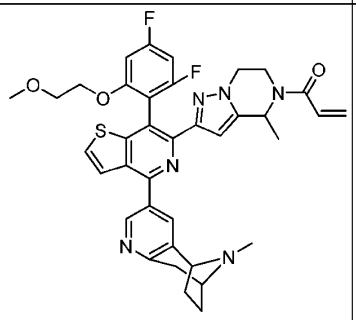
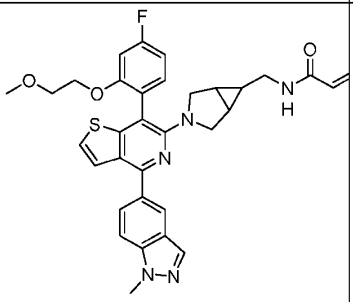
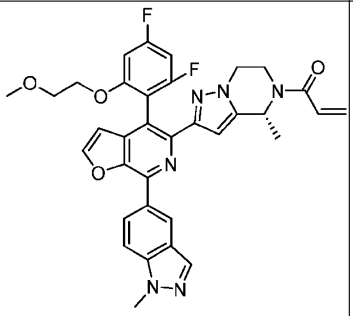
Cmpd. No.	Structure	Analytical data
75a		
76		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.17 (s, 1H), 8.10 - 8.05 (m, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.72 - 7.67 (m, 2H), 6.91 - 6.77 (m, 2H), 6.75 - 6.64 (m, 1H), 6.61 - 6.53 (m, 1H), 6.35 - 6.20 (m, 1H), 5.88 - 5.43 (m, 2H), 4.16 (s, 3H), 4.12-3.86 (m, 3H), 3.44 - 3.38 (m, 2H), 3.02 (d, J = 2.5 Hz, 3H), 1.58 - 1.42 (m, 3H), 1.37 (dd, J = 11.8, 6.4 Hz, 3H), 1.32-1.25 (m, 1H).
77		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.23 (s, 1H), 8.05 - 8.03 (m, 2H), 7.86 - 7.82 (m, 2H), 7.01 (d, J = 10.6 Hz, 1H), 6.92 - 6.77 (m, 2H), 6.29 (t, J = 16.2 Hz, 1H), 5.99 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.62 - 5.30 (m, 1H), 4.33 - 4.29 (m, 1H), 4.18 (s, 3H), 4.18 - 4.16 (m, 2H), 3.47 (s, 2H), 3.09 (s, 3H), 1.81 - 1.78 (m, 2H), 1.32 - 1.28 (m, 2H), 0.91 - 0.89 (m, 3H).
77a		

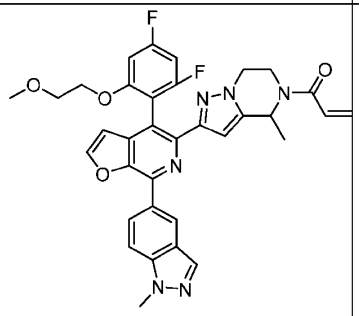
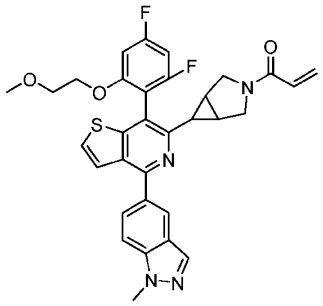
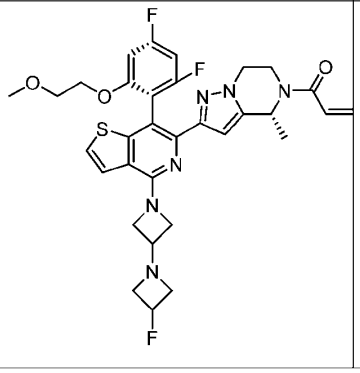
Cmpd. No.	Structure	Analytical data
78		LCMS m/z [M+1]: 618.7 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (d, J = 11.2 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.03 (dd, J = 10.6, 3.4 Hz, 2H), 7.89 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.04 (d, J = 10.7 Hz, 1H), 6.90 (t, J = 9.3 Hz, 1H), 6.33 – 6.21 (m, 2H), 5.74 (dd, J = 9.0, 3.2 Hz, 1H), 4.75 – 4.61 (m, 2H), 4.39 (t, J = 8.8 Hz, 1H), 4.29 (td, J = 8.6, 4.3 Hz, 2H), 4.21 (s, 3H), 4.20 – 4.12 (m, 2H), 4.04 (td, J = 9.8, 6.0 Hz, 1H), 3.63 – 3.49 (m, 2H), 3.40 (ddd, J = 8.9, 7.4, 4.5 Hz, 1H), 3.20 – 3.14 (m, 3H).
79		LCMS m/z [M+1]: 667.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.15 (s, 1H), 8.07 (dd, J = 8.8, 1.5 Hz, 1H), 7.78 – 7.67 (m, 3H), 6.89 – 6.83 (m, 1H), 6.73 – 6.65 (m, 1H), 6.17 (s, 1H), 5.75 – 5.52 (m, 1H), 4.69– 4.52(m, 2H) 4.20 – 4.01 (m, 7H), 3.43 (t, J = 4.8 Hz, 2H), 3.04 (s, 3H), 2.33 – 2.23 (m, 2H), 2.12 – 2.05 (m, 1H), 1.54 – 1.39 (s, 3H), 1.32 – 1.19 (m, 2H).
79a		

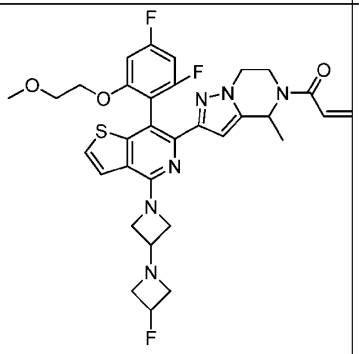
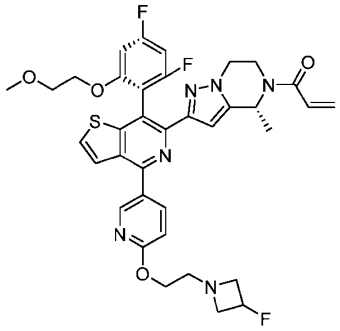
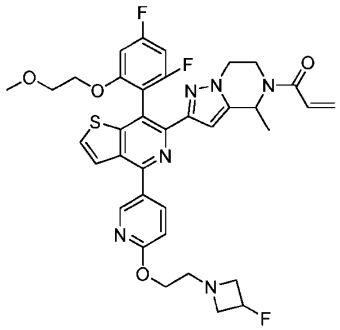
Cmpd. No.	Structure	Analytical data
80		LCMS m/z [M+1]: 637.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 -8.35 (m, 1H), 8.17 (s, 1H), 8.14 – 8.08 (m, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.71 - 7.62 (m, 2H), 7.17 - 7.13 (m, 1H), 6.86 – 6.73 (m, 2H), 6.70 – 6.60 (m, 1H), 6.34 – 6.26 (m, 1H), 5.84 – 5.76 (m, 1H), 4.96 – 4.89 (m, 1H), 4.83 – 4.73 (m, 1H), 4.54 – 4.45 (m, 1H), 4.28 – 4.17 (m, 2H), 4.17 – 4.06 (m, 4H), 3.97 – 3.87 (m, 1H), 1.61 – 1.48 (m, 2H), 1.24 – 0.86 (m, 6H).
81		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.31 – 8.22 (m, 1H), 8.11 – 8.00 (m, 2H), 7.91 – 7.80 (m, 2H), 6.96 (d, J = 10.9 Hz, 1H), 6.91 – 6.76 (m, 2H), 6.36 – 6.21 (m, 2H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.79 – 5.46 (m, 1H), 4.23 – 4.09 (m, 4H), 4.04 – 3.95 (m, 1H), 3.44 (t, J = 4.3 Hz, 2H), 3.09 (s, 3H), 1.59 – 1.38 (m, 6H).
82		LCMS m/z [M+1]: 601.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 – 8.36 (m, 1H), 8.27 – 8.24 (m, 1H), 8.05 (d, J = 5.6 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.73 (d, J = 5.6 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.92 – 6.85 (m, 1H), 6.27 – 6.14 (m, 2H), 5.64 (dd, J = 8.6, 3.3 Hz, 1H), 4.27 – 4.11 (m, 5H), 3.56 – 3.46 (m, 2H), 3.33 (s, 2H), 3.12 (s, 3H), 2.06 (s, 6H).
83		LCMS m/z [M+1]: 657.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (d, J = 5.6 Hz, 1H), 7.45 (d, J = 5.6 Hz, 1H), 6.88 – 6.73 (m, 2H), 6.65 – 6.56 (m, 1H), 6.27 (d, J = 15.0 Hz, 1H), 6.00 (s, 1H), 5.80 (d, J = 10.6 Hz, 1H), 5.73 – 5.36 (m, 1H), 4.60 – 4.30 (m, 3H), 4.27 – 4.11 (m, 3H), 4.09 – 3.91 (m, 3H), 3.87 – 3.63 (m, 6H), 3.40 (t, J = 4.6 Hz, 2H), 3.03 (s, 3H), 1.49 – 1.32 (m, 3H).

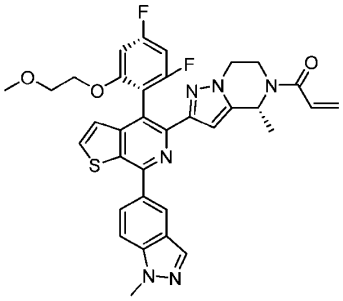
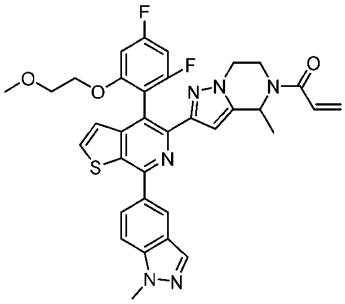
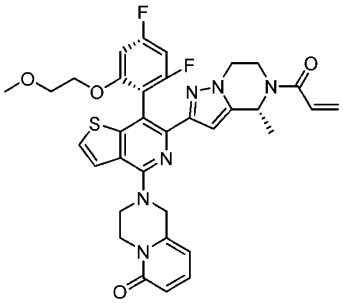
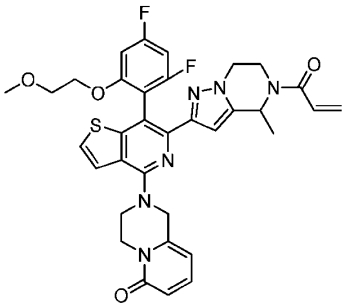
Cmpd. No.	Structure	Analytical data
83a		
84		LCMS m/z [M+1]: 667.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, J = 5.6 Hz, 1H), 7.45 (d, J = 5.6 Hz, 1H), 6.87 - 6.74 (m, 2H), 6.65 - 6.56 (m, 1H), 6.33 - 6.19 (m, 1H), 6.02 (s, 1H), 5.85 - 5.78 (m, 1H), 5.65 - 5.36 (m, 1H), 4.80 - 4.60 (m, 1H), 4.56 - 4.47 (m, 2H), 4.33 - 4.21 (m, 2H), 4.19 - 4.11 (m, 1H), 4.06 - 3.92 (m, 3H), 3.44 - 3.36 (m, 3H), 3.04 (s, 3H), 2.67 - 2.55 (m, 2H), 2.55 - 2.45 (m, 2H), 2.02 - 1.82 (m, 4H), 1.50 - 1.32 (m, 3H).
84a		

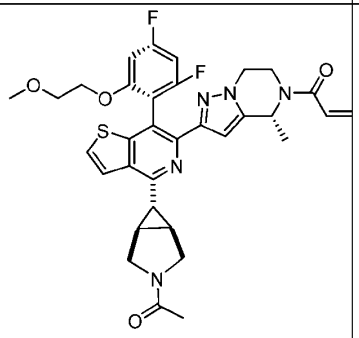
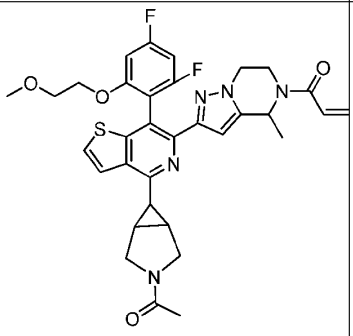
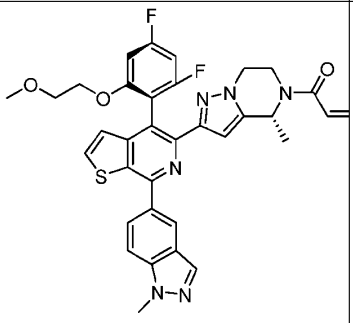
Cmpd. No.	Structure	Analytical data
85		LCMS m/z [M+1]: 651.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 - 7.48 (m, 2H), 6.88 - 6.73 (m, 2H), 6.66 - 6.57 (m, 1H), 6.36 - 6.21 (m, 1H), 6.15 (s, 1H), 5.81 (d, J = 11.2 Hz, 1H), 5.75 - 5.40 (m, 1H), 4.74 (t, J = 6.6 Hz, 2H), 4.69 (t, J = 6.2 Hz, 2H), 4.16 - 4.08 (m, 1H), 4.07 - 3.89 (m, 3H), 3.76 - 3.68 (m, 4H), 3.67 - 3.59 (m, 1H), 3.39 (t, J = 4.6 Hz, 2H), 3.01 (s, 3H), 2.68 - 2.59 (m, 4H), 1.56-1.33 (m, 3H).
85a		
86		LCMS m/z [M+1]: 683.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (d, J = 1.5 Hz, 1H), 8.35 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.5 Hz, 1H), 6.94 – 6.67 (m, 3H), , 6.29 (d, J = 16.6 Hz, 1H), 6.14 (s, 1H), 5.82 (dd, J = 10.6, 1.5 Hz, 1H), 5.70 - 5.48 (m, 1H), 5.02 (s, 1H), 4.44 – 4.36 (m, 1H), 4.22 (dd, J = 12.7, 2.9 Hz, 1H), 4.14 - 3.93 (m, 3H), 3.75 - 3.71 (m, 1H), 3.42 (t, J = 4.5 Hz, 2H), 3.04 (s, 6H), 2.65 - 2.60 (m, 2H), 2.41 (t, J = 10.9 Hz, 1H), 2.19 - 2.03 (m, 1H), 1.44 - 1.39 (m, 3H).

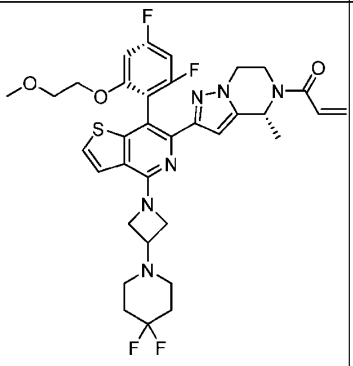
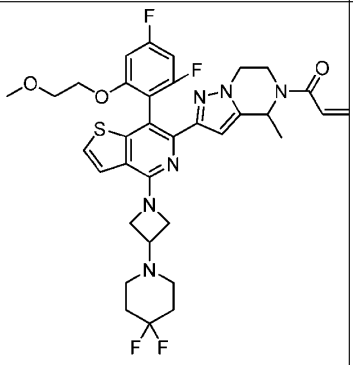
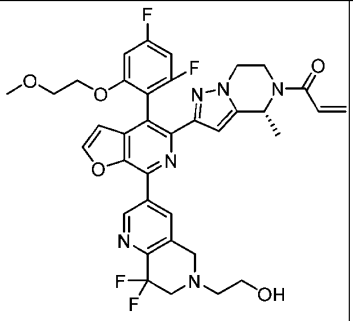
Cmpd. No.	Structure	Analytical data
86a		
87		LCMS m/z [M+1]: 598.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.20 (s, 1H), 7.91-7.89 (m, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.46-7.39 (m, 3H), 7.04 (dd, J = 10.6, 1.7 Hz, 1H), 6.92-6.87 (m, 1H), 6.21-6.20 (m, 2H), 5.65 (dd, J = 7.1, 4.8 Hz, 1H), 4.26-4.21 (m, 1H), 4.16 (s, 3H), 4.13-4.08 (m, 1H), 3.62 (t, J = 10.04 Hz, 2H), 3.56 (t, J = 4.36 Hz, 2H), 3.49 (t, J = 10.28 Hz, 2H), 3.18 (s, 3H), 3.15-3.13 (m, 2H), 1.61-1.55 (m, 2H).
88		LCMS m/z [M+1]: 625.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (s, 1H), 8.62 (d, J = 8.8 Hz, 1H), 8.15 (s, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 6.88 – 6.76 (m, 2H), 6.69 – 6.61 (m, 2H), 6.26 (d, J = 16.4 Hz, 1H), 6.15 (s, 1H), 5.80 (d, J = 10.6 Hz, 1H), 5.59 (d, J = 85.4 Hz, 1H), 4.19 (dt, J = 12.0, 3.8 Hz, 1H), 4.12 (s, 3H), 4.11 – 4.02 (m, 2H), 3.98 – 3.62 (m, 2H), 3.41 (q, J = 4.4 Hz, 2H), 3.27 – 3.10 (m, 1H), 3.08 (d, J = 1.4 Hz, 3H), 1.42 (s, 3H).

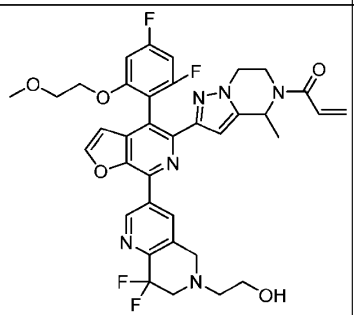
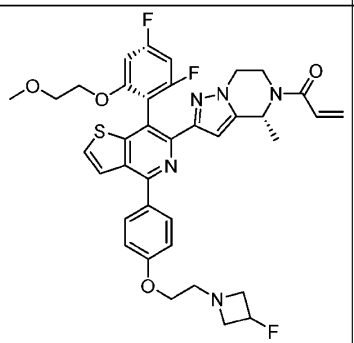
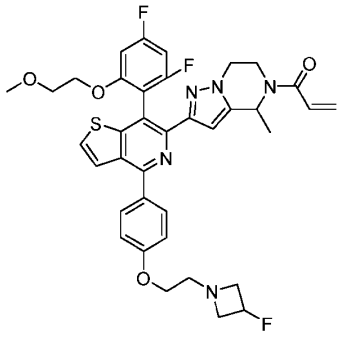
Cmpd. No.	Structure	Analytical data
88a		
89		LCMS m/z [M+1]: 587.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 8.07 (d, J = 0.7 Hz, 1H), 7.92 (dd, J = 8.8, 1.4 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 5.6 Hz, 1H), 7.52 (dd, J = 5.6, 1.0 Hz, 1H), 6.85 (d, J = 10.9 Hz, 1H), 6.76 – 6.68 (m, 1H), 6.42 (dd, J = 16.8, 10.4 Hz, 1H), 6.14 (dd, J = 16.8, 1.9 Hz, 1H), 5.63 (dt, J = 10.4, 1.8 Hz, 1H), 4.15 – 4.00 (m, 5H), 3.76 – 3.66 (m, 3H), 3.54 – 3.42 (m, 3H), 3.03 (d, J = 1.1 Hz, 3H), 2.47 – 2.37 (m, 1H), 2.33 – 2.20 (m, 1H), 1.55 (dt, J = 6.8, 3.3 Hz, 1H).
90		LCMS m/z [M+1]: 639.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (d, J = 5.6 Hz, 1H), 7.43 (d, J = 5.6 Hz, 1H), 6.90 - 6.27 (m, 2H), 6.65 - 6.56 (m, 1H), 6.34 - 6.20 (m, 1H), 6.01 (s, 1H), 5.80 (d, J = 10.6 Hz, 1H), 5.72 - 5.39 (m, 1H), 5.30 - 5.07 (m, 1H), 4.53 - 4.41 (m, 2H), 4.26 - 4.10 (m, 3H), 4.06 - 3.92 (m, 3H), 3.81 - 3.68 (m, 3H), 3.49 - 3.43 (m, 1H), 3.40 (t, J = 4.6 Hz, 3H), 3.03 (s, 3H), 1.50 - 1.31 (m, 3H).

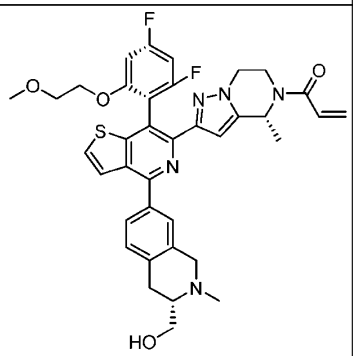
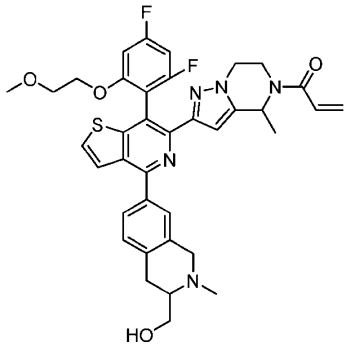
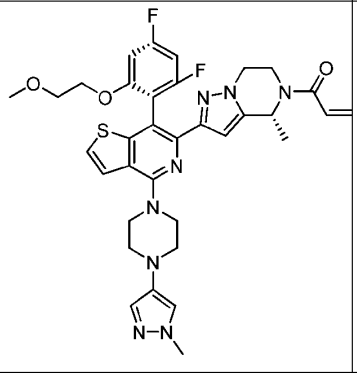
Cmpd. No.	Structure	Analytical data
90a		
91		LCMS m/z [M+1]: 705.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (s, 1H), 8.38 (dd, J = 8.6, 2.4 Hz, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 6.96 – 6.79 (m, 2H), 6.74 (td, J = 9.2, 2.2 Hz, 1H), 6.31-6.25 (m, 1H), 6.12 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.76 – 5.34 (m, 2H), 4.79 – 4.39 (m, 7H), 4.24 (dd, J = 12.8, 2.9 Hz, 1H), 4.16 – 3.96 (m, 3H), 3.83 – 3.67 (m, 2H), 3.43 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.52 – 1. 36 (m, 3H).
91a		

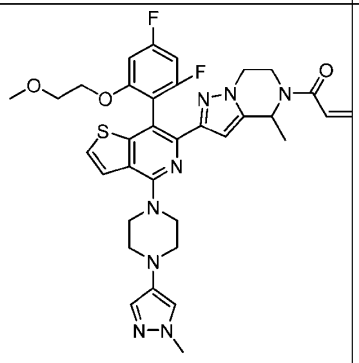
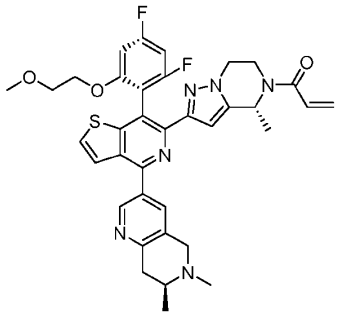
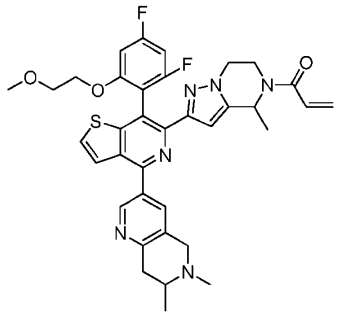
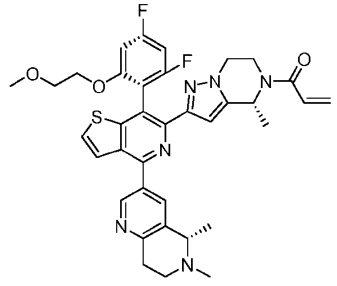
Cmpd. No.	Structure	Analytical data
92		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.26 (s, 1H), 8.17 (dd, J = 8.8, 1.6 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 5.5 Hz, 1H), 7.00 – 6.72 (m, 3H), 6.30 (d, J = 16.9 Hz, 1H), 6.01 (s, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.71-5.42 (m, 1H), 4.19 (s, 3H), 4.17 – 4.03 (m, 3H), 3.44 (t, J = 4.5 Hz, 2H), 3.09 (s, 3H), 1.47-1.35 (m, 3H).
92a		
93		LCMS m/z [M+1]: 659.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (d, J = 5.7 Hz, 1H), 7.81 (d, J = 5.7 Hz, 1H), 7.57 (dd, J = 9.2, 6.9 Hz, 1H), 6.99 – 6.70 (m, 3H), 6.58 (d, J = 8.8 Hz, 1H), 6.55(d, J = 6.8 Hz, 1H), 6.29 (d, J = 16.4 Hz, 1H), 5.91 – 5.75 (m, 2H), 5.75 - 5.40 (m, 1H), 5.17 (s, 2H), 4.66 – 4.42 (m, 2H), 4.36 – 4.23 (m, 3H), 4.20 - 3.98 (m, 3H), 3.40 (t, J = 4.5 Hz, 2H), 3.06 - 3.04 (m, 3H), 1.43 - 1.38 (m, 3H).
93a		

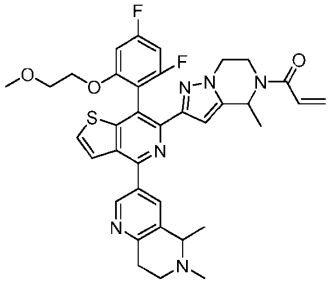
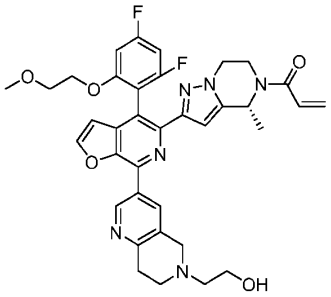
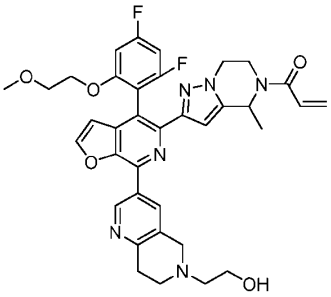
Cmpd. No.	Structure	Analytical data
94		LCMS m/z [M+1]: 634.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 5.6 Hz, 1H), 7.65 (d, J = 5.5 Hz, 1H), 6.94 – 6.79 (m, 2H), 6.66 (t, J = 9.2 Hz, 1H), 6.31 (s, 1H), 6.17 (s, 1H), 5.84 (d, J = 10.8 Hz, 1H), 5.60 (d, J = 85.7 Hz, 1H), 4.39 (s, 1H), 4.21 – 3.83 (m, 7H), 3.75 (s, 1H), 3.63 (dd, J = 12.2, 4.2 Hz, 1H), 3.40 (t, J = 4.6 Hz, 2H), 3.03 (d, J = 0.9 Hz, 3H), 2.62 (s, 1H), 2.58 – 2.53 (m, 1H), 2.49 (t, J = 3.2 Hz, 1H), 2.13 (s, 3H), 1.43 (s, 3H).
94a		
95		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.40 (d, J = 5.5 Hz, 1H), 8.25 (s, 1H), 8.17 (dd, J = 8.8, 1.7 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 5.3 Hz, 1H), 6.97 – 6.77 (m, 3H), 6.30 (d, J = 16.7 Hz, 1H), 6.02 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.33 (dd, J = 12.9, 2.8 Hz, 1H), 4.22 – 4.07 (m, 5H), 4.00 – 3.95 (m, 1H), 3.44 (t, J = 4.6 Hz, 2H), 3.11 (s, 3H), 1.47-1.35 (m, 3H).

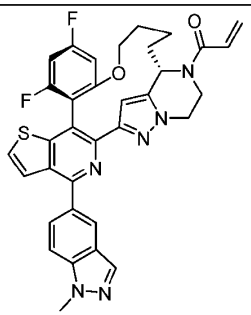
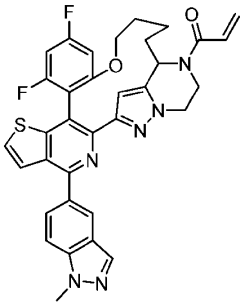
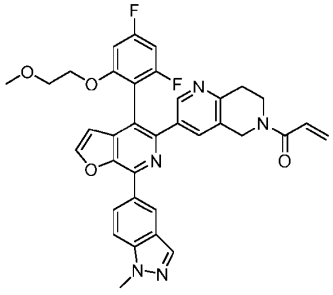
Cmpd. No.	Structure	Analytical data
96		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, J = 5.2 Hz, 1H), 7.46 (d, J = 5.6 Hz, 1H), 6.88 - 6.74(m, 2H), 6.65 - 6.57 (m, 1H), 6.34 - 6.21(m, 1H), 6.01 (s, 1H), 5.81 (d, J = 10.8 Hz, 1H), 5.70 - 5.44 (m, 1H), 4.59 - 4.48 (m, 2H), 4.33 - 4.24 (m, 2H), 4.20 - 4.12 (m, 1H), 4.08 - 3.93 (m, 3H), 3.50 - 3.43 (m, 1H), 3.41 (t, J = 4.78Hz , 1H), 3.04 (s, 3H), 2.70 - 2.52 (m, 4H), 2.12 - 1.95 (m, 1H), 1.50 - 1.32 (m, 3H).
96a		
97		LCMS m/z [M+1]: 707.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.83 (s, 1H), 8.99 (s, 1H), 8.17 (d, J = 1.8 Hz, 1H), 6.88 (dd, J = 18.6, 9.6 Hz, 2H), 6.73 (dd, J = 20.4, 11.0 Hz, 2H), 6.31 (d, J = 16.8 Hz, 1H), 6.20 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.79 – 5.52 (m, 1H), 4.59 (s, 2H), 4.30 – 4.22 (m, 1H), 4.20 – 4.05 (m, 2H), 4.05 – 3.88 (m, 5H), 3.88 – 3.55 (m, 2H), 3.44 (dd, J = 8.6, 4.4 Hz, 2H), 3.38 – 3.33 (m, 2H), 3.12 (d, J = 0.8 Hz, 3H), 1.47 (s, 3H).

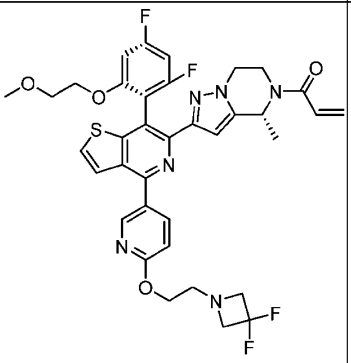
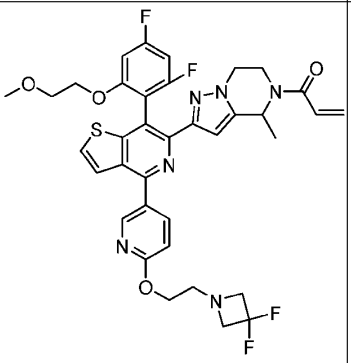
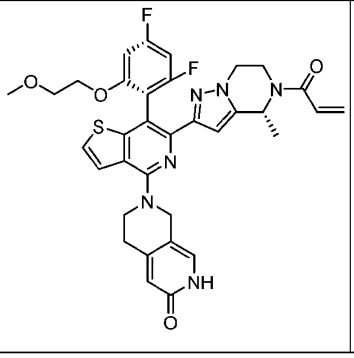
Cmpd. No.	Structure	Analytical data
97a		
98		LCMS m/z [M+1]: 704.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 7.27 (d, J = 8.6 Hz, 2H), 6.94 - 6.88 (m, 1H), 6.87 - 6.79 (m, 1H), 6.76 - 6.70 (m, 1H), 6.34 - 6.23 (m, 1H), 6.09 (s, 1H), 5.84 - 5.78 (m, 1H), 5.75 - 5.59 (m, 1H), 5.53 - 5.38 (m, 1H), 4.81 - 4.64 (m, 3H), 4.57 - 4.47 (m, 2H), 4.43 - 4.38 (m, 2H), 4.28 - 4.20 (m, 1H), 4.14 - 4.02 (m, 3H), 3.90 - 3.69 (m, 3H), 3.44 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.52 - 1.38 (s, 3H).
98a		

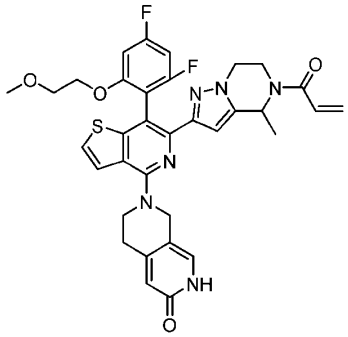
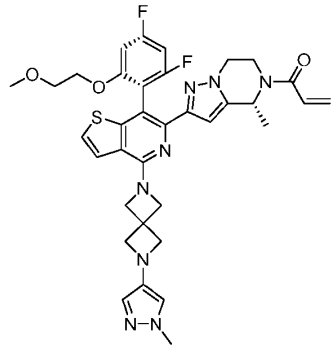
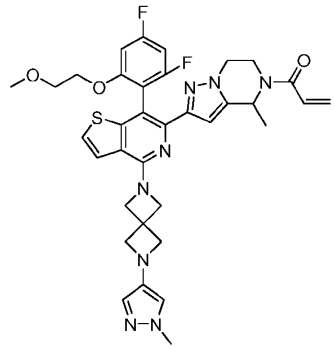
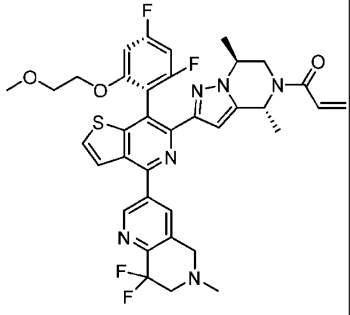
Cmpd. No.	Structure	Analytical data
99		LCMS m/z [M+1]: 686.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (d, J = 7.4 Hz, 1H), 7.87 (s, 1H), 7.81 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 6.91-6.80 (m, 2H), 6.71 (td, J = 9.2, 2.0 Hz, 1H), 6.28 (d, J = 15.6 Hz, 1H), 6.12 (s, 1H), 5.82 (dd, J = 10.4, 1.4 Hz, 1H), 5.70 - 5.48 (m, 1H), 4.71 - 4.54 (m, 2H), 4.24 - 4.02 (m, 6H), 3.79 - 3.71 (m, 3H), 3.44 - 3.41 (m, 3H), 3.14 (s, 2H), 3.04 (s, 3H), 1.42 - 1.40 (m, 3H).
99a		
100		LCMS m/z [M+1]: 675.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (s, 2H), 7.32 (d, J = 9.2 Hz, 2H), 6.88 - 6.75 (m, 2H), 6.66 - 6.58 (m, 1H), 6.34 - 6.22 (m, 1H), 6.15 (s, 1H), 5.81 (d, J = 11.6 Hz, 1H), 5.76 - 5.47 (m, 1H), 4.61 - 4.32 (m, 1H), 4.16 - 4.09 (m, 1H), 4.08 - 3.91 (m, 3H), 3.82 (s, 3H), 3.80 - 3.74 (m, 4H), 3.40 (t, J = 4.8 Hz, 2H), 3.24 - 3.12 (m, 4H), 3.02 (s, 3H), 1.53 - 1.35 (m, 3H).

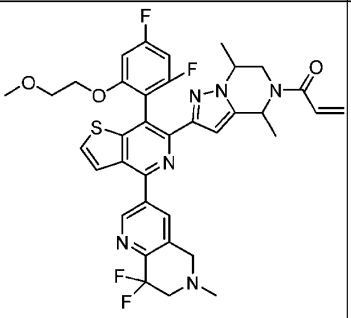
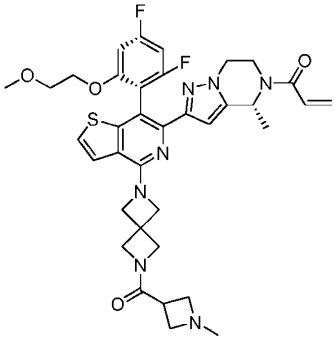
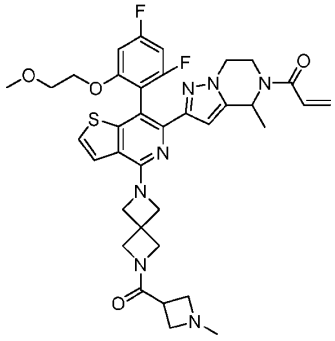
Cmpd. No.	Structure	Analytical data
100a		
101		LCMS m/z [M+1]: 671.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1H), 8.09 (s, 1H), 7.68 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 5.6 Hz, 1H), 6.81 - 6.67 (m, 2H), 6.66 - 6.55 (m, 1H), 6.25 - 6.12 (m, 1H), 6.12 - 6.04 (m, 1H), 5.71 (d, J = 10.8 Hz, 1H), 5.66 - 5.31 (m, 1H), 4.02 - 3.84 (m, 4H), 3.68 (d, J = 15.8 Hz, 1H), 3.31 (t, J = 4.6 Hz, 2H), 3.13 - 3.02 (m, 1H), 2.93 (s, 3H), 2.88 - 2.71 (m, 2H), 2.41 (s, 3H), 1.45 - 1.28 (m, 3H), 1.20 (d, J = 6.0 Hz, 3H).
101a		
102		LCMS m/z [M+1]: 671.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (d, J = 1.6 Hz, 1H), 8.28 (d, J = 1.4 Hz, 1H), 7.79 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 5.7 Hz, 1H), 6.90 - 6.78 (m, 2H), 6.75 - 6.65 (m, 1H), 6.33 - 6.23 (m, 1H), 6.19 - 6.08 (m, 1H), 5.81 (d, J = 11.8 Hz, 1H), 5.74 - 5.40 (m, 1H), 4.25 - 4.13 (m, 1H), 4.12 - 3.97 (m, 3H), 3.95 - 3.83 (m, 1H), 3.41 (t, J = 4.6

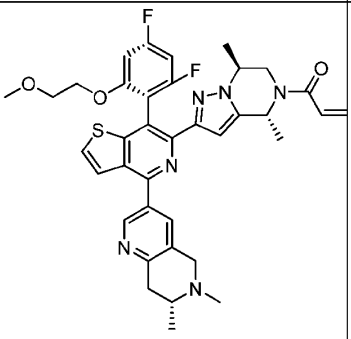
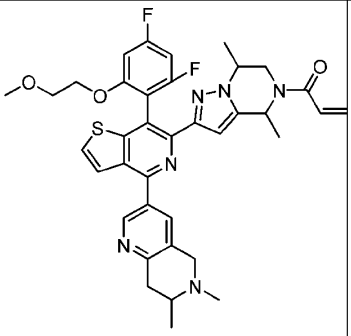
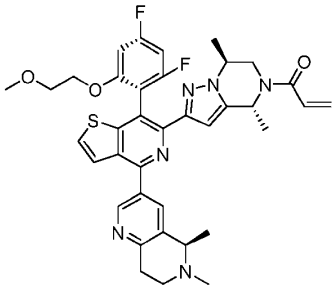
Cmpd. No.	Structure	Analytical data
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102a		
103		LCMS m/z [M+1]: 671.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.68 (s, 1H), 8.91 (s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 6.88 (dd, J = 18.3, 9.7 Hz, 2H), 6.72 (dd, J = 19.2, 9.9 Hz, 2H), 6.32 (d, J = 15.7 Hz, 1H), 6.15 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.63 (d, J = 86.0 Hz, 1H), 4.81 (s, 2H), 4.47 (s, 1H), 4.25 (d, J = 12.7 Hz, 1H), 4.18 – 4.02 (m, 4H), 4.01 – 3.68 (m, 4H), 3.59 – 3.52 (m, 2H), 3.51 – 3.42 (m, 4H), 3.12 (d, J = 1.8 Hz, 3H), 1.47 (s, 3H).
103a		

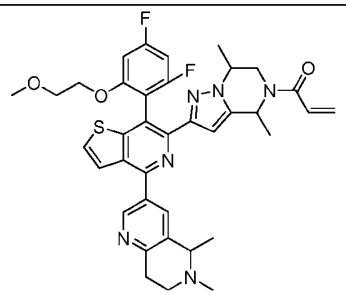
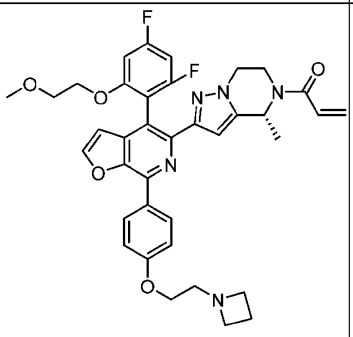
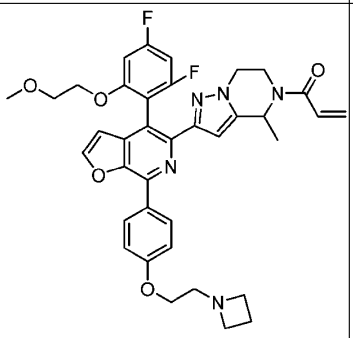
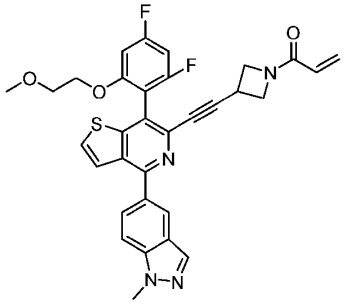
Cmpd. No.	Structure	Analytical data
104		LCMS m/z [M+1]: 623.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.27 (s, 1H), 8.10-8.03 (m, 2H), 7.89 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.16-7.13 (m, 1H), 6.95-6.80 (m, 2H), 6.35-6.25 (m, 1H), 6.03 (s, 1H), 5.90-5.80 (m, 1H), 5.70-5.40 (m, 1H), 4.70-4.40 (m, 3H), 4.40-4.21 (m, 1H), 4.20 (s, 3H), 3.90-3.75 (m, 2H), 2.50-2.20 (m, 1H), 1.70-1.55 (m, 1H), 1.55-1.15 (m, 5H).
104a		
105		LCMS m/z [M+1]: 622.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.99 (s, 1H), 8.69 – 8.59 (m, 2H), 8.33 (d, J = 20.5 Hz, 1H), 8.24 – 8.16 (m, 2H), 7.78 (d, J = 8.9 Hz, 1H), 6.88 (d, J = 11.1 Hz, 2H), 6.76 (dd, J = 20.5, 11.2 Hz, 2H), 6.32 (d, J = 17.0 Hz, 1H), 5.86 (d, J = 10.2 Hz, 1H), 4.97 (s, 2H), 4.17 (s, 3H), 4.14 – 3.97 (m, 4H), 3.51 (t, J = 4.4 Hz, 2H), 3.18 (d, J = 23.2 Hz, 5H)

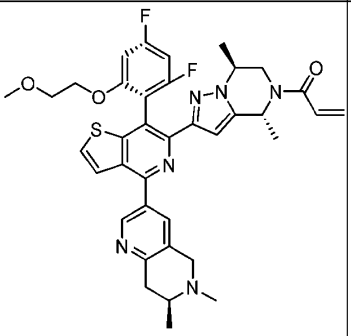
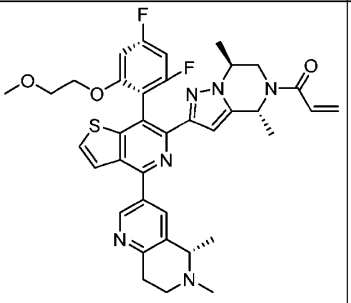
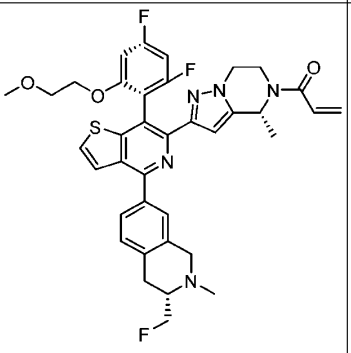
Cmpd. No.	Structure	Analytical data
106		LCMS m/z [M+1]: 723.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (d, J = 2.2 Hz, 1H), 8.32 (dd, J = 8.6, 2.4 Hz, 1H), 7.75 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 5.6 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 6.90 – 6. 77 (m, 2H), 6.69 (td, J = 9.2, 2.3 Hz, 1H), 6.38 – 6. 10 (m, 2H), 5.81 (d, J = 12.1 Hz, 1H), 5.74 – 5. 40 (m, 1H), 4.53 – 4. 44 (m, 2H), 4.22 – 3.95 (m, 4H), 3.86 – 3. 69 (m, 4H), 3.41 (t, J = 4.6 Hz, 2H), 3.10 – 2.97 (m, 5H), 1.52 – 1.37 (m, 3H).
106a		
107		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 5.7 Hz, 1H), 7.89 (d, J = 5.7 Hz, 1H), 7.58 (s, 1H), 6.99 (d, J = 10.8 Hz, 1H), 6.90 – 6.75 (m, 2H), 6.58 (s, 1H), 6.34 – 6.22 (m, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.77 – 5.45 (m, 2H), 5.03 (s, 2H), 4.55 – 4.33 (m, 2H), 4.22 – 4.03 (m, 5H), 3.87 – 3.65 (m, 1H), 3.44 – 3.37 (m, 2H), 3.20 (t, J = 5.8 Hz, 2H), 3.05 (s, 3H), 1.50 – 1.35 (m, 3H).

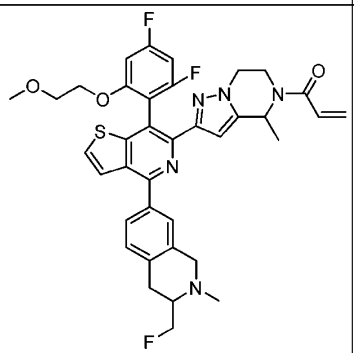
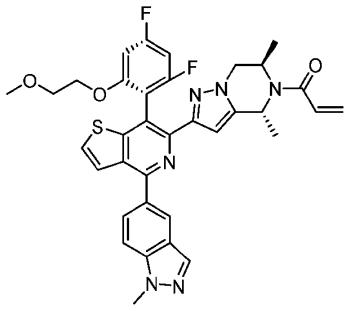
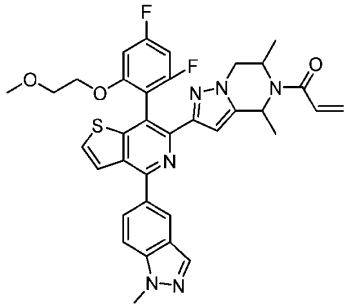
Cmpd. No.	Structure	Analytical data
107a		
108		LCMS m/z [M+1]: 687.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 6.0 Hz, 1H), 7.36 (s, 1H), 7.25 (s, 1H), 6.97 (d, J = 10.8 Hz, 1H), 6.90 - 6.71 (m ,2H), 6.29 (d, J = 16.0 Hz, 1H), 5.82 (dd, J = 10.4, 1.6 Hz, 1H), 5.74 (s, 1H), 5.70-5.42 (m, 1H), 5.05 - 4.91 (m, 4H), 4.42 - 4.31 (m, 1H), 4.30-4.04 (m, 6H), 3.83 (s, 3H), 3.46 -3.36 (m, 2H), 3.08 (s, 3H), 1.50 - 1.28(m, 3H).
108a		
109		LCMS m/z [M+1]: 707.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (d, J = 1.4 Hz, 1H), 8.35 (s, 1H), 7.81 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 6.92 – 6.80 (m, 2H), 6.73 – 6.64 (m, 1H), 6.37 – 6.23 (m, 2H), 5.83 (d, J = 10.6 Hz, 1H), 5.79 – 5.45 (m, 1H), 4.77 – 4.62 (m, 0.5H), 4.44 – 4.33 (m, 1H), 4.30 – 4.15 (m, 0.5H), 4.13 – 3.97 (m, 2H), 3.89 (s, 2H),

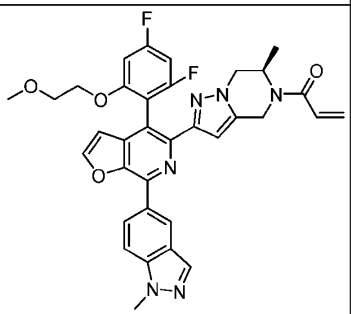
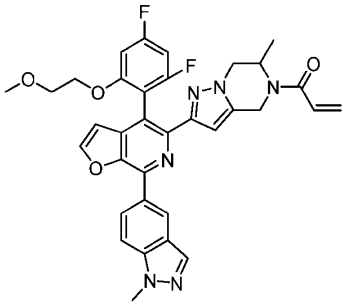
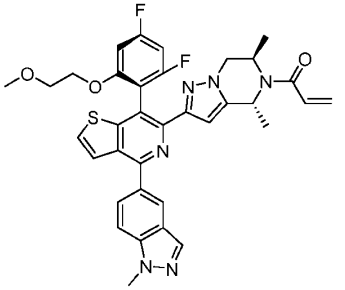
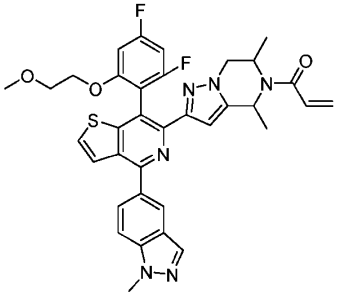
Cmpd. No.	Structure	Analytical data
		3.42 (t, J = 4.6 Hz, 2H), 3.30 – 3.22 (m, 1H), 3.04 (s, 3H), 2.59 (s, 3H), 1.55 – 1.37 (m, 3H), 1.28 (s, 3H).
109a		
110		LCMS m/z [M+1]: 704.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.84-7.82 (m, 1H), 7.76-7.74 (m, 1H), 6.94 (d, J = 10.7 Hz, 1H), 6.90-6.73 (m, 2H), 6.29 (d, J = 16.2 Hz, 1H), 5.82 (dd, J= 10.6, 1.7 Hz, 1H), 5.80-5.74 (m, 1H), 5.72-5.40 (m, 1H), 4.90 (s, 4H), 4.52-4.38 (m, 3H), 4.36-4.28 (m, 3H), 4.25-4.02 (m, 5H), 3.73-3.65 (m, 1H), 3.42 (t, J = 4.8 Hz, 2H), 3.07 (s, 3H), 2.95 (s, 3H), 1.49-1.28 (m, 3H).
110a		

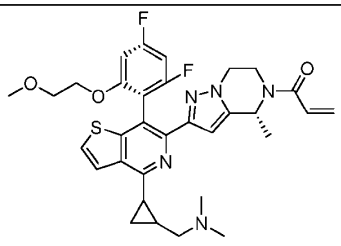
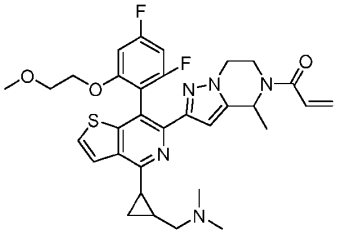
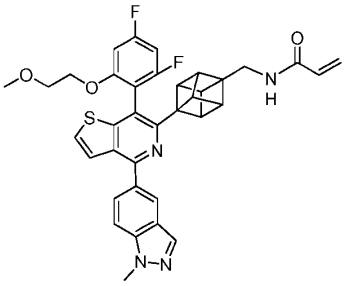
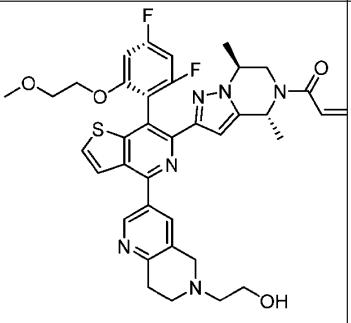
Cmpd. No.	Structure	Analytical data
111		LCMS m/z [M+1]: 685.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (d, J = 1.5 Hz, 1H), 8.34 (s, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.91 - 6.83 (m, 2H), 6.69 (td, J = 9.2, 2.2 Hz, 1H), 6.33 (d, J = 16.7 Hz, 1H), 6.21 (s, 1H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.73 - 5.11 (m, 1H), 4.76 - 4.70 (m, 2H), 4.51 - 4.38 (s, 1H), 4.13– 3.97 (m, 2H), 3.60 – 3.38 (m, 3H), 3.24 - 3.19 (m, 1H), 3.17 – 2.96 (m, 6H), 1.58 (d, J = 5.1 Hz, 3H), 1.43 - 1.40 (m, 3H), 1.3 - 1.21 (m, 3H).
111a		
112		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (d, J = 1.7 Hz, 1H), 8.42 (s, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 6.91 - 6.83 (m, 2H), 6.69 (td, J = 9.2, 2.2 Hz, 1H), 6.33 (d, J = 16.6 Hz, 1H), 6.18 (s, 1H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.73 - 5.49 (m, 1H), 4.51 -4.40 (m, 1H), 4.10 - 4.02 (m, 2H), 3.89 - 3.86 (m, 1H), 3.76-3.65 (m, 1H), 3.53 – 3.37 (m, 4H), 3.11 (s, 3H), 3.06 (s, 3H), 1.86 - 1.82 (m, 3H), 1.46 - 1.40 (m, 3H), 1.33 - 1.20 (m, 3H).

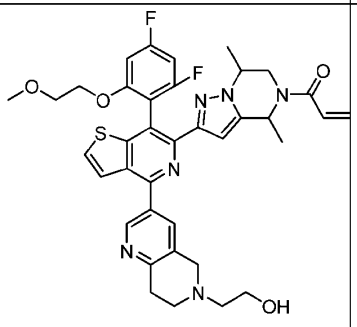
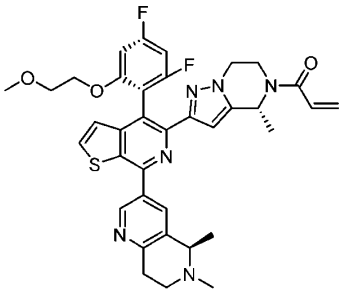
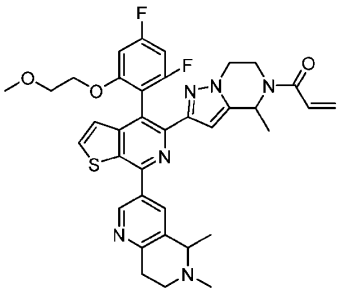
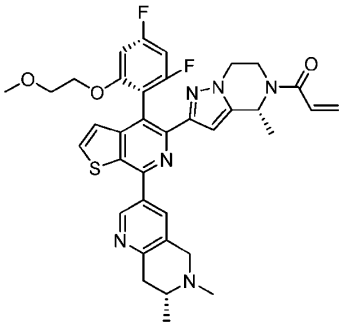
Cmpd. No.	Structure	Analytical data
112a		
113		LCMS m/z [M+1]: 670.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, J = 7.9 Hz, 2H), 8.27 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 8.9 Hz, 2H), 6.93 – 6.80 (m, 3H), 6.74 (dd, J = 20.9, 9.9 Hz, 1H), 6.32 (d, J = 16.0 Hz, 1H), 6.10 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.62 (d, J = 89.8 Hz, 1H), 4.56 – 4.24 (m, 8H), 4.14 (dt, J = 16.2, 5.7 Hz, 2H), 3.98 (ddd, J = 25.1, 9.9, 5.3 Hz, 1H), 3.76 – 3.71 (m, 2H), 3.47 (dd, J = 7.7, 4.5 Hz, 2H), 3.14 (d, J = 4.1 Hz, 3H), 2.76 – 2.61 (m, 2H), 2.51 (dd, J = 11.6, 5.3 Hz, 1H), 1.46 (s, 3H).
113a		
114		LCMS m/z [M+1]: 585.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.17 (s, 1H), 7.94 – 7.89 (m, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.67 (d, J = 5.5 Hz, 1H), 6.97 – 6.87 (m, 1H), 6.83 - 6.73 (m, 1H), 6.30 – 6.25 (m, 2H), 5.80 – 5.72 (m, 1H), 4.60 – 4.49 (m, 1H), 4.32 - 4.24 (m,

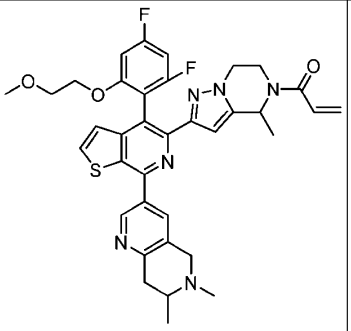
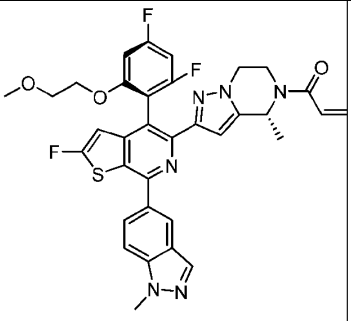
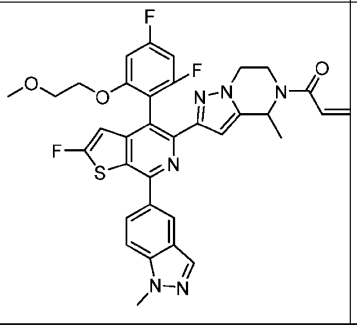
Cmpd. No.	Structure	Analytical data
		1H), 4.11 - 4.00 (m, 5H), 3.90 – 3.79 (m, 1H), 3.55 - 3.45 (m, 3H), 3.16 - 3.11 (m, 1H), 3.10 (s, 3H).
115		LCMS m/z [M+1]: 685.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.93 (d, J = 1.42 Hz, 1H), 8.17 (d, J = 0.9 Hz, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.66 (d, J = 5.6 Hz, 1H), 6.77-6.93 (m, 2H), 6.73-6.62 (m, 1H), 6.36-6.18 (m, 2H), 5.83 (d, J = 11.2 Hz, 1H), 5.77-5.40 (m, 1H), 4.47-4.33 (m, 1H), 4.14-3.96 (m, 3H), 3.85-3.73 (m, 1H), 3.42 (t, J = 4.6 Hz, 2H), 3.34 (s, 3H), 3.22-3.09 (m, 1H), 3.03 (s, 3H), 2.97-2.83 (m, 2H), 2.51 (s, 3H), 1.52-1.36 (m, 3H), 1.35 - 1.20 (m, 6H)
116		LCMS m/z [M+1]: 685.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.91 (d, J = 1.9 Hz, 1H), 8.27 (d, J = 1.6 Hz, 1H), 7.79 (d, J = 5.6 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 10.8 Hz, 2H), 6.72 - 6.62 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.27 - 6.15 (m, 1H), 5.83 (dd, J = 10.6 Hz, 1.4 Hz, 1H), 5.76-5.46 (m, 1H), 4.76 - 4.52 (m, 1H), 4.47 - 4.34 (m, 1H), 4.13 - 3.97 (m, 2H), 3.94 - 3.81 (m, 1H), 3.42 (t, J = 4.6 Hz, 2H), 3.28 - 3.20 (m, 1H), 3.16 - 3.08 (m, 2H), 3.04 (s, 3H), 2.95 - 2.80 (m, 1H), 2.55 (s, 3H), 1.89 (s, 4H), 1.53 (d, J = 6.6 Hz, 3H), 1.50 - 1.36 (m, 3H).
117		LCMS m/z [M+1]: 688.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 7.8 Hz, 1H), 7.90 - 7.87 (m, 2H), 7.71 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 6.93 - 6.80 (m, 2H), 6.74 (td, J = 9.2, 2.2 Hz, 1H), 6.28 (d, J = 15.8 Hz, 1H), 6.10 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.69 - 5.48 (m, 1H), 5.05 (dd, J = 46.7, 11.6 Hz, 1H), 4.81 - 4.73 (m, 3H), 4.24 (dd, J = 12.6, 2.8 Hz, 1H), 4.12 - 4.04 (m, 4H), 3.44 - 3.35 (m, 4H), 3.15 (s, 3H), 3.05 (s, 3H), 1.45 - 1.42 (m, 3H).

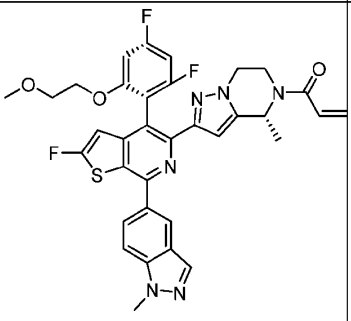
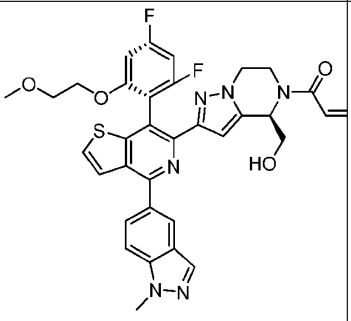
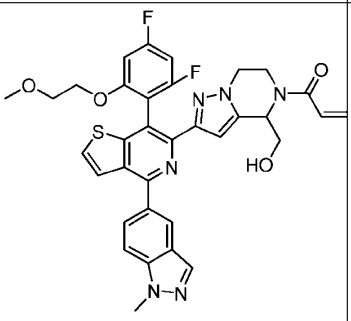
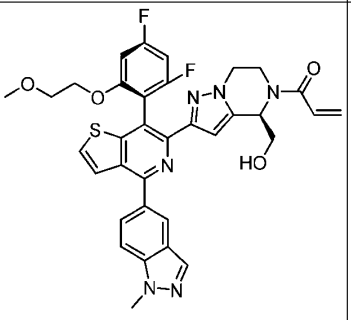
Cmpd. No.	Structure	Analytical data
117a		
118		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.28 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 8.05 (dd, J = 8.8, 1.6 Hz, 1H), 7.98 -7.85 (m, 2H), 7.00 (d, J = 10.7 Hz, 1H), 6.92 – 6.77 (m, 2H), 6.35 (dd, J = 16.6, 1.9 Hz, 1H), 6.17 (s, 1H), 5.82 (dd, J = 10.5, 1.9 Hz, 1H), 5.39 (q, J = 6.5 Hz, 1H), 4.61 – 4.51 (m, 1H), 4.38 (dd, J = 13.8, 1.6 Hz, 1H), 4.27 – 4.00 (m, 5H), 3.47 (t, J = 4.5 Hz, 2H), 3.12 (d, J = 7.6 Hz, 3H), 1.44 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H).
118a		

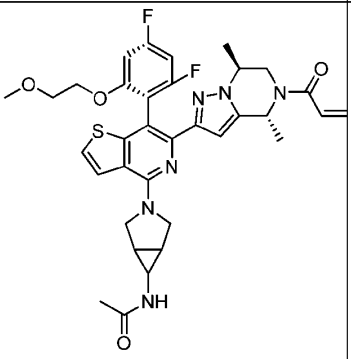
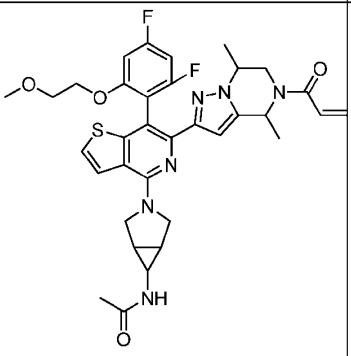
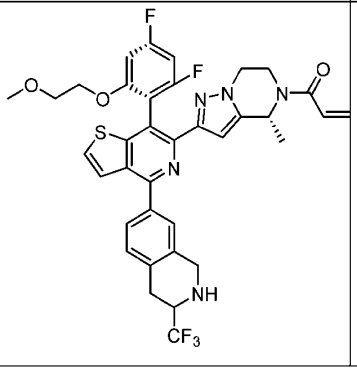
Cmpd. No.	Structure	Analytical data
119		LCMS m/z [M+1]: 625.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.67 (d, J = 8.8 Hz, 1H), 8.19 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 6.96 – 6.79 (m, 2H), 6.73 – 6.64 (m, 2H), 6.35 – 6.25 (m, 2H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.25 – 5.09 (m, 1H), 4.87 (s, 2H), 4.32 – 4.19 (m, 1H), 4.16 (s, 3H), 4.10 (td, J = 10.6, 5.2 Hz, 2H), 3.93 (dd, J = 10.8, 4.6 Hz, 1H), 3.46 (dd, J = 8.6, 4.4 Hz, 2H), 3.12 (d, J = 2.6 Hz, 3H), 1.22 (s, 3H).
119a		
120		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.17 (s, 1H), 8.12 - 8.07 (m, 1H), 7.79 - 7.68 (m, 3H), 6.92 - 6.78 (m, 2H), 6.73 - 6.64 (m, 1H), 6.38 - 6.28 (m, 2H), 5.84 - 5.76 (m, 1H), 5.41 - 5.31 (m, 1H), 4.79 - 4.65 (m, 1H), 4.53 - 4.43 (m, 1H), 4.22 - 4.10 (m, 4H), 4.10 - 4.02 (m, 1H), 4.00 - 3.92 (m, 1H), 3.44 (t, J = 4.8 Hz, 1H), 3.05 (s, 3H), 1.46 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H).
120a		

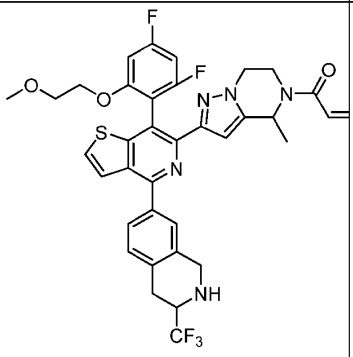
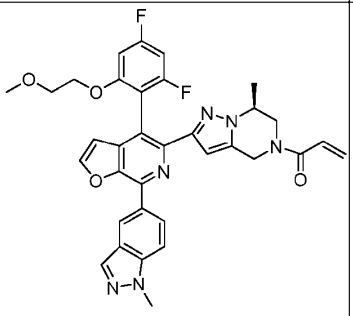
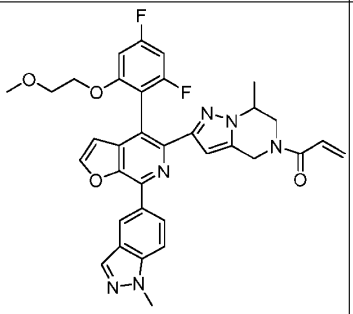
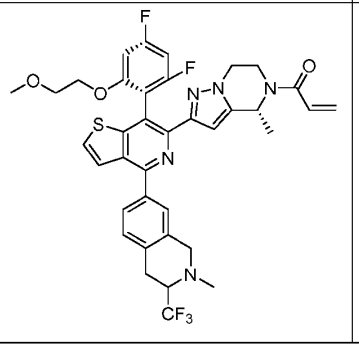
Cmpd. No.	Structure	Analytical data
121		LCMS m/z [M+1]: 608.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (s, 2H), 7.69 (d, J = 15.1 Hz, 1H), 7.39 (dt, J = 15.1, 7.7 Hz, 1H), 6.90 (d, J = 10.7 Hz, 2H), 6.72 (t, J = 9.1 Hz, 1H), 6.32 (s, 1H), 6.02 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.50 (s, 1H), 4.45 (s, 1H), 4.29 (t, J = 12.1 Hz, 3H), 4.06 (tt, J = 11.3, 5.6 Hz, 3H), 3.77 (s, 1H), 3.40 (t, J = 4.6 Hz, 2H), 3.26 (s, 6H), 3.02 (s, 3H), 2.90 (s, 1H), 1.51 – 1.26 (m, 6H).
121a		
122		LCMS m/z [M+1]: 637.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 8.17 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.64 (dd, J = 13.6, 5.6 Hz, 2H), 6.91 (d, J = 10.9 Hz, 1H), 6.78 (td, J = 9.1, 2.2 Hz, 1H), 6.38 – 6.15 (m, 2H), 5.66 (dd, J = 9.6, 2.4 Hz, 1H), 4.22 – 4.14 (m, 4H), 4.11 (dd, J = 10.5, 5.6 Hz, 4H), 3.71 – 3.57 (m, 3H), 3.51 (t, J = 4.5 Hz, 2H), 3.47 (s, 2H), 3.05 (s, 3H).
123		LCMS m/z [M+1]: 701.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.14 - 9.11 (m, 1H), 8.35 (s, 1H), 7.84 (d, J = 5.5 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.93 – 6.84 (m, 2H), 6.72 - 6.63 (m, 1H), 6.37 - 6.26 (m, 1H), 6.21 (s, 1H), 5.84 (dd, J = 10.5, 1.9 Hz, 1H), 5.71 - 5.49 (m, 1H), 4.79 - 4.67 (m, 3H), 4.49 - 4.36 (m, 1H), 4.29 - 4.16 (m, 1H), 4.14 - 4.04 (m, 2H), 4.04 – 4.01 (m, 2H), 3.93 - 3.79 (m, 2H), 3.54 - 3.49 (m, 2H), 3.49 – 3.45 (m, 2H), 3.45 - 3.40 (m, 3H), 3.05 (s, 3H), 1.40 - 1.39 (s, 3H), 1.32 - 1.26 (s, 3H).

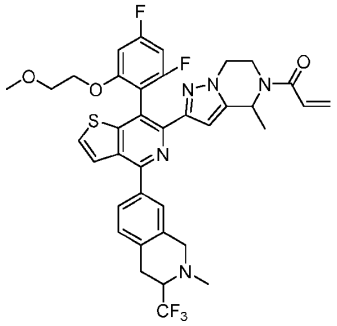
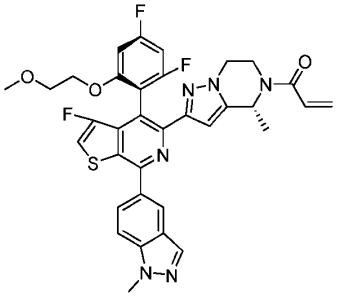
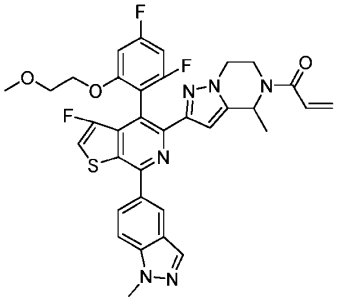
Cmpd. No.	Structure	Analytical data
123a		
124		LCMS m/z [M+1]: 671.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.37 - 9.32 (m, 1H), 8.60 (s, 1H), 8.01 (d, J = 5.5 Hz, 1H), 7.15 (d, J = 5.5 Hz, 1H), 6.92 - 6.79 (m, 1H), 6.74 - 6.66 (m, 2H), 6.35 - 6.23 (m, 1H), 6.05 (s, 1H), 5.86 - 5.78 (m, 1H), 5.70 - 5.47 (m, 1H), 4.91 - 4.88 (m, 1H), 4.50 - 4.35 (m, 1H), 4.28 – 4.21 (m, 1H), 4.14 – 3.91 (m, 4H), 3.82 - 3.64 (m, 2H), 3.47 – 3.38 (m, 4H), 3.16 - 3.07 (m, 3H), 3.05 (s, 3H), 1.92 - 1.76 (m, 3H), 1.50 - 1.36 (m, 3H).
124a		
125		LCMS m/z [M+1]: 671.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.38 - 9.33 (m, 1H), 8.54 - 8.49 (m, 1H), 8.01 (d, J = 5.5 Hz, 1H), 7.14 (d, J = 5.5 Hz, 1H), 6.92 - 6.79 (m, 2H), 6.72 – 6.65 (m, 1H), 6.34 - 6.22 (m, 1H), 6.10 (s, 1H), 5.84 - 5.78 (m, 1H), 5.70 - 5.44 (m, 1H), 4.82 - 4.62 (m, 2H), 4.79 - 4.33 (m, 1H), 4.26 – 4.18 (m, 1H), 4.14 - 4.04 (m, 2H), 4.04 – 3.91 (m, 2H), 3.85 - 3.67 (m, 1H), 3.56 - 3.48 (m,

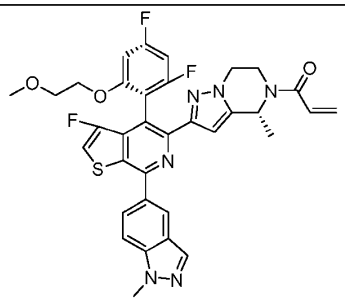
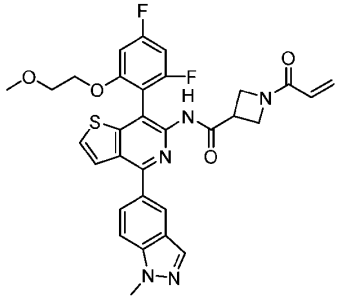
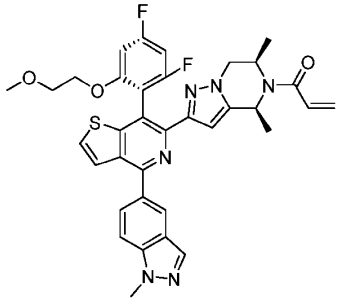
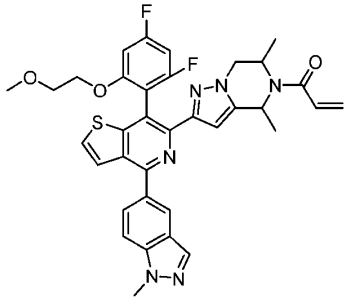
Cmpd. No.	Structure	Analytical data
		1H), 3.41 (t, J = 4.6 Hz, 2H), 3.28 - 3.16 (m, 2H), 3.12 - 3.06 (m, 2H), 3.04 (s, 3H), 1.65 - 1.52 (m, 3H), 1.50 - 1.37 (m, 3H).
125a		
126		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.23 (s, 1H), 8.10 (dd, J = 1.7, 8.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 6.98 – 6.71 (m, 4H), 6.29 (d, J = 16.1 Hz, 1H), 6.04 (s, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.71 -5.42 (m, 1H), 4.29 (dd, J = 12.9, 2.8 Hz, 1H), 4.24 – 4.04 (m, 5H), 4.04 – 3.93 (m, 1H), 3.44 (t, J = 4.5 Hz, 2H), 3.15 (s, 3H), 1.47-1.35 (m, 3H).
126a		

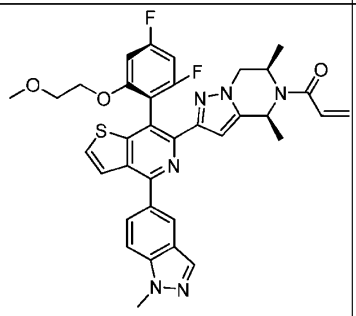
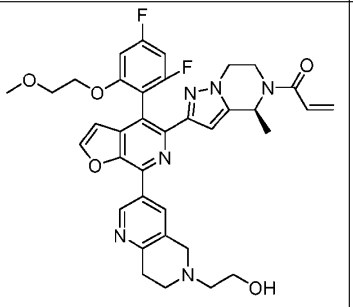
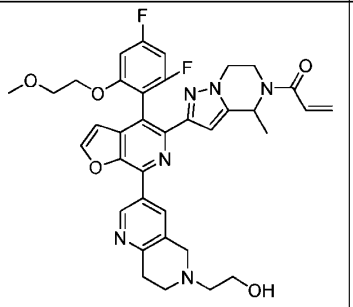
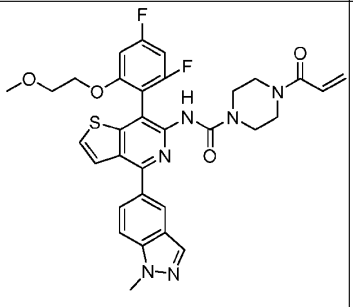
Cmpd. No.	Structure	Analytical data
127		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.21 (s, 1H), 8.07 (dd, J = 8.8, 1.6 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 6.98 – 6.71 (m, 4H), 6.29 (d, J = 16.6 Hz, 1H), 5.98 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.74 – 5.42 (m, 1H), 4.29 (dd, J = 12.8, 2.9 Hz, 1H), 4.23 – 3.99 (m, 6H), 3.48 (t, J = 4.5 Hz, 2H), 3.14 (s, 3H), 1.47 – 1.35 (m, 3H).
128		LCMS m/z [M+1]: 657.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.27 (s, 1H), 8.15 – 8.01 (m, 2H), 7.91 - 7.86 (m, 2H), 7.01 – 6.82 (m, 3H), 6.29 (dd, J = 16.8, 1.6 Hz, 1H), 6.12 (d, J = 18.8 Hz, 1H), 5.84 – 5.67 (m, 2H), 4.36 (d, J = 12.6 Hz, 1H), 4.27 – 4.00 (m, 6H), 3.79 – 3.65 (m, 2H), 3.45 (t, J = 4.5 Hz, 2H), 3.08 (s, 3H).
128a		
129		LCMS m/z [M+1]: 657.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.27 (s, 1H), 8.10 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 8.8, 1.5 Hz, 1H), 7.89 (dd, J = 12.5, 7.2 Hz, 2H), 7.04 – 6.81 (m, 3H), 6.29 (d, J = 17.0 Hz, 1H), 6.11 (d, J = 9.1 Hz, 1H), 5.79 (d, J = 10.7 Hz, 1H), 5.71 – 5.42 (m, 2H), 4.98 (d, J = 12.2 Hz, 1H), 4.37 (d, J = 11.8 Hz, 1H), 4.25 – 3.92 (m, 6H), 3.85 – 3.70 (m, 2H), 3.50 – 3.41 (m, 2H), 3.11 (s, 3H).

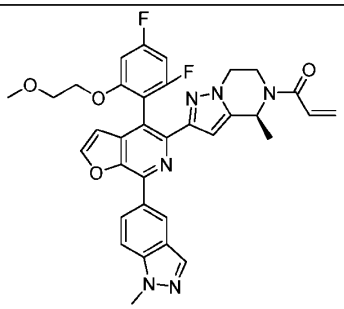
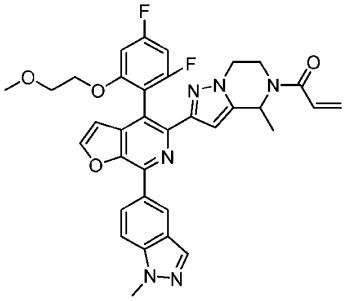
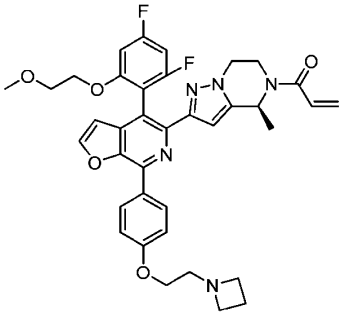
Cmpd. No.	Structure	Analytical data
130		LCMS m/z [M+1]: 663.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 – 8.04 (m, 1H), 7.90 - 7.86 (m, 1H), 7.02 (d, J = 10.8 Hz, 1H), 6.86 - 6.82 (m, 2H), 6.33 (d, J = 16.6 Hz, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.78 – 5.36 (m, 2H), 4.66 (s, 1H), 4.42 (d, J = 10.4 Hz, 2H), 4.33 (d, J = 9.7 Hz, 2H), 4.10 (s, 2H), 3.45 – 3.36 (m, 2H), 3.12 – 2.95 (m, 3H), 2.65-2.18 (m, 2H), 21.96 -1.87 (m, 3H), 1.44 - 1.38 (m, 6H).
130a		
131		LCMS m/z [M+1]: 710.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 – 7.91 (m, 2H), 7.85 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 6.95 – 6. 79 (m, 2H), 6.77 – 6. 69 (m, 1H), 6.36 – 6. 23 (m, 1H), 6.11 (s, 1H), 5.85 – 5. 77 (m, 1H), 5.75 – 5. 44 (m, 1H), 4.64 – 4. 56 (m, 1H), 4.23 (d, J = 12.0 Hz, 1H), 4.16 – 3.98 (m, 3H), 3.61 – 3. 36 (m, 4H), 3.05 (s, 3H), 1.52 – 1. 36 (m, 1H).

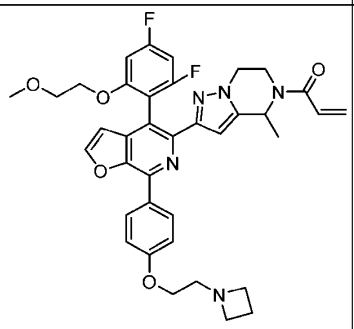
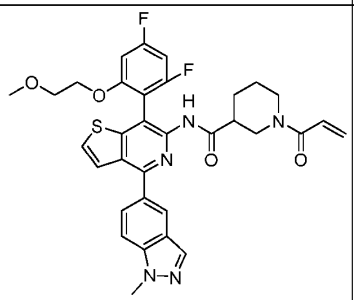
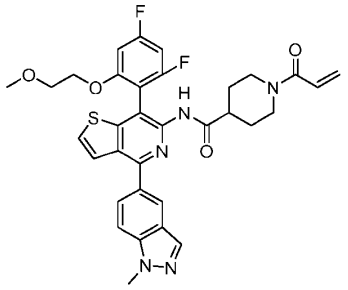
Cmpd. No.	Structure	Analytical data
131a		
132		LCMS m/z [M+1]: 625.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.66 (d, J = 8.9 Hz, 1H), 8.19 (s, 1H), 8.09 (d, J = 2.1 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 6.95 – 6.76 (m, 2H), 6.76 – 6.60 (m, 2H), 6.47 – 6.26 (m, 2H), 5.85 (d, J = 11.8 Hz, 1H), 4.94 (s, 2H), 4.85 (s, 1H), 4.33 (s, 1H), 4.15 (s, 3H), 4.11 – 3.84 (m, 3H), 3.45 (dt, J = 18.4, 4.8 Hz, 2H), 3.10 (d, J = 5.5 Hz, 3H), 1.37 (dd, J = 13.5, 6.4 Hz, 3H).
132a		
133		LCMS m/z [M+1]: 724.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 7.8 Hz, 1H), 7.76 (s, 1H), 7.71 (d, J = 5.6 Hz, 1H), 7.65 (d, J = 5.6 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 6.91 – 6. 79 (m, 2H), 6.69 (td, J = 9.2, 2.3 Hz, 1H), 6.38 – 6. 21 (m, 1H), 6.15 (s, 1H), 5.81 (d, J = 10.6 Hz, 1H), 5.73 – 5. 39 (m, 1H), 4.23 – 3.86 (m, 6H), 3.60 – 3. 48 (m, 1H), 3.44 – 3. 37

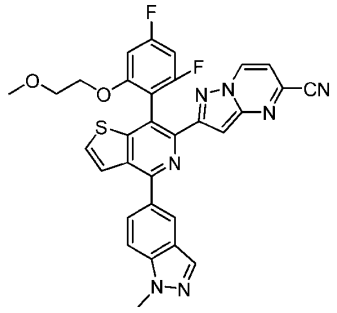
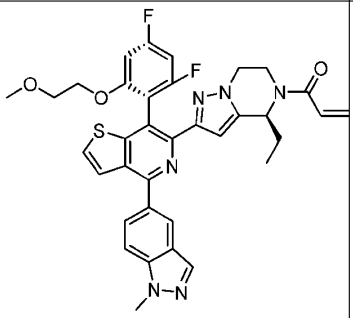
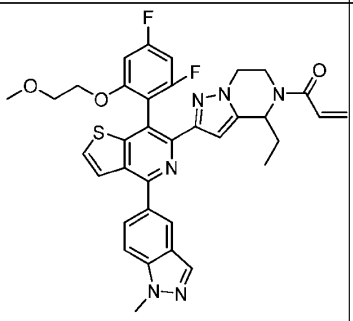
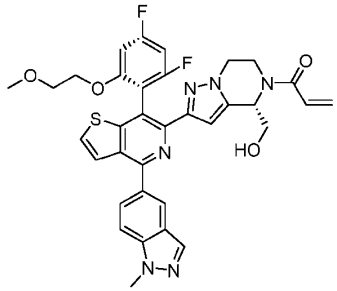
Cmpd. No.	Structure	Analytical data
		(m, 2H), 3.29 – 3.21 (m, 1H), 3.09 – 2.97 (m, 4H), 2.63 (s, 1H), 1.51 – 1. 38 (m, 3H).
133a		
134		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.55 - 7.50 (m, 1H), 6.89-6.73 (m, 2H), 6.68-6.60 (m, 1H), 6.37-6.21 (m, 1H), 6.10 (s, 1H), 5.85 - 5.78 (m, 1H), 5.75 - 5.37 (m, 1H), 4.51 - 4.30 (m, 1H), 4.25 - 4.18 (m, 1H), 4.16 (s, 3H), 4.13 - 3.99 (m, 2H), 3.98 - 3.91 (m, 1H), 3.85 - 3.62 (m, 1H), 3.45 (t, J = 4.7 Hz, 2H), 3.08 (s, 3H), 1.55 - 1.35 (m, 3H).
134a		

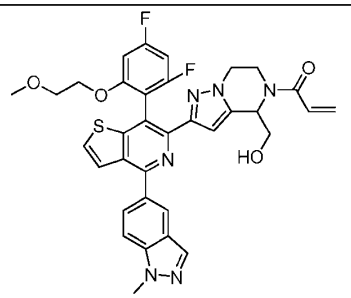
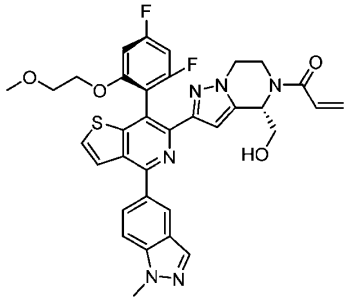
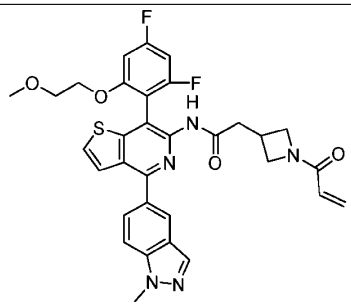
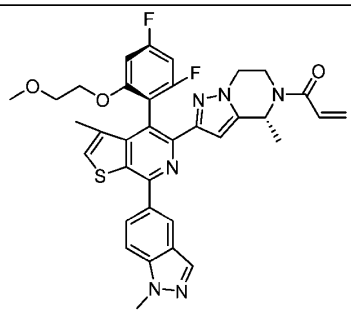
Cmpd. No.	Structure	Analytical data
135		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.55 - 7.50 (m, 1H), 6.89 - 6.75 (m, 2H), 6.66 - 6.57 (m, 1H), 6.37 - 6.21 (m, 1H), 6.08 (s, 1H), 5.85 - 5.78 (m, 1H), 5.75 - 5.37 (m, 1H), 4.51 - 4.30 (m, 1H), 4.24 - 4.17 (m, 1H), 4.16 (s, 3H), 4.12 - 3.96 (m, 3H), 3.85 - 3.64 (m, 1H), 3.46 (t, J = 4.7 Hz, 2H), 3.08 (s, 3H), 1.55 - 1.35 (m, 3H).
136		LCMS m/z [M+1]: 604.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.19 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.83 – 7.75 (m, 2H), 7.71 (d, J = 5.6 Hz, 1H), 6.93 (d, J = 10.8 Hz, 1H), 6.81 (t, J = 9.3 Hz, 1H), 6.26 (dd, J = 20.8, 11.1 Hz, 2H), 5.74 (dd, J = 9.3, 2.5 Hz, 1H), 4.37 (d, J = 8.6 Hz, 2H), 4.26 – 3.92 (m, 7H), 3.69 – 3.48 (m, 3H), 3.25 (d, J = 5.4 Hz, 3H).
137		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.25 (s, 1H), 8.07-8.03 (m, 2H), 7.89-7.84 (m, 2H), 6.96 (d, J = 10.8 Hz, 1H), 6.87-6.80 (m, 2H), 6.35-6.20 (m, 1H), 6.15 (s, 1H), 5.83-5.80 (m, 1H), 5.60-5.45 (m, 1H), 4.25 (s, 2H), 4.19 (s, 3H), 4.15-4.10 (m, 1H), 4.05-3.95 (m, 1H), 3.46 (t, J = 4.8 Hz, 2H), 3.11 (s, 3H), 1.50 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H).
137a		

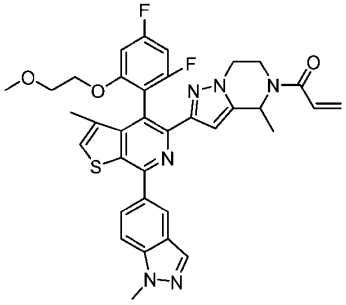
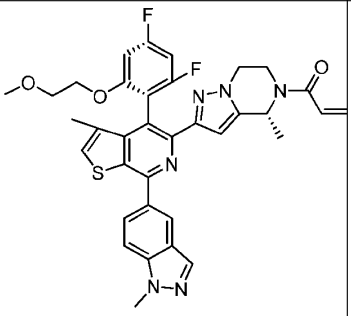
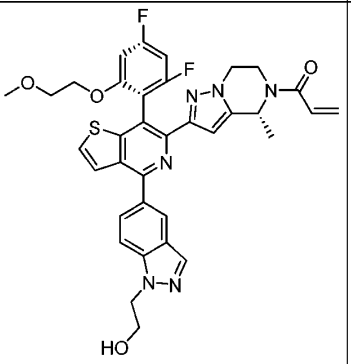
Cmpd. No.	Structure	Analytical data
138		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.27 (s, 1H), 8.11 (d, J = 5.6 Hz, 1H), 8.04 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.91-7.86 (m, 2H), 7.00 (d, J = 10.8 Hz, 1H), 6.87-6.80 (m, 2H), 6.35-6.20 (m, 1H), 6.16 (s, 1H), 5.83-5.80 (m, 1H), 5.60-5.45 (m, 1H), 4.27 (s, 2H), 4.20 (s, 3H), 4.15-4.08 (m, 2H), 3.47 (t, J = 4.4 Hz, 2H), 3.11 (s, 3H), 1.49 (d, J = 6.4 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H).
139		LCMS m/z [M+1]: 671.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.56 (s, 1H), 8.78 (s, 1H), 8.04 (d, J = 2.0 Hz, 1H), 6.76 (dd, J = 18.5, 9.6 Hz, 2H), 6.65 – 6.52 (m, 2H), 6.21 (s, 1H), 6.03 (s, 1H), 5.74 (d, J = 12.0 Hz, 1H), 5.50 (d, J = 92.1 Hz, 1H), 4.68 (s, 2H), 4.32 (s, 1H), 4.13 (d, J = 12.0 Hz, 1H), 4.07 – 3.53 (m, 8H), 3.50 – 3.40 (m, 2H), 3.33 (dd, J = 8.8, 4.6 Hz, 4H), 3.00 (d, J = 1.9 Hz, 3H), 1.35 (s, 3H).
139a		
140		LCMS m/z [M+1]: 633.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 8.25 (s, 1H), 8.06 – 7.99 (m, 1H), 7.88 (t, J = 7.5 Hz, 2H), 7.80 (d, J = 5.7 Hz, 1H), 7.00 (d, J = 10.6 Hz, 1H), 6.88 (d, J = 1.9 Hz, 1H), 6.78 (dd, J = 16.8, 10.6 Hz, 1H), 6.26 (dd, J = 16.8, 1.9 Hz, 1H), 5.80 (dd, J = 10.6, 1.9 Hz, 1H), 4.28 – 4.17 (m, 5H), 3.71 – 3.56 (m, 6H), 3.52 (s, 4H), 3.24 (s, 3H).

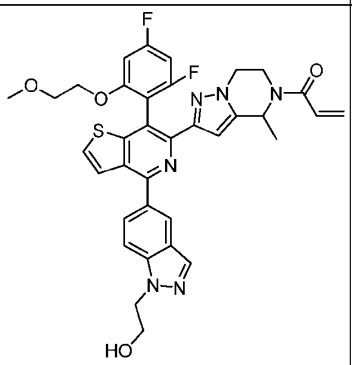
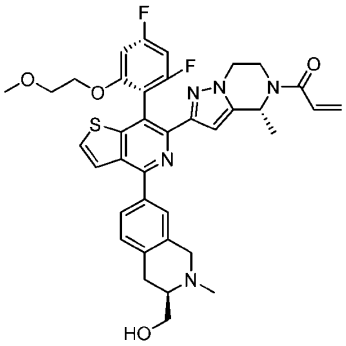
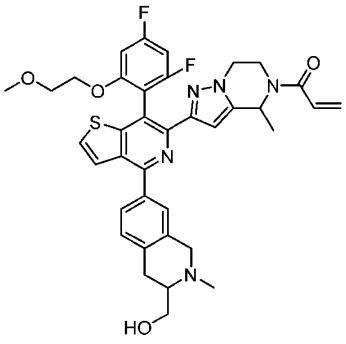
Cmpd. No.	Structure	Analytical data
141		LCMS m/z [M+1]: 625.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (s, 1H), 8.59 (d, J = 9.6 Hz, 1H), 8.20 (s, 1H), 8.14 (d, J = 1.4 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 6.88 (dd, J = 17.0, 10.2 Hz, 2H), 6.78 – 6.69 (m, 2H), 6.33 (s, 1H), 6.13 (s, 1H), 5.85 (dd, J = 10.6, 1.2 Hz, 1H), 5.75 (s, 1H), 5.54 (s, 1H), 4.53 – 4.40 (m, 1H), 4.28 (dt, J = 6.0, 4.2 Hz, 1H), 4.17 (s, 3H), 4.16 – 4.05 (m, 2H), 4.00 – 3.91 (m, 1H), 3.46 (dd, J = 7.6, 4.6 Hz, 2H), 3.12 (d, J = 3.4 Hz, 3H), 1.47 (s, 3H).
141a		
142		LCMS m/z [M+1]: 670.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, J = 8.4 Hz, 2H), 8.20 (s, 1H), 7.26 (d, J = 8.6 Hz, 2H), 6.88 (dd, J = 17.0, 9.4 Hz, 2H), 6.79 – 6.67 (m, 2H), 6.37 – 6.26 (m, 1H), 6.11 (s, 1H), 5.85 (d, J = 10.8 Hz, 1H), 5.77 – 5.52 (m, 1H), 4.40 – 4.26 (m, 7H), 4.20 – 4.06 (m, 2H), 4.00 – 3.78 (m, 2H), 3.77 – 3.70 (m, 2H), 3.46 (dd, J = 7.6, 4.0 Hz, 2H), 3.28 (s, 1H), 3.13 (d, J = 3.2 Hz, 3H), 2.74 – 2.62 (m, 1H), 2.49 (s, 1H), 1.46 (s, 3H).

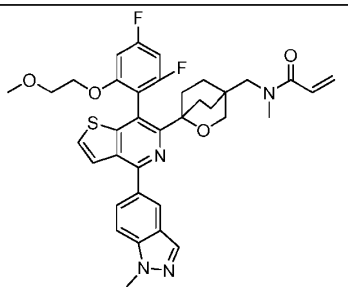
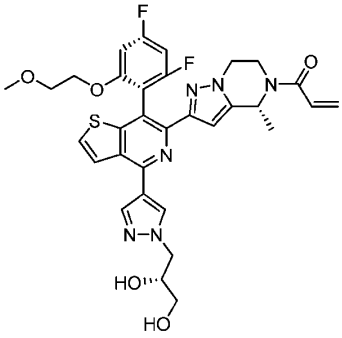
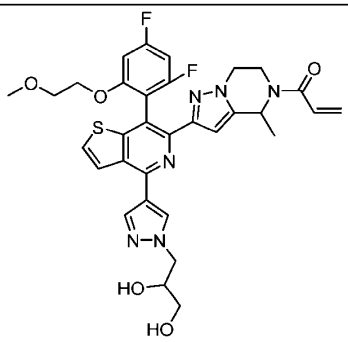
Cmpd. No.	Structure	Analytical data
142a		
143		LCMS m/z [M+1]: 632.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.19 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 7.0 Hz, 2H), 7.74 – 7.67 (m, 1H), 6.94 (s, 1H), 6.85 – 6.69 (m, 2H), 6.20 (dd, J = 15.8, 6.4 Hz, 1H), 5.79 – 5.70 (m, 1H), 4.37 (s, 1H), 4.23 – 4.14 (m, 4H), 4.06 (s, 1H), 3.72 – 3.56 (m, 2H), 3.30 – 3.20 (m, 3H), 3.17 – 3.00 (m, 1H), 2.86 – 2.70 (m, 1H), 2.47 (s, 1H), 1.96 (s, 1H), 1.74 (dd, J = 28.2, 17.0 Hz, 2H), 1.59 (d, J = 12.9 Hz, 1H), 1.47 (s, 1H).
144		LCMS m/z [M+1]: 632.0 ^{1}H NMR (400 MHz, CD_3OD) δ 10.03 (s, 1H), 8.29 (s, 1H), 8.22 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.84 (t, J = 8.2 Hz, 2H), 7.71 (d, J = 5.6 Hz, 1H), 6.98 (dd, J = 16.4, 7.2 Hz, 2H), 6.77 (dd, J = 16.6, 10.5 Hz, 1H), 6.07 (dd, J = 16.7, 2.4 Hz, 1H), 5.65 (dd, J = 10.5, 2.3 Hz, 1H), 4.22 – 4.05 (m, 6H), 3.93 (s, 1H), 3.51 (s, 2H), 3.05 (s, 4H), 2.70 (d, J = 11.3 Hz, 1H), 1.66 – 1.52 (m, 2H), 1.18 (d, J = 45.4 Hz, 3H).

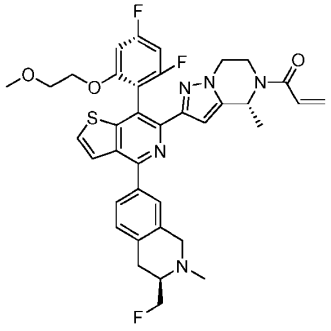
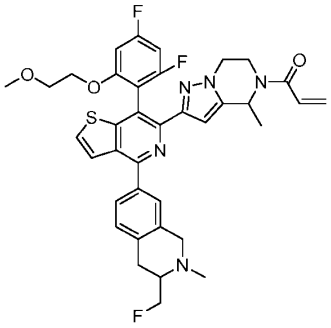
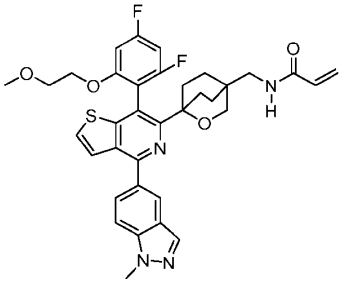
Cmpd. No.	Structure	Analytical data
145		LCMS m/z [M+1]: 594.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.65 (d, J = 7.2 Hz, 1H), 8.36 (s, 1H), 8.14 – 8.08 (m, 2H), 7.75 (d, J = 5.6 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.19 (s, 1H), 7.00 (d, J = 7.1 Hz, 1H), 6.68 – 6.57 (m, 2H), 4.17 (s, 3H), 4.05 – 3.92 (m, 2H), 3.38 (t, J = 4.9 Hz, 2H), 3.03 (s, 3H).
146		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.16 (s, 1H), 8.08 (dd, J = 8.7, 1.4 Hz, 1H), 7.77– 7.65 (m, 3H), 6. 94 – 6.80 (m, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6. 36– 6.21 (m, 1H), 6.16 (d, J = 9.6 Hz, 1H), 5.81 (d, J = 10.6 Hz, 1H), 5.66 – 5. 21 (m, 1H), 4.28 – 4. 12 (m, 4H), 4.10 – 3.89 (m, 3H), 3.41 (t, J = 4.6 Hz, 2H), 3.04 (s, 3H), 1.92 – 1. 73 (m, 2H), 1.01 – 0.88 (m, 3H).
146a		
147		LCMS m/z [M+1]: 657.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (s, 1H), 8.24 (s, 1H), 8.06 - 8.02 (m, 2H), 7.88 - 7.82 (m, 2H), 6.97 - 6.80 (m, 3H), 6.28 (d, J = 16.6 Hz, 1H), 6.13 (s, 1H), 5.84 - 5.77 (m, 1H), 5.65 - 5.40 (m, 1H), 4.98 - 4.86 (m, 1H), 4.48 - 4.32 (m, 1H), 4.19 (s, 3H), 4.15 - 4.01 (m, 3H), 3.82 - 3.71 (m, 2H), 3.48 - 3.40 (m, 3H), 3.09 (s, 3H).

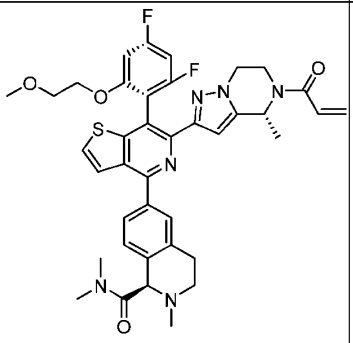
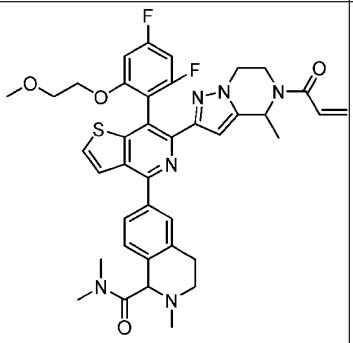
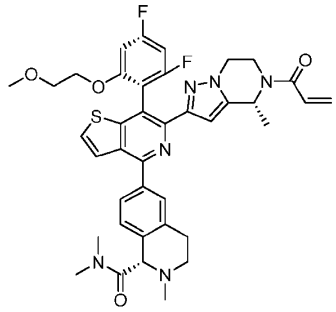
Cmpd. No.	Structure	Analytical data
147a		
148		LCMS m/z [M+1]: 657.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.25 (s, 1H), 8.05 - 8.03 (m, 2H), 7.89 - 7.84 (m, 2H), 6.97 - 6.80 (m, 3H), 6.98 (d, J = 10.6 Hz, 1H), 6.93 - 6.80 (m, 2H), 6.28 (dd, J = 16.6, 1.2 Hz, 1H), 6.12 (d, J = 18.6 Hz, 1H), 5.84 - 5.77 (m, 1H), 5.67 - 5.40 (m, 1H), 4.98 - 4.86 (m, 1H), 4.48 - 4.32 (m, 1H), 4.19 (s, 3H), 4.15 - 4.01 (m, 3H), 3.79 - 3.68 (m, 2H), 3.48 - 3.43 (m, 3H), 3.07 (s, 3H).
149		LCMS m/z [M+1]: 618.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.23 (s, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.86 (dd, J = 17.4, 7.2 Hz, 2H), 7.79 (d, J = 5.6 Hz, 1H), 7.00 (d, J = 10.7 Hz, 1H), 6.87 (t, J = 9.3 Hz, 1H), 6.39 – 6.19 (m, 2H), 5.74 (d, J = 9.1 Hz, 1H), 4.40 (dd, J = 13.2, 8.7 Hz, 1H), 4.33 – 4.04 (m, 6H), 3.99 – 3.84 (m, 1H), 3.71 (ddd, J = 17.1, 10.7, 6.0 Hz, 1H), 3.60 (s, 2H), 3.23 (d, J = 1.7 Hz, 3H), 3.08 – 2.96 (m, 1H), 2.81 – 2.68 (m, 2H).
150		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (d, J = 2.0 Hz, 1H), 8.26 (s, 1H), 8.19 (s, 1H), 8.10 (dd, J = 8.8, 1.7 Hz, 1H), 7.93 – 7.87 (m, 1H), 6.98 - 6.91 (m, 1H), 6.90 - 6.79 (m, 1H), 6.77 (td, J = 9.1, 2.3 Hz, 1H), 6.29 (d, J = 16.6 Hz, 1H), 5.93 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.70 - 5.48 (m, 1H), 4.52 - 4.40 (m, 1H), 4.36 – 4.31 (m, 1H),

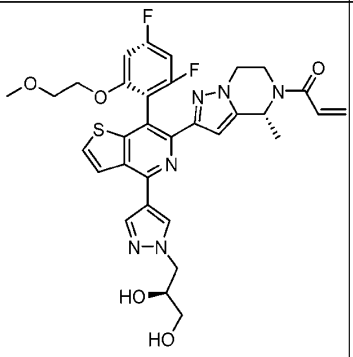
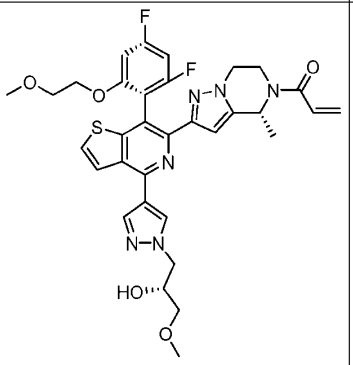
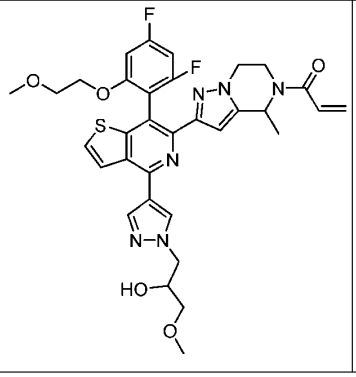
Cmpd. No.	Structure	Analytical data
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150a		
151		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (d, J = 2.0 Hz, 1H), 8.26 (s, 1H), 8.19 (s, 1H), 8.10 (dd, J = 8.8, 1.7 Hz, 1H), 7.93 – 7.87 (m, 1H), 6.98 - 6.91 (m, 1H), 6.90 - 6.79 (m, 1H), 6.77 (td, J = 9.1, 2.3 Hz, 1H), 6.29 (d, J = 16.6 Hz, 1H), 5.93 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.70 - 5.48 (m, 1H), 4.52 - 4.40 (m, 1H), 4.36 – 4.31 (m, 1H), 4.19 (s, 3H), 4.19 – 4.10 (m, 2H), 3.83 - 3.71 (m, 1H), 3.49 (t, J = 4.5 Hz, 2H), 3.10 (s, 3H), 2.04 (d, J = 1.1 Hz, 3H), 1.48 - 1.34 (s, 3H).
152		LCMS m/z [M+1]: 671.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.22 (s, 1H), 8.08 (dd, J = 8.8, 1.3 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.73 (q, J = 5.6 Hz, 2H), 6.86 (dd, J = 16.8, 10.6 Hz, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.37 – 6.18 (m, 2H), 5.83 (d, J = 10.7 Hz, 1H), 5.61 (d, J = 82.5 Hz, 1H), 4.61 (t, J = 5.4 Hz, 2H), 4.43 (s, 1H), 4.21 (dd, J = 12.6, 2.6 Hz, 1H), 4.08 (ddd, J = 17.0, 10.8, 5.0 Hz, 5H), 3.77 (s, 1H), 3.45 (t, J = 4.6 Hz, 2H), 3.06 (s, 3H), 1.45 (s, 3H).

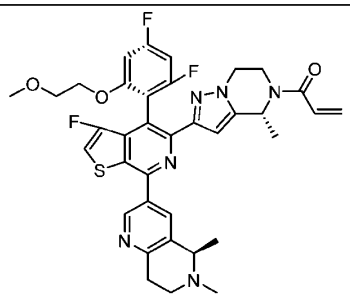
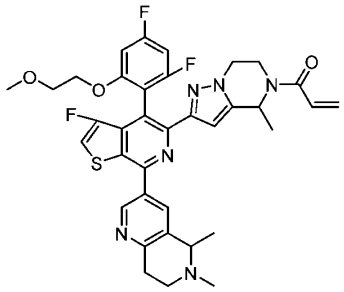
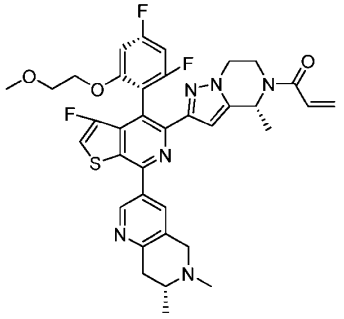
Cmpd. No.	Structure	Analytical data
152a		
153		LCMS m/z [M+1]: 686.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 – 7.93 (m, 2H), 7.89 (s, 1H), 7.75 (d, J = 5.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.00 – 6.71 (m, 3H), 6.29 (d, J = 15.0 Hz, 1H), 6.09 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.71 - 5.42 (m, 1H), 4.71 - 4.56 (m, 2H), 4.28 (dd, J = 12.8, 2.9 Hz, 1H), 4.21 – 4.02 (m, 4H), 3.85 – 3.71 (m, 2H), 3.44 (t, J = 4.5 Hz, 2H), 3.15 (s, 2H), 3.06 (s, 3H), 1.47 - 1.35 (m, 3H).
153a		

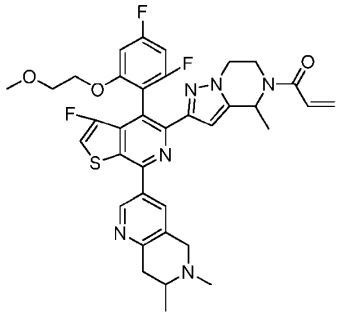
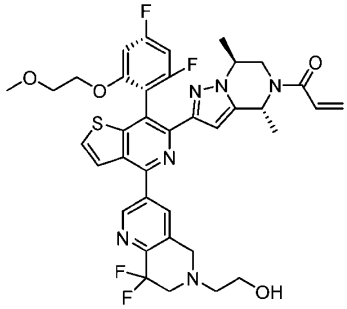
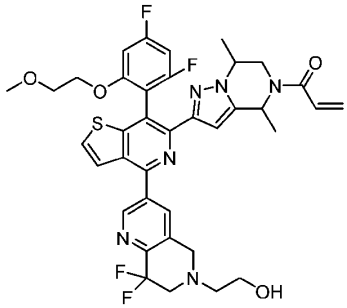
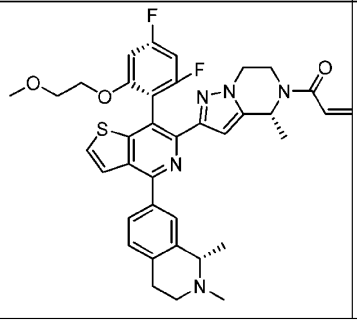
Cmpd. No.	Structure	Analytical data
154		LCMS m/z [M+1]: 659.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (s, 1H), 8.29 (s, 1H), 8.17 – 8.09 (m, 1H), 8.02 – 7.87 (m, 3H), 7.06 (d, J = 10.9 Hz, 1H), 6.92 (td, J = 9.2, 2.1 Hz, 1H), 6.81 – 6.68 (m, 1H), 6.32 – 6.13 (m, 1H), 5.77 – 5.69 (m, 1H), 4.28 – 4.18 (m, 4H), 4.17 – 4.10 (m, 1H), 4.03 – 3.96 (m, 2H), 3.51 – 3.46 (m, 2H), 3.14 (s, 2H), 3.10 (s, 3H), 2.27 – 1.95 (m, 4H), 1.80 – 1.60 (m, 4H).
155		LCMS m/z [M+1]: 651.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.33 (s, 1H), 7.91 (d, J = 5.6 Hz, 1H), 7.78 (d, J = 5.6 Hz, 1H), 6.87 (dd, J = 18.8, 8.4 Hz, 2H), 6.71 (td, J = 9.2, 2.2 Hz, 1H), 6.32 (s, 1H), 6.14 (s, 1H), 5.84 (d, J = 10.7 Hz, 1H), 5.61 (d, J = 82.2 Hz, 1H), 4.47 (dd, J = 14.0, 4.1 Hz, 2H), 4.35 – 4.19 (m, 2H), 4.18 – 3.97 (m, 4H), 3.78 (s, 1H), 3.61 (d, J = 5.1 Hz, 2H), 3.43 (t, J = 4.6 Hz, 2H), 3.04 (s, 3H), 1.44 (s, 3H).
155a		

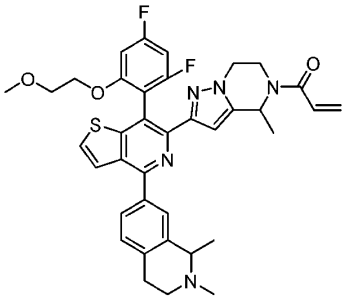
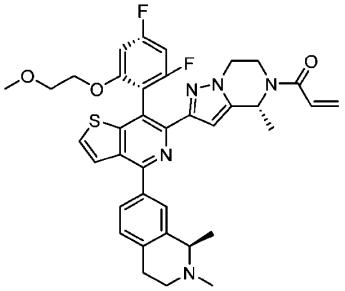
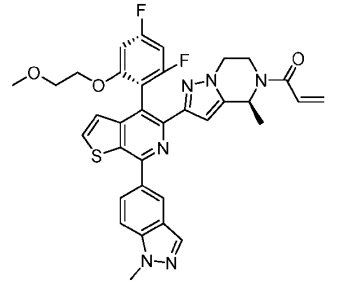
Cmpd. No.	Structure	Analytical data
156		LCMS m/z [M+1]: 688.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 6.94 – 6.69 (m, 3H), 6.29 (d, J = 15.9 Hz, 1H), 6.12 (s, 1H), 5.82 (dd, J = 10.6, 1.5 Hz, 1H), 5.71 - 5.42 (m, 1H), 5.12 (d, J = 8.0 Hz, 1H), 5.13 – 4.74 (m, 3H), 4.23 (dd, J = 12.8, 2.6 Hz, 1H), 4.17 – 3.98 (m, 4H), 3.50 – 3.37 (m, 4H), 3.16 (s, 3H), 3.05 (s, 3H), 1.47 - 1.35 (m, 3H).
156a		
157		LCMS m/z [M+1]: 645.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.29 (s, 1H), 8.13 (d, J = 5.6 Hz, 1H), 8.00 – 7.89 (m, 3H), 7.09 – 7.03 (m, 1H), 6.96 – 6.88 (m, 1H), 6.30 – 6.16 (m, 2H), 5.66 (dd, J = 8.8, 3.1 Hz, 1H), 4.29 – 4.10 (m, 5H), 3.95 (s, 2H), 3.54 – 3.44 (m, 2H), 3.14 – 3.07 (m, 5H), 2.26 – 2.14 (m, 2H), 2.10 – 1.95 (m, 2H), 1.76 – 1.66 (m, 2H), 1.65 – 1.53 (m, 2H).

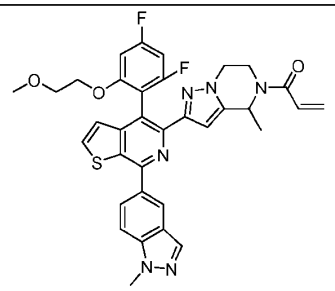
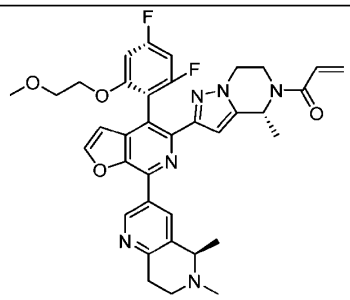
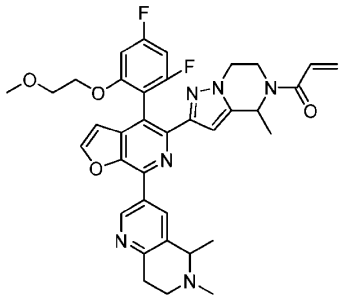
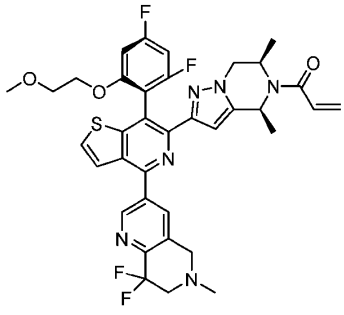
Cmpd. No.	Structure	Analytical data
158		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, J = 5.2 Hz, 1H), 7.41 - 7.31 (m, 2H), 7.20 (d, J = 6.8 Hz, 1H), 7.04 (d, J = 5.6 Hz, 1H), 6.92 - 6.77(m, 2H), 6.74 - 6.66 (m, 1H), 6.23 - 6.17 (m, 1H), 5.81 (d, J = 10.4 Hz, 1H), 5.72 - 5.56 (m, 1H), 4.16 - 3.94 (m, 4H), 3.44 (t, J = 4.4 Hz, 2H), 3.24 - 3.12 (m, 1H), 3.05 (s, 3H), 2.89 - 2.76 (m, 2H), 2.49 (d, J = 3.6 Hz, 6H), 2.15 (s, 3H), 1.52 - 1.36 (m, 3H).
158a		
159		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (d, J = 5.6 Hz, 1H), 7.43 - 7.33 (m, 1H), 7.22 - 7.16 (m, 1H), 7.05 (d, J = 5.2 Hz, 1H), 6.94 - 6.78 (m, 2H), 6.72 - 6.66 (m, 1H), 6.32 - 6.15 (m, 2H), 5.85 - 5.78 (m, 1H), 5.70 - 5.53 (m, 1H), 4.21 - 3.98 (m, 4H), 3.51 - 3.38 (m, 3H), 3.22 - 3.12 (m, 4H), 2.94 - 2.78 (m, 2H), 2.48 - 2.36 (m, 6H), 2.24 (s, 3H), 1.50 - 1.36 (m, 3H).

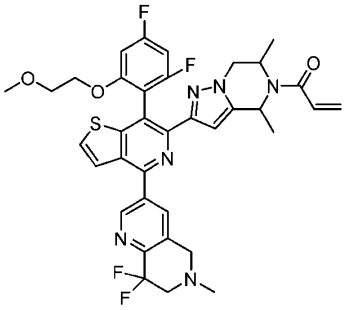
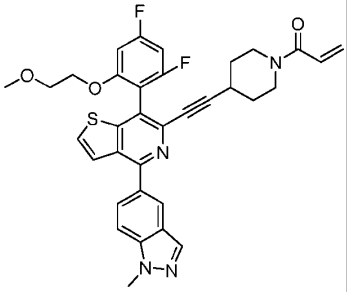
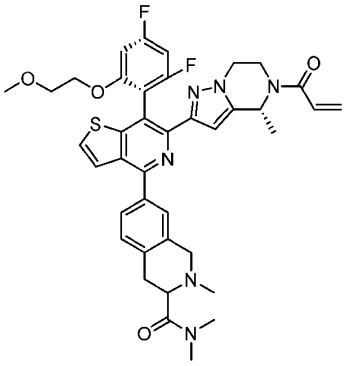
Cmpd. No.	Structure	Analytical data
160		LCMS m/z [M+1]: 651.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, J = 21.4 Hz, 1H), 8.34 (s, J = 6.9 Hz, 1H), 7.90 (d, J = 5.6 Hz, 1H), 7.76 (d, J = 5.6 Hz, 1H), 6.87 (dd, J = 17.8, 9.3 Hz, 2H), 6.71 (td, J = 9.1, 2.2 Hz, 1H), 6.32 (s, 1H), 6.14 (s, 1H), 5.84 (d, J = 10.4 Hz, 1H), 5.61 (d, J = 83.4 Hz, 1H), 4.47 (dd, J = 14.0, 4.1 Hz, 2H), 4.34 – 4.20 (m, J = 15.7, 13.3, 5.4 Hz, 2H), 4.17 – 3.91 (m, 4H), 3.78 (s, 1H), 3.61 (d, J = 5.1 Hz, 2H), 3.43 (t, J = 4.6 Hz, 2H), 3.04 (s, 3H), 1.44 (s, 3H).
161		LCMS m/z [M+1]: 665.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.33 (s, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.76 (d, J = 5.6 Hz, 1H), 6.87 (dd, J = 18.7, 8.5 Hz, 2H), 6.71 (td, J = 9.2, 2.3 Hz, 1H), 6.32 (s, 1H), 6.16 (d, J = 11.8 Hz, 1H), 5.84 (d, J = 10.6 Hz, 1H), 5.72 (s, 1H), 4.37 (ddd, J = 21.4, 13.8, 5.8 Hz, 3H), 4.25 – 4.16 (m, 2H), 4.15 – 3.98 (m, 3H), 3.78 (s, 1H), 3.52 – 3.39 (m, 7H), 3.04 (s, 3H), 1.55 – 1.35 (m, 3H).
161a		

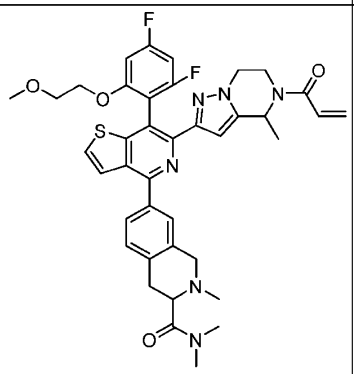
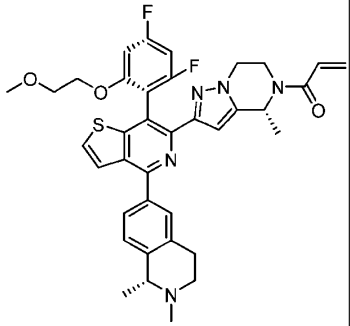
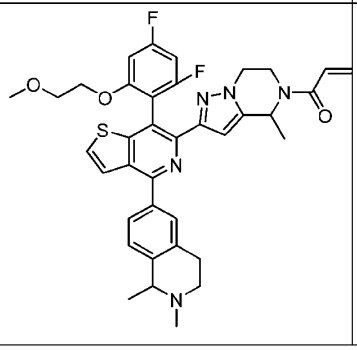
Cmpd. No.	Structure	Analytical data
162		LCMS m/z [M+1]: 689.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (s, 1H), 8.35 (s, 1H), 7.57 (d, J = 2.3 Hz, 1H), 6.90 - 6.76 (m, 2H), 6.67 - 6.58 (m, 1H), 6.37 - 6.21 (m, 1H), 6.06 (s, 1H), 5.86-5.79 (m, 1H), 5.74 - 5.40 (m, 1H), 4.27 - 4.17 (m, 1H), 4.15 - 3.96 (m, 4H), 3.92 - 3.80 (m, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.25 - 3.10 (m, 2H), 3.06 (s, 3H), 2.96 - 2.86 (m, 1H), 2.59 - 2.52 (m, 3H), 1.60 (d, J = 6.6 Hz, 3H), 1.53 - 1.37 (m, 3H).
162a		
163		LCMS m/z [M+1]: 689.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (s, 1H), 8.46 (d, J = 1.6 Hz, 1H), 7.58 (d, J = 2.3 Hz, 1H), 6.92 - 6.75 (m, 2H), 6.67 - 6.58 (m, 1H), 6.37 - 6.20 (m, 1H), 6.04 (s, 1H), 5.86 - 5.78 (m, 1H), 5.76 - 5.40 (m, 1H), 4.27 - 4.17 (m, 1H), 4.15 - 3.96 (m, 4H), 3.44 (t, J = 4.6 Hz, 2H), 3.22 - 3.15 (m, 2H), 3.07 (s, 3H), 3.05 - 2.96 (m, 1H), 2.65 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H), 1.55 - 1.37 (m, 3H).

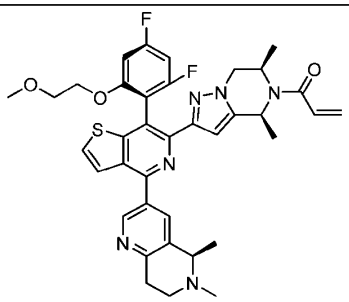
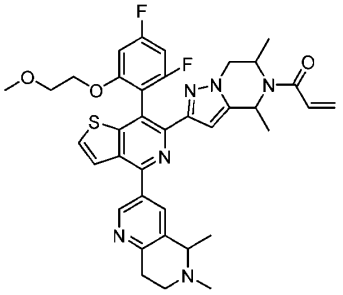
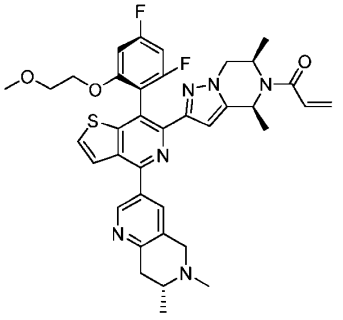
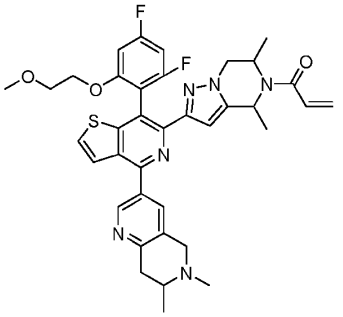
Cmpd. No.	Structure	Analytical data
163a		
164		LCMS m/z [M+1]: 737.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.28 (s, 1H), 8.45 (s, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.67-6.91 (m, 3H), 6.33 (d, J = 16.7 Hz, 1H), 6.25 (s, 1H), 5.84 (d, J = 10.5 Hz, 1H), 5.71 - 5.42 (m, 1H), 4.72 (s, 1H), 4.50 - 4.42 (m, 3H), 4.13 - 4.01 (m, 2H), 3.95 - 3.84 (m, 4H), 3.43 (t, J = 4.6 Hz, 2H), 3.30 - 3.25 (m, 2H), 3.05 (s, 3H). 1.47-1.31 (m, 3H), 1.35 - 1.25 (m, 3H).
164a		
165		LCMS m/z [M+1]: 670.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 7.62 (d, J = 5.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 6.93 - 6.77 (m, 2H), 6.73 - 6.65 (m, 1H), 6.34 - 6.23 (m, 1H), 6.13 (s, 1H), 5.84 - 5.78 (m, 1H), 5.72 - 5.54 (m, 1H), 4.25 - 4.15 (m, 1H), 4.12 - 3.98 (m, 4H), 3.46 - 3.39 (m, 2H),

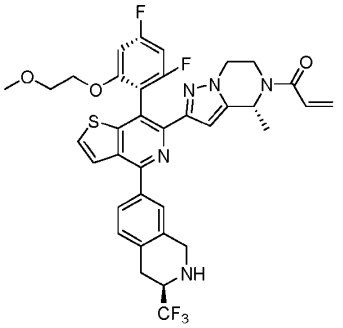
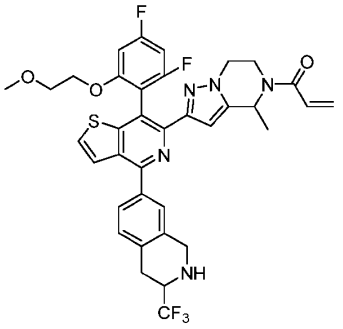
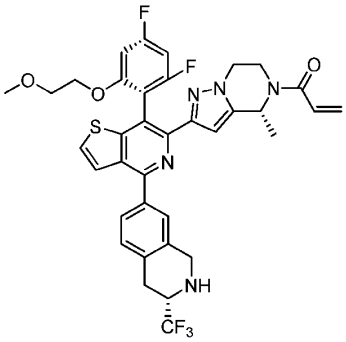
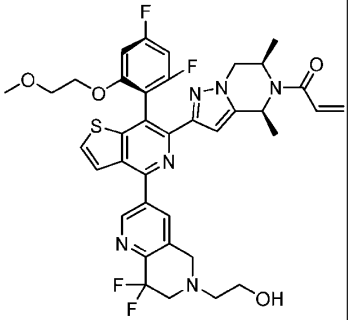
Cmpd. No.	Structure	Analytical data
		3.12 - 3.01 (m, 5H), 2.97 - 2.87 (m, 1H), 2.63 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H), 1.48 - 1.37 (m, 3H).
165a		
166		LCMS m/z [M+1]: 670.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (s, 1H), 7.76 - 7.70 (m, 2H), 7.62 (d, J = 5.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 6.93 - 6.77 (m, 2H), 6.73 - 6.65 (m, 1H), 6.34 - 6.23 (m, 1H), 6.13 (s, 1H), 5.84 - 5.78 (m, 1H), 5.72 - 5.54 (m, 1H), 4.15-4.25 (m,1H), 3.98-4.12 (m, 3H), 3.85-3.93 (m,1H), 3.46 - 3.39 (m, 2H), 3.24 - 3.15 (m, 1H), 3.06 - 2.96 (m, 5H), 2.85 - 2.75 (m, 1H), 2.56 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H), 1.48 - 1.37 (m, 3H).
167		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.47 (d, J = 5.4 Hz, 1H), 8.26 (s, 1H), 8.16 (d, J = 5.4 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 5.32 Hz, 1H), 6.95 (d, J = 10.7 Hz, 1H), 6.90 – 6.76 (m, 2H), 6.30 (d, J = 16.8 Hz, 1H), 6.01 (s, 1H), 5.83 (d, J = 10.3 Hz, 1H), 5.77 – 5.41 (m, 1H), 4.39 – 4.31 (m, 1H), 4.24 – 4.06 (m, 5H), 4.03 – 3.93 (m, 1H), 3.44 (t, J = 4.0 Hz, 2H), 3.11 (s, 3H), 1.54 – 1.34 (m, 3H).

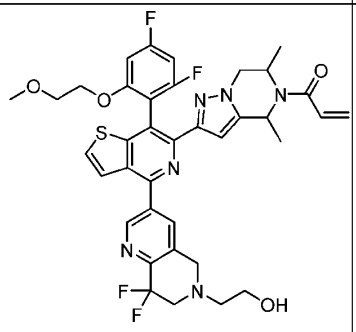
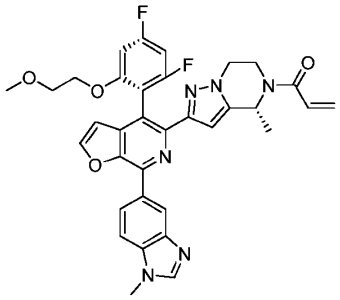
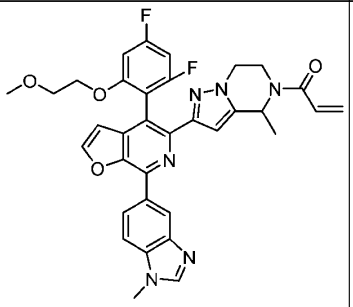
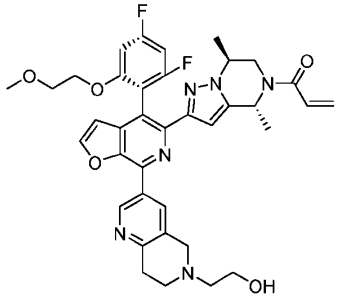
Cmpd. No.	Structure	Analytical data
167a		
168		LCMS m/z [M+1]: 655.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.47 (d, J = 1.9 Hz, 1H), 8.80 (d, J = 1.7 Hz, 1H), 8.14 (d, J = 2.2 Hz, 1H), 6.98 – 6.81 (m, 2H), 6.78 – 6.66 (m, 2H), 6.32 (s, 1H), 6.14 (s, 1H), 5.85 (d, J = 12.0 Hz, 1H), 5.64 (d, J = 77.3 Hz, 1H), 4.42 (s, 1H), 4.31 – 4.22 (m, 1H), 4.17 – 4.03 (m, 2H), 4.00 – 3.89 (m, 2H), 3.45 (t, J = 4.6 Hz, 2H), 3.31 – 3.24 (m, 1H), 3.18 – 3.06 (m, 5H), 2.93 – 2.86 (m, 1H), 2.58 (s, 3H), 2.50 (d, J = 9.7 Hz, 1H), 1.58 (d, J = 6.7 Hz, 3H), 1.50 – 1.39 (m, 3H).
168a		
169		LCMS m/z [M+1]: 707.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.29 (s, 1H), 8.45 (s, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.89 - 6.80 (m, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.30 - 6.25 (m, 2H), 5.80 (d, J = 10.4 Hz, 1H), 5.48 - 5.47 (m, 1H), 4.39 (s, 2H), 4.18 - 4.06 (m, 3H), 4.02 - 3.97 (m, 1H), 3.85 (t, J = 11.8 Hz, 2H), 3.42 (t, J = 4.6 Hz,

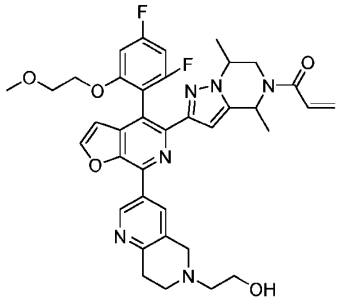
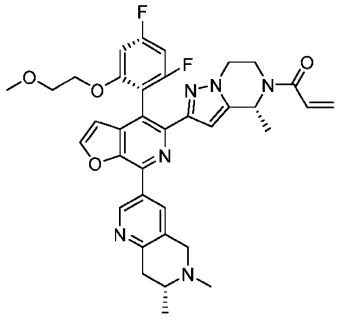
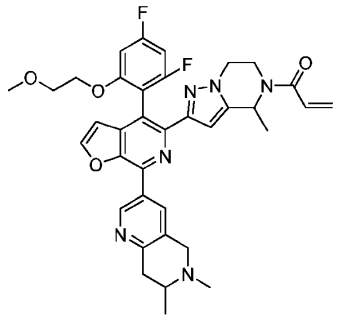
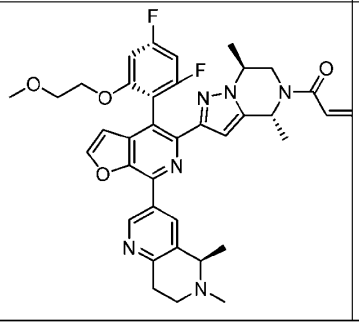
Cmpd. No.	Structure	Analytical data
		2H), 3.05 (s, 3H), 2.94 (s, 3H), 1.52 (d, J = 6.0 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H).
169a		
170		LCMS m/z [M+1]: 613.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.16 (s, 1H), 7.90 (dd, J = 8.8, 1.5 Hz, 1H), 7.79 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 5.6 Hz, 1H), 6.93 (d, J = 11.0 Hz, 1H), 6.81-6.70 (m, 2H), 6.17 (dd, J = 16.8, 1.9 Hz, 1H), 5.73 (dd, J = 10.6, 1.8 Hz, 1H), 4.19-4.10 (m, 5H), 3.69-3.59 (m, 1H), 3.58-3.45 (m, 5H), 3.08 (s, 3H), 2.98-2.90 (m, 1H), 1.85-1.70 (m, 2H), 1.61-1.48 (m, 2H).
171		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 - 7.94 (m, 1H), 7.92 - 7.88 (m, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 6.92 - 6.79 (m, 2H), 6.77 – 6.68 (m, 1H), 6.33 - 6.22 (s, , 1H), 6.16 - 6.06 (m, 1H), 5.86 - 5.76 (m, 1H), 5.68 - 5.49 (m,1H), 4.96 – 4.88 (m, 2H), 4.83 - 4.73 (m , 2H), 4.64 - 4.58 (m, 1H), 4.25 - 4.17 (m, 1H), 4.13 - 3.99 (m, 3H), 3.82 - 3.68(m,1H), 3.64 - 3.55 (m, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.25 (s, 3H), 3.11 - 3.06 (m, 5H), 3.04 (s, 3H), 1.53 - 1.38 (m, 3H).

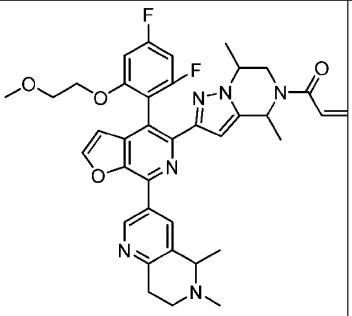
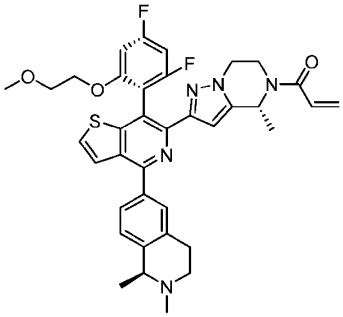
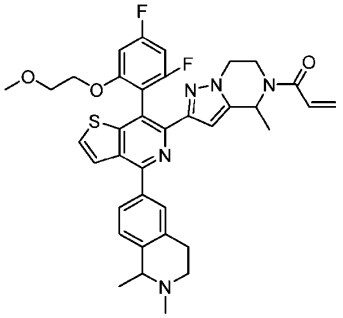
Cmpd. No.	Structure	Analytical data
171a		
172		LCMS m/z [M+1]: 670.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 – 7.79 (m, 2H), 7.76 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 6.87 (dd, J = 17.1, 10.7 Hz, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.32 (s, 1H), 6.18 (s, 1H), 5.84 (d, J = 11.9 Hz, 1H), 5.61 (d, J = 86.3 Hz, 1H), 4.42 (s, 1H), 4.25 (dd, J = 46.4, 4.7 Hz, 1H), 4.08 (dd, J = 10.7, 5.9 Hz, 3H), 3.80 (s, 1H), 3.60 – 3.41 (m, 4H), 3.22 (d, J = 8.8 Hz, 3H), 3.06 (s, 3H), 2.85 (d, J = 17.6 Hz, 3H), 1.66 (d, J = 6.8 Hz, 3H), 1.45 (s, 3H).
172a		

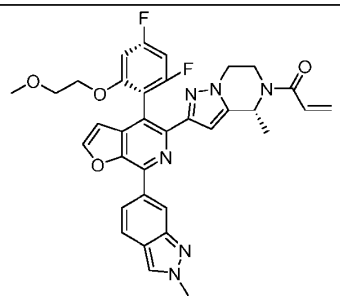
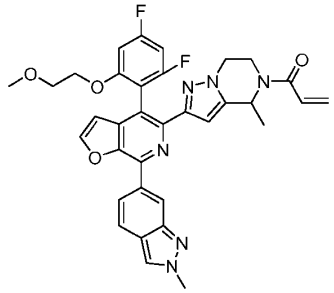
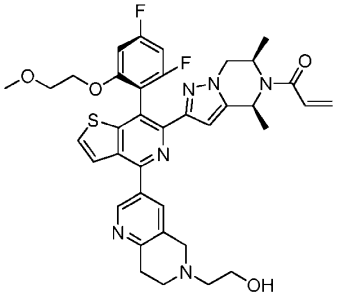
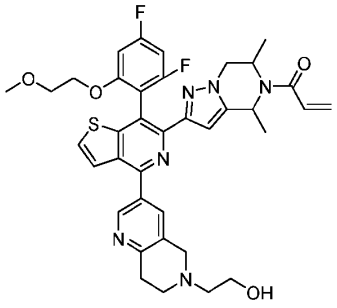
Cmpd. No.	Structure	Analytical data
173		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.45 (s, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.93 - 6.85 (m, 2H), 6.78 - 6.70 (t, J = 8.9 Hz, 1H), 6.31 - 6.21 (m, 2H), 5.85 - 5.80 (m, 1H), 5.50 - 5.46 (m, 1H), 4.23 - 4.01 (m, 5H), 3.51 - 3.38 (m, 6H), 3.22 - 3.09 (m, 4H), 3.08 (s, 3H), 1.91 - 1.79 (m, 3H), 1.57 - 1.47 (m, 3H), 1.21 (d, J = 7.0 Hz, 3H).
173a		
174		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (s, 1H), 8.34 - 8.30 (m, 1H), 7.84 (d, J = 5.5 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.90 - 6.81 (m, 2H), 6.73 - 6.67 (m, 1H), 6.30 - 6.21 (m, 2H), 5.82 - 5.78 (m, 1H), 5.48 - 5.43 (m, 1H), 4.16 – 3.98 (m, 5H), 3.58 – 3.40 (m, 6H), 3.22 – 3.11 (m, 4H), 3.05 (s, 3H), 1.53 - 1.45 (m, 3H), 1.32 - 1.24 (m, 3H), 1.19 (d, J = 7.0 Hz, 3H).
174a		

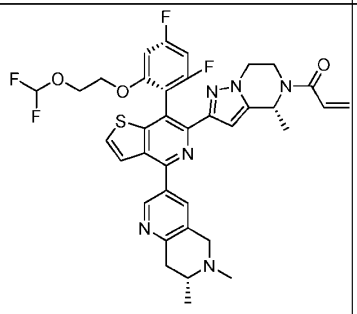
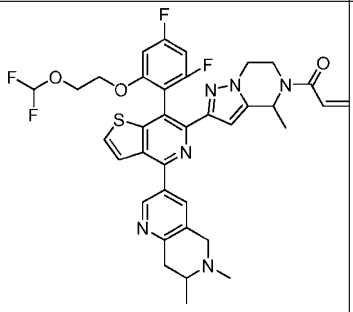
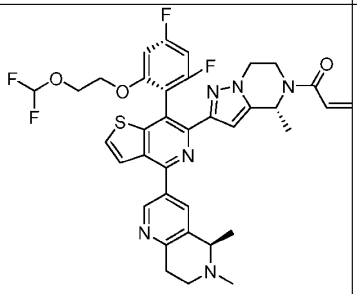
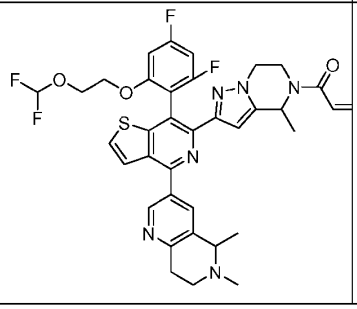
Cmpd. No.	Structure	Analytical data
175		LCMS m/z [M+1]: 710.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 – 7.75 (m, 3H), 7.67 (d, J = 5.7 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 6.95 – 6. 81 (m, 2H), 6.78 – 6. 65 (m, 1H), 6.36 – 6. 23 (m, 1H), 6.17 (s, 1H), 5.84 (dd, J = 10.8, 1.5 Hz, 1H), 5.75 – 5. 41 (m, 1H), 4.28 – 3.95 (m, 6H), 3.85 – 3.73 (m, 1H), 3.61 – 3. 36 (m, 2H), 3.25-3.01 (m, 5H), 1.37 – 1. 52 (m, 1H).
175a		
176		LCMS m/z [M+1]: 710.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 – 7.81 (m, 1H), 7.77 (d, J = 11.7 Hz, 2H), 7.67 (d, J = 5.7 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 6.95 – 6. 81 (m, 2H), 6.78 – 6. 65 (m, 1H), 6.36 – 6. 23 (m, 1H), 6.17 (s, 1H), 5.84 (dd, J = 10.8, 1.5 Hz, 1H), 5.75 – 5. 41 (m, 1H), 4.28 – 3.95 (m, 6H), 3.85 – 3.73 (m, 1H), 3.61 – 3. 36 (m, 2H), 3.25-3.01 (m, 5H), 1.37 – 1. 52 (m, 1H).
177		LCMS m/z [M+1]: 737.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (s, 1H), 8.49 (s, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 5.6 Hz, 1H), 6.90 - 6.71 (m, 3H), 6.29 (s, 2H), 5.81 (d, J = 10.7 Hz, 1H), 5.48 (s, 1H), 4.66 (s, 2H), 4.27 – 4.05 (m, 5H), 4.05 – 3.91 (m, 3H), 3.49 - 3.40 (m, 4H), 3.06 (s, 3H), 1.52 (d, J = 5.5 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H).

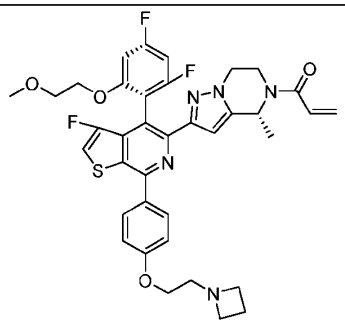
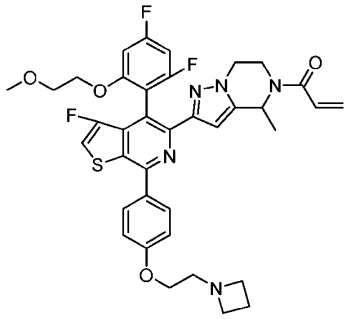
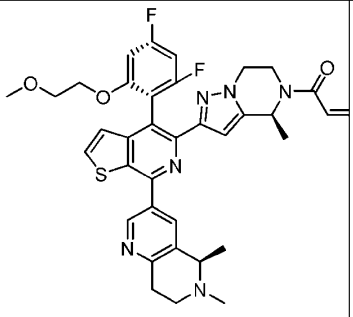
Cmpd. No.	Structure	Analytical data
177a		
178		LCMS m/z [M+1]: 625.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.87 (d, J = 0.9 Hz, 1H), 8.58 (dd, J = 8.6, 1.5 Hz, 1H), 8.24 (s, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 6.95 – 6.79 (m, 2H), 6.72 – 6.63 (m, 2H), 6.29 (d, J = 29.5 Hz, 2H), 5.84 (d, J = 10.6 Hz, 2H), 4.51 – 4.04 (m, 4H), 4.02 – 3.83 (m, 5H), 3.46 (dd, J = 9.7, 4.9 Hz, 2H), 3.12 (s, 3H), 1.47 (s, 3H).
178a		
179		LCMS m/z [M+1]: 685.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (d, J = 1.9 Hz, 1H), 8.56 (s, 1H), 7.99 (dd, J = 2.1, 0.9 Hz, 1H), 6.73 (d, J = 10.8 Hz, 2H), 6.63 – 6.47 (m, 2H), 6.27 – 6.06 (m, 2H), 5.75 (d, J = 11.5 Hz, 1H), 5.53 (d, J = 84.5 Hz, 1H), 4.37 – 4.26 (m, 1H), 4.12 (s, 1H), 4.05 – 3.97 (m, 1H), 3.88 – 3.64 (m, 7H), 3.35 (t, J = 4.7 Hz, 3H), 3.10 – 2.91 (m, 8H), 2.72 (t, J = 5.9 Hz, 2H), 1.37 (d, J = 23.4 Hz, 3H).

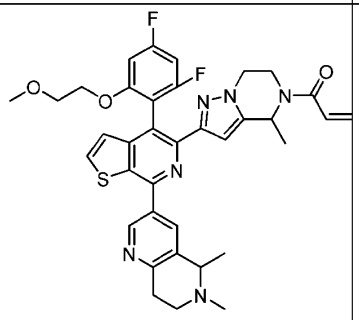
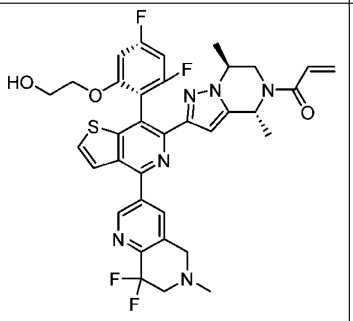
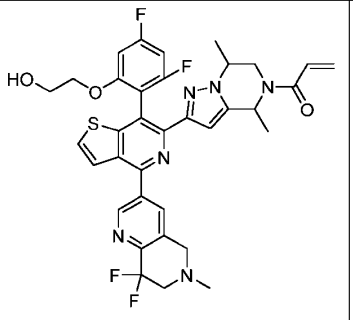
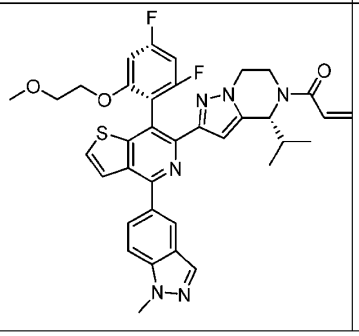
Cmpd. No.	Structure	Analytical data
179a		
180		LCMS m/z [M+1]: 655.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.55 (s, 1H), 8.75 (s, 1H), 8.13 (d, J = 2.0 Hz, 1H), 6.88 (dd, J = 17.6, 10.1 Hz, 2H), 6.76 – 6.62 (m, 2H), 6.33 (s, 1H), 6.17 (s, 1H), 5.85 (d, J = 10.7 Hz, 1H), 5.62 (d, J = 82.8 Hz, 1H), 4.45 (s, 1H), 4.37 – 4.28 (m, 1H), 4.23 (dd, J = 12.6, 3.0 Hz, 1H), 4.17 – 4.06 (m, 3H), 3.99 – 3.92 (m, 1H), 3.45 (t, J = 4.6 Hz, 2H), 3.28 (s, 2H), 3.11 (s, 3H), 3.01 (dd, J = 18.4, 9.4 Hz, 1H), 2.78 – 2.62 (m, 4H), 1.46 (s, 3H), 1.41 (d, J = 5.9 Hz, 3H).
180a		
181		LCMS m/z [M+1]: 669.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.48 (s, 1H), 8.79 (s, 1H), 8.13 (d, J = 1.8 Hz, 1H), 6.98 – 6.83 (m, 2H), 6.68 (dd, J = 21.0, 12.6 Hz, 2H), 6.35 (d, J = 16.4 Hz, 1H), 6.20 (s, 1H), 5.87 (d, J = 10.6 Hz, 1H), 5.80 – 5.47 (m, 1H), 4.52 – 4.22 (m, 2H), 4.17 – 4.08 (m, 1H), 4.05 – 3.79 (m, 3H), 3.47 (t, J = 4.4 Hz, 2H), 3.30 (s, 1H), 3.16

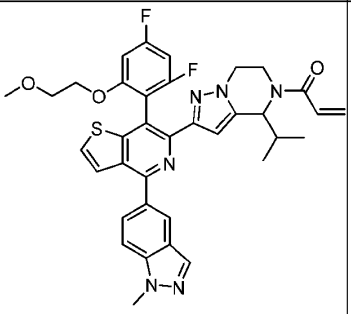
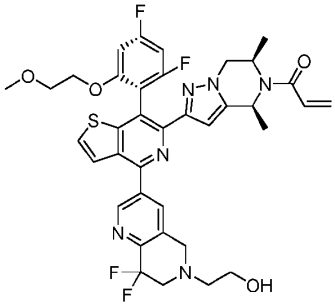
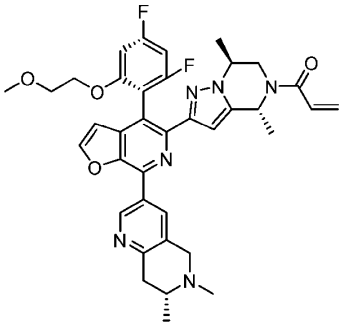
Cmpd. No.	Structure	Analytical data
		(d, J = 2.4 Hz, 2H), 3.13 (s, 3H), 3.01 – 2.91 (m, 1H), 2.62 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H), 1.49 (d, J = 24.0 Hz, 3H), 1.34 (s, 3H)
181a		
182		LCMS m/z [M+1]: 670.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 – 7.79 (m, 2H), 7.75 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 6.93 – 6.82 (m, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.38 – 6.13 (m, 3H), 5.84 (d, J = 10.7 Hz, 1H), 5.73 – 5.57 (m, 1H), 4.32 – 3.97 (m, 6H), 3.50 – 3.39 (m, 3H), 3.17 (t, J = 6.0 Hz, 2H), 3.10 – 3.01 (m, 4H), 2.74 (s, 3H), 1.62 (d, J = 6.7 Hz, 3H), 1.44 (s, 3H).
182a		

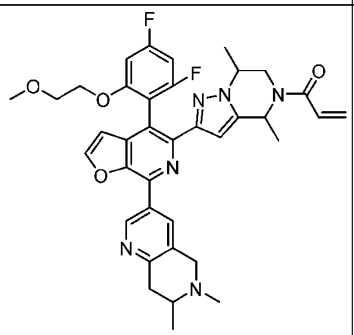
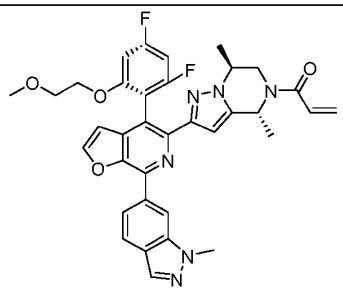
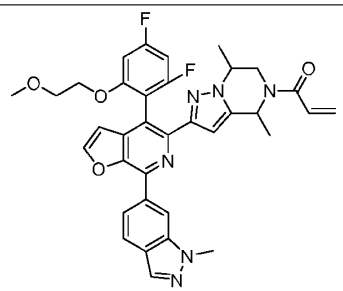
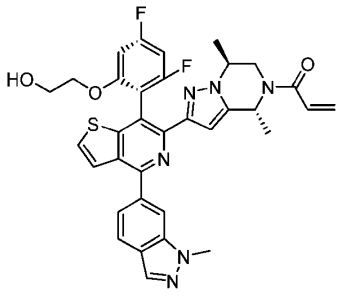
Cmpd. No.	Structure	Analytical data
183		LCMS m/z [M+1]: 625.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 8.37 – 8.24 (m, 2H), 8.11 (d, J = 2.1 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 6.94 – 6.80 (m, 2H), 6.75 – 6.61 (m, 2H), 6.28 (d, J = 26.4 Hz, 2H), 5.74 (dd, J = 81.2, 46.9 Hz, 2H), 4.35 (d, J = 50.0 Hz, 4H), 4.20 (dd, J = 12.8, 3.4 Hz, 1H), 4.16 – 4.00 (m, 2H), 3.98 – 3.92 (m, 1H), 3.78 (s, 1H), 3.46 (t, J = 4.7 Hz, 2H), 3.12 (s, 3H), 1.47 (s, 3H).
183a		
184		LCMS m/z [M+1]: 701.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.00 (s, 1H), 8.23 (s, 1H), 7.81 (d, J = 5.2 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 6.87 - 6.80 (m, 2H), 6.73 - 6.68 (m, 1H), 6.31(s, 2H), 5.81 (d, J = 10.8 Hz, 1H), 5.53-5.35 (d, J = 3.2 Hz, 1H), 4.61 (s, 1H), 4.21 - 3.98 (m, 5H), 3.91 - 3.88 (m, 3H), 3.44 - 3.42 (m, 2H), 3.31 - 3.27 (m, 2H), 3.06 (s, 5H), 1.52 (d, J = 6.0 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H).
184a		

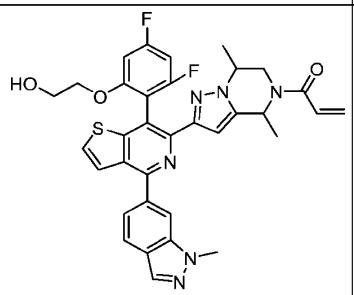
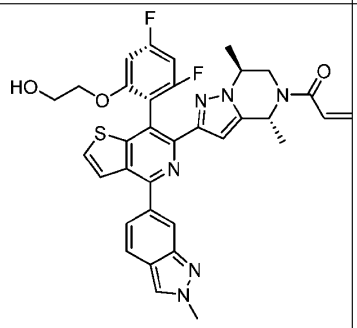
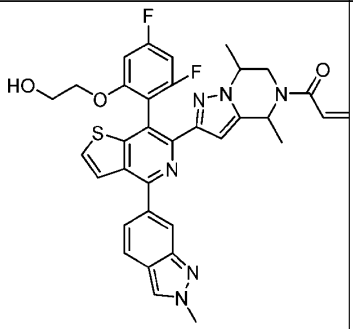
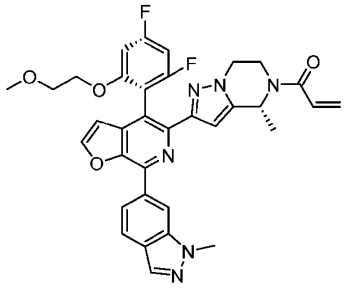
Cmpd. No.	Structure	Analytical data
185		LCMS m/z [M+1]: 707.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (d, J = 1.7 Hz, 1H), 8.19 (s, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 5.6 Hz, 1H), 6.91 – 6.69 (m, 3H), 6.35 – 6.17 (m, 2H), 6.17 – 5.76 (m, 2H), 5.74 – 5.43 (m, 1H), 4.49 – 4.31 (m, 1H), 4.22 – 3.94 (m, 5H), 3.89 – 3.79 (m, 3H), 3.24 – 3.15 (m, 1H), 3.06 – 2.87 (m, 2H), 2.55 (s, 3H), 1.53 – 1.38 (m, 3H), 1.32 (d, J = 6.2 Hz, 3H).
185a		
186		LCMS m/z [M+1]: 707.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.41 (d, J = 1.3 Hz, 1H), 7.84 (d, J = 5.5 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 6.95 – 6.73 (m, 3H), 6.35 – 6.23 (m, 1H), 6.17 – 5.77 (m, 3H), 5.75 – 5.42 (m, 1H), 4.50 – 4.35 (m, 1H), 4.25 – 4.00 (m, 4H), 3.97 – 3.80 (m, 3H), 3.77 – 3.67 (m, 1H), 3.44 (t, J = 6.4 Hz, 2H), 3.10 (s, 3H), 1.84 (d, J = 6.7 Hz, 3H), 1.52 – 1.37 (m, 3H).
186a		

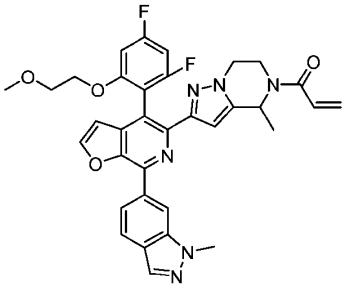
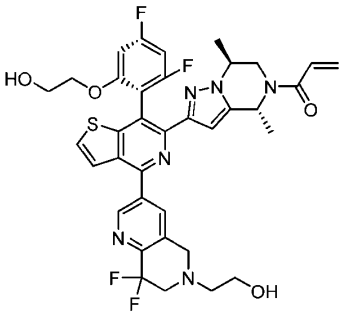
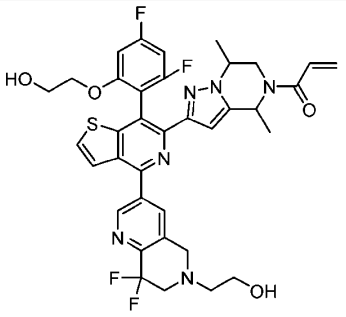
Cmpd. No.	Structure	Analytical data
187		LCMS m/z [M+1]: 704.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 – 8.11 (m, 2H), 7.59 (d, J = 2.4 Hz, 1H), 7.26 – 7.21 (m, 2H), 6.89 – 6.78 (m, 2H), 6.62 (td, J = 9.2, 2.3 Hz, 1H), 6.33 - 6.23 (m, 1H), 6.03 (s, 1H), 5.82 (dd, J = 10.6, 1.8 Hz, 1H), 5.70 - 5.46 (m, 1H), 4.39 – 4.34 (m, 2H), 4.34 – 4.28 (m, 4H), 4.25 - 4.19 (m, 1H), 4.11 – 3.98 (m, 3H), 3.71 (t, J = 4.9 Hz, 2H), 3.45 (t, J = 4.6 Hz, 2H), 3.07 (s, 3H), 2.71 - 2.59 (m, 1H), 2.53 – 2.41 (m, 1H), 1.48 - 1.36 (s, 3H).
187a		
188		LCMS m/z [M+1]: 671.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (d, J = 1.9 Hz, 1H), 8.58 (s, 1H), 8.00 (d, J = 5.5 Hz, 1H), 7.14 (d, J = 5.4 Hz, 1H), 6.90 – 6.79 (m, 2H), 6.76 – 6.68 (m, 1H), 6.29 (d, J = 16.6 Hz, 1H), 6.07 (s, 1H), 5.82 (dd, J = 10.7, 1.6 Hz, 1H), 5.75 – 5.40 (m, 1H), 4.30 – 4.19 (m, 1H), 4.17 – 4.02 (m, 2H), 4.00 – 3.85 (m, 2H), 3.84 – 3.37 (m, 6H), 3.11 (s, 3H), 3.06 (s, 3H), 1.92-1.70 (m, 3H), 1.52-1.35 (m, 3H).

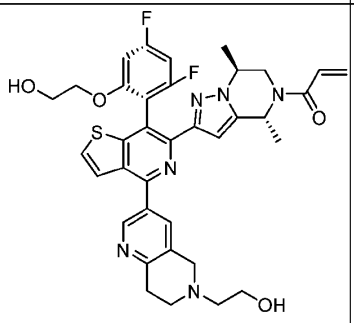
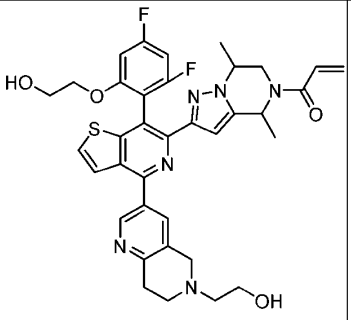
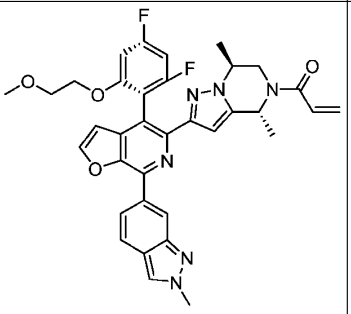
Cmpd. No.	Structure	Analytical data
188a		
189		LCMS m/z [M+1]: 693.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.19 (d, J = 1.9 Hz, 1H), 8.38 (s, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.92 (d, J = 10.8 Hz, 2H), 6.68 (dd, J = 9.2, 7.3 Hz, 1H), 6.35 (d, J = 15.4 Hz, 2H), 5.86 (d, J = 10.5 Hz, 1H), 5.66 (d, J = 87.4 Hz, 1H), 4.42 (d, J = 3.1 Hz, 1H), 4.28 – 3.84 (m, 5H), 3.72 – 3.42 (m, 3H), 3.29 (d, J = 12.1 Hz, 2H), 2.61 (s, 3H), 1.50 (d, J = 23.0 Hz, 3H), 1.27 (s, 3H).
189a		
190		LCMS m/z [M+1]: 669.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.16 (s, 1H), 8.08 (dd, J = 8.6, 1.4 Hz, 1H), 7.76 - 7.69 (m, 3H), 6.92 - 6.81 (m, 2H), 6.66 (td, J = 9.2, 2.0 Hz, 1H), 6.26 (t, J = 15.0 Hz, 1H), 6.08 (d, J = 17.2 Hz, 1H), 5.80 (d, J = 11.0 Hz, 1H), 5.37-5.10 (m, 1H), 4.44 - 4.40 (m, 1H), 4.26 - 4.22 (m, 1H), 4.15 - 4.06 (m, 6H), 3.89 -

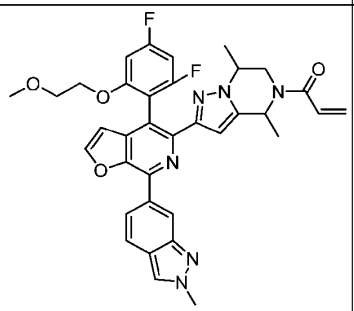
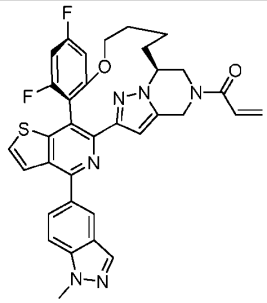
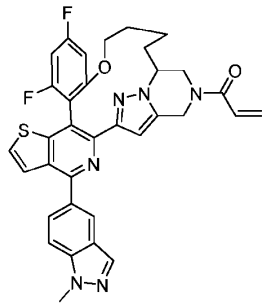
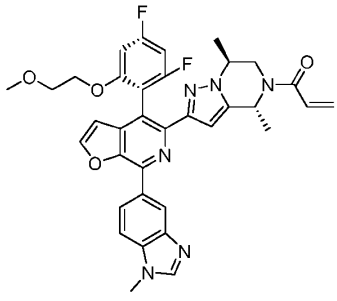
Cmpd. No.	Structure	Analytical data
		3.82 (m, 1H), 3.49 - 3.46 (m, 2H), 3.06 (s, 3H), 2.10-2.00 (m, 1H), 0.94 - 0.91 (m, 6H).
190a		
191		LCMS m/z [M+1]: 737.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (s, 1H), 8.49 (s, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 5.6 Hz, 1H), 6.90 - 6.71 (m, 3H), 6.29 (s, 2H), 5.81 (d, J = 10.7 Hz, 1H), 5.48 (s, 1H), 4.66 (s, 2H), 4.27 – 4.05 (m, 5H), 4.05 – 3.91 (m, 3H), 3.46 - 3.40 (m, 4H), 3.06 (s, 3H), 1.52 (d, J = 5.5 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H).
192		LCMS m/z [M+1]: 669.0 ^{1}H NMR (400 MHz, CD_3OD) δ 9.36 (d, J = 1.8 Hz, 1H), 8.58 (d, J = 1.6 Hz, 1H), 7.99 (d, J = 2.2 Hz, 1H), 6.84 – 6.70 (m, 2H), 6.60 (d, J = 2.0 Hz, 1H), 6.54 (td, J = 9.2, 2.2 Hz, 1H), 6.23 (d, J = 16.4 Hz, 1H), 6.12 (s, 1H), 5.75 (d, J = 11.4 Hz, 1H), 5.67 – 5.35 (m, 1H), 4.76 – 4.53 (m, 1H), 4.34 – 4.28 (m, 1H), 4.26 – 4.07 (m, 1H), 4.06 – 3.97 (m, 2H), 3.87 – 3.80 (m, 1H), 3.71 (d, J = 15.8 Hz, 1H), 3.35 (t, J = 4.6 Hz, 2H), 3.06 (dd, J = 16.4, 2.8 Hz, 1H), 3.00 (s, 3H), 2.87 – 2.75 (m, 2H), 2.42 (s, 3H), 1.37 (d, J = 25.4 Hz, 3H), 1.21 (s, 3H), 1.19 (d, J = 2.6 Hz, 3H).

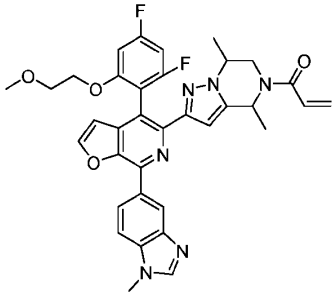
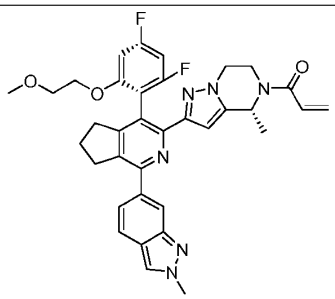
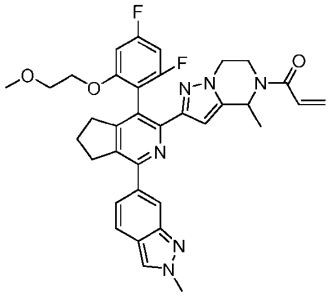
Cmpd. No.	Structure	Analytical data
192a		
193		LCMS m/z [M+1]: 639.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.14 (dd, J = 5.0, 3.0 Hz, 2H), 8.01 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 6.83 – 6.68 (m, 3H), 6.59 (td, J = 9.2, 2.0 Hz, 1H), 6.24 (d, J = 16.4 Hz, 1H), 6.09 (s, 1H), 5.75 (dd, J = 10.6, 1.4 Hz, 1H), 5.70 – 5.36 (m, 1H), 4.76 – 4.56 (m, 1H), 4.45 – 4.34 (m, 1H), 4.11 (s, 3H), 4.09 – 3.71 (m, 3H), 3.37 (t, J = 4.6 Hz, 2H), 3.03 (s, 3H), 1.37 (d, J = 21.0 Hz, 3H), 1.24 (s, 3H).
193a		
194		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 8.14 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 7.0, 1.2 Hz, 1H), 7.76 – 7.71 (m, 2H), 6.91 (d, J = 10.8 Hz, 2H), 6.68 (t, J = 8.2 Hz, 1H), 6.39 – 6.28 (m, 2H), 5.86 (d, J = 11.8 Hz, 1H), 5.79 – 5.50 (m, 1H), 4.88 – 4.63 (m, 1H), 4.49 – 4.41 (m, 1H), 4.19 (s, 3H), 4.14 – 3.80 (m, 3H), 3.72 – 3.56 (m, 2H), 1.49 (d, J = 23.8 Hz, 3H), 1.28 (s, 3H).

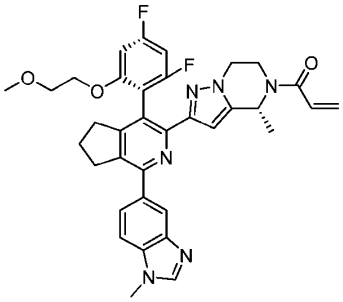
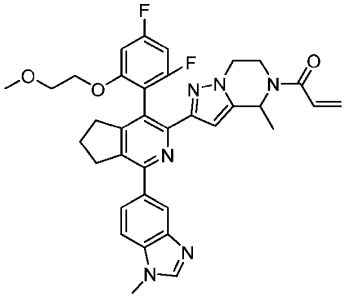
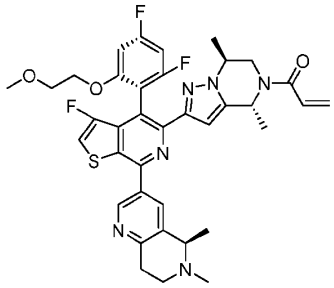
Cmpd. No.	Structure	Analytical data
194a		
195		LCMS m/z [M+1]: 641.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 8.04 (s, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 5.6 Hz, 1H), 7.62 – 7.58 (m, 2H), 6.78 (d, J = 10.8 Hz, 2H), 6.54 (t, J = 8.2 Hz, 1H), 6.22 (d, J = 16.2 Hz, 2H), 5.73 (d, J = 11.4 Hz, 1H), 5.69 – 5.36 (m, 1H), 4.76 – 4.55 (m, 1H), 4.36 – 4.24 (m, 1H), 4.18 (s, 3H), 4.11 – 3.69 (m, 3H), 3.58 – 3.45 (m, 2H), 1.38 (d, J = 22.2 Hz, 3H), 1.14 (s, 3H).
195a		
196		LCMS m/z [M+1]: 625.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (d, J = 6.4 Hz, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.22 (d, J = 2.1 Hz, 1H), 8.13 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 6.88 (t, J = 11.1 Hz, 2H), 6.80 (d, J = 2.0 Hz, 1H), 6.72 (td, J = 9.3, 2.2 Hz, 1H), 6.34 (s, 1H), 6.12 (d, J = 11.2 Hz, 1H), 5.86 (dd, J = 10.6, 1.6 Hz, 1H), 5.73 (s, 1H), 4.45 (s, 1H), 4.31 –

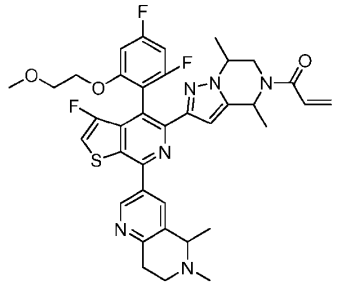
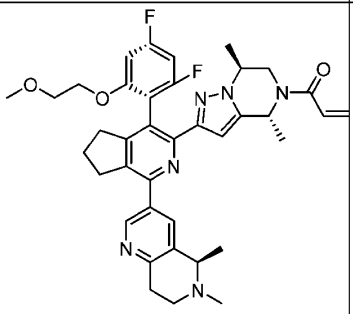
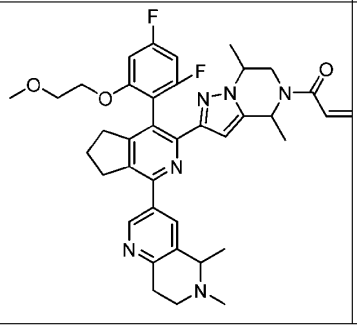
Cmpd. No.	Structure	Analytical data
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196a		
197		LCMS m/z [M+1]: 722.9 ^{1}H NMR (400 MHz, CD_3OD) δ 9.18 (d, J = 1.7 Hz, 1H), 8.37 (s, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.92 (d, J = 10.9 Hz, 2H), 6.68 (t, J = 8.3 Hz, 1H), 6.35 (d, J = 15.9 Hz, 2H), 5.92 – 5.48 (m, 2H), 4.51 – 4.16 (m, 2H), 4.06 (s, 4H), 3.84 (t, J = 5.6 Hz, 2H), 3.60 (tdd, J = 17.4, 12.2, 5.0 Hz, 3H), 3.44 (t, J = 12.1 Hz, 2H), 2.90 (t, J = 5.6 Hz, 2H), 1.50 (d, J = 20.9 Hz, 3H), 1.27 (s, 3H).
197a		

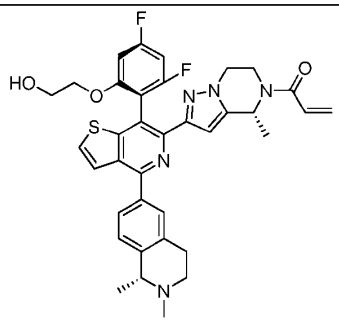
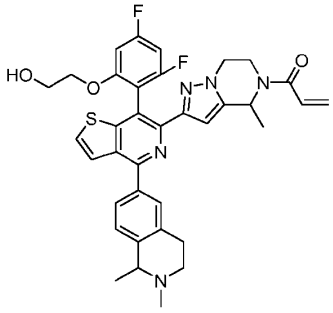
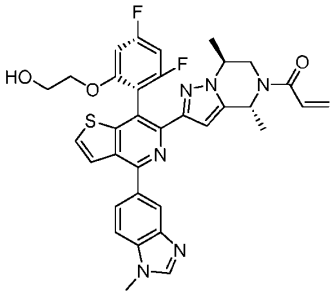
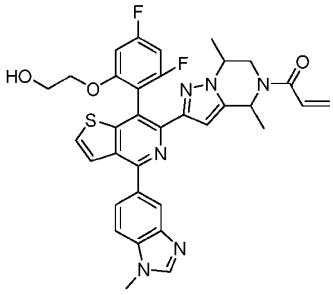
Cmpd. No.	Structure	Analytical data
198		LCMS m/z [M+1]: 687.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (d, J = 1.8 Hz, 1H), 8.18 (s, 1H), 7.81 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 6.91 (d, J = 11.0 Hz, 2H), 6.67 (t, J = 8.4 Hz, 1H), 6.34 (d, J = 17.3 Hz, 2H), 5.86 (d, J = 10.6 Hz, 1H), 5.65 (d, J = 85.4 Hz, 1H), 4.43 (s, 1H), 4.06 (t, J = 4.7 Hz, 2H), 3.98 (s, 2H), 3.91 – 3.77 (m, 4H), 3.68 – 3.53 (m, 2H), 3.20 (t, J = 5.8 Hz, 2H), 3.09 (t, J = 5.8 Hz, 2H), 2.85 (t, J = 5.7 Hz, 2H), 1.47 (s, 3H), 1.27 (s, 3H).
198a		
199		LCMS m/z [M+1]: 639.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (d, J = 0.8 Hz, 1H), 8.21 – 8.13 (m, 2H), 7.99 (dd, J = 2.1, 0.9 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 6.74 (t, J = 12.0 Hz, 2H), 6.54 (ddd, J = 11.8, 11.4, 2.1 Hz, 2H), 6.28 – 6.14 (m, 2H), 5.74 (d, J = 10.5 Hz, 1H), 5.55 (d, J = 84.0 Hz, 1H), 4.29 (d, J = 4.6 Hz, 1H), 4.15 (d, J = 17.6 Hz, 4H), 4.06 – 4.00 (m, 1H), 3.90 – 3.81 (m, 1H), 3.62 (dd, J = 90.8, 21.4 Hz, 1H), 3.37 (t, J = 4.5 Hz, 2H), 3.00 (t, J = 4.2 Hz, 3H), 1.39 (d, J = 21.3 Hz, 3H), 1.19 (s, 3H)..

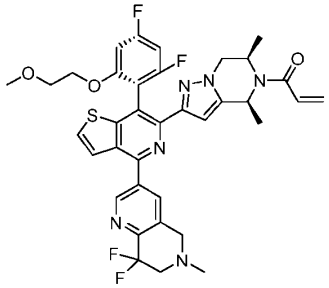
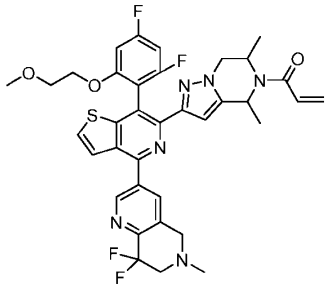
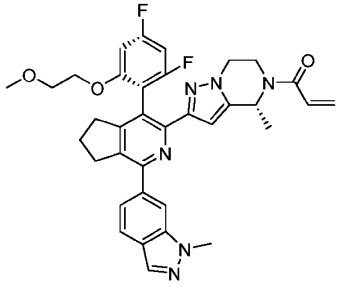
Cmpd. No.	Structure	Analytical data
199a		
200		LCMS m/z [M+1]: 623.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (1H, s), 8.25 (s, 1H), 8.10 (d, J = 5.6 Hz. 1H), 8.04 (dd, J =8.7, 1.3 Hz, 1H), 7.94 -7.83 (m, 2H), 6.95 - 6.76 (m, 2H), 6.70 (d, J =11.2 Hz, 1H), 6.37 - 6.25 (m, 1H), 6.02 (s, 1H), 5.90 - 5.81 (m, 1H), 5.20 - 5.05 (m, 1H), 4.74 - 4.55 (m, 2H), 4.48 - 4.22 (m, 1H), 4.19 (s, 3H), 4.15 - 3.90 (m, 1H), 3.80 - 3.71 (m, 1H), 2.13 - 1.95 (m, 1H), 1.92 - 1.65 (m, 2H), 1.61 - 1.45 (m, 1H), 1.20 - 1.05 (m, 1H), 0.61 - 0.48 (m, 1H).
200a		
201		LCMS m/z [M+1]: 639.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (d, J = 1.0 Hz, 1H), 8.47 (dd, J = 8.6, 1.5 Hz, 1H), 8.13 (s, 1H), 7.98 (d, J = 2.2 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 6.74 (t, J = 12.6 Hz, 2H), 6.58 (d, J = 2.1 Hz, 1H), 6.52 (td, J = 9.3, 2.1 Hz, 1H), 6.22 (dd, J = 20.2, 10.0 Hz, 2H), 5.75 (d, J = 10.8 Hz, 1H), 5.55 (d, J = 86.1 Hz, 1H), 4.37 – 4.06 (m,

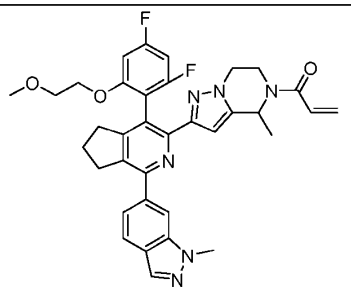
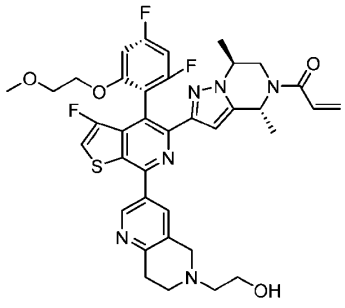
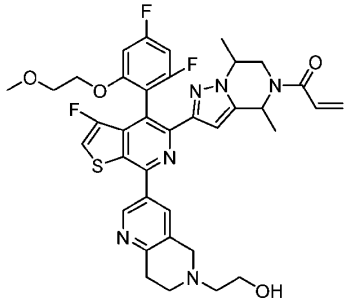
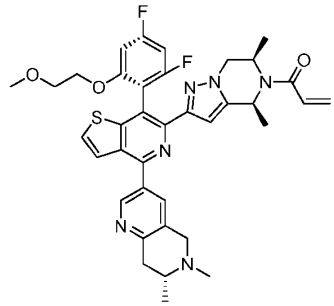
Cmpd. No.	Structure	Analytical data
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201a		
202		LCMS m/z [M+1]: 625.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 8.04 (d, J = 0.8 Hz, 1H), 7.83 (dd, J = 8.7, 0.7 Hz, 1H), 7.70 (dd, J = 8.7, 1.3 Hz, 1H), 6.91 – 6.75 (m, 2H), 6.62 (td, J = 9.2, 2.3 Hz, 1H), 6.31 (s, 1H), 6.07 (s, 1H), 5.88 – 5.78 (m, 1H), 5.59 (d, J = 80.5 Hz, 1H), 4.47 – 4.19 (m, 4H), 4.19 – 4.10 (m, 2H), 4.08 – 3.92 (m, 2H), 3.87 – 3.59 (m, 1H), 3.56 (t, J = 4.6 Hz, 2H), 3.27 (d, J = 7.2 Hz, 2H), 3.24 (s, 3H), 2.96 – 2.84 (m, 1H), 2.80 – 2.70 (m, 1H), 2.19 – 2.08 (m, 2H), 1.42 (s, 3H).
202a		

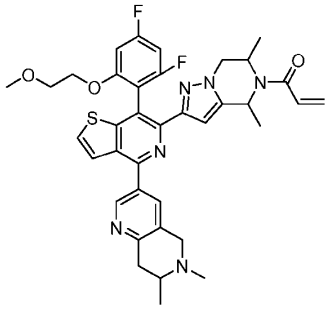
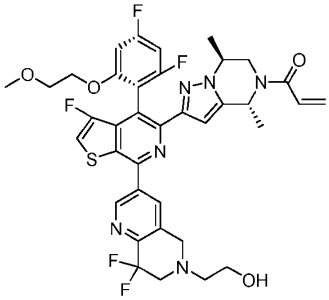
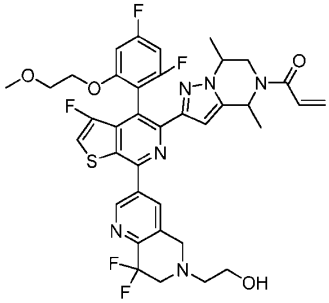
Cmpd. No.	Structure	Analytical data
203		LCMS m/z [M+1]: 625.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 8.16 (s, 1H), 7.96 (dd, J = 8.5, 1.3 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 6.91 – 6.74 (m, 2H), 6.62 (td, J = 9.2, 2.3 Hz, 1H), 6.31 (s, 1H), 6.08 (s, 1H), 5.83 (d, J = 10.7 Hz, 1H), 5.59 (d, J = 81.4 Hz, 1H), 4.51 – 4.08 (m, 3H), 4.08 – 3.89 (m, 5H), 3.78 (dd, J = 43.6, 24.1 Hz, 1H), 3.56 (t, J = 4.6 Hz, 2H), 3.29 – 3.20 (m, 5H), 2.90 (dt, J = 15.4, 7.5 Hz, 1H), 2.81 – 2.68 (m, 1H), 2.19 – 2.07 (m, 2H), 1.42 (s, 3H).
203a		
204		LCMS m/z [M+1]: 703.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.6 Hz, 1H), 8.55 (s, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.95 - 6.78 (m, 2H), 6.67 - 6.57 (m, 1H), 6.33 (d, J = 16.4 Hz, 1H), 6.10 (s, 1H), 5.91 - 5.79 (m, 1H), 5.77 - 5.46 (m, 1H), 4.45 (s, 1H), 4.14 - 4.06 (m, 1H), 4.06 - 3.98 (m, 1H), 3.94 - 3.81 (m, 1H), 3.77 - 3.67 (m, 1H), 3.50 - 3.35 (m, 5H), 3.11 (s, 3H), 3.08 (s, 3H), 1.84 (d, J = 8.0Hz, 3H), 1.54 - 1.37 (m, 3H), 1.32 (s, 3H).

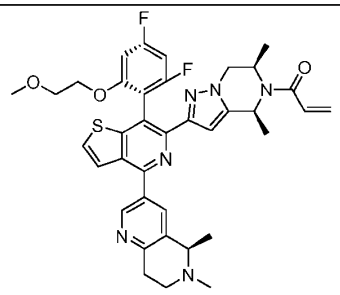
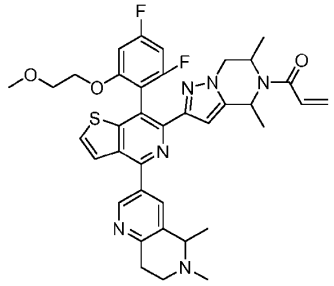
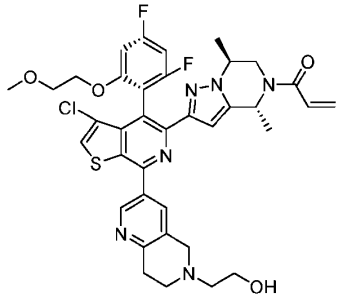
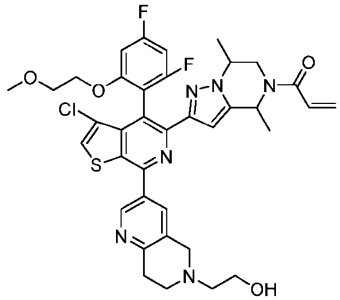
Cmpd. No.	Structure	Analytical data
204a		
205		LCMS m/z [M+1]: 669.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.04 (d, J = 1.8 Hz, 1H), 8.36 (s, 1H), 6.94 – 6.56 (m, 4H), 6.32 (d, J = 16.4 Hz, 1H), 6.02 (s, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 - 5.42 (m, 1H), 4.74 (s, 1H), 4.46 (s, 1H), 4.20 – 4.10 (m, 1H), 4.06 – 3.99 (m, 1H), 3.89 (s, 2H), 3.75 – 3.64 (m, 1H), 3.55 (t, J = 4.5 Hz, 2H), 3.40 (t, J = 6.3 Hz, 2H), 3.28 – 3.19 (m, 5H), 3.09 (s, 3H), 3.04 – 2.91 (m, 1H), 2.84 – 2.69 (m, 1H), 2.23 - 2.11 (m, 2H), 1.81 (d, J = 6.6 Hz, 3H), 1.49 - 1.39 (m, 3H), 1.47 - 1.35 (m, 3H).
205a		

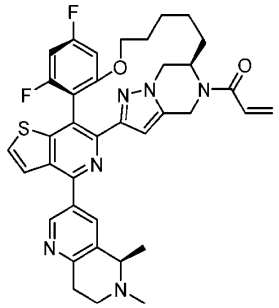
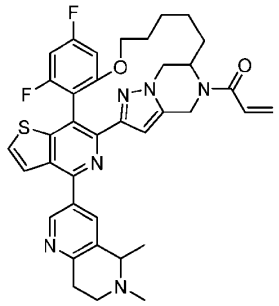
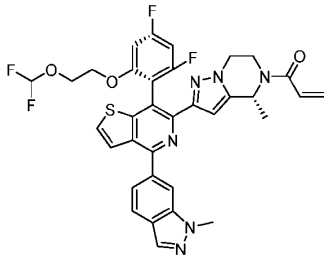
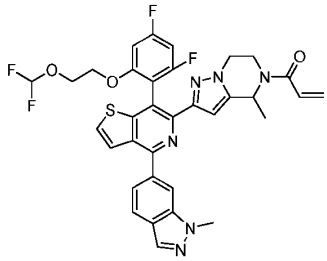
Cmpd. No.	Structure	Analytical data
206		LCMS m/z [M+1]: 656.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 – 7.74 (m, 2H), 7.61 (dd, J = 35.2, 5.6 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 6.74 (t, J = 12.0 Hz, 2H), 6.61 (td, J = 9.1, 2.1 Hz, 1H), 6.26 – 6.02 (m, 2H), 5.60 (dd, J = 90.7, 50.9 Hz, 2H), 4.53 (q, J = 6.8 Hz, 1H), 4.45 – 3.69 (m, 6H), 3.66 – 3.24 (m, 6H), 2.90 (s, 3H), 1.64 (d, J = 6.8 Hz, 3H), 1.34 (s, 3H).
206a		
207		LCMS m/z [M+1]: 640.8 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (d, J = 3.3 Hz, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.82 – 7.65 (m, 3H), 6.90 (d, J = 11.0 Hz, 2H), 6.66 (t, J = 8.4 Hz, 1H), 6.34 (d, J = 16.0 Hz, 2H), 5.85 (d, J = 10.5 Hz, 1H), 5.66 (d, J = 83.9 Hz, 1H), 4.76 – 4.20 (m, 2H), 4.17 – 4.05 (m, 2H), 4.02 (s, 3H), 3.89 – 3.42 (m, 3H), 1.49 (d, J = 23.4 Hz, 3H), 1.26 (s, 3H).
207a		

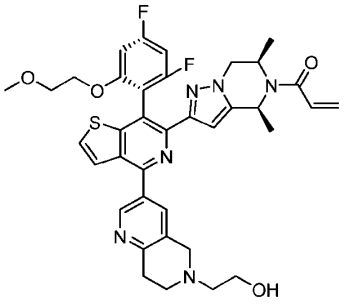
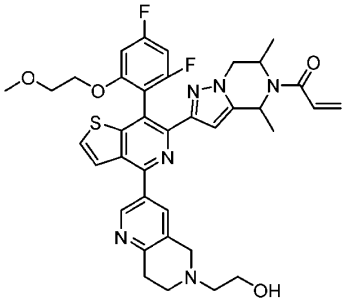
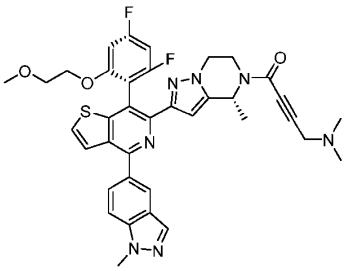
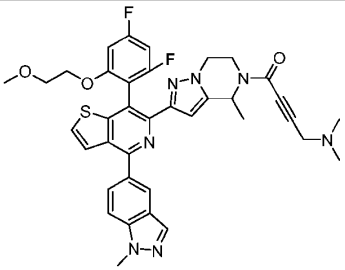
Cmpd. No.	Structure	Analytical data
208		LCMS m/z [M+1]: 707.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (d, J = 1.6 Hz, 1H), 8.47 (s, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.89 - 6.80 (m, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.30 - 6.25 (m, 2H), 5.80 (d, J = 10.4 Hz, 1H), 5.48 - 5.47 (m, 1H), 4.46 (s, 2H), 4.16 - 4.05 (m, 3H), 3.99 - 3.90 (m, 3H), 3.41 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 2.99 (s, 3H), 1.52 (d, J = 6.0 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H).
208a		
209		LCMS m/z [M+1]: 625.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (d, J = 12.9 Hz, 2H), 8.03 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 10.6 Hz, 1H), 6.92 – 6.74 (m, 2H), 6.32 (d, J = 17.0 Hz, 1H), 5.88 (t, J = 10.4 Hz, 2H), 5.61 (d, J = 89.8 Hz, 1H), 4.61 – 4.33 (m, 2H), 4.20 (t, J = 6.9 Hz, 7H), 3.81 (s, 1H), 3.60 (t, J = 4.3 Hz, 2H), 3.30 (d, J = 7.9 Hz, 4H), 3.18 (dd, J = 16.6, 8.8 Hz, 1H), 3.00 (dd, J = 16.6, 9.1 Hz, 1H), 2.29 (dd, J = 15.1, 7.6 Hz, 2H), 1.41 (s, 3H).

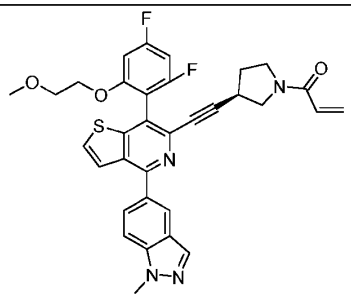
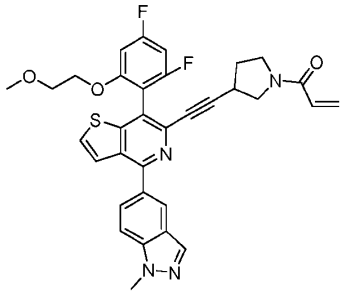
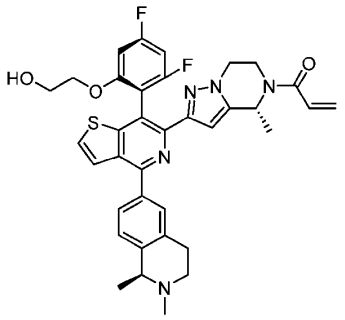
Cmpd. No.	Structure	Analytical data
209a		
210		LCMS m/z [M+1]: 719.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.29 (d, J = 1.6 Hz, 1H), 8.48 (d, J = 1.6 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.96 - 6.77 (m, 2H), 6.65 - 6.58 (m, 1H), 6.33 (d, J = 16.8 Hz, 1H), 6.13 (s, 1H), 5.89 - 5.81 (m, 1H), 5.77 - 5.52 (m, 1H), 4.77 (s, 2H), 4.44 (s, 1H), 4.14 - 4.07 (m, 1H), 4.04 - 3.98 (m, 3H), 3.94 - 3.76 (m, 2H), 3.56 - 3.50 (m, 2H), .50 - 3.41 (m, 4H), 3.08 (s, 3H), 1.51 - 1.38 (m, 3H), 1.34 - 1.28 (m, 3H).
210a		
211		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (s, 1H), 8.38 - 8.34 (m, 1H), 7.87 (d, J = 5.5 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.90 – 6.80 (m, 2H), 6.77 - 6.70 (m, 1H), 6.30 - 6.17 (m, 2H), 5.83 - 5.77 (m, 1H), 5.50 - 5.42 (m, 1H), 4.78 - 4.69 (m, 2H), 4.22 - 4.13 (m, 2H), 4.13 - 3.96 (m, 4H), 3.57 - 3.50 (m, 1H), 3.42 (t, J = 4.6 Hz, 2H), 3.28 - 3.17 (m, 2H), 3.09 (s, 2H), 3.05 (s, 3H), 1.59 (d, J= 6.5

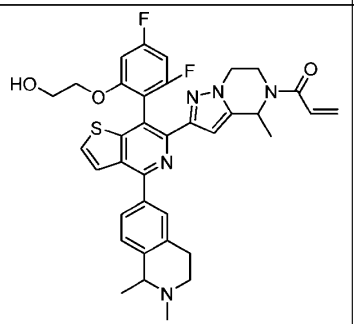
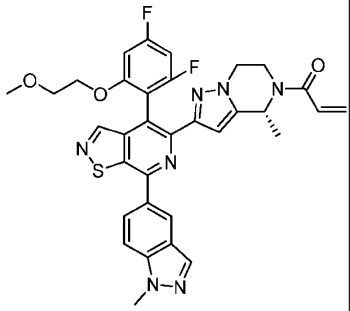
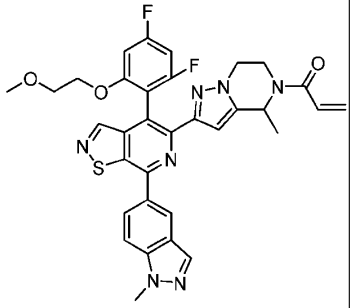
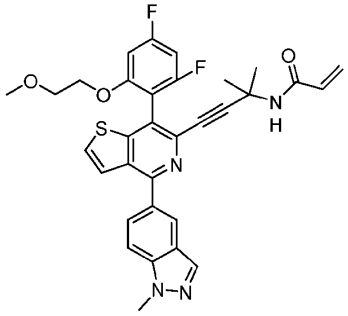
Cmpd. No.	Structure	Analytical data
		Hz, 3H), 1.52 (d, J = 6.7 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H).
211a		
212		LCMS m/z [M+1]: 755.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (d, J = 1.2 Hz, 1H), 8.59 (s, 1H), 7.61 (d, J = 2.0 Hz, 1H), 6.92 - 6.77 (m,2H), 6.66 - 6.57 (m, 1H), 6.33 (d, J = 16.4 Hz, 1H), 6.17 (s, 1H), 5.89 - 5.81 (m, 1H), 5.78 - 5.50 (m, 1H), 4.50 (s, 2H), 4.47- 4.38 (m, 1H), 4.12 - 4.07 (m, 1H), 4.98 - 4.03 (m, 1H), 3.98 - 3.90 (m, 4H), 3.48 - 3.41 (m, 3H), 3.29 - 3.24 (m, 2H), 3.08 (s, 3H), 1.53 - 1.38 (m, 3H), 1.33 - 1.24 (m, 3H).
212a		

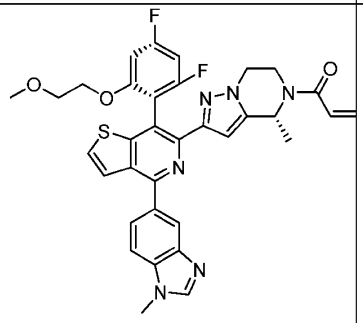
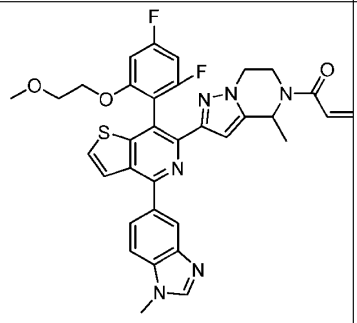
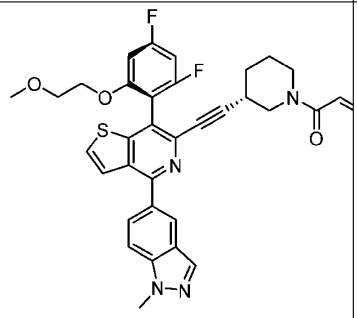
Cmpd. No.	Structure	Analytical data
213		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.46 - 8.41 (m, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 6.90 – 6.80 (m, 2H), 6.77 - 6.71 (m, 1H), 6.42 - 6.30 (m, 2H), 5.83 - 5.76 (m, 1H), 5.50 - 5.42 (m, 1H), 4.24 - 3.88 (m, 6H), 3.78 – 3.67 (m, 1H), 3.47 - 3.40 (m, 4H), 3.11 (s, 3H), 3.06 (s, 3H), 1.84 (d, J = 6.9 Hz, 3H), 1.51 (d, J = 6.7 Hz, 3H), 1.22 (d, J = 7.0 Hz, 3H).
213a		
214		LCMS m/z [M+1]: 735.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.25 (d, J = 1.7 Hz, 1H), 8.44 (d, J = 1.5 Hz, 1H), 8.00 (s, 1H), 6.89 - 6.77 (m, 2H), 6.59 (td, J = 9.1, 2.1 Hz, 1H), 6.34 (d, J = 16.1 Hz, 1H), 6.10 (s, 1H), 5.85 (dd, J =10.5, 1.5 Hz, 1H), 5.70 - 5.46 (m, 1H), 4.75 (s, 2H), 4.43 (s, 1H), 4.00 - 4.12 (m, 5H), 3.53 - 3.45 (m, 7H), 3.06 (s, 3H), 1.50 -1.36 (m, 3H), 1.35-1.21 (m, 3H).
214a		

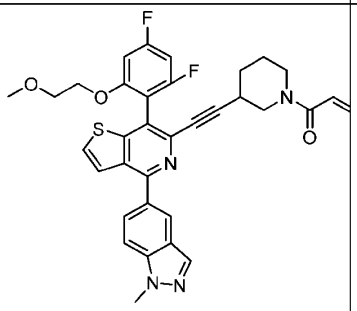
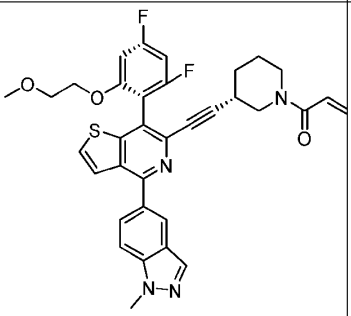
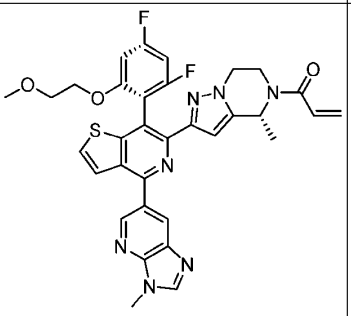
Cmpd. No.	Structure	Analytical data
215		LCMS m/z [M+1]: 667.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (s, 1H), 8.51 – 8.44 (m, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 6.89 – 6.69 (m, 3H), 6.31 (d, J = 16.6 Hz, 1H), 5.86 – 5.78 (m, 2H), 5.07 – 5.00 (m, 1H), 4.83 – 4.76 (m, 1H), 4.70 – 4.61 (m, 1H), 4.57 – 4.32 (m, 3H), 4.12 – 4.04 (m, 1H), 3.80 – 3.69 (m, 2H), 3.49 – 3.40 (m, 2H), 3.17 – 3.06 (m, 3H), 1.95 – 1.78 (m, 3H), 1.68 – 1.50 (m, 2H), 1.27 – 0.90 (m, 6H).
215a		
216		LCMS m/z [M+1]: 677.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.20 (s, 1H), 8.13-8.03 (m, 2H), 7.85 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 10.8 Hz, 1H), 6.90-6.80 (m, 2H), 6.35-6.25 (m, 1H), 6.08 (s, 1H), 6.03 (s, 1H), 5.83 (d, J= 10.8 Hz, 1H), 5.80-5.40 (m, 1H), 4.40-4.30 (m, 1H), 4.25-4.10 (m, 5H), 3.95-3.85 (m, 2H), 1.55-1.35 (m, 3H).
216a		

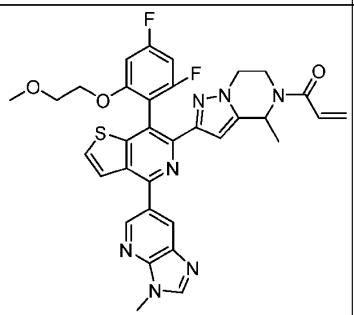
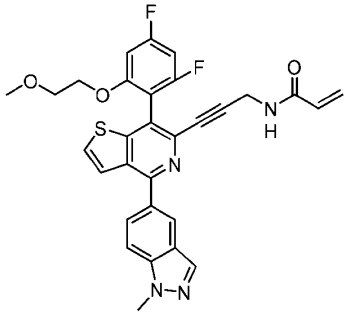
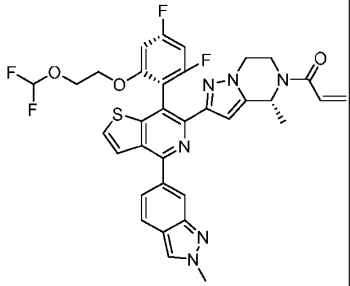
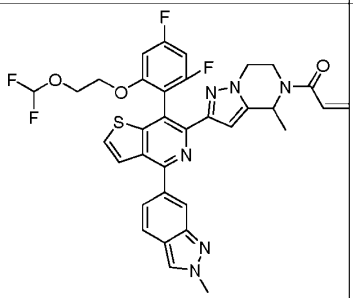
Cmpd. No.	Structure	Analytical data
217		LCMS m/z [M+1]: 701.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (d, J = 1.9 Hz, 1H), 8.39 (s, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.91 - 6.74 (m, 3H), 6.29 - 6.24 (m, 2H), 5.84 (d, J = 10.0 Hz, 1H), 5.71 - 5.42 (m, 2H), 4.85 - 4.75 (m, 2H), 4.25 – 3.96 (m, 7H), 3.59 – 3.53 (m, 2H), 3.50 - 3.44 (m, 4H), 3.08 (s, 3H), 1.54 (d, J = 6.5 Hz, 3H), 1.24 (d, J = 6.9 Hz, 3H).
217a		
218		LCMS m/z [M+1]: 696.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.24 (s, 1H), 8.05 (dd, J = 8.6, 0.8 Hz, 1H), 8.00 (t, J = 5.2 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.82 (dd, J = 5.6, 1.8 Hz, 1H), 6.97 (d, J = 10.6 Hz, 1H), 6.79 (t, J = 8.8 Hz, 1H), 6.15 (d, J = 9.2 Hz, 1H), 5.67 - 5.62 (m, 1H), 4.80 - 4.62 (m, 1H), 4.38 - 4.31 (m, 3H), 4.19 (s, 3H), 4.13 - 3.89 (m, 3H), 3.46 (t, J = 4.4 Hz, 2H), 3.08 (d, J = 3.8 Hz, 3H), 3.00 (d, J = 6.8 Hz, 6H), 1.54 (d, J = 6.8 Hz, 1H), 1.41 (d, J = 6.8 Hz, 2H).
218a		

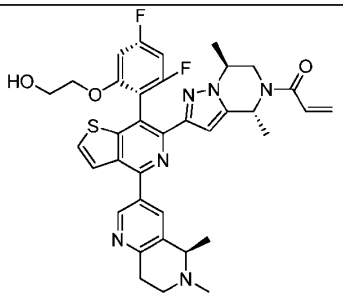
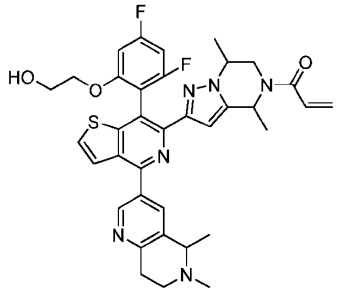
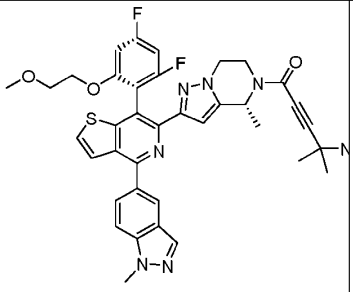
Cmpd. No.	Structure	Analytical data
219		LCMS m/z [M+1]: 599.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 - 8.29 (m, 1H), 8.24 - 8.19 (m, 1H), 8.06 - 7.99 (m, 1H), 7.94 - 7.88 (m, 1H), 7.86 - 7.80 (m, 1H), 7.78 - 7.74 (m, 1H), 7.02- 6.91 (m, 1H), 6.89 - 6.79 (m, 1H), 6.59 - 6.44 (m 1H), 6.35 - 6.25 (m, 1H), 5.81 - 5.73 (m, 1H), 4.21 - 4.12 (m, 5H), 4.00 - 3.77 (m, 1H), 3.71 - 3.62 (m, 1H), 3.60 - 3.38 (m, 5H), 3.16 - 3.08 (m, 3H), 2.30 - 2.10 (m, 1H), 2.06 - 1.87 (m, 1H).
219a		
220		LCMS m/z [M+1]: 656.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, J = 8.1 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.55 (d, J = 5.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.79 – 6.70 (m, 2H), 6.60 (td, J = 9.2, 2.2 Hz, 1H), 6.23 – 6.04 (m, 2H), 5.69 (dd, J = 32.2, 21.6 Hz, 2H), 4.38 – 4.01 (m, 2H), 3.98 – 3.58 (m, 5H), 3.51 – 3.41 (m, 2H), 3.08 (dt, J = 11.9, 5.8 Hz, 1H), 2.95 (t, J = 5.8 Hz, 2H), 2.68 (dt, J = 11.8, 5.8 Hz, 1H), 2.45 (s, 3H), 1.38 (t, J = 15.5 Hz, 6H).

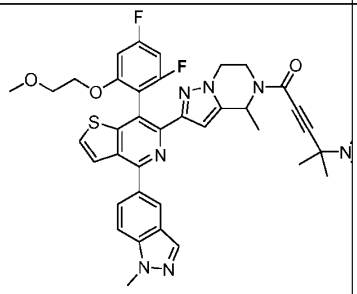
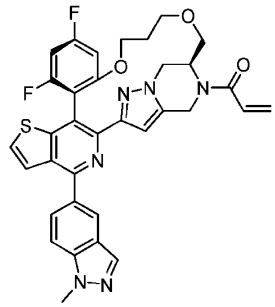
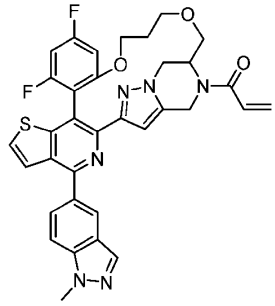
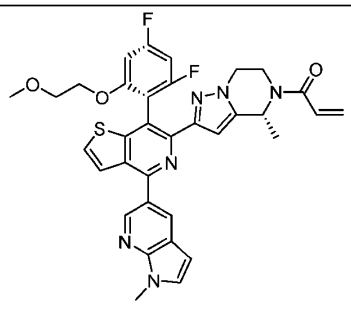
Cmpd. No.	Structure	Analytical data
220a		
221		LCMS m/z [M+1]: 642.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (s, 1H), 8.61 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 6.93 – 6.80 (m, 2H), 6.75 – 6.67 (m, 1H), 6.35 – 6.23 (m, 2H), 5.83 (d, J = 10.7 Hz, 1H), 5.78 – 5.45 (m, 1H), 4.50 – 4.35 (m, 0.5H), 4.22 – 3.90 (m, 7H), 3.85 – 3.68 (m, 0.5H), 3.45 – 3.35 (m, 2H), 3.03 (s, 3H), 1.57 – 1.40 (m, 3H).
221a		
222		LCMS m/z [M+1]: 587.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.16 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 5.5 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 5.6 Hz, 1H), 6.87 (d, J = 10.6 Hz, 1H), 6.74 (t, J = 9.5 Hz, 1H), 6.18-6.16 (m, 2H), 5.61(dd, J = 7.6, 4.2Hz, 1H), 4.57 (s, 2H), 4.27-4.13 (m, 5H), 3.58-3.50 (m, 2H), 3.09 (s, 3H), 1.55 (s, 3H), 1.52 (s, 3H).

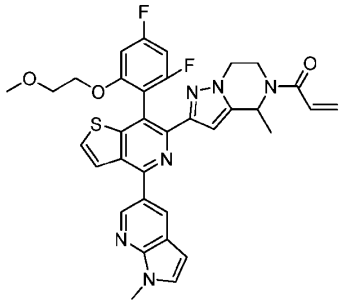
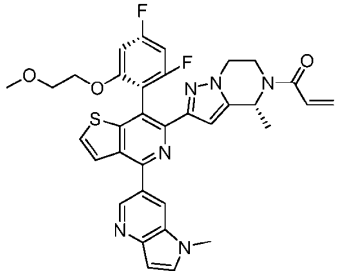
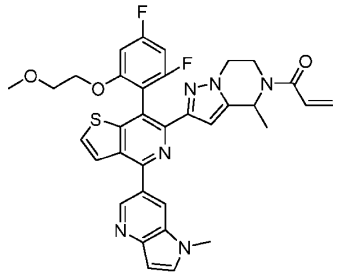
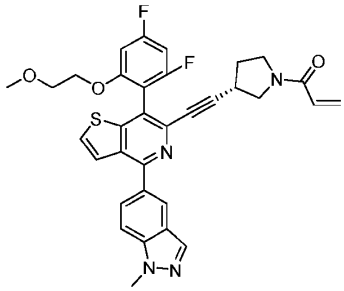
Cmpd. No.	Structure	Analytical data
223		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 - 8.20 (m, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 6.89 - 6.78 (m, 2H), 6.73 - 6.65 (m, 1H), 6.32- 6.17 (m, 2H), 5.81 (d, J = 10.8 Hz, 1H), 5.73 - 5.46 (m, 1H), 4.62 - 4.35 (m, 1H), 4.22 - 4.15 (m, 1H), 4.11 - 4.03 (m, 5H), 4.00 (s, 3H), 3.44 (t, J = 4.4 Hz, 2H) , 3.04 (s, 3H), 1.55 - 1.34 (m, 3H),
223a		
224		LCMS m/z [M+1]: 613.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 - 8.27 (m, 1H), 8.24 - 8.17 (m, 1H), 8.03 - 7.89 (m, 2H), 7.86 - 7.84 (m, 1H), 7.77 - 7.70 (m, 1H), 7.04 - 6.94 (m, 1H), 6.89 – 6.80 (m, 1H), 6.76 - 6.64 (m, 1H), 6.19 - 6.08 (m, 1H), 5.75 - 5.64 (m, 1H), 4.22 - 4.13 (m, 4H), 4.04 - 3.88 (m, 1H), 3.74 - 3.60 (m, 2H), 3.56 - 3.46 (m, 2H), 3.46 - 3.33 (m, 2H), 3.46 - 3.03 (m, 3H), 2.87 - 2.77 (m, 1H), 1.96 - 1.86 (m, 1H), 1.65 - 1.59 (m, 1H), 1.53 - 1.39 (m, 1H).

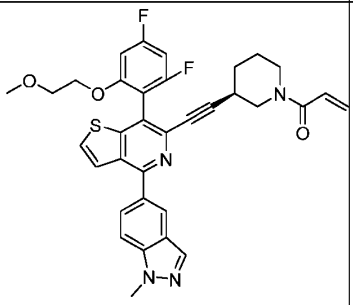
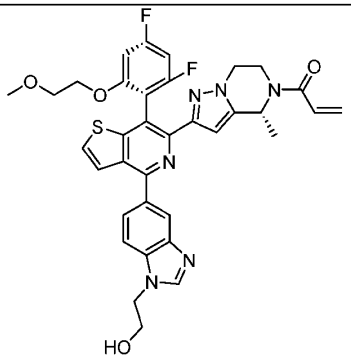
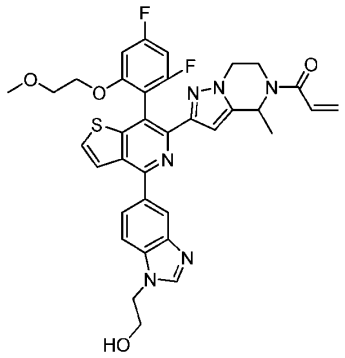
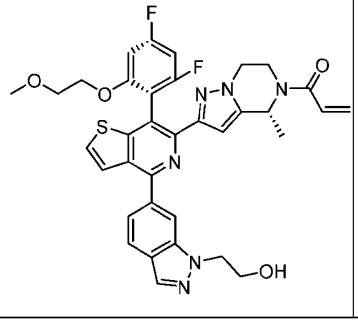
Cmpd. No.	Structure	Analytical data
224a		
225		LCMS m/z [M+1]: 613.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 - 8.27 (m, 1H), 8.24 - 8.17 (m, 1H), 8.03 - 7.89 (m, 2H), 7.86 - 7.84 (m, 1H), 7.77 - 7.70 (m, 1H), 7.04 - 6.94 (m, 1H), 6.89 – 6.80 (m, 1H), 6.76 - 6.64 (m, 1H), 6.19 - 6.08 (m, 1H), 5.75 - 5.64 (m, 1H), 4.22 - 4.13 (m, 4H), 4.04 - 3.88 (m, 1H), 3.74 - 3.60 (m, 2H), 3.56 - 3.46 (m, 2H), 3.46 - 3.33 (m, 2H), 3.46 - 3.03 (m, 3H), 2.87 - 2.77 (m, 1H), 1.96 - 1.86 (m, 1H), 1.65 - 1.59 (m, 1H), 1.53 - 1.39 (m, 1H).
226		LCMS m/z [M+1]: 642.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.19 (s, 1H), 9.08 (s, 1H), 8.78 (s, 1H), 7.97 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 5.6 Hz, 1H), 6.95 (d, J = 10.8 Hz, 1H), 6.90-6.75 (m, 2H), 6.35-6.25 (m, 1H), 6.12 (s, 1H), 5.83 (d, J = 10.8 Hz, 1H), 5.80-5.45 (m, 1H), 4.32-4.25 (m, 1H), 4.20-4.05 (m, 6H), 3.85-3.75 (m, 1H), 3.44 (t, J = 4.8 Hz, 2H), 3.07 (s, 3H), 1.55-1.35 (m, 3H).

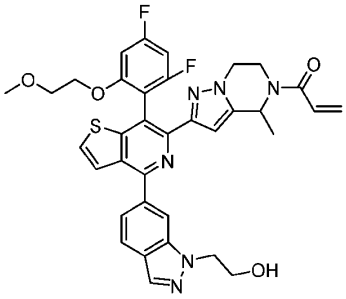
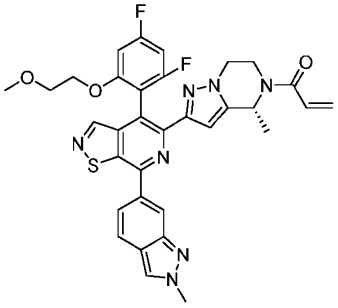
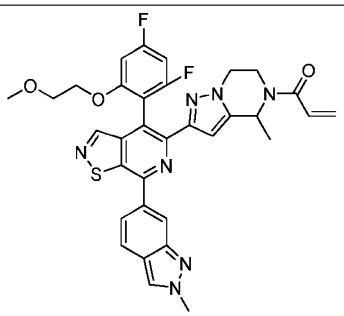
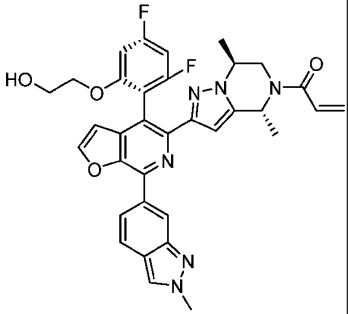
Cmpd. No.	Structure	Analytical data
226a		
227		LCMS m/z [M+1]: 559.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.16 (s, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 5.66 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 10.6 Hz, 1H), 6.77 - 6.69 (m, 1H), 6.27 - 6.12 (m, 2H), 5.69 (dd, J = 9.2, 2.6 Hz, 1H), 4.18-4.12 (m, 7H), 3.62 - 3.45 (m, 2H), 3.10 (s, 3H).
228		LCMS m/z [M+1]: 677.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 8.25 (s, 1H), 8.10-8.03 (m, 2H), 7.84 (d, J = 5.6 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 10.8 Hz, 1H), 6.90-6.75 (m, 2H), 6.35-6.20 (m, 1H), 6.06 (s, 1H), 5.87-5.81 (m, 1H), 5.80-5.45 (m, 1H), 4.40-4.30 (m, 4H), 4.20-4.10 (m, 3H), 3.95-3.85 (m, 2H), 3.85-3.75 (m, 1H), 3.07 (s, 1H), 1.55-1.35 (m, 3H), 1.35-1.25 (m, 2H).
228a		

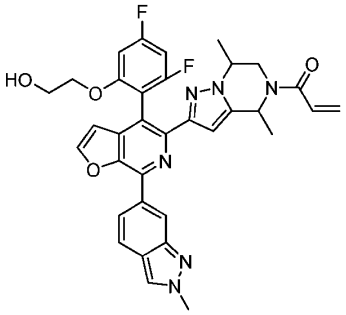
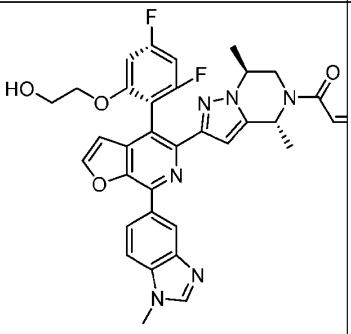
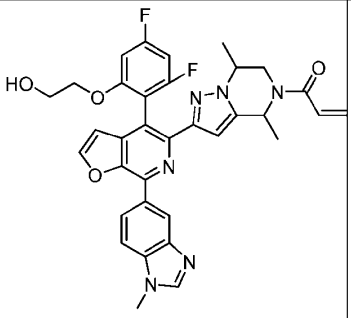
Cmpd. No.	Structure	Analytical data
229		LCMS m/z [M+1]: 671.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.14 (d, J = 1.7 Hz, 1H), 8.41 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.5 Hz, 1H), 6.94 – 6.80 (m, 2H), 6.72 – 6.63 (m, 1H), 6.33 (d, J = 16.4 Hz, 1H), 6.24 (s, 1H), 5.84 (dd, J = 10.6, 1.4 Hz, 1H), 5.78 – 5.45 (m, 1H), 4.80 – 4.65 (m, 0.5H), 4.49 – 4.40 (m, 1H), 4.32 – 4.18 (m, 0.5H), 4.05 (t, J = 4.8 Hz, 2H), 3.99 – 3.80 (m, 1H), 3.77 – 3.67 (m, 1H), 3.66 – 3.51 (m, 2H), 3.44 (t, J = 6.3 Hz, 2H), 3.11 (s, 3H), 1.83 (d, J = 6.8 Hz, 3H), 1.55 – 1.38 (m, 3H), 1.27 (s, 3H).
229a		
230		LCMS m/z [M+1]: 724.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.24 (s, 1H), 8.05 (dd, J = 8.8, 0.8 Hz, 1H), 8.00 (t, J = 5.6 Hz, 1H), 7.87-7.81 (m, 2H), 6.97 (d, J = 10.8 Hz, 1H), 6.80-6.70 (m, 1H), 6.23-6.15 (m, 1H), 5.65-5.55 (m, 1H), 4.85-4.75 (m, 1H), 4.65-4.20 (m, 2H), 4.19 (s, 3H), 4.18-3.85 (m, 3H), 3.46 (t, J = 4.4 Hz, 2H), 3.08 (s, 3H), 3.00 (d, J = 6.4 Hz, 6H), 1.78-1.81 (m, 6H), 1.55 (d, J = 7.2 Hz, 1H), 1.41 (d, J = 6.8 Hz, 2H).

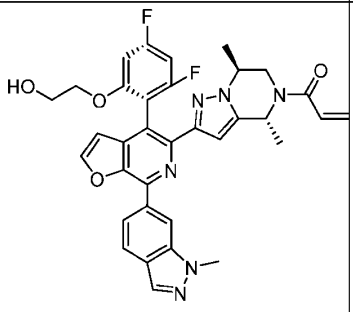
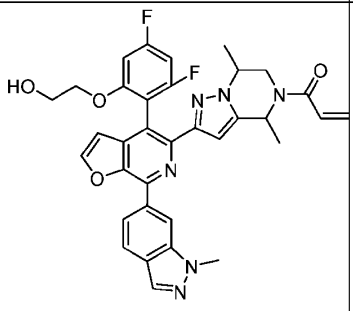
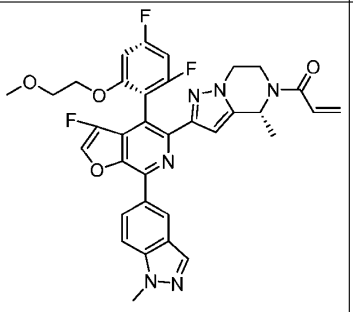
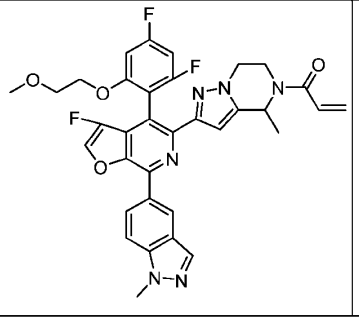
Cmpd. No.	Structure	Analytical data
230a		
231		LCMS m/z [M+1]: 639.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.28 (s, 1H), 8.14 – 8.05 (m, 2H), 7.92 (d, J = 8.9 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.00 (t, J = 9.0 Hz, 1H), 6.91 (d, J = 10.7 Hz, 1H), 6.86 – 6.75 (m, 1H), 6.43 – 6.27 (m, 1H), 5.89 – 5.81 (m, 1H), 5.77 – 5.68 (m, 1H), 5.17 – 4.92 (m, 2H), 4.78 – 4.64 (m, 2H), 4.63 – 4.42 (m, 1H), 4.20 (s, 3H), 4.10 – 3.92 (m, 1H), 3.88 – 3.60 (m, 3H), 2.98-2.93 (m, 1H), 1.82-1.73 (m, 1H), 1.60 – 1.45 (m, 1H).
231a		
232		LCMS m/z [M+1]: 641.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.89 (d, J = 2.4 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 5.6 Hz, 1H),7.84 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 3.6 Hz, 1H), 7.09 - 6.72 (m, 4H), 6.29 (d, J = 17.2 Hz, 1H), 6.05 (s, 1H), 5.85 - 5.50 (m, 2H), 4.35 - 4.31 (m, 1H), 4.13 (d, J = 4.4 Hz, 3H), 4.00 (s, 3H), 3.47 - 3.44 (m, 2H), 3.09 (s, 3H), 1.52 1.35 (s, 3H).

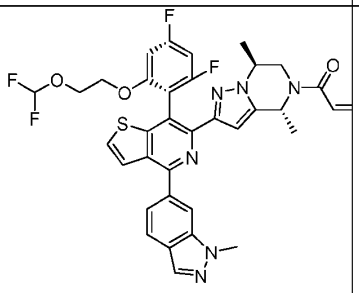
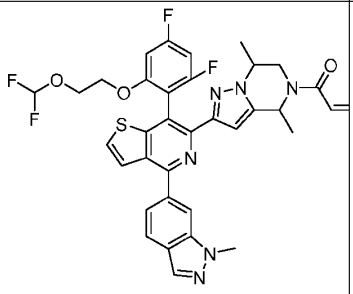
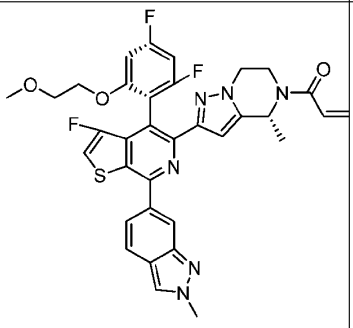
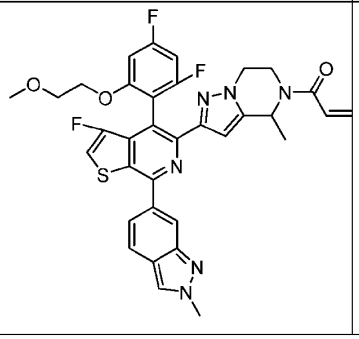
Cmpd. No.	Structure	Analytical data
232a		
233		LCMS m/z [M+1]: 641.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.93 (d, J = 1.6 Hz, 1H), 8.54 (s, 1H), 7.77 (q, J = 5.5 Hz, 2H), 7.68 (d, J = 3.2 Hz, 1H), 6.89 - 6.81 (m, 2H), 6.73 - 6.68 (m, 2H), 6.15 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.75 - 5.41(m, 1H), 4.23 - 4.20 (m, 1H), 4.10 - 3.99 (m, 6H), 3.43 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.46 - 1.40 (m, 3H).
233a		
234		LCMS m/z [M+1]: 599.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 8.16 (s, 1H), 7.91 (dd, J = 8.8, 1.2 Hz, 1H), 7.80 (dd, J = 5.5, 0.9 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.65 (d, J = 5.5 Hz, 1H), 6.89 (m, 1H), 6.75 - 6.78 (m, 1H), 6.54 - 6.51 (m, 1H), 6.30 (m, 1H), 5.77 - 5.74 (m, 1H), 4.15 (m, 5H), 3.63 - 3.42 (m, 6H), 3.30 (m, 1H), 3.08 (s, 3H), 2.24 - 2.07 (m, 1H), 2.03 - 1.85 (m, 1H).

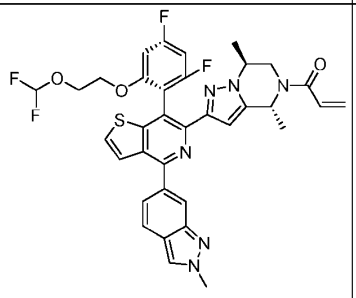
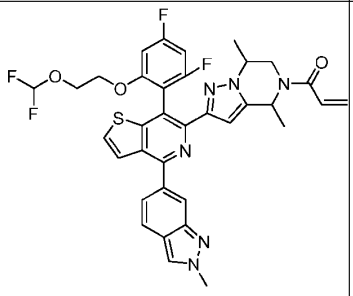
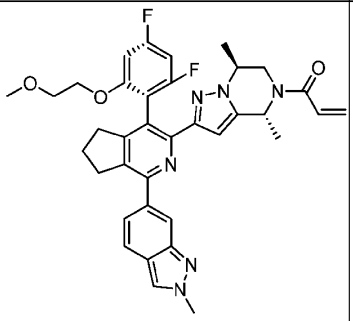
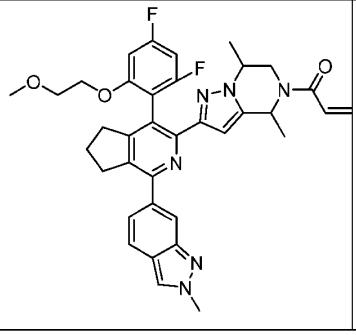
Cmpd. No.	Structure	Analytical data
235		LCMS m/z [M+1]: 613.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.16 (s, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.64 (d, J = 5.5 Hz, 1H), 6.97 –6.87 (m, 1H), 6.84 – 6.65 (m, 2H), 6.20 – 6.05 (m, 1H), 5.75 – 5.64 (m, 1H), 4.20 – 4.07 (m, 6H), 3.68 – 3.40 (m, 5H), 3.09 (s, 2H), 2.85 – 2.60 (m, 1H), 2.00 – 1.82 (m, 1H), 1.75 – 1.41 (m, 4H).
236		LCMS m/z [M+1]: 671.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.37 (s, 1H), 8.44 (s, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.94-6.72 (m, 3H), 6.35-6.25 (m, 1H), 6.14 (s, 1H), 5.83 (dd, J = 10.8 Hz, 1.6 Hz, 1H), 5.80-5.45 (m, 1H), 4.69 (t, J = 4.8 Hz, 2H), 4.28-4.20 (m, 1H), 4.18-4.00 (m, 5H), 3.85-3.70 (m, 1H), 3.44 (t, J = 4.8 Hz, 2H), 3.06 (s, 3H), 1.55-1.35 (m, 3H).
236a		
237		LCMS m/z [M+1]: 671.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.15 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.73 (s, 2H), 6.91 - 6.79 (m, 2H), 6.74 - 6.66 (m, 1H), 6.34 - 6.21 (m, 1H), 6.17 (s, 1H), 5.86 - 5.77 (m, 1H), 5.73 - 5.45 (m, 1H), 4.65 - 4.54 (m, 5H), 4.24 - 4.17 (m,

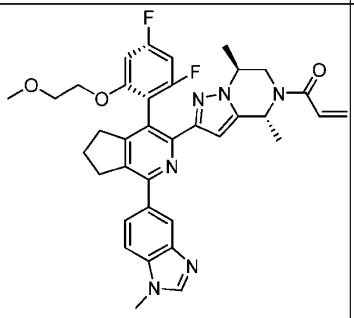
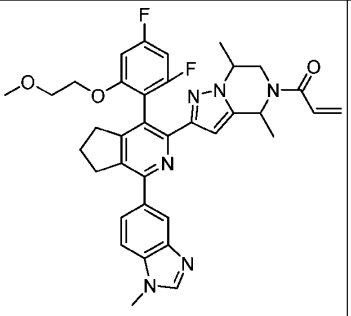
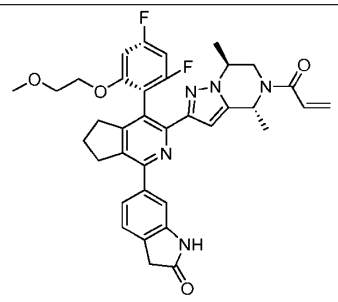
Cmpd. No.	Structure	Analytical data
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237a		
238		LCMS m/z [M+1]: 642.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 - 8.67 (m, 1H), 8.41 (s, 1H), 8.31 (s, 1H), 8.07 - 8.02 (m, 1H), 7.94 (d, J =9.6 Hz, 1H), 6.91- 6.81 (m, 2H), 6.75 - 6.68 (m, 1H), 6.39 - 6.23 (m, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.76 - 5.51 (m, 1H), 4.59 (s, 1H), 4.29 (s, 3H), 4.21 - 4.10 (m, 2H), 4.02 - 3.95 (m, 1H), 3.43 - 3.38 (m, 2H), 3.03 (s, 1H), 1.55 - 1.42 (m, 3H).
238a		
239		LCMS m/z [M+1]: 625.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 8.33 – 8.24 (m, 2H), 8.10 (d, J = 2.1 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 6.85 (d, J = 10.9 Hz, 2H), 6.73 – 6.57 (m, 2H), 6.35 (d, J = 15.5 Hz, 2H), 5.77 (dd, J = 75.4, 47.8 Hz, 2H), 4.41 (d, J = 6.0 Hz, 1H), 4.29 (s, 3H), 4.26 – 3.86 (m,

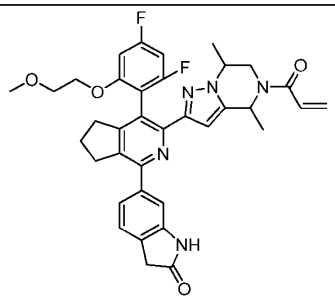
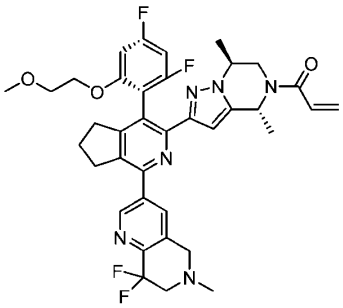
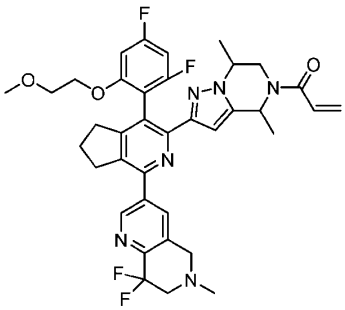
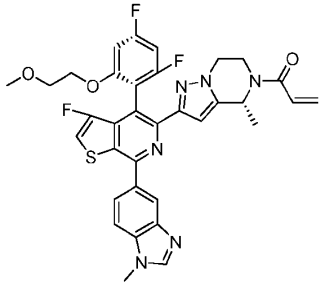
Cmpd. No.	Structure	Analytical data
		3H), 3.85 – 3.35 (m, 3H), 1.52 (d, J = 20.5 Hz, 3H), 1.28 (s, 3H).
239a		
240		LCMS m/z [M+1]: 625.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.86 (d, J = 0.9 Hz, 1H), 8.56 (dd, J = 8.6, 1.5 Hz, 1H), 8.24 (s, 1H), 8.09 (d, J = 2.2 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 6.87 (dd, J = 16.8, 6.6 Hz, 2H), 6.73 – 6.56 (m, 2H), 6.33 (t, J = 13.8 Hz, 2H), 5.77 (dd, J = 74.6, 48.9 Hz, 2H), 4.42 (d, J = 5.8 Hz, 1H), 4.32 – 4.02 (m, 2H), 3.99 (s, 3H), 3.97 – 3.73 (m, 1H), 3.72 – 3.34 (m, 3H), 1.61 – 1.44 (m, 3H), 1.29 (d, J = 9.1 Hz, 3H).
240a		

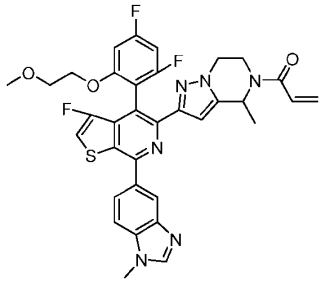
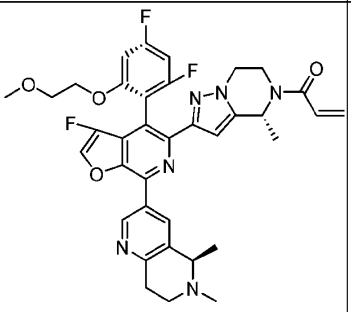
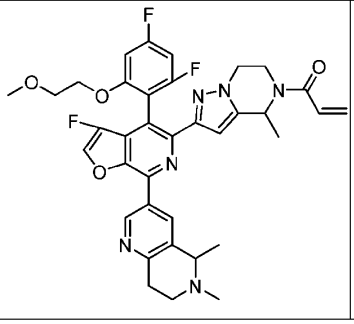
Cmpd. No.	Structure	Analytical data
241		LCMS m/z [M+1]: 625.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (s, 1H), 8.36 (dd, J = 8.6, 1.0 Hz, 1H), 8.16 – 8.05 (m, 2H), 7.95 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 10.9 Hz, 2H), 6.77 – 6.59 (m, 2H), 6.42 – 6.23 (m, 2H), 5.77 (dd, J = 80.7, 47.2 Hz, 2H), 4.84 – 4.25 (m, 2H), 4.22 (s, 3H), 4.11 – 3.43 (m, 3H), 1.51 (d, J = 22.3 Hz, 3H), 1.31 (s, 3H).
241a		
242		LCMS m/z [M+1]: 643.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 8.59 (dd, J = 8.9, 1.4 Hz, 1H), 8.19 – 8.15 (m, 2H), 7.71 (d, J = 8.9 Hz, 1H), 6.90 – 6.76 (m, 2H), 6.66 – 6.60 (m, 1H), 6.36 – 6.24 (m, 1H), 6.20 (s, 1H), 5.82 (d, J = 10.7 Hz, 1H), 5.78 – 5.45 (m, 1H), 4.50 – 4.32 (m, 0.5H), 4.23 – 4.16 (m, 1H), 4.15 – 3.92 (m, 6H), 3.85 – 3.65 (m, 0.5H), 3.47 (t, J = 4.6 Hz, 2H), 3.12 (s, 3H), 1.56 – 1.38 (m, 3H).
242a		

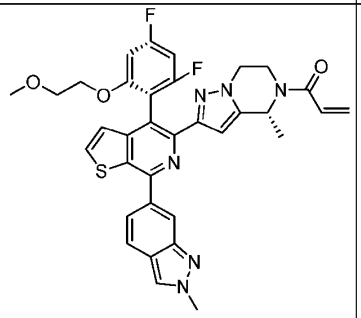
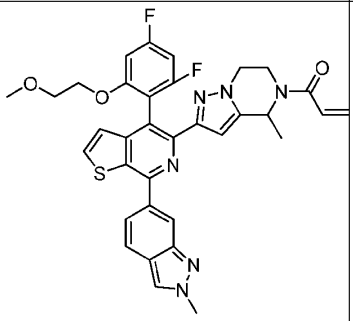
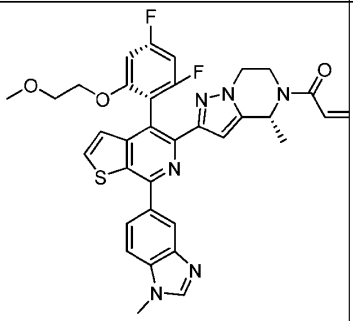
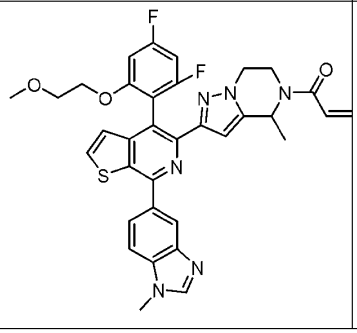
Cmpd. No.	Structure	Analytical data
243		LCMS m/z [M+1]: 691.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 8.21 (s, 1H), 8.12 – 8.06 (m, 2H), 7.85 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 12.4 Hz, 1H), 6.90 – 6.82 (m, 2H), 6.37 –6.29 (m, 1H), 6.17 – 6.07 (m, 1H), 5.92 –5.81 (m, 1H), 5.67-5.53 (m, 1H), 4.22 (s, 1H), 4.21 – 4.03 (m, 4H), 3.90 (t, J = 4.3 Hz, 2H), 1.45-1.31 (m, 6H).
243a		
244		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 2H), 7.95 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 6.90 – 6.61 (m, 3H), 6.29 (d, J = 16.0 Hz, 1H), 6.04 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.72 - 5.41 (m, 1H), 4.30 (s, 3H), 4.25 (dd, J = 12.7, 2.9 Hz, 1H), 4.17 – 3.97 (m, 3H), 3.47 (t, J = 4.5 Hz, 2H), 3.09 (s, 3H), 1.47 - 1.35 (m, 3H).
244a		

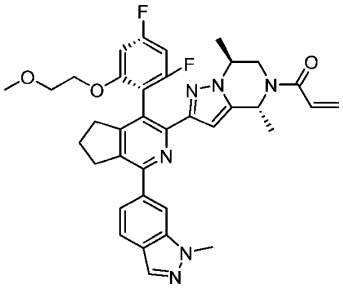
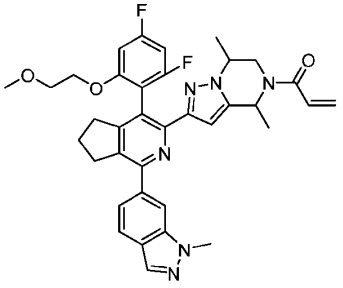
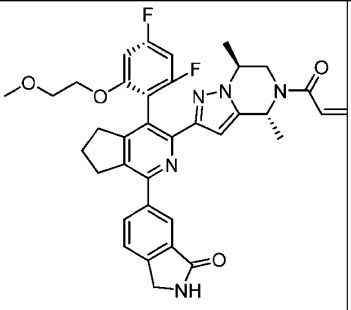
Cmpd. No.	Structure	Analytical data
245		LCMS m/z [M+1]: 691.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1H), 8.27 (s, 1H), 8.09 (d, J = 5.6 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 8.03 – 6.80 (m, 3H), 5.81 – 6.39 (m, 4H), 5.71 - 5.42 (m, 1H), 4.78 - 4.52 (m, 2H), 4.33 (s, 3H), 4.29 – 4.02 (m, 3H), 3.92 - 3.81 (m, 2H), 1.53 - 1.42 (m, 3H), 1.41 - 1.31 (m, 3H).
245a		
246		LCMS m/z [M+1]: 639.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 7.91 (s, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 6.86 – 6.63 (m, 2H), 6.47 (t, J = 8.3 Hz, 1H), 6.22 (d, J = 16.6 Hz, 1H), 6.02 (s, 1H), 5.73 (d, J = 10.7 Hz, 1H), 5.50 (d, J = 85.3 Hz, 1H), 4.28 (s, 1H), 4.23 – 3.99 (m, 5H), 3.97 – 3.86 (m, 1H), 3.74 (s, 1H), 3.47 (t, J = 4.5 Hz, 2H), 3.13 (s, 5H), 2.88 – 2.77 (m, 1H), 2.69 – 2.54 (m, 1H), 2.17 – 1.90 (m, 2H), 1.34 (d, J = 24.1 Hz, 3H), 1.16 (s, 3H).
246a		

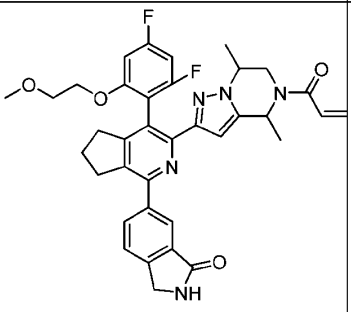
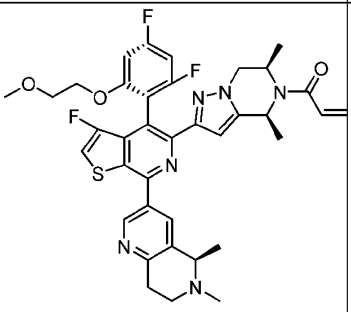
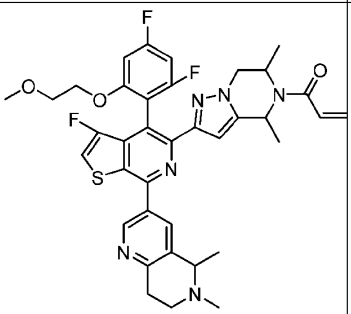
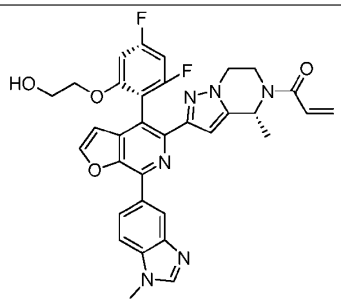
Cmpd. No.	Structure	Analytical data
247		LCMS m/z [M+1]: 639.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 25.6 Hz, 2H), 7.82 (d, J = 8.5 Hz, 1H), 7.58 (dd, J = 8.5, 1.9 Hz, 1H), 6.86 – 6.60 (m, 2H), 6.46 (td, J = 9.2, 2.1 Hz, 1H), 6.21 (d, J = 16.4 Hz, 1H), 6.04 (s, 1H), 5.73 (d, J = 10.7 Hz, 1H), 5.50 (d, J = 83.8 Hz, 1H), 4.28 (s, 1H), 4.18 – 3.98 (m, 2H), 3.94 – 3.81 (m, 4H), 3.73 (s, 1H), 3.47 (t, J = 4.2 Hz, 2H), 3.13 (d, J = 1.0 Hz, 5H), 2.89 – 2.76 (m, 1H), 2.68 – 2.52 (m, 1H), 2.10 – 1.90 (m, 2H), 1.42 – 1.27 (m, 3H), 1.13 (s, 3H).
247a		
248		LCMS m/z [M+1]: 640.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 – 7.24 (m, 3H), 6.86 – 6.61 (m, 2H), 6.46 (td, J = 9.2, 2.2 Hz, 1H), 6.22 (d, J = 16.7 Hz, 1H), 5.98 (s, 1H), 5.73 (dd, J = 10.6, 1.5 Hz, 1H), 5.48 (d, J = 88.7 Hz, 1H), 4.28 (s, 1H), 4.20 – 3.96 (m, 2H), 3.93 – 3.85 (m, 1H), 3.74 (s, 1H), 3.56 – 3.41 (m, 4H), 3.17 – 3.02 (m, 5H), 2.86 – 2.73 (m, 1H), 2.64 – 2.50 (m, 1H), 2.07 – 1.91 (m, 2H), 1.40 – 1.27 (m, 3H), 1.16 (s, 3H).

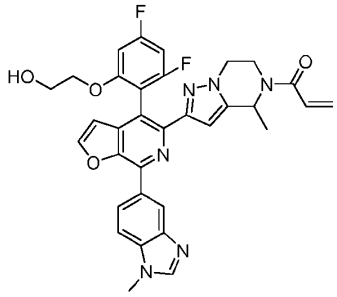
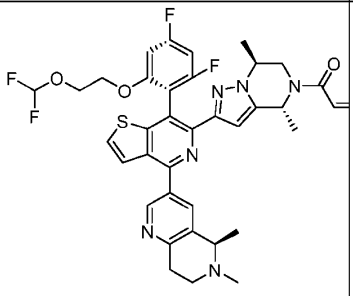
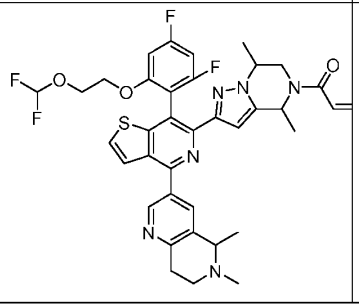
Cmpd. No.	Structure	Analytical data
248a		
249		LCMS m/z [M+1]: 691.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.00 (d, J = 1.9 Hz, 1H), 8.19 (s, 1H), 6.84 – 6.64 (m, 2H), 6.48 (td, J = 9.3, 2.2 Hz, 1H), 6.22 (d, J = 16.9 Hz, 1H), 6.03 (s, 1H), 5.73 (dd, J = 10.6, 1.6 Hz, 1H), 5.49 (d, J = 81.9 Hz, 1H), 4.35 – 4.22 (m, 1H), 4.20 – 3.97 (m, 2H), 3.94 – 3.83 (m, 1H), 3.76 (s, 3H), 3.44 (t, J = 4.6 Hz, 2H), 3.19 – 3.07 (m, 7H), 2.91 – 2.74 (m, 1H), 2.67 – 2.55 (m, 1H), 2.48 (s, 3H), 2.12 – 1.98 (m, 2H), 1.31 (s, 3H), 1.17 (s, 3H).
249a		
250		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.45 (s, 1H), 8.60 (s, 1H), 8.46 (dd, J = 8.7, 1.4 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.93 – 6.58 (m, 3H), 6.29 (d, J = 15.4 Hz, 1H), 6.06 (s, 1H), 5.83 (dd, J = 10.6, 1.5 Hz, 1H), 5.71 - 5.42 (m, 1H), 4.26 – 4.20 (m, 4H), 4.13

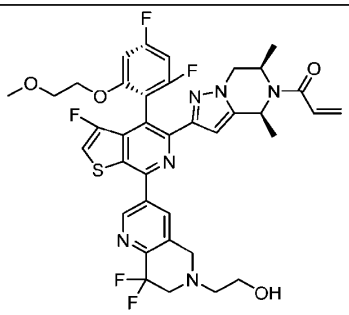
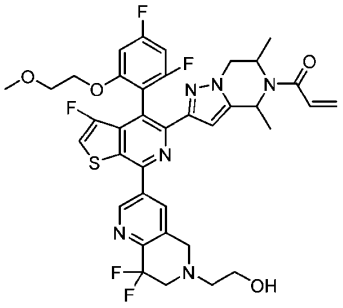
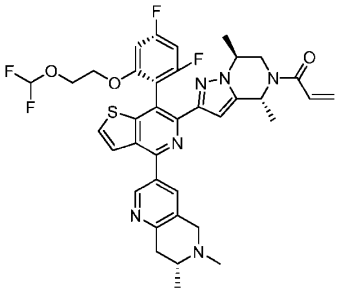
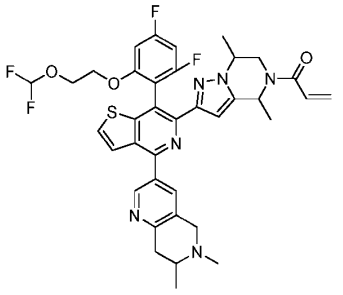
Cmpd. No.	Structure	Analytical data
		- 4.01 (m, 3H), 3.46 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 1.47 - 1.31 (m, 3H).
250a		
251		LCMS m/z [M+1]: 673.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.60 (s, 1H), 8.86 (s, 1H), 8.26 (d, J = 4.4 Hz, 1H), 6.91 – 6.80 (m, 2H), 6.69 – 6.62 (m, 1H), 6.37 – 6.25 (m, 1H), 6.10 (s, 1H), 5.83 (dd, J = 10.6, 1.5 Hz, 1H), 5.78 – 5.42 (m, 1H), 4.51 – 4.35 (m, 0.5H), 4.28 – 4.20 (m, 1H), 4.17 – 3.85 (m, 4H), 3.85 – 3.65 (m, 2H), 3.52 – 3.37 (m, 4H), 3.16 – 3.05 (m, 6H), 1.85 (d, J = 6.0 Hz, 3H), 1.54 – 1.37 (m, 3H).
251a		

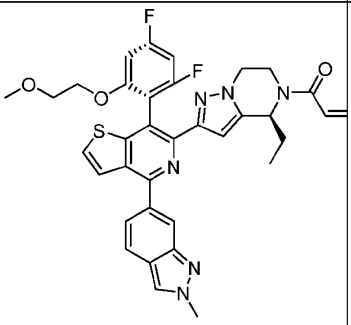
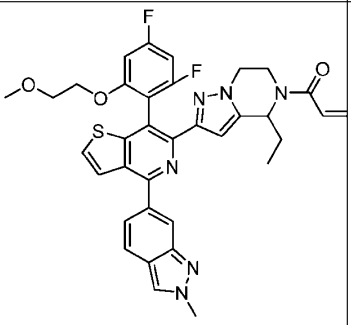
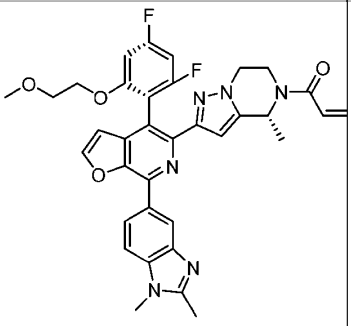
Cmpd. No.	Structure	Analytical data
252		LCMS m/z [M+1]: 641.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 -8.39 (m, 3H), 8.03 (d, J = 8.8 Hz, 1H), 7.81 - 7.78 (m, 1H), 7.32 (d, J = 5.6 Hz, 1H), 6.96 (d, J = 10.8 Hz, 1H), 6.86 - 6.75 (m, 2H), 6.30 (d, J = 16.0 Hz, 1H), 6.03 (s, 1H), 5.85 (d, J = 2.0 Hz, 1H), 5.82 - 5.48 (m, 1H), 4.33 (s, 4H), 4.17 - 4.05 (m, 3H), 3.51 - 3.43 (m, 2H), 3.09 (s, 3H), 1.55 - 1.34 (m, 3H).
252a		
253		LCMS m/z [M+1]: 641.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.36 (s, 1H), 8.63 (s, 1H), 8.48 (d, J = 10.0 Hz, 1H), 8.14 - 8.06 (m, 2H), 7.18 (d, J = 5.6 Hz, 1H), 6.91 - 6.82 (m, 2H), 6.74 - 6.69 (m, 1H), 6.29 (d, J = 16.4 Hz, 1H), 6.09 (s, 1H), 5.83 (d, J = 12.0 Hz, 1H), 5.69 - 5.47 (m, 1H), 4.25 - 4.21 (m, 4H), 4.12 - 4.04 (m, 3H), 3.42 - 3.38 (m, 2H), 3.06 (s, 3H), 1.54-1.34 (m, 3H).
253a		

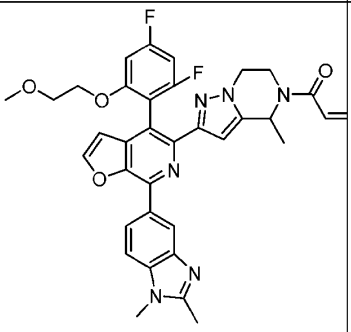
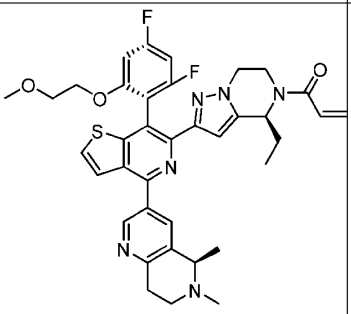
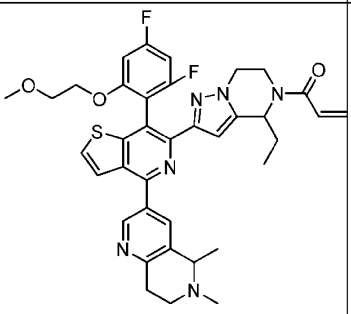
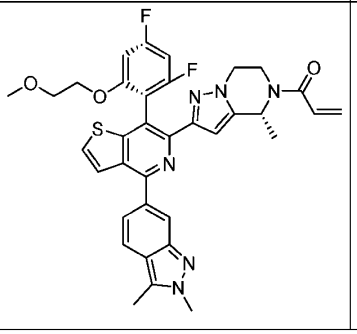
Cmpd. No.	Structure	Analytical data
254		LCMS m/z [M+1]: 639.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (d, J = 3.4 Hz, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 6.88 (s, 1H), 6.80 (d, J = 11.0 Hz, 1H), 6.60 (t, J = 9.0 Hz, 1H), 6.34 (d, J = 16.6 Hz, 1H), 6.09 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.61 (d, J = 83.8 Hz, 1H), 4.43 (s, 1H), 4.26 – 4.13 (m, 4H), 4.06 – 3.77 (m, 2H), 3.58 (t, J = 4.2 Hz, 2H), 3.48 – 3.36 (m, 1H), 3.37 – 3.27 (m, 5H), 2.99 – 2.89 (m, 1H), 2.78 – 2.67 (m, 1H), 2.21 – 2.07 (m, 2H), 1.52 – 1.36 (m, 3H), 1.35 – 1.22 (m, 3H).
254a		
255		LCMS m/z [M+1]: 640.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.29 (s, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 6.89 (d, J = 15.0 Hz, 1H), 6.80 (d, J = 10.8 Hz, 1H), 6.59 (t, J = 8.6 Hz, 1H), 6.34 (d, J = 16.4 Hz, 1H), 6.21 (d, J = 21.2 Hz, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.63 (d, J = 86.8 Hz, 1H), 4.58 (s, 2H), 4.39 (s, 1H), 4.31 – 4.10 (m, 2H), 4.05 – 3.99 (m, 1H), 3.94 – 3.70 (m, 1H), 3.58 (t, J = 4.4 Hz, 2H), 3.30 – 3.19 (m, 5H), 2.99 – 2.87 (m, 1H), 2.78 – 2.65 (m, 1H), 2.22 – 2.07 (m, 2H), 1.50 – 1.37 (m, 3H), 1.31 – 1.23 (m, 3H).

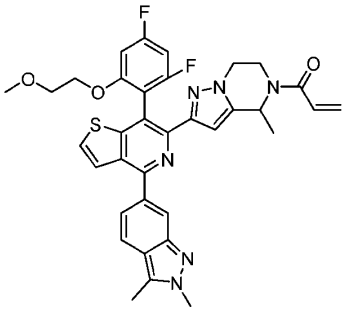
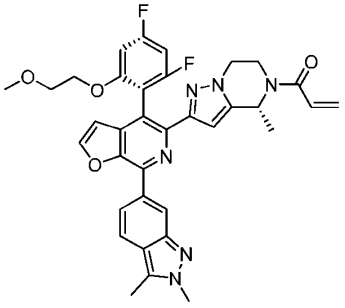
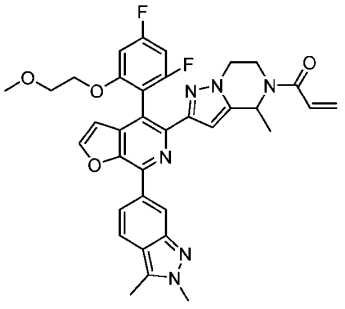
Cmpd. No.	Structure	Analytical data
255a		
256		LCMS m/z [M+1]: 703.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (d, J = 2.0 Hz, 1H), 8.56 (s, 1H), 7.62 (d, J = 2.4 Hz, 1H), 6.87 - 6.78 (m, 2H), 6.68 - 6.64 (m, 1H), 6.40-6.21(m, 1H), 6.09 (s, 1H), 5.82 (d, J = 10.4 Hz, 1H), 5.60 - 5.41(m, 1H), 4.18-4.09 (m, 2H), 4.08-4.05 (t, J = 5.2 Hz, 1H), 3.96-3.91 (m, 2H), 3.45-3.42 (m, 4H), 3.11 (d, J = 7.2 Hz, 6H), 1.85 (d, J = 6.0 Hz, 3H), 1.51 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 7.2 Hz, 3H).
256a		
257		LCMS m/z [M+1]: 611.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.86 (d, J = 1.0 Hz, 1H), 8.57 (dd, J = 8.6, 1.5 Hz, 1H), 8.24 (s, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 6.91 – 6.79 (m, 2H), 6.72 – 6.61 (m, 2H), 6.41 – 6.21 (m, 2H), 5.84 (d, J = 10.9 Hz, 1H), 5.64 (d, J = 80.0 Hz, 1H), 4.36 (d, J = 40.9 Hz, 1H), 4.21 (dd, J = 12.6, 2.7 Hz, 1H), 4.11 –

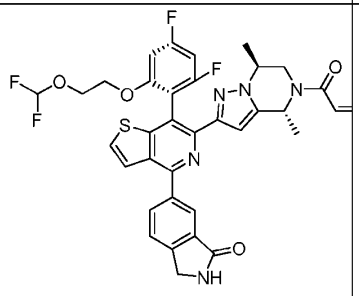
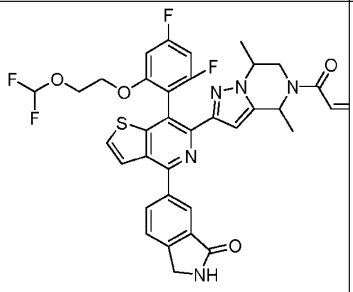
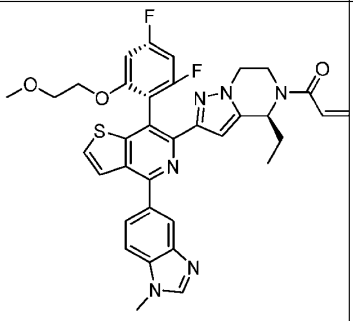
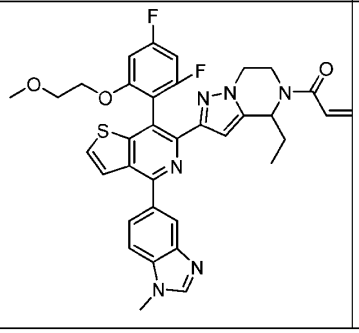
Cmpd. No.	Structure	Analytical data
		3.97 (m, 5H), 3.92 (dq, J = 5.5, 3.8 Hz, 1H), 3.61 (dd, J = 9.7, 4.1 Hz, 3H), 1.48 (d, J = 9.2 Hz, 3H).
257a		
258		LCMS m/z [M+1]: 721.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (d, J = 1.9 Hz, 1H), 8.40 (s, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 6.95 - 6.67 (m, 3H), 6.37-6.28 (m, 1H), 6.28-6.15 (m, 1H), 5.98 (s, 1H), 5.88 - 5.78 (m, 1H), 5.77 - 5.41 (m, 1H), 4.48 - 4.35 (m, 1H), 4.29 - 4.04 (m, 2H), 4.02 - 3.89 (m, 1H), 3.88 - 3.83 (m, 2H), 3.83 - 3.77 (m, 1H), 3.77 - 3.63 (m, 1H), 3.43 (t, J = 6.5 Hz, 2H), 3.11 (s, 3H), 1.93 - 1.74 (m, 3H), 1.55 - 1.37 (m, 3H), 1.36 - 1.19 (m, 3H).
258a		

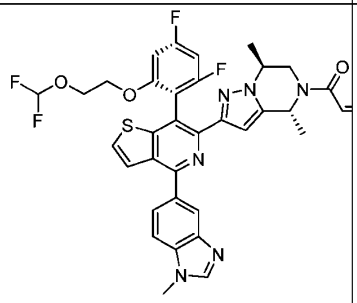
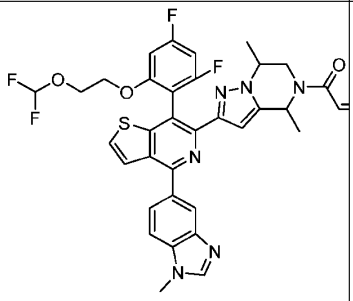
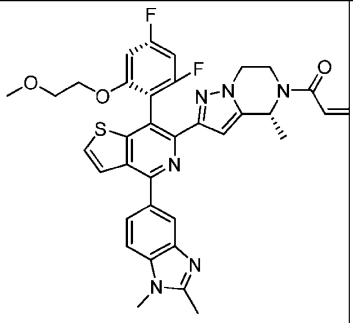
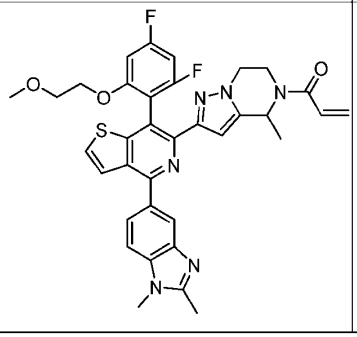
Cmpd. No.	Structure	Analytical data
259		LCMS m/z [M+1]: 755.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (s, 1H), 8.61 (s, 1H), 7.63 (d, J = 2.2 Hz, 1H), 6.87 - 6.64 (m, 3H), 6.28 (s, 1H), 6.16 (s, 1H), 5.81 (d, J = 10.2 Hz, 1H), 5.46 (s, 1H), 4.46 (s, 2H), 4.20 – 4.05 (m, 3H), 3.99 – 3.78 (m, 5H), 3.44 (t, J = 4.6 Hz, 2H), 3.24 (t, J = 5.2 Hz, 2H), 3.09 (s, 3H), 1.51 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).
259a		
260		LCMS m/z [M+1]: 721.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.14 (s, 1H), 8.33 (s, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 4.9 Hz, 1H), 6.93 – 6.68 (m, 3H), 6.38 – 6.21 (m, 2H), 6.19 – 5.77 (m, 2H), 5.71 - 5.42 (m, 1H), 4.74 (s, 1H), 4.40 (s, 1H), 4.27 – 3.76 (m, 8H), 3.57 - 3.48 (m, 1H), 3.28 – 3.20 (m, 1H), 3.09 (s, 3H), 1.64 - 1.55 (m, 3H), 1.53 - 1.41 (m, 3H), 1.26 (d, J = 6.9 Hz, 3H).
260a		

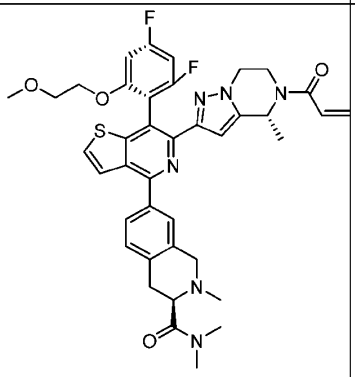
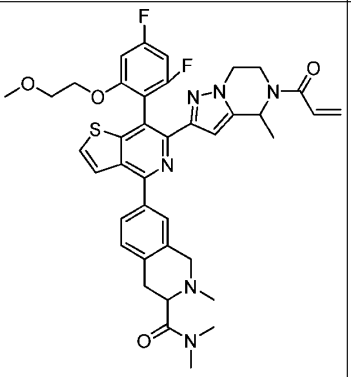
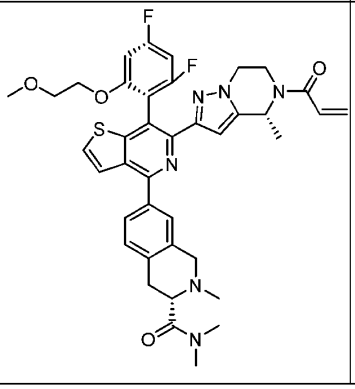
Cmpd. No.	Structure	Analytical data
261		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (s, 1H), 8.25 (s, 1H), 8.05 - 7.98 (m, 2H), 7.81 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.51 - 7.32 (m, 1H), 6.95 (d, J = 10.8 Hz, 1H), 6.90 - 6.79 (m, 2H), 6.36 - 6.22 (m, 1H), 6.06 (s, 1H), 5.83 (d, J = 10.8 Hz, 1H), 5.65 - 5.28 (m, 1H), 4.32 (s, 3H), 4.31 - 4.26 (m, 1H), 4.16 - 4.07 (m, 2H), 4.03 - 3.96 (m, 1H), 3.44 (t, J = 4.4 Hz, 2H), 3.09 (s, 3H), 1.88 - 1.76 (m, 2H), 0.98 - 0.90 (m, 3H).
261a		
262		LCMS m/z [M+1]: 639.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (s, 1H), 8.50 (dd, J = 8.6, 1.4 Hz, 1H), 8.09 (d, J = 2.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 6.94 – 6.85 (m, 1H), 6.83 (d, J = 11.4 Hz, 1H), 6.71 – 6.63 (m, 2H), 6.28 (d, J = 33.0 Hz, 2H), 5.84 (d, J = 10.2 Hz, 1H), 5.64 (d, J = 86.8 Hz, 1H), 4.44 (d, J = 15.8 Hz, 1H), 4.20 (dd, J = 12.4, 2.8 Hz, 1H), 4.13 – 3.91 (m, 3H), 3.87 (s, 3H), 3.83 – 3.59 (m, 1H), 3.46 (t, J = 4.6 Hz, 2H), 3.12 (s, 3H), 2.67 (s, 3H), 1.47 (s, 3H).

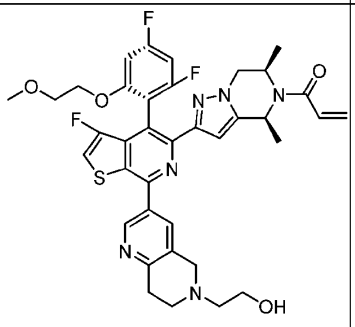
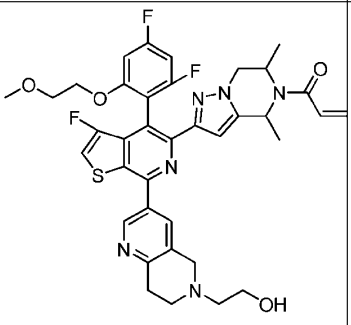
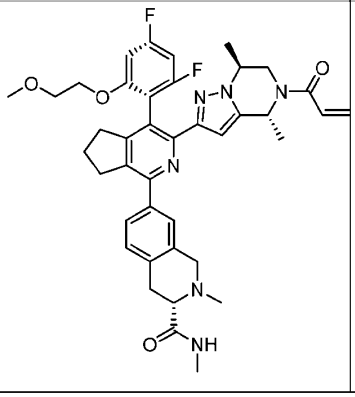
Cmpd. No.	Structure	Analytical data
262a		
263		LCMS m/z [M+1]: 685.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.18 - 9.11 (m , 1H), 8.43 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 6.94 - 6.82 (m, 2H), 6.79 - 7.68 (m, 1H), 6.33 - 6.21 (m, 1H), 6.16 - 6.04 (m, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.65 - 5.26 (m, 1H), 4.25 - 4.17 (m, 1H), 4.14 - 4.03 (m, 2H), 4.02 - 3.88 (m, 2H), 3.85 - 3.63 (m, 2H), 3.48 - 3.37 (m, 4H), 3.11 (s, 3H), 3.04 (s, 3H), 1.90 - 1.70 (m, 5H), 1.03 - 0.87 (m, 3H).
263a		
264		LCMS m/z [M+1]: 655.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.71 (dt, J = 15.6, 7.7 Hz, 3H), 6.86 (dd, J = 16.6, 10.6 Hz, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.27 (d, J = 28.6 Hz, 2H), 5.83 (d, J = 10.7 Hz, 1H), 5.62 (d, J = 85.2 Hz, 1H), 4.37 (d, J = 17.9 Hz, 1H), 4.19 (d, J = 8.3 Hz, 4H), 4.13 – 3.94 (m, 3H), 3.90 – 3.58 (m,

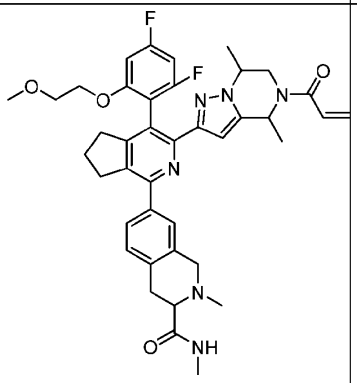
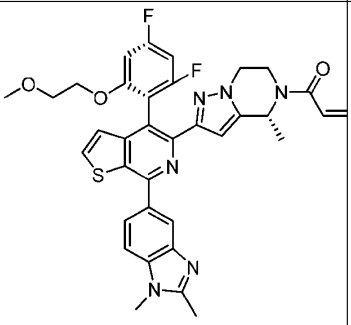
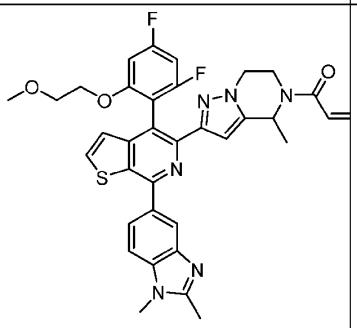
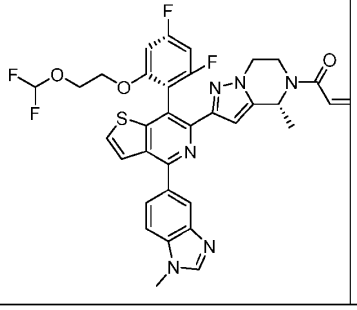
Cmpd. No.	Structure	Analytical data
		1H), 3.45 (t, J = 4.6 Hz, 2H), 3.06 (s, 3H), 2.73 (s, 3H), 1.44 (s, 3H).
264a		
265		LCMS m/z [M+1]: 639.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.24 (dd, J = 8.9, 1.3 Hz, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 6.92 – 6.80 (m, 2H), 6.69 (dt, J = 9.3, 5.2 Hz, 2H), 6.29 (d, J = 28.8 Hz, 2H), 5.84 (d, J = 11.0 Hz, 1H), 5.64 (d, J = 83.9 Hz, 1H), 4.38 (d, J = 27.9 Hz, 1H), 4.24 – 4.15 (m, 4H), 4.15 – 4.02 (m, 2H), 3.99 – 3.72 (m, 2H), 3.46 (t, J = 4.7 Hz, 2H), 3.12 (s, 3H), 2.72 (s, 3H), 1.47 (s, 3H).
265a		

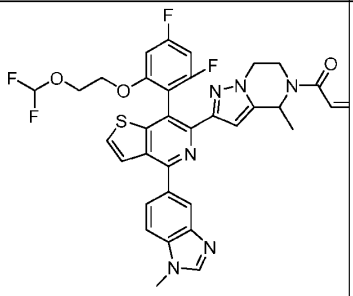
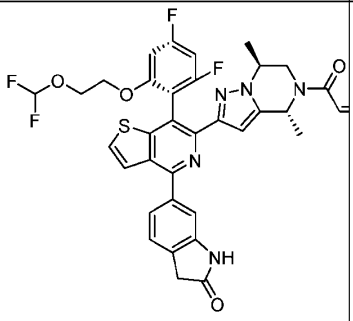
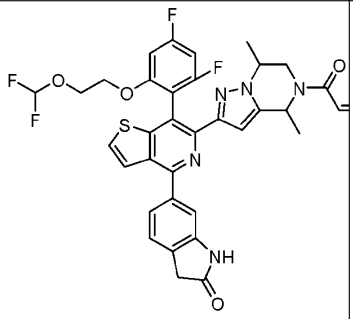
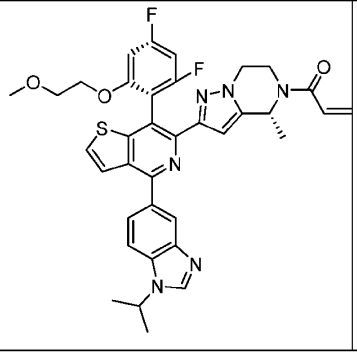
Cmpd. No.	Structure	Analytical data
266		LCMS m/z [M+1]: 692.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.24 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 5.6 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 5.6 Hz, 1H), 6.97 - 6.78 (m, 3H), 6.33 (d, J = 16.6 Hz, 1H), 6.33 – 5.83 (m, 3H), 5.71 - 5.42 (m, 2H), 4.65 (s, 2H), 4.55 - 4.47 (m, 1H), 4.33 – 4.09 (m, 3H), 3.88 (t, J = 4.4 Hz, 2H), 1.53 - 1.41 (m, 3H), 1.37 - 1.25 (m, 3H).
266a		
267		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.44 (s, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.5 Hz, 1H), 6.93 – 6.74 (m, 3H), 6.36 – 6.05 (m, 2H), 5.82 (d, J = 10.6 Hz, 1H), 5.57-5.31 (m, 1H), 4.24 (s, 4H), 4.15 – 3.91 (m, 3H), 3.43 (t, J = 4.5 Hz, 2H), 3.06 (s, 3H), 1.90 – 1.76 (m, 2H), 0.94 (s, 3H).
267a		

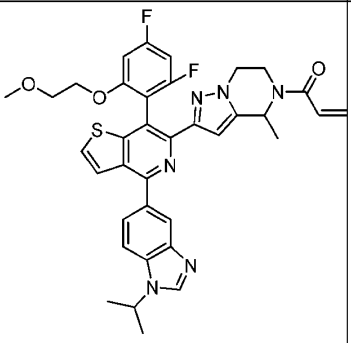
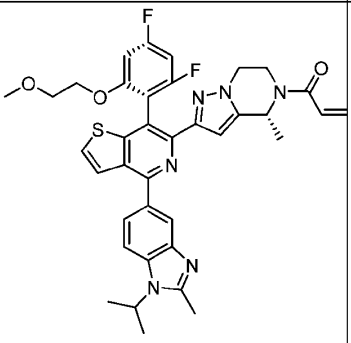
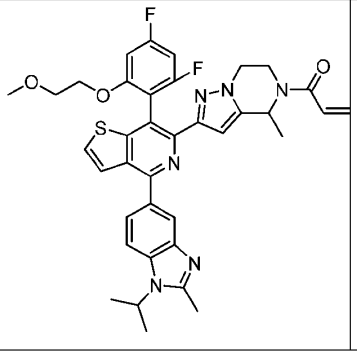
Cmpd. No.	Structure	Analytical data
268		LCMS m/z [M+1]: 691.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.37 (s, 1H), 8.44 (s, 1H), 8.28 (d, J = 9.6 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.95 - 6.76 (m, 3H), 6.37 - 6.20 (m, 2H), 6.01 (t, J = 75.6 Hz, 1H), 5.88 - 5.82 (m, 1H), 5.75 - 5.40 (m, 1H), 4.45 (s, 1H), 4.25 - 4.12 (m, 5H), 4.05 - 3.84 (m, 3H), 1.56 - 1.40 (m, 3H), 1.40 -1.25 (m, 3H).
268a		
269		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 7.99 – 7.88 (m, 1H), 7.77 – 7.60 (m, 3H), 6.85 (t, J = 13.0 Hz, 2H), 6.71 (td, J = 9.2, 2.1 Hz, 1H), 6.38 – 6.16 (m, 2H), 5.82 (d, J = 10.5 Hz, 1H), 5.61 (d, J = 80.0 Hz, 1H), 4.42 (s, 1H), 4.19 (d, J = 12.6 Hz, 1H), 4.14 – 3.99 (m, 3H), 3.97 – 3.86 (m, 3H), 3.75 (s, 1H), 3.45 (s, 2H), 3.06 (d, J = 1.5 Hz, 3H), 2.70 (d, J = 1.7 Hz, 3H), 1.45 (s, 3H).
269a		

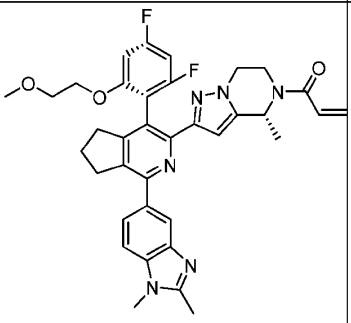
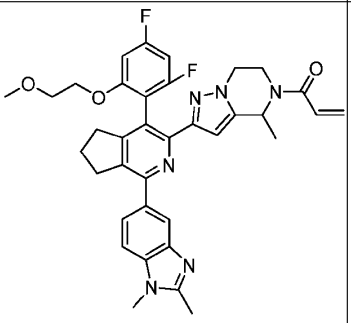
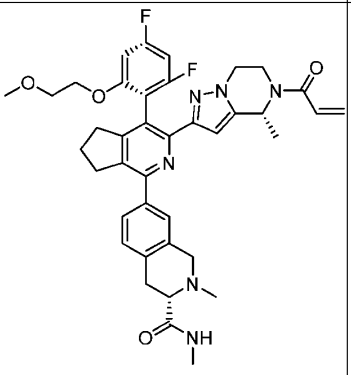
Cmpd. No.	Structure	Analytical data
270		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 8.0 Hz, 1H), 7.71 – 7.69 (m, 2H), 7.65 (d, J = 5.6 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 6.86 – 6.80 (m, 2H), 6.69 – 6.68 (m, 1H), 6.38 – 6.21 (m, 1H), 6.16 (s, 1H), 5.81 (d, J = 12.4 Hz, 1H), 5.75-5.40(m, 1H), 4.17 – 4.01 (m, 5H), 3.90 – 3.83 (m, 2H), 3.42 (t, J = 4.8 Hz, 2H), 3.33 – 3.20 (m, 4H), 3.13 – 3.02 (m, 7H), 2.44 (s, 3H), 1.52 – 1.38 (m, 3H).
270a		
271		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, J = 5.6 Hz, 1H), 7.71 – 7.69 (m, 2H), 7.65 (d, J = 5.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.86 – 6.80 (m, 2H), 6.69 – 6.68 (m, 1H), 6.38 – 6.21(m, 1H), 6.16 (s, 1H), 5.81 (d, J = 12.4 Hz, 1H), 5.75-5.40(m, 1H), 4.17 – 4.01 (m, 5H), 3.90 – 3.83 (m, 2H), 3.42 (t, J = 4.8 Hz, 2H), 3.33 – 3.20 (m, 4H), 3.13 – 3.02 (m, 7H), 2.44 (s, 3H), 1.52 – 1.38 (m, 3H).

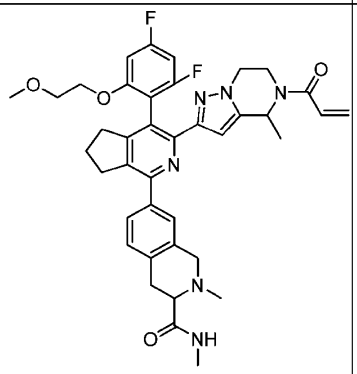
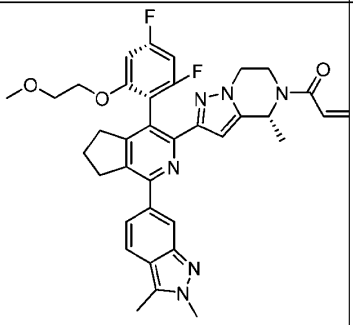
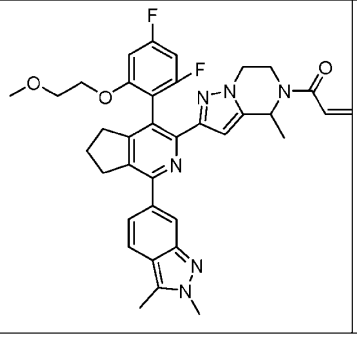
Cmpd. No.	Structure	Analytical data
272		LCMS m/z [M+1]: 719.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.6 Hz, 1H), 8.49 (s, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.87 - 6.78 (m, 2H), 6.66 (d, J = 2.4 Hz, 1H), 6.41-6.20(m ,1H), 6.11 (s, 1H), 5.82 (d, J = 11.2 Hz, 1H), 5.60 - 5.41(m, 1H), 4.15 - 4.07 (m, 3H), 4.06 - 4.00 (m, 2H), 3.95 - 3.92 (m, 1H), 3.51 (t, J = 5.2 Hz, 2H), 3.47 - 3.43 (m, 3H), 3.08 (s, 3H), 1.51 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H).
272a		
273		LCMS m/z [M+1]: 711.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 – 7.61 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 6.98 – 6.73 (m, 2H), 6.58 (t, J = 9.1 Hz, 1H), 6.34 (d, J = 16.6 Hz, 1H), 6.09 (s, 1H), 5.86 (d, J = 10.5 Hz, 1H), 5.60 (d, J = 85.9 Hz, 1H), 4.51 – 4.07 (m, 4H), 4.04 – 3.74 (m, 3H), 3.57 (t, J = 4.5 Hz, 2H), 3.47 (s, 2H), 3.28 – 3.09 (m, 6H), 3.03 – 2.54 (m, 8H), 2.12 (dd, J = 12.7, 6.6 Hz, 2H), 1.45 (d, J = 23.0 Hz, 3H), 1.29 (s, 3H).

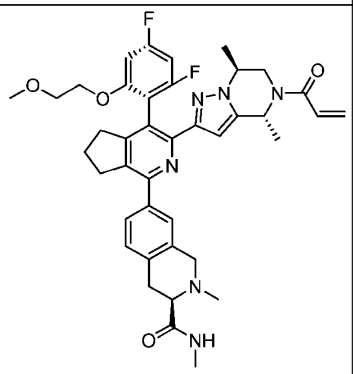
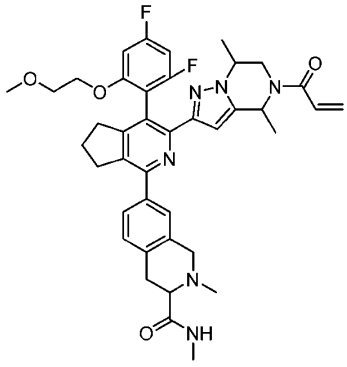
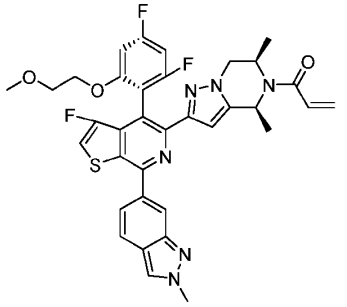
Cmpd. No.	Structure	Analytical data
273a		
274		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.44 (dd, J = 8.6, 1.2 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 5.6 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 6.90-6.81 (m, 2H), 6.73-6.68 (m, 1H), 6.37-6.23 (m, 1H), 6.08 (s, 1H), 5.82 (d, J = 11.9 Hz, 1H), 5.78 - 5.40 (m, 1H), 4.29 - 4.21 (m, 1H), 4.18-3.97 (m, 6H), 3.42 (t, J = 4.6 Hz, 1H), 3.05 (s, 3H), 2.93 (s, 3H), 1.54-1.35 (m, 3H).
274a		
275		LCMS m/z [M+1]: 677.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (s, 1H), 8.42 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.95-6.70 (m, 3H), 6.35-6.25 (m, 1H), 6.20-6.10 (m, 1H), 6.00-5.50 (m, 2H), 4.25-4.20 (m, 4H), 4.20-4.15 (m, 2H), 4.15-4.00 (m, 1H), 3.90-3.80 (m, 2H), 3.50-3.45

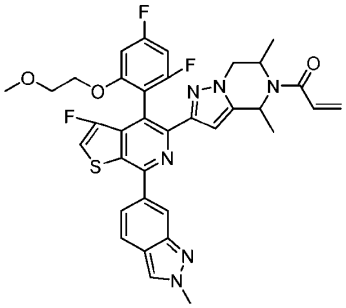
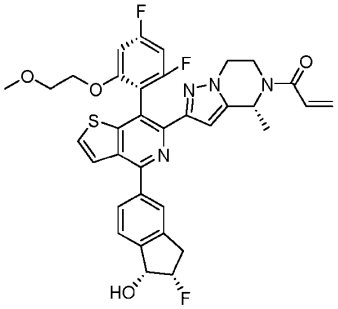
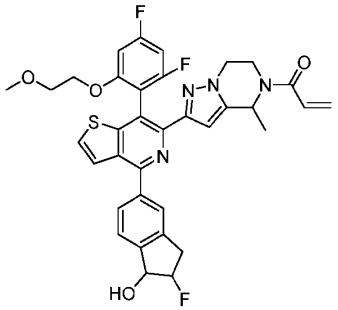
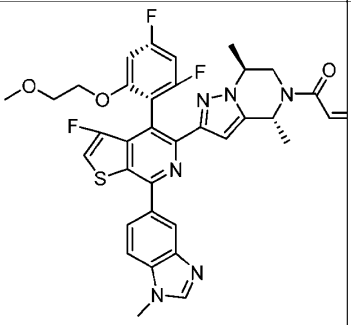
Cmpd. No.	Structure	Analytical data
		(m, 1H), 3.15-3.10 (m, 1H), 1.55-1.40 (m, 3H), 1.40-1.25 (m, 2H).
275a		
276		LCMS m/z [M+1]: 692.1 ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 5.6 Hz, 1H), 7.76 (d, J = 5.6 Hz,1H), 7.59 - 7.55 (m, 2H), 7.48 (s, 1H), 6.95 - 6.76 (m, 3H), 6.33 (d, J = 17.2 Hz, 1H), 6.21 - 5.83 (m, 3H), 5.73 - 5.48 (m, 1H), 4.49 (s, 1H), 4.20 - 4.10 (m, 3H), 3.88 - 3.86 (m, 3H), 3.70 (s, 2H), 1.55 - 1.20 (m, 6H).
276a		
277		LCMS m/z [M+1]: 669.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (s, 1H), 8.35 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 5.5 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.93 – 6.78 (m, 2H), 6.76 – 6.68 (m, 1H), 6.28 (d, J = 15.9 Hz, 1H), 6.17 (s, 1H), 5.82 (d, J = 10.5 Hz, 1H), 5.76 – 5.39 (m, 1H), 5.09 – 4.95 (m, 2H), 4.24 – 4.16 (m, 1H),

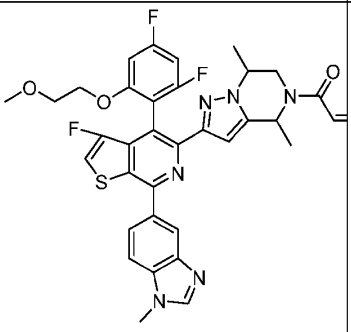
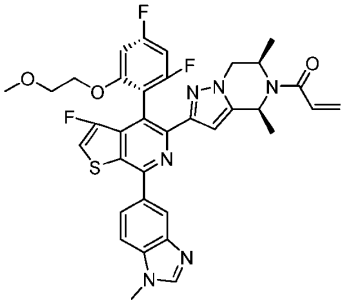
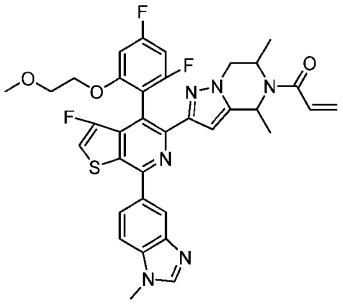
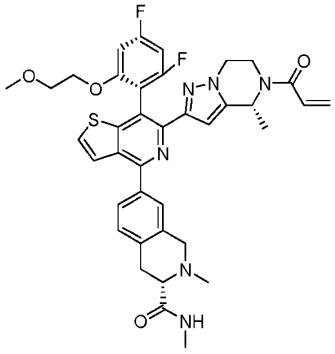
Cmpd. No.	Structure	Analytical data
		4.15 – 3.95 (m, 3H), 3.44 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.74 (d, J = 6.7 Hz, 6H), 1.53 – 1.34 (m, 3H).
277a		
278		LCMS m/z [M+1]: 683.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.18 (dd, J = 8.6, 1.0 Hz, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.96 – 6.70 (m, 3H), 6.28 (d, J = 17.2 Hz, 1H), 6.13 (s, 1H), 5.82 (dd, J = 10.6, 1.3 Hz, 1H), 5.77 – 5.37 (m, 1H), 5.18 – 5.06 (m, 1H), 4.29 – 4.20 (m, 1H), 4.17 – 3.98 (m, 3H), 3.44 (t, J = 4.6 Hz, 2H), 3.06 (s, 3H), 2.97 (s, 3H), 1.83 (d, J = 6.9 Hz, 6H), 1.53 – 1.36 (m, 3H).
278a		

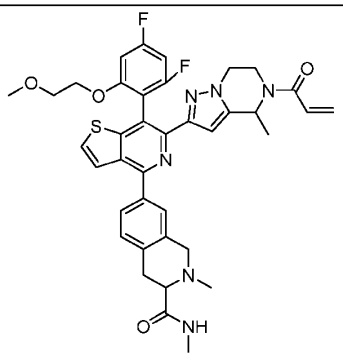
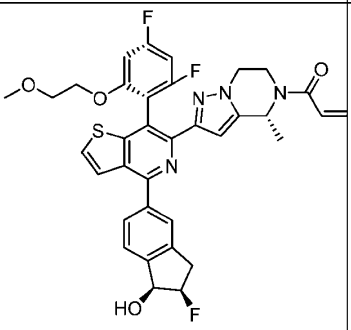
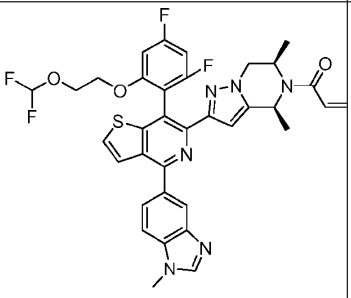
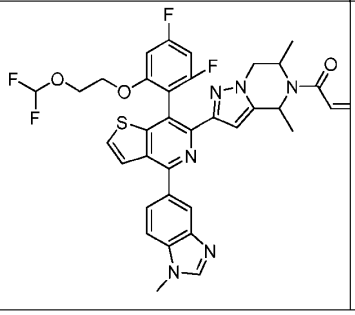
Cmpd. No.	Structure	Analytical data
279		LCMS m/z [M+1]: 639.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 6.91 – 6.73 (m, 2H), 6.61 (td, J = 9.2, 2.2 Hz, 1H), 6.31 (s, 1H), 6.07 (s, 1H), 5.83 (d, J = 10.8 Hz, 1H), 5.59 (d, J = 84.2 Hz, 1H), 4.55 – 3.94 (m, 5H), 3.87 (d, J = 1.5 Hz, 4H), 3.56 (t, J = 4.5 Hz, 2H), 3.29 – 3.11 (m, 5H), 2.94 – 2.82 (m, 1H), 2.79 – 2.69 (m, 1H), 2.66 (s, 3H), 2.18 – 2.03 (m, 2H), 1.42 (s, 3H).
279a		
280		LCMS m/z [M+1]: 697.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 7.63 – 7.52 (m, 2H), 7.18 (d, J = 7.8 Hz, 1H), 6.80 – 6.60 (m, 2H), 6.49 (dd, J = 10.2, 8.2 Hz, 1H), 6.17 (d, J = 15.6 Hz, 1H), 5.89 (s, 1H), 5.71 (d, J = 11.8 Hz, 1H), 5.33 (dd, J = 98.6, 42.6 Hz, 1H), 4.23 (d, J = 29.4 Hz, 1H), 4.12 – 3.85 (m, 5H), 3.67 (d, J = 15.2 Hz, 1H), 3.43 (t, J = 4.4 Hz, 2H), 3.18 (s, 2H), 3.14 – 3.05 (m, 6H), 2.99 (dd, J = 16.4, 5.2 Hz, 1H), 2.74 (dd, J = 16.2, 8.2 Hz, 1H), 2.68 (s, 3H), 2.61 (dd, J = 16.0, 8.2 Hz, 1H), 2.41 (s, 3H), 1.99 (p, J = 7.2 Hz, 2H), 1.31 (dd, J = 10.2, 5.8 Hz, 3H).

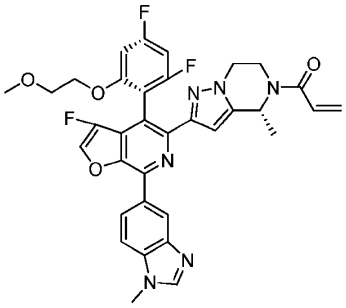
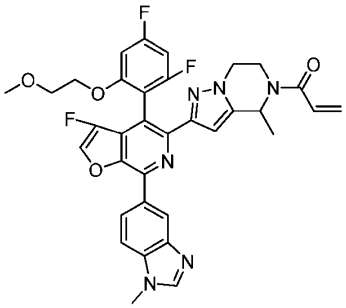
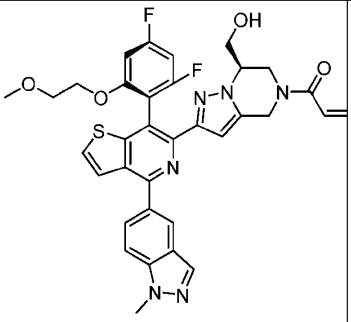
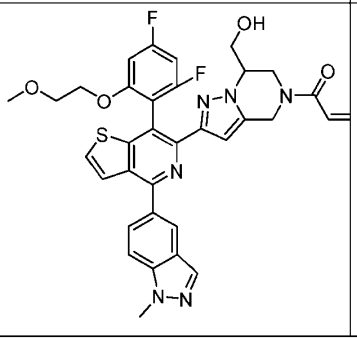
Cmpd. No.	Structure	Analytical data
280a		
281		LCMS m/z [M+1]: 639.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (s, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 6.89 – 6.75 (m, 2H), 6.62 (td, J = 9.2, 2.3 Hz, 1H), 6.31 (s, 1H), 6.07 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.69 (s, 1H), 4.40 (s, 1H), 4.34 – 4.04 (m, 6H), 4.00 (d, J = 11.2 Hz, 3H), 3.56 (t, J = 4.6 Hz, 2H), 3.28 – 3.23 (m, 4H), 2.89 (d, J = 7.8 Hz, 1H), 2.82 – 2.67 (m, 4H), 2.19 – 2.07 (m, 2H), 1.43 (s, 3H).
281a		

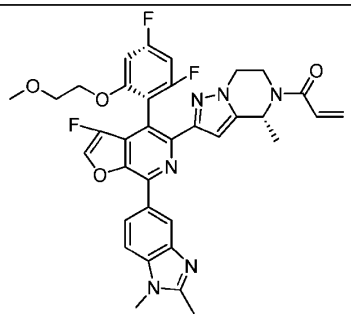
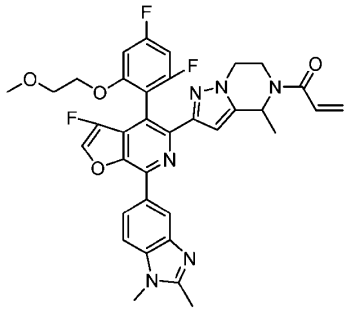
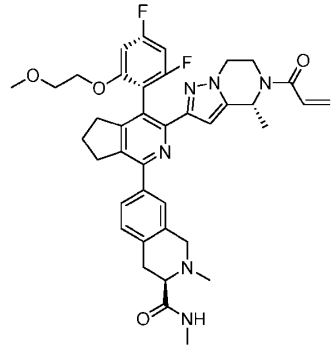
Cmpd. No.	Structure	Analytical data
282		LCMS m/z [M+1]: 711.0 ^{1}H NMR (400 MHz, CD_3OD) δ 7.68 (d, J = 7.9 Hz, 2H), 7.64 (s, 1H), 7.29 (d, J = 7.9 Hz, 1H), 6.86 (s, 1H), 6.78 (d, J = 10.9 Hz, 1H), 6.58 (t, J = 8.2 Hz, 1H), 6.34 (d, J = 16.5 Hz, 1H), 6.08 (s, 1H), 5.85 (d, J = 11.6 Hz, 1H), 5.61 (d, J = 77.6 Hz, 1H), 4.40 (d, J = 5.6 Hz, 1H), 4.29 – 4.07 (m, 3H), 4.00 (dt, J = 10.7, 3.9 Hz, 1H), 3.87 (s, 1H), 3.71 (d, J = 15.0 Hz, 1H), 3.60 – 3.55 (m, 2H), 3.24 (s, 3H), 3.23 – 3.13 (m, 4H), 3.07 (dd, J = 19.6, 8.6 Hz, 1H), 2.96 – 2.87 (m, 1H), 2.79 (s, 3H), 2.75 – 2.65 (m, 1H), 2.47 (s, 3H), 2.11 (dd, J = 14.0, 6.8 Hz, 2H), 1.45 (d, J = 25.3 Hz, 3H), 1.30 (d, J = 6.5 Hz, 3H).
282a		
283		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.35 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.81 (m, 1H), 7.72 (d, J = 2.4 Hz, 1H), 6.79 - 6.88 (m, 2H), 6.63 - 6.71 (m, 1H), 6.21 - 6.32 (m, 1H), 6.16 (s, 1H), 5.81 (d, J = 10.8Hz, 1H), 5.41 - 5.51 (m, 1H), 4.30 (s, 3H), 4.14 - 4.22 (m, 2H), 4.04 - 4.2 (m, 1H), 3.92 - 3.99 (m, 1H), 3.47 (t, J = 4.8 Hz, 2H), 3.11 (s, 3H), 1.51 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 7.2Hz, 3H).

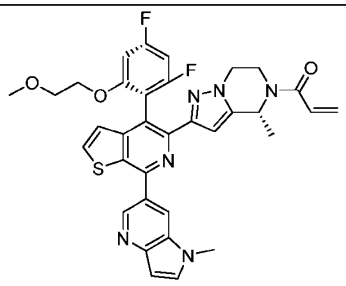
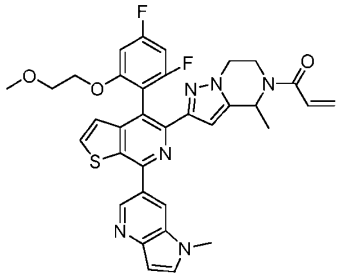
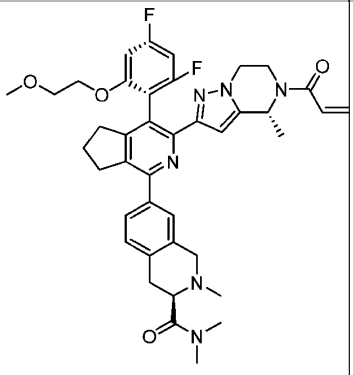
Cmpd. No.	Structure	Analytical data
283a		
284		LCMS m/z [M+1]: 661.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 5.6 Hz, 1H), 7.97 - 7.88 (m, 2H), 7.87 – 7.73 (m, 2H), 7.04 (d, J = 10.8 Hz, 1H), 6.90 – 6.83 (m, 2H), 6.32 (d, J = 17.0 Hz, 1H), 6.06 – 5.97 (m, 1H), 5.87 (d, J = 10.6 Hz, 1H), 5.80 – 5.47 (m, 1H), 5.47 – 5.24 (m, 2H), 4.40 – 4.30 (m, 1H), 4.16 (s, 3H), 3.52 – 3.41 (m, 2H), 3.11 (s, 3H), 1.52 – 1.30 (m, 3H).
284a		
285		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.39 (s, 1H), 8.59 (s, 1H), 8.44 (d, J = 8.1 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 6.83 (t, J = 11.0 Hz, 2H), 6.61 (t, J = 9.2 Hz, 1H), 6.33 (d, J = 16.6 Hz, 1H), 6.14 (s, 1H), 5.85 (d, J = 10.7 Hz, 1H), 5.80 – 5.45 (m, 1H), 4.44 (s, 1H), 4.22 (s, 4H), 4.14 – 3.99 (m, 3H), 3.88 (s, 1H), 3.47 (t, J = 4.5 Hz, 3H), 3.09 (s, 3H), 1.55 – 1.25 (m, 6H).

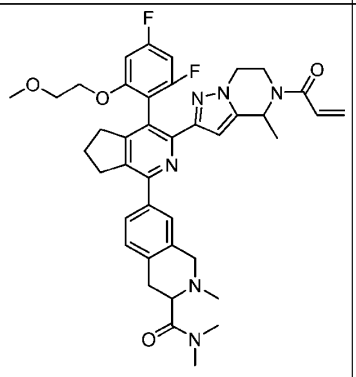
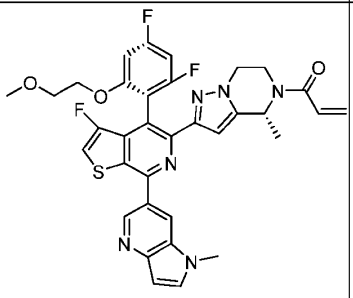
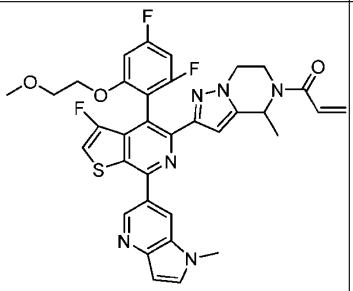
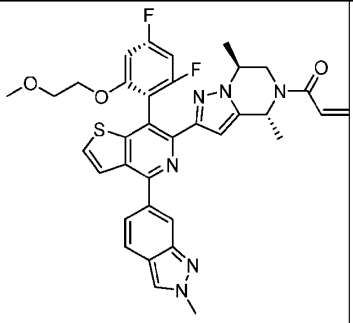
Cmpd. No.	Structure	Analytical data
285a		
286		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.39 (s, 1H), 8.59 (s, 1H), 8.47 - 8.43 (m, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 6.88 - 6.76 (m, 2H), 6.70 - 6.62 (m, 1H), 6.38 - 6.19 (m, 1H), 6.14 (s, 1H), 5.81 (d, J = 10.6 Hz, 1H), 5.51 - 5.39 (m, 1H), 4.22 (s, 3H), 4.20 - 4.05 (m, 3H), 3.99 - 3.92 (m, 1H), 3.46 (t, J = 4.7 Hz, 2H), 3.09 (s, 3H), 1.51 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H).
286a		
287		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 8.7 Hz, 1H), 7.89 (s, 1H), 7.84 - 7.78 (m, 1H), 7.68 (d, J = 5.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 6.93 - 6.78 (m, 2H), 6.75 - 6.67 (m, 1H), 6.37 - 6.22 (m, 1H), 6.12 (s, 1H), 5.88 - 5.78 (m, 1H), 5.77 - 5.38 (m, 1H), 4.81 -4.70 (m, 1H), 4.66 - 4.57 (m, 1H), 4.52 - 4.34 (m, 1H), 4.31 - 4.16 (m, 2H), 4.14 - 3.98 (m, 3H), 3.84 - 3.62 (m, 1H), 3.58 -

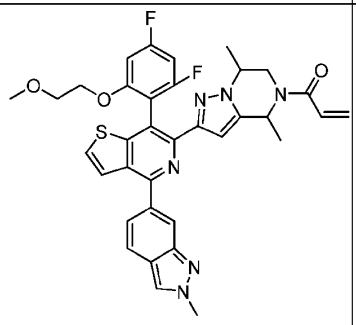
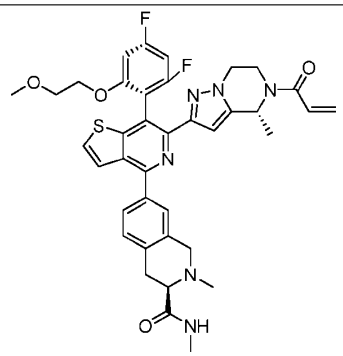
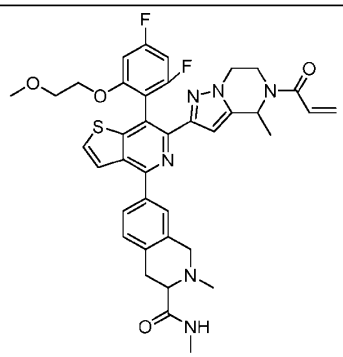
Cmpd. No.	Structure	Analytical data
		3.45 (m, 2H), 3.42 (t, J = 4.7 Hz, 2H), 3.09 (s, 3H), 3.04 (s, 3H), 2.91 - 2.86 (m, 3H), 1.54 - 1.33 (m, 3H).
287a		
288		LCMS m/z [M+1]: 661.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 5.6 Hz, 1H), 7.96 – 7.89 (m, 2H), 7.83 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 10.7 Hz, 1H), 6.90 – 6.82 (m, 2H), 6.32 (d, J = 16.6 Hz, 1H), 5.99 (s, 1H), 5.87 (d, J = 10.6 Hz, 1H), 5.80 – 5.42 (m, 1H), 5.30 (d, J = 3.2 Hz, 1H), 4.34 (d, J = 10.3 Hz, 1H), 4.20 – 4.09 (m, 3H), 3.48 (d, J = 4.4 Hz, 2H), 3.11 (s, 3H), 1.50 – 1.29 (m, 3H).
289		LCMS m/z [M+1]: 691.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 - 9.28 (s, 1H), 8.42 (s, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.89 - 7.83 (m, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.92 – 6.74 (m, 3H), 6.35 - 5.79 (m, 4H), 5.54 - 5.39 (m, 1H), 4.21 (s, 3H), 4.19 - 4.00 (m, 4H), 3.90 - 3.83 (m, 2H), 1.52 (d, J = 6.7 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H).
289a		

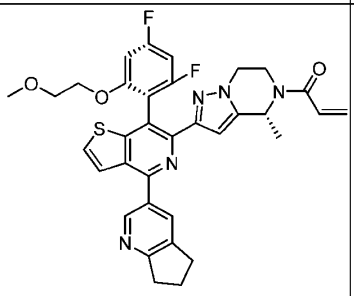
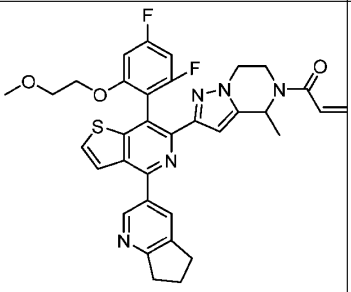
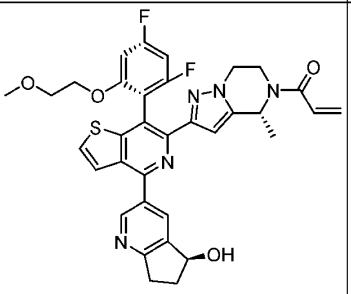
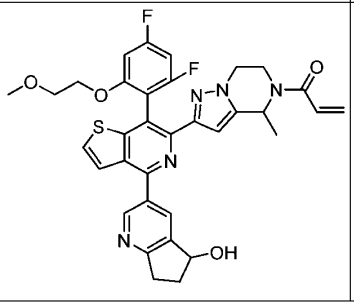
Cmpd. No.	Structure	Analytical data
290		LCMS m/z [M+1]: 643.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.22 – 9.14 (m, 1H), 8.94 (s, 1H), 8.79 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 4.5 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 6.91 – 6.78 (m, 2H), 6.69 – 6.60 (m, 1H), 6.36 – 6.24 (m, 1H), 6.19 (s, 1H), 5.83 (dd, J = 10.4, 1.3 Hz, 1H), 5.78 – 5.44 (m, 1H), 4.50 – 4.36 (m, 0.5H), 4.26 – 3.95 (m, 7H), 3.84 – 3.68 (m, 0.5H), 3.47 (t, J = 4.6 Hz, 2H), 3.12 (s, 3H), 1.56 – 1.40 (m, 3H).
290a		
291		LCMS m/z [M+1]: 657.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.26 (s, 1H), 8.08 – 8.02 (m, 2H), 7.89 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.00 – 6.75 (m, 3H), 6.29 (d, J = 16.8 Hz, 1H), 6.23 – 6.10 (m, 1H), 5.83 (d, J = 10.2 Hz, 1H), 4.97 – 4.87 (m, 1H), 4.42 – 4.33 (m, 1H), 4.32 – 4.13 (m, 4H), 4.12 – 3.97 (m, 2H), 3.95 – 3.75 (m, 2H), 3.41 (t, J = 4.5 Hz, 2H), 3.06 (s, 3H).
291a		

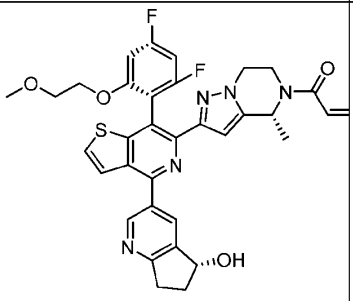
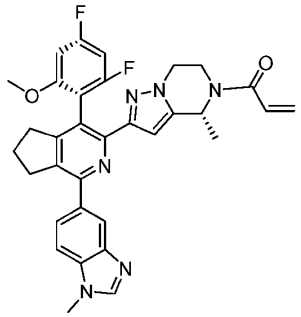
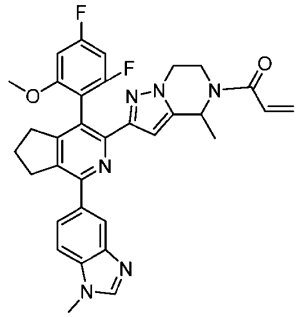
Cmpd. No.	Structure	Analytical data
292		LCMS m/z [M+1]: 657.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (s, 1H), 8.80 (d, J = 8.8 Hz, 1H), 8.24 (d, J = 4.5 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 6.91 – 6.80 (m, 2H), 6.69 – 6.61 (m, 1H), 6.36 – 6.24 (m, 1H), 6.17 (s, 1H), 5.85 – 5.81 (m, 1H), 5.78 – 5.45 (m, 1H), 4.50 – 4.35 (m, 0.5H), 4.27 – 4.18 (m, 1H), 4.15 – 4.04 (m, 4H), 4.03 – 3.96 (m, 1H), 3.85 – 3.67 (m, 1H), 3.47 (t, J = 4.6 Hz, 2H), 3.12 (s, 3H), 2.92 (s, 3H), 1.55 – 1.40 (m, 3H).
292a		
293		LCMS m/z [M+1]: 697.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (s, 2H), 7.28 (d, J = 7.9 Hz, 1H), 6.89 – 6.74 (m, 2H), 6.60 (td, J = 9.2, 2.2 Hz, 1H), 6.29 (d, J = 17.0 Hz, 1H), 6.01 (s, 1H), 5.83 (dd, J = 10.7, 1.6 Hz, 1H), 5.57 (d, J = 82.6 Hz, 1H), 4.35 - 3.95(m, 6H), 3.70 (d, J = 15.2 Hz, 2H), 3.55 (t, J = 4.6 Hz, 2H), 3.24 – 3.15 (m, 7H), 3.10 – 3.03 (m, 1H), 2.86 (dd, J = 16.1, 8.3 Hz, 1H), 2.79 (s, 3H), 2.75 – 2.67 (m, 1H), 2.46 (s, 3H), 2.12 (dd, J = 15.0, 7.5 Hz, 2H), 1.42 (s, 3H).

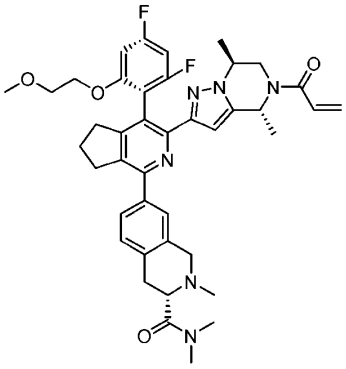
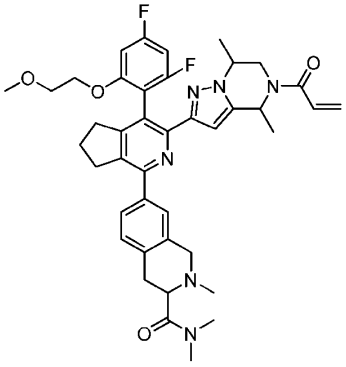
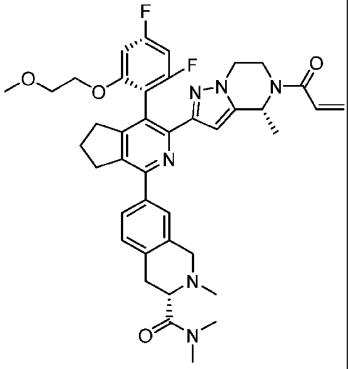
Cmpd. No.	Structure	Analytical data
294		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.53 - 9.41 (m, 2H), 8.24 (d, J = 3.2 Hz, 1H), 8.07 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 6.97 (d, J = 2.7 Hz, 1H), 6.94 - 6.79 (m, 2H), 6.73 (td, J = 9.2, 2.2 Hz, 1H), 6.30 (d, J = 17.0 Hz, 1H), 6.03 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.72 - 5.41 (m, 1H), 4.29 (dd, J = 12.7, 2.9 Hz, 1H), 4.23 - 4.06 (m, 5H), 4.05 - 3.97 (m, 1H), 3.42 (t, J = 4.6 Hz, 2H), 3.07 (s, 3H), 1.52 - 1.35 (m, 3H).
294a		
295		LCMS m/z [M+1]: 711.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 – 7.62 (m, 2H), 7.29 (d, J = 7.9 Hz, 1H), 6.90 – 6.74 (m, 2H), 6.60 (td, J = 9.2, 2.2 Hz, 1H), 6.29 (d, J = 15.0 Hz, 1H), 6.01 (s, 1H), 5.82 (dd, J = 10.7, 1.4 Hz, 1H), 5.55 (t, J = 42.0 Hz, 1H), 4.50 (d, J = 76.4 Hz, 1H), 4.24 - 3.96 (m, 5H), 3.92 – 3.63 (m, 3H), 3.54 (t, J = 4.5 Hz, 2H), 3.25 (d, J = 7.1 Hz, 3H), 3.23 – 3.11 (m, 6H), 3.02 (s, 4H), 2.85 (dd, J = 16.2, 8.2 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.45 (s, 3H), 2.16 – 2.06 (m, 2H), 1.41 (d, J = 10.9 Hz, 3H).

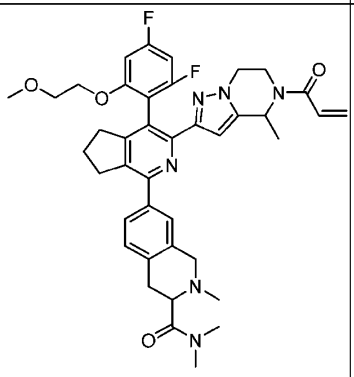
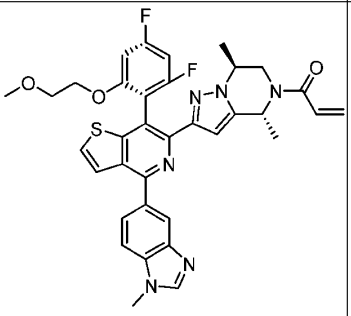
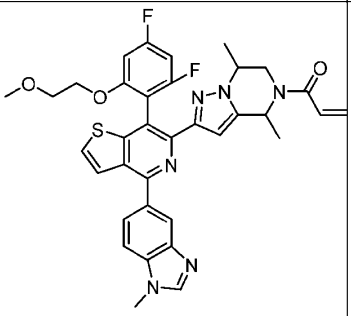
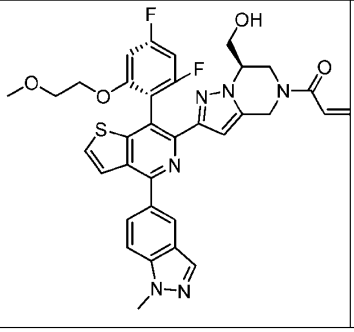
Cmpd. No.	Structure	Analytical data
295a		
296		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.38 (s, 2H), 8.20 (d, J = 3.1 Hz, 1H), 7.66 (d, J = 2.2 Hz, 1H), 6.95 (d, J = 3.1 Hz, 1H), 6.85 (dd, J = 18.1, 7.3 Hz, 2H), 6.66 (td, J = 9.1, 2.1 Hz, 1H), 6.30 (d, J = 16.4 Hz, 1H), 6.00 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.72 - 5.41 (m, 1H), 4.33 - 4.25 (m, 1H), 4.21 - 3.99 (m, 7H), 3.45 (t, J = 4.5 Hz, 2H), 3.09 (s, 3H), 1.52 - 1.35 (m, 3H).
296a		
297		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.15 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.75 – 7.69 (m, 3H), 6.88 (d, J = 10.9 Hz, 2H), 6.73 – 6.64 (m, 1H), 6.33 (d, J = 17.0 Hz, 2H), 5.88 – 5.81 (m, 1H), 5.79 – 5.46 (m, 1H), 4.79 – 4.35 (m, 2H), 4.29 (s, 3H), 4.26 – 3.97 (m, 3H), 3.47 (t, J = 4.7 Hz, 2H), 3.07 (s, 3H), 1.45 (s, 3H), 1.30 (s, 3H).

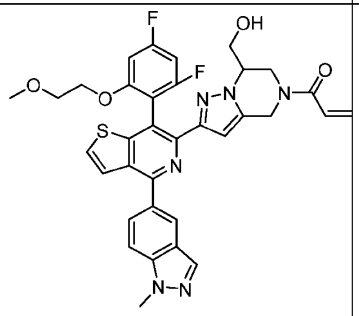
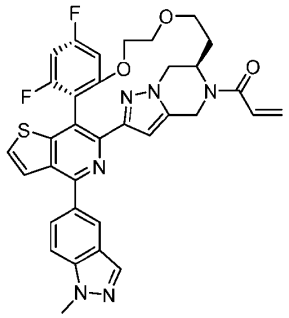
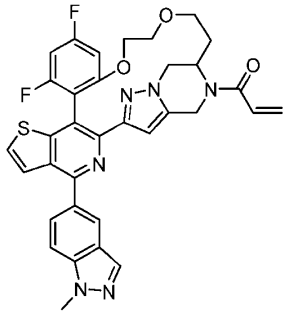
Cmpd. No.	Structure	Analytical data
297a		
298		LCMS m/z [M+1]: 713.1 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 - 7.94 (m, 1H), 7.89 (s, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 6.90 (d, 1H), 6.87 - 6.79 (m, J = 12.0 Hz, 1H), 6.73 (td, J = 9.2, 2.3 Hz, 1H), 6.33 - 6.22 (m, 1H), 6.14 - 6.06 (m, 1H), 5.85 - 5.79 (m, 1H), 5.71 - 5.46 (m, 1H), 4.82 - 4.73 (m, 2H), 4.63 (d, J = 15.6 Hz, 1H), 4.48 - 4.35 (m, 1H), 4.33 – 4.20 (m, 2H), 4.14 - 4.01 (m, 3H), 3.85 - 3.66 (m, 1H), 3.58 – 3.46 (m, 2H), 3.43 (t, J = 4.6 Hz, 2H), 3.09 (s, 3H), 3.05 (s, 3H), 2.90 - 2.86 (m, 3H), 1.50 - 1.36 (m, 3H)
298a		

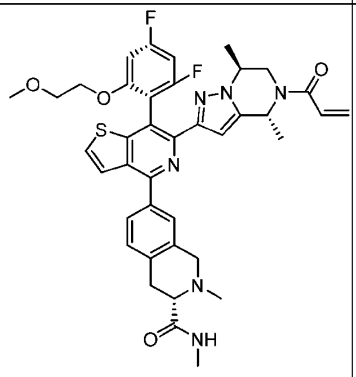
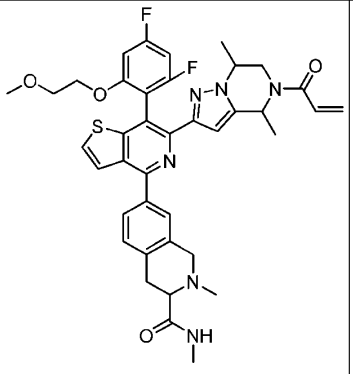
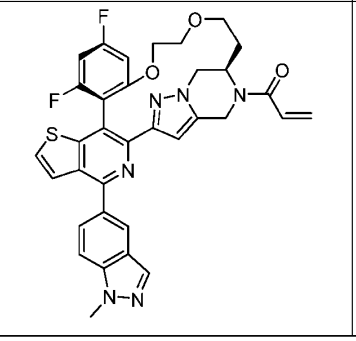
Cmpd. No.	Structure	Analytical data
299		LCMS m/z [M+1]: 628.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (s, 1H), 8.90 (s, 1H), 7.90 (d, J = 5.6 Hz, 1H), 7.79 (d, J = 5.6 Hz, 1H), 6.93 - 6.71 (m, 3H), 6.29 (d, J = 16 Hz, 1H), 6.13 (s, 1H), 5.82 (dd, J = 10.4, 1.2 Hz, 1H), 5.71 - 5.38 (m, 1H), 4.23 (dd, J = 15.6, 3.2Hz, 1H), 4.11 - 4.03 (m, 3H), 3.42 - 3.37 (m, 5H), 3.08 (s, 3H), 2.48 - 2.42 (m, 2H), 1.55 - 1.35 (m, 3H).
299a		
300		LCMS m/z [M+1]: 644.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.24 (s, 1H), 8.85 (s, 1H), 7.92 (d, J = 5.6 Hz, 1H), 7.79 (d, J = 5.6 Hz, 1H), 6.93 - 6.72 (m, 3H), 6.31 (d, J = 16.8 Hz, 1H), 6.15 (s, 1H), 5.83 (d, J = 10.8 Hz, 1H), 5.75 - 5.41 (m, 3H), 4.26 (d, J = 16.0 Hz, 1H), 4.11 - 4.05 (m, 3H), 3.43 - 3.37 (m, 4H), 3.07 (s, 3H), 2.83 - 2.72 (m, 2H), 2.33 - 2.25 (m, 1H), 1.55 - 1.35 (m, 3H).
300a		

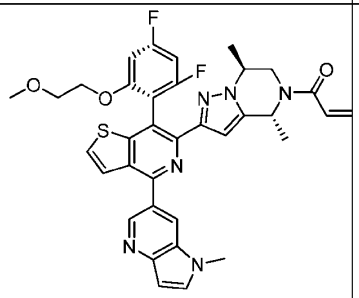
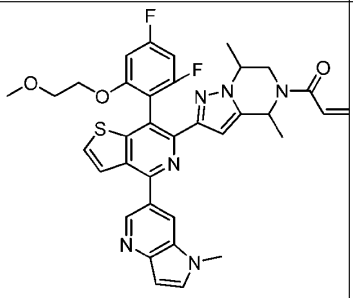
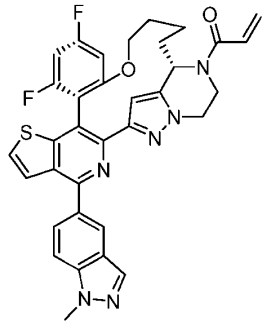
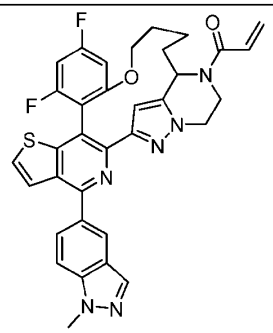
Cmpd. No.	Structure	Analytical data
301		LCMS m/z [M+1]: ^{1}H NMR (400 MHz, CD_3OD) δ 9.23 (s, 1H), 8.82 (s, 1H), 7.91 (d, J = 5.6 Hz, 1H), 7.78 (d, J = 5.6 Hz, 1H), 6.93 - 6.72 (m, 3H), 6.29 (d, J = 16.4 Hz, 1H), 6.14 (s, 1H), 5.83 (d, J = 10.8 Hz, 1H), 5.71 - 5.46 (m, 2H), 4.23 (d, J = 12.0 Hz, 1H), 4.11 - 4.05 (m, 3H), 3.77 - 3.38 (m, 4H), 3.27 - 3.12 (m, 1H), 3.04 (s, 3H), 2.81 - 2.72 (m, 1H), 2.24 - 2.18 (m, 1H),1.55 - 1.35 (m, 3H).
302		LCMS m/z [M+1]: 581.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.16 (s, 1H), 7.95 (t, J = 7.3 Hz, 1H), 7.74 – 7.67 (m, 1H), 6.86 (dd, J = 16.7, 10.7 Hz, 1H), 6.76 (d, J = 10.7 Hz, 1H), 6.62 (td, J = 9.2, 2.2 Hz, 1H), 6.37 – 6.22 (m, 1H), 6.10 – 5.95(m, 1H), 5.83 (d, J = 10.7 Hz, 1H), 5.75 – 5.50 (m, 1H), 4.45 – 4.30 (m, 1H), 4.25 – 4.05 (m, 2H), 4.03 – 3.89 (m, 4H), 3.73 (s, 3H), 3.26 (t, J = 7.3 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 2.17 – 2.06 (m, 2H), 1.51 – 1.36 (m, 3H).
302a		

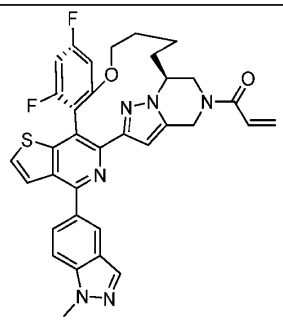
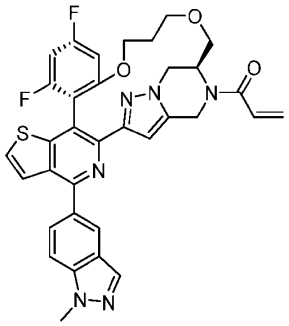
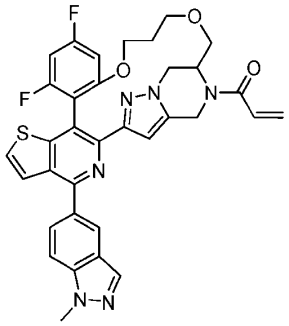
Cmpd. No.	Structure	Analytical data
303		LCMS m/z [M+1]: 725.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 7.80 – 7.62 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 6.88 (s, 1H), 6.79 (d, J = 10.8 Hz, 1H), 6.58 (t, J = 9.1 Hz, 1H), 6.34 (d, J = 16.6 Hz, 1H), 6.09 (s, 1H), 5.86 (d, J = 10.6 Hz, 1H), 5.61 (d, J = 85.7 Hz, 1H), 4.69 (s, 6H), 4.41 (s, 1H), 4.32 – 3.78 (m, 3H), 3.57 (t, J = 4.5 Hz, 2H), 3.46 (s, 1H), 3.28 – 2.98 (m, 12H), 2.95 – 2.84 (m, 1H), 2.76 – 2.63 (m, 1H), 2.56 (s, 3H), 2.19 – 2.05 (m, 2H), 1.45 (d, J = 25.2 Hz, 3H), 1.29 (s, 3H).
303a		
304		LCMS m/z [M+1]: 711.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.77 – 7.59 (m, 2H), 7.30 (d, J = 7.9 Hz, 1H), 6.95 – 6.75 (m, 2H), 6.61 (td, J = 9.2, 2.0 Hz, 1H), 6.31 (s, 1H), 6.01 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.58 (d, J = 87.5 Hz, 1H), 4.40 (s, 1H), 4.25 – 3.67 (m, 8H), 3.55 (t, J = 4.5 Hz, 2H), 3.30 – 3.10 (m, 9H), 3.09 – 2.94 (m, 4H), 2.86 (dd, J = 15.9, 8.3 Hz, 1H), 2.77 – 2.66 (m, 1H), 2.53 – 2.40 (m, 3H), 2.12 (dd, J = 14.6, 7.3 Hz, 2H), 1.44 (d, J = 23.6 Hz, 3H).

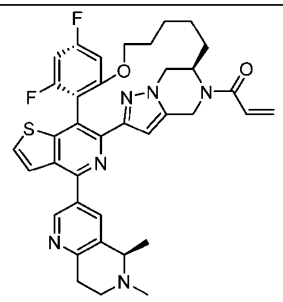
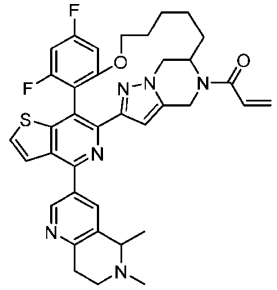
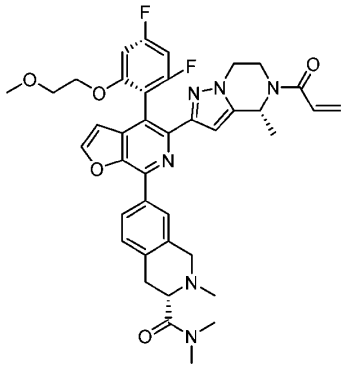
Cmpd. No.	Structure	Analytical data
304a		
305		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 2H), 7.88 (d, J = 8.3 Hz, 1H), 7.70 – 7.54 (m, 3H), 6.76 (d, J = 10.1 Hz, 2H), 6.61 – 6.50 (m, 1H), 6.22 (d, J = 16.9 Hz, 2H), 5.73 (d, J = 10.7 Hz, 1H), 5.52 (d, J = 88.0 Hz, 1H), 4.34 – 4.24 (m, 1H), 4.16 – 3.81 (m, 6H), 3.73 (s, 1H), 3.36 (t, J = 4.6 Hz, 2H), 2.95 (s, 3H), 1.33 (s, 3H), 1.10 (s, 3H).
305a		
306		LCMS m/z [M+1]: 657.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (d, J = 10.0 Hz, 1H), 8.25 (d, J = 10.9 Hz, 1H), 8.15 – 7.94 (m, 2H), 7.92 – 7.72 (m, 2H), 7.12 – 6.68 (m, 3H), 6.38 – 6.03 (m, 2H), 5.81 (s, 1H), 4.31 – 3.71 (m, 8H), 3.53 – 3.38 (m, 2H), 3.08 (s, 3H).

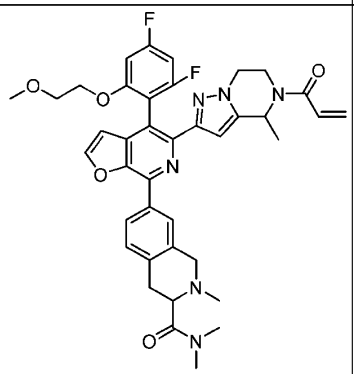
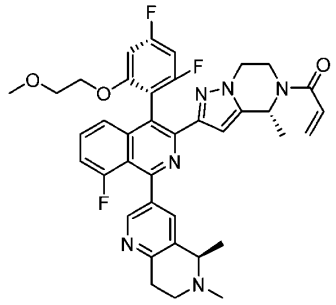
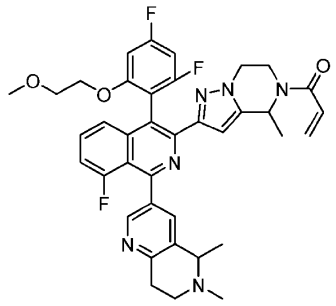
Cmpd. No.	Structure	Analytical data
306a		
307		LCMS m/z [M+1]: 639.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.88 - 7.80 (m, 2H), 7.75 - 7.71 (m, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.90 - 6.75 (m, 2H), 6.75 - 6.65 (m, 1H), 6.34 - 6.27 (m, 1H), 5.82 (t, J = 10.8 Hz, 1H), 5.12 - 4.90 (m, 2H), 4.75 - 4.50 (m, 2H), 4.19 (s, 4H), 4.15 - 4.08 (m, 1H), 3.85 - 3.81 (m, 1H), 3.70 - 3.55 (m, 1H), 3.40 - 3.35 (m, 1H), 3.20 - 3.10 (m, 1H), 1.95 - 1.60 (m, 2H).
307a		

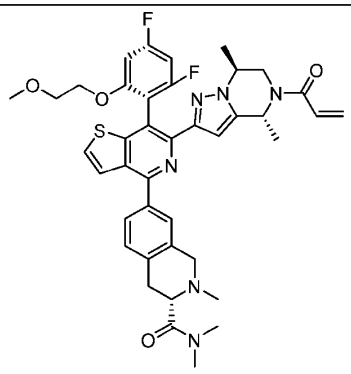
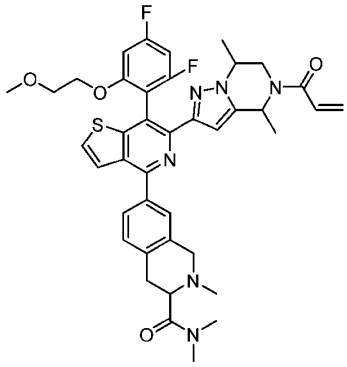
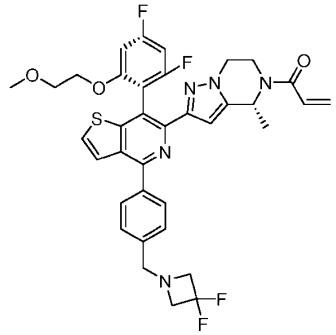
Cmpd. No.	Structure	Analytical data
308		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.87 – 7.79 (m, 1H), 7.70 (dd, J = 5.5, 1.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 16.2 Hz, 2H), 6.72 (t, J = 9.1 Hz, 1H), 6.35 (d, J = 16.1 Hz, 1H), 6.21 (s, 1H), 5.86 (dd, J = 10.6, 1.6 Hz, 1H), 5.64 (d, J = 85.7 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 4.65 (d, J = 15.2 Hz, 1H), 4.46 (s, 1H), 4.37 – 3.99 (m, 4H), 3.89 (s, 1H), 3.65 – 3.37 (m, 4H), 3.10 (d, J = 18.0 Hz, 6H), 2.91 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H).
308a		
309		LCMS m/z [M+1]: 639.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.27 (s, 1H), 8.11 - 8.08 (m, 2H), 7.91 - 7.85 (m, 2H), 7.00 - 6.70 (m, 3H), 6.34 - 6.29 (m, 1H), 5.98 - 5.95 (m, 1H), 5.84 - 5.81 (m, 1H), 5.00 - 4.90 (m, 2 H), 4.70 - 4.60 (m, 1H), 4.60 - 4.40 (m, 2H), 4.19 (s, 4H), 3.90 - 3.81 (m, 1H), 3.60 - 3.40 (m, 3H), 2.10 - 1.70 (m, 2H).

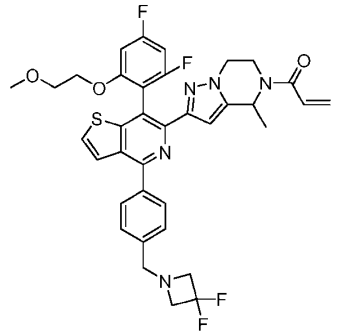
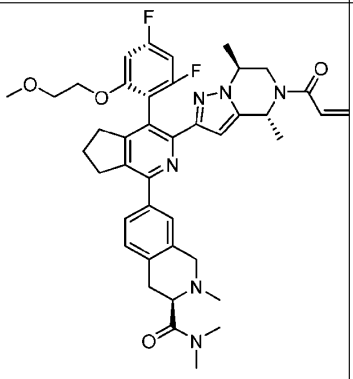
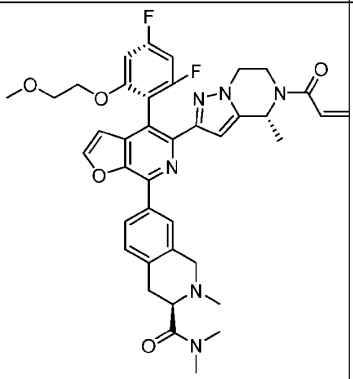
Cmpd. No.	Structure	Analytical data
310		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1H), 9.27 (s, 1H), 8.21 (d, J = 3.2 Hz, 1H), 7.90 - 7.85 (m, 2H), 7.00 - 6.83 (m, 3H), 6.72 (td, J = 9.6 Hz, 2.4 Hz, 1H), 6.35 - 6.29 (m, 1H), 6.17 (s, 1H), 5.84 (d, J = 10.4 Hz, 1.6 Hz, 1H), 5.80 - 5.45 (m, 1H), 4.50 - 4.40 (m, 1H), 4.18 (s, 3H), 4.15 - 4.00 (m, 2H), 3.95 - 3.81 (m, 1H), 3.43 (t, J = 4.4 Hz, 2H), 3.07 (s, 3H), 1.55 - 1.35 (m, 3H), 1.35 - 1.25 (m, 3H).
310a		
311		LCMS m/z [M+1]: 623.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1H), 8.24 (s, 1H), 8.10-8.00 (m, 2H), 7.90-7.80 (m, 2H), 6.93-6.75 (m, 3H), 6.57-6.54 (m, 1H), 6.35-6.25 (m, 1H), 5.90-5.50 (m, 2H), 4.40-4.25 (m, 2H), 4.19 (s, 3H), 4.10-3.90 (m, 2H), 3.90-3.40 (m, 2H), 2.30-2.20 (m, 1H), 1.90-1.75 (m, 1H), 1.70-1.40 (m, 3H).
311a		

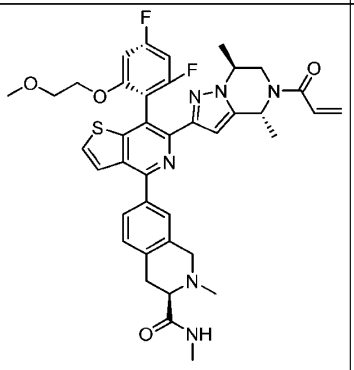
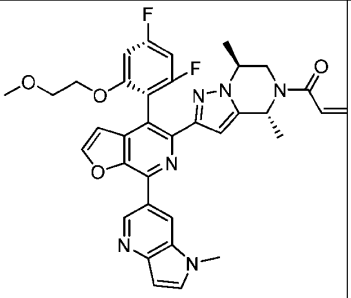
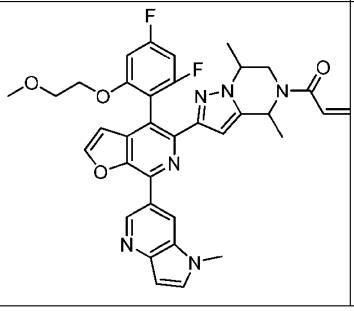
Cmpd. No.	Structure	Analytical data
312		LCMS m/z [M+1]: 623.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (1H, s), 8.16 (s, 1H), 8.05 - 8.11 (m, 1H), 7.74 (d, J = 8.7 Hz,1 H), 7.69 - 7.60 (m, 2H), 7.08 - 6.99 (m, 1H), 6.91- 6.75 (m, 2H), 6.64 - 6.55 (m, 1H), 6.35-6.22 (m, 1H), 5.82 (d, J = 9.7 Hz, 1H), 5.55 - 5.20 (m, 1H), 4.75 - 4.60 (m, 1H), 4.55(dd, J = 12.8, 5.2 Hz, 1H), 4.38 - 4.20 (m, 2H), 4.16 (s, 3H), 3.84 - 3.80 (m, 1H), 3.50 -3.33 (m, 1H), 2.16 - 2.00 (m, 1H), 1.76 - 1.40 (m, 3H), 1.26 -1.00 (m, 2H)
313		LCMS m/z [M+1]: 639.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.22 (s, 1H), 8.10 (dd, J = 8.7, 4.6 Hz, 1H), 7.86 – 7.80 (m, 2H), 7.76 – 7.70 (m, 1H), 7.22 – 7. 13 (m, 1H), 6.89 – 6. 64 (m, 3H), 6.40 – 6. 25 (m, 1H), 5.90 – 5.79 (m, 1H), 5.11 – 4.93 (m, 2H), 4.83 – 4. 59 (m, 2H), 4.57 – 4. 38 (m, 1H), 4.29 – 4. 06 (m, 6H), 3.60 – 3.50 (m, 1H), 3.24 – 2.91 (m, 2H), 2.71 – 2. 43 (m, 1H), 1.83 – 1. 69 (m, 1H), 1.58 – 1. 42 (m, 1H).
313a		

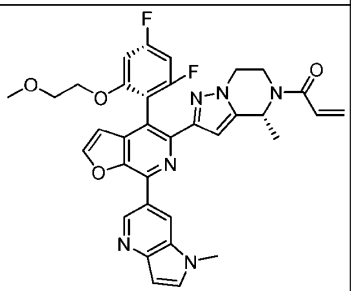
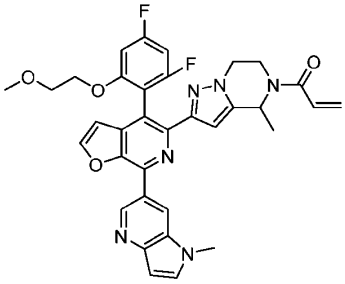
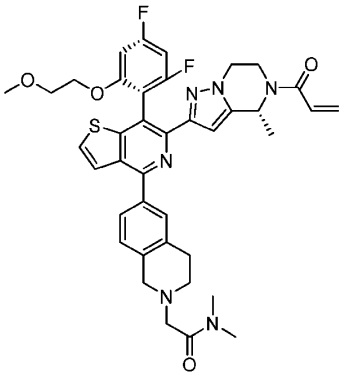
Cmpd. No.	Structure	Analytical data
314		LCMS m/z [M+1]: 667.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (d, J = 1.7 Hz, 1H), 8.41 – 8.36 (m, 1H), 7.76 (d, J = 5.6 Hz, 1H), 7.69 - 7.65 (m, 1H), 7.14 (d, J = 5.8 Hz, 1H), 6.88 - 6.75 (m, 2H), 6.71 - 6.64 (m, 1H), 6.36 - 6.27 (m, 1H), 5.86 - 5.78 (m, 1H), 4.98 - 4.94 (m, 1H), 4.82 - 4.71 (m, 1H), 4.56 - 4.47 (m, 1H), 4.28 – 4.09 (m, 3H), 4.02 - 3.86 (m, 2H), 3.78 -3.68 (m, 1H), 3.47 - 3.41 (m, 2H), 3.17 - 3.08 (m, 3H), 1.90 - 1.76 (m, 1H), 1.61 -1.50 (m, 2H), 1.35 -1.03 (m, 6H).
314a		
315		LCMS m/z [M+1]: 711.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (d, J = 8.2 Hz, 1H), 8.41 (s, 1H), 8.07 (d, J = 2.1 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 6.84 (t, J = 12.7 Hz, 2H), 6.72 – 6.61 (m, 2H), 6.29 (s, 1H), 6.10 (s, 1H), 5.81 (d, J = 10.6 Hz, 1H), 5.58 (d, J = 90.3 Hz, 1H), 4.77 (d, J = 15.4 Hz, 2H), 4.60 (d, J = 15.5 Hz, 1H), 4.39 (s, 1H), 4.20 (d, J = 10.2 Hz, 1H), 4.13 – 3.98 (m, 2H), 3.96 – 3.87 (m, 1H), 3.75 (s, 1H), 3.60 – 3.49 (m, 1H), 3.46 – 3.30 (m, 3H), 3.23 (d, J = 11.8 Hz, 4H), 3.07 (s, 9H), 1.41 (s, 3H).

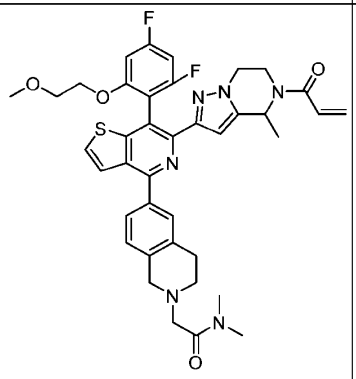
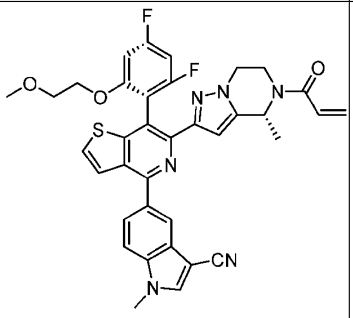
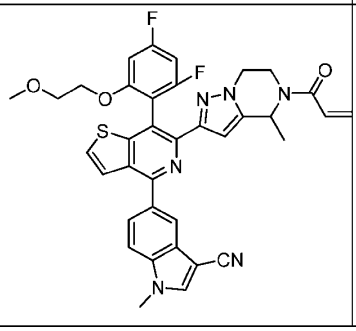
Cmpd. No.	Structure	Analytical data
315a		
316		LCMS m/z [M+1]: 683.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.78 (s, 1H),8.20 (s, 1H), 7.81 - 7.70 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.44 - 7.33 (m, 1H), 6.94 (d, J = 10.8 Hz, 1H), 6.90 - 6.79 (m, 1H), 6.79 - 6.69 (m, 1H), 6.30 (d, J = 16.2 Hz, 1H), 6.05 (s, 1H), 5.88 - 5.79 (m, 1H), 5.76 - 5.40 (m, 1H), 4.22 (dd, J = 12.6 Hz, 2.6 Hz, 1H), 4.15 - 4.02 (m, 3H), 4.01 - 3.87 (m, 1H), 3.83 - 3.66 (m, 1H), 3.45 (t, J = 6.4 Hz, 2H), 3.40 (t, J = 4.4 Hz, 2H), 3.12 (s, 3H), 3.02 (s, 3H), 1.83 (d, J = 6.6 Hz, 3H), 1.55-1.34 (m, 3H).
316a		

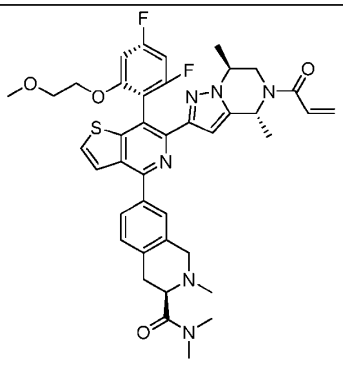
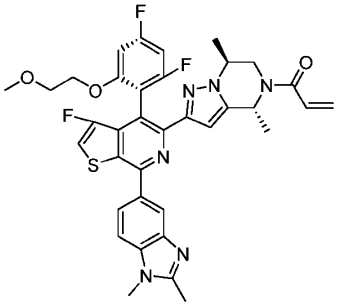
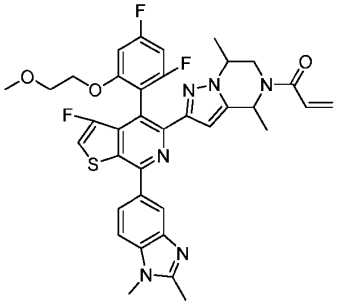
Cmpd. No.	Structure	Analytical data
317		LCMS m/z [M+1]: 741.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (dd, J = 7.9, 1.4 Hz, 1H), 7.87 (s, 1H), 7.83 (s, 1H), 7.66 (d, J = 5.0 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 6.93 – 6.77 (m, 2H), 6.68 (t, J = 9.1 Hz, 1H), 6.30 (d, J = 16.3 Hz, 1H), 6.15 (s, 1H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.59 (d, J = 91.8 Hz, 1H), 4.90 (s, 1H), 4.76 (d, J = 15.4 Hz, 1H), 4.60 (d, J = 15.2 Hz, 1H), 4.43 (s, 1H), 4.22 (d, J = 14.6 Hz, 1H), 4.12 – 3.97 (m, 2H), 3.84 (s, 1H), 3.58 (dd, J = 17.6, 5.1 Hz, 1H), 3.47 – 3.38 (m, 2H), 3.32 (d, J = 10.8 Hz, 1H), 3.22 (s, 3H), 3.05 (d, J = 16.6 Hz, 9H), 1.41 (d, J = 19.6 Hz, 3H), 1.29 (s, 3H).
317a		
318		LCMS m/z [M+1]: 692.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 7.9 Hz, 2H), 7.69 (d, J = 5.6 Hz, 1H), 6.93 - 6.88 (m, 1H), 6.87 - 6.78 (m, 1H), 6.74 (td, J = 9.2, 2.3 Hz, 1H), 6.32 - 6.23 (m, 1H), 6.13 (s, 1H), 5.82 (dd, J = 10.7, 1.8 Hz, 1H), 5.71 - 5.46 (m, 1H), 4.71 (t, J = 11.0 Hz, 4H), 4.60 (s, 2H), 4.48 - 4.35 (m, 1H), 4.28 – 4.20 (m, 1H), 4.15 - 3.90 (m, 3H), 3.82 - 3.65 (m, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.50 - 1.36 (m, 3H)

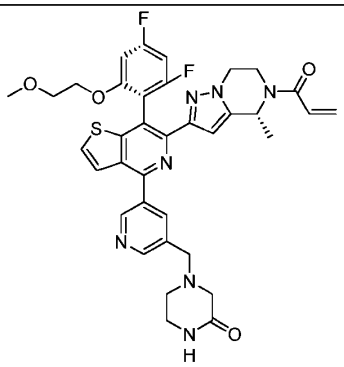
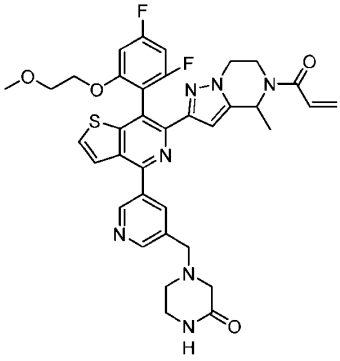
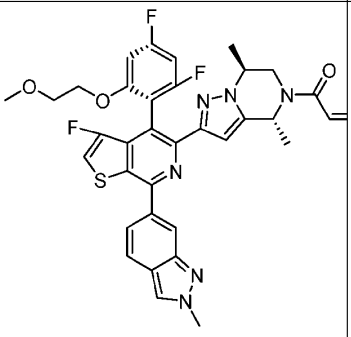
Cmpd. No.	Structure	Analytical data
318a		
319		LCMS m/z [M+1]: 725.1 ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (d, J = 8.0 Hz, 1H), 7.59 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 25.4 Hz, 1H), 6.74 (d, J = 10.9 Hz, 1H), 6.54 (t, J = 9.2 Hz, 1H), 6.30 (d, J = 16.4 Hz, 1H), 6.04 (s, 1H), 5.82 (d, J = 10.3 Hz, 1H), 5.57 (d, J = 79.7 Hz, 1H), 4.36 (d, J = 6.8 Hz, 1H), 4.27 – 4.03 (m, 3H), 3.96 (dt, J = 10.8, 3.9 Hz, 1H), 3.82 (dd, J = 9.6, 4.8 Hz, 2H), 3.53 (t, J = 4.6 Hz, 2H), 3.23 (s, 3H), 3.20 (s, 6H), 3.03 – 2.83 (m, 6H), 2.66 (dd, J = 15.7, 9.0 Hz, 1H), 2.40 (s, 3H), 2.12 – 2.02 (m, 2H), 1.47 – 1.35 (m, 3H), 1.26 (d, J = 9.2 Hz, 3H).
320		LCMS m/z [M+1]: 711.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (d, J = 8.1 Hz, 1H), 8.45 (s, 1H), 8.11 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 6.93 – 6.81 (m, 2H), 6.71 (dd, J = 12.3, 2.0 Hz, 2H), 6.32 (d, J = 16.3 Hz, 1H), 6.14 (s, 1H), 5.85 (dd, J = 10.7, 1.6 Hz, 1H), 5.62 (d, J = 86.0 Hz, 1H), 4.95 – 4.89 (m, 3H), 4.85 – 4.78 (m, 1H), 4.67 (s, 1H), 4.24 (d, J = 10.4 Hz, 1H), 4.18 – 4.05 (m, 2H), 3.98 (dd, J = 10.0, 5.4 Hz, 1H), 3.60 (dd, J = 17.6, 5.2 Hz, 1H), 3.46 (t, J = 4.6 Hz, 2H), 3.39 – 3.35 (m, 1H), 3.26 (s, 3H), 3.12 (d, J = 1.1 Hz, 9H), 1.47 (s, 3H).

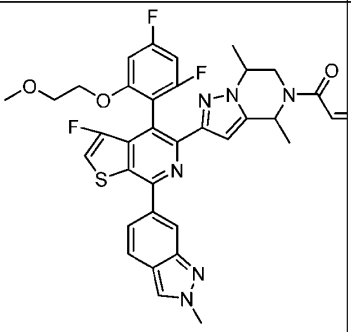
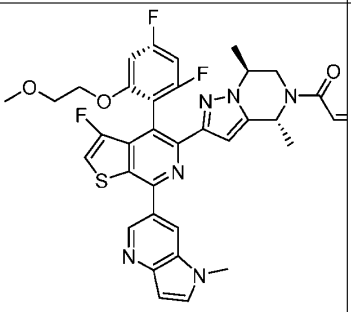
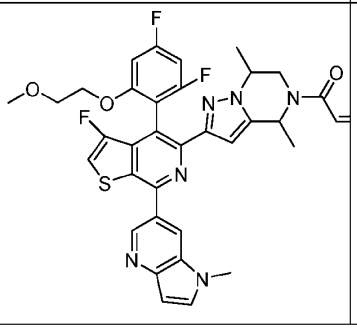
Cmpd. No.	Structure	Analytical data
321		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (dd, J = 7.9, 1.4 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.71 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 6.96 – 6.81 (m, 2H), 6.73 (td, J = 9.2, 2.2 Hz, 1H), 6.33 (d, J = 16.7 Hz, 1H), 6.16 (s, 1H), 5.84 (dd, J = 10.6, 1.8 Hz, 1H), 5.62 (d, J = 86.3 Hz, 1H), 4.79 (d, J = 15.7 Hz, 2H), 4.64 (d, J = 15.5 Hz, 1H), 4.48 (s, 1H), 4.29 (d, J = 5.4 Hz, 1H), 4.18 - 4.04 (m, 2H), 3.98 (s, 1H), 3.54 – 3.41 (m, 4H), 3.10 (s, 3H), 3.06 (s, 3H), 2.89 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H).
322		LCMS m/z [M+1]: 639.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.39 (d, J = 1.6 Hz, 1H), 8.90 (s, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.56 (d, J = 3.2 Hz, 1H), 6.75 (t, J = 14.2 Hz, 2H), 6.59 (dd, J = 9.4, 2.6 Hz, 2H), 6.54 (dd, J = 9.2, 2.0 Hz, 1H), 6.23 (d, J = 16.2 Hz, 1H), 6.10 (s, 1H), 5.75 (d, J = 10.6 Hz, 1H), 5.54 (d, J = 85.0 Hz, 1H), 4.73 – 4.53 (m, 1H), 4.40 – 4.31 (m, 1H), 4.24 – 4.08 (m, 1H), 4.05 – 3.99 (m, 1H), 3.91 (s, 3H), 3.87 – 3.81 (m, 1H), 3.37 (t, J = 4.6 Hz, 2H), 3.02 (s, 3H), 1.38 (d, J = 23.0 Hz, 3H), 1.22 (s, 3H).
322a		

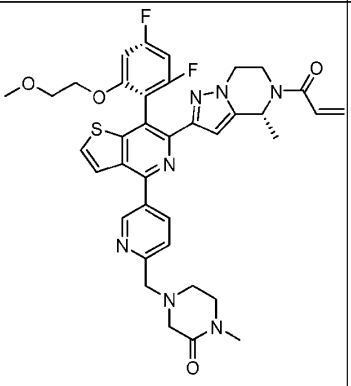
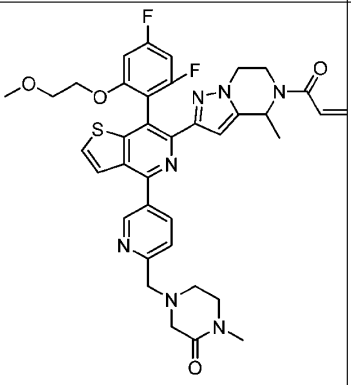
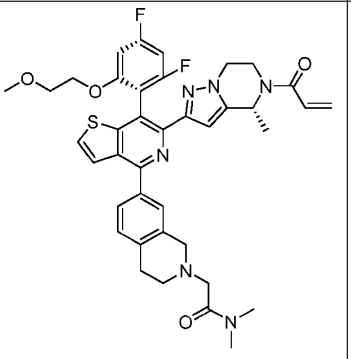
Cmpd. No.	Structure	Analytical data
323		LCMS m/z [M+1]: 625.0 ^{1}H NMR (400 MHz, CD_3OD) δ 9.39 (d, J = 1.6 Hz, 1H), 8.91 (s, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 3.2 Hz, 1H), 6.82 – 6.70 (m, 2H), 6.57 (td, J = 9.0, 2.0 Hz, 3H), 6.19 (d, J = 16.2 Hz, 1H), 6.03 (s, 1H), 5.72 (dd, J = 10.6, 1.4 Hz, 1H), 5.66 – 5.28 (m, 1H), 4.47 – 4.21 (m, 1H), 4.19 – 4.10 (m, 1H), 4.01 (dd, J = 10.6, 5.0 Hz, 1H), 3.90 (s, 3H), 3.88 – 3.80 (m, 1H), 3.77 – 3.53 (m, 1H), 3.35 (t, J = 4.6 Hz, 2H), 3.32 – 3.22 (m, 1H), 3.01 (s, 3H), 1.34 (s, 3H).
323a		
324		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 - 7.86 (m, 3H), 7.72 (d, J = 5.6 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 6.96 - 6.71 (m, 3H), 6.29 (d, J = 16.4 Hz, 1H), 6.10 (s, 1H), 5.83 (d, J = 11.9 Hz, 1H), 5.71 - 5.49 (m, 1H), 4.68 (s, 2H), 4.45 (s, 2H), 4.29 (dd, J = 12.7, 2.9 Hz, 1H), 4.16 - 4.04 (m, 3H), 3.75 (s, 2H), 3.45 - 3.38 (m, 4H), 3.06 (s, 9H), 1.52 - 1.35 (m, 3H).

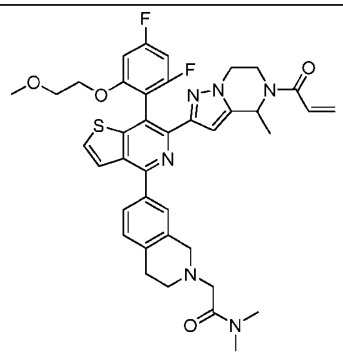
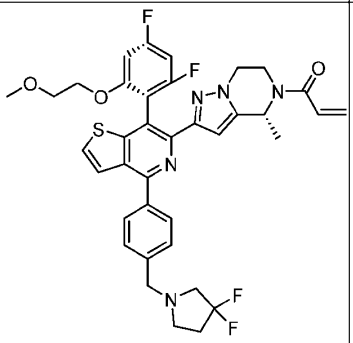
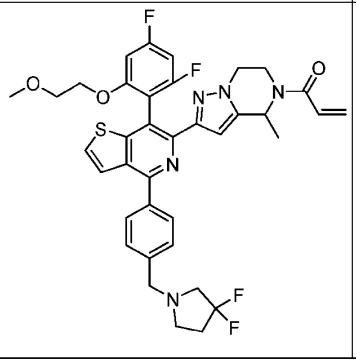
Cmpd. No.	Structure	Analytical data
324a		
325		LCMS m/z [M+1]: 664.9 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (d, J = 0.9 Hz, 1H), 8.07 (s, 1H), 8.01 (dd, J = 8.6, 1.5 Hz, 1H), 7.81 – 7.68 (m, 3H), 6.86 (dd, J = 16.7, 10.7 Hz, 2H), 6.72 (td, J = 9.2, 2.3 Hz, 1H), 6.39 – 6.11 (m, 2H), 5.83 (dd, J = 10.7, 1.5 Hz, 1H), 5.62 (d, J = 79.6 Hz, 1H), 4.60 – 4.16 (m, 2H), 4.16 – 3.97 (m, 6H), 3.80 (d, J = 21.1 Hz, 1H), 3.51 – 3.44 (m, 2H), 3.05 (d, J = 18.1 Hz, 3H), 1.47 (s, 3H).
325a		

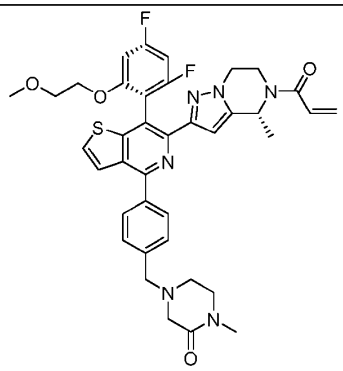
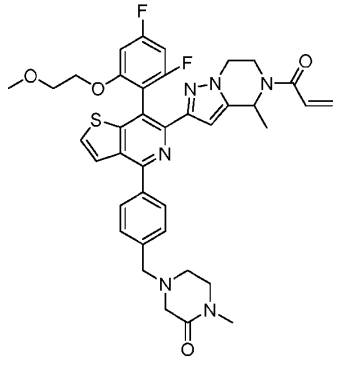
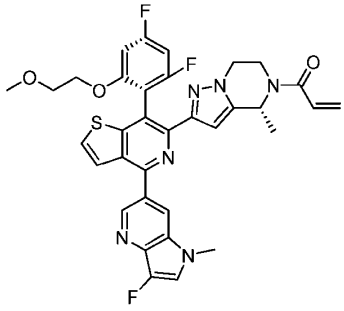
Cmpd. No.	Structure	Analytical data
326		LCMS m/z [M+1]: 641.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.87 (s, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 5.6 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 10.9 Hz, 2H), 6.66 (td, J = 9.2, 2.2 Hz, 1H), 6.30 (d, J = 16.3 Hz, 1H), 6.16 (s, 1H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.59 (d, J = 89.0 Hz, 1H), 4.89 (dd, J = 10.6, 5.4 Hz, 1H), 4.75 (d, J = 15.5 Hz, 1H), 4.62 (s, 1H), 4.41 (s, 1H), 4.20 (s, 1H), 4.11 – 3.99 (m, 2H), 3.84 (s, 1H), 3.57 (dd, J = 17.6, 5.3 Hz, 1H), 3.42 (t, J = 4.6 Hz, 2H), 3.34 (s, 1H), 3.22 (s, 3H), 3.07 (s, 6H), 3.03 (s, 3H), 1.40 (s, 3H), 1.28 (s, 3H).
327		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.40 (dd, J = 8.6 Hz, 1.2 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 6.92 - 6.77 (m, 2H), 6.66 - 6.55 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.12 (s, 1H), 5.84 (dd, J = 10.6 Hz, 1.4 Hz, 1H), 5.78 - 5.41 (m, 1H), 4.52 - 4.40 (m, 1H), 4.09 (s, 3H), 4.06 - 3.97 (m, 1H), 3.47 (t, J = 4.4 Hz, 2H), 3.08 (s, 3H), 2.93 (s, 3H), 1.50-1.36 (m, 3H), 1.35 - 1.22 (m, 3H).
327a		

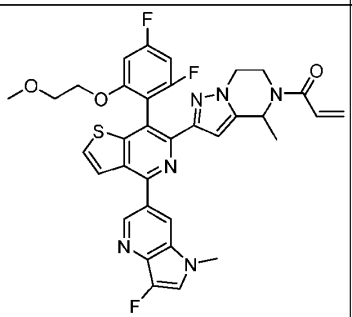
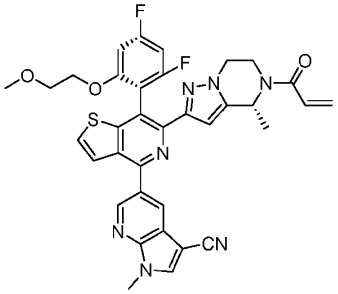
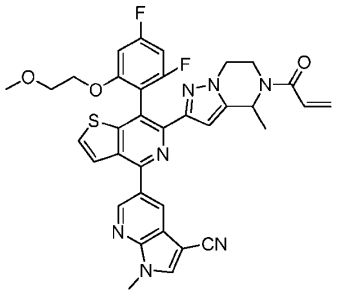
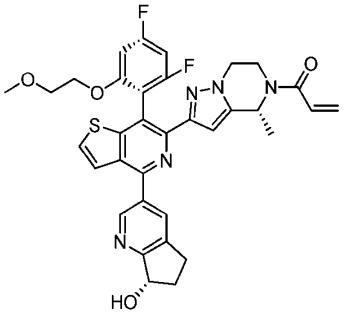
Cmpd. No.	Structure	Analytical data
328		LCMS m/z [M+1]: 700.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.89 (d, J = 10.4 Hz, 2H), 7.90 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 5.6 Hz, 1H), 6.92 - 6.80 (m, 2H), 6.73 (td, J = 9.2 Hz, 2.0 Hz, 1H), 6.35 - 6.25 (m, 1H), 6.15 (s, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.80 - 5.45 (m, 1H), 4.30 - 4.20 (m, 3H), 4.15 - 4.00 (m, 3H), 3.80 - 3.70 (m, 1H), 3.55 (s, 2H), 3.47 (t, J = 5.2 Hz, 2H), 3.41 (t, J = 4.4 Hz, 2H), 3.17 (t, J = 4.2 Hz, 2H), 3.04 (s, 3H), 1.55 - 1.35 (m, 3H).
328a		
329		LCMS m/z [M+1]: 673.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (d, J = 6.8 Hz, 2H), 7.97 (d, J = 8.6 Hz, 1H), 7.80 (dd, J = 8.6, 1.2 Hz, 1H), 7.72 (s, 1H), 6.89 – 6.81 (m, 2H), 6.63 (td, J = 9.2, 2.2 Hz, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.14 (s, 1H), 5.84 (d, J = 10.4 Hz, 1H), 5.72 – 5.51 (m, 1H), 4.47 – 4.45 (m, 1H), 4.30 (s, 3H), 4.13 – 4.00 (m, 2H), 3.47 (t, J = 4.8 Hz, 2H), 3.09 (s, 3H), 1.45 – 1.42 (m, 3H), 1.31 – 1.28 (m, 3H).

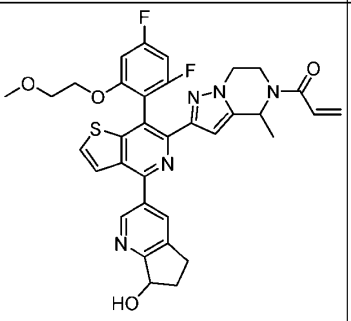
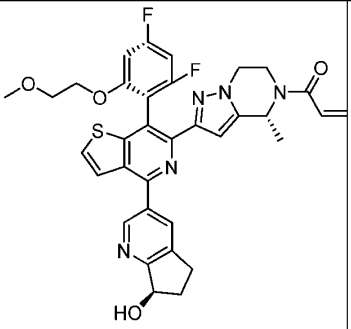
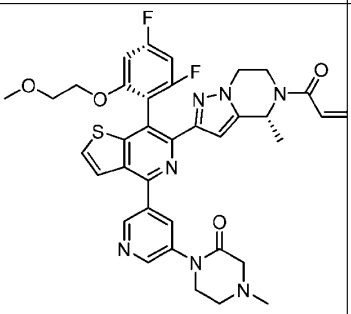
Cmpd. No.	Structure	Analytical data
329a		
330		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (s, 1H), 9.40 (s, 1H), 8.24 (d, J = 3.2 Hz, 1H), 7.66 (d, J = 2.2 Hz, 1H), 6.97 (d, J = 2.8 Hz, 1H), 6.92 - 6.77 (m, 2H), 6.68 - 6.57 (m, 1H), 6.33 (d, J = 16.2 Hz, 1H), 6.08 (s, 1H), 5.84 (dd, J = 10.6 Hz, 1.4 Hz, 1H), 5.79 - 5.43 (m, 1H), 4.48 (s, 1H), 4.18 (s, 3H),4.16-4.07 (m, 1H), 4.06 - 3.97 (m, 1H), 3.45 (t, J = 4.4 Hz, 2H), 3.10 (s, 3H), 1.53-1.38 (m, 3H), 1.37-1.24 (s, 3H).
330a		

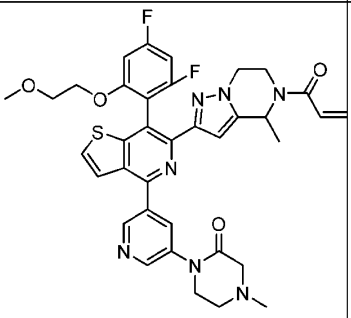
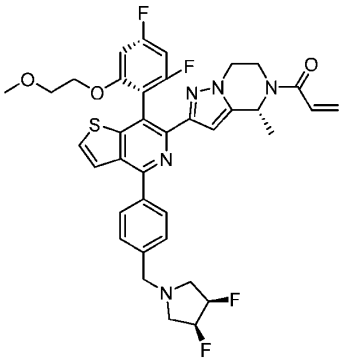
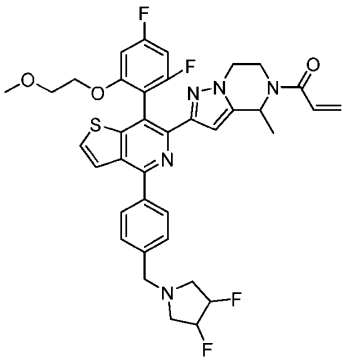
Cmpd. No.	Structure	Analytical data
331		LCMS m/z [M+1]: 714.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.6 Hz, 1H), 8.64 (dd, J = 8.0, 2.0 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.94 – 6.79 (m, 2H), 6.76 – 6.69 (m, 1H), 6.29 (d, J = 16.8 Hz, 1H), 6.16 (s, 1H), 5.86 - 5.78 (m, 1H), 5.75 - 5.43 (m, 1H), 4.62 (s, 2H), 4.25 - 4.18 (m, 1H), 4.15 – 4.01 (m, 3H), 3.95 (s, 2H), 3.69 (t, J = 5.2 Hz, 2H), 3.59 (t, J = 5.6 Hz, 2H), 3.42 (t, J = 4.8 Hz, 2H), 3.05 (d, J = 6.0 Hz, 6H), 1.52 – 1.36 (m, 3H).
331a		
332		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (d, J = 7.6 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.64 (d, J = 5.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 6.89 – 6.78 (m, 2H), 6.72-6.64 (m, 1H), 6.34-6.22 (m, 1H), 6.16 (s, 1H), 5.84 - 5.77 (m, 1H), 5.71 - 5.46 (m, 1H), 4.57 - 4.41 (m, 1H), 4.21 – 3.94 (m, 7H), 3.67 (s, 2H), 3.42 (t, J = 4.4Hz, 2H), 3.15 - 3.05 (m, 7H), 3.03 (s, 3H), 2.99 (s, 3H), 1.48-1.38 (m, 3H).

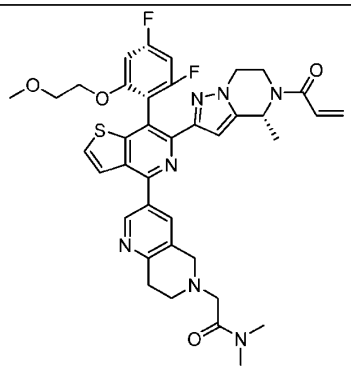
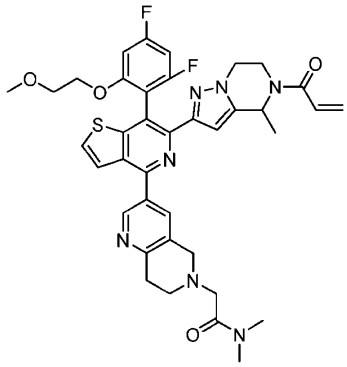
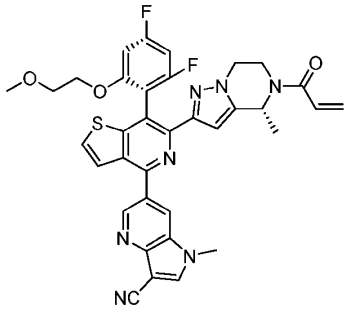
Cmpd. No.	Structure	Analytical data
332a		
333		LCMS m/z [M+1]: 706.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (d, J = 8.1 Hz, 2H), 7.72 – 7.65 (m, 2H), 7.57 (d, J = 8.1 Hz, 2H), 6.88 – 6.79 (m, 2H), 6.69 (t, J = 9.2 Hz, 1H), 6.32 – 6.15 (m, 2H), 5.81 (d, J = 10.7 Hz, 1H), 5.70 – 5.49 (m, 1H), 4.54 (s, 2H), 4.17 – 3.95 (m, 4H), 3.78 (s, 2H), 3.42 (t, J = 4.6 Hz, 2H), 3.03 (s, 3H), 2.95 (t, J = 13.2 Hz, 2H), 2.84 (t, J = 6.9 Hz, 2H), 2.38 – 2.21 (m, 2H), 1.50 – 1.25 (m, 3H).
333a		

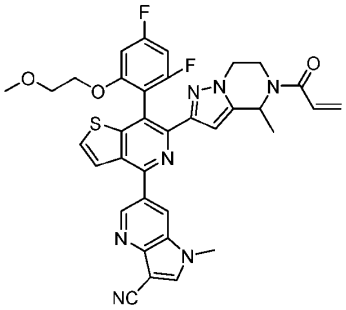
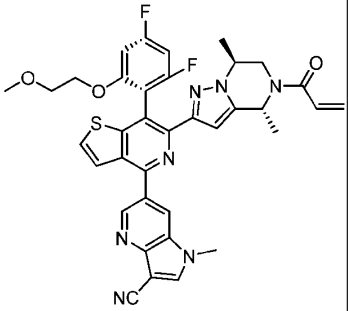
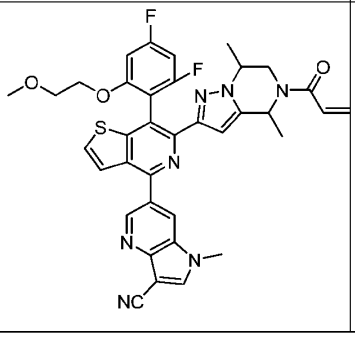
Cmpd. No.	Structure	Analytical data
334		LCMS m/z [M+1]: 713.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 8.1 Hz, 2H), 7.91 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 5.6 Hz, 1H), 6.93 (d, J = 10.6 Hz, 1H), 6.89 – 6.70 (m, 2H), 6.28 (d, J = 16.5 Hz, 1H), 6.12 (s, 1H), 5.82 (dd, J = 10.6, 1.5 Hz, 1H), 5.76 – 5.38 (m, 1H), 4.40 (s, 2H), 4.29 – 4.21 (m, 1H), 4.17 – 4.00 (m, 3H), 3.76 (s, 2H), 3.65 – 3.60 (m, 2H), 3.52 – 3.46 (m, 2H), 3.43 (t, J = 4.5 Hz, 2H), 3.05 (s, 3H), 3.02 (s, 3H), 1.55 – 1.29 (m, 3H).
334a		
335		LCMS m/z [M+1]: 658.9 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (d, J = 1.3 Hz, 1H), 9.03 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.97 (d, J = 5.6 Hz, 1H), 7.88 (d, J = 5.6 Hz, 1H), 6.97 (d, J = 10.8 Hz, 1H), 6.91 – 6.75 (m, 2H), 6.32 (d, J = 16.6 Hz, 1H), 6.10 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.62 (d, J = 84.6 Hz, 1H), 4.62 – 4.23 (m, 2H), 4.18 – 4.05 (m, 6H), 3.78 (s, 1H), 3.46 (t, J = 4.6 Hz, 2H), 3.09 (s, 3H), 1.45 (s, 3H).

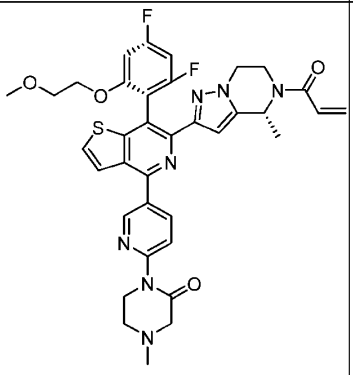
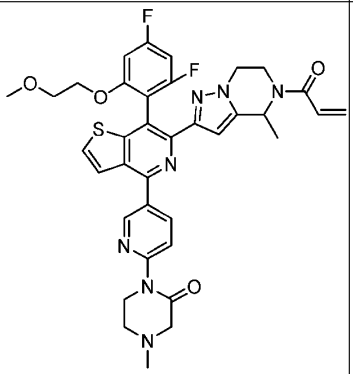
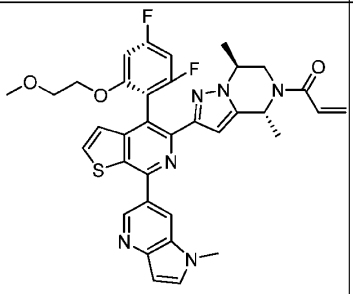
Cmpd. No.	Structure	Analytical data
335a		
336		LCMS m/z [M+1]: 666.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (d, J = 1.9 Hz, 1H), 8.62 (d, J = 1.8 Hz, 1H), 8.18 (s, 1H), 7.70 (d, J = 5.6 Hz, 1H), 7.62 (d, J = 5.6 Hz, 1H), 6.81 – 6.71 (m, 2H), 6.62 (td, J = 9.2, 2.3 Hz, 1H), 6.25 – 6.02 (m, 2H), 5.72 (d, J = 12.1 Hz, 1H), 5.51 (d, J = 84.4 Hz, 1H), 4.46 – 4.05 (m, 2H), 4.03 – 3.91 (m, 6H), 3.65 (s, 1H), 3.34 (t, J = 4.6 Hz, 2H), 2.96 (s, 3H), 1.34 (s, 3H).
336a		
337		LCMS m/z [M+1]: 644.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.14 (s, 1H), 8.71 (s, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.95 - 6.78 (m, 2H), 6.77 - 6.68 (m, 1H), 6.28 (d, J = 11.2 Hz, 1H), 6.13 (s, 1H), 5.82 (dd, J = 10.6, 1.4 Hz, 1H), 5.76 - 5.46 (m, 1H), 5.42 (t, J = 7.0 Hz, 1H), 4.27 - 4.17 (m, 1H), 4.14 - 3.95 (m, 3H), 3.41 (t, J = 4.6 Hz, 2H), 3.29 - 3.19 (m, 1H), 3.16 - 3.05 (m, 1H), 3.04 (s,

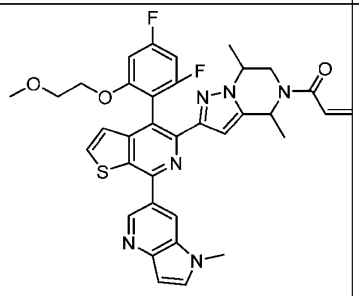
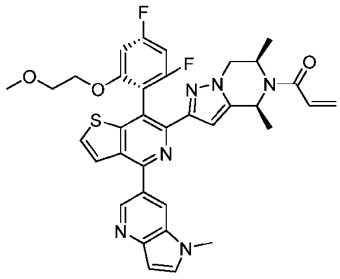
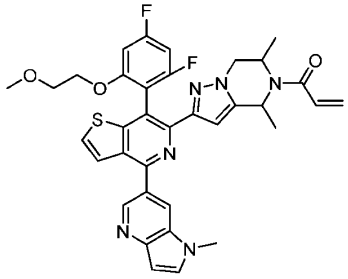
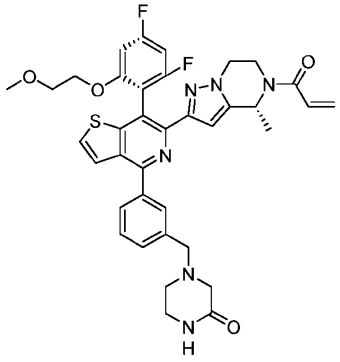
Cmpd. No.	Structure	Analytical data
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337a		
338		LCMS m/z [M+1]: 644.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.73 (s, 1H), 7.89 (d, J = 5.5 Hz, 1H), 7.75 (d, J = 5.4 Hz, 1H), 6.95 - 6.78 (m, 2H), 6.77 - 6.69 (m, 1H), 6.28 (d, J = 11.2 Hz, 1H), 6.13 (s, 1H), 5.82 (d, J = 10.4 Hz, 1H), 5.76 - 5.46 (m, 1H), 5.42 (t, J = 6.9 Hz, 1H), 4.26 - 4.17 (m, 1H), 4.15 - 4.00 (m, 3H), 3.41 (t, J = 4.5 Hz, 2H), 3.29 - 3.17 (m, 1H), 3.16 - 3.06 (m, 1H), 3.04 (s, 3H), 2.78 - 2.67 (m, 1H), 2.23 - 2.11 (m, 1H), 1.50 - 1.36 (m, 3H).
339		LCMS m/z [M+1]: 700.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (d, J = 1.5 Hz, 1H), 8.76 (d, J = 1.9 Hz, 1H), 8.52 - 8.48 (m, 1H), 7.81 (d, J = 5.5 Hz, 1H), 7.74 (d, J = 5.5 Hz, 1H), 6.92 - 6.78 (m, 2H), 6.75 - 6.66 (m, 1H), 6.28 (d, J = 16.2 Hz, 1H), 6.17 (s, 1H), 5.81 (dd, J = 10.5, 1.2 Hz, 1H), 5.75 - 5.38 (m, 1H), 4.24 - 4.15 (m, 1H), 4.14 - 3.96 (m, 5H), 3.67 (s, 3H), 3.41 (t, J = 4.6 Hz, 2H), 3.28 - 3.22 (m, 1H), 3.03 (s, 3H), 2.71 (s, 3H), 1.50 - 1.36 (m, 3H).

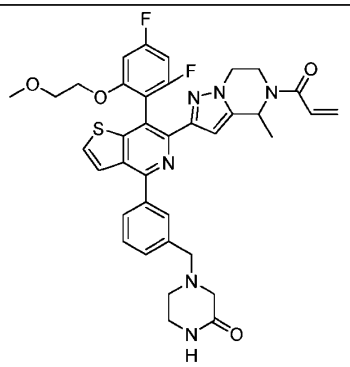
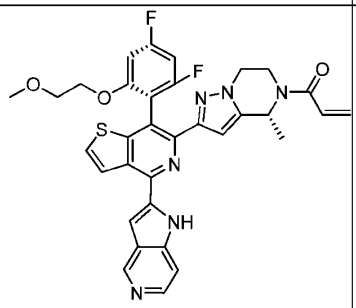
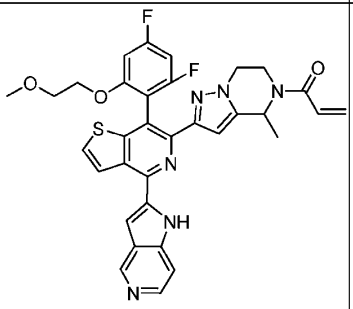
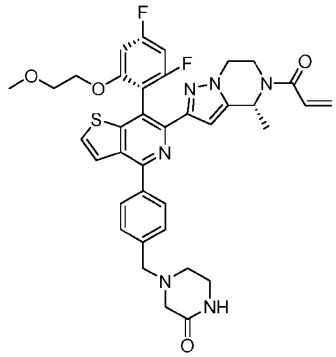
Cmpd. No.	Structure	Analytical data
339a		
340		LCMS m/z [M+1]: 706.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 5.6 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 5.6 Hz, 1H), 6.93 – 6.79 (m, 2H), 6.73 (td, J = 9.2, 2.2 Hz, 1H), 6.29 (d, J = 17.7 Hz, 1H), 6.14 (s, 1H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.60 – 5.52 (m, 1H), 5.48 – 5.40 (m, 1H), 4.61 (s, 2H), 4.23 (dd, J = 12.8, 2.8 Hz, 1H), 4.15 – 4.00 (m, 3H), 3.92 – 3.73 (m, 4H), 3.43 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.50 – 1.28 (m, 3H).
340a		

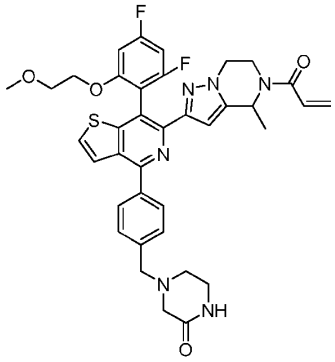
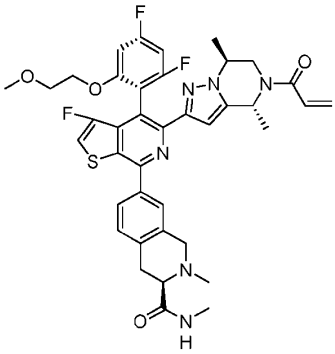
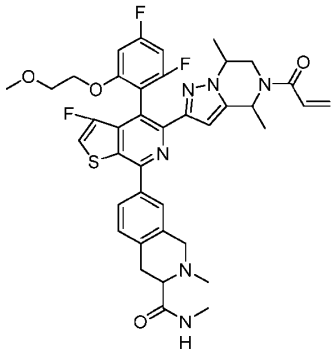
Cmpd. No.	Structure	Analytical data
341		LCMS m/z [M+1]: 728.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (d, J = 2.0 Hz, 1H), 8.35 (d, J = 1.9 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.93 - 6.64 (m, 3H), 6.28 (d, J = 16.9 Hz, 1H), 6.14 (s, 1H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.72 - 5.41 (m, 1H), 4.75 (s, 2H), 4.48 (s, 2H), 4.22 (dd, J = 12.6, 2.8 Hz, 1H), 4.12 - 3.99 (m, 3H), 3.89 - 3.82 (m, 2H), 3.49 (t, J = 6.2 Hz, 2H), 3.42 (t, J = 4.6 Hz, 2H), 3.05 (s, 6H), 3.04 (s, 3H), 1.52 - 1.35 (m, 3H).
341a		
342		LCMS m/z [M+1]: 666.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (d, J = 1.7 Hz, 1H), 8.73 (d, J = 1.8 Hz, 1H), 8.38 (s, 1H), 7.80 (d, J = 11.5 Hz, 2H), 6.93 – 6.83 (m, 2H), 6.74 (td, J = 9.2, 2.3 Hz, 1H), 6.37 – 6.16 (m, 2H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.62 (d, J = 78.9 Hz, 1H), 4.51 (d, J = 64.6 Hz, 1H), 4.24 (dd, J = 12.6, 2.7 Hz, 1H), 4.15 – 4.02 (m, 6H), 3.85 (s, 1H), 3.45 (t, J = 4.6 Hz, 2H), 3.07 (s, 3H), 1.45 (s, 3H).

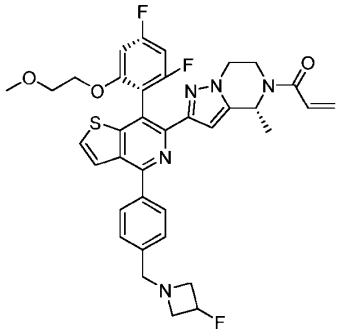
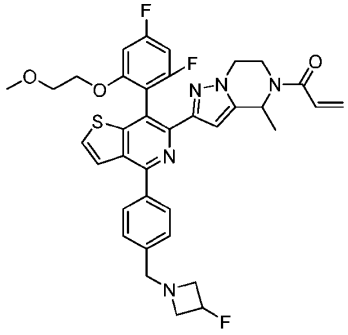
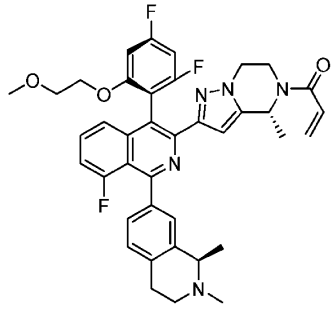
Cmpd. No.	Structure	Analytical data
342a		
343		LCMS m/z [M+1]: 680.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (d, J = 1.6 Hz, 1H), 8.77 (d, J = 1.7 Hz, 1H), 8.44 (s, 1H), 7.90 (d, J = 5.6 Hz, 1H), 7.81 (d, J = 5.6 Hz, 1H), 6.94 (d, J = 10.9 Hz, 2H), 6.75 (d, J = 2.2 Hz, 1H), 6.35 (d, J = 16.3 Hz, 1H), 6.23 (s, 1H), 5.86 (dd, J = 10.6, 1.7 Hz, 1H), 5.75 (s, 1H), 4.74 (s, 1H), 4.48 (d, J = 6.2 Hz, 1H), 4.30 – 3.88 (m, 6H), 3.47 (t, J = 4.6 Hz, 2H), 3.09 (s, 3H), 1.45 (s, 3H), 1.34 (s, 3H).
343a		

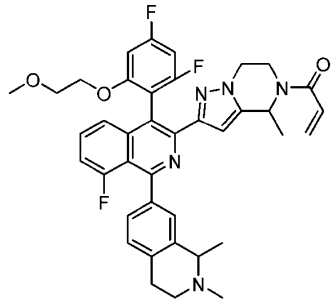
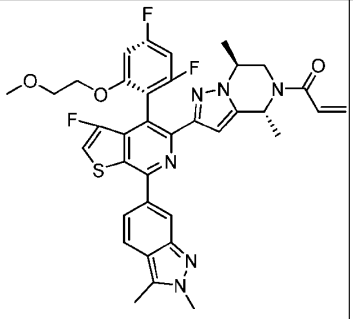
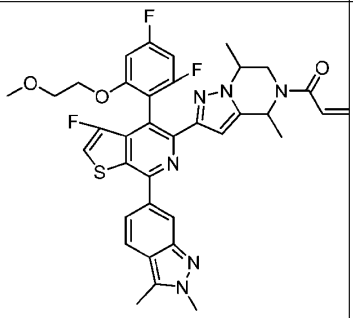
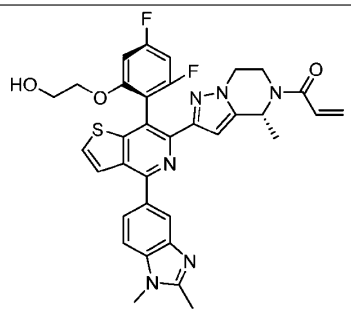
Cmpd. No.	Structure	Analytical data
344		LCMS m/z [M+1]: 700.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.08 (d, J = 1.8 Hz, 1H), 8.47 (dd, J = 8.6, 2.4 Hz, 1H), 8.22 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.94 – 6.62 (m, 3H), 6.35 – 6.22 (m, 1H), 6.16 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.78 – 5.40 (m, 1H), 4.49 – 4.37 (m, 2H), 4.26 – 4.17 (m, 3H), 4.15 – 3.97 (m, 3H), 3.85 – 3.65 (m, 2.5H), 3.42 (t, J = 4.6 Hz, 2H), 3.11 (s, 3H), 3.04 (s, 3H), 1.55 – 1.35 (m, 3H).
344a		
345		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.47 (s, 1H), 9.44(s, 1H), 8.23 (d, J = 3.2 Hz, 1H), 8.06 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 6.98 (d, J = 3.1 Hz, 1H), 6.94 – 6.81 (m, 2H), 6.70 (td, J = 9.2, 2.3 Hz, 1H), 6.33 (d, J = 16.9 Hz, 1H), 6.11 (s, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.80 – 5.38 (m, 1H), 4.32 – 4.08 (m, 5H), 4.05 – 3.95 (m, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.07 (s, 3H), 1.54 – 1.25 (m, 6H).

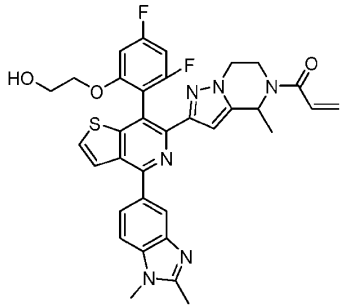
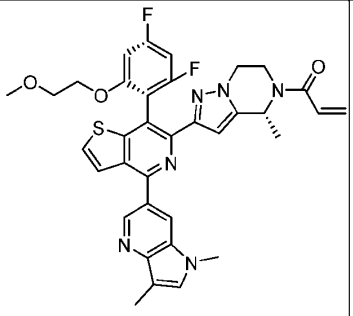
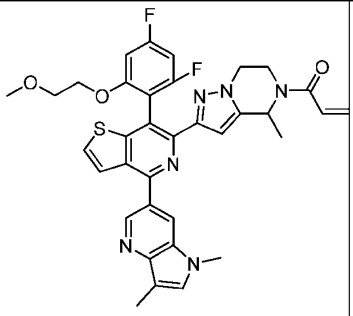
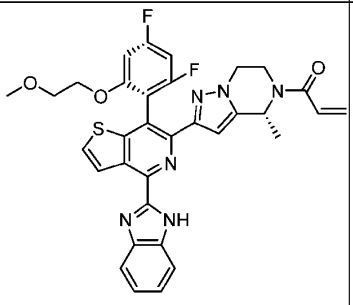
Cmpd. No.	Structure	Analytical data
345a		
346		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (s, 1H), 9.28 (d, J = 1.4 Hz, 1H), 8.21 (d, J = 3.2 Hz, 1H), 7.92 – 7.87 (m, 2H), 6.96 (dd, J = 3.2, 0.7 Hz, 1H), 6.93 – 6.73 (m, 3H), 6.35 – 6.21 (s, 1H), 6.16 (s, 1H), 5.81 (d, J = 11.5 Hz, 1H), 5.52 – 5.42 (m, 1H), 4.25 – 4.15 (m, 5H), 4.14 – 4.07 (m, 1H), 4.03 – 3.95 (m, 1H), 3.43 (t, J = 4.7 Hz, 2H), 3.08 (s, 3H), 1.51 (d, J = 6.7 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H).
346a		
347		LCMS m/z [M+1]: 699.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1H), 8.14 – 8.09 (m, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.80 – 7.71 (m, 3H), 6.95 – 6.71 (m, 3H), 6.34 – 6.24 (m, 1H), 6.10 (s, 1H), 5.82 (dd, J = 10.6, 1.8 Hz, 1H), 5.76 – 5.42 (m, 1H), 4.56 – 4.36 (m, 2.5H), 4.29 – 4.21 (m, 1H), 4.17 – 4.00 (m, 3H), 3.87 – 3.68 (m, 2.5H), 3.61 – 3.50 (m, 4H), 3.43 (t, J = 4.6 Hz, 2H), 3.06 (s, 3H), 1.51 – 1.35 (m, 3H).

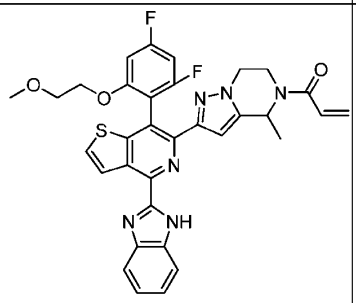
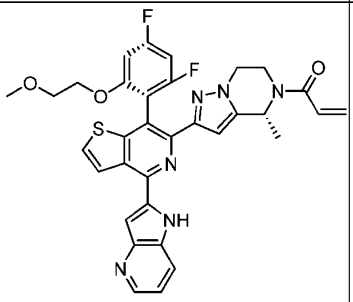
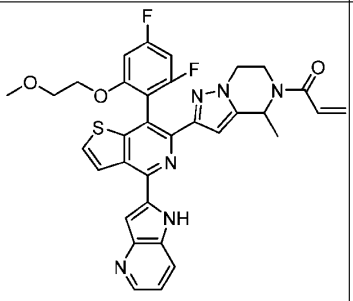
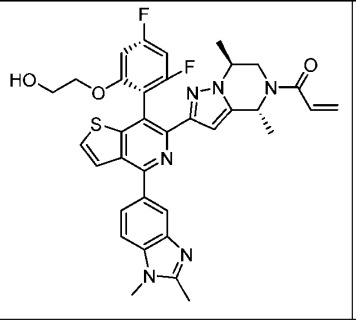
Cmpd. No.	Structure	Analytical data
347a		
348		LCMS m/z [M+1]: 627.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.25 (s, 1H), 8.41 (d, J = 6.7 Hz, 1H), 8.21 (d, J = 5.6 Hz, 1H), 8.07 – 7.84 (m, 3H), 7.01 – 6.75 (m, 3H), 6.31 (d, J = 16.6 Hz, 1H), 5.98 – 5.78 (m, 2H), 5.61 (d, J = 82.1 Hz, 1H), 4.61 – 4.31 (m, 2H), 4.22 (s, 1H), 4.15 – 4.04 (m, 2H), 3.83 (s, 1H), 3.41 (t, J = 4.5 Hz, 2H), 3.00 (s, 3H), 1.44 (s, 3H).
348a		
349		LCMS m/z [M+1]: 699.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 - 8.08 (m, 2H), 7.91 (d, J = 5.6 Hz, 1H), 7.82 - 7.70 (m, 2H), 7.73 (d, J = 5.6 Hz, 1H), 6.96 – 6.91 (m, 1H), 6.88 – 6.78 (m, 1H), 6.77 – 6.70 (m, 1H), 6.36 – 6.22 (m, 1H), 6.11 (s, 1H), 5.82 (dd, J1 = 10.6, 1.7 Hz, 1H), 5.78 - 5.40 (m, 1H), 4.48 (s, 2H), 4.28 - 4.22 (m, 1H), 4.17 - 4.03 (m, 3H), 3.80 (s, 2H), 3.61 - 3.55 (m, 2H), 3.54 - 3.49 (m, 2H),

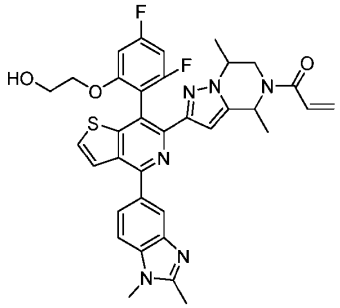
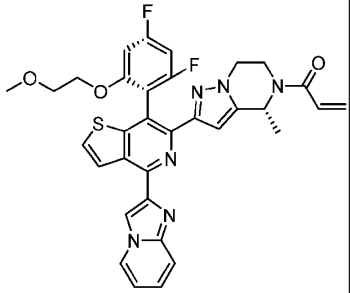
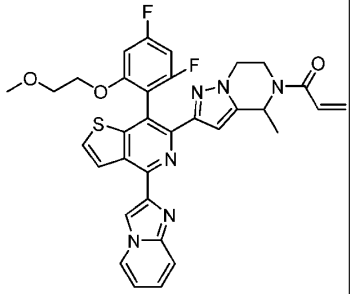
Cmpd. No.	Structure	Analytical data
		3.43 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.55 - 1.35 (m, 3H).
349a		
350		LCMS m/z [M+1]: 745.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (dd, J = 7.8, 1.4 Hz, 1H), 8.02 (s, 1H), 7.55 – 7.53 (m, 2H), 6.89 – 6.78 (m, 2H), 6.59 (td, J = 9.2, 2.2 Hz, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.11 (s, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 – 5.48 (m, 1H), 4.77 (d, J = 14.8 Hz, 2H), 4.62 (d, J = 15.4 Hz, 1H), 4.42 – 4.25 (m, 2H), 4.12 – 4.06 (m, 1H), 4.04 – 3.99 (m, 1H), 3.51 – 3.41 (m, 5H), 3.09 (s, 3H), 3.07 (s, 3H), 2.88 (s, 3H), 1.44 – 1.41 (m, 3H), 1.32 – 1.30 (m, 3H).
350a		

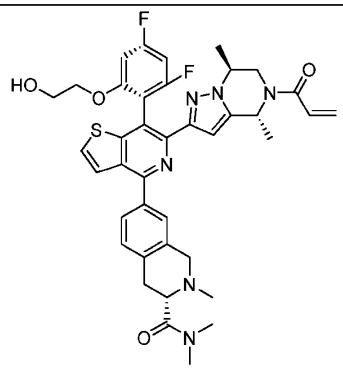
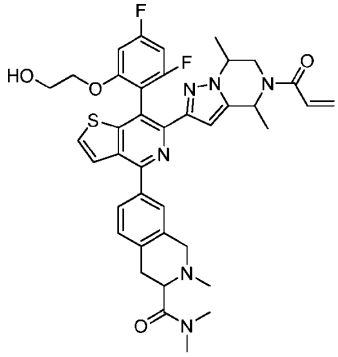
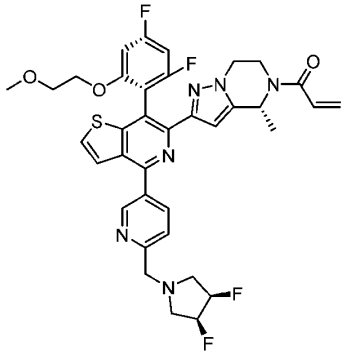
Cmpd. No.	Structure	Analytical data
351		LCMS m/z [M+1]: 674.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 5.6 Hz, 1H), 7.73 - 7.68 (m, 2H), 7.66 (d, J = 5.6 Hz, 1H), 6.92 – 6.80 (m, 2H), 6.72 (td, J = 9.2, 2.3 Hz, 1H), 6.32 - 6.23 (m, 1H), 6.15 (s, 1H), 5.82 (dd, J = 10.6, 1.9 Hz, 1H), 5.75 - 5.48 (m, 1H), 5.52 - 5.38 (m, 1H), 4.69 – 4.54 (m, 4H), 4.50 - 4.32 (m, 3H), 4.24 - 4.16 (m, 1H), 4.12 - 3.99 (m, 3H), 3.84 - 3.66 (m, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.04 (s, 3H), 1.50 - 1.37 (m, 3H).
351a		
352		LCMS m/z [M+1]: 683.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1H), 8.17 (s, 1H),7.80-7.68 (m, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.41 - 7.30 (m, 1H), 6.92 - 6.70 (m, 3H), 6.28 (d, J = 16.6 Hz, 1H), 6.07 (s, 1H), 5.81 (dd, J = 10.6 Hz, 1.6 Hz, 1H), 5.75 - 5.37 (m, 1H), 4.19 (dd, J = 12.8 Hz, 3.0 Hz, 1H), 4.13 - 4.01 (m, 2H), 4.00 - 3.84 (m, 2H), 3.80 - 3.60 (m, 1H), 3.43 (t, J = 6.2 Hz, 2H), 3.36 (t, J = 4.6 Hz, 2H), 3.10 (s, 3H), 3.01 (s, 3H), 1.80 (d, J = 6.6 Hz, 3H), 1.52-1.31 (m, 3H).

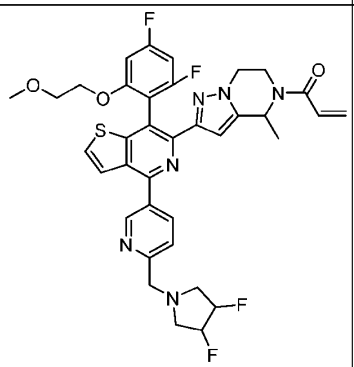
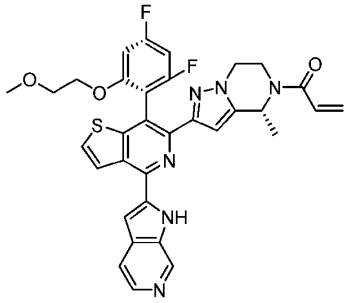
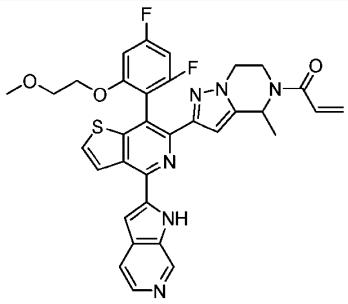
Cmpd. No.	Structure	Analytical data
352a		
353		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.80 - 7.75 (m, 1H), 7.73 - 7.67 (m, 1H), 6.93 - 6.78 (m, 2H), 6.66 - 6.58 (m, 1H), 6.37 - 6.28 (m, 1H), 6.15 (s, 1H), 5.84 (dd, J = 10.5, 1.7 Hz, 1H), 5.79 - 5.43 (m, 1H), 4.50 - 4.40 (m, 1H), 4.19 (s, 3H), 4.14 - 4.07 (m, 1H), 4.06 - 3.98 (m, 1H), 3.93 - 3.77 (m, 1H), 3.47 (t, J = 4.9 Hz, 2H), 3.09 (s, 3H), 2.75 (s, 3H), 1.56 - 1.37 (m, 3H), 1.36 - 1.24 (m, 3H).
353a		
354		LCMS m/z [M+1]: 641.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 1.0 Hz, 1H), 7.91 (dd, J = 8.4, 1.4 Hz, 1H), 7.73 – 7.60 (m, 3H), 6.92 – 6.78 (m, 2H), 6.70 (td, J = 9.2, 2.3 Hz, 1H), 6.25 (d, J = 28.9 Hz, 2H), 5.81 (d, J = 11.9 Hz, 1H), 5.60 (d, J = 81.4 Hz, 1H), 4.47 – 4.14 (m, 2H), 4.12 – 3.90 (m, 3H), 3.88 (s, 3H), 3.72 (d, J = 18.0 Hz, 1H), 3.62 – 3.51 (m, 2H), 2.66 (s, 3H), 1.41 (d, J = 10.3 Hz, 3H).

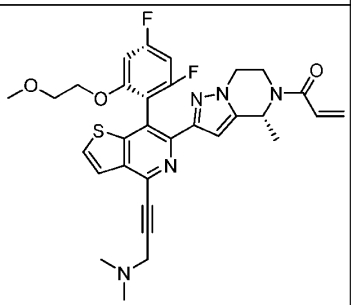
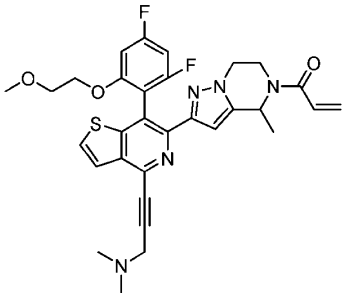
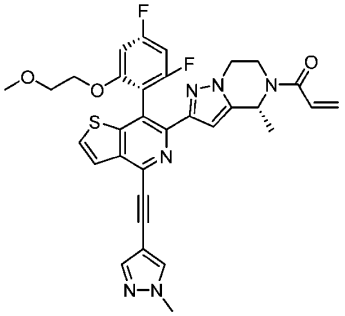
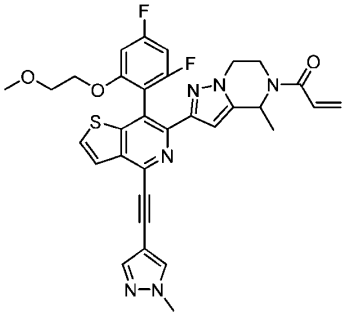
Cmpd. No.	Structure	Analytical data
354a		
355		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.27 (s, 1H), 9.22 (s, 1H), 8.03 (s, 1H), 7.90 (dd, J = 13.2, 5.6 Hz, 2H), 6.95 (d, J = 10.8 Hz, 1H), 6.87 (dd, J = 16.6, 10.8 Hz, 1H), 6.77 (td, J = 9.2, 2.0 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 6.11 (s, 1H), 5.85 (dd, J = 10.6, 1.4 Hz, 1H), 5.78 – 5.45 (m, 1H), 4.61 – 4.19 (m, 2H), 4.16 – 3.75 (m, 7H), 3.45 (t, J = 4.4 Hz, 2H), 3.09 (s, 3H), 2.55 (s, 3H), 1.45 (s, 3H).
355a		
356		LCMS m/z [M+1]: 627.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (d, J = 5.6 Hz, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.86 (dd, J = 6.0, 3.0 Hz, 2H), 7.52 (dd, J = 6.0, 3.0 Hz, 2H), 6.99 (d, J = 10.8 Hz, 1H), 6.92 – 6.78 (m, 2H), 6.33 (d, J = 15.6 Hz, 1H), 5.97 (s, 1H), 5.86 (dd, J = 10.6, 1.6 Hz, 1H), 5.77 – 5.43 (m, 1H), 4.42 – 4.20 (m, 2H), 4.15 – 4.07 (m, 2H),3.41 (t, J = 4.4 Hz, 2H), 3.01 (s, 3H), 2.68 (s, 2H), 1.47 (s, 3H).

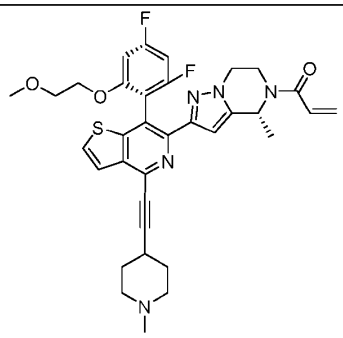
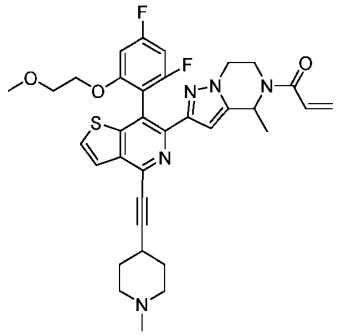
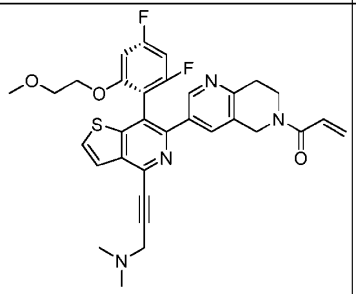
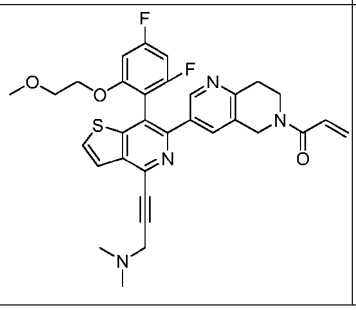
Cmpd. No.	Structure	Analytical data
356a		
357		LCMS m/z [M+1]: 627.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 (dd, J = 4.7, 1.3 Hz, 1H), 8.21 (d, J = 5.7 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 5.6 Hz, 1H), 7.52 (s, 1H), 7.31 (dd, J = 8.2, 4.7 Hz, 1H), 6.91 (dd, J = 39.4, 11.1 Hz, 2H), 6.79 (td, J = 9.2, 2.2 Hz, 1H), 6.32 (d, J = 16.1 Hz, 1H), 5.94 (s, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.61 (d, J = 79.2 Hz, 1H), 4.40 (dd, J = 30.9, 21.4 Hz, 2H), 4.18 (d, J = 35.1 Hz, 1H), 4.13 – 4.03 (m, 2H), 3.83 (s, 1H), 3.42 (t, J = 4.6 Hz, 2H), 3.02 (s, 3H), 1.56 – 1.37 (m, 3H).
357a		
358		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.24 (dd, J = 8.6, 1.3 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.85 (dd, J = 5.5, 2.4 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.90 (dd, J = 25.4, 13.7 Hz, 2H), 6.70 (t, J = 9.2 Hz, 1H), 6.35 (d, J = 16.7 Hz, 1H), 6.28 (s, 1H), 5.86 (dd, J = 10.6, 1.7 Hz, 1H), 5.65 (d, J = 85.2 Hz, 1H), 4.46 (s, 1H), 4.38 –

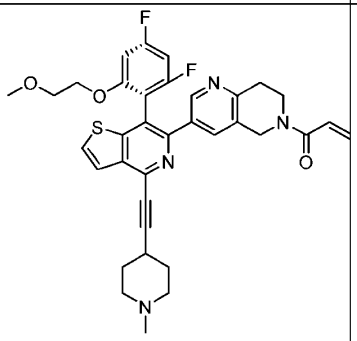
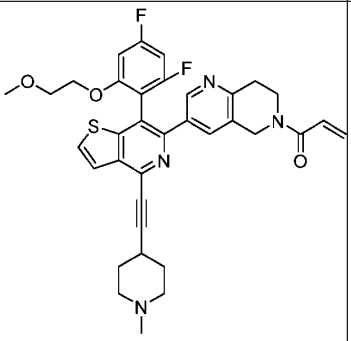
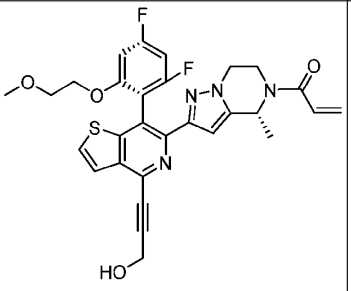
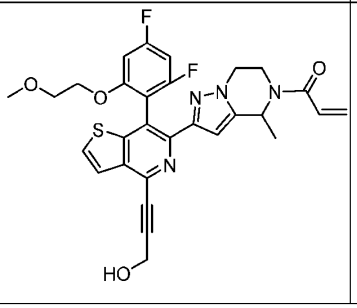
Cmpd. No.	Structure	Analytical data
		4.17 (m, 1H), 4.15 – 4.01 (m, 5H), 3.89 (s, 1H), 3.72 – 3.53 (m, 2H), 2.96 (s, 3H), 1.46 (s, 3H), 1.31 (s, 3H).
358a		
359		LCMS m/z [M+1]: 627.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.89 (d, J = 7.0 Hz, 1H), 8.39 (s, 1H), 7.95 (t, J = 4.9 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.58 – 7.47 (m, 1H), 7.14 (t, J = 6.8 Hz, 1H), 6.87 (dd, J = 16.3, 10.8 Hz, 2H), 6.73 (td, J = 9.2, 2.2 Hz, 1H), 6.41 – 6.19 (m, 2H), 5.84 (d, J = 10.6 Hz, 1H), 5.64 (d, J = 81.7 Hz, 1H), 4.42 (s, 1H), 4.26 – 4.17 (m, 1H), 4.07 (dtd, J = 15.4, 10.8, 4.4 Hz, 3H), 3.78 (s, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.48 (s, 3H).
359a		

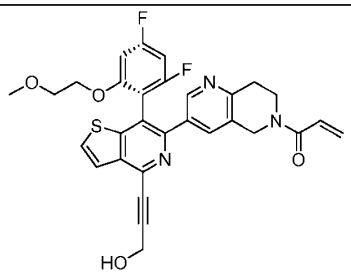
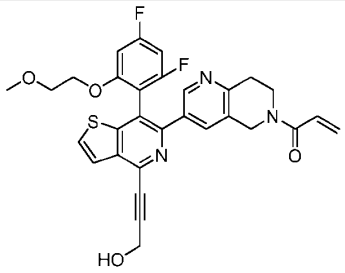
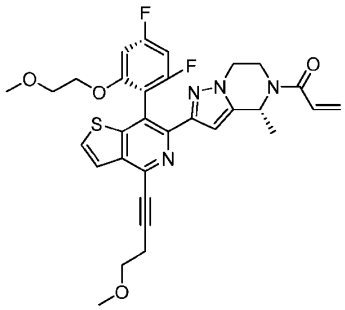
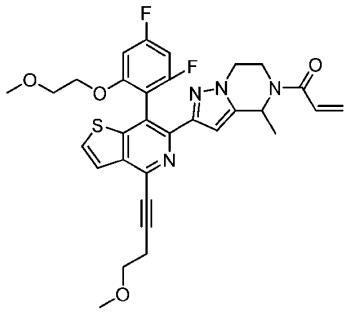
Cmpd. No.	Structure	Analytical data
360		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 7.8 Hz, 1H), 7.91 (s, 1H), 7.86 (s, 1H), 7.70 (s, 1H), 7.58 (d, J = 7.2 Hz, 1H), 6.92 (t, J = 11.2 Hz, 2H), 6.70 (s, 1H), 6.35 (d, J = 17.1 Hz, 1H), 6.26 (s, 1H), 5.87 (dd, J = 10.5, 1.6 Hz, 1H), 5.65 (d, J = 85.0 Hz, 1H), 4.93 (s, 2H), 4.81 (d, J = 15.4 Hz, 1H), 4.64 (d, J = 15.6 Hz, 1H), 4.47 (s, 1H), 4.28 (s, 1H), 4.08 (t, J = 4.8 Hz, 2H), 3.88 (s, 1H), 3.71 – 3.54 (m, 3H), 3.27 (s, 3H), 3.12 (s, 6H), 1.47 (d, J = 5.8 Hz, 3H), 1.29 (s, 3H).
360a		
361		LCMS m/z [M+1]: 707.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.28 (d, J = 1.6 Hz, 1H), 8.52 (dd, J = 8.0, 2.4 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 6.0 Hz, 2H), 6.93 – 6.79 (m, 2H), 6.76 – 6.70 (m, 1H), 6.35 - 6.24 (m, 1H), 6.16 (s, 1H), 5.82 (dd, J = 10.8, 1.6 Hz, 1H), 5.64 – 5.42 (m, 3H), 4.83 (s, 3H), 4.25 - 4.18 (m, 1H), 4.14 – 3.82 (m, 8H), 3.42 (t, J = 4.8 Hz, 2H), 3.04 (s, 3H), 1.53 – 1.37 (m, 3H).

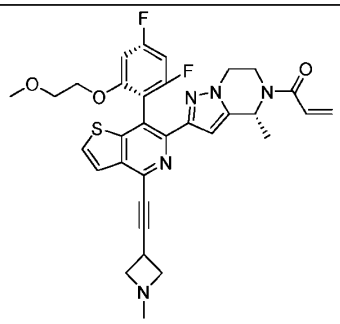
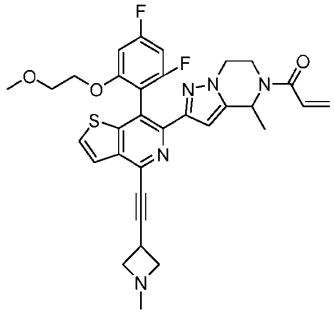
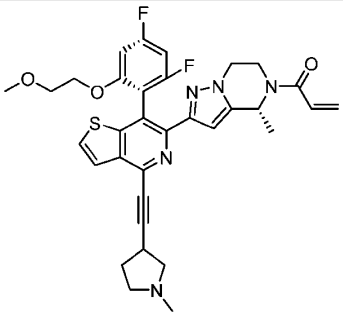
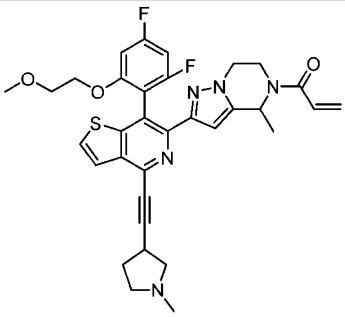
Cmpd. No.	Structure	Analytical data
361a		
362		LCMS m/z [M+1]: 626.9 ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (s, 1H), 8.08 (d, J = 5.7 Hz, 1H), 8.03 (d, J = 5.6 Hz, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 7.37 (s, 1H), 6.84 (d, J = 10.9 Hz, 1H), 6.81 – 6.71 (m, 1H), 6.67 (td, J = 9.2, 2.3 Hz, 1H), 6.20 (d, J = 16.1 Hz, 1H), 5.86 (s, 1H), 5.73 (dd, J = 10.6, 1.8 Hz, 1H), 5.49 (d, J = 76.2 Hz, 1H), 4.55 – 4.19 (m, 2H), 4.10 (s, 1H), 4.00 – 3.94 (m, 2H), 3.68 (d, J = 28.6 Hz, 1H), 3.30 (t, J = 4.6 Hz, 2H), 2.90 (d, J = 6.0 Hz, 3H), 1.32 (d, J = 12.8 Hz, 3H).
362a		

Cmpd. No.	Structure	Analytical data
363		LCMS m/z [M+1]: 592.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (d, J = 5.5 Hz, 1H), 7.71 (d, J = 5.5 Hz, 1H), 6.81 - 6.88 (m, 2H), 6.70 (td, J = 2.2, 9.3 Hz, 1H), 6.29 (d, J = 15.0 Hz, 1H), 6.08 (s, 1H), 5.83 (dd, J = 1.6, 10.6 Hz, 1H), 5.49 - 5.69 (m, 1H), 4.53 (s, 2H), 4.41 (s, 1H), 4.20 (dd, J = 2.8, 12.8 Hz, 1H), 3.98 - 4.08 (m, 3H), 3.40 (t, J = 4.6 Hz, 2H), 3.13 (s, 6H), 3.03 (s, 3H), 1.40 - 1.49 (m, 3H).
363a		
364		LCMS m/z [M+1]: 615.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.81 (s, 1H), 7.78 (d, J = 5.5 Hz, 1H), 7.72 (d, J = 5.5 Hz, 1H), 6.78-6.89 (m, 2H), 6.63-6.71 (m, 1H), 6.28 (d, J = 15.4 Hz, 1H), 6.14 (s, 1H), 5.81 (d, J = 10.6 Hz, 1H), 5.40-5.76 (m, 1H), 4.27-4.50 (m, 1H), 4.11-4.19 (m, 1H), 3.93-4.09 (m, 6H), 3.54-3.89 (m, 1H), 3.40 (t, J = 4.6 Hz, 2H), 3.02 (s, 3H), 1.37-1.54 (m, 3H).
364a		

Cmpd. No.	Structure	Analytical data
365		LCMS m/z [M+1]: 632.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (dd, J = 3.2, 5.6 Hz, 1H), 7.64 -7.71 (m, 1H), 6.79-6.89 (m, 2H), 6.65-6.73 (m, 1H), 6.28 (d, J = 15.0 Hz, 1H), 6.00-6.12 (m, 1H), 5.82 (d, J = 11.0 Hz, 1H), 5.42-5.76 (m, 1H), 4.14-4.27 (m, 1H), 3.93-4.13 (m, 3H), 3.44-3.67 (m, 4H), 3.40 (q, J = 4.4 Hz, 2H), 3.05-3.21 (m, 2H), 3.03 (d, J= 7.6 Hz, 3H), 2.93 (d, J= 13.8 Hz, 3H), 2.39-2.50 (m, 1H), 1.98-2.32 (m, 3H), 1.35-1.52 (m, 3H).
365a		
366		LCMS m/z [M+1]: 589.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 7.89 (d, J = 5.5 Hz, 1H), 7.83 – 7.74 (m, 2H), 6.95 – 6.79 (m, 2H), 6.76 – 6.63 (m, 1H), 6.28 (d, J = 16.8 Hz, 1H), 5.82 (d, J = 10.6 Hz, 1H), 4.83 (d, J = 22.4 Hz, 2H), 4.12 – 3.96 (m, 4H), 3.76 (s, 2H), 3.53 – 3.44 (m, 2H), 3.15 (s, 3H), 3.09 – 2.94 (m, 2H), 2.52 (s, 6H).
366a		

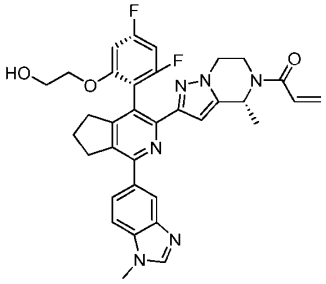
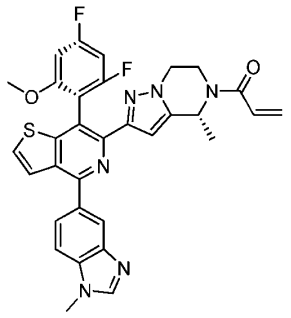
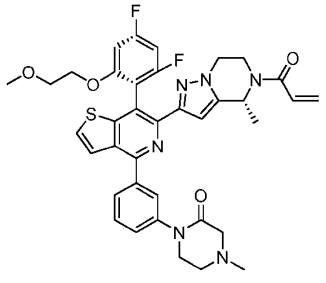
Cmpd. No.	Structure	Analytical data
367		LCMS m/z [M+1]: 629.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 7.75 (d, J = 5.5 Hz, 1H), 7.66 (d, J = 1.8 Hz, 1H), 7.59 (d, J = 5.5 Hz, 1H), 6.84 – 6.68 (m, 2H), 6.60 – 6.51 (m, 1H), 6.21 – 6.11 (m, 1H), 5.70 (d, J = 10.5 Hz, 1H), 4.70 (d, J = 20.5 Hz, 2H), 4.03 – 3.80 (m, 4H), 3.42 – 3.30 (m, 2H), 3.04 (s, 3H), 2.96 – 2.75 (m, 5H), 2.46 (s, 2H), 2.39 – 2.29 (m, 3H), 2.10 – 2.00 (m, 2H), 1.94 – 1.84 (m, 2H).
367a		
368		LCMS m/z [M+1]: 565.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, J = 5.6 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 6.71-6.96 (m, 3H), 6.20-6.38 (m, 1H), 6.05 (s, 1H), 5.83 (dd, J = 1.6, 10.4 Hz, 1H), 5.46-5.76 (m, 1H), 4.63 (s, 2H), 4.22-4.32 (m, 1H), 4.17-3.97 (m, 3H), 3.37-3.44 (m, 2H), 3.03 (s, 3H), 1.35-1.52 (m, 3H).
368a		

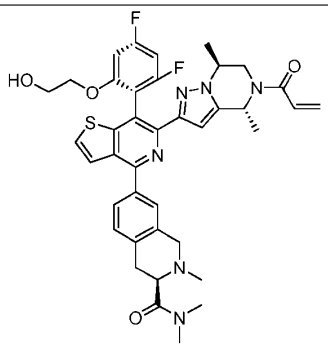
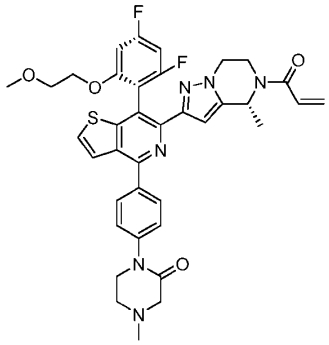
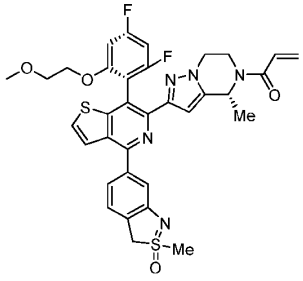
Cmpd. No.	Structure	Analytical data
369		LCMS m/z [M+1]: 562.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 7.75 (d, J = 5.5 Hz, 1H), 7.65 (d, J = 5.5 Hz, 2H), 6.82 – 6.67 (m, 2H), 6.60 – 6.51 (m, 1H), 6.15 (dd, J = 17.0, 6.4 Hz, 1H), 5.70 (d, J = 10.7 Hz, 1H), 4.70 (d, J = 21.6 Hz, 2H), 4.48 (s, 2H), 3.99 – 3.80 (m, 4H), 3.40 – 3.28 (m, 2H), 3.02 (s, 3H), 2.95 – 2.83 (m, 2H).
369a		
370		LCMS m/z [M+1]: 593.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 5.5 Hz, 1H), 7.66 (d, J = 5.5 Hz, 1H), 6.80-6.87 (m, 2H), 6.64-6.69 (m, 1H), 6.20-6.38 (m, 1H), 6.10 (s, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.40-5.73 (m, 1H), 4.06-4.16 (m, 1H), 3.93-4.03 (m, 3H), 3.71 (t, J = 6.6 Hz, 2H), 3.45 (s, 3H), 3.39 (t, J = 4.8 Hz, 2H), 3.01 (s, 3H), 2.87 (t, J = 6.6 Hz, 2H), 1.35-1.52 (m, 3H).
370a		

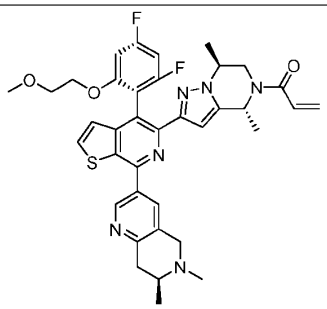
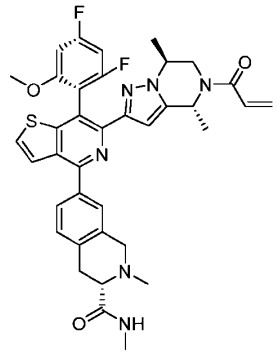
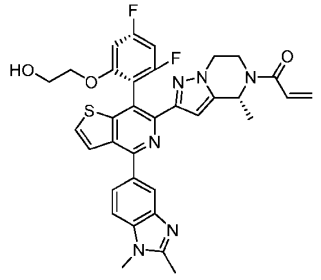
Cmpd. No.	Structure	Analytical data
371		LCMS m/z [M+1]: 604.1 ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (d, J = 5.4 Hz, 1H), 7.72 (d, J = 5.4 Hz, 1H), 6.87 (dd, J = 18.0, 9.0 Hz, 2H), 6.71 (t, J = 8.2 Hz, 1H), 6.39 – 6.25 (m, 1H), 6.12 (s, 1H), 5.84 (d, J = 10.6 Hz, 1H), 5.74 – 5.55 (m, 1H), 4.43 (d, J = 18.8 Hz, 1H), 4.32 – 4.11 (m, 4H), 4.08 – 3.97 (m, 5H), 3.77 (s, 1H), 3.42 (t, J = 4.2 Hz, 2H), 3.04 (s, 3H), 2.83 (s, 3H), 1.46 (d, J = 22.6 Hz, 3H).
371a		
372		LCMS m/z [M+1]: 618.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, J = 5.5 Hz, 1H), 7.56 (d, J = 5.5 Hz, 1H), 6.75 (dd, J = 16.4, 10.7 Hz, 2H), 6.60 – 6.55 (m, 1H), 6.20 (s, 1H), 6.01 (s, 1H), 5.72 (d, J = 10.7 Hz, 1H), 5.46 – 5.23 (m, 1H), 4.35 – 4.19 (m, 1H), 4.06 – 3.76 (m, 6H), 3.35 – 3.27 (m, 3H), 3.06 – 2.98 (m, 1H), 2.92 (s, 3H), 2.64 (dt, J = 15.7, 6.8 Hz, 3H), 2.34 (d, J = 6.1 Hz, 3H), 2.10 – 2.02 (m, 1H), 1.40 (s, 3H).
372a		

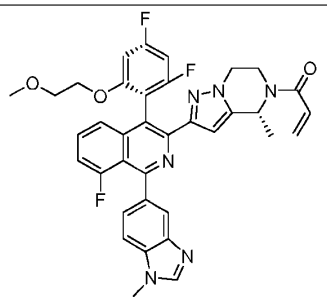
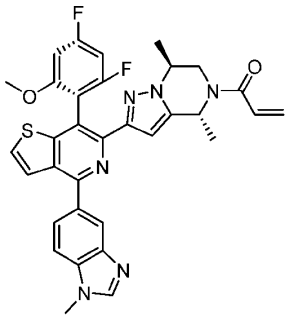
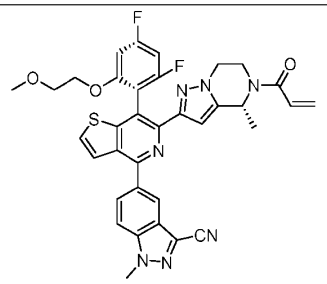
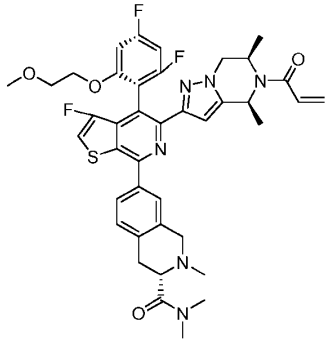
[000780] Table 2 includes additional selected compounds of the present disclosure.

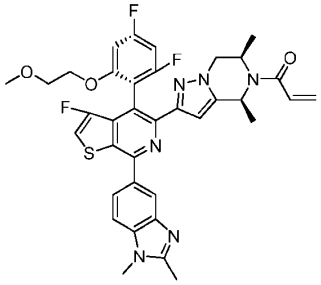
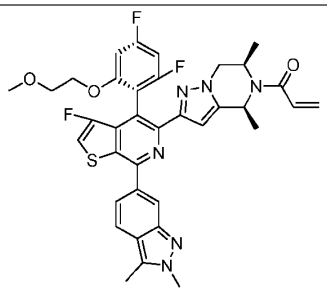
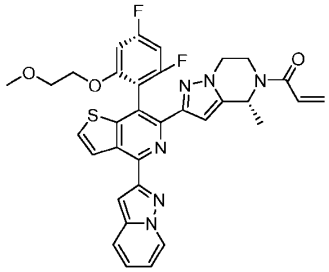
Table 2. Selected compounds of the present disclosure.

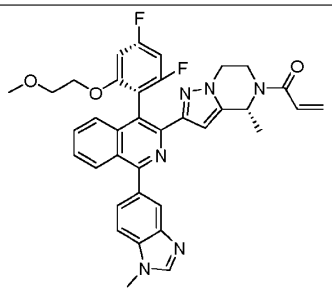
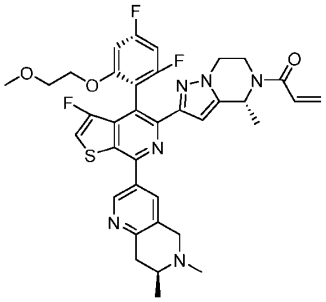
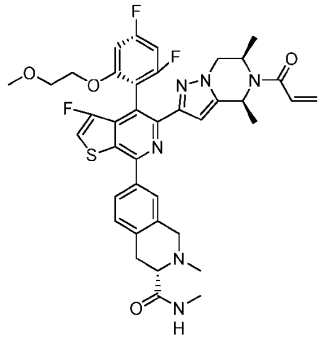
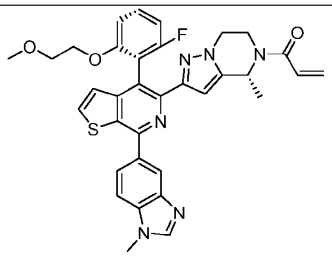
Cmpd. No.	Structure	Analytical data
373		LCMS m/z [M+1]: 611.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1H), 8.37 (s, 1H), 8.12 (d, J = 0.8 Hz, 2H), 7.00 – 6.67 (m, 3H), 6.31 (d, J = 16.0 Hz, 1H), 6.01 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.71 – 5.40 (m, 1H), 4.55 – 4.24 (m, 2H), 4.24 – 3.97 (m, 6H), 3.85 – 3.58 (m, 3H), 3.32 – 3.23 (m, 2H), 3.19 – 3.05 (m, 1H), 3.01 – 2.86 (m, 1H), 2.34 – 2.18 (m, 2H), 1.52 – 1.35 (m, 3H).
374		LCMS m/z [M+1]: 597.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 2H), 8.02 (dd, J = 8.4, 1.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 16.6, 5.6 Hz, 2H), 6.92 – 6.81 (m, 2H), 6.70 (td, J = 9.2, 2.2 Hz, 1H), 6.36 – 6.17 (m, 2H), 5.83 (dd, J = 10.6, 1.4 Hz, 1H), 5.76 – 5.46 (m, 1H), 4.85 – 4.80 (m, 1H), 4.56 – 4.06 (m, 2H), 4.02 (s, 3H), 3.85 – 3.64 (m, 4H), 1.46 (s, 3H).
375		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 – 7.96 (m, 2H), 7.84 (d, J = 5.6 Hz, 1H), 7.74 (dd, J = 13.3, 6.7 Hz, 2H), 7.59 (d, J = 8.5 Hz, 1H), 6.92 – 6.80 (m, 2H), 6.73 (td, J = 9.2, 2.2 Hz, 1H), 6.29 (d, J = 17.7 Hz, 1H), 6.12 (s, 1H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.71-5.48 (m, 1H), 4.43 (s, 1H), 4.18 – 4.02 (m, 7H), 3.80 (d, J = 5.5 Hz, 3H), 3.43 (t, J = 4.6 Hz, 2H), 3.10 (s, 3H), 3.05 (s, 3H), 1.53 - 1.32 (m, 3H).

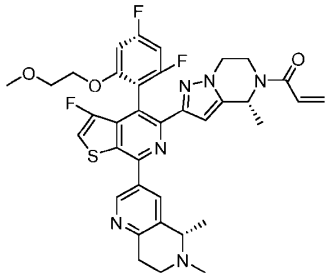
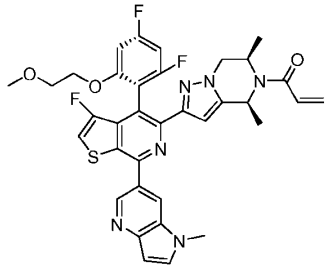
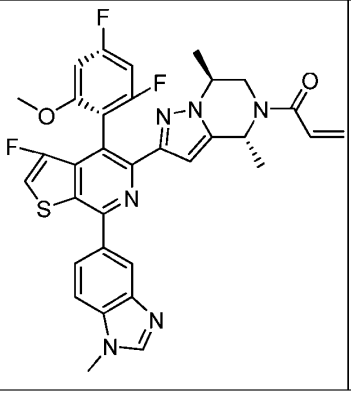
376		LCMS m/z [M+1]: 727.0 ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (d, J = 9.0 Hz, 1H), 7.88 (s, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 5.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 6.87 (dd, J = 23.9, 13.1 Hz, 2H), 6.70 – 6.64 (m, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.24 (s, 1H), 5.84 (dd, J = 10.6, 1.5 Hz, 1H), 5.63 (d, J = 87.5 Hz, 1H), 4.92 (dd, J =10.6, 5.4 Hz, 2H), 4.77 (d, J=15.5 Hz, 1H), 4.63 (d, J=15.4 Hz, 1H), 4.44 (s, 1H), 4.24 (d, J=15.0 Hz, 1H), 4.05 (t, J=4.7 Hz, 2H), 3.83 (d, J=29.7 Hz, 1H), 3.66 – 3.52 (m, 3H), 3.24 (s, 3H), 3.09 (s, 6H), 1.43 (s, 3H), 1.27 (d, J=6.3 Hz, 3H).
377		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 6.96 – 6.80 (m, 2H), 6.73 (td, J = 9.2, 2.2 Hz, 1H), 6.29 (d, J = 17.6 Hz, 1H), 6.14 (s, 1H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.71 -5.45 (m, 1H), 4.42 (s, 1H), 4.17 – 3.98 (m, 7H), 3.86 – 3.69 (m, 3H), 3.43 (t, J = 4.6 Hz, 2H), 3.10 (s, 3H), 3.05 (s, 3H), 1.53 - 1.32 (m, 3H).
378		LCMS m/z [M+1]: 676.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 5.6 Hz, 1H), 7.80 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.44 - 7.35 (m, 2H), 6.97 (d, J = 10.8 Hz, 1H), 6.90 - 7.76 (m, 2H), 6.38 - 6.21 (m, 1H), 6.06 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.79 - 5.40 (m, 1H), 5.19 - 5.07 (m, 1H), 4.77 - 4.68 (m, 1H), 4.36 - 4.25 (m, 1H), 4.22 - 3.96 (m, 3H), 3.57 (s, 3H), 3.44 (t, J = 4.5 Hz, 2H), 3.07 (s, 3H), 1.54 - 1.35 (m, 1H).

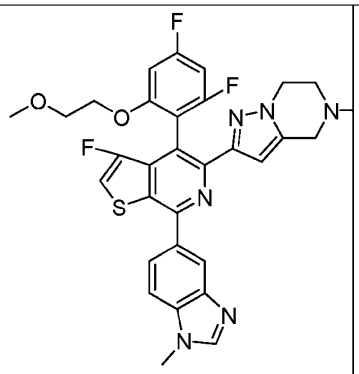
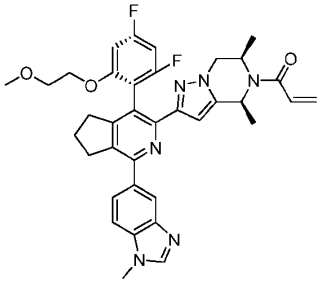
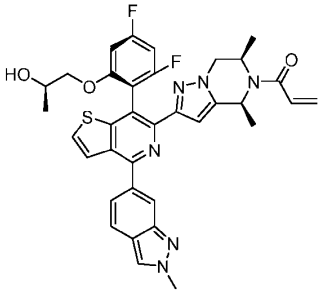
379		LCMS m/z [M+1]: 685.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (d, J = 2.2 Hz, 1H), 8.51 (d, J = 2.2 Hz, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.15 (d, J = 5.5 Hz, 1H), 6.91 - 6.80 (m, 2H), 6.67 (td, J = 9.2, 2.3 Hz, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.16 (s, 1H), 5.85 (dd, J = 10.5, 2.0 Hz, 1H), 5.75 - 5.62 (m, 1H), 4.78 - 4.60 (m, 2H), 4.47 - 4.39 (m, 1H), 4.22 (s, 1H), 4.15 – 4.08 (m, 1H), 4.02 - 3.95 (m, 1H), 3.92 - 3.77 (m, 1H), 3.57 - 3.45 (m, 2H), 3.42 (t, J = 4.6 Hz, 2H), 3.27 - 3.18 (m, 2H), 3.14 - 3.06 (m, 2H), 3.05 (s, 3H), 1.66 - 1.53 (m, 3H), 1.49 - 1.37 (m, 3H), 1.34 - 1.28 (m 3H).
380		LCMS m/z [M+1]: 683.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.85 (dd, J = 8.7, 5.6 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.57 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 9.8 Hz, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.35 (d, J = 16.7 Hz, 1H), 6.17 (s, 1H), 5.86 (dd, J = 10.6, 1.8 Hz, 1H), 5.64 (d, J = 88.9 Hz, 1H), 4.80 (d, J = 15.5 Hz, 2H), 4.65 (d, J = 15.5 Hz, 1H), 4.47 (s, 1H), 4.31 (s, 1H), 3.86 (s, 1H), 3.73 (s, 3H), 3.60 – 3.44 (m, 2H), 3.10 (d, J = 14.4 Hz, 3H), 2.91 (s, 3H), 1.45 (s, 3H), 1.32 (s, 3H).
381		LCMS m/z [M+1]: 641.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.74 – 7.63 (m, 3H), 6.84 (m, J = 16.1, 10.7 Hz, 2H), 6.67 (t, J = 8.4 Hz, 1H), 6.25 (s, 2H), 5.81 (d, J = 10.6 Hz, 1H), 5.60 (d, J = 82.0 Hz, 1H), 4.33 (d, J = 35.0 Hz, 1H), 4.17 (d, J = 12.3 Hz, 1H), 4.01 (s, 3H), 3.87 (s, 3H), 3.75 (s, 1H), 3.58 (m, J = 17.3, 6.2 Hz, 2H), 2.66 (s, 3H), 1.44 (s, 3H).

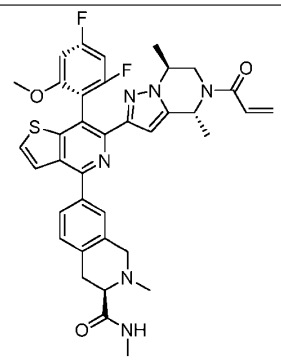
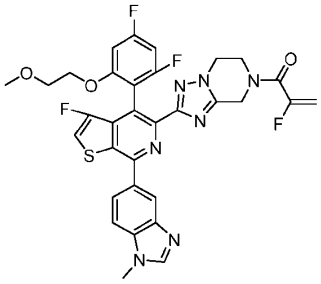
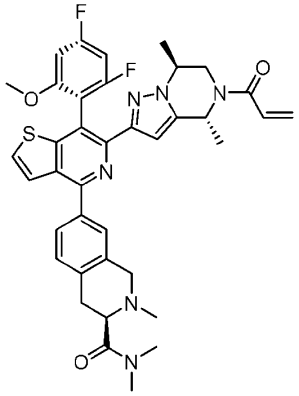
382		LCMS m/z [M+1]: 653.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.46 (s, 1H), 8.17 (s, 1H), 8.05 (d, J =8.8 Hz, 1H), 8.01 - 7.95 (m, 1H), 7.80 - 7.71 (m, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.39 - 7.30 (m, 1H), 6.94 (d, J = 11.2 Hz, 1H), 6.89 - 6.71 (m, 2H), 6.37 - 6.23 (m, 1H), 6.06 (s, 1H), 5.86 - 5.80 (m, 1H), 5.71 - 5.44 (m, 1H), 4.25 (s, 3H), 4.21 - 4.18 (m, 1H), 4.15 – 4.03 (m, 3H), 3.42 (t, J = 4.8 Hz, 2H), 3.03 (s, 3H), 1.53 - 1.36 (m, 3H).
383		LCMS m/z [M+1]: 611.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.30 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 5.5 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 10.9 Hz, 2H), 6.69 (t, J = 9.3 Hz, 1H), 6.34 (d, J = 17.0 Hz, 1H), 6.24 (s, 1H), 5.86 (d, J = 11.7 Hz, 1H), 5.75 (s, 1H), 4.43 (s, 1H), 4.32 – 3.79 (m, 5H), 3.74 (s, 3H), 1.45 (s, 3H), 1.31 (s, 3H).
384		LCMS m/z [M+1]: 666.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (s, 1H), 8.22 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.5 Hz, 1H), 6.97 – 6.81 (m, 2H), 6.75 (td, J = 9.3, 2.3 Hz, 1H), 6.33 (s, 1H), 6.16 (s, 1H), 5.84 (d, J = 10.5 Hz, 1H), 5.62 (d, J = 83.4 Hz, 1H), 4.67 – 4.21 (m, 5H), 4.20 – 3.61 (m, 4H), 3.46 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 1.44 (s, 3H).
385		LCMS m/z [M+1]: 759.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 7.8 Hz, 1H), 8.04 (s, 1H), 7.59 - 7.52 (m, 2H), 6.88 - 6.73 (m, 2H), 6.68 - 6.58 (m, 1H), 6.37 - 6.18 (m, 1H), 6.11 (s, 1H), 5.81 (d, J = 10.6 Hz, 1H), 5.51-5.33 (m, 1H), 4.94 - 4.88 (m, 1H), 4.79 - 4.73 (m, 3H), 4.68 - 4.52 (m, 1H), 4.26 - 4.12 (m, 2H), 4.11 - 4.02 (m, 1H), 4.00 - 3.88 (m, 1H), 3.59 (dd, J = 17.8 Hz, 5.2 Hz, 1H), 3.45 (t, J = 4.4 Hz,

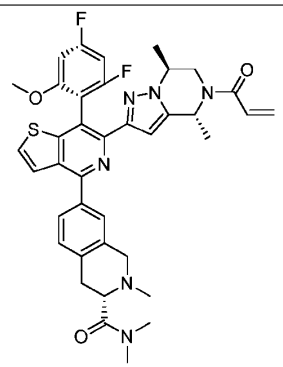
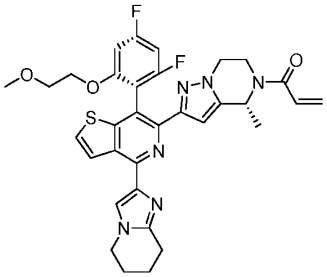
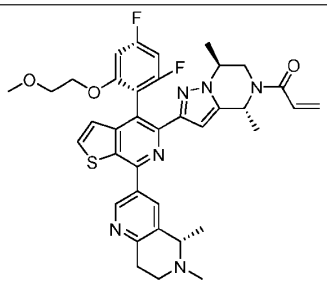
		2H), 3.24 (s, 3H), 3.09 (d, J = 1.2 Hz, 6H), 3.08 (s, 3H), 1.50 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H).
386		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J = 1.1 Hz, 1H), 8.06 (dd, J = 8.4, 1.5 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 6.88 – 6.72 (m, 2H), 6.66 – 6.59 (m, 1H), 6.34 –6.18 (m, 2H), 5.80 (d, J = 10.8 Hz, 1H), 5.52 – 5.40 (m, 1H), 4.20 - 4.03 (m, 3H), 3.98 – 3.91 (m, 1H), 3.88 (s, 3H), 3.46 (t, J = 4.7 Hz, 2H), 3.09 (s, 3H), 2.66 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H).
387		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.95 – 7.90 (m, 1H), 7.82 – 7.75 (m, 1H), 7.71 – 7.67 (m, 1H), 6.88 – 6.76 (m, 2H), 6.71 – 6.63 (m, 1H), 6.34 – 6.20 (m, 1H), 6.16 (s, 1H), 5.81 (d, J = 10.1 Hz, 1H), 5.52 – 5.41 (m, 1H), 4.25 – 4.13 (m, 5H), 4.12 – 4.05 (m, 1H), 3.99 – 3.92 (m, 1H), 3.47 (t, J = 4.6 Hz, 2H), 3.10 (s, 3H), 2.74 (s, 3H), 1.51 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).
388		LCMS m/z [M+1]: 627.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.67 (dd, J = 12.2, 6.3 Hz, 2H), 7.73 (dd, J = 19.9, 12.2 Hz, 2H), 7.54 (s, 1H), 7.26 (dd, J = 8.3, 7.3 Hz, 1H), 6.95 (t, J = 6.9 Hz, 1H), 6.91 – 6.79 (m, 2H), 6.71 (td, J = 9.2, 2.3 Hz, 1H), 6.30 (s, 2H), 5.84 (d, J = 11.4 Hz, 1H), 5.64 (d, J = 82.2 Hz, 1H), 4.74 – 4.13 (m, 2H), 4.12 – 3.51 (m, 4H), 3.42 (t, J = 4.6 Hz, 2H), 3.08 – 2.95 (m, 3H), 1.45 (dd, J = 34.3, 12.8 Hz, 3H).

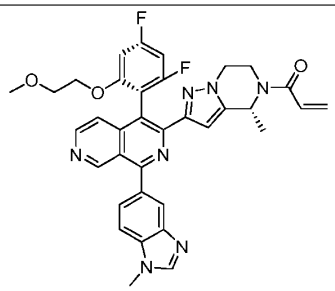
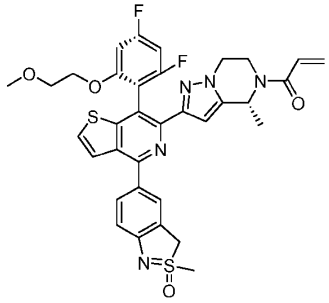
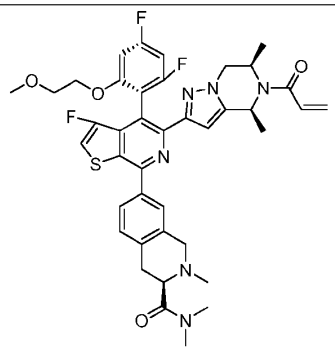
389		LCMS m/z [M+1]: 635.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (s, 1H), 8.16 - 8.09 (m, 2H), 7.88 (s, 2H), 7.77 - 7.70 (m, 1H), 7.66 - 7.56 (m, 2H), 6.92 - 6.78 (m, 2H), 6.71 (td, J = 9.1, 2.2 Hz, 1H), 6.29 (d, J = 16.7 Hz, 1H), 6.04 (s, 1H), 5.82 (dd, J = 10.6, 1.5 Hz, 1H), 5.75 - 5.43 (m, 1H), 4.25 - 4.17 (dd, J = 12.8, 2.9 Hz, 1H), 4.12 - 3.98 (m, 6H), 3.39 (t, J = 4.9 Hz, 2H), 2.98 (s, 3H), 1.51 - 1.35 (m, 3H), 1.34-1.22 (m, 2H).
390		LCMS m/z [M+1]: 689.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.32 (s, 1H), 8.48 (s, 1H), 7.61 (s, 1H), 6.82 (d, J = 10.8 Hz, 2H), 6.66 – 6.61 (m, 1H), 6.3 (d, J = 16 Hz, 1H), 6.05 (s, 1H), 5.83 (d, J = 10.4 Hz, 1H), 5.69 - 5.45 (m, 1H), 4.41 (s, 1H), 4.22 (d, J = 12.8 Hz, 1H), 4.17-4.02 (m, 4H), 3.81-3.72 (m, 1H), 3.59-3.44 (m, 3H), 3.29-3.22 (m, 2H), 3.20-3.01(m, 6H), 1.58 (d, J = 4.4 Hz, 3H), 1.53-1.35 (m, 3H).
391		LCMS m/z [M+1]: 745.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (dd, J = 7.9, 1.5 Hz, 1H), 8.04 (s, 1H), 7.58 - 7.52 (m, 2H), 6.88 - 6.74 (m, 2H), 6.64 (td, J = 9.2, 2.2 Hz, 1H), 6.28 (s, 1H), 6.16 - 6.06 (m, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.45 (d, J = 4.2 Hz, 1H), 4.82 - 4.73 (m, 3H), 4.64 (d, J = 15.4 Hz, 1H), 4.36 - 4.03 (m, 4H), 3.98 - 3.90 (m, 1H), 3.57 - 3.42 (m, 4H), 3.10 - 3.07 (m, 6H), 2.90 - 2.87 (m, 3H), 1.51 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).
392		LCMS m/z [M+1]: 623.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.25 (s, 1H), 8.20 (dd, J = 8.5, 1.5 Hz, 1H), 7.92 (d, J = 5.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.45 (dd, J = 15.1, 8.3 Hz, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.87 – 6.76 (m, 2H), 6.27 (d, J = 16.7 Hz, 1H), 6.00 (s, 1H), 5.81 (dd, J = 10.6, 1.7 Hz, 1H), 5.71 – 5.42 (m,

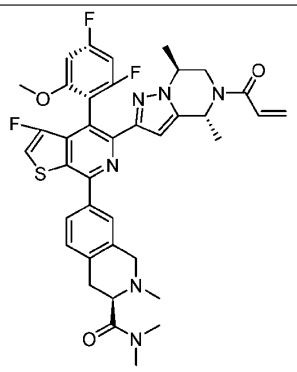
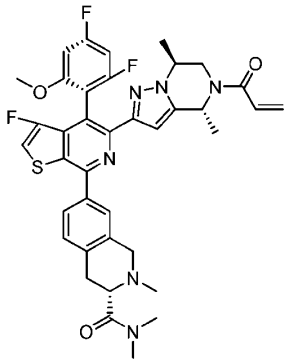
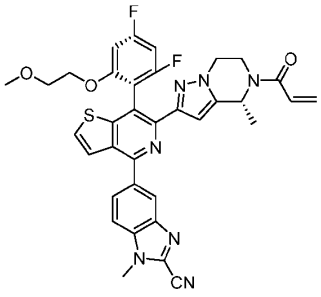
		1H), 4.21 (dd, J = 12.4, 2.9 Hz, 1H), 4.13 – 3.94 (m, 7H), 3.43 (t, J = 4.7 Hz, 2H), 3.04 (s, 3H), 1.52 – 1.35 (m, 3H).
393		LCMS m/z [M+1]: 689.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.6 Hz, 1H), 8.55 (s, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.85 - 6.81 (m, 2H), 6.64 - 6.61 (m, 1H), 6.30 (d, J = 12.0 Hz, 1H), 6.02 (s, 1H), 5.83 (dd, J = 10.4, 1.6 Hz, 1H), 5.65 – 5.45 (m, 1H), 4.24 (dd, J = 12.8, 2.8 Hz, 1H), 4.11 – 4.01 (m, 3H), 3.95 (s, 1H), 3.73 (s, 2H), 3.46 – 3.42 (m, 4H), 3.32 (s, 2H), 3.12 (s, 2H), 3.09 (s, 2H), 1.85 (d, J = 4.0 Hz, 3H), 1.53 - 1.35 (m, 3H).
394		LCMS m/z [M+1]: 673.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.42 (d, J = 10.4 Hz, 2H), 8.23 (d, J = 3.2 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.87 – 6.80 (m, 2H), 6.72 - 6.67 (m, 1H), 6.27 (s, 1H), 6.05 (s, 1H), 5.82 (d, J = 11.2 Hz, 1H), 5.45 (s, 1H), 4.27 - 4.18 (m, 5H), 4.13-4.09 (m, 1H), 4.08-3.93 (m, 1H), 3.46-3.44 (m, 2H), 3.11 (s, 3H), 1.50 (d, J = 6.4 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H).
395		LCMS m/z [M+1]: 629.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.45 (s, 1H), 8.59 (s, 1H), 8.46 (dd, J = 8.8, 1.6 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.94 - 6.74 (m, 2H), 6.65 - 6.56 (m, 1H), 6.37- 6.28 (m, 1H), 6.10 (s, 1H), 5.85 (dd, J = 10.4, 1.6 Hz, 1H), 5.75 - 5.51 (m, 1H), 4.48 - 4.39 (m, 1H), 4.23 (s, 3H), 3.71 (s, 3H), 1.52 -1.38 (m, 3H), 1.34 - 1.24 (m, 3H).

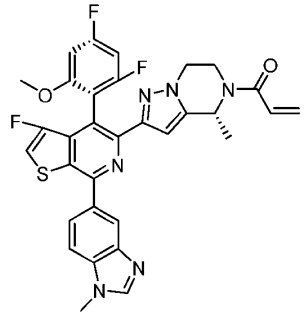
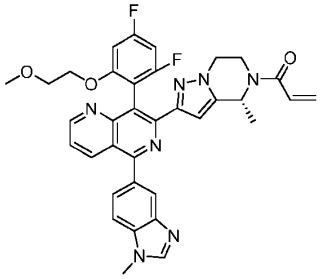
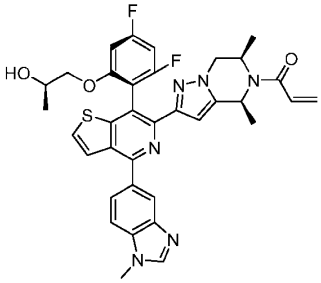
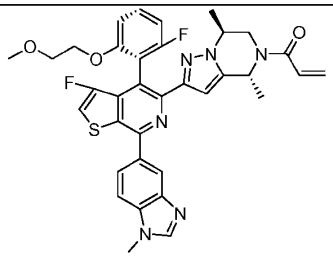
396		LCMS m/z [M+1]: 663.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1H), 8.26 (s, 1H), 8.13 (dd, J = 8.4, 1.3 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.5 Hz, 1H), 6.79 - 6.74 (m, 1H), 6.65 - 6.58 (m, 1H), 6.17 (s, 1H), 5.40 - 5.31 (m, 1H), 5.29 - 5.26 (m, 1H), 4.23 - 4.14 (m, 2H), 4.12 - 4.04 (m, 3H), 4.03 - 3.97 (m, 4H), 3.45 (t, J = 4.7 Hz, 2H), 3.06 (s, 3H).
397		LCMS m/z [M+1]: 639.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 8.14 (s, 1H), 7.95 - 7.91 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 6.87 - 6.71 (m, 2H), 6.64 - 6.56 (m, 1H), 6.37 - 6.18 (m, 1H), 6.15 (s, 1H), 5.80 (d, J = 10.2 Hz, 1H), 5.51 - 5.37 (m, 1H), 4.18 - 4.04 (m, 3H), 3.99 - 3.89 (m, 4H), 3.54 (t, J = 4.6 Hz, 2H), 3.26 - 3.20 (m, 5H), 2.92 - 2.69 (m, 2H), 2.18 - 2.06 (m, 2H), 1.50 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H).
398		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.30 (s, 1H), 8.11 (t, J = 7.6 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.86 (t, J = 6.1 Hz, 1H), 7.66 (dd, J = 8.6, 1.3 Hz, 1H), 6.97 (d, J = 10.9 Hz, 1H), 6.87 – 6.78 (m, 2H), 6.35 – 6.16 (m, 2H), 5.82 (d, J = 10.8 Hz, 1H), 5.49 (d, J = 6.2 Hz, 1H), 4.34 (s, 3H), 4.30 – 4.17 (m, 2H), 3.94 – 3.78 (m, 3H), 1.51 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 8.1 Hz, 3H).

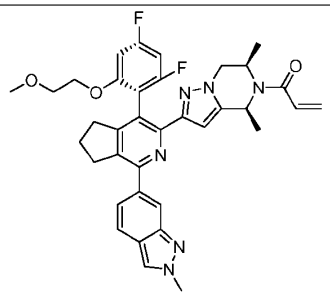
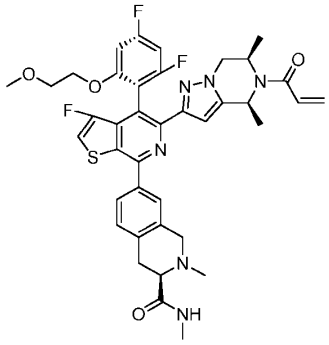
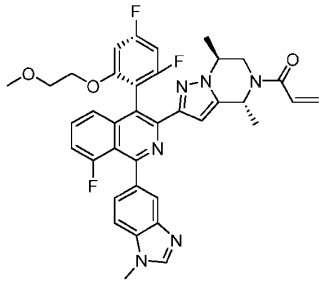
399		LCMS m/z [M+1]: 683.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 – 7.88 (m, 3H), 7.72 (d, J = 5.7 Hz, 1H), 7.60 (d, J = 6.9 Hz, 1H), 6.95 – 6.85 (m, 2H), 6.73 (d, J = 8.0 Hz, 1H), 6.35 (d, J = 16.6 Hz, 1H), 6.15 (s, 1H), 5.87 (dd, J = 10.6, 1.7 Hz, 1H), 5.64 (d, J = 86.6 Hz, 1H), 4.81 (d, J = 15.8 Hz, 3H), 4.66 (d, J = 15.8 Hz, 1H), 4.49 (s, 1H), 4.32 (s, 1H), 3.90 (s, 1H), 3.74 (s, 1H), 3.58 – 3.46 (m, 3H), 3.12 (s, 3H), 2.91 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H).
400		LCMS m/z [M+1]: 644.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.64 (s, 1H), 8.52 (s, 1H), 8.27 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.76 - 6.69 (m, 1H), 6.64 - 6.56 (m, 1H), 5.47 - 5.29 (m, 2H), 4.92 (s, 2H), 4.22 - 4.10 (m, 4H), 4.07 (s, 3H), 4.04 (t, J = 5.0 Hz, 1H), 3.99 - 3.93 (m, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.06 (s, 3H).
401		LCMS m/z [M+1]: 697.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.82 (d, J = 5.5 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 10.6 Hz, 2H), 6.74 – 6.65 (m, 1H), 6.35 (d, J = 16.5 Hz, 1H), 6.18 (s, 1H), 5.87 (m, J = 10.6, 1.7 Hz, 1H), 5.66 (d, J = 76.6 Hz, 1H), 4.94 (m, J = 10.6, 5.4 Hz, 1H), 4.80 (d, J = 15.5 Hz, 2H), 4.65 (d, J = 15.4 Hz, 1H), 4.46 (s, 1H), 4.24 (t, J = 34.0 Hz, 1H), 3.74 (s, 3H), 3.27 (s, 3H), 3.12 (s, 6H), 2.68 (s, 2H), 1.45 (s, 3H), 1.31 (s, 3H).

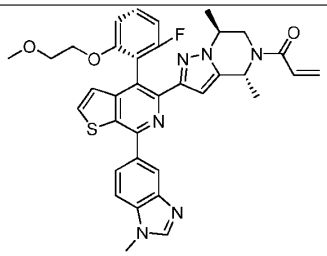
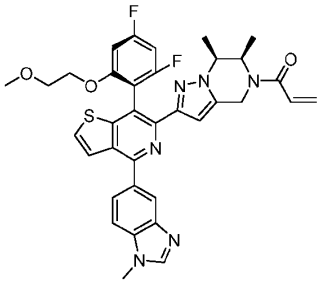
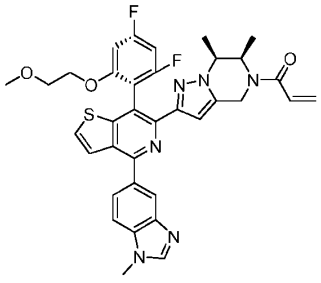
402		LCMS m/z [M+1]: 697.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, J = 7.9 Hz, 1H), 7.74 – 7.69 (m, 2H), 7.67 – 7.62 (m, 1H)., 7.38 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 10.8 Hz, 2H), 6.73 – 6.58 (m, 1H), 6.34 (d, J = 16.7 Hz, 1H), 6.21 (s, 1H), 5.85 (d, J = 10.7 Hz, 1H), 5.63 (d, J = 86.0 Hz, 1H), 4.49 – 4.12 (m, 3H), 4.07 – 3.79 (m, 3H), 3.72 (s, 3H), 3.31 – 3.19 (m, 4H), 3.13 – 2.98 (m, 4H), 2.52 (s, 3H), 1.46 (d, J = 9.3 Hz, 3H), 1.29 (s, 3H).
403		LCMS m/z [M+1]: 631.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.03 – 7.91 (m, 2H), 7.00 (d, J = 10.8 Hz, 1H), 6.82 (t, J = 9.1 Hz, 2H), 6.32 (d, J = 15.8 Hz, 1H), 5.86 (dd, J = 10.6, 1.7 Hz, 1H), 5.78 (s, 1H), 5.58 (d, J = 79.2 Hz, 1H), 4.59 – 4.17 (m, 5H), 4.14 – 4.04 (m, 2H), 3.84 (s, 1H), 3.44 – 3.37 (m, 2H), 3.24 (t, J = 6.1 Hz, 2H), 3.00 (s, 3H), 2.27 – 2.09 (m, 4H), 1.43 (s, 3H).
404		LCMS m/z [M+1]: 685.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (d, J = 2.1 Hz, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.00 (d, J = 5.5 Hz, 1H), 7.15 (d, J = 5.5 Hz, 1H), 6.95 - 6.80 (m, 2H), 6.67 (td, J = 9.2, 2.4 Hz, 1H), 6.37 - 6.29 (m, 1H), 6.13 (s, 1H), 5.87 - 5.78 (m, 1H), 5.73 - 5.47 (m, 1H), 4.80 - 4.60(m, 2H), 4.48 - 4.40 (m, 1H), 4.37 - 4.18 (m, 1H), 4.15 – 4.07 (m, 1H), 4.01 – 3.96 (m, 1H), 3.93 - 3.83 (m, 1H), 3.75 - 3.69 (m, 1H), 3.49 – 3.39 (m, 4H), 3.17 - 3.07 (m, 3H), 3.06 (s, 3H), 1.96 - 1.75 (m, 3H), 1.50 - 1.37 (m, 3H), 1.35 - 1.26 (m, 3H).

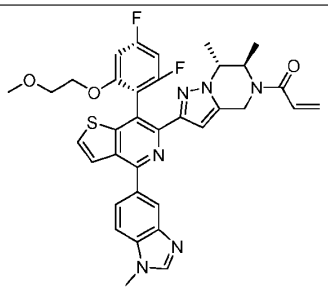
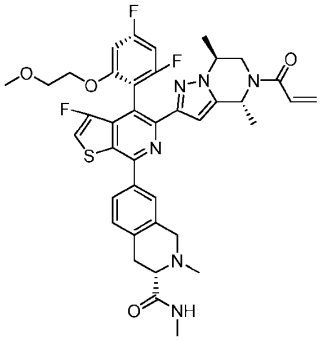
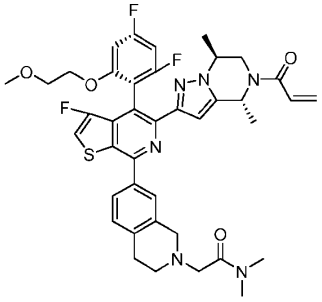
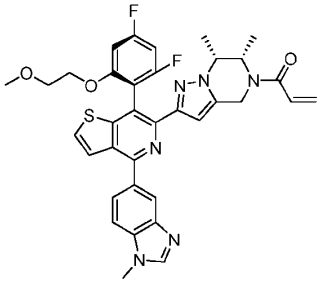
405		LCMS m/z [M+1]: 636.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.46 (d, J = 11.8 Hz, 2H), 8.66 (d, J = 6.2 Hz, 1H), 8.38 (s, 1H), 8.23 – 8.12 (m, 2H), 7.61 (d, J = 6.2 Hz, 1H), 6.95 (d, J = 10.7 Hz, 1H), 6.89 – 6.72 (m, 2H), 6.28 (d, J = 10.6 Hz, 2H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.25 (s, 3H), 4.22 – 3.97 (m, 4H), 3.39 (t, J = 4.5 Hz, 2H), 3.01 (s, 3H), 1.52 – 1.35 (m, 3H).
406		LCMS m/z [M+1]: 676.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 5.6 Hz, 1H), 7.97(s, 1H), 7.94 (d, J = 5.6 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.16(d, J = 8.3 Hz, 1H), 7.01(d, J = 9.6 Hz, 1H), 6.92- 7.76 (m, 2H), 6.38 - 6.21 (m, 1H), 5.99 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.79 - 5.40 (m, 1H), 5.19 - 5.10 (m, 1H), 4.81 - 4.71 (m, 1H), 4.41 - 4.32 (m, 1H), 4.28 - 4.03 (m, 3H), 3.60 (s, 3H), 3.48 - 3.40 (m, 2H), 3.08 (s, 3H), 1.54 - 1.35 (m, 1H)
407		LCMS m/z [M+1]: 759.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.57 - 7.55 (m, 2H), 6.87 - 6.77 (m, 2H), 6.65 - 6.57 (m, 1H), 6.41 (s, 1H), 6.12 (s, 1H), 5.81 (d, J = 10.4 Hz, 1H), 5.49 (s, 2H), 4.77 (s, 1H), 4.64 (d, J = 15.2 Hz, 1H), 4.25 - 4.05 (m, 3H), 3.96 - 3.91 (m, 1H), 3.60 (dd, J = 17.6, 5.2 Hz, 1H), 3.48-3.42 (m, 2H), 3.34 (s, 1H), 3.27 (s, 3H), 3.10 (s, 5H), 3.09 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H).

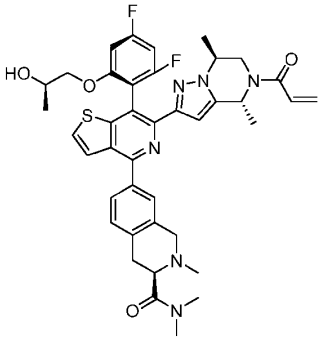
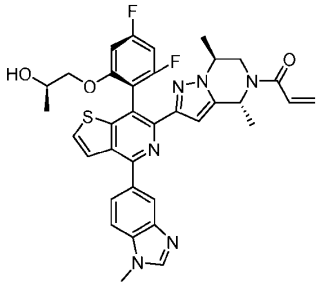
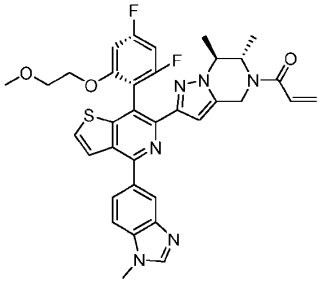
408		LCMS m/z [M+1]: 715.1 ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 - 7.89 (m, 1H), 7.85 (s, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 6.93 - 6.78 (m, 1H), 6.76 - 6.70 (m, 1H), 6.61-6.53 (m, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.13 - 6.05 (m, 1H), 5.84 (dd, J = 10.8, 1.6 Hz, 1H), 5.75 - 5.49 (m, 1H), 4.63 - 4.51 (m, 1H), 4.45 - 4.36 (m, 1H), 4.21 (d, J = 15.6 Hz, 1H), 4.05 - 3.91 (m, 2H), 3.69 (s, 3H), 3.25 (s, 3H), 3.24 - 3.18 (m, 1H), 3.14 - 3.05 (m, 1H), 3.02 (s, 3H), 2.52 (s, 3H), 1.52 - 1.37 (m, 3H), 1.30 - 1.22 (m, 3H).
409		LCMS m/z [M+1]: 715.1 ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 - 7.89 (m, 1H), 7.85 (s, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 6.93 - 6.78 (m, 1H), 6.76 - 6.70 (m, 1H), 6.61 - 6.53 (m, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.13 - 6.05 (m, 1H), 5.84 (dd, J = 10.8, 1.6 Hz, 1H), 5.75 - 5.49 (m, 1H), 4.63 - 4.51 (m, 1H), 4.45 - 4.36 (m, 1H), 4.21 (d, J = 15.6 Hz, 1H), 4.05 – 3.91 (m, 2H), 3.69 (s, 3H), 3.25 (s, 3H), 3.24 - 3.18 (m, 1H), 3.14 - 3.05 (m, 1H), 3.02 (s, 3H), 2.52 (s, 3H), 1.52 - 1.37 (m, 3H), 1.30 - 1.22 (m, 3H).
410		LCMS m/z [M+1]: 666.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.21 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 6.86 (dd, J = 16.8, 10.6 Hz, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.36 – 6.17 (m, 2H), 5.83 (d, J = 10.7 Hz, 1H), 5.62 (d, J = 80.3 Hz, 1H), 4.60 – 3.59 (m, 9H), 3.46 (t, J = 4.6 Hz, 2H), 3.06 (s, 3H), 1.46 (s, 3H).

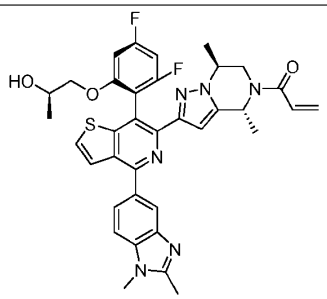
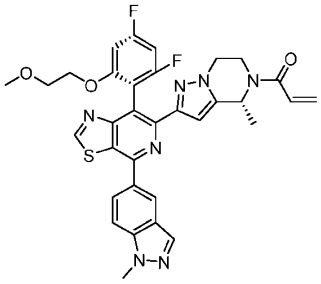
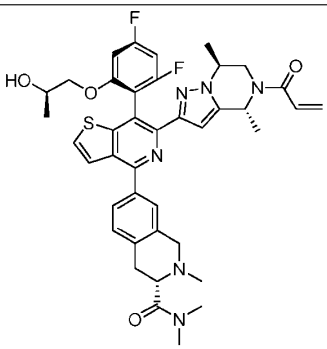
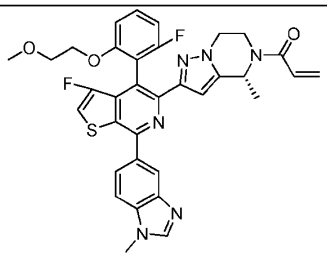
411		LCMS m/z [M+1]: 615.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.37 (s, 1H), 8.58 (d, J = 0.8 Hz, 1H), 8.43 (dd, J = 8.8 Hz, 1.4 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 6.92 - 6.73 (m, 2H), 6.71 - 6.52 (m, 1H), 6.38 - 6.20 (m, 1H), 6.02 (s, 1H), 5.82 (dd, J = 10.6 Hz, 1.8 Hz, 1H), 5.74 - 5.25 (m, 1H), 4.21 (s, 4H), 3.70 (s, 3H), 1.54 - 1.34 (m, 3H).
412		LCMS m/z [M+1]: 636.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.40 (s, 1H), 9.03 (dd, J = 4.2, 1.6 Hz, 1H), 8.51 (dd, J = 8.5, 1.6 Hz, 1H), 8.30 (s, 1H), 8.16 – 8.07 (m, 2H), 7.65 (dd, J = 8.4, 4.2 Hz, 1H), 6.90 – 6.79 (m, 2H), 6.74 – 6.66 (m, 1H), 6.29 (d, J = 16.9 Hz, 1H), 6.09 (d, J = 6.6 Hz, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.29 – 4.20 (m, 4H), 4.14 – 3.89 (m, 3H), 3.38 – 3.34 (m, 2H), 3.02 – 2.98 (m, 3H), 1.52 – 1.35 (m, 3H).
413		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (s, 1H), 8.42 (s, 1H), 8.27 (dd, J = 8.6, 1.4 Hz, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.92 – 6.79 (m, 2H), 6.72 (td, J = 9.2, 2.1 Hz, 1H), 6.37 – 6.18 (m, 2H), 5.81 (d, J = 10.8 Hz, 1H), 5.53 – 5.43 (m, 1H), 4.22 (s, 3H), 4.18 – 4.09 (m, 2H), 3.90 – 3.77 (m, 3H), 1.53 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H).
414		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.19 (s, 1H), 8.57 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.46-7.40 (m, 1H), 6.95 (d, J = 12.1 Hz, 1H), 6.89-6.75 (m, 2H), 6.32 (d, J = 16.8 Hz, 1H), 5.96 (s, 1H), 5.83 (dd, J = 10.8, 1.8 Hz,), 5.73 - 5.35 (m, 1H), 4.48 (s, 1H), 4.13-4.01 (m, 3H), 3.49-3.46 (m, 2H), 3.09 (s, 3H), 1.43-1.29 (m, 6H).

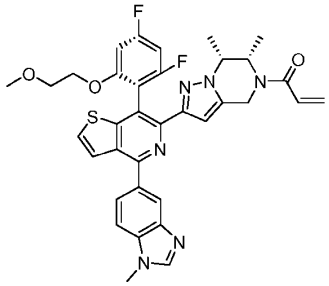
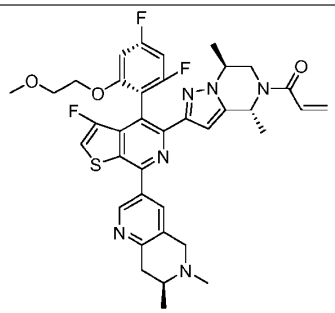
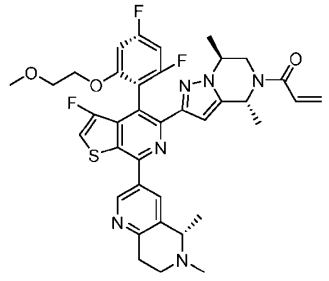
415		LCMS m/z [M+1]: 639.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 8.15 - 8.13 (m, 1H), 8.03 - 7.98 (m, 1H), 7.49 (dd, J = 8.6, 1.4 Hz, 1H), 6.96 - 6.90 (m, 1H), 6.87 - 6.76 (m, 2H), 6.27 (d, J = 15.3 Hz, 1H), 6.02 (s, 1H), 5.81 (dd, J = 12.1, 1.5 Hz, 1H), 5.52 - 5.39 (m, 1H), 4.36 - 4.15 (m, 6H), 4.04 - 3.95 (m, 1H), 3.58 - 3.53 (m, 2H), 3.42 - 3.32 (m, 2H), 3.27 (s, 3H), 3.18 - 2.98 (m, 2H), 2.35 - 2.22 (m, 2H), 1.47 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).
416		LCMS m/z [M+1]: 745.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (dd, J = 7.9, 1.8 Hz, 1H), 8.04 (s, 1H), 7.60 – 7.51 (m, 2H), 6.88 – 6.75 (m, 2H), 6.64 (td, J = 9.2, 2.3 Hz, 1H), 6.35 - 6.18 (m, 1H), 6.16 - 6.07 (m, 1H), 5.81 (d, J = 10.6 Hz, 1H), 5.48 - 5.39 (m, 1H), 4.81 - 4.74 (m, 3H), 4.67 - 4.57 (m, 1H), 4.30 - 4.20 (m, 1H), 4.19 – 4.04 (m, 3H), 3.98 - 3.90 (dt, J = 10.9, 4.3 Hz, 1H), 3.56 – 3.41 (m, 4H), 3.14 - 3.02 (m, 6H), 2.89 (s, 3H), 1.51 (d, J = 6.7 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H).
417		LCMS m/z [M+1]: 667.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.45 (s, 1H), 8.15 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 1.2 Hz, 1H), 7.74 - 7.71 (m, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.35 – 7.30 (m, 1H), 6.93 – 6.82 (m, 2H), 6.71 – 6.69 (m, 1H), 6.34 (d, J = 8.0 Hz, 1H), 6.11 (s, 1H), 5.83 (dd, J = 2.8, 2.0 Hz, 1H), 5.69 – 5.43 (m, 1H), 4.42 (s, 1H), 4.25 (s, 3H), 4.17 – 4.03 (m, 2H), 3.43 – 3.40 (m, 2H), 3.02 (s, 3H), 1.40 (s, 3H), 1.29 (s, 3H).

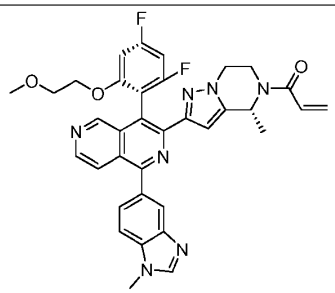
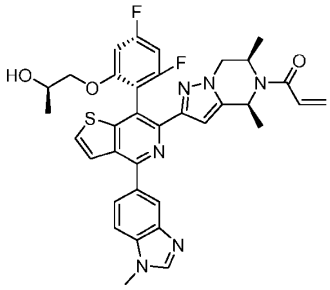
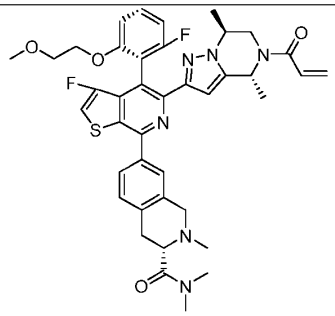
418		LCMS m/z [M+1]: 637.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.32 (s, 1H), 8.63 (s, 1H), 8.48 (dd, J = 8.6, 1.5 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 5.5 Hz, 1H), 7.49 (dd, J = 15.1, 8.4 Hz, 1H), 7.15 (d, J = 5.6 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.86 (dd, J = 17.7, 9.5 Hz, 2H), 6.32 (d, J = 16.6 Hz, 1H), 5.99 (s, 1H), 5.84 (dd, J = 10.6, 1.8 Hz, 1H), 5.75 -5.46 (m, 1H), 4.49 (s, 1H), 4.21 (s, 3H), 4.16 – 4.10 (m, 1H), 4.07 – 3.99 (m, 1H), 3.87 (s, 1H), 3.52 – 3.38 (m, 3H), 3.06 (s, 3H), 1.53 - 1.28 (m, 3H).
419		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 – 8.22 (m, 2H), 8.02 – 7.96 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.71 (q, J = 5.6 Hz, 2H), 6.82 (d, J = 10.9 Hz, 2H), 6.73 (td, J = 9.3, 2.3 Hz, 1H), 6.69 (s, 1H), 6.29 (dd, J = 16.7, 1.7 Hz, 1H), 5.85 – 5.78 (m, 1H), 5.16 (t, J = 37.4 Hz, 1H), 4.67 (d, J = 63.1 Hz, 1H), 4.52 – 4.17 (m, 2H), 4.11 – 3.96 (m, 4H), 3.95 – 3.88 (m, 1H), 3.45 – 3.37 (m, 2H), 3.03 (s, 3H), 1.35 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 10.5 Hz, 3H).
420		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 3.6 Hz, 2H), 7.88 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.59 (q, J = 5.6 Hz, 2H), 6.74 (d, J = 10.9 Hz, 2H), 6.58 (dd, J = 9.2, 2.3 Hz, 1H), 6.54 (s, 1H), 6.16 (dd, J = 16.7, 1.7 Hz, 1H), 5.69 (dd, J = 10.6, 1.7 Hz, 1H), 5.00 (d, J = 55.7 Hz, 1H), 4.55 (d, J = 55.8 Hz, 1H), 4.40 – 4.06 (m, 2H), 4.02 – 3.95 (m, 1H), 3.95 – 3.81 (m, 4H), 3.32 (dd, J = 10.6, 5.8 Hz, 2H), 2.91 (s, 3H), 1.25 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 20.2 Hz, 3H).

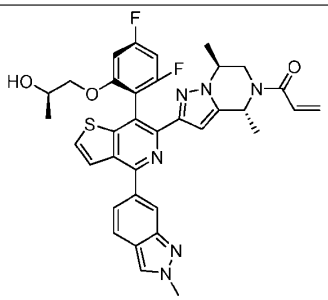
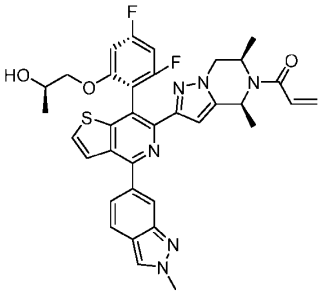
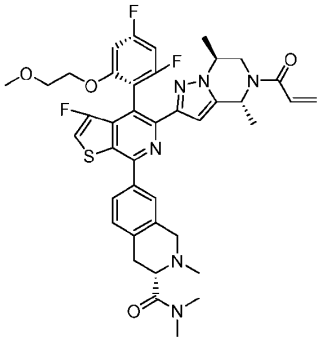
421		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 – 8.22 (m, 2H), 8.03 – 7.96 (m, 1H), 7.82 – 7.66 (m, 3H), 6.93 – 6.75 (m, 2H), 6.70 (t, J = 9.2 Hz, 1H), 6.38 – 6.25(m, 2H), 5.84 (dd, J = 10.6, 1.8 Hz, 1H), 5.39 – 4.98 (m, 2H), 4.72 – 4.55 (d, J = 26.2 Hz, 1H), 4.31 – 4.24 (m, 1H), 4.16 – 4.07 (m, 1H), 4.06 – 3.94 (m, 4H), 3.47 (t, J = 4.7 Hz, 2H), 3.07 (s, 3H), 1.35 – 1.28 (m, 3H), 1.26 – 1.14 (m, 3H).
422		LCMS m/z [M+1]: 745.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 8.1 Hz, 1H), 8.02 (s, 1H), 7.55-7.53 (m, 2H), 6.89-6.78 (m, 2H), 6.62 – 6.57 (m, 1H), 6.33 (d, J = 16.2 Hz, 1H), 6.11 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.73 - 5.35 (m, 1H), 4.78 (s, 1H), 4.74 (s, 1H), 4.60 (d, J = 15.4 Hz, 1H), 4.43 (s, 1H), 4.42 (s, 1H), 4.12 - 3.99 (m, 2H), 3.5-3.43 (m, 4H), 3.07 (s, 6H), 2.89 (s, 3H), 1.58 - 1.20 (m, 6H).
423		LCMS m/z [M+1]: 759.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (dd, J = 8.0, 1.6 Hz, 1H), 7.98 (s, 1H), 7.58 – 7.53 (m, 2H), 6.94 - 6.75 (m, 2H), 6.63 - 6.54 (m, 1H), 6.33 (d, J = 16.4 Hz, 1H), 6.11 (s, 1H), 5.84 (dd, J = 10.4, 1.6 Hz, 1H), 5.79 - 5.43 (m, 1H), 4.69 (s, 2H), 4.44 (s, 3H), 4.18 - 3.96 (m, 2H), 3.90 - 3.62 (m, 2H), 3.46 (t, J = 4.8 Hz, 2H), 3.44 - 3.35 (m, 2H), 3.07 (s, 3H), 3.05 (s, 6H), 1.54 - 1.36 (m, 3H), 1.35 - 1.23 (m, 3H).
424		LCMS m/z [M+1]: 655.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (d, J = 5.3 Hz, 2H), 8.00 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.71 (q, J = 5.5 Hz, 2H), 6.87 (d, J = 11.1 Hz, 2H), 6.73 – 6.64 (m, 2H), 6.29 (dd, J = 16.7, 1.6 Hz, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.22 (d, J = 18.8 Hz, 1H), 4.78 – 4.57 (m, 1H), 4.25 – 4.46 (m, 2H), 4.15 – 3.98 (m, 5H), 3.45

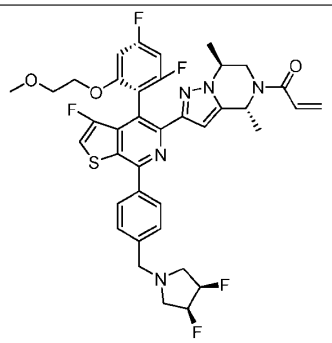
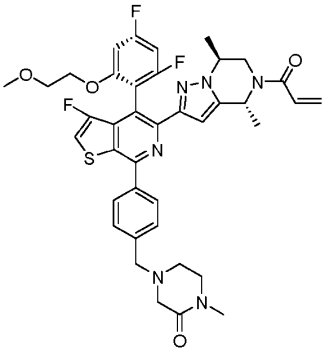
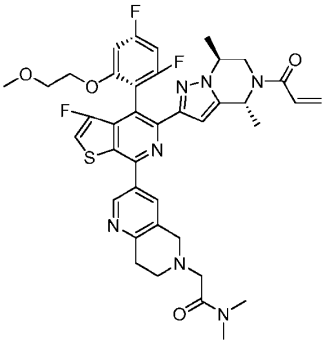
		(t, J = 4.7 Hz, 2H), 3.04 (s, 3H), 1.38 (d, J = 6.7 Hz, 3H), 1.05 (s, 3H).
425		LCMS m/z [M+1]: 741.0 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (dd, J = 7.9, 1.4 Hz, 1H), 7.92 (s, 1H), 7.88 – 7.82 (m, 1H), 7.71 (d, J = 5.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 13.5 Hz, 2H), 6.81 – 6.74 (m, 1H), 6.35 (d, J = 15.6 Hz, 1H), 6.26 (s, 1H), 5.86 (dd, J = 10.6, 1.8 Hz, 1H), 5.64 (d, J = 91.1 Hz, 1H), 4.94 (dd, J = 10.5, 5.4 Hz, 1H), 4.80 (d, J = 15.5 Hz, 2H), 4.65 (d, J = 15.5 Hz, 1H), 4.45 (s, 1H), 3.85 (dd, J = 9.4, 5.6 Hz, 1H), 3.75 (dd, J = 11.5, 5.3 Hz, 1H), 3.70 – 3.58 (m, 2H), 3.43 – 3.33 (m, 2H), 3.27 (s, 3H), 3.12 (s, 6H), 1.47 (s, 3H), 1.32 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H).
426		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 2H), 8.01 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 12.4, 5.6 Hz, 2H), 6.88 (s, 1H), 6.82 (d, J = 10.8 Hz, 1H), 6.77 – 6.72 (m, 1H), 6.37 – 6.32 (m, 2H), 5.86 (d, J = 11.8 Hz, 1H), 5.77 – 5.54 (m, 1H), 4.86 – 4.83 (m, 1H), 4.39 (s, 1H), 4.02 (s, 3H), 3.90 – 3.72 (m, 3H), 3.68 – 3.60 (m, 1H), 1.47 (s, 3H), 1.29 (s, 3H), 0.89 (d, J = 6.2 Hz, 3H).
427		LCMS m/z [M+1]: 655.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 2H), 8.01 (d, J = 8.4 Hz, 1H), 7.81 – 7.69 (m, 3H), 6.86 (d, J = 10.9 Hz, 2H), 6.70 (m, J = 9.2, 2.1 Hz, 1H), 6.37 – 6.28 (m, 2H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.23 (dd, J = 50.3, 16.9 Hz, 2H), 4.65 (d, J = 27.6 Hz, 1H), 4.31 – 4.26 (m, 1H), 4.11 (dt, J = 10.0, 4.8 Hz, 1H), 4.05 – 4.00 (m, 4H), 3.47 (t, J = 4.7 Hz, 2H), 3.08 (s, 3H), 1.31 (s, 3H), 1.20 (d, J = 14.7 Hz, 3H).

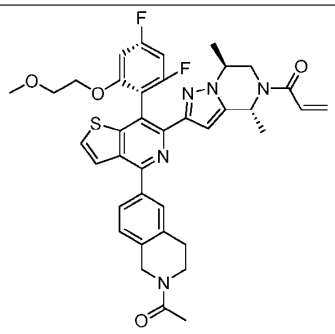
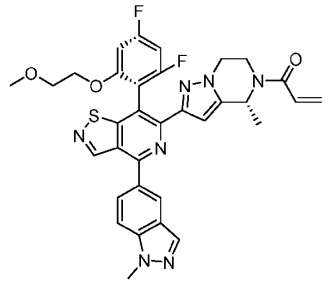
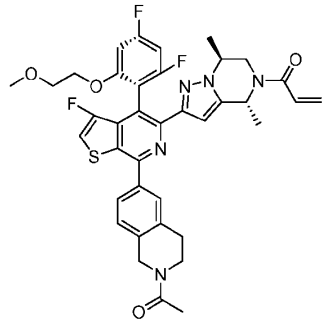
428		LCMS m/z [M+1]: 669.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 1.0 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.73 – 7.61 (m, 3H), 6.88 (s, 1H), 6.79 (d, J = 10.8 Hz, 1H), 6.75 – 6.67 (m, 1H), 6.39 – 6.26 (m, 2H), 5.83 (d, J = 10.5 Hz, 1H), 5.62 (d, J = 92.3 Hz, 1H), 4.36 (s, 1H), 4.21 (d, J = 14.4 Hz, 1H), 3.87 (d, J = 1.3 Hz, 3H), 3.83 – 3.67 (m, 3H), 3.61 (s, 1H), 2.66 (s, 3H), 1.44 (s, 3H), 1.25 (s, 3H), 0.86 (d, J = 6.3 Hz, 3H).
429		LCMS m/z [M+1]: 642.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.57 (s, 1H), 8.59 (s, 1H), 8.26 (dd, J = 8.8, 1.5 Hz, 1H), 8.21 (s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 6.91 – 6.65 (m, 3H), 6.29 (d, J = 17.1 Hz, 1H), 6.17 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.27 (dd, J = 12.8, 2.9 Hz, 1H), 4.20 – 4.03 (m, 5H), 4.02 – 3.93 (m, 1H), 3.42 – 3.38 (m, 2H), 3.05 (s, 3H), 1.52 – 1.35 (m, 3H).
430		LCMS m/z [M+1]: 741.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (d, J = 7.8 Hz, 1H), 7.71- 7.67 (m, 2H), 7.64 (d, J = 5.6 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 6.85 (s, 1H), 6.79 (d, J = 10.9 Hz, 1H), 6.75- 6.65 (m, 1H), 6.38- 6.24 (m, 2H), 5.83 (d, J = 10.4 Hz, 1H), 5.61 (d, J = 88.0 Hz, 1H), 4.36 (s, 1H), 4.31- 4.04 (m, 2H), 3.95- 3.66 (m, 5H), 3.60 (s, 1H), 3.27- 3.19 (m, 4H), 3.06- 2.97 (m, 4H), 2.44 (s, 3H), 1.52- 1.40 (m, 3H), 1.26 (s, 3H), 0.85 (d, J = 6.3 Hz, 3H).
431		LCMS m/z [M+1]: 641.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (s, 1H), 8.59 (s, 1H), 8.43 (d, J = 8.6 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.49 - 7.41 (m, 1H), 6.99 - 6.90 (m, 1H), 6.88 - 6.74 (m, 2H), 6.36 - 6.20 (m, 1H), 5.88 (d, J = 5.0 Hz, 1H), 5.81 (dd, J = 10.6, 1.8 Hz, 1H), 5.69 - 5.34 (m, 1H), 4.51 - 4.32 (m, 1H), 4.29 - 4.22 (m, 1H), 4.20 (s, 3H), 4.16 - 3.89 (m, 3H), 3.85 - 3.62 (m, 1H),

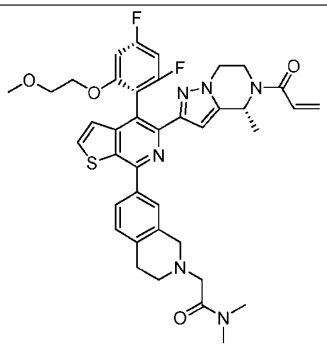
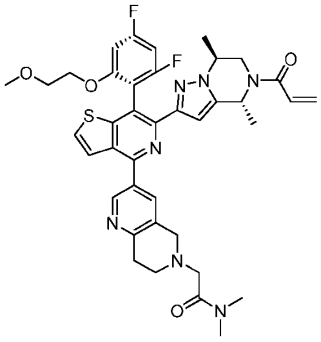
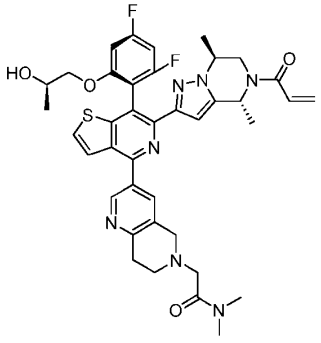
		3.49 - 3.41 (m, 2H), 3.08 (d, J = 5.3 Hz, 3H), 1.48 - 1.25 (m, 3H).
432		LCMS m/z [M+1]: 655.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 6.1 Hz, 2H), 7.88 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.59 (q, J = 5.6 Hz, 2H), 6.70 (d, J = 11.0 Hz, 2H), 6.65 – 6.56 (m, 2H), 6.17 (dd, J = 16.8, 1.6 Hz, 1H), 5.70 (d, J = 10.8 Hz, 1H), 5.02 – 5.12 (m, 1H), 4.65 – 4.44 (m, 1H), 4.37 – 4.11 (m, 2H), 3.99 – 3.89 (m, 4H), 3.85 – 3.76 (m, 1H), 3.30 (t, J = 4.7 Hz, 2H), 2.92 (s, 3H), 1.23 (d, J = 6.6 Hz, 3H), 0.91 (s, 3H).
433		LCMS m/z [M+1]: 703.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (d, J = 2.0 Hz, 1H), 8.47 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.93 – 6.82 (m, 2H), 6.68 – 6.61 (m, 1H), 6.35 – 6.31 (m, 1H), 6.31 (s, 1H), 5.85 (dd, J = 10.8, 2.0 Hz, 1H), 5.79 – 5.53 (m, 1H), 4.76 - 4.74 (m, 2H), 4.43 (s, 1H), 4.11 – 4.01 (m, 3H), 3.57 – 3.44 (m, 3H), 3.27 – 3.23 (m, 1H), 3.08 (d, J = 3.6 Hz, 6H), 1.58 (d, J = 5.6 Hz, 3H), 1.42 (s, 3H), 1.30 (s, 3H).
434		LCMS m/z [M+1]: 703.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.6 Hz, 1H), 8.54 (d, J = 4.0 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.91 – 6.80 (m, 2H), 6.64 – 6.59 (m, 1H), 6.35 – 6.31 (m, 1H), 6.11 (s, 1H), 5.85 (dd, J = 10.8, 1.6 Hz, 1H), 5.79 – 5.51 (m, 1H), 4.45 (s, 1H), 4.11 – 3.99 (m, 2H), 3.97 – 3.72 (m, 3H), 3.47 – 3.43 (m, 4H), 3.10 (d, J = 9.6 Hz, 6H), 1.85 (d, J = 6.4 Hz, 3H), 1.42 (s, 3H), 1.31 (s, 3H).

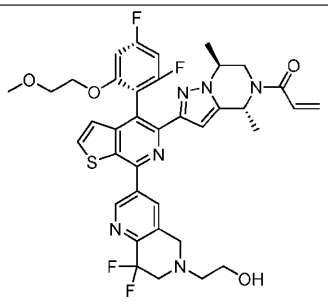
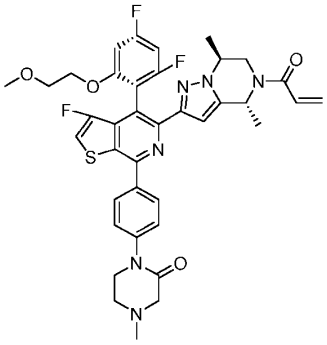
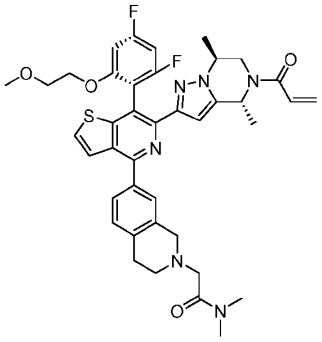
435		LCMS m/z [M+1]: 636.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (s, 1H), 9.01 (s, 1H), 8.65 (d, J = 5.9 Hz, 1H), 8.33 (s, 1H), 8.15 (s, 2H), 8.03 (dd, J = 5.9, 0.6 Hz, 1H),7.00 - 6.92 (m, 1H), 6.89 - 6.74 (m, 2H), 6.34 - 6.16 (m, 2H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.75 - 5.45 (m, 1H), 4.24 (s, 3H), 4.22 - 4.01 (m, 4H), 3.38 (t, J = 4.2 Hz, 2H), 2.99 (s, 3H), 1.55 - 1.37 (m, 3H).
436		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.38 (s, 1H), 8.44 (s, 1H), 8.27 (dd, J = 8.6 Hz, 1.2 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.96 - 6.69 (m, 3H), 6.38 - 6.15 (m, 2H), 5.81 (d, J = 10.2 Hz, 1H), 5.57 - 5.38 (m, 1H), 4.22 (s, 3H), 4.19 - 4.10 (m, 2H), 3.80 (d, J = 5.2 Hz, 2H), 3.78 - 3.70 (m, 1H),1.50 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.2 Hz, 3H).
437		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (dd, J = 7.9, 1.4 Hz, 1H), 8.06 - 8.02 (m, 1H), 7.58 - 7.51 (m, 2H), 7.45 - 7.38 (m, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.89 - 6.79 (m, 1H), 6.75 (t, J = 8.5 Hz, 1H), 6.32 (d, J = 16.6 Hz, 1H), 5.93 (s, 1H), 5.83 (dd, J = 10.5, 1.8 Hz, 1H), 5.72 - 5.36 (m, 1H), 4.96 - 4.88 (m, 1H), 4.81 - 4.75 (m, 2H), 4.66 - 4.58 (m, 1H), 4.52 - 4.38 (m, 1H), 4.14 - 3.98 (m, 2H), 3.64 - 3.54 (m, 1H), 3.50 - 3.32 (m, 3H), 3.24 (s, 3H), 3.09 (s, 6H), 3.07 (s, 3H), 1.45 - 1.25 (m, 6H).

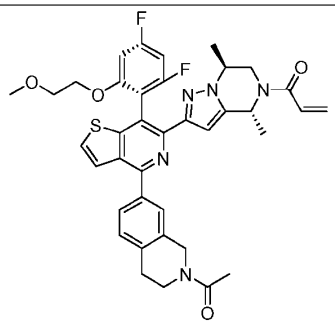
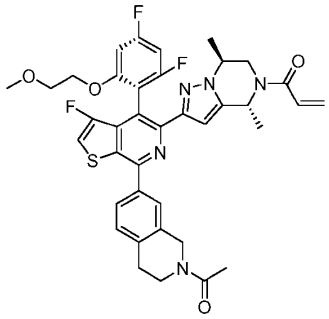
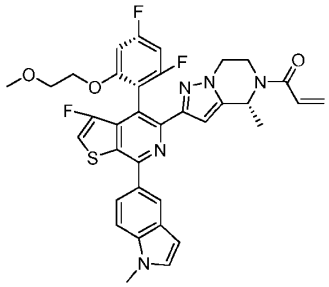
438		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.15 (s, 1H), 7.89 (t, J = 7.6 Hz, 2H), 7.70 (d, J = 5.6 Hz, 1H), 7.57 (dd, J = 8.6, 1.2 Hz, 1H), 6.83 – 6.68 (m, 3H), 6.23 (d, J = 16.4 Hz, 1H), 6.10 (s, 1H), 5.75 (dd, J = 10.6, 1.6 Hz, 1H), 5.65 – 5.43 (m, 1H), 4.73 – 4.62 (m, 1H), 4.39 (s, 1H), 4.22 (s, 3H), 3.85 – 3.53 (m, 4H), 1.34 (s, 3H), 1.22 (d, J = 6.2 Hz, 3H), 0.81 (d, J = 6.2 Hz, 3H).
439		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1H), 8.29 (s, 1H), 8.11 (d, J = 5.6 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.61 (dd, J = 8.6 Hz, 1.4 Hz, 1H), 6.96 (d, J = 10.8 Hz, 1H), 6.88 - 6.76 (m, 2H), 6.39 - 6.19 (m, 1H), 6.15 (s, 1H), 5.81 (d, J = 10.8 Hz, 1H), 5.60 - 5.39 (m, 1H), 4.33 (s, 3H), 4.29 - 4.21 (m, 2H), 3.94 - 3.84 (m, 1H), 3.83 - 3.73 (m, 2H), 1.49 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 5.8 Hz, 3H).
440		LCMS m/z [M+1]: 759.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 8.1 Hz, 1H), 8.03 (s, 1H), 7.57-7.54 (m, 2H), 6.89-6.79 (m, 2H), 6.61 – 6.57 (m, 1H), 6.33 (d, J = 16.2 Hz, 1H), 6.11 (s, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 5.73 - 5.35 (m, 1H), 4.78 (s, 2H), 4.64 – 4.60 (d, J = 14.9 Hz, 2H), 4.44 - 4.40 (m, 1H), 4.13 - 4.07 (m, 1H), 4.04 - 3.98 (m, 1H), 4.33 (d, J = 16.2 Hz, 1H), 3.61 (t, J = 5.2 Hz, 1H), 3.57 (t, J = 5.2 Hz, 1H), 3.46 (t, J = 4.84 Hz, 3H), 3.24 (s, 3H), 3.09 - 3.07 (m, 9H), 1.42 - 1.30 (m, 6H).

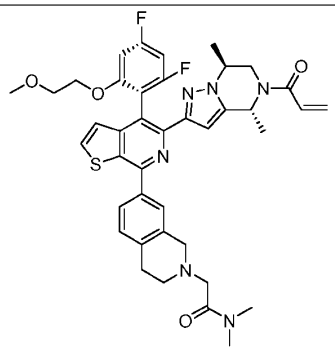
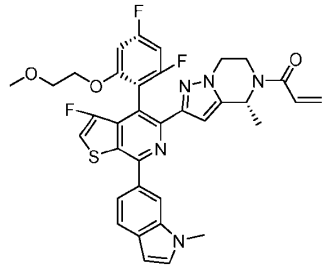
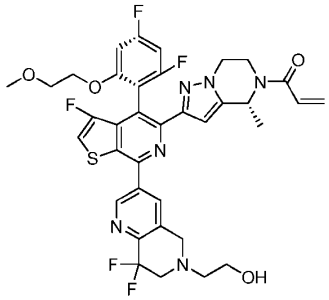
441		LCMS m/z [M+1]: 738.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 2.4 Hz, 1H), 6.93 – 6.77 (m, 2H), 6.60 (td, J = 9.2, 2.2 Hz, 1H), 6.33 (d, J = 16.8 Hz, 1H), 6.14 (s, 1H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.57 - 5.42 (m, 2H), 4.60 (s, 2H), 4.43 (s, 1H), 4.26 (s, 1H), 4.13 – 4.07 (m, 1H), 4.05 – 3.98 (m, 1H), 3.93 – 3.71 (m, 5H), 3.47 (t, J = 4.6 Hz, 2H), 3.07 (s, 3H), 1.56 - 1.21 (m, 6H).
442		LCMS m/z [M+1]: 745.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 2.4 Hz, 1H), 6.87 – 6.76 (m, 2H), 6.59 (t, J = 9.2 Hz, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.15 (s, 1H), 5.84 (d, J = 12.2 Hz, 1H), 5.71 (s, 1H), 4.89 – 4.87 (m, 2H), 4.83 – 4.79 (m, 4H), 4.42 (s, 1H), 4.18 (s, 2H), 4.12 – 3.99 (m, 2H), 3.61 – 3.52 (m, 3H), 3.49 – 3.44 (m, 2H), 3.07 (s, 2H), 3.00 (s, 2H), 1.56 - 1.21 (m, 6H).
443		LCMS m/z [M+1]: 760.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.4 Hz, 1H), 8.47 (s, 1H), 7.60 (d, J = 2.1 Hz, 1H), 6.92 – 6.77 (m, 2H), 6.61 (td, J = 9.2, 2.0 Hz, 1H), 6.33 (d, J = 16.6 Hz, 1H), 6.13 (s, 1H), 5.84 (dd, J = 10.6, 1.2 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.77 (s, 2H), 4.52 – 4.40 (m, 3H), 4.13 – 4.06 (m, 1H), 4.05 – 3.98 (m, 1H), 3.90 – 3.81 (m, 2H), 3.52 – 3.42 (m, 4H), 3.08 (s, 3H), 3.05 (s, 6H), 1.52 – 1.36 (m, 3H), 1.35 – 1.27 (m, 3H).

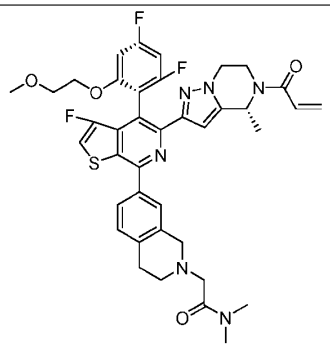
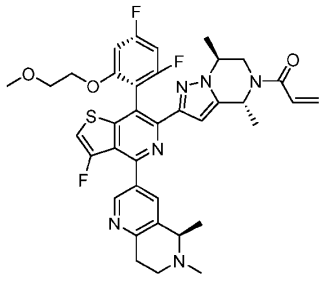
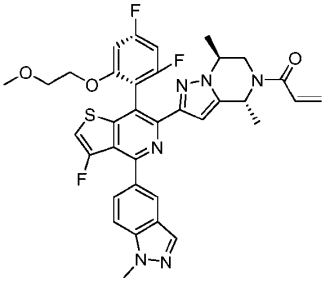
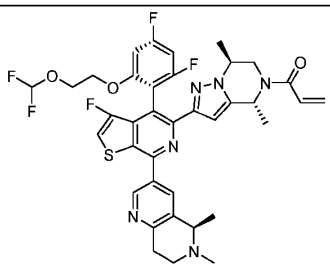
444		LCMS m/z [M+1]: 698.1 ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (s, 2H), 7.73 (d, J = 5.6 Hz, 1H), 7.66 (d, J = 5.6 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 10.8 Hz, 2H), 6.68 (td, J = 9.2, 2.2 Hz, 1H), 6.38 – 6.22 (m, 2H), 5.86 (dd, J = 10.6, 1.6 Hz, 1H), 5.63 (d, J = 86.8 Hz, 1H), 4.84 (d, J = 8.2 Hz, 2H), 4.42 (dd, J = 6.2, 3.2 Hz, 1H), 4.08 (m, J = 15.4, 10.8, 4.5 Hz, 2H), 3.87 (m, J = 11.7, 5.9 Hz, 3H), 3.46 (t, J = 4.7 Hz, 3H), 3.14 – 3.00 (m, 5H), 2.26 (d, J = 6.8 Hz, 3H), 1.45 (s, 3H), 1.31 (s, 3H).
445		LCMS m/z [M+1]: 642.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.32 (s, 1H), 8.53 (s, 1H), 8.22 - 8.18 (m, 2H), 7.82 (d, J = 8.8 Hz, 1H), 6.93 - 6.81 (m, 2H), 6.76 - 6.73 (m, 1H), 6.37 (d, J = 14.4 Hz, 1H), 6.31 - 6.22 (m, 1H), 5.82 (d, J = 8.8 Hz, 1H), 5.74 - 5.47 (m, 1H), 4.82 - 4.77 (m, 1H), 4.49 - 4.02 (m, 4H), 3.46 - 3.41 (m, 2H), 3.05 (m, 3H), 1.47 (s, 3H), 1.29 (s, 1H).
446		LCMS m/z [M+1]: 716.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 – 7.90 (m, 2H), 7.55 – 7.50 (m, 1H), 7.47 – 7.36 (m, 1H), 6.98 – 6.84 (m, 1H), 6.80 (d, J = 10.9 Hz, 1H), 6.65 – 6.55 (m, 1H), 6.34 (d, J = 16.5 Hz, 1H), 6.17 (s, 1H), 5.86 (d, J = 10.6 Hz, 1H), 5.75 – 5.45 (m, 1H), 4.85 – 4.80 (m, 2H), 4.70 –4.20 (m, 2H), 4.14 – 3.98 (m, 2H), 3.95– 3.75 (m, 3H), 3.48 (t, J = 4.6 Hz, 2H), 3.18 – 3.07 (m, 4H), 3.05 – 2.98 (m, 1H), 2.30 – 2.20 (m, 3H), 1.55 – 1.40 (m, 3H), 1.37 – 1.28 (m, 3H).

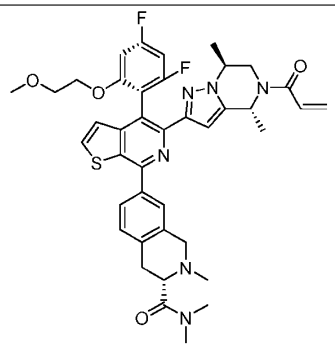
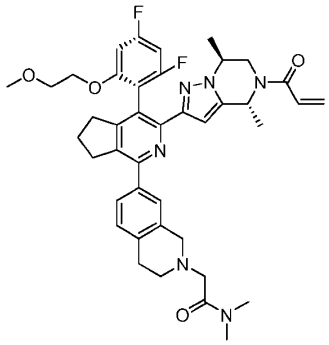
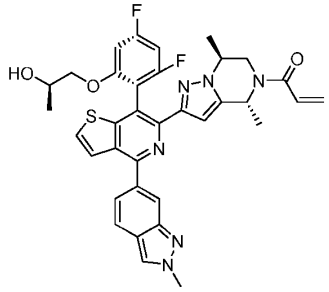
447		LCMS m/z [M+1]: 727.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 7.8 Hz, 1H), 8.04 – 8.03 (m, 2H), 7.56 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 5.4 Hz, 1H), 6.89 – 6.81 (m, 2H), 6.72 – 6.67 (m, 1H), 6.28 (d, J = 15.4 Hz, 1H), 6.06 (s, 1H), 5.82 (dd, J = 10.6, 1.8 Hz, 1H), 5.69 – 5.47 (m, 1H), 4.69 (s, 2H), 4.44 (s, 3H), 4.25- 4.22 (m, 2H), 4.11 – 4.07 (m, 2H), 4.02 – 3.98 (m, 2H), 3.77 (s, 2H), 3.43 – 3.38 (m, 6H), 3.04 (s, 6H), 1.42 – 1.39 (m, 3H).
448		LCMS m/z [M+1]: 742.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.83 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 1.7 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 5.6 Hz, 1H), 6.77 (d, J = 10.9 Hz, 2H), 6.57 (t, J = 9.2 Hz, 1H), 6.26 – 6.11 (m, 2H), 5.74 (d, J = 10.6 Hz, 1H), 5.52 (d, J = 82.5 Hz, 1H), 4.34 – 4.23 (m, 1H), 4.16 – 3.69 (m, 6H), 3.51 (s, 2H), 3.33 (t, J = 4.7 Hz, 2H), 3.13 – 3.06 (m, 2H), 3.04 (s, 3H), 3.02 – 2.97 (m, 2H), 2.94 (s, 3H), 2.89 (s, 3H), 1.42 – 1.30 (m, 3H), 1.21 – 1.18 (m, 3H).
449		LCMS m/z [M+1]: 742.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (d, J = 2.0 Hz, 1H), 8.16 (s, 1H), 7.80 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 6.96 – 6.80 (m, 2H), 6.75 (t, J = 9.2 Hz, 1H), 6.41 – 6.28 (m, 2H), 5.86 (d, J = 11.9 Hz, 1H), 5.65 (d, J = 87.7 Hz, 1H), 4.54 – 4.10 (m, 2H), 3.98 (s, 2H), 3.90 – 3.68 (m, 3H), 3.67 – 3.53 (m, 3H), 3.24 – 3.13 (m, 5H), 3.09 (t, J = 5.9 Hz, 2H), 3.00 (s, 3H), 1.48 (s, 3H), 1.32 – 1.26 (m, 3H), 0.87 (d, J = 6.3 Hz, 3H).

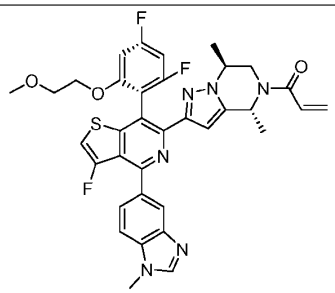
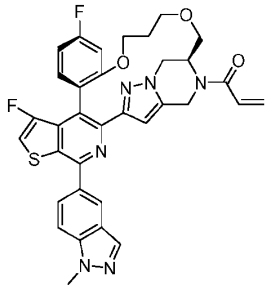
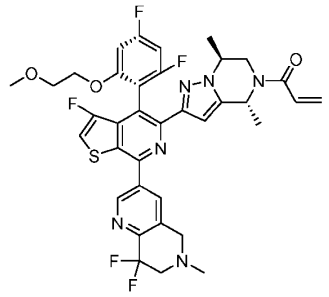
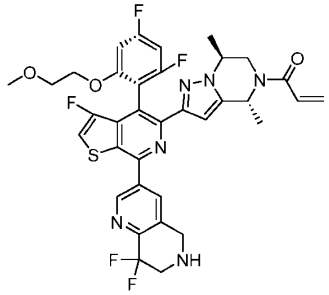
450		LCMS m/z [M+1]: 737 ^{1}H NMR (400 MHz, CD_3OD) δ 9.49 (d, J = 1.76 Hz, 1H), 8.63 (s, 1H), 8.02 (d, J = 5.52 Hz, 1H), 7.16 (d, J = 5.52 Hz, 1H), 6.93 – 6.80 (m, 2H), 6.70 – 6.64 (m, 1H), 6.33 (d, J = 16.6 Hz, 1H), 6.19 (s, 1H), 5.86 – 5.83 (m, 1H), 5.80 – 5.40 (m, 1H), 4.48 – 4.38 (m, 1H), 4.13 – 4.08 (m, 1H), 4.01 – 3.94 (m, 4H), 3.42 (t, J = 4.4 Hz, 2H), 3.05 (s, 3H), 1.53 – 1.38 (m, 3H), 1.37 – 1.25 (m, 3H).
451		LCMS m/z [M+1]: 731.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 2.4 Hz, 1H), 6.91 – 6.77 (m, 2H), 6.63 – 6.56 (m, 1H), 6.37 - 6.26 (m, 1H), 6.16 (s, 1H), 5.87 – 5.80 (m, 1H), 5.72 - 5.55 (m, 1H), 4.44 - 4.38 (m, 1H), 4.16 (s, 2H), 4.13 - 4.05 (m, 3H), 4.05 – 3.98 (m, 1H), 3.82 - 3.75 (m, 2H), 3.46 (t, J = 4.6 Hz, 2H), 3.11 (s, 2H), 3.07 (s, 3H), 1.50 - 1.3 (m, 3H), 1.32 - 1.25 (m, 3H).
452		LCMS m/z [M+1]: 741.0 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 6.6 Hz, 2H), 7.72 (d, J = 5.6 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 6.93 (d, J = 9.6 Hz, 1H), 6.87 (d, J = 15.0 Hz, 1H), 6.73 (t, J = 9.2 Hz, 1H), 6.35 (d, J = 16.2 Hz, 1H), 6.20 (s, 1H), 5.92 – 5.85 (m, 1H), 5.80 – 5.43 (m, 1H), 5.00 – 4.93 (m, 1H), 4.71 (s, 2H), 4.47 (s, 3H), 4.27 (d, J = 15.8 Hz, 1H), 4.16 – 4.04 (m, 2H), 3.96 – 3.72 (m, 2H), 3.47 (t, J = 4.6 Hz, 2H), 3.42 (s, 1H), 3.31 – 3.21 (m, 2H), 3.07 (d, J = 3.0 Hz, 8H), 1.47 (d, J = 21.0 Hz, 3H), 1.33 (s, 3H).

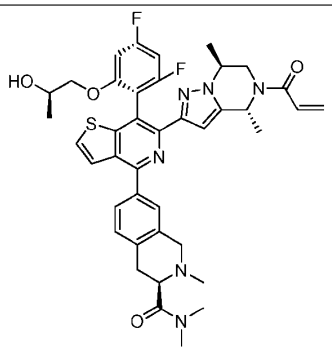
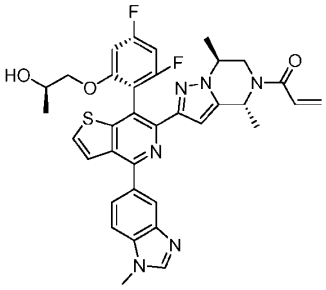
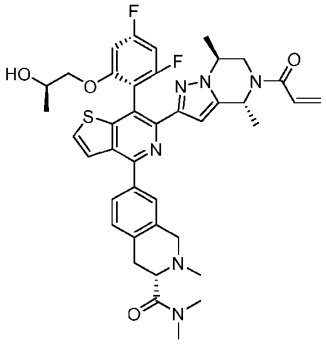
453		LCMS m/z [M+1]: 698.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (s, 1H), 7.68 (s, 1H), 7.60 (t, J = 8.8 Hz, 1H), 7.50 (dd, J = 12.0, 5.4 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 6.89 (s, 1H), 6.76 (dd, J = 16.6, 10.6 Hz, 2H), 6.23 (d, J = 16.6 Hz, 1H), 5.75 (d, J = 10.6 Hz, 1H), 5.65 – 5.47 (m, 1H), 4.89 – 4.85 (m, 1H), 4.77 (s, 1H), 4.74 – 4.63 (m, 1H), 4.19 (s, 1H), 4.04 – 3.91 (m, 2H), 3.81 – 3.73 (m, 3H), 3.55 – 3.34 (m, 1H), 3.29 (d, J = 3.0 Hz, 2H), 2.98 (t, J = 5.8 Hz, 1H), 2.90 (d, J = 3.0 Hz, 4H), 2.14 (d, J = 11.6 Hz, 3H), 1.37 (s, 3H), 1.32 (s, 3H).
454		LCMS m/z [M+1]: 716.0 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (t, J = 6.8 Hz, 2H), 7.65 (dd, J = 10.6, 2.2 Hz, 1H), 7.48 (dd, J = 7.6, 4.0 Hz, 1H), 6.89 (s, 1H), 6.83 (d, J = 10.8 Hz, 1H), 6.64 (t, J = 9.2 Hz, 1H), 6.35 (d, J = 16.2 Hz, 1H), 6.15 (s, 1H), 5.87 (dd, J = 10.6, 1.6 Hz, 1H), 5.79 – 5.46 (m, 1H), 4.97 – 4.92 (m, 1H), 4.88 (s, 3H), 4.74 (s, 1H), 4.47 (s, 1H), 4.27 (d, J = 17.0 Hz, 1H), 4.15 – 3.99 (m, 2H), 3.91 – 3.85 (m, 2H), 3.48 (t, J = 4.6 Hz, 2H), 3.12 – 3.08 (m, 3H), 3.01 (t, J = 5.8 Hz, 1H), 2.26 (d, J = 5.2 Hz, 2H), 1.46 (d, J = 20.8 Hz, 3H), 1.34 (s, 3H).
455		LCMS m/z [M+1]: 658.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (d, J = 1.2 Hz, 1H), 7.91 (dd, J = 8.6 Hz, 1.6 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 3.2 Hz, 1H), 6.92 - 6.76 (m, 2H), 6.75 - 6.61 (m, 2H), 6.29 (d, J = 16.6 Hz, 1H), 5.98 (s, 1H), 5.82 (dd, J = 10.6 Hz, 1.6 Hz, 1H), 5.76 - 5.41 (m, 1H), 4.30 (dd, J = 12.8 Hz, 2.8 Hz, 1H), 4.21-3.99 (m, 3H), 3.92 (s, 3H), 3.47 (t, J = 4.6 Hz, 2H), 3.10 (s, 3H), 1.50 - 1.38 (m, 3H).

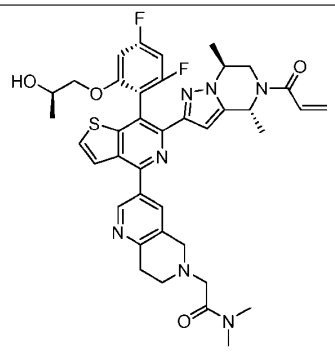
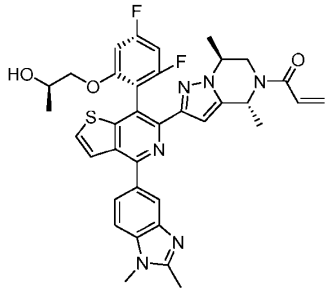
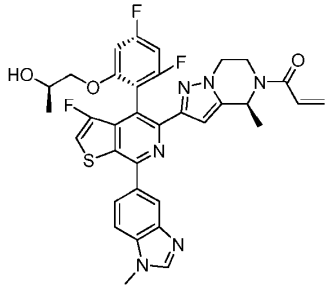
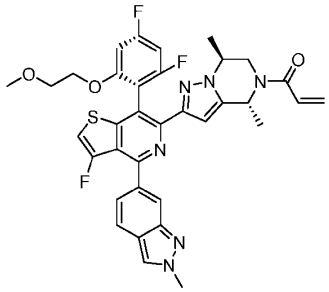
456		LCMS m/z [M+1]: 741.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 8.0 Hz, 1H), 8.05 – 8.00 (m, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 5.5 Hz, 1H), 6.86 (t, J = 11.3 Hz, 2H), 6.72 – 6.61 (m, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.13 (s, 1H), 5.85 (d, J = 12.2 Hz, 1H), 5.75- 5.35(m, 1H), 4.78 – 4.58 (m, 2H), 4.45 (s, 3H), 4.19 – 4.06 (m, 1H), 4.04 – 3.93 (m, 1H), 3.51 – 3.34 (m, 4H), 3.08 – 2.99 (m, 9H), 1.53 – 1.38 (m, 3H), 1.36 – 1.25 (m, 3H).
457		LCMS m/z [M+1]: 658.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 7.91 (d, J = 2.3 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.70 - 7.65 (m, 1H), 7.42 (d, J = 3.1 Hz, 1H), 6.91 - 6.81 (m, 2H), 6.68 (td, J = 9.2, 2.3 Hz, 1H), 6.60 (dd, J = 3.1, 0.9 Hz, 1H), 6.33 - 6.27 (m, 1H), 5.88 – 5.81 (m, 2H), 5.72 - 5.57 (m, 1H), 4.49 - 4.37 (m, 1H), 4.27 - 4.22 (m, 1H), 4.17 - 4.06 (m, 3H), 3.88 (s, 3H), 3.52 - 3.41 (m, 3H), 3.10 (s, 3H), 1.45 - 1.34 (m, 3H).
458		LCMS m/z [M+1]: 741.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.40 (d, J = 2.2 Hz, 1H), 8.58 (s, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.89 - 6.78 (m, 2H), 6.67 – 6.60 (m, 1H), 6.34 - 6.23 (m, 1H), 6.09 (s, 1H), 5.85 – 5.80 (m, 1H), 5.69 - 5.53 (m, 1H), 5.01 - 4.90 (m, 3H), 4.48 - 4.37 (m, 1H), 4.32 (s, 1H), 4.24 - 4.18 (m, 1H), 4.12 – 3.98 (m, 3H), 3.89 (t, J = 5.5 Hz, 2H), 3.73 (t, J = 11.8 Hz, 2H), 3.44 (t, J = 4.6 Hz, 2H), 3.15 - 3.08 (m, 2H), 3.07 (s, 3H), 1.52 - 1.38 (m, 3H).

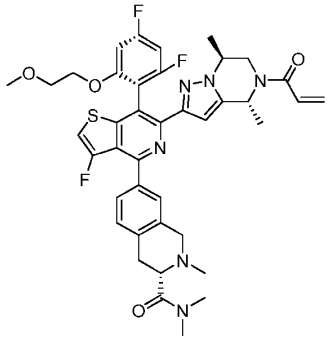
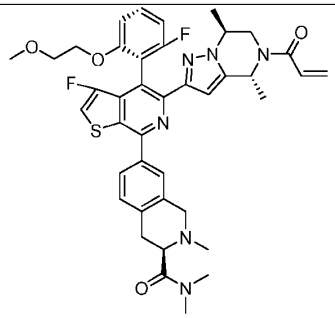
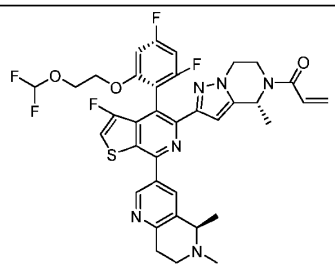
459		LCMS m/z [M+1]: 745.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 7.6 Hz, 1H), 8.00 (s, 1H), 7.59 – 7.51 (m, 2H), 6.88 – 6.78 (m, 2H), 6.65 – 6.57 (m, 1H), 6.29 (d, J = 14.5 Hz, 1H), 6.04 - 5.98 (m, 1H), 5.85 – 5.79 (m, 1H), 5.68 - 5.60 (m, 1H), 4.44 (s, 2H), 4.26 - 4.16 (m, 2H), 4.11 – 3.98 (m, 4H), 3.51 - 3.34 (m, 7H), 3.06 (d, J = 9.4 Hz, 10H), 1.47 - 1.36 (m, 3H).
460		LCMS m/z [M+1]: 703.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.99 (s, 1H), 8.30 (s, 1H), 7.40 (d, J = 2.8 Hz, 1H), 6.92 - 6.85 (m, 2H), 6.74 - 6.71 (m, 1H), 6.34 - 6.25 (m, 2H), 5.84 (dd, J = 10.8, 2.4 Hz, 1H), 5.78 - 5.54 (m, 1H), 4.40 (s, 1H), 4.13 - 4.09 (m, 1H), 4.07 - 4.02 (m, 1H), 3.92 (s, 1H), 3.75 – 3.70 (m, 1H), 3.45 - 3.42 (m, 4H), 3.11 (s, 3H), 3.08 (s, 3H), 1.82 (d, J = 9.2 Hz, 3H), 1.43 (s, 3H), 1.29 (s, 3H).
461		LCMS m/z [M+1]: 673.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (d, J = 2.4 Hz, 1H), 8.24 (s, 1H), 7.94 – 7.92 (m, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 10.8 Hz, 1H), 6.89 – 6.82 (m, 1H), 6.76 – 6.72 (m, 1H), 6.34 – 6.24 (m, 2H), 5.84 (dd, J = 10.8, 1.6 Hz, 1H), 5.78 – 5.52 (m, 1H), 4.44 – 4.42 (m, 1H), 4.16 – 4.11 (m, 3H), 4.10 – 4.04 (m, 2H), 3.51 – 3.47 (m, 3H), 3.09 (s, 3H), 1.44 (d, J = 12.8 Hz, 3H), 1.29 (s, 3H).
462		LCMS m/z [M+1]: 739.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.28 (d, J = 1.8 Hz, 1H), 8.52 (s, 1H), 7.59 (d, J = 2.2 Hz, 1H), 6.92 - 6.78 (m, 2H), 6.67 - 6.59 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.23 - 6.01 (m, 2H), 5.87 - 5.81 (m, 1H), 5.78 - 5.43 (m, 1H), 4.49 - 4.37 (m, 1H), 4.32 - 4.04 (m, 3H), 4.03 - 3.61 (m, 5H), 3.43 (t, J = 6.3 Hz, 2H), 3.11 (s, 3H), 1.84 (s, 3H), 1.51 - 1.36 (m, 3H), 1.30 (s, 3H).

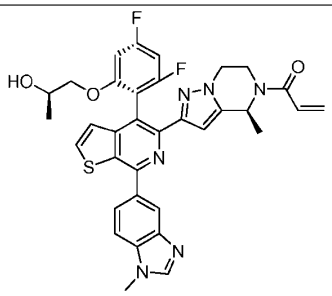
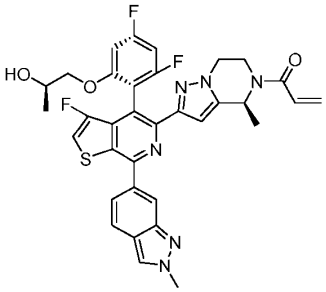
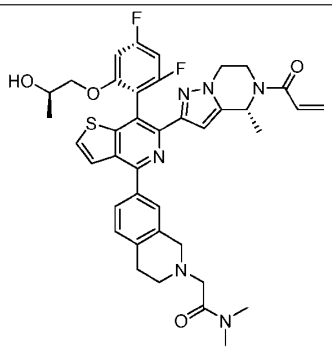
463		LCMS m/z [M+1]: 741.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 8.1 Hz, 1H), 8.09 – 8.00 (m, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 5.5 Hz, 1H), 6.94 – 6.80 (m, 2H), 6.68 (td, J = 9.2, 2.1 Hz, 1H), 6.33 (d, J = 16.7 Hz, 1H), 6.13 (s, 1H), 5.85 (d, J = 12.0 Hz, 1H), 5.78 – 5.44 (m, 1H), 4.97 – 4.90 (m, 1H), 4.83 – 4.75 (m, 1H), 4.68 – 4.57 (m, 1H), 4.51 – 4.39 (m, 1H), 4.15-4.05 (m, 1H), 4.03 – 3.94 (m, 1H), 3.65 – 3.56 (m, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.38 – 3.32 (m, 1H), 3.24 (s, 3H), 3.10 (s, 6H), 3.06 (s, 3H), 1.52 – 1.37 (m, 3H), 1.36 – 1.23 (m, 3H).
464		LCMS m/z [M+1]: 725.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 - 7.79 (m, 1H), 7.73 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 6.92 - 6.79 (m, 2H), 6.74 - 6.64 (m, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.01 (s, 1H), 5.84 (dd, J = 10.5, 1.5 Hz, 1H), 5.76 - 5.40 (m, 1H), 4.68 (s, 2H), 4.53 (s, 1H), 4.44 (s, 2H), 4.40 - 4.09 (m, 2H), 4.07 - 3.99 (m, 1H), 3.91 - 3.64 (m, 2H), 3.54 (t, J = 4.0 Hz, 2H), 3.43 - 3.33 (m, 2H), 3.27 - 3.17 (m, 5H), 3.14 - 2.99 (m, 7H), 2.95 - 2.83 (m, 1H), 2.28 - 2.14 (m, 2H), 1.50 - 1.26 (m, 6H).
465		LCMS m/z [M+1]: 655.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 8.28 (s, 1H), 8.03 (t, J = 6.8 Hz, 2H), 7.84 (d, J = 5.6 Hz, 1H), 7.70 (dd, J = 8.6, 1.2 Hz, 1H), 6.98 (d, J = 10.8 Hz, 1H), 6.89 (dd, J = 16.4, 10.6 Hz, 1H), 6.82 – 6.77 (m, 1H), 6.35 (d, J = 16.2 Hz, 1H), 6.23 (s, 1H), 5.87 (dd, J = 10.6, 1.6 Hz, 1H), 5.76 – 5.57 (m, 1H), 4.85 – 4.66 (m, 1H), 4.55 (s, 1H), 4.34 (s, 3H), 3.97 – 3.86 (m, 3H), 3.84 – 3.77 (m, 1H), 1.45 (s, 3H), 1.34 (s, 3H), 0.97 (d, J = 6.4 Hz, 3H).

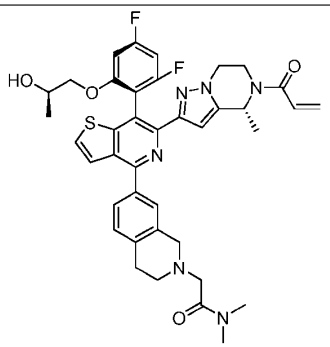
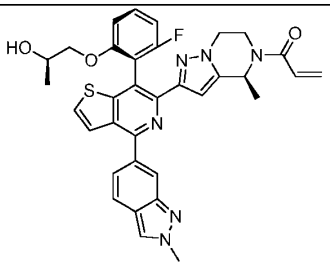
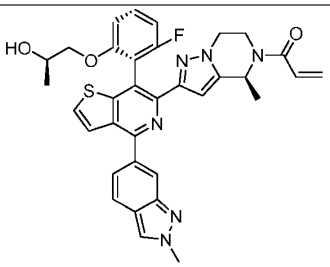
466		LCMS m/z [M+1]: 673 ^{1}H NMR (400 MHz, CD_3OD) δ 9.46 (s, 1H), 8.28 (s, 1H), 8.16 – 8.14 (m, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 2.6 Hz, 1H), 6.95 – 6.80 (m, 2H), 6.74 – 6.69 (m, 1H), 6.32 (d, J = 16.7 Hz, 1H), 6.26 (s, 1H), 5.85 – 5.82 (m, 1H), 5.78 – 5.40 (m, 1H), 4.45 – 4.35 (m, 1H), 4.23 (s, 3H), 4.15 – 4.03 (m, 2H), 3.46 (t, J = 4.7 Hz, 2H), 3.08 (s, 3H), 1.53 – 1.35 (m, 3H), 1.34 – 1.22 (m, 3H).
467		LCMS m/z [M+1]: 639 ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.35 - 8.20 (m, 1H), 8.18 (s, 1H), 7.78 (d, J = 8.84 Hz, 1H), 7.50 (d, J = 1.9 Hz, 1H), 7.41-7.33 (m, 1H), 6.92 – 6.75 (m, 3H), 6.36 – 6.26 (m, 1H), 5.82 (d, J = 10.3 Hz, 1H), 5.42 (d, J = 15.6 Hz, 1H), 4.72 – 4.41 (m, 3H), 3.96 – 3.83 (m, 1H), 3.76 – 3.65 (m, 2H), 3.06 – 2.94 (m, 1H), 1.85 – 1.72 (m, 1H), 1.63 – 1.52 (m, 1H).
468		LCMS m/z [M+1]: 725 ^{1}H NMR (400 MHz, CD_3OD) δ 9.48 (s, 1H), 8.62 (s, 1H), 7.64 (d, J = 2.3 Hz, 1H), 6.95 – 6.82 (m, 2H), 6.66 – 6.61 (m, 1H), 6.34 (d, J = 17.2 Hz, 1H), 6.19 (s, 1H), 5.90 – 5.83 (m, 1H), 5.81 - 5.45 (m, 1H), 4.51 – 4.40 (m, 3H), 4.15 – 4.09 (m, 1H), 4.06 – 4.01 (m, 1H), 3.93 (t, J = 11.6 Hz, 2H), 3.47 (t, J = 4.72 Hz, 2H), 3.10 (s, 3H), 3.00 (s, 3H), 1.56 – 1.40 (m, 3H), 1.37 – 1.28 (m, 3H).
469		LCMS m/z [M+1]: 711 ^{1}H NMR (400 MHz, CD_3OD) δ 9.51 (d, J = 1.56 Hz, 1H), 8.66 (s, 1H), 7.63 (d, J = 2.2 Hz, 1H), 6.89 – 6.80 (m, 2H), 6.64 – 6.59 (m, 1H), 6.33 (d, J = 16.6 Hz, 1H), 6.15 (s, 1H), 5.86 – 5.83 (m, 1H), 5.78 – 5.41 (m, 1H), 4.48 – 4.35 (m, 1H), 4.21 (t, J = 11.4 Hz, 2H), 4.13 – 3.99 (m, 2H), 3.45 (t, J = 4.8 Hz, 2H), 3.08 (s, 3H), 1.53 – 1.36 (m, 3H), 1.35 – 1.25 (m, 3H).

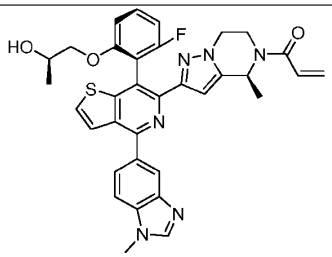
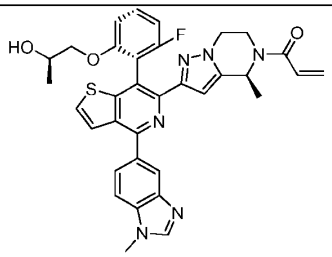
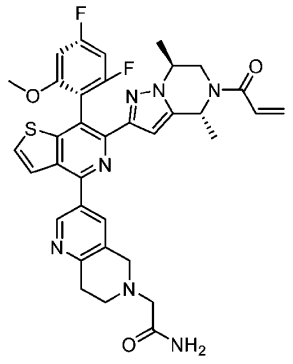
470		LCMS m/z [M+1]: 741.0 ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, J = 7.8 Hz, 1H), 7.90 (s, 1H), 7.84 (d, J = 5.5 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 16.4 Hz, 2H), 6.70 (t, J = 9.1 Hz, 1H), 6.34 (d, J = 16.2 Hz, 1H), 6.26 (s, 1H), 5.86 (d, J = 10.5 Hz, 1H), 5.64 (d, J = 87.8 Hz, 1H), 4.92 (d, J = 5.3 Hz, 1H), 4.79 (d, J = 15.5 Hz, 2H), 4.66 (s, 1H), 4.45 (s, 1H), 3.92 (d, J = 6.4 Hz, 1H), 3.86 – 3.81 (m, 1H), 3.76 (s, 1H), 3.62 (dd, J = 17.6, 5.1 Hz, 1H), 3.35 (s, 2H), 3.26 (s, 3H), 3.11 (s, 6H), 1.46 (s, 3H), 1.28 (s, 3H), 0.93 (d, J = 6.3 Hz, 3H).
471		LCMS m/z [M+1]: 655.0 ^{1}H NMR (400 MHz, CD_3OD) δ 9.40 (d, J = 12.4 Hz, 1H), 8.45 (s, 1H), 8.30 (d, J = 8.6 Hz, 1H), 8.14 (dd, J = 8.6, 2.2 Hz, 1H), 7.88 (d, J = 5.4 Hz, 1H), 7.75 (d, J = 5.6 Hz, 1H), 6.99 – 6.83 (m, 2H), 6.72 (t, J = 9.0 Hz, 1H), 6.40 – 6.25 (m, 2H), 5.86 (d, J = 10.6 Hz, 1H), 5.78 – 5.55 (m, 1H), 4.84 – 4.74 (m, 1H), 4.47 (s, 1H), 4.25 (s, 3H), 4.03 – 3.72 (m, 4H), 1.46 (s, 3H), 1.30 (s, 3H), 0.95 (d, J = 6.2 Hz, 3H).
472		LCMS m/z [M+1]: 741.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (d, J = 7.9 Hz, 1H), 7.88 (s, 1H), 7.86 – 7.77 (m, 1H), 7.68 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 6.95 – 6.78 (m, 2H), 6.67 (t, J = 8.5 Hz, 1H), 6.31 (d, J = 16.7 Hz, 1H), 6.23 (s, 1H), 5.83 (d, J = 10.6, 1.7 Hz, 1H), 5.61 (d, J = 86.0 Hz, 1H), 4.92 (d, J = 5.2 Hz, 1H), 4.77 (d, J = 15.4 Hz, 1H), 4.61 (d, J = 15.1 Hz, 1H), 4.43 (s, 1H), 4.21 (s, 1H), 3.97 – 3.65 (m, 4H), 3.64 – 3.54 (m, 1H), 3.34 (d, J = 10.4 Hz, 1H), 3.23 (s, 3H), 3.08 (s, 6H), 1.42 (s, 3H), 1.26 (s, 3H), 0.90 (d, J = 6.3 Hz, 3H).

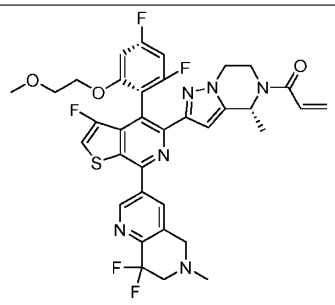
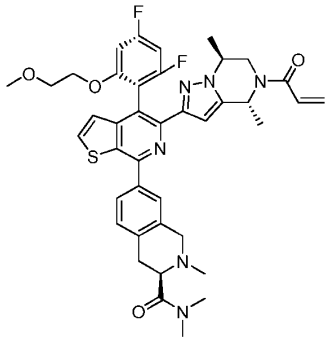
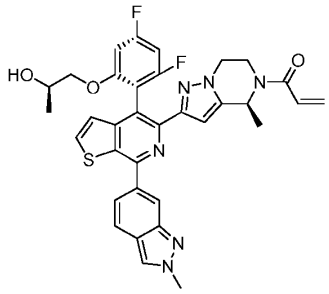
473		LCMS m/z [M+1]: 742.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (s, 1H), 8.32 (s, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.95 – 6.79 (m, 2H), 6.66 (dd, J = 10.2, 8.1 Hz, 1H), 6.37 – 6.24 (m, 2H), 5.83 (d, J = 10.6 Hz, 1H), 5.62 (d, J = 87.6 Hz, 1H), 4.74 (s, 2H), 4.54 – 4.33 (m, 3H), 4.24 (s, 1H), 4.07 – 3.61 (m, 6H), 3.48 (t, J = 6.2 Hz, 2H), 3.04 (s, 6H), 1.43 (s, 3H), 1.24 (s, 3H), 0.89 (d, J = 6.3 Hz, 3H).
474		LCMS m/z [M+1]: 669.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.20 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 5.4 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 6.92 – 6.78 (m, 2H), 6.67 (t, J = 8.3 Hz, 1H), 6.30 (d, J = 16.9 Hz, 1H), 6.24 (s, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.61 (d, J = 85.7 Hz, 1H), 4.74 – 4.19 (m, 2H), 4.07 (s, 3H), 3.95 – 3.68 (m, 4H), 2.92 (s, 3H), 1.41 (s, 3H), 1.24 (s, 3H), 0.90 (d, J = 6.3 Hz, 3H).
475		LCMS m/z [M+1]: 659.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1H), 8.59 (s, 1H), 8.43 (d, J = 8.7 Hz, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 6.92 – 6.74 (m, 2H), 6.67 (td, J = 9.3, 2.0 Hz, 1H), 6.27 (s, 1H), 6.09 (s, 1H), 5.83 (d, J = 12.0 Hz, 1H), 5.69 -5.43 (m, 1H), 4.44 – 4.05 (m, 5H), 3.81 – 3.70 (m, 3H), 1.48 - 1.30 (m, 3H), 0.93 (d, J = 5.8 Hz, 3H).
476		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.96 (d, J = 3.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 6.94 - 6.75 (m, 2H), 6.73 - 6.36 (m, 1H), 6.42 - 6.22 (m, 2H), 5.83 (d, J = 11.8 Hz, 1H), 5.76-5.41 (m, 1H), 4.58 (s, 1H), 4.42 - 4.31 (m, 1H), 4.27 (s, 3H), 4.16 - 4.98 (m, 2H), 3.46 (t,

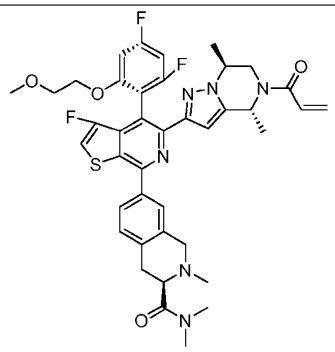
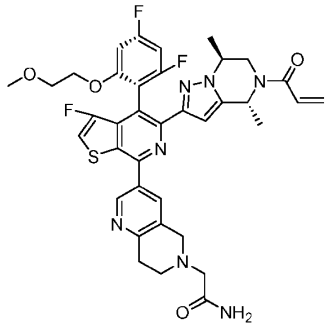
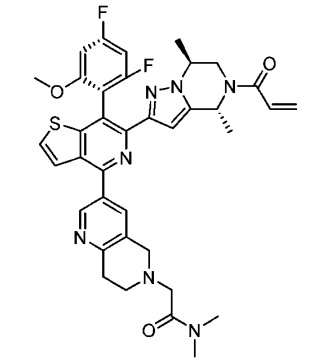
		J = 4.8 Hz, 2H), 3.07 (s, 3H), 2.03 (s, 2H), 1.54 - 1.34 (m, 3H).
477		LCMS m/z [M+1]: 759.1 ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (d, J = 6.0 Hz, 1H), 7.73 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 6.92 - 6.85 (m, 2H), 6.75 - 6.67 (m, 1H), 6.34 - 6.24 (m, 2H), 5.86 - 5.83 (m, 1H), 5.75 - 5.51 (m, 1H), 4.75 (d, J = 15.6, 2H), 4.60 (d, J = 15.6 Hz, 1H), 4.39 (s, 1H), 4.29 - 4.21 (m, 1H), 4.13 - 4.09 (m, 2H), 3.89 - 3.81 (m, 1H), 3.61 – 3.55 (m, 1H), 3.47 - 3.44 (m, 3H), 3.21 (s, 3H), 3.11 – 3.07 (m, 9H), 1.43 (s, 3H), 1.28 (s, 3H).
478		LCMS m/z [M+1]: 741.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 - 7.91 (m, 1H), 7.86 (s, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.44 - 7.35 (m, 2H), 6.91 (d, J = 8.4 Hz, 1H), 6.89 - 6.79 (m, 1H), 6.74 (t, J = 8.5 Hz, 1H), 6.31 (d, J = 16.6 Hz, 1H), 6.04 - 5.88 (m, 1H), 5.83 (dd, J = 10.6, 1.5 Hz, 1H), 5.74 - 5.37 (m, 1H), 4.65 - 4.38 (m, 2H), 4.28 - 3.94 (m, 5H), 3.93 - 3.77 (m, 1H), 3.45 (t, J = 5.0 Hz, 2H), 3.28 - 3.19 (m, 4H), 3.12 - 3.04 (m, 4H), 3.02 (s, 3H), 2.50 (s, 3H), 1.47 - 1.21 (m, 6H).
479		LCMS m/z [M+1]: 725.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.29 (d, J = 1.6 Hz, 1H), 8.54 (s, 1H), 7.59 (d, J = 2.2 Hz, 1H), 6.83 – 6.81 (m, 2H), 6.66 (td, J = 9.2, 1.9 Hz, 1H), 6.28 (d, J = 15.6 Hz, 1H), 6.21 – 5.81 (m, 1H), 6.03 (s, 1H), 5.84 – 5.81 (m, 1H), 5.68 – 5.48 (m, 1H), 4.25 – 4.21 (m, 1H), 4.15 – 4.10 (m, 3H), 3.92 – 3.73 (m, 2H), 3.86 (t, J = 4.4 Hz, 2H), 3.43 (t, J = 6.1 Hz, 2H), 3.11 (s, 3H), 3.10 (s, 3H), 1.45 – 1.41 (m, 3H).

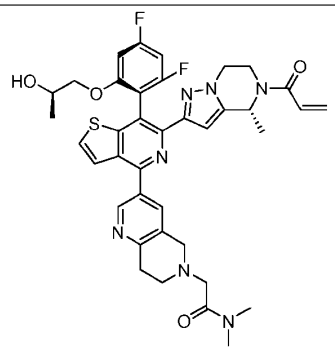
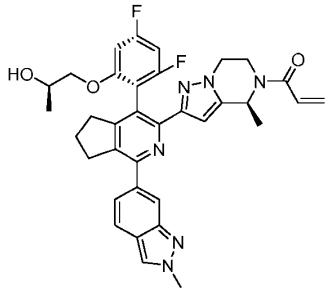
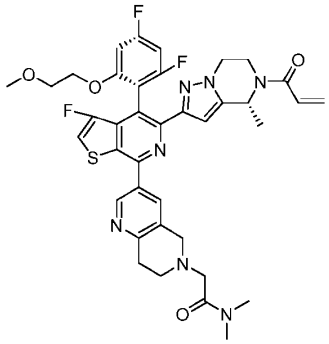
480		LCMS m/z [M+1]: 641.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.36 (s, 1H), 8.63 (s, 1H), 8.48 (d, J = 8.7 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 5.5 Hz, 1H), 7.17 (d, J = 5.4 Hz, 1H), 6.85 (dd, J = 18.5, 8.2 Hz, 2H), 6.78 – 6.70 (m, 1H), 6.29 (d, J = 13.8 Hz, 1H), 6.11 (s, 1H), 5.83 (dd, J = 10.6, 1.5 Hz, 1H), 5.75 – 5.56 (m, 1H), 4.44 (s, 1H), 4.31 – 4.18 (m, 4H), 4.11 (s, 1H), 3.86 – 3.64 (m, 4H), 1.48 - 1.30 (m, 3H), 0.91 (d, J = 6.1 Hz, 3H).
481		LCMS m/z [M+1]: 659.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (d, J = 7.4 Hz, 2H), 7.96 (d, J = 8.7 Hz, 1H), 7.82 (dd, J = 8.7, 1.3 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 6.91 – 6.77 (m, 2H), 6.72 – 6.64 (m, 1H), 6.28 (d, J = 16.4 Hz, 1H), 6.08 (s, 1H), 5.83 (d, J = 11.8 Hz, 1H), 5.59 (d, J = 84.2 Hz, 1H), 4.53 – 4.21 (m, 5H), 4.09 (s, 1H), 3.87 – 3.67 (m, 4H), 1.48 - 1.30 (m, 3H), 0.95 (d, J = 5.7 Hz, 3H).
482		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.36 (d, J = 7.8 Hz, 1H), 6.90 – 6.82 (m, 2H), 6.74 – 6.67 (m, 1H), 6.35 – 6.19 (m, 2H), 5.84 (d, J = 11.0 Hz, 1H), 5.74 – 5.49 (m, 1H), 4.88 – 4.81 (m, 1H), 4.42 – 4.03 (m, 3H), 3.93 – 3.86 (m, 3H), 3.80 – 3.73 (m, 2H), 3.51 (s, 2H), 3.17 (s, 3H), 3.07 (t, J = 5.6 Hz, 2H), 3.00 (s, 3H), 2.94 (t, J = 5.6 Hz, 2H), 1.48 (d, J = 18.8 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H).

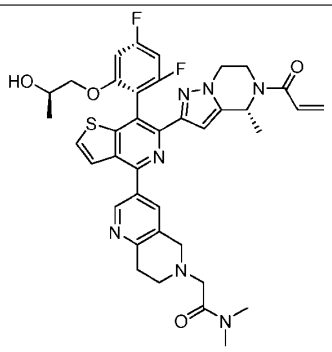
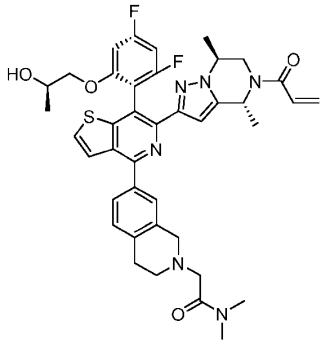
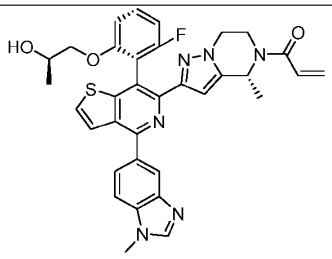
483		LCMS m/z [M+1]: 727 ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.56 (d, J = 5.4 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 6.74 (dd, J = 16.6, 10.8 Hz, 2H), 6.65 (s, 1H), 6.19 (d, J = 15.6 Hz, 1H), 6.04 (s, 1H), 5.72 (dd, J = 10.6, 1.4 Hz, 1H), 5.65 – 5.36 (m, 1H), 4.74 – 4.68 (m, 1H), 4.41 – 3.98 (m, 5H), 3.91 (s, 2H), 3.76 – 3.64 (m, 4H), 3.28 (s, 2H), 3.15 – 3.08 (m, 2H), 3.00 (s, 3H), 2.92 (s, 3H), 1.40 – 1.32 (m, 3H), 0.77 (d, J = 6.0 Hz, 3H).
484		LCMS m/z [M+1]: 623 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.18 (s, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.73 (dd, J = 12.4, 5.6 Hz, 3H), 7.49 (dd, J = 15.0, 8.2 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.85 (dd, J = 17.0, 9.2 Hz, 2H), 6.29 (d, J = 17.0 Hz, 1H), 6.14 (s, 1H), 5.83 (dd, J = 10.6, 1.4 Hz, 1H), 5.70 – 5.38 (m, 1H), 4.87 – 4.74 (m, 1H), 4.40 (s, 1H), 4.31 (s, 3H), 4.21 (dd, J = 12.4, 2.6 Hz, 1H), 4.01 (s, 1H), 3.89 – 3.82 (m, 3H), 1.43 (s, 3H), 0.92 (d, J = 6.0 Hz, 3H).
485		LCMS m/z [M+1]: 623 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.18 (s, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.75 (dt, J = 12.0, 3.4 Hz, 3H), 7.50 (dd, J = 15.0, 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.93 – 6.79 (m, 2H), 6.29 (d, J = 16.4 Hz, 1H), 6.09 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.72 – 5.32 (m, 1H), 4.86 – 4.77 (m, 1H), 4.50 (s, 1H), 4.31 (s, 3H), 4.21 (dd, J = 12.4, 3.0 Hz, 1H), 4.07 (s, 1H), 3.91 – 3.82 (m, 1H), 3.79 – 3.72 (m, 2H), 1.42 (s, 3H), 0.92 (d, J = 6.0 Hz, 3H).

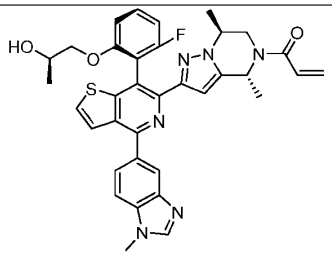
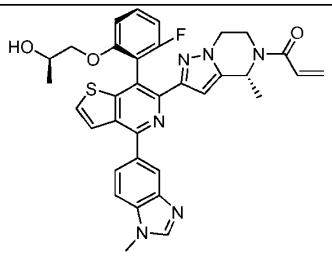
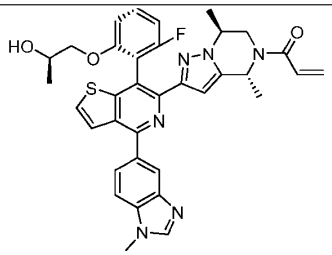
486		LCMS m/z [M+1]: 623 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.31 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 7.50 (dd, J = 15.2, 8.2 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.92 – 6.79 (m, 2H), 6.30 (d, J = 16.4 Hz, 1H), 6.12 (s, 1H), 5.83 (dd, J = 10.6, 1.4 Hz, 1H), 5.75 – 5.42 (m, 1H), 4.87 – 4.78 (m, 1H), 4.41 (s, 1H), 4.23 (dd, J = 12.4, 2.8 Hz, 1H), 4.07 (s, 3H), 3.88 – 3.83 (m, 4H), 1.43 (s, 3H), 0.92 (d, J = 6.1 Hz, 3H).
487		LCMS m/z [M+1]: 623 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.27 (s, 1H), 8.03 (dd, J = 8.4, 1.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 12.2, 5.6 Hz, 2H), 7.50 (dd, J = 15.0, 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.93 – 6.83 (m, 2H), 6.29 (d, J = 14.8 Hz, 1H), 6.10 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.73 – 5.36 (m, 1H), 4.86 – 4.81 (m, 1H), 4.41 (s, 1H), 4.21 (dd, J = 12.6, 2.8 Hz, 1H), 4.02 (s, 3H), 3.92 – 3.70 (m, 4H), 1.42 (s, 3H), 0.92 (d, J = 5.8 Hz, 3H).
488		LCMS m/z [M+1]: 670 ^{1}H NMR (400 MHz, CD_3OD) δ 8.93 (s, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.81 (d, J = 4.8 Hz, 1H), 7.66 (d, J = 5.4 Hz, 1H), 6.87 (d, J = 10.0 Hz, 2H), 6.71 (s, 1H), 6.34 (d, J = 16.4 Hz, 1H), 6.20 (s, 1H), 5.86 (dd, J = 10.6, 1.4 Hz, 1H), 5.79 – 5.50 (m, 1H), 4.86 – 4.83 (m, 1H), 4.78 – 4.21 (m, 2H), 3.98 (s, 2H), 3.85 (s, 1H), 3.72 (s, 3H), 3.50 (s, 1H), 3.22 (t, J = 5.8 Hz, 2H), 3.08 (t, J = 5.8 Hz, 2H), 1.48 (d, J = 19.8 Hz, 3H), 1.31 (s, 3H).

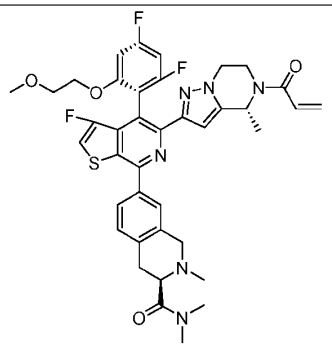
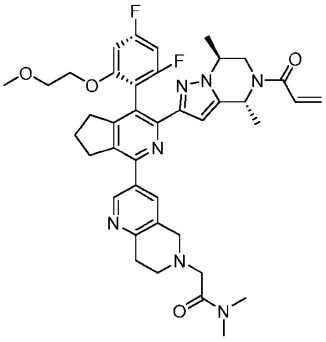
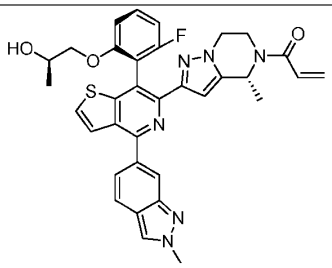
489		LCMS m/z [M+1]: 711.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.43 (d, J = 1.8 Hz, 1H), 8.58 (s, 1H), 7.61 (d, J = 2.7 Hz, 1H), 6.89 - 6..75 (m, 2H), 6.68 – 6.60 (m, 1H), 6.33 - 6.21 (m, 1H), 6.09 (s, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.68 - 5.52 (m, 1H), 4.31 (s, 2H), 4.25 - 4.16 (m, 2H), 4.11 – 3.97 (m, 4H), 3.76 (t, J = 11.6 Hz, 2H), 3.43 (t, J = 4.5 Hz, 2H), 3.07 (s, 3H), 2.88 (s, 3H), 1.48 - 1.37 (m, 3H).
490		LCMS m/z [M+1]: 741.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 8.1 Hz, 1H), 8.07 (s, 1H), 8.02 (d, J = 5.5 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.15 (d, J = 5.5 Hz, 1H), 6.92 – 6.81 (m, 2H), 6.67 (td, J = 9.2, 2.2 Hz, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.14 (s, 1H), 5.85 (dd, J = 10.6, 1.6 Hz, 1H), 5.78 – 5.43 (m, 1H), 4.92 (dd, J = 10.7, 5.3 Hz, 1H), 4.77 (s, 1H), 4.68-4.58 (m, 1H), 4.45 (s, 1H), 4.19 – 4.05 (m, 1H), 4.06 – 3.94 (m, 1H), 3.66 – 3.54 (m, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.35 (d, J = 11.1 Hz, 1H), 3.24 (s, 3H), 3.10 (s, 6H), 3.05 (s, 3H), 1.51 – 1.38 (m, 3H), 1.36 – 1.26 (m, 3H).
491		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 – 8.39 (m, 3H), 8.03 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 5.4 Hz, 1H), 6.96 – 6.76 (m, 3H), 6.32 (s, 1H), 6.02 (s, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.76 – 5.43 (m, 1H), 4.62 – 4.25 (m, 5H), 4.23 – 4.01 (m, 1H), 3.89 – 3.82 (m, 1H), 3.81 – 3.70 (m, 2H), 1.48 - 1.30 (m, 3H), 0.95 (d, J = 5.9 Hz, 3H).

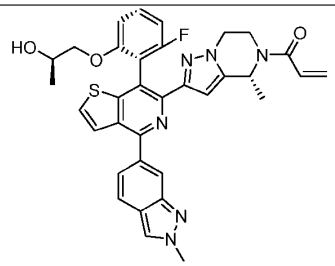
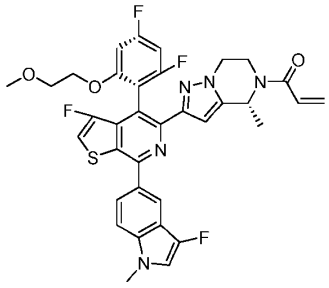
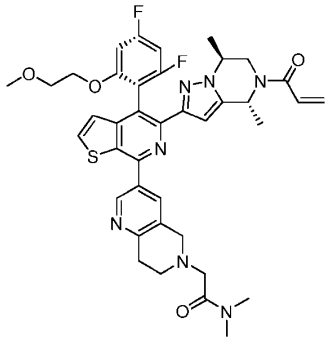
492		LCMS m/z [M+1]: 759.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (dd, J = 8.0, 1.2 Hz, 1H), 8.03 (s, 1H), 7.58 – 7.52 (m, 2H), 6.92 – 6.77 (m, 2H), 6.59 (td, J = 9.3, 2.2 Hz, 1H), 6.33 (d, J = 16.4 Hz, 1H), 6.12 (s, 1H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.79 – 5.41 (m, 1H), 4.95 – 4.88 (m, 1H), 4.82 – 4.75 (m, 1H), 4.63 (d, J = 15.5 Hz, 1H), 4.48 – 4.38 (m, 1H), 4.15 – 3.98 (m, 2H), 3.65 – 3.55 (m, 1H), 3.46 (t, J = 4.6 Hz, 2H), 3.24 (s, 3H), 3.10 (s, 6H), 3.08 (s, 3H), 1.51 – 1.38 (m, 3H), 1.34 – 1.27 (m, 3H).
493		LCMS m/z [M+1]: 732.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (d, J = 1.7 Hz, 1H), 8.30 (d, J = 1.4 Hz, 1H), 7.55 (d, J = 2.3 Hz, 1H), 6.94 – 6.76 (m, 2H), 6.64 – 6.56 (m, 1H), 6.32 (d, J = 16.9 Hz, 1H), 6.15 (s, 1H), 5.88 – 5.80 (m, 1H), 5.76 – 5.44 (m, 1H), 4.68 – 4.50 (m, 2H), 4.46 – 4.38 (m, 1H), 4.28 – 4.18 (m, 0.5H), 4.12 – 4.04 (m, 1H), 4.03 – 3.94 (m, 3H), 3.90 – 3.78 (m, 0.5H), 3.45 (t, J = 4.6 Hz, 2H), 3.34 (s, 2H), 3.21 (t, J = 5.6 Hz, 2H), 3.10 – 3.04 (m, 5H), 1.52 – 1.38 (m, 3H), 1.34 – 1.24 (m, 3H).
494		LCMS m/z [M+1]: 698.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (d, J = 1.8 Hz, 1H), 8.35 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.88 (d, J = 10.8 Hz, 2H), 6.70 (td, J = 9.3, 2.2 Hz, 1H), 6.35 (d, J = 16.3 Hz, 1H), 6.20 (s, 1H), 5.87 (dd, J = 10.6, 1.6 Hz, 1H), 5.65 (d, J = 87.0 Hz, 1H), 4.78 (s, 2H), 4.54 – 4.22 (m, 3H), 3.87 (s, 3H), 3.73 (s, 3H), 3.51 (t, J = 6.1 Hz, 2H), 3.08 (s, 6H), 1.54 – 1.41 (m, 3H), 1.31 (s, 4H).

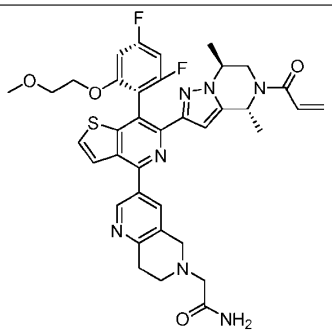
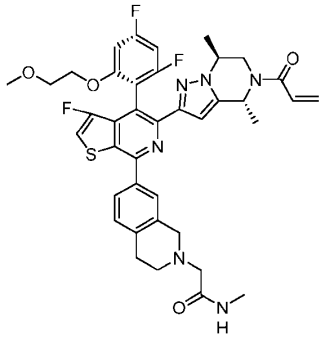
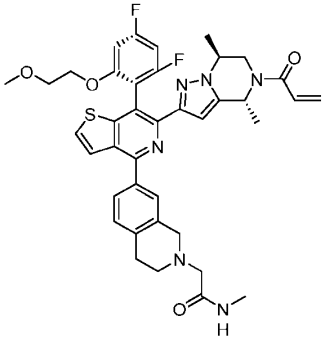
495		LCMS m/z [M+1]: 728.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (d, J = 1.8 Hz, 1H), 8.18 (s, 1H), 7.80 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.92 – 6.82 (m, 2H), 6.74 (t, J = 9.2 Hz, 1H), 6.38 – 6.23 (m, 2H), 5.84 (d, J = 10.7 Hz, 1H), 5.63 (d, J = 84.6 Hz, 1H), 4.42 (s, 1H), 4.25 – 4.01 (m, 2H), 3.95 (s, 2H), 3.91 – 3.67 (m, 4H), 3.56 (s, 2H), 3.24 – 3.13 (m, 5H), 3.06 (t, J = 5.9 Hz, 2H), 3.01 (s, 3H), 1.46 (s, 3H), 0.89 (d, J = 6.0 Hz, 3H).
496		LCMS m/z [M+1]: 625.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.01 (s, 1H), 7.81 (d, J = 8.72 Hz, 1H), 7.67 (dd, J = 8.7, 1.2 Hz, 1H), 6.86 - 6.79 (m, 1H), 6.72 (d, J = 10.9 Hz, 1H), 6.65 – 6.60 (m, 1H), 6.36 – 6.20 (m, 1H), 6.06 (s, 1H), 5.82 - 5.79 (m, 1H), 5.75 - 5.40 (m, 1H), 4.25 (s, 3H), 4.21 - 4.15 (m, 1H), 4.12 – 3.91 (m, 1H), 3.89 – 3.72 (m, 3H), 3.27 – 3.22 (m, 2H), 2.77 (t, J = 7.3 Hz, 2H), 2.17 – 2.05 (m, 2H), 1.51 – 1.34 (m, 3H), 1.03 (d, J = 6.24 Hz, 3H).
497		LCMS m/z [M+1]: 746.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (d, J = 1.92 Hz, 1H), 8.47 (d, J = 1.6 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.87-6.78 (m, 2H), 6.65 – 6.60 (m, 1H), 6.29 (d, J = 18.3 Hz, 1H), 6.04 (s, 1H), 5.84 - 5.79 (m, 1H), 5.75 - 5.40 (m, 1H), 4.50 - 4.32 (m, 3H), 4.25 - 4.20 (m, 1H), 4.11 - 3.99 (m, 3H), 3.91 – 3.58 (m, 2H), 3.48 (t, J = 6.2 Hz, 2H), 3.44 (t, J = 4.7 Hz, 2H), 3.07 (s, 3H), 3.05 (s, 6H), 1.52 - 1.35 (m, 3H).

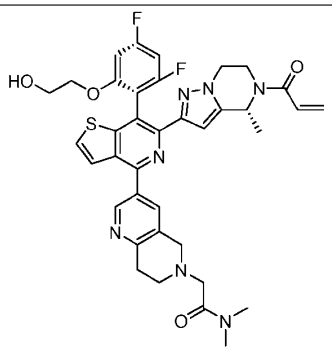
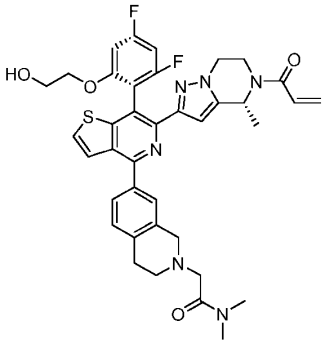
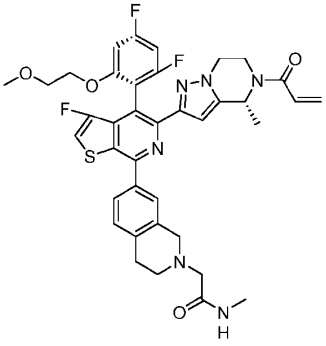
498		LCMS m/z [M+1]: 728.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (d, J = 1.9 Hz, 1H), 8.17 (d, J = 1.6 Hz, 1H), 7.81 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.93 – 6.81 (m, 2H), 6.72 (t, J = 9.2 Hz, 1H), 6.39 – 6.18 (m, 2H), 5.84 (d, J = 10.6, 1.4 Hz, 1H), 5.63 (d, J = 77.8 Hz, 1H), 4.45 (s, 1H), 4.25 – 4.01 (m, 2H), 3.97 (s, 2H), 3.92 – 3.67 (m, 4H), 3.57 (s, 2H), 3.25 – 3.13 (m, 5H), 3.08 (t, J = 5.8 Hz, 2H), 3.01 (s, 3H), 1.47 (s, 3H), 0.91 (d, J = 6.2 Hz, 3H).
499		LCMS m/z [M+1]: 741.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (dd, J = 7.9, 1.4 Hz, 1H), 7.87 (d, J = 5.6 Hz, 2H), 7.73 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 6.95 – 6.84 (m, 2H), 6.71 (m, J = 9.2, 2.1 Hz, 1H), 6.39 – 6.25 (m, 2H), 5.87 (dd, J = 10.6, 1.7 Hz, 1H), 5.65 (d, J = 87.6 Hz, 1H), 4.72 (s, 2H), 4.47 (s, 4H), 3.89 (dd, J = 26.8, 5.6 Hz, 3H), 3.81 – 3.70 (m, 2H), 3.58 – 3.34 (m, 3H), 3.07 (s, 6H), 1.46 (s, 3H), 1.29 (s, 3H), 0.94 (d, J = 6.3 Hz, 3H).
500		LCMS m/z [M+1]: 623.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (d, J = 4.0 Hz, 2H), 8.02 (m, J = 8.4, 1.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.72 (m, J = 12.4, 5.6 Hz, 2H), 7.48 (d, J = 6.8 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.84 (m, J = 17.7, 9.4 Hz, 2H), 6.18 (dd, J = 81.8, 16.4 Hz, 2H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.56 (d, J = 73.9 Hz, 1H), 4.19 (d, J = 2.7 Hz, 2H), 4.01 (s, 4H), 3.91 (d, J = 2.9 Hz, 1H), 3.77 (dd, J = 11.2, 4.3 Hz, 3H), 1.44 (d, J = 16.1 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H).

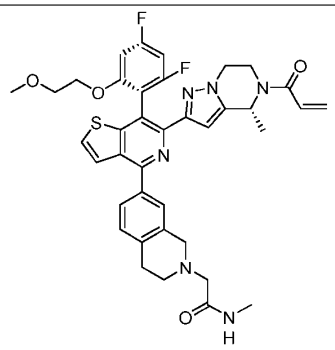
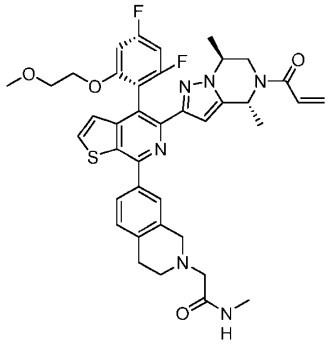
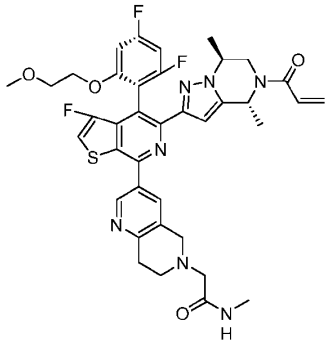
501		LCMS m/z [M+1]: 637.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.28 (s, 1H), 8.06 – 7.97 (m, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 15.8, 5.6 Hz, 2H), 7.48 (dd, J = 15.1, 8.4 Hz, 1H), 7.00 – 6.78 (m, 3H), 6.33 (d, J = 16.7 Hz, 1H), 6.21 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.75 –5.40 (m, 1H), 4.63 – 4.14 (m, 2H), 4.02 (s, 3H), 3.89 – 3.38 (m, 4H), 1.55 – 1.35 (m, 3H), 1.33 – 1.25 (m, 3H), 0.89 (d, J = 6.3 Hz, 3H).
502		LCMS m/z [M+1]: 623.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (d, J = 4.1 Hz, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 13.0, 5.6 Hz, 2H), 7.47 (d, J = 6.8 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.90 – 6.76 (m, 2H), 6.08 (s, 2H), 5.80 (d, J = 10.7 Hz, 1H), 5.56 (d, J = 79.9 Hz, 1H), 4.15 (d, J = 3.0 Hz, 2H), 3.99 (s, 4H), 3.89 – 3.54 (m, 4H), 1.39 (s, 3H), 0.88 (d, J = 5.9 Hz, 3H).
503		LCMS m/z [M+1]: 637.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 2H), 7.89 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 13.5, 5.6 Hz, 2H), 7.34 (dd, J = 15.1, 8.2 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.85 – 6.60 (m, 2H), 6.17 (dd, J = 33.6, 21.5 Hz, 2H), 5.73 (d, J = 10.6 Hz, 1H), 5.65 – 5.32(m, 1H), 4.67 – 4.02 (m, 2H), 4.00 – 3.78 (m, 4H), 3.76 – 3.27 (m, 3H), 1.45 – 1.25 (m, 3H), 1.15 – 1.02 (m, 3H), 0.83 (d, J = 6.3 Hz, 3H).

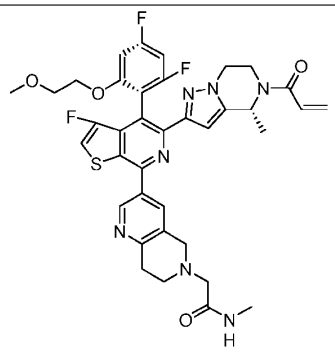
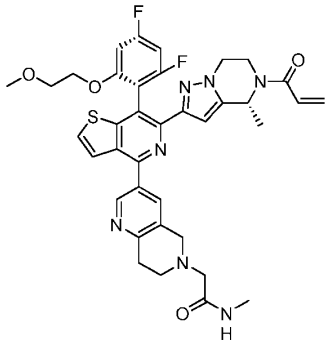
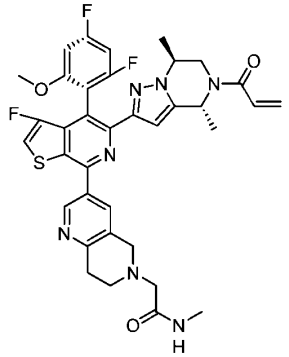
504		LCMS m/z [M+1]: 745.1 ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (d, J = 7.6 Hz, 1H), 7.90 (s, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.89 - 6.75 (m, 2H), 6.65 - 6.55 (m, 1H), 6.35 - 6.22 (m, 1H), 6.05 (s, 1H), 5.82 (d, J = 10.4 Hz,1H), 5.73 - 5.53 (m, 1H), 4.59 (s, 3H), 4.30 – 4.17 (m, 2H), 4.15 – 3.94 (m, 5H), 3.45 (t, J = 4.4 Hz, 2H), 3.25 (s, 3H), 3.15 (d, J = 4.8 Hz, 1H), 3.07 (s, 3H), 3.03 (s, 3H), 2.56 (s, 3H), 1.50 – 1.32 (m, 3H).
505		LCMS m/z [M+1]: 726.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.05 (d, J = 1.5 Hz, 1H), 8.30 - 8.27 (m, 1H), 6.91 - 6.78 (m, 2H), 6.66 - 6.57 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.05 (s, 1H), 5.84 (dd, J = 10.5, 1.5 Hz, 1H), 5.77 - 5.38 (m, 1H), 4.73 (s, 2H), 4.50 - 4.40 (m, 3H), 4.19 - 4.09 (m, 1H), 4.04 - 3.97 (m, 1H), 3.83 (t, J = 6.2 Hz, 2H), 3.54 (t, J = 4.3 Hz, 2H), 3.46 (t, J = 6.2 Hz, 2H), 3.28 - 3.19 (m, 5H), 3.04 (s, 6H), 3.02 - 2.92 (m, 1H), 2.82 - 2.72 (m, 1H), 2.26 - 2.10 (m, 2H), 1.51 - 1.23 (m, 6H).
506		LCMS m/z [M+1]: 623.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.18 (s, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.80 – 7.76 (m, 1H), 7.75 – 7.71 (m, 2H), 7.50 (dd, J = 15.2, 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.87 (dt, J = 17.0, 9.9 Hz, 2H), 6.21 (d, J = 81.0 Hz, 2H), 5.83 (d, J = 10.6 Hz, 1H), 5.59 (d, J = 80.8 Hz, 1H), 4.36 (d, J = 40.1 Hz, 4H), 4.19 (d, J = 9.5 Hz, 1H), 4.10 (s, 1H), 3.93 – 3.58 (m, 4H), 1.42 (s, 3H), 0.91 (d, J = 6.0 Hz, 3H).

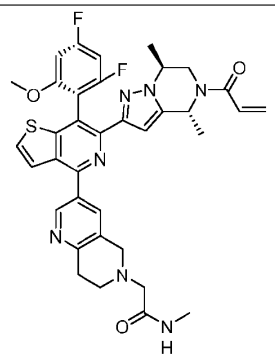
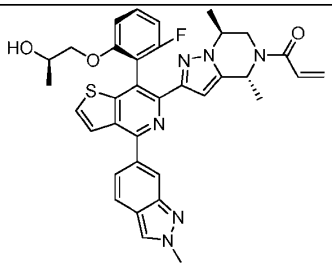
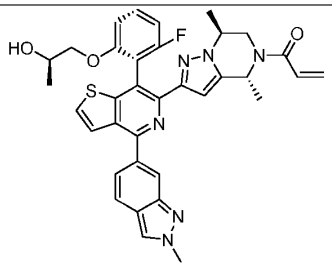
507		LCMS m/z [M+1]: 623.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.18 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.74 (dd, J = 12.4, 5.7 Hz, 3H), 7.49 (dd, J = 15.3, 8.4 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.85 (dd, J = 17.0, 8.7 Hz, 2H), 6.20 (d, J = 84.7 Hz, 2H), 5.83 (d, J = 10.6 Hz, 1H), 5.57 (d, J = 79.4 Hz, 1H), 4.35 (d, J = 34.8 Hz, 4H), 4.22 (d, J = 12.6 Hz, 1H), 4.02 (d, J = 5.6 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.87 – 3.48 (m, 3H), 1.41 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.0 Hz, 3H).
508		LCMS m/z [M+1]: 676.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.95 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.85 (s, 1H), 7.65 (dd, J = 10.8 Hz, 2.0 Hz, 1H), 7.25 (s, 1H), 6.90 - 6.80 (m, 2H), 6.67 (td, J = 9.2 Hz, 2.0 Hz, 1H), 6.35 - 6.25 (m, 1H), 5.97 (s, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.80 - 5.40 (m, 1H), 4.32 - 4.25 (m, 1H), 4.20 - 4.05 (m, 3H), 3.85 (s, 3H), 3.80 - 3.70 (m, 1H), 3.47 (t, J = 4.4 Hz, 2H), 3.12 (s, 3H), 1.55 - 1.35 (m, 3H).
509		LCMS m/z [M+1]: 742.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (d, J = 1.6 Hz, 1H), 8.51 (s, 1H), 8.00 (d, J = 5.2 Hz, 1H), 7.15 (d, J = 5.6 Hz, 1H), 6.93 - 6.78 (m, 2H), 6.73 - 6.62 (m, 1H), 6.33 (d, J = 16.8 Hz, 1H), 6.15 (s, 1H), 5.88 - 5.81 (m, 1H), 5.79 - 5.46 (m, 1H), 4.77 (s, 3H), 4.49 (s, 2H),4.46 - 4.40 (m, 1H), 4.30 - 4.17 (m, 1H), 4.16 – 4.07 (m, 1H), 4.03 – 3.95 (m, 1H), 3.89 - 3.81 (m, 2H), 3.49 (t, J = 6.0 Hz, 2H), 3.42 (t, J = 4.8 Hz, 2H), 3.07 - 3.01 (m, 9H), 1.51 - 1.38 (m, 3H), 1.34 - 1.28 (m, 3H).

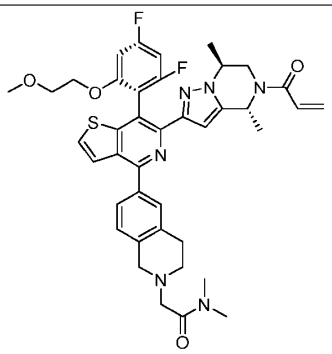
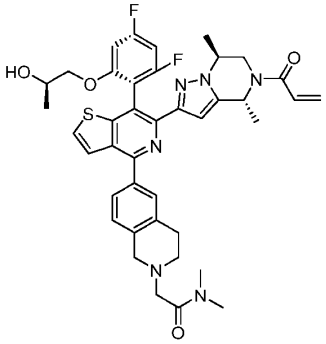
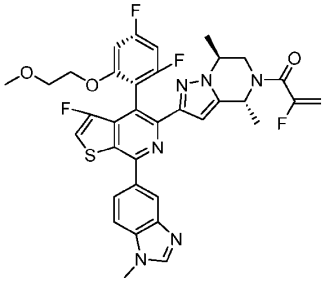
510		LCMS m/z [M+1]: 714.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (d, J = 1.5 Hz, 1H), 8.38 (s, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.94 – 6.80 (m, 2H), 6.75 – 6.63 (m, 1H), 6.33 (d, J = 16.1 Hz, 1H), 6.21 (s, 1H), 5.84 (d, J = 12.1 Hz, 1H), 5.78 – 5.39 (m, 1H), 4.72 (s, 2H), 4.48 – 4.39 (m, 1H), 4.17 (s, 2H), 4.14 – 4.00 (m, 2H), 3.82 (t, J = 6.1 Hz, 3H), 3.51 – 3.41 (m, 5H), 3.05 (s, 3H), 1.52 – 1.38 (m, 3H), 1.37 – 1.26 (m, 3H).
511		LCMS m/z [M+1]: 745.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 – 8.06 (m, 1H), 7.98 (s, 1H), 7.58 – 7.51 (m, 2H), 6.92 – 6.74 (m, 2H), 6.64 – 6.53 (m, 1H), 6.33 (d, J = 16.3 Hz, 1H), 6.11 (s, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.77 – 5.43 (m, 1H), 4.68 (s, 2H), 4.43 (s, 1H), 4.32 – 3.97 (m, 5H), 3.91 – 3.62 (m, 3H), 3.46 (t, J = 4.6 Hz, 2H), 3.41 – 3.34 (m, 2H), 3.07 (s, 3H), 2.85 (s, 3H), 1.48 -1.21 (m, 6H).
512		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, J = 8.1 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.70 (d, J = 5.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 6.95 – 6.81 (m, 2H), 6.75 – 6.67 (m, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.17 (s, 1H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.77 – 5.45 (m, 1H), 4.68 (s, 2H), 4.47 (s, 1H), 4.32 – 3.97 (m, 5H), 3.94 – 3.65 (m, 3H), 3.44 (t, J = 4.6 Hz, 2H), 3.38 (t, J = 6.0 Hz, 2H), 3.06 (s, 3H), 2.85 (s, 3H), 1.48 - 1.31 (m, 6H).

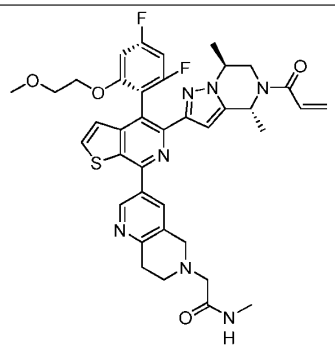
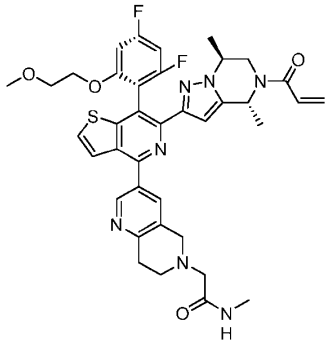
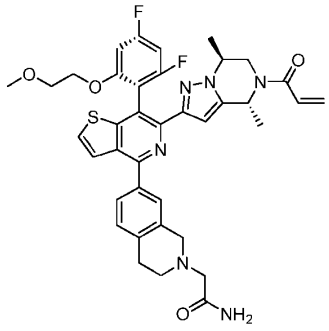
513		LCMS m/z [M+1]: 714.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (d, J = 1.6 Hz, 1H), 8.35 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.94 – 6.78 (m, 2H), 6.75 - 6.66 (m, 1H), 6.29 (d, J = 16.0 Hz, 1H), 6.19 (s, 1H), 5.87 – 5.79 (m, 1H), 5.75 - 5.46 (m, 1H), 4.76 (s, 2H), 4.48 (s, 3H), 4.25 - 4.16 (m, 1H), 4.12 – 3.98 (m, 3H), 3.86 (t, J = 6.0 Hz, 2H), 3.62 – 3.53 (m, 2H), 3.50 (t, J = 6.4 Hz, 2H), 3.05 (s, 6H), 1.57 - 1.31 (m, 3H).
514		LCMS m/z [M+1]: 713.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 - 7.92 (m, 1H), 7.87 - 7.81 (m, 2H), 7.70 (d, J = 5.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 6.93 – 6.78 (m, 2H), 6.75 - 6.66 (m, 1H), 6.33 - 6.23 (m, 1H), 6.16 (s, 1H), 5.83 - 5.79 (m, 1H), 5.74 - 5.48 (m, 1H), 4.68 (s, 2H), 4.44 (s, 1H), 4.36 (s, 2H), 4.27 - 4.19 (m, 1H), 4.05 - 3.99 (m, 2H), 3.86 - 3.68 (m, 2H), 3.62 - 3.52 (m, 2H), 3.39 (s, 2H), 3.05 (s, 6H), 3.02 (d, J = 2.8 Hz, 3H), 1.52 - 1.35 (m, 3H).
515		LCMS m/z [M+1]: 731.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (dd, J = 8.0, 1.4 Hz, 1H), 8.00 (s, 1H), 7.57 – 7.52 (m, 2H), 6.89 – 6.77 (m, 2H), 6.66 - 6.58 (m, 1H), 6.34 – 6.24 (m, 1H), 6.03 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.74 – 5.42 (m, 1H), 4.67 (s, 2H), 4.48 – 4.34 (m, 0.5H), 4.26 – 4.19 (m, 1H), 4.15 – 3.98 (m, 5H), 3.81 – 3.66 (m, 2H), 3.45 (t, J = 4.6 Hz, 2H), 3.40 – 3.33 (m, 2H), 3.07 (s, 3H), 2.85 (s, 3H), 1.50 – 1.36 (m, 3H).

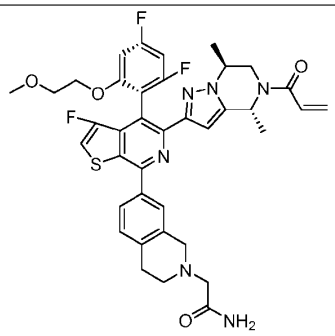
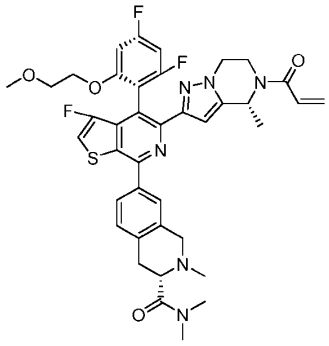
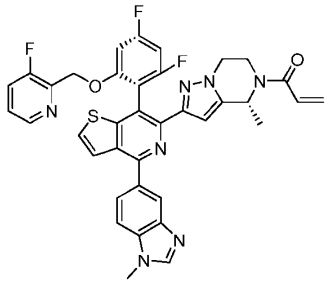
516		LCMS m/z [M+1]: 713.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (dd, J = 8.0, 1.2 Hz, 1H), 7.90 – 7.84 (m, 2H), 7.73 – 7.68 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 6.95 – 6.70 (m, 3H), 6.34 – 6.24 (m, 1H), 6.11 (s, 1H), 5.82 (dd, J = 10.6, 1.7 Hz, 1H), 5.75 – 5.42 (m, 1H), 4.67 (s, 2H), 4.50 – 4.35 (m, 0.5H), 4.28 – 4.21 (m, 1H), 4.16 – 4.02 (m, 5H), 3.79 – 3.69 (m, 2H), 3.43 (t, J = 4.6 Hz, 2H), 3.37 (t, J = 6.1 Hz, 2H), 3.05 (s, 3H), 2.85 (s, 3H), 1.50 – 1.37 (m, 3H).
517		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 8.0 Hz, 1H), 8.07 – 7.96 (m, 2H), 7.55 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 6.87 (d, J = 10.6 Hz, 2H), 6.66 (td, J = 9.2, 2.3 Hz, 1H), 6.33 (d, J = 16.6 Hz, 1H), 6.13 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.75 – 5.47 (m, 1H), 4.68 (s, 2H), 4.45 (s, 1H), 4.31 – 4.07 (m, 4H), 4.04 – 3.95 (m, 1H), 3.73 (s, 3H), 3.43 (t, J = 4.6 Hz, 2H), 3.37 (s, 2H), 3.05 (s, 3H), 2.85 (s, 3H), 1.48 - 1.21 (m, 6H).
518		LCMS m/z [M+1]: 746.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.8 Hz, 1H), 8.49 (d, J = 1.6 Hz, 1H), 7.59 (d, J = 2.2 Hz, 1H), 6.92 - 6.84 (m, 1H), 6.81 (d, J = 11.0 Hz, 1H), 6.65 - 6.53 (m, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.12 (s, 1H), 5.84 (dd, J = 10.6 Hz, 1.6 Hz, 1H), 5.77 - 5.44 (m, 1H), 4.72 (s, 2H), 4.48 - 4.38 (m, 1H), 4.14 (s, 2H), 4.12 - 4.05 (m, 1H), 4.04 - 3.96 (m, 1H), 3.81 (t, J = 6.4 Hz, 2H), 3.51 - 3.39 (m, 4H), 3.07 (s, 3H), 2.85 (s, 3H), 1.52 - 1.36 (m, 3H), 1.34 - 1.21 (m, 3H).

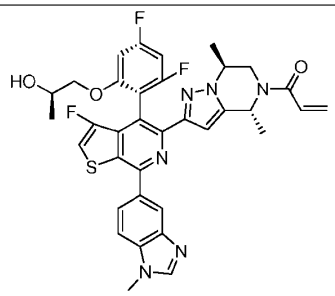
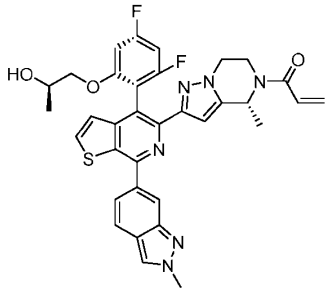
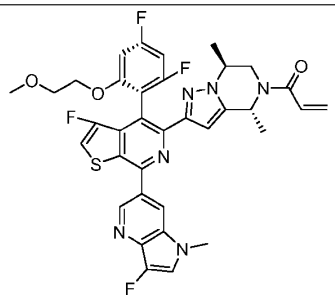
519		LCMS m/z [M+1]: 732.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31(d, J = 1.8 Hz, 1H), 8.50 (s, 1H), 7.60 (d, J = 2.2 Hz, 1H), 6.92 - 6.75 (m, 2H), 6.71 - 6.54 (m, 1H), 6.28 (d, J = 16.2 Hz, 1H), 6.04 (s, 1H), 5.82 (dd, J = 10.6 Hz, 1.4 Hz, 1H), 5.74 - 5.39 (m, 1H), 4.72 (s, 2H), 4.22 (dd, J = 12.6 Hz, 2.6 Hz, 1H), 4.14 (s, 2H), 4.11 - 3.97 (m, 3H), 3.81 (t, J = 6.2 Hz, 2H), 3.50 - 3.38 (m, 4H), 3.06 (s, 3H), 2.85 (m, 3H), 2.04-1.97 (m, 1H), 1.52 - 1.35 (m, 3H), 1.23 (t, J = 7.2 Hz, 1H).
520		LCMS m/z [M+1]: 714.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (d, J = 1.6 Hz, 1H), 8.39 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.89 (d, J = 10.8 Hz, 1H), 6.85 - 6.77 (m, 1H), 6.75 - 6.67 (m, 1H), 6.28 (d, J = 16.2 Hz, 1H), 6.13 (s, 1H), 5.82 (dd, J = 10.6 Hz, 1.6 Hz, 1H), 5.75 - 5.40 (m, 1H), 4.67 (s, 2H), 4.50 - 4.31 (m, 1H), 4.21 (dd, J = 12.8 Hz, 2.8 Hz, 1H), 4.12 - 4.08 (m, 2H), 4.07 - 3.99 (m, 2H), 3.77 (t, J = 6.2 Hz, 2H), 3.45 (t, J = 6.2 Hz, 2H), 3.41 (t, J = 4.6 Hz, 2H), 3.03 (s, 3H), 2.85 (s, 3H), 1.54 - 1.35 (m, 3H).
521		LCMS m/z [M+1]: 702.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (d, J = 2.0 Hz, 1H), 8.35 - 8.25 (m, 1H), 7.56 (d, J = 2.4 Hz, 1H), 6.92 - 6.78 (m, 1H), 6.78 - 6.71 (m, 1H), 6.65 - 6.54 (m, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.11 (s, 1H), 5.87 - 5.78 (m, 1H), 5.75 - 5.53 (m, 1H), 4.47 - 4.37 (m, 1H), 4.01 (s, 2H), 3.68 (s, 3H), 3.39 (s, 2H), 3.23 (t, J = 5.6 Hz, 2H), 3.15 - 3.07 (m, 2H), 2.81 (s, 3H), 1.54 - 1.35 (m, 3H), 1.34 - 1.23 (m, 3H).

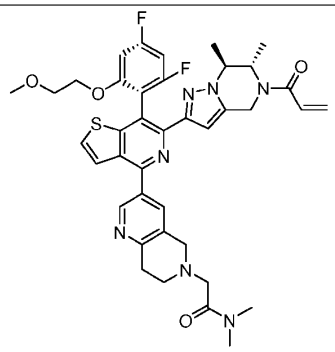
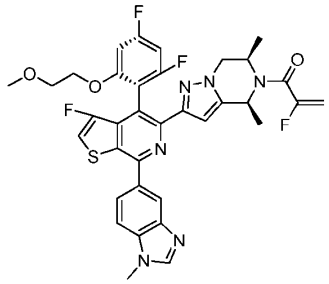
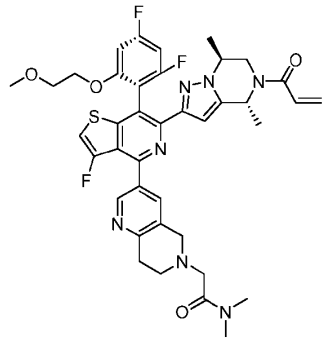
522		LCMS m/z [M+1]: 684.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.18 (d, J = 1.7 Hz, 1H), 8.41 (s, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.88 (d, J = 10.6 Hz, 2H), 6.71 (m, J = 9.2, 2.2 Hz, 1H), 6.35 (d, J = 16.7 Hz, 1H), 6.20 (s, 1H), 5.87 (dd, J = 10.6, 1.7 Hz, 1H), 5.64 (d, J = 86.8 Hz, 1H), 4.88 – 4.85 (m, 1H), 4.72 (s, 2H), 4.45 (s, 1H), 4.13 (s, 3H), 3.81 (d, J = 6.2 Hz, 2H), 3.73 (s, 3H), 3.49 (t, J = 6.2 Hz, 2H), 2.88 (s, 3H), 1.46 (s, 3H), 1.31 (s, 3H).
523		LCMS m/z [M+1]: 637.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.17 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.73 (dd, J = 13.6, 6.8 Hz, 3H), 7.48 (dd, J = 15.2, 8.1 Hz, 1H), 6.98 – 6.82 (m, 3H), 6.33 (d, J = 16.9 Hz, 1H), 6.21 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.62 (d, J = 86.5 Hz, 1H), 4.56 (d, J = 120.9 Hz, 2H), 4.30 (s, 3H), 3.80 (ddt, J = 23.4, 12.0, 5.9 Hz, 3H), 3.63 (dd, J = 9.1, 4.8 Hz, 1H), 1.45 (d, J = 21.9 Hz, 3H), 1.29 (d, J = 13.2 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H).
524		LCMS m/z [M+1]: 637.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.17 (s, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.78 – 7.68 (m, 3H), 7.47 (dd, J = 15.2, 8.3 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.82 (t, J = 8.2 Hz, 2H), 6.29 (dd, J = 34.1, 22.7 Hz, 2H), 5.85 (d, J = 10.6 Hz, 1H), 5.62 (d, J = 80.9 Hz, 1H), 4.49 (dd, J = 59.1, 56.2 Hz, 2H), 4.30 (s, 3H), 4.04 – 3.94 (m, 1H), 3.92 – 3.71 (m, 3H), 1.46 (d, J = 28.1 Hz, 3H), 1.24 (s, 3H), 0.95 (d, J = 6.1 Hz, 3H).

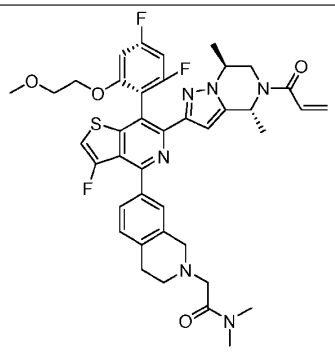
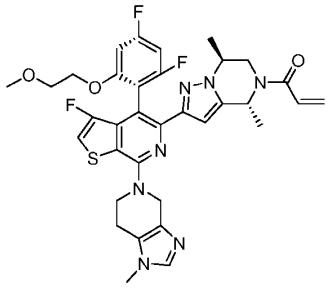
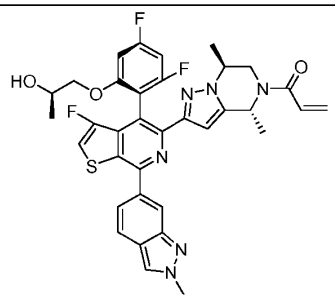
525		LCMS m/z [M+1]: 741.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (d, J = 8.0 Hz, 2H), 7.87 – 7.81 (m, 1H), 7.70 (t, J = 5.0 Hz, 1H), 7.50 – 7.45 (m, 1H), 6.90 (t, J = 16.1 Hz, 2H), 6.72 (s, 1H), 6.35 (d, J = 16.9 Hz, 1H), 6.21 (s, 1H), 5.86 (dd, J = 10.6, 1.7 Hz, 1H), 5.79 – 5.49 (m, 1H), 4.69 (s, 2H), 4.47 (s, 3H), 4.08 (s, 3H), 3.46 (dd, J = 10.6, 6.1 Hz, 7H), 3.09 – 3.04 (m, 9H), 1.46 (s, 3H), 1.33 (s, 3H).
526		LCMS m/z [M+1]: 741.0 ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 – 7.79 (m, 3H), 7.72 (d, J = 5.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 6.90 (t, J = 17.1 Hz, 2H), 6.72 (d, J = 8.8 Hz, 1H), 6.42 – 6.19 (m, 2H), 5.86 (dd, J = 10.6, 1.6 Hz, 1H), 5.76 (s, 1H), 4.70 (s, 2H), 4.47 (s, 3H), 4.25 (s, 1H), 4.08 – 3.70 (m, 5H), 3.47 (d, J = 23.4 Hz, 3H), 3.08 (s, 6H), 1.47 (s, 3H), 1.29 (s, 3H), 0.95 (d, J = 6.3 Hz, 3H).
527		LCMS m/z [M+1]: 691.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.61 (s, 1H), 8.47 (dd, J = 8.7, 1.4 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 10.9 Hz, 1H), 6.63 (td, J = 9.3, 2.3 Hz, 1H), 6.20 (s, 1H), 5.55 (s, 1H), 5.45 – 5.32 (m, 1H), 5.29 (s, 1H), 4.49-4.41 (m, 1H), 4.24 (s, 3H), 4.20 – 3.98 (m, 2H), 3.50 (t, J = 4.6 Hz, 2H), 3.11 (s, 3H), 1.49 (d, J = 6.5 Hz, 3H), 1.34 (d, J = 6.7 Hz, 3H).

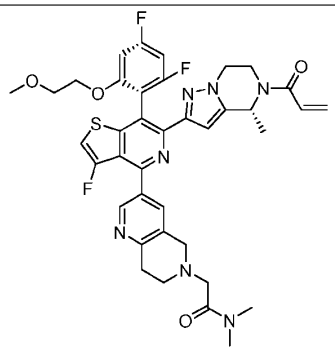
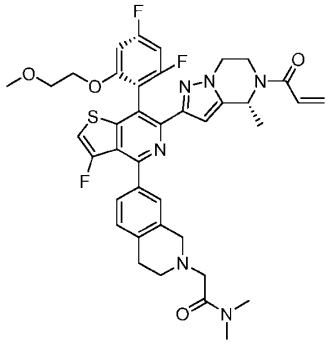
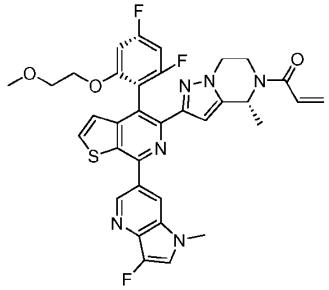
528		LCMS m/z [M+1]: 728.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (s, 1H), 8.52 (s, 1H), 7.99 (d, J = 5.6 Hz, 1H), 7.14 (d, J = 5.6 Hz, 1H), 6.92 - 6.80 (m, 2H), 6.67 (td, J = 9.2 Hz, 2.0 Hz, 1H), 6.35 - 6.30 (m, 1H), 6.15 (s, 1H), 5.84 (dd, J = 10.8 Hz, 1.6 Hz, 1H), 5.80 - 5.40 (m, 1H), 4.66 (s, 2H), 4.50 - 4.40 (m, 1H), 4.15 - 4.05 (m, 3H), 4.05 - 3.95 (m, 1H), 3.90 - 3.70 (m, 3H), 3.50 - 3.40 (m, 4H), 3.05 (s, 3H), 2.86 (s, 3H), 1.55 - 1.35 (m, 3H), 1.35 - 1.25 (m, 3H).
529		LCMS m/z [M+1]: 728.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (s, 1H), 8.38 (s, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.92 - 6.80 (m, 2H), 6.69 (td, J = 9.2 Hz, 2.4 Hz, 1H), 6.35 - 6.30 (m, 1H), 6.21 (s, 1H), 5.84 (dd, J = 10.8 Hz, 1.6 Hz, 1H), 5.80 - 5.40 (m, 1H), 4.67 (s, 2H), 4.50 - 4.40 (m, 1H), 4.15 - 4.00 (m, 4H), 3.76 (t, J = 6.0 Hz, 2H), 3.50 - 3.40 (m, 4H), 3.04 (s, 3H), 2.89 (s, 3H), 1.55 - 1.35 (m, 3H), 1.35 - 1.25 (m, 3H).
530		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 5.6 Hz, 2H), 7.68 (d, J = 5.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.73 – 6.68 (m, 1H), 6.35 – 6.31 (m, 1H), 6.17 (s, 1H), 5.84 (dd, J = 10.4, 1.6 Hz, 1H), 5.83 – 5.48 (m, 1H), 4.69 (s, 3H), 4.45 (s, 1H), 4.18 – 4.03 (m, 4H), 3.89 – 3.74 (m, 3H), 3.49 – 3.42 (m, 2H), 3.35 (s, 2H), 3.06 (s, 3H), 1.43 (s, 3H), 1.31 (d, J = 4.4 Hz, 3H).

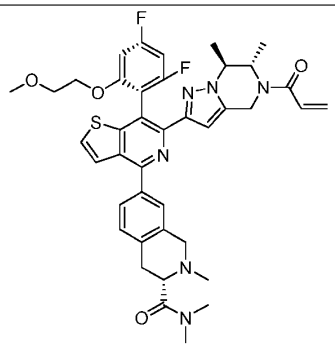
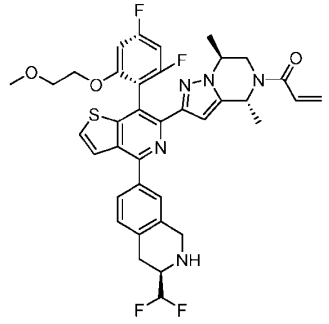
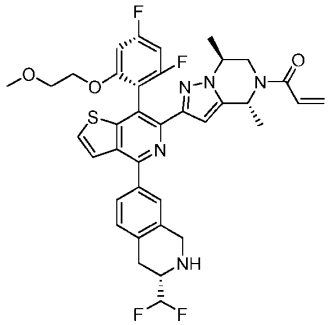
531		LCMS m/z [M+1]: 731.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 7.57 (d, J = 7.2 Hz, 2H), 6.92 – 6.80 (m, 2H), 6.64 – 6.59 (m, 1H), 6.35 (d, J = 16.8, 1H), 6.13 (s, 1H), 5.87 (d, J = 10.8, 1H), 5.73 – 5.51 (m, 1H), 4.71 (s, 3H), 4.46 (s, 1H), 4.28 – 4.18 (m, 3H), 4.13 – 4.02 (m, 2H), 3.97 – 3.72 (m, 3H), 3.50 - 3.47 (m, 3H), 3.10 (s, 3H), 1.46 - 1.44 (m, 3H), 1.32 (s, 3H).
532		LCMS m/z [M+1]: 745.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (dd, J = 8.1, 2.0 Hz, 1H), 8.05 (d, J = 1.7 Hz, 1H), 7.58 – 7.51 (m, 2H), 6.88 – 6.77 (m, 2H), 6.62 (td, J = 9.3, 2.3 Hz, 1H), 6.33 - 6.23 (m, 1H), 6.04 (d, J = 1.8 Hz, 1H), 5.82 (dd, J = 10.6, 1.9 Hz, 1H), 5.72 - 5.55 (m, 1H), 4.92 - 4.87 (m, 1H), 4.80 - 4.72 (m, 2H), 4.65 - 4.57 (m, 1H), 4.48 - 4.33 (m, 1H), 4.25 – 4.18 (m, 1H), 4.12 – 3.98 (m, 3H), 3.81 - 3.67 (m, 1H), 3.59 (dd, J = 17.6, 5.5 Hz, 1H), 3.45 (t, J = 4.6 Hz, 2H), 3.37 - 3.32 (m, 1H), 3.24 (s, 3H), 3.11 – 3.04 (m, 8H), 1.48 - 1.36 (m, 3H).
533		LCMS m/z [M+1]: 691.9 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.25 (d, J = 3.1 Hz, 2H), 7.99 (d, J = 8.3 Hz, 1H), 7.76 (dd, J = 8.3, 2.4 Hz, 1H), 7.69 (ddd, J = 7.0, 4.8, 2.8 Hz, 2H), 7.49 (t, J = 9.0 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.14 (d, J = 10.7 Hz, 1H), 6.88 (dd, J = 16.7, 10.9 Hz, 1H), 6.75 (td, J = 9.2, 2.2 Hz, 1H), 6.32 (d, J = 16.0 Hz, 1H), 6.06 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.56 (d, J = 75.2 Hz, 1H), 5.21 (s, 2H), 4.27 (dd, J = 78.4, 29.1 Hz, 2H), 4.11 – 3.94 (m, 4H), 3.63 (d, J = 100.9 Hz, 1H), 1.45 (d, J = 28.1 Hz, 3H).

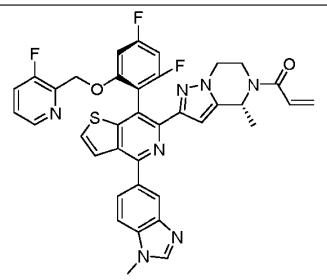
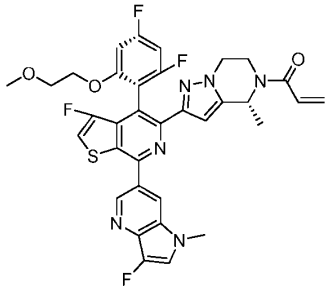
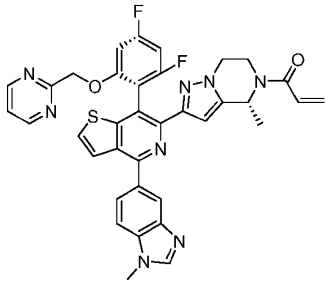
534		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.59 (s, H), 8.44 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 6.96 – 6.73 (m, 2H), 6.65 - 6.55 (m, 1H), 6.33 (d, J = 16.8 Hz, 1H), 6.22 (s, 1H), 5.85 (d, J = 10.4 Hz, 1H), 5.79 - 5.70 (m, 1H), 4.43 (s, 1H), 4.21 (s, 4H), 3.97 - 3.87 (m, 1H), 3.86 - 3.72 (m, 2H), 1.52 - 1.37 (m, 3H), 1.33 - 1.19 (m, 3H), 0.95 (d, J = 6.0 Hz, 3H).
535		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 – 8.37 (m, 3H), 8.04 (d, J = 8.7 Hz, 1H), 7.79 (dd, J = 8.7, 1.4 Hz, 1H), 7.32 (d, J = 5.4 Hz, 1H), 6.98 – 6.72 (m, 3H), 6.29 (d, J = 16.8 Hz, 1H), 6.06 (s, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.36 – 4.28 (m, 4H), 4.25 – 4.05 (m, 1H), 3.91 – 3.70 (m, 4H), 1.43 (s, 3H), 0.95 (d, J = 6.3 Hz, 3H).
536		LCMS m/z [M+1]: 691.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.24 (d, J = 1.3 Hz, 1H), 8.95 (s, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 2.3 Hz, 1H), 6.86 (dd, J = 24.9, 13.0 Hz, 2H), 6.64 (m, J = 9.3, 2.2 Hz, 1H), 6.34 (d, J = 16.6 Hz, 1H), 6.13 (s, 1H), 5.86 (dd, J = 10.6, 1.6 Hz, 1H), 5.62 (d, J = 86.6 Hz, 1H), 4.74 (s, 1H), 4.48 (s, 1H), 4.26 – 3.85 (m, 6H), 3.48 (t, J = 4.6 Hz, 2H), 3.11 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H).

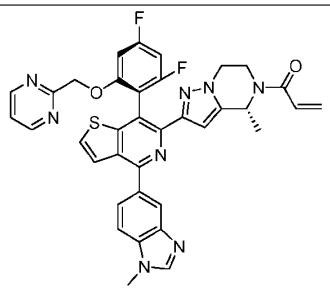
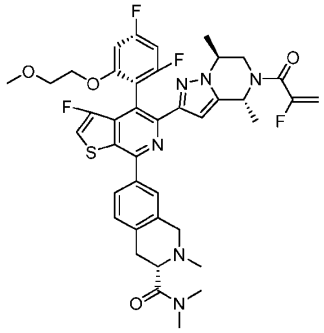
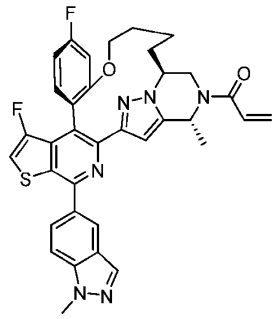
537		LCMS m/z [M+1]: 742.0 ^{1}H NMR (400 MHz, CD_3OD) δ 9.13 (d, J = 1.7 Hz, 1H), 8.34 (s, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 6.84 (t, J = 14.5 Hz, 2H), 6.70 (m, J = 9.2, 2.2 Hz, 1H), 6.32 – 6.18 (m, 2H), 5.81 (dd, J = 10.6, 1.8 Hz, 1H), 5.24 (d, J = 18.0 Hz, 1H), 5.09 (s, 1H), 4.74 (s, 2H), 4.62 (d, J = 15.9 Hz, 1H), 4.47 (s, 2H), 4.30 – 4.26 (m, 1H), 4.11 – 4.04 (m, 1H), 4.01 – 3.94 (m, 1H), 3.84 (s, 2H), 3.47 (t, J = 6.2 Hz, 2H), 3.40 (t, J = 4.6 Hz, 2H), 3.03 (d, J = 4.5 Hz, 9H), 1.33 – 1.27 (m, 3H), 1.22 – 1.11 (m, 3H).
538		LCMS m/z [M+1]: 691.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.32 (s, 1H), 8.58 (s, 1H), 8.44 (dd, J = 8.6, 1.3 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 10.8 Hz, 1H), 6.65 (td, J = 9.3, 2.2 Hz, 1H), 6.20 (s, 1H), 5.46 (q, J = 6.7 Hz, 1H), 5.36 - 5.20 (m, 2H), 4.20 (s, 4H), 4.17 - 4.04 (m, 2H), 4.00 - 3.91 (m, 1H), 3.45 (t, J = 4.7 Hz, 2H), 3.09 (s, 3H), 1.52 (d, J = 6.7 Hz, 3H), 1.40 - 1.27 (m, 2H), 1.24 (d, J = 6.8 Hz, 3H).
539		LCMS m/z [M+1]: 760.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.20 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 6.92 - 6.82 (m, 2H), 6.73 - 6.68 (m, 1H), 6.34 - 6.27 (m, 2H), 5.85 - 5.47 (m, 2H), 4.74 (s, 3H), 4.47 (s, 2H), 4.39 (s, 1H), 4.13 - 4.03 (m, 2H), 3.85 (s, 2H), 3.48 - 3.43 (m, 5H), 3.05 (m, 9H), 1.44 (s, 3H), 1.28 (d, J = 6.0 Hz, 3H).

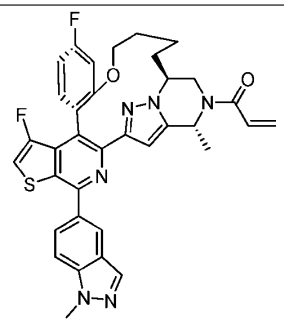
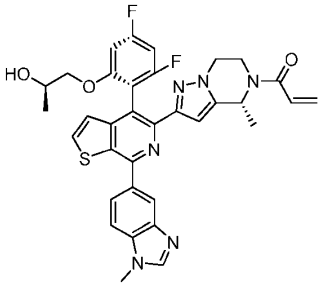
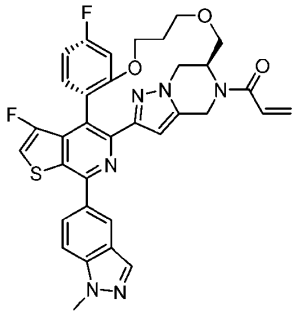
540		LCMS m/z [M+1]: 759.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 7.2 Hz, 1H), 7.66 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 6.90 - 6.87 (m, 2H), 6.71 - 6.67 (m, 1H), 6.34 - 6.25 (m, 2H), 5.83 (d, J = 10.0 Hz, 1H), 5.57 - 5.51 (m, 1H), 4.61 (s, 3H), 4.37 (s, 3H), 4.12 - 4.03 (m, 3H), 3.46 - 3.44 (m, 5H), 3.07 - 3.04 (m, 9H), 1.43 (s, 3H), 1.29 (s, 3H).
541		LCMS m/z [M+1]: 678.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 6.85 (q, J = 11.1 Hz, 1H), 6.74 (d, J = 10.6 Hz, 1H), 6.52 (td, J = 9.2, 2.2 Hz, 1H), 6.34 (d, J = 15.4 Hz, 1H), 6.03 (s, 1H), 5.85 (dd, J = 10.6, 1.6 Hz, 1H), 5.76 - 5.39 (m, 1H), 5.01 - 4.86 (m, 5H), 4.45 - 4.32 (m, 1H), 4.27 - 4.16 (m, 2H), 4.09 - 3.95 (m, 2H), 3.84 (s, 3H), 3.43 (t, J = 4.7 Hz, 2H), 3.06 (s, 3H), 3.05 - 2.98 (m, 2H), 1.49 - 1.36 (m, 3H), 1.28 (d, J = 6.2 Hz, 3H).
542		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.31 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.84 (dd, J = 8.7, 1.4 Hz, 1H), 7.52 (d, J = 2.5 Hz, 1H), 6.86 (s, 1H), 6.72 (d, J = 11.0 Hz, 1H), 6.69 – 6.60 (m, 2H), 6.32 (d, J = 17.0 Hz, 1H), 6.24 (s, 1H), 5.84 (d, J = 12.0 Hz, 1H), 5.76 – 5.47 (m, 1H), 4.79 – 4.65 (m, 1H), 4.40 (s, 1H), 4.29 (s, 3H), 4.27 – 4.15 (m, 1H), 3.89 – 3.70 (m, 2H), 3.65 – 3.54 (m, 1H), 1.45 (s, 3H), 1.28 (d, J = 5.7 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H).

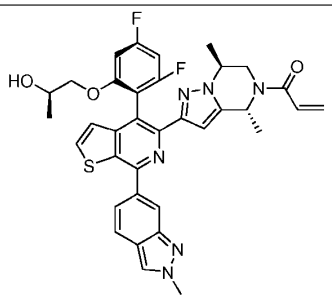
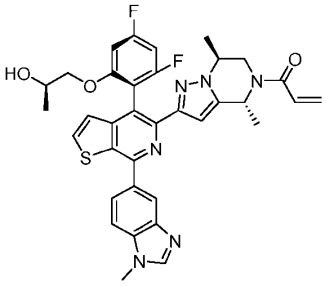
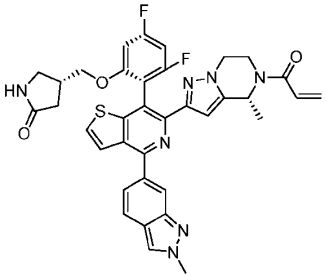
543		LCMS m/z [M+1]: 746.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.97 (s, 1H), 8.22 (s, 1H), 7.39 (d, J = 2.7 Hz, 1H), 6.95 – 6.78 (m, 2H), 6.78 – 6.71 (m, 1H), 6.28 (d, J = 16.3 Hz, 1H), 6.21 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.75 – 5.43 (m, 1H), 4.74 (s, 2H), 4.47 (s, 3H), 4.18 (dd, J = 12.7, 2.9 Hz, 1H), 4.13 – 3.95 (m, 3H), 3.92 – 3.64 (m, 3H), 3.48 (t, J = 6.2 Hz, 2H), 3.42 (t, J = 4.6 Hz, 2H), 3.06 (d, J = 4.3 Hz, 9H), 1.52-1.33 (m, 3H).
544		LCMS m/z [M+1]: 745.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, J = 5.5 Hz, 1H), 7.69 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 2.5 Hz, 1H), 6.92 – 6.78 (m, 2H), 6.73 (dd, J = 12.7, 5.7 Hz, 1H), 6.28 (d, J = 16.5 Hz, 1H), 6.19 (s, 1H), 5.82 (d, J = 10.5 Hz, 1H), 5.73 – 5.49 (m, 1H), 4.79 – 4.54 (m, 2H), 4.49 – 4.22 (m, 3H), 4.21 – 4.13 (m, 1H), 4.12 – 3.97 (m, 3H), 3.93 – 3.66 (m, 2H), 3.64 – 3.35 (m, 5H), 3.05 (d, J = 6.7 Hz, 9H), 1.52-1.33 (m, 3H).
545		LCMS m/z [M+1]: 658.9 ^{1}H NMR (400 MHz, CD_3OD) δ 9.25 (s, 1H), 8.99 (s, 1H), 8.13 (d, J = 5.4 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 5.4 Hz, 1H), 6.95 – 6.84 (m, 2H), 6.77 – 6.72 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.00 (d, J = 7.2 Hz, 1H), 5.86 (d, J = 10.6 Hz, 1H), 5.77 – 5.46 (m, 1H), 4.58 – 4.34 (m, 1H), 4.28 (d, J = 12.4 Hz, 1H), 4.18 – 4.02 (m, 4H), 4.00 (d, J = 2.8 Hz, 3H), 3.44 (t, J = 4.4 Hz, 2H), 3.09 (s, 3H), 1.44 (s, 3H).

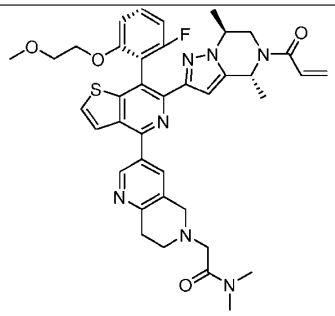
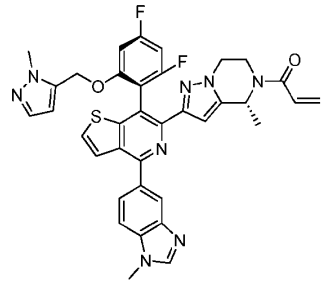
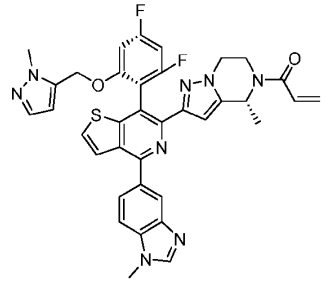
546		LCMS m/z [M+1]: 741.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 7.9 Hz, 1H), 7.92 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 6.95 – 6.79 (m, 2H), 6.74 (t, J = 9.2 Hz, 1H), 6.32 (d, J = 16.7 Hz, 1H), 6.24 (d, J = 17.4 Hz, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.39 – 5.08 (m, 2H), 5.00 – 4.93 (m, 1H), 4.80 (d, J = 15.5 Hz, 1H), 4.65 (d, J = 15.1 Hz, 2H), 4.36 – 4.30 (m, 1H), 4.16 – 4.07 (m, 1H), 4.06 – 3.98 (m, 1H), 3.63 (dd, J = 17.6, 5.3 Hz, 1H), 3.46 (t, J = 4.6 Hz, 2H), 3.41 – 3.34 (m, 1H), 3.27 (s, 3H), 3.12 (s, 6H), 3.07 (s, 3H), 1.35 (s, 3H), 1.26 – 1.12 (m, 3H).
547		LCMS m/z [M+1]: 706.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, J = 8.5 Hz, 1H), 7.90 (s, 1H), 7.80 (t, J = 4.3 Hz, 1H), 7.67 (d, J = 5.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 6.95 – 6.79 (m, 2H), 6.68 (t, J = 9.2 Hz, 1H), 6.57 – 6.25 (m, 2H), 6.16 (s, 1H), 5.88 – 5.79 (m, 1H), 5.60 (d, J = 87.8 Hz, 1H), 4.66 (s, 2H), 4.43 (s, 1H), 4.21 (s, 1H), 4.13 – 3.99 (m, 2H), 3.86 (s, 1H), 3.48 – 3.36 (m, 3H), 3.31 (s, 1H), 3.28 – 3.19 (m, 1H), 3.04 (s, 3H), 1.58 – 1.36 (m, 3H), 1.29 (s, 3H).
548		LCMS m/z [M+1]: 706.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.83 (d, J = 5.4 Hz, 1H), 7.72 – 7.63 (m, 1H), 7.55 (d, J = 7.9 Hz, 1H), 6.96 – 6.77 (m, 2H), 6.69 (t, J = 8.9 Hz, 1H), 6.56 – 6.24 (m, 2H), 6.16 (s, 1H), 5.87 – 5.78 (m, 1H), 5.60 (d, J = 89.6 Hz, 1H), 4.73 – 4.61 (m, 2H), 4.43 (s, 1H), 4.22 (d, J = 10.3 Hz, 1H), 4.13 – 3.98 (m, 2H), 3.85 (s, 1H), 3.50 – 3.35 (m, 3H), 3.31 (s, 1H), 3.27 – 3.18 (m, 1H), 3.04 (s, 3H), 1.58 – 1.34 (m, 3H), 1.29 (s, 3H).

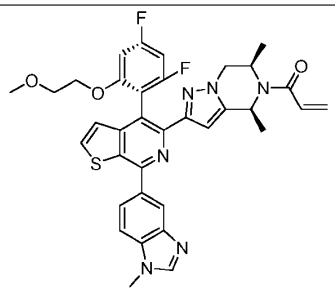
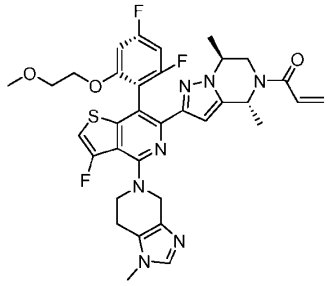
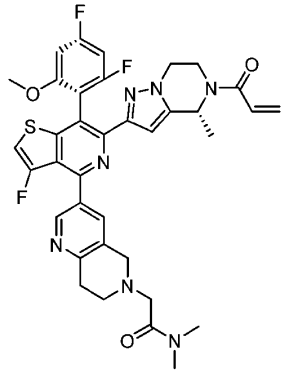
549		LCMS m/z [M+1]: 691.9 ^{1}H NMR (400 MHz, CD_3OD) δ 9.29 (s, 1H), 8.40 (s, 1H), 8.29 (d, J = 4.6 Hz, 1H), 8.24 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 7.52 (t, J = 9.1 Hz, 1H), 7.39 (dt, J = 8.6, 4.5 Hz, 1H), 7.16 (d, J = 10.7 Hz, 1H), 6.93 – 6.79 (m, 2H), 6.33 (d, J = 16.1 Hz, 1H), 6.15 (s, 1H), 5.86 (dd, J = 10.6, 1.5 Hz, 1H), 5.73 (s, 1H), 5.17 (s, 2H), 4.46 (s, 1H), 4.21 (s, 4H), 3.89 (d, J = 90.6 Hz, 2H), 1.46 (s, 3H).
550		LCMS m/z [M+1]: 677.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.24 (s, 1H), 8.96 (s, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 2.2 Hz, 1H), 6.95 – 6.79 (m, 2H), 6.74 – 6.62 (m, 1H), 6.40 – 6.25 (m, 1H), 6.04 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.76 – 5.55 (m, 1H), 4.60 – 4.20 (m, 2H), 4.20 – 3.86 (m, 6H), 3.85 – 3.65 (m, 1H), 3.48 (t, J = 4.5 Hz, 2H), 3.11 (s, 3H), 1.55 – 1.35 (m, 3H).
551		LCMS m/z [M+1]: 674.9 ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (t, J = 5.1 Hz, 2H), 8.15 (d, J = 6.2 Hz, 2H), 7.88 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 5.5 Hz, 1H), 7.56 (d, J = 5.6 Hz, 1H), 7.24 (t, J = 4.9 Hz, 1H), 6.76 (dd, J = 16.9, 10.7 Hz, 2H), 6.60 (td, J = 9.2, 2.1 Hz, 1H), 6.19 (d, J = 25.2 Hz, 2H), 5.73 (d, J = 10.8 Hz, 1H), 5.48 (d, J = 82.5 Hz, 1H), 5.09 (d, J = 17.3 Hz, 2H), 4.30 (s, 1H), 4.09 (d, J = 11.3 Hz, 1H), 3.94 (d, J = 44.2 Hz, 4H), 3.77 – 3.43 (m, 1H), 1.28 (s, 3H).

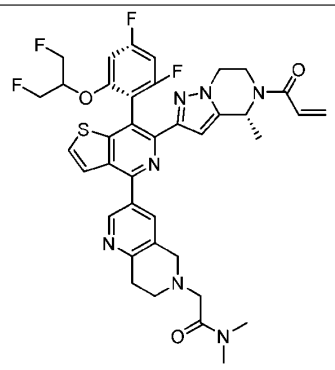
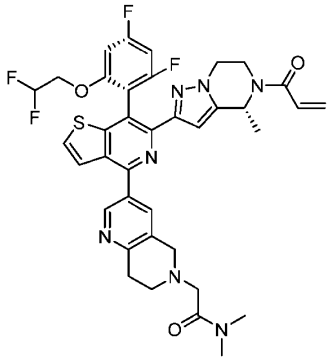
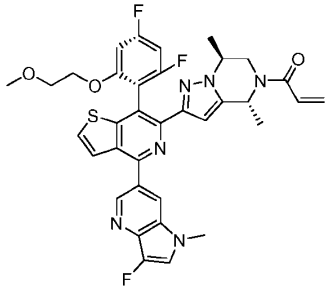
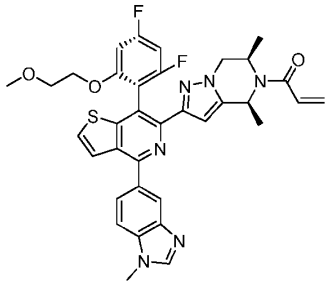
552		LCMS m/z [M+1]: 674.9 ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (d, J = 4.9 Hz, 2H), 8.13 (d, J = 4.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 5.5 Hz, 1H), 7.55 (d, J = 5.5 Hz, 1H), 7.23 (t, J = 4.9 Hz, 1H), 6.82 – 6.71 (m, 2H), 6.67 – 6.59 (m, 1H), 6.19 (d, J = 21.2 Hz, 2H), 5.73 (d, J = 10.4 Hz, 1H), 5.48 (d, J = 80.2 Hz, 1H), 5.03 (dd, J = 38.6, 13.6 Hz, 2H), 4.29 (s, 1H), 4.06 (dd, J = 12.6, 2.9 Hz, 1H), 3.88 (s, 4H), 3.74 – 3.41 (m, 1H), 1.33 (d, J = 20.0 Hz, 3H).
553		LCMS m/z [M+1]: 777.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 7.9 Hz, 1H), 8.03 (s, 1H), 7.59 – 7.51 (m, 2H), 6.80 (d, J = 10.9 Hz, 1H), 6.59 (td, J = 9.2, 2.2 Hz, 1H), 6.16 (s, 1H), 5.52 (s, 1H), 5.40 – 5.29 (m, 1H), 5.27 (s, 1H), 4.91 (dd, J = 10.7, 5.3 Hz, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.62 (d, J = 15.5 Hz, 1H), 4.48 – 4.39 (m, 1H), 4.14 – 3.98 (m, 2H), 3.64 – 3.55 (m, 1H), 3.47 (t, J = 4.6 Hz, 2H), 3.24 (s, 3H), 3.10 (s, 6H), 3.07 (s, 3H), 1.46 (d, J = 6.5 Hz, 3H), 1.32 (d, J = 6.6 Hz, 3H).
554		LCMS m/z [M+1]: 637.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (1H, s), 8.19(d, J = 9.2 Hz,1H), 8.17(s, 1H), 7.77(d, J = 8.8 Hz,1 H), 7.53 (d, J =2.3 Hz, 1H), 7.37 - 7.32(m, 1H), 6.96 - 6.71 (m, 2H), 6.65 - 6.56 (m, 1H), 6.40 - 6.28 (m, 1H), 5.89 - 5.81 (m, 1H), 5.72 -5.62(m, 1H), 5.61 - 5.35 (m, 1H), 4.58 - 4.45 (m, 1H), 4.33 - 4.23 (m, 0.5H), 4.20 - 4.04(m, 4H), 3.97 - 3.90 (m, 0.5H), 3.74 - 3.64 (m, 1H), 2.07 - 1.85 (m, 2H), 1.45 - 1.40 (m, 1H), 1.40-1.26 (m, 5H)

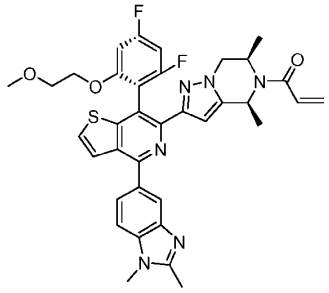
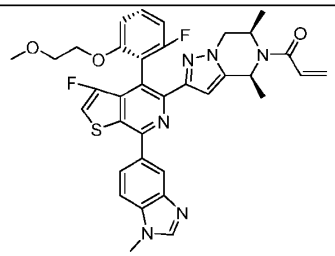
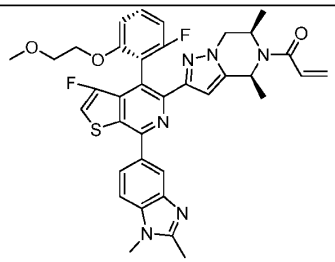
555		LCMS m/z [M+1]: 637.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.20 (dd, J = 12.7, 5.7 Hz, 2H), 7.79 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 7.3, 2.2 Hz, 1H), 7.06 – 6.74 (m, 4H), 6.62 (t, J = 8.3 Hz, 1H), 6.30 (t, J = 15.8 Hz, 1H), 5.90 – 5.53 (m, 2H), 4.58 (dd, J = 12.5, 4.0 Hz, 1H), 4.35 – 4.25 (m, 1H), 4.21 – 4.12 (m, 3H), 3.94 – 3.76 (m, 2H), 3.54 – 3.47 (m, 1H), 2.29 – 2.13 (m, 1H), 1.64 (d, J = 10.7 Hz, 1H), 1.68 – 1.42 (m, 6H).
556		LCMS m/z [M+1]: 641.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.63 (s, 1H), 8.48 (dd, J = 8.8, 1.2Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 5.6 Hz, 1H), 7.18 (d, J = 5.2 Hz, 1H), 6.89 - 6.81 (m, 2H), 6.74 – 6.69 (m, 1H), 6.32 - 6.28 (m, 1H), 6.13 (s, 1H), 5.83 (dd, J = 10.4, 1.6 Hz, 1H), 5.78 – 5.49 (m, 1H), 4.51 – 4.45 (m, 1H), 4.23 (s, 3H), 4.13 – 4.06 (m, 1H), 3.87 – 3.72 (m, 3H), 3.51 – 3.41 (m, 1H), 1.45 (s, 3H), 0.91 (d, J = 6.4 Hz, 3H).
557		LCMS m/z [M+1]: 639 ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (d, J = 5.2 Hz, 1H), 8.30 - 8.20 (m, 1H), 8.17 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.70 - 7.34 (m, 1H), 7.19 (d, J = 12.3 Hz, 1H), 7.01 - 7.08 (m, 1H), 6.86 (dd, J = 11.4 Hz, 2.4 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.73 – 6.65 (m, 1H), 6.35 – 6.28 (m, 1H), 5.85 – 5.75 (m, 1H), 4.67 – 4.58 (m, 1H), 4.18 – 4.07 (m, 6H), 3.52 – 3.45 (m, 1H), 3.01 – 2.90 (m, 1H), 2.38 – 2.24 (m, 1H), 1.81 – 1.68 (m, 1H), 1.64 – 1.47 (m, 1H).

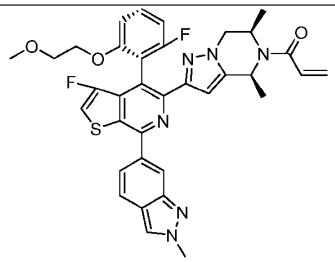
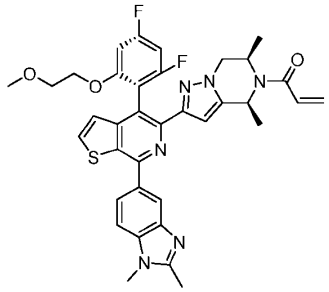
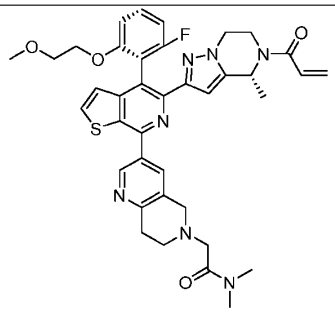
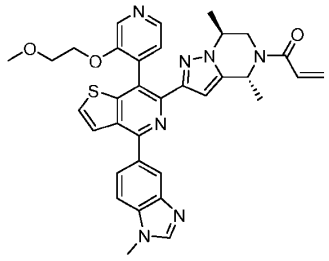
558		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (d, J = 5.4 Hz, 1H), 8.43 (s, 2H), 8.06 (d, J = 8.6 Hz, 1H), 7.78 (dd, J = 7.5, 1.2 Hz, 1H), 7.37 (d, J = 5.4 Hz, 1H), 6.95 - 6.78 (m, 3H), 6.35 (d, J = 17.0 Hz, 1H), 6.10 (s, 1H), 5.86 (dd, J = 10.5, 1.5 Hz, 1H), 5.81 - 5.46 (m, 1H), 4.55 (s, 1H), 4.33 (s, 3H), 3.88 - 3.81 (m, 1H), 3.80 - 3.74 (m, 1H), 3.73 - 3.68 (m, 1H), 1.53 - 1.39 (m, 3H), 1.36 (d, J = 6.2 Hz, 3H), 0.94 (d, J = 6.2 Hz, 3H).
559		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.63 (s, 1H), 8.50 (dd, J = 8.6, 1.3 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 5.5 Hz, 1H), 7.19 (d, J = 5.5 Hz, 1H), 6.94 - 6.71 (m, 3H), 6.35 (d, J = 16.2 Hz, 1H), 6.22 (s,1H), 5.86 (dd, J = 10.5, 1.5 Hz, 1H), 5.80 - 5.44 (m, 1H), 4.44 (s, 1H), 4.22 (s, 3H), 3.88 - 3.79 (m, 1H), 3.78 - 3.69 (m, 1H), 3.66 - 3.56 (m, 1H), 1.54 - 1.39 (m, 3H), 1.32 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H).
560		LCMS m/z [M+1]: 680.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (d, J = 22.2 Hz, 2H), 8.16 – 8.04 (m, 2H), 7.86 (t, J = 4.6 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 10.5 Hz, 1H), 6.95 – 6.76 (m, 2H), 6.30 (d, J = 16.3 Hz, 1H), 6.05 (d, J = 14.4 Hz, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.73 – 5.49 (m, 1H), 4.54 – 4.28 (m, 5H), 4.16 (s, 1H), 4.10 – 3.91 (m, 2H), 3.79 (s, 1H), 3.27 (d, J = 10.2 Hz, 1H), 2.81 (dd, J = 10.0, 3.7 Hz, 1H), 2.73 – 2.58 (m, 1H), 2.22 (dd, J = 17.1, 9.7 Hz, 1H), 1.87 – 1.60 (m, 1H), 1.52-1.33 (m, 3H).

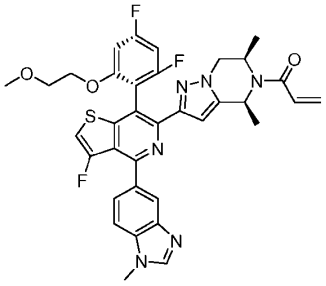
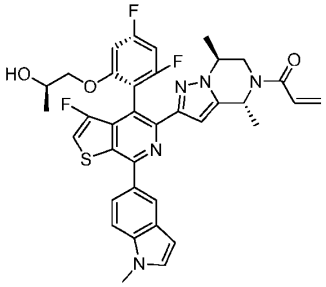
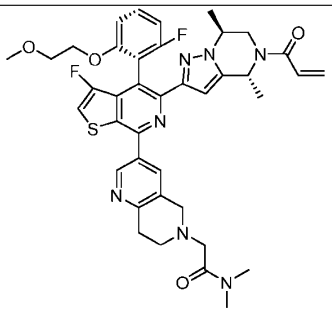
561		LCMS m/z [M+1]: 680.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.38 (s, 1H), 8.11 (d, J = 5.6 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.71 (dd, J = 8.6, 1.3 Hz, 1H), 6.98 (d, J = 10.8 Hz, 1H), 6.95 – 6.78 (m, 2H), 6.30 (d, J = 16.3 Hz, 1H), 6.03 (s, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.76 – 5.52 (m, 1H), 4.52 – 4.28 (m, 5H), 4.22 (s, 1H), 4.06 – 3.70 (m, 3H), 3.26 (s, 1H), 2.81 (dd, J = 10.1, 4.0 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.22 (dd, J = 17.1, 9.7 Hz, 1H), 1.65 (dd, J = 17.0, 4.7 Hz, 1H), 1.52 - 1.38 (m, 3H).
562		LCMS m/z [M+1]: 676.9 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 2H), 8.01 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.72 (s, 2H), 7.28 (s, 1H), 7.05 (d, J = 10.9 Hz, 1H), 6.93 – 6.74 (m, 2H), 6.25 (t, J = 20.6 Hz, 3H), 5.84 (d, J = 10.3 Hz, 1H), 5.61 (d, J = 80.3 Hz, 1H), 5.19 – 5.06 (m, 2H), 4.79 – 4.05 (m, 2H), 3.98 (d, J = 24.3 Hz, 4H), 3.74 (s, 1H), 3.34 (s, 3H), 1.44 (s, 3H).
563		LCMS m/z [M+1]: 677.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (d, J = 2.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 10.6 Hz, 2H), 7.29 (d, J = 1.7 Hz, 1H), 7.10 (d, J = 10.8 Hz, 1H), 6.87 (dd, J = 16.7, 10.6 Hz, 1H), 6.81 – 6.71 (m, 1H), 6.42 – 6.05 (m, 3H), 5.84 (d, J = 10.7 Hz, 1H), 5.58 (d, J = 79.2 Hz, 1H), 5.16 (dd, J = 33.3, 13.0 Hz, 2H), 4.76 – 4.03 (m, 2H), 4.02 (s, 4H), 3.80 (d, J = 31.9 Hz, 1H), 3.34 (s, 3H), 1.47 (d, J = 27.2 Hz, 3H).

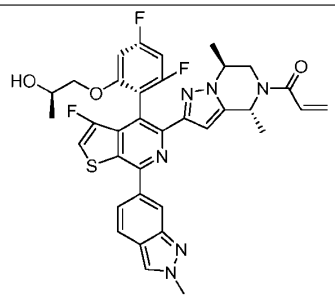
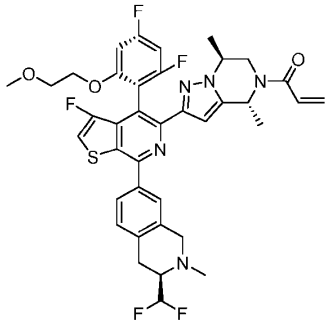
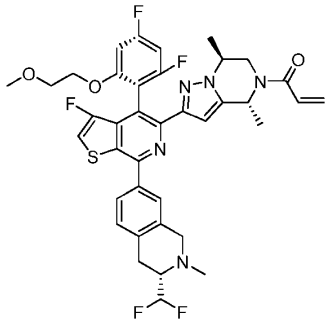
564		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.64 (s, 1H), 8.50 (dd, J = 8.7, 1.1 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.4 Hz, 1H), 6.94 – 6.67 (m, 3H), 6.28 (d, J = 8.8 Hz, 1H), 6.17 (s, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.28 – 4.05 (m, 6H), 4.00 – 3.90 (m, 1H), 3.44 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H).
565		LCMS m/z [M+1]: 678.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.77 (s, 1H), 7.19 (s, 1H), 6.83 (d, J = 10.4 Hz, 2H), 6.66 – 6.61(m, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.28 (s, 1H), 5.84 (d, J = 10.8 Hz, 1H), 5.72 – 5.44 (m, 1H), 4.74 (s, 1H), 4.45 – 4.21 (m, 3H), 4.06 – 3.91 (m, 5H), 3.87 (s, 4H), 3.44 – 3.41 (m, 2H), 3.05 (s, 4H), 1.44 - 1.46 (m, 3H), 1.26 (d, J = 6.0 Hz, 3H).
566		LCMS m/z [M+1]: 702.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.19 (s, 1H), 7.38 (d, J = 2.5 Hz, 1H), 6.91 - 6.67 (m, 3H), 6.35 - 6.23 (m, 1H), 6.17 (s, 1H), 5.83 (d, J = 10.4 Hz, 1H), 5.75 - 5.40 (m, 1H), 4.73 (s, 2H), 4.47 (s, 2H), 4.23 - 4.12 (m, 1H), 4.11 - 3.92 (m, 1H), 3.91 - 3.77 (m, 2H), 3.70 (s, 3H), 3.56 - 3.41 (m, 3H), 3.04 (s, 6H), 1.51 - 1.36 (m, 3H).

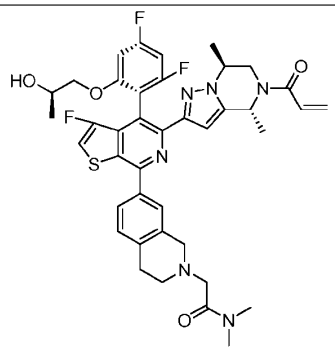
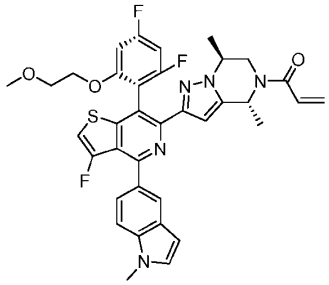
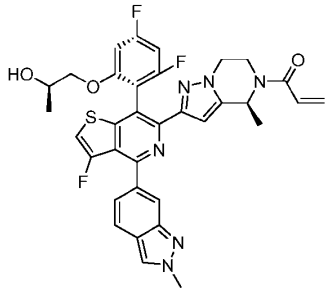
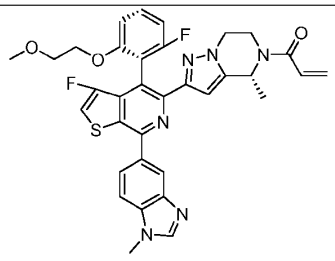
567		LCMS m/z [M+1]: 748.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.06 (d, J = 1.6 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 6.89 (d, J = 10.7 Hz, 1H), 6.79 – 6.64 (m, 2H), 6.19 (d, J = 15.9 Hz, 1H), 6.11 (s, 1H), 5.73 (dd, J = 10.6, 1.6 Hz, 1H), 5.64 – 5.48 (m, 1H), 4.64 (s, 2H), 4.44 – 4.27 (m, 5H), 4.24 – 4.16 (m, 2H), 4.13 – 4.03 (m, 2H), 3.96 (s, 1H), 3.75 (s, 3H), 3.41 – 3.36 (m, 2H), 2.96 (s, 6H), 1.52-1.31 (m, 3H)
568		LCMS m/z [M+1]: 734.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (s, 1H), 8.38 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.95 (d, J = 10.6 Hz, 1H), 6.89 – 6.77 (m, 2H), 6.25 (dd, J = 30.2, 12.7 Hz, 2H), 5.92 – 5.74 (m, 2H), 5.73 – 5.42 (m, 1H), 4.77 (s, 2H), 4.55 – 4.31 (m, 3H), 4.27 – 4.11 (m, 3H), 4.06 (s, 1H), 3.86 (t, J = 5.7 Hz, 2H), 3.75 (s, 1H), 3.50 (t, J = 6.0 Hz, 2H), 3.38 – 3.27 (m, 6H), 1.52-1.31 (m, 3H).
569		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (s, 1H), 8.56 (s, 1H), 7.83 (d, J = 5.5 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 6.92 (d, J = 10.5 Hz, 2H), 6.74 (t, J = 8.7 Hz, 1H), 6.35 (d, J = 16.7 Hz, 1H), 6.20 (s, 1H), 5.86 (d, J = 10.7 Hz, 1H), 5.65 (d, J = 85.0 Hz, 1H), 4.50 (s, 1H), 4.10 (d, J = 18.7 Hz, 3H), 3.95 (s, 4H), 3.47 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 1.45 (s, 3H), 1.33 (d, J = 13.8 Hz, 3H).
570		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.38 (s, 1H), 8.44 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.94 - 6.72 (m, 3H), 6.36 - 6.14 (m, 2H), 5.82 (d, J = 10.4 Hz, 1H), 5.48 (s, 1H), 4.22 (s, 3H), 4.21 - 4.07 (m, 3H),

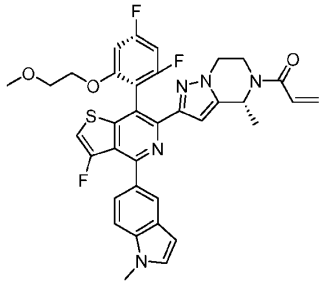
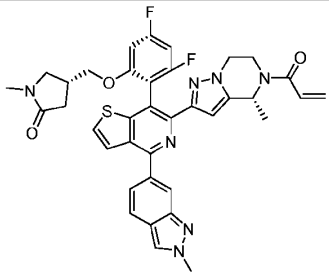
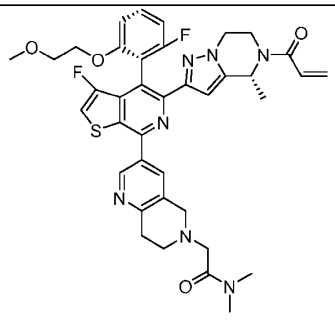
		4.03 - 3.94 (m, 1H), 3.44 (t, J = 4.5 Hz, 2H), 3.07 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H).
571		LCMS m/z [M+1]: 669.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.24 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 5.5 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.94 - 6.70 (m, 3H), 6.36 - 6.16 (m, 2H), 5.82 (d, J = 10.6 Hz, 1H), 5.47 (d, J = 3.8 Hz, 1H), 4.23 - 4.06 (m, 6H), 4.03 - 3.95 (m, 1H), 3.44 (t, J = 4.6 Hz, 2H), 3.07 (s, 3H), 2.94 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H).
572		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.27 (s, 1H), 8.59 (s, 1H), 8.42 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.50 - 7.40 (m, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.87 - 6.76 (m, 2H), 6.42 - 6.12 (m, 1H), 5.94 (s, 1H), 5.80 (d, J = 10.0 Hz, 1H), 5.48 - 5.32 (m, 1H), 4.24 - 4.14 (m, 5H), 4.13 - 4.06 (m, 1H), 3.98 - 3.89 (m, 1H), 3.46 (t, J = 4.8 Hz, 2H), 3.10 (s, 3H), 1.45 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H).
573		LCMS m/z [M+1]: 669.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.44 - 8.38 (m, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.50 - 7.40 (m, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.87 - 6.77 (m, 2H), 6.35 - 6.16 (m, 1H), 5.92 (s, 1H), 5.80 (d, J = 10.8 Hz, 1H), 5.47 - 5.33 (m, 1H), 4.24 - 4.14 (m, 2H), 4.13 - 4.04 (m, 4H), 3.97 - 3.88 (m, 1H), 3.46 (t, J = 4.8 Hz, 2H), 3.10 (s, 3H), 2.93 (s, 3H), 1.44 (d, J = 6.4 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H).

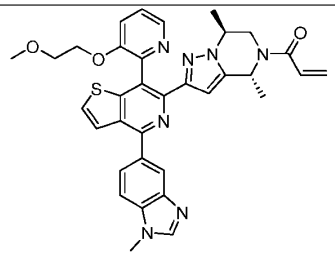
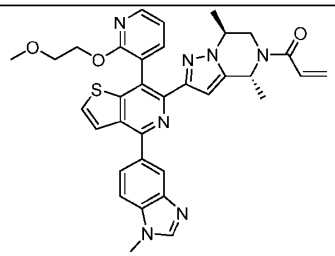
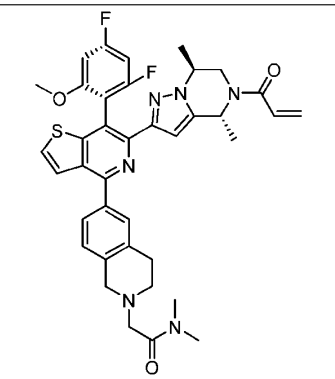
574		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.34 (s, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.85 - 7.80 (m, 1H), 7.68 (s, 1H), 7.50 - 7.40 (m, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.87 - 6.77 (m, 2H), 6.38 - 6.15 (m, 1H), 5.96 (s, 1H), 5.80 (d, J = 10.9 Hz, 1H), 5.48 - 5.35 (m, 1H), 4.30 (s, 3H), 4.18 (s, 2H), 4.14 - 4.04 (m, 1H), 3.97 - 3.88 (m, 1H), 3.46 (t, J = 4.8 Hz, 2H), 3.10 (s, 3H), 1.45 (d, J = 6.2 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H).
575		LCMS m/z [M+1]: 669.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.48 (dd, J = 8.6, 1.7 Hz, 1H), 8.10 (dd, J = 8.7, 2.5 Hz, 1H), 8.06 – 8.02 (m, 1H), 7.20 (d, J = 5.4 Hz, 1H), 6.94 – 6.67 (m, 3H), 6.28 (d, J = 8.8 Hz, 1H), 6.17 (s, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.28 – 4.05 (m, 6H), 4.00 – 3.90 (m, 1H), 3.44 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 2.96 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H).
576		LCMS m/z [M+1]: 710.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.36 (s, 1H), 8.53 (s, 1H), 7.99 (d, J = 5.5 Hz, 1H), 7.49 (dd, J = 15.2, 8.4 Hz, 1H), 7.11 (d, J = 5.5 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.88 – 6.79 (m, 2H), 6.28 (d, J = 16.8 Hz, 1H), 5.91 (s, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.71 – 5.42 (m, 2H), 4.76 (s, 2H), 4.49 (s, 2H), 4.29 – 4.22 (m, 1H), 4.06 (m, 3H), 3.85 (s, 2H), 3.49 (t, J = 5.9 Hz, 2H), 3.41 (t, J = 4.6 Hz, 2H), 3.05 (s, 6H), 3.04 (s, 3H), 1.52 – 1.35 (m, 3H).
577		LCMS m/z [M+1]: 620.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (d, J = 32.0 Hz, 1H), 8.37 – 8.25 (m, 3H), 7.99 (d, J = 8.4 Hz, 1H), 7.81 – 7.71 (m, 3H), 7.59 – 7.35 (m, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.39 (dd, J = 39.2, 19.2 Hz, 2H), 5.85 (d, J = 10.4 Hz, 1H), 5.77 – 5.54 (m, 1H), 4.71 (s, 1 H), 4.36 – 4.08 (m, 3H), 4.02 (s, 3H), 3.96 – 3.85 (m, 1H), 3.51 (t, J =

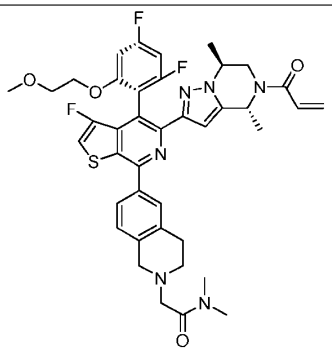
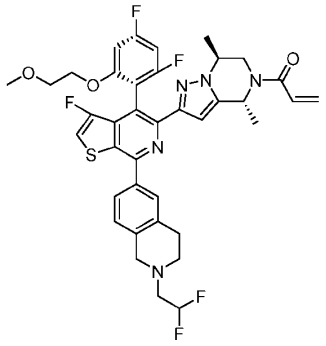
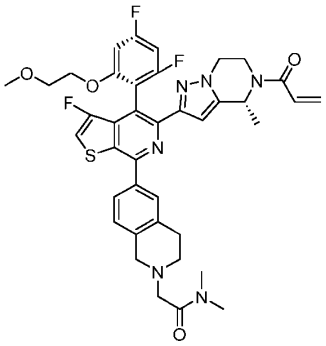
		4.6 Hz, 1H), 3.44 (t, J = 4.6 Hz, 1H), 3.13 (d, J = 7.4 Hz, 3H), 1.49 (s, 3H), 1.19 (d, J = 6.0 Hz, 3H).
578		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.29 (d, J = 1.0 Hz, 1H), 8.18 – 8.12 (m, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 6.93 – 6.72 (m, 3H), 6.36 – 6.20 (m, 2H), 5.80 (d, J = 10.1 Hz, 1H), 5.52 – 5.41 (m, 1H), 4.22 (s, 3H), 4.19 – 4.06 (m, 3H), 4.03 – 3.95 (m, 1H), 3.44 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H).
579		LCMS m/z [M+1]: 672.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 7.95 – 7.93 (m, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.42(d, J = 3.2 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.75 – 6.67 (m, 2H), 6.36 (d, J = 16.0 Hz, 1H), 6.13 (s, 1H), 5.87 (d, J = 8.4 Hz, 1H), 5.75 – 5.51 (m, 1H), 4.57 (s, 1H), 3.96 (s, 3H), 3.93 – 3.80 (m, 4H), 1.46 - 1.44 (m, 3H), 1.35 - 1.33 (m, 3H), 1.00 (d, J = 2.4 Hz, 3H).
580		LCMS m/z [M+1]: 742.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.5 Hz, 1H), 8.49 - 8.45 (m, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.47 - 7.39 (m, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.90 - 6.80 (m, 1H), 6.76 (t, J = 8.6 Hz, 1H), 6.32 (d, J = 16.3 Hz, 1H), 5.93 (s, 1H), 5.83 (dd, J = 10.5, 1.4 Hz, 1H), 5.73 - 5.35 (m, 1H), 4.76 (s, 2H), 4.52 - 4.40 (m, 3H), 4.15 - 3.98 (m, 2H), 3.93 - 3.73 (m, 3H), 3.56 - 3.38 (m, 5H), 3.07 (s, 3H), 3.05 (s, 6H), 1.47 - 1.25 (m, 6H).

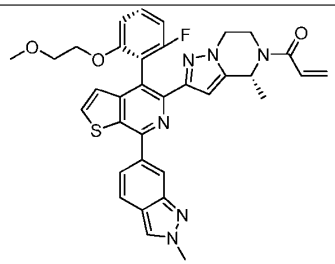
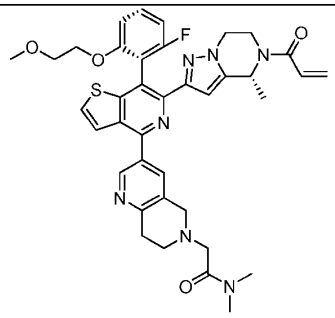
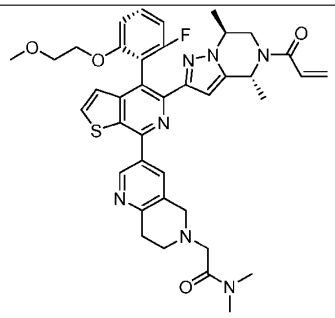
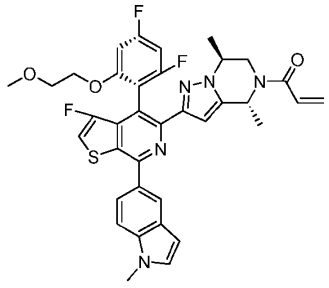
581		LCMS m/z [M+1]: 673.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (d, J = 1.2 Hz, 2H), 7.99 (d, J = 7.2 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.72 (s, 1H), 6.88 – 6.82 (m, 2H), 6.65 – 6.61 (m, 1H), 6.37 – 6.24 (m, 2H), 5.87 (d, J = 10.8 Hz, 1H), 5.82 – 5.51 (m, 1H), 4.48 (s, 1H), 4.33 (s, 3H), 4.29 – 4.23 (m, 1H), 3.92 (d, J = 7.2 Hz, 1H), 3.86 – 3.81 (m, 2H), 3.59 – 3.40 (m, 1H), 1.46 (s, 3H), 1.31 (s, 3H), 0.99 (d, J = 6.0 Hz, 3H).
582		LCMS m/z [M+1]: 738.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 7.8 Hz, 1H), 7.90 (s, 1H), 7.53 (s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 6.89 (s, 1H), 6.80 (d, J = 10.9 Hz, 1H), 6.61 (t, J = 9.2 Hz, 1H), 6.35 (d, J = 16.3 Hz, 1H), 6.25 – 5.92 (m, 2H), 5.86 (d, J = 10.6 Hz, 1H), 5.63 (d, J = 89.6 Hz, 1H), 4.43 (s, 1H), 4.25 (d, J = 15.4 Hz, 1H), 4.16 – 3.98 (m, 3H), 3.91 (d, J = 15.4 Hz, 2H), 3.48 (t, J = 4.6 Hz, 2H), 3.24 – 2.97 (m, 6H), 2.62 (s, 3H), 1.46 (d, J = 24.0 Hz, 3H), 1.31 (s, 3H).
583		LCMS m/z [M+1]: 738.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 7.9 Hz, 1H), 7.90 (s, 1H), 7.53 (d, J = 2.3 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 6.89 (s, 1H), 6.80 (d, J = 10.9 Hz, 1H), 6.61 (dd, J = 10.2, 8.1 Hz, 1H), 6.35 (d, J = 16.5 Hz, 1H), 6.23 – 5.93 (m, 2H), 5.86 (d, J = 10.6 Hz, 1H), 5.63 (d, J = 87.7 Hz, 1H), 4.44 (s, 1H), 4.33 – 4.20 (m, 1H), 4.16 – 3.98 (m, 3H), 3.92 (d, J = 15.5 Hz, 2H), 3.48 (t, J = 4.5 Hz, 2H), 3.26 – 3.00 (m, 6H), 2.62 (s, 3H), 1.46 (d, J = 23.0 Hz, 3H), 1.31 (s, 3H).

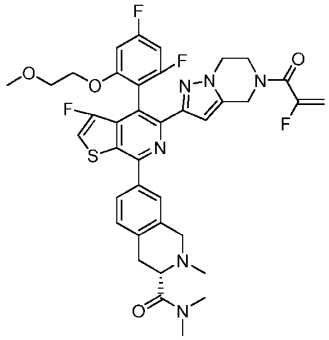
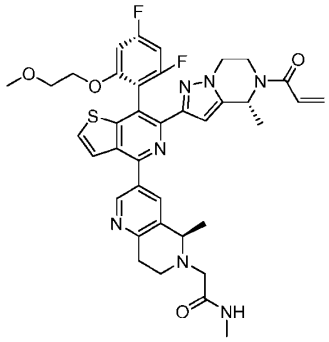
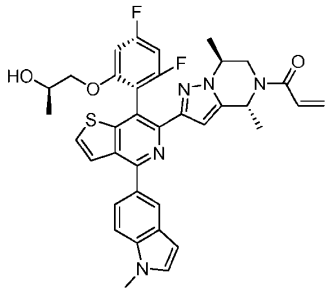
584		LCMS m/z [M+1]: 759.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (d, J = 1.6 Hz, 1H), 8.15 (s, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 6.90 - 6.77 (m, 2H), 6.74 - 6.65 (m, 1H), 6.33 - 6.22(m, 1H), 6.18 (s, 1H), 5.81 (d, J = 10.8 Hz, 1H), 5.73 - 5.48 (m, 1H),4.22 - 4.14 (m, 1H), 4.12 – 3.96 (m, 3H), 3.93 (s, 2H), 3.54 (s, 2H), 3.41 (t, J = 4.6 Hz, 2H), 3.19 – 3.12 (m, 5H), 3.07 – 3.01 (m, 5H), 2.98 (s, 3H), 1.51 - 1.36 (m,3H).
585		LCMS m/z [M+1]: 672.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.73 – 7.65 (m, 2H), 7.59 (s, 1H), 7.38 (d, J = 2.8 Hz, 1H), 7.00 (d, J = 10.4 Hz, 1H), 6.90 – 6.80 (m, 2H), 6.68 (d, J = 2.8 Hz, 1H), 6.35 (d, J = 16.8 Hz, 1H), 6.16 (s, 1H), 5.87 (d, J = 10.4 Hz, 1H), 5.75 – 5.51 (m, 1H), 4.55 (s, 1H), 4.18 – 4.08 (m, 2H), 3.95 (s, 3H), 3.48 (d, J = 15.6 Hz, 2H), 3.14 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H).
586		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.08 (d, J = 2.7 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 2.0 Hz,, 1H), 6.92 – 6.76 (m, 3H), 6.27 (d, J = 16.0 Hz, 1H), 6.20 (s, 1H), 5.81 (dd, J = 10.8, 1.4 Hz, 1H), 5.70 – 5.50 (m, 1H), 4.42 – 4.39 (m, 0.5H), 4.29 (s, 3H), 4.22 (dd, J = 12.8, 2.6 Hz, 1H), 4.12 – 4.07 (m, 1H), 3.82 (d, J = 5.3 Hz, 2H), 3.79 – 3.73 (m, 1.5H), 1.47 – 1.43 (m, 3H), 0.93 (d, J = 6.2 Hz, 3H).
587		LCMS m/z [M+1]: 641.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.37 (s, 1H), 8.60 (s, 1H), 8.45 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.50 - 7.41 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.90 - 6.75 (m, 2H), 6.34 - 6.21 (m, 1H), 5.87 (s, 1H), 5.81 (dd, J = 10.5, 1.5 Hz, 1H), 5.71 - 5.33 (m, 1H), 4.51 - 4.33 (m, 1H), 4.29 - 4.22 (m, 1H), 4.21

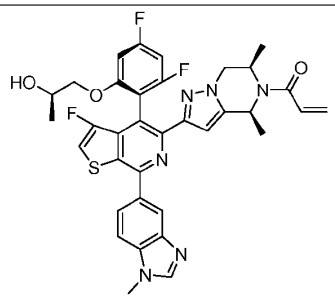
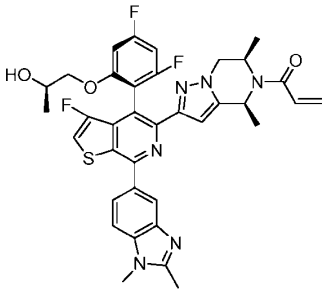
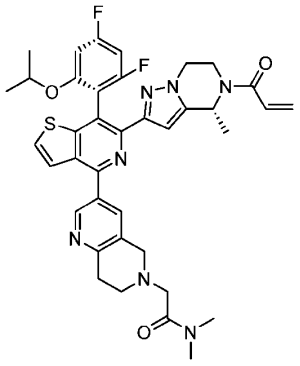
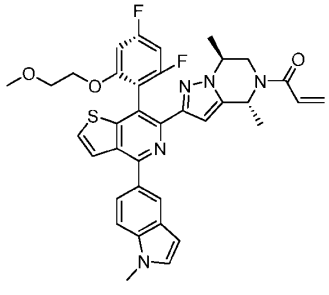
		(s, 3H), 4.16 - 4.00 (m, 3H), 3.83 - 3.64 (m, 1H), 3.46 (t, J = 4.9 Hz, 2H), 3.08 (s, 3H), 1.47 - 1.29 (m, 3H).
588		LCMS m/z [M+1]: 658.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 7.75 – 7.58 (m, 3H), 7.37 (d, J = 2.9 Hz, 1H), 7.00 (d, J = 10.8 Hz, 1H), 6.83 (t, J = 8.2 Hz, 2H), 6.66 (d, J = 2.9 Hz, 1H), 6.29 (d, J = 16.7 Hz, 1H), 6.06 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.73 - 5.45 (m, 1H), 4.44 (s, 1H), 4.36 – 4.27 (m, 1H), 4.22 – 4.03 (m, 3H), 3.92 (s, 3H), 3.75 (s, 1H), 3.47 (t, J = 4.4 Hz, 2H), 3.11 (s, 3H), 1.52-1.31 (m, 3H).
589		LCMS m/z [M+1]: 694.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1H), 8.38 (s, 1H), 8.12 – 8.04 (m, 2H), 7.85 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 10.4 Hz, 1H), 6.91 – 6.78 (m, 2H), 6.29 (d, J = 17.2 Hz, 1H), 6.05 (s, 1H), 5.83 (d, J = 11.4 Hz, 1H), 5.77 – 5.49 (m, 1H), 4.45 (s, 1H), 4.41 – 4.30 (m, 4H), 4.20 (s, 1H), 4.09 (d, J = 5.4 Hz, 1H), 4.00 (dd, J = 8.9, 4.0 Hz, 1H), 3.80 (s, 1H), 3.40 – 3.34 (m, 1H), 2.95 (dd, J = 9.8, 2.9 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.46 (s, 3H), 2.32 (dd, J = 17.0, 9.8 Hz, 1H), 1.73 (dd, J = 17.0, 3.6 Hz, 1H), 1.52-1.31 (m, 3H).
590		LCMS m/z [M+1]: 728.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (d, J = 1.7 Hz, 1H), 8.48 (s, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.52 - 7.39 (m, 1H), 6.95 (d, J = 8.6 Hz, 1H), 6.90 - 6.73 (m, 2H), 6.38 - 6.21 (m, 1H), 5.88 - 5.77 (m, 2H), 5.70 - 5.31 (m, 1H), 4.75 (s, 2H), 4.48 (s, 2H), 4.45 - 4.34 (m, 1H), 4.29 - 4.21 (m, 1H), 4.17 - 3.98 (m, 3H), 3.94 - 3.63 (m, 3H), 3.53 - 3.40 (m, 5H), 3.06 (s, 3H), 3.05 (s, 6H), 1.49 - 1.27 (m, 3H).

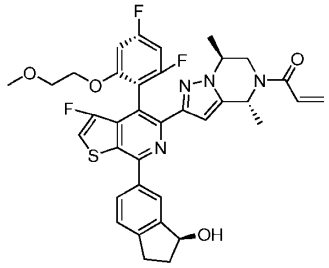
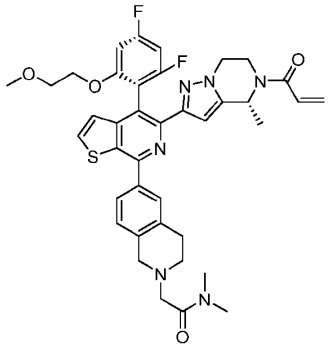
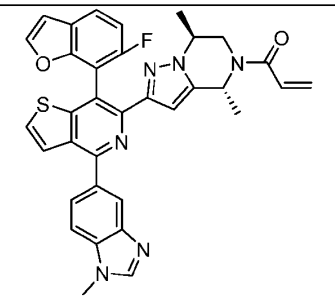
591		LCMS m/z [M+1]: 620.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (d, J = 6.7 Hz, 3H), 8.01 (d, J = 8.4 Hz, 1H), 7.77 (dd, J = 24.5, 8.3 Hz, 3H), 7.55 (d, J = 9.2 Hz, 2H), 7.02 – 6.73 (m, 1H), 6.39 (s, 2H), 5.86 (d, J = 10.8 Hz, 1H), 5.81 – 5.46 (m, 1H), 4.32 (s, 1H), 4.26 – 4.12 (m, 1H), 4.03 (s, 4H), 3.96 – 3.72 (m, 2H), 3.48 (s, 1H), 3.42 (t, J = 4.6 Hz, 1H), 3.12 (d, J = 2.0 Hz, 3H), 1.49 (d, J = 23.0 Hz, 3H), 1.20 (s, 3H).
592		LCMS m/z [M+1]: 620.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (d, J = 4.9 Hz, 1H), 8.40 (s, 1H), 8.31 – 8.21 (m, 2H), 8.10 (d, J = 8.6 Hz, 1H), 7.88 – 7.69 (m, 3H), 7.13 (m, J = 20.0, 7.3, 5.1 Hz, 1H), 6.89 – 6.80 (m, 1H), 6.31 (d, J = 16.3 Hz, 1H), 6.17 (d, J = 30.5 Hz, 1H), 5.85 – 5.80 (m, 1H), 5.47 (s, 1H), 4.48 – 4.24 (m, 3H), 4.20 (s, 3H), 3.83 (s, 1H), 3.48 (s, 3H), 3.12 (d, J = 2.0 Hz, 3H), 1.42 (s, 3H), 1.24 (d, J = 6.6 Hz, 3H).
593		LCMS m/z [M+1]: 697.0 ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.77 (m, 3H), 7.65 (d, J = 5.6 Hz, 1H), 7.45 (s, 1H), 6.85 (d, J = 10.5 Hz, 2H), 6.67 (s, 1H), 6.31 (d, J = 16.6 Hz, 1H), 6.12 (s, 1H), 5.86 – 5.78 (m, 1H), 5.71 (s, 1H), 4.87 (s, 3H), 4.66 (s, 2H), 4.43 (s, 3H), 3.85 (s, 1H), 3.69 (s, 3H), 3.39 (s, 2H), 3.03 (s, 6H), 1.40 (s, 3H), 1.28 (s, 3H).

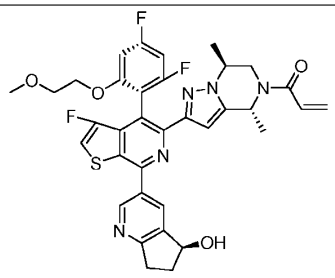
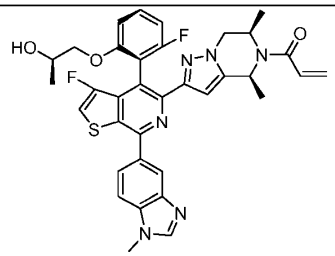
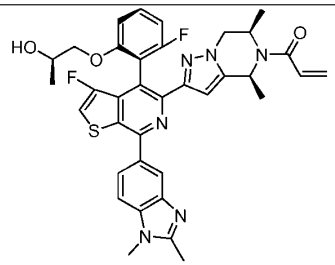
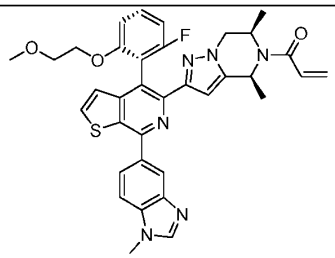
594		LCMS m/z [M+1]: 759.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (d, J = 5.9 Hz, 2H), 7.51 (d, J = 2.3 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 6.87 (s, 1H), 6.78 (d, J = 10.8 Hz, 1H), 6.59 (t, J = 9.2 Hz, 1H), 6.33 (d, J = 16.8 Hz, 1H), 6.14 (s, 1H), 5.84 (d, J = 11.5 Hz, 1H), 5.62 (d, J = 83.4 Hz, 1H), 4.41 (d, J = 5.5 Hz, 1H), 4.21 (s, 1H), 4.11 – 3.97 (m, 2H), 3.86 (s, 2H), 3.47 (dd, J = 10.5, 5.5 Hz, 5H), 3.16 (s, 3H), 3.09 (d, J = 8.3 Hz, 5H), 2.99 (s, 3H), 2.93 (t, J = 5.9 Hz, 2H), 1.45 (d, J = 23.1 Hz, 3H), 1.29 (s, 3H).
595		LCMS m/z [M+1]: 737.9 ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 6.87 – 6.76 (m, 2H), 6.66 – 6.49 (m, 2H), 6.30 (d, J = 16.6 Hz, 1H), 6.09 (s, 1H), 5.85 – 5.79 (m, 1H), 5.47 (s, 1H), 4.68 (s, 2H), 4.41 (s, 1H), 4.22 (d, J = 17.0 Hz, 1H), 4.06 (d, J = 4.8 Hz, 1H), 3.99 (d, J = 4.3 Hz, 1H), 3.84 (m, J = 32.0, 13.9, 8.9 Hz, 5H), 3.40 (m, J = 12.4, 5.5 Hz, 4H), 3.05 (s, 3H), 1.41 (d, J = 19.4 Hz, 3H), 1.28 (s, 3H).
596		LCMS m/z [M+1]: 744.9 ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, J = 5.8 Hz, 2H), 7.58 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 6.85 (dd, J = 16.2, 8.2 Hz, 2H), 6.68 – 6.62 (m, 1H), 6.31 (d, J = 16.1 Hz, 1H), 6.07 (s, 1H), 5.84 (d, J = 11.6 Hz, 1H), 5.61 (d, J = 83.9 Hz, 1H), 4.68 (s, 2H), 4.46 (s, 3H), 4.27 – 4.22 (m, 1H), 4.14 – 4.01 (m, 3H), 3.78 (s, 2H), 3.46 (dd, J = 12.8, 8.4 Hz, 5H), 3.09 (s, 3H), 3.07 (s, 6H), 1.44 (s, 3H).

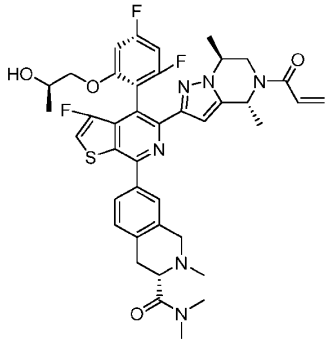
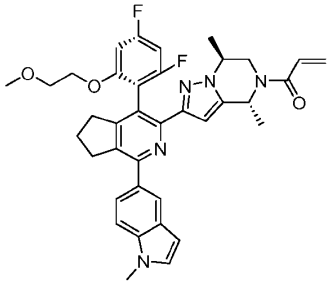
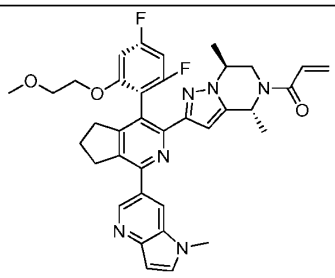
597		LCMS m/z [M+1]: 623.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, J = 5.4 Hz, 1H), 8.41 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.78 (dd, J = 8.6, 1.2 Hz, 1H), 7.59 (q, J = 8.3 Hz, 1H), 7.31 (d, J = 5.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.92 (t, J = 8.6 Hz, 1H), 6.89 - 6.75 (m, 1H), 6.30 (d, J = 16.3 Hz, 1H), 5.86 - 5.79 (m, 2H), 5.73 - 5.36 (m, 1H), 4.37 - 4.30 (m, 4H), 4.21 - 4.03 (m, 3H), 3.45 (t, J = 4.5 Hz, 2H), 3.08 (s, 3H), 1.47 - 1.29 (m, 3H).
598		LCMS m/z [M+1]: 710.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (s, 1H), 8.39 (s, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 7.56 - 7.50 (m, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.90 - 6.75 (m, 2H), 6.35 - 6.20 (m, 1H), 5.95 (s, 1H), 5.83 - 5.75 (m, 1H), 5.73 – 5.35 (m, 1H), 4.49 (s, 2H), 4.30 – 4.23 (m, 1H), 4.15 – 4.00 (m, 3H), 3.91 – 3.82 (m, 2H), 3.50 (t, J = 6.24 Hz, 2H), 3.42 (t, J = 4.8 Hz, 2H), 3.10 – 3.00 (m, 9H), 1.55 – 1.37 (m, 3H).
599		LCMS m/z [M+1]: 724.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.52 (s, 1H), 7.99 (d, J = 5.5 Hz, 1H), 7.50 - 7.44 (m, 1H), 7.12 (d, J = 5.6 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.90 - 6.80 (m, 2H), 6.32 (d, J = 16.5 Hz, 1H), 5.98 (s, 1H), 5.87 - 5.80 (m, 1H), 5.73 - 5.40 (m, 1H), 4.54 – 4.41 (m, 3H), 4.15 – 4.08 (m, 1H), 4.03 – 3.92 (m, 1H), 3.91 – 3.78 (m, 2H), 3.49 (t, J = 6.28 Hz, 2H), 3.42 (t, J = 4.6 Hz, 2H), 3.06 – 3.02 (m, 9H), 1.48 – 1.25 (m, 6H).
600		LCMS m/z [M+1]: 672.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.95 (s, 1H), 7.92 - 7.89 (m, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 2.9 Hz, 1H), 6.92 - 6.80 (m, 2H), 6.73 - 6.65 (m, 2H), 6.33 (d, J = 16.5 Hz, 1H), 6.05 (s, 1H), 5.88 - 5.80 (m, 1H), 5.79 - 5.40 (m, 1H), 4.15 – 4.10 (m, 1H), 4.06

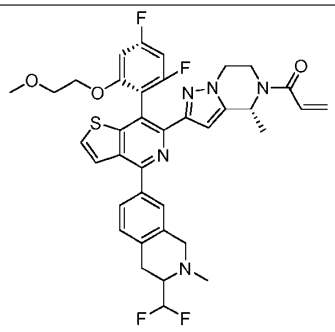
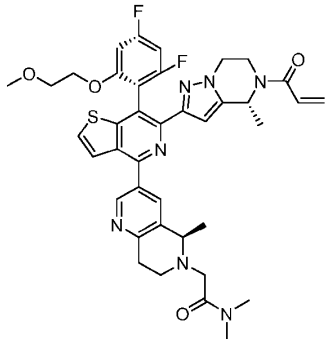
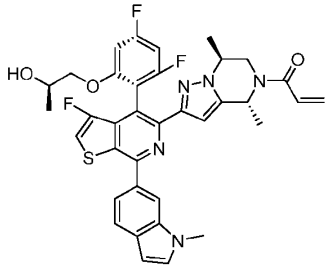
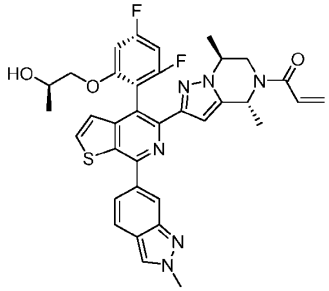
		– 4.01 (m, 1H), 3.96 – 3.80 (m, 3H), 3.47 (t, J = 4.6 Hz, 2H), 3.11 (s, 3H), 1.53 – 1.26 (m, 6H).
601		LCMS m/z [M+1]: 649.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 - 7.90 (m, 1H), 7.86 (s, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 6.79 - 6.72 (m, 1H), 6.64 - 6.52 (m, 1H), 6.12 (s, 1H), 5.41 - 5.30 (m, 1H), 5.29 - 5.25 (m, 1H), 4.81 - 4.73 (m, 1H), 4.23 - 3.83 (m, 9H), 3.43 (t, J = 4.4 Hz, 2H), 3.27 - 3.10 (m, 5H), 3.05 (s, 3H), 3.01 (s, 3H), 2.45 (s, 3H).
602		LCMS m/z [M+1]: 728.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.18 (s, 1H), 8.48 (s, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.98 – 6.80 (m, 2H), 6.74 (t, J = 9.1 Hz, 1H), 6.31 (d, J = 16.2 Hz, 1H), 6.13 (s, 1H), 5.84 (d, J = 10.7 Hz, 1H), 5.61 (d, J = 85.3 Hz, 1H), 4.45 (s, 1H), 4.25 (d, J = 12.4 Hz, 1H), 4.19 – 4.02 (m, 5H), 4.00 – 3.62 (m, 3H), 3.44 (t, J = 4.4 Hz, 5H), 3.07 (s, 3H), 2.87 (s, 3H), 1.85 (d, J = 6.8 Hz, 3H), 1.44 (s, 3H).
603		LCMS m/z [M+1]: 654.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.58 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 2.9 Hz, 1H), 6.86 (d, J = 10.9 Hz, 2H), 6.62 (dd, J = 19.1, 5.5 Hz, 2H), 6.32 (d, J = 15.8 Hz, 2H), 5.83 (d, J = 10.5 Hz, 1H), 5.74 (s, 1H), 4.40 (s, 1H), 4.20 (s, 1H), 3.98 – 3.88 (m, 4H), 3.87 – 3.68 (m, 3H), 1.48 (d, J = 18.1 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.1 Hz, 3H).

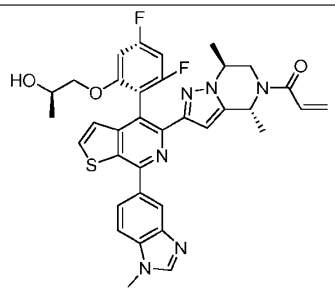
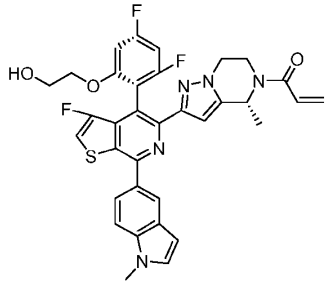
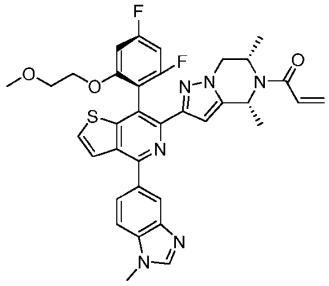
604		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.58 (s, 1H), 8.43 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 2.1 Hz, 1H), 6.86 – 6.76 (m, 2H), 6.62 (dd, J = 9.2, 2.1 Hz, 1H), 6.36 -6.25 (m, 2H), 5.81 (d, J = 10.6 Hz, 1H), 5.47 (s, 1H), 4.21 (s, 3H), 4.15 – 4.09 (m, 2H), 3.85 – 3.83 (m, 3H), 1.51 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 5.6 Hz, 3H).
605		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.40 (dd, J = 8.6, 1.4 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 2.2 Hz, 1H), 6.86 – 6.76 (m, 2H), 6.62 (dd, J = 9.2, 2.2 Hz, 1H), 6.31 – 6.23 (m, 2H), 5.81 (d, J = 10.4 Hz, 1H), 5.46 (s, 1H), 4.21 – 4.13 (m, 2H), 4.09 (s, 3H), 3.85 – 3.83 (m, 3H), 2.93 (s, 3H), 1.51 (d, J = 6.3 Hz, 3H), 1.20 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 5.7 Hz, 3H).
606		LCMS m/z [M+1]: 712.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.18 (s, 1H), 8.39 (s, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.90 – 6.78 (m, 2H), 6.74 – 6.63 (m, 1H), 6.29 (d, J = 16.2 Hz, 1H), 6.07 (s, 1H), 5.82 (d, J = 11.9 Hz, 1H), 5.77 – 5.49 (m, 1H), 4.76 (s, 2H), 4.61 – 4.52 (m, 1H), 4.49 (s, 3H), 4.28 – 4.19 (m, 1H), 4.08 (s, 1H), 3.86 (t, J = 6.1 Hz, 2H), 3.75 (s, 1H), 3.50 (t, J = 6.3 Hz, 2H), 3.05 (s, 6H), 1.52-1.31 (m, 3H), 1.09 (d, J = 6.0 Hz, 3H), 0.96 (d, J = 6.0 Hz, 3H).
607		LCMS m/z [M+1]: 654.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.72 - 7.65 (m, 1H), 7.62 - 7.53 (m, 2H), 7.46 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 3.0 Hz, 1H), 6.82 - 6.68 (m, 2H), 6.60 - 6.54 (m, 1H), 6.49 (d, J = 2.8 Hz, 1H), 6.27 - 6.08 (m, 2H), 5.73 (d, J = 10.48 Hz, 1H), 5.68 - 5.35 (m, 1H), 4.35 - 4.25 (m, 1H), 4.04 – 3.87 (m, 2H), 3.82 – 3.65 (m, 3H),

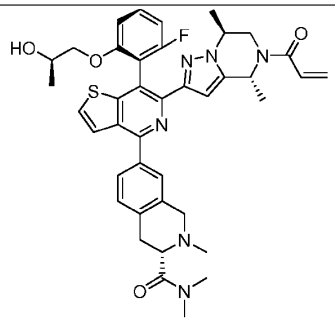
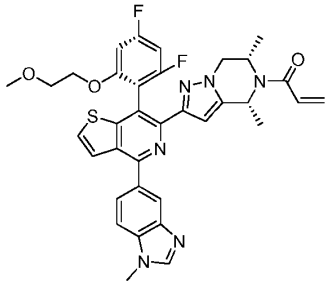
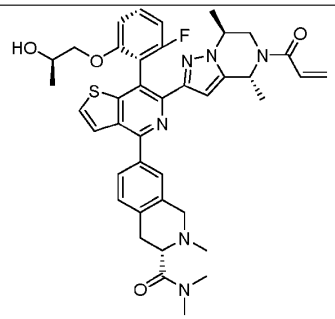
		3.35 (t, J = 4.8 Hz, 2H), 2.95 (s, 3H), 1.42 – 1.26 (m, 3H), 1.24 – 1.11 (m, 3H).
608		LCMS m/z [M+1]: 675.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.93 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 7.72 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 6.78 (d, J = 11.0 Hz, 2H), 6.63 - 6.54 (m, 1H), 6.28 (d, J = 16.6 Hz, 1H), 6.07 (s, 1H), 5.80 (dd, J = 10.6 Hz, 1.4 Hz, 1H), 5.72 - 5.40 (m, 1H), 5.28 (t, J = 6.4 Hz, 1H), 4.49 - 4.35 (m, 1H), 4.12 - 3.93 (m, 2H), 3.42 (t, J = 4.2 Hz, 2H), 3.18 - 3.07 (m, 1H), 3.05 (s, 3H), 2.97 - 2.84 (m, 1H), 2.58 - 2.43 (m, 1H), 2.05 - 1.92 (m, 1H), 1.47 - 1.33 (m, 3H), 1.32 - 1.17 (m, 6H).
609		LCMS m/z [M+1]: 727 ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 6.0 Hz, 2H), 8.06 (d, J = 5.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 5.4 Hz, 1H), 6.88 (dd, J = 20.1, 10.8 Hz, 2H), 6.73 (t, J = 9.2 Hz, 1H), 6.31 (d, J = 16.8 Hz, 1H), 6.09 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.78 – 5.44 (m, 1H), 4.88 – 4.82 (m, 1H), 4.69 (s, 2H), 4.47 (s, 2H), 4.30 – 4.01 (m, 5H), 3.88 – 3.58 (m, 2H), 3.45 (t, J = 4.4 Hz, 4H), 3.08 (s, 9H), 1.45 (s, 3H).
610		LCMS m/z [M+1]: 603 ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (d, J = 12.2 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.64 – 7.47 (m, 4H), 7.16 – 7.00 (m, 1H), 6.86 – 6.62 (m, 2H), 6.22 – 5.99 (m, 2H), 5.70 (d, J = 10.4 Hz, 1H), 5.58 – 5.19 (m, 1H), 4.61 – 3.96 (m, 2H), 3.90 (s, 3H), 3.72 – 3.24 (m, 1H), 1.24 (s, 3H), 0.97 (d, J = 59.0 Hz, 3H).

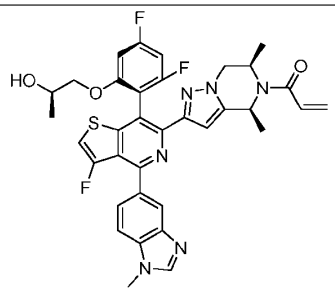
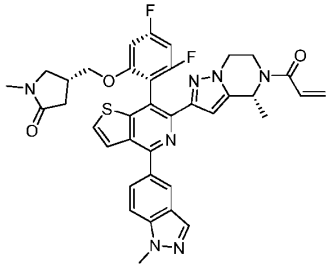
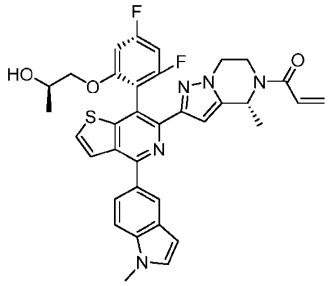
611		LCMS m/z [M+1]: 676.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.99 (s, 1H), 7.63 (s, 1H), 6.95-6.75 (m, 2H), 6.62 (t, J = 8.8 Hz, 2H), 6.33 (d, J = 16.2 Hz, 1H), 6.15 (s, 1H), 5.84 (d, J = 10.4 Hz, 1H), 5.76 - 5.41 (m, 2H), 4.53 - 4.35 (m, 1H), 4.28 - 3.77 (m, 3H), 3.44 (t, J = 4.2 Hz, 3H), 3.26 - 3.14 (m, 1H), 3.07 (s, 3H), 2.84 - 2.66 (m, 1H), 2.30 - 2.11 (m, 1H), 1.55 - 1.36 (m, 3H), 1.36 - 1.18 (m, 3H).
612		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.45 (s, 1H), 8.61 (s, 1H), 8.47 (dd, J = 8.7, 1.3 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 2.2 Hz, 1H), 7.43 (dd, J = 15.2, 8.3 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.86 – 6.72 (m, 2H), 6.40 – 6.15 (m, 1H), 6.06 (s, 1H), 5.81 (d, J = 10.7 Hz, 1H), 5.53 – 5.32 (m, 1H), 4.23 (s, 3H), 4.15 (s, 2H), 3.92 – 3.79 (m, 3H), 1.46 (d, J = 5.9 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 0.98 – 0.87 (m, 3H).
613		LCMS m/z [M+1]: 669.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.43 (dd, J = 15.3, 8.5 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.88 – 6.72 (m, 2H), 6.43 – 6.14 (m, 1H), 6.05 (s, 1H), 5.81 (d, J = 10.2 Hz, 1H), 5.51 – 5.33 (m, 1H), 4.15 (s, 2H), 4.09 (s, 3H), 3.91 – 3.78 (m, 3H), 2.94 (s, 3H), 1.45 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 0.99 – 0.87 (m, 3H).
614		LCMS m/z [M+1]: 637.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.63 (s, 1H), 8.51 - 8.45 (m, 1H), 8.13 (d, J = 8.6 Hz, 1H), 8.08 (d, J = 5.5 Hz, 1H), 7.55 - 7.46 (m, 1H), 7.17 (d, J = 5.5 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.95 - 6.77 (m, 2H), 6.39 - 6.15 (m, 1H), 5.99 (s, 1H), 5.80 (d, J = 10.5 Hz, 1H), 5.48 - 5.33 (m, 1H), 4.26 - 4.16 (m, 5H), 4.15 - 4.07 (m, 1H), 3.97 - 3.88 (m, 1H), 3.43 (t, J = 4.6 Hz,

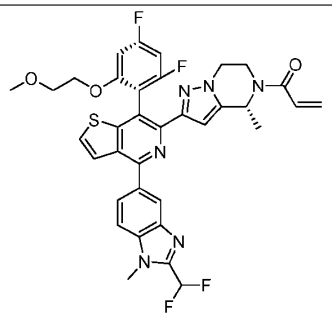
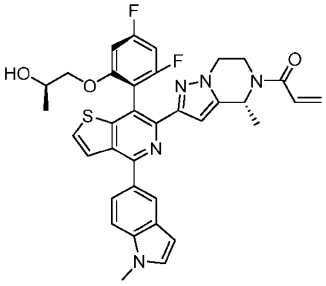
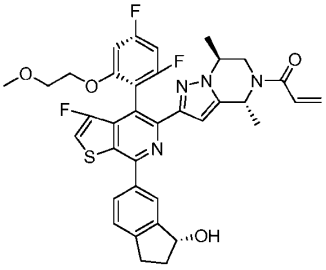
		2H), 3.08 (s, 3H), 1.45 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.6 Hz, 3H).
615		LCMS m/z [M+1]: 759.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (d, J = 1.7 Hz, 1H), 8.12 (d, J = 7.4 Hz, 1H), 8.03 (s, 1H), 7.59 - 7.52 (m, 2H), 6.93 - 6.76 (m, 2H), 6.61 - 6.53 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.19 (s, 1H), 5.88 - 5.80 (m, 1H), 5.79 - 5.43 (m, 1H), 4.79 - 4.69 (m, 2H), 4.66 - 4.57 (m, 1H), 4.49 - 4.35 (m, 1H), 4.31 - 4.16 (m, 1H), 3.95 - 3.85 (m, 1H), 3.82 - 3.72 (m, 2H), 3.64 - 3.55 (m, 1H), 3.24 (s, 3H), 3.11 - 3.07 (m, 6H), 1.53 - 1.37 (m, 3H), 1.30 - 1.22 (m, 3H), 0.94 (d, J = 6.0 Hz, 3H) .
616		LCMS m/z [M+1]: 638.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 7.72 – 7.64 (m, 2H), 7.40 (d, J = 3.1 Hz, 1H), 6.96 – 6.74 (m, 3H), 6.69 (d, J = 3.0 Hz, 1H), 6.33 (d, J = 16.5 Hz, 1H), 5.95 (s, 1H), 5.85 (dd, J = 10.6, 1.4 Hz, 1H), 5.61 (d, J = 81.2 Hz, 1H), 4.63 (s, 1H), 4.44 – 4.12 (m, 2H), 4.09 – 4.03 (m, 1H), 3.90 (d, J = 19.6 Hz, 4H), 3.55 (t, J = 4.1 Hz, 2H), 3.36 (t, J = 7.4 Hz, 2H), 3.26 (s, 3H), 3.13 (dd, J = 16.9, 9.1 Hz, 1H), 3.02 – 2.94 (m, 1H), 2.27 (p, J = 7.3 Hz, 2H), 1.39 (s, 6H).
617		LCMS m/z [M+1]: 639.0 ^{1}H NMR (400 MHz, CD_3OD) δ 9.20 (d, J = 14.6 Hz, 2H), 8.17 (d, J = 3.1 Hz, 1H), 6.92 – 6.81 (m, 3H), 6.63 (t, J = 9.2 Hz, 1H), 6.32 (d, J = 16.9 Hz, 1H), 6.01 (s, 1H), 5.84 (d, J = 10.6 Hz, 1H), 5.58 (d, J = 89.9 Hz, 1H), 4.48 (s, 1H), 4.30 – 4.09 (m, 5H), 4.03 – 3.98 (m, 1H), 3.86 (d, J = 13.8 Hz, 1H), 3.54 (t, J = 4.5 Hz, 2H), 3.38 (dd, J = 15.1, 7.5 Hz, 2H), 3.23 (s, 3H), 3.02 – 2.93 (m, 1H), 2.81 – 2.72 (m, 1H), 2.25 – 2.16 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H).

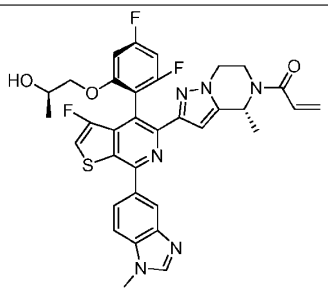
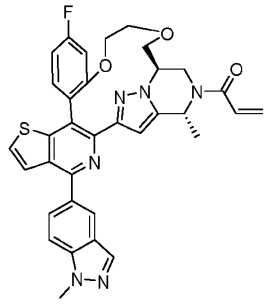
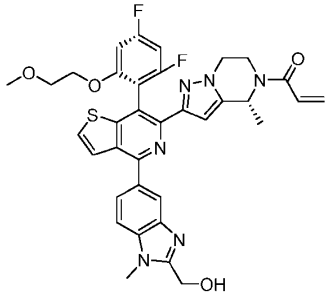
618		LCMS m/z [M+1]: 706.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.1 Hz, 1H), 7.94 (s, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 6.98 – 6.80 (m, 2H), 6.76 (t, J = 9.2 Hz, 1H), 6.53 (td, J = 53.5, 2.7 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 6.15 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.62 (d, J = 84.8 Hz, 1H), 4.73 (s, 2H), 4.53 – 3.96 (m, 6H), 3.60 – 3.35 (m, 5H), 3.19 (s, 3H), 3.07 (s, 3H), 1.45 (s, 3H).
619		LCMS m/z [M+1]: 742 ^{1}H NMR (400 MHz, CD_3OD) δ 9.18 (s, 1H), 8.44 (s, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.99 – 6.82 (m, 2H), 6.80 – 6.68 (m, 1H), 6.31 (d, J = 15.6 Hz, 1H), 6.14 (s, 1H), 5.85 (d, J = 10.7 Hz, 1H), 5.62 (d, J = 81.6 Hz, 1H), 5.02 – 4.93 (m, 1H), 4.57 – 4.34 (m, 3H), 4.30 – 4.21 (m, 1H), 4.16 – 3.95 (m, 4H), 3.82 – 3.41 (m, 6H), 3.05 (d, J = 13.8 Hz, 9H), 1.91 (d, J = 6.8 Hz, 3H), 1.44 (s, 3H).
620		LCMS m/z [M+1]: 672.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.80 (d, J = 6.7 Hz, 2H), 7.59 (s, 1H), 7.35 (s, 1H), 6.93 - 6.76 (m, 2H), 6.58 (s, 2H), 6.34 (d, J = 16.9 Hz, 1H), 6.19 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.80 - 5.46 (m, 1H), 4.45 (s, 1H), 3.93 (s, 3H), 3.92 - 3.75 (m, 4H), 1.54 - 1.39 (m, 3H), 1.31 - 1.27 (m, 4H), 1.01 - 0.94 (m, 3H).
621		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 - 8.42 (m, 3H), 8.05(dd, J = 8.7, 0.7 Hz, 1H), 7.78 (dd, J = 8.7, 1.5 Hz, 1H), 7.34 (d, J = 5.4 Hz, 1H), 6.96 - 6.81(m, 2H), 6.80 - 6.73 (m, 1H), 6.33 (d, J = 16.4 Hz, 1H), 6.13 (s, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.79 - 5.40 (m, 1H), 4.61 - 4.52 (m, 1H), 4.33 (s, 3H), 3.90 - 3.84 (m, 2H), 3.80 - 3.72 (m, 1H), 1.52 - 1.25 (m, 6H), 0.95 (d, J = 6.4 Hz, 3H)

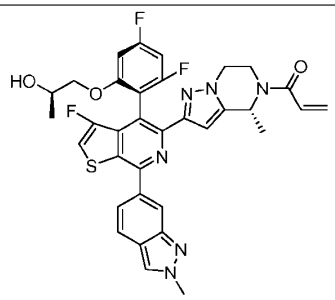
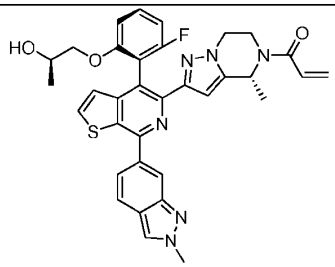
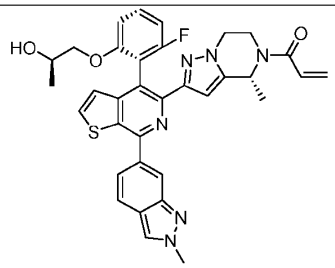
622		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.34(s, 1H), 8.62 (s, 1H), 8.47(dd, J = 8.7, 1.4 Hz, 1H), 8.12(d, J = 8.7 Hz, 1H), 8.04 (d, J = 5.5 Hz, 1H), 7.16(d, J = 5.5 Hz, 1H), 6.90 - 6.81(m, 2H), 6.70 - 6.63 (m, 1H), 6.33 (d, J = 16.4 Hz, 1H), 6.24 (s, 1H), 5.84 (dd, J = 10.6, 1.8 Hz, 1H), 5.79 - 5.40 (m, 1H), 4.51 - 4.40 (m, 1H), 4.21 (s, 3H), 3.92 - 3.80 (m, 2H), 3.77 - 3.71 (m, 1H), 1.55 - 1.22 (m, 6H), 0.92 (d, J = 6.4 Hz, 3H)
623		LCMS m/z [M+1]: 644.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (d, J = 1.4 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 8.6, 1.7 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 3.1 Hz, 1H), 6.92 – 6.78 (m, 2H), 6.74 – 6.67 (m, 2H), 6.36 – 6.24 (m, 1H), 5.99 (s, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.76 – 5.42 (m, 1H), 4.52 – 4.38 (m, 0.5H), 4.36 – 4.28 (m, 1H), 4.22 – 4.08 (m, 1H), 4.07 – 3.98 (m, 2H), 3.93 (s, 3H), 3.84 – 3.70 (m, 0.5H), 3.68 – 3.56 (m, 2H), 1.50 – 1.34 (m, 3H).
624		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 2H), 8.02 (d, J = 8.4 Hz, 1H), 7.84 – 7.67 (m, 3H), 6.86 (dd, J = 18.7, 8.5 Hz, 2H), 6.73 (td, J = 9.2, 2.3 Hz, 1H), 6.32 (s, 2H), 5.82 (d, J = 10.5 Hz, 1H), 5.49 (s, 1H), 4.88 (s, 1H), 4.25 – 4.06 (m, 3H), 4.06 – 3.95 (m, 4H), 3.47 (t, J = 4.5 Hz, 2H), 3.08 (d, J = 0.6 Hz, 3H), 1.55 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.6 Hz, 3H).

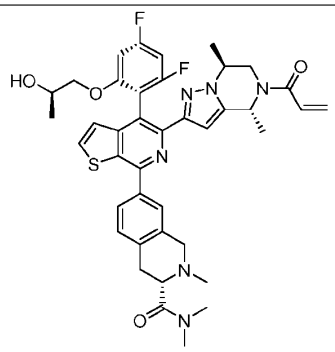
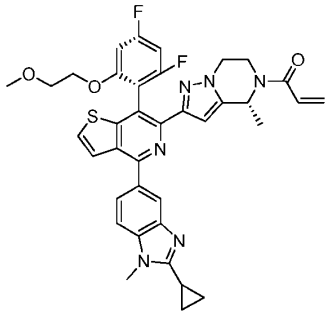
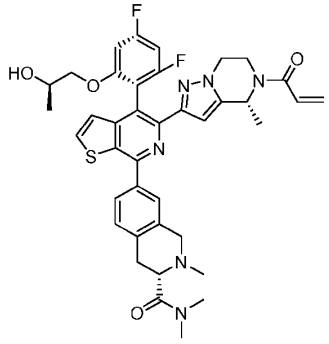
625		LCMS m/z [M+1]: 723.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, J = 7.6 Hz, 1H), 7.71 (s, 2H), 7.67 (d, J = 5.6 Hz, 1H), 7.47 (d, J = 6.8 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.00 – 6.79 (m, 3H), 6.34 (d, J = 16.6 Hz, 1H), 6.16 (s, 1H), 5.85 (d, J = 10.5 Hz, 1H), 5.60 (d, J = 87.4 Hz, 1H), 4.41 (s, 1H), 4.30 – 4.12 (m, 2H), 3.96 – 3.70 (m, 5H), 3.67 – 3.57 (m, 1H), 3.31 – 3.17 (m, 4H), 3.10 – 2.97 (m, 4H), 2.46 (s, 3H), 1.45 (d, J = 20.6 Hz, 3H), 1.29 (d, J = 11.9 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H).
626		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (s, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.70 – 7.57 (m, 3H), 6.74 (dd, J = 18.5, 8.9 Hz, 2H), 6.65 – 6.54 (m, 1H), 6.33 – 6.05 (m, 2H), 5.70 (d, J = 10.3 Hz, 1H), 5.37 (s, 1H), 4.77 – 4.74 (m, 1H), 4.12 – 3.94 (m, 3H), 3.93 – 3.83 (m, 4H), 3.36 (t, J = 4.6 Hz, 2H), 2.96 (s, 3H), 1.43 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H).
627		LCMS m/z [M+1]: 723.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 11.1 Hz, 2H), 7.72 (d, J = 4.5 Hz, 1H), 7.66 – 7.45 (m, 2H), 7.06 (d, J = 8.1 Hz, 1H), 6.94 – 6.79 (m, 2H), 6.35 (d, J = 16.2 Hz, 1H), 6.12 (s, 1H), 5.91 – 5.80 (m, 1H), 5.61 (d, J = 86.0 Hz, 1H), 4.96 (s, 1H), 4.82 (d, J = 15.3 Hz, 1H), 4.66 (d, J = 15.2 Hz, 1H), 4.49 (s, 1H), 4.25 (s, 1H), 4.04 – 3.72 (m, 4H), 3.63 (d, J = 16.5 Hz, 1H), 3.38 (d, J = 9.5 Hz, 1H), 3.27 (s, 3H), 3.12 (s, 6H), 1.42 (s, 3H), 1.30 (s, 3H), 0.94 (d, J = 6.3 Hz, 3H).

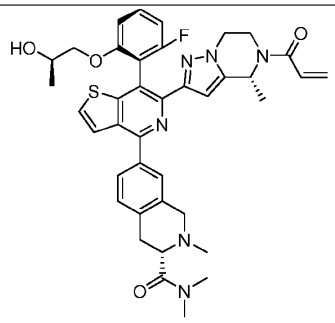
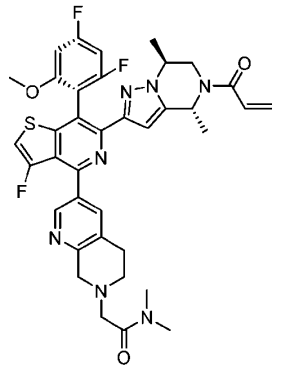
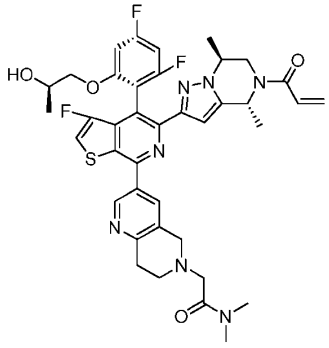
628		LCMS m/z [M+1]: 673.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.29 (s, 1H), 8.29 – 8.23 (m, 1H), 8.16 – 8.09 (m, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H), 6.92 – 6.77 (m, 2H), 6.72 (td, J = 9.4, 2.5 Hz, 1H), 6.41 (s, 1H), 6.35 - 6.20 (m, 1H), 5.80 (d, J = 10.8 Hz, 1H), 5.51 - 5.42 (m, 1H), 4.20 (s, 3H), 4.15 – 4.04 (m, 2H), 3.88 – 3.78 (m, 3H), 1.53 (d, J = 7.0 Hz, 3H), 1.19 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H).
629		LCMS m/z [M+1]: 694.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.07 (d, J = 0.8 Hz, 1H), 8.03 (dd, J = 8.7, 1.5 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.60 (s, 2H), 6.74 (dd, J = 16.3, 10.7 Hz, 2H), 6.65 – 6.57 (m, 1H), 6.18 (d, J = 14.7 Hz, 2H), 5.72 (dd, J = 10.6, 1.6 Hz, 1H), 5.70 - 5.44 (m, 1H), 4.47 (s, 1H), 4.32 (s, 1H), 4.13 – 3.94 (m, 5H), 3.89 – 3.82 (m, 2H), 3.68 (s, 1H), 3.14 – 3.07 (m, 1H), 2.79 (dd, J = 10.1, 4.7 Hz, 1H), 2.52 – 2.41 (m, 1H), 2.35 (s, 3H), 2.18 (dd, J = 17.0, 9.6 Hz, 1H), 1.78 (dd, J = 17.1, 5.5 Hz, 1H), 1.52-1.31 (m, 3H).
630		LCMS m/z [M+1]: 640.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 1.0 Hz, 1H), 7.83 (dd, J = 8.4, 1.6 Hz, 1H), 7.72 (dd, J = 16.2, 5.6 Hz, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 3.0 Hz, 1H), 6.91 – 6.82 (m, 2H), 6.70 (td, J = 9.2, 2.2 Hz, 1H), 6.62 (d, J = 3.0 Hz, 1H), 6.28 (d, J = 20.2 Hz, 2H), 5.84 (d, J = 10.6 Hz, 1H), 5.72 - 5.51 (m, 1H), 4.55 – 3.93 (m, 4H), 3.92 (s, 3H), 3.89 – 3.70 (m, 3H), 1.48 (d, J = 22.6 Hz, 3H), 0.94 (d, J = 6.0 Hz, 3H).

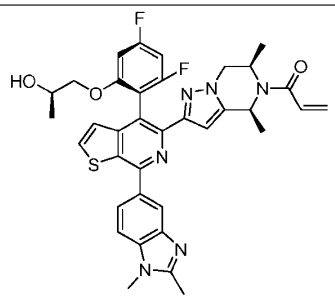
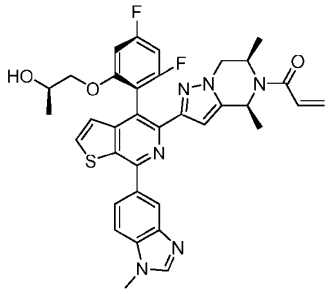
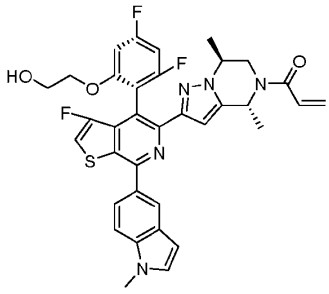
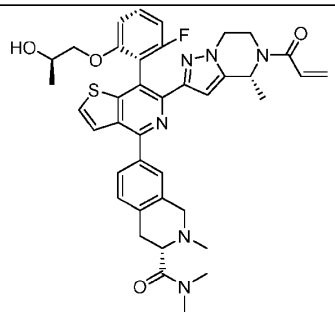
631		LCMS m/z [M+1]: 691.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 - 8.37 (m, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 5.6 Hz, 1H), 7.22 (t, J = 52.3 Hz, 1H), 6.97 (d, J = 10.6 Hz, 1H), 6.89 - 6.75 (m, 2H), 6.35 - 6.22 (m, 1H), 6.10 (s, 1H), 5.82 (dd, J = 10.6, 1.8 Hz, 1H), 5.77 - 5.41 (m, 1H), 4.57 - 4.36 (m, 1H), 4.33 - 4.26 (m, 1H), 4.21 - 4.01 (m, 6H), 3.86 - 3.65 (m, 1H), 3.45 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 1.55 - 1.34 (m, 3H) .
632		LCMS m/z [M+1]: 640.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 7.70 (dd, J = 8.4, 1.4 Hz, 1H), 7.59 (dd, J = 16.6, 5.6 Hz, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 3.0 Hz, 1H), 6.78 – 6.69 (m, 2H), 6.60 (td, J = 9.2, 2.2 Hz, 1H), 6.49 (d, J = 3.0 Hz, 1H), 6.16 (d, J = 24.4 Hz, 2H), 5.71 (d, J = 10.4 Hz, 1H), 5.61 - 5.40 (m, 1H), 4.38 – 3.84 (m, 3H), 3.79 (s, 3H), 3.75 – 3.53 (m, 4H), 1.36 (d, J = 21.6 Hz, 3H), 0.80 (d, J = 5.8 Hz, 3H).
633		LCMS m/z [M+1]: 675.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 – 8.09 (m, 1H), 7.98 (dd, J = 7.8, 1.8 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 6.89 – 6.79 (m, 2H), 6.62 (td, J = 9.2, 2.3 Hz, 1H), 6.36 – 6.30 (m, 1H), 6.14 (s, 1H), 5.84 (dd, J = 10.5, 2.0 Hz, 1H), 5.71 - 5.50 (m, 1H), 5.31 (t, J = 6.5 Hz, 1H), 4.77 - 4.61 (m, 1H), 4.48 - 4.50 (m, 1H), 4.24 (d, J = 12.8 Hz, 1H), 4.13 – 3.98 (m, 1H), 3.90 - 3.78 (m, 1H), 3.49 – 3.44 (m, 2H), 3.21 - 3.10 (m, 1H), 3.08 (s, 3H), 2.98 – 2.88 (m, 1H), 2.59 - 2.50 (m, 1H), 2.08 – 1.97 (m, 2H), 1.49 - 1.38 (m, 3H), 1.34 – 1.30 (m, 4H).

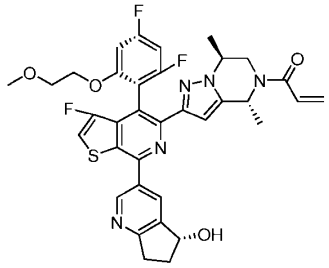
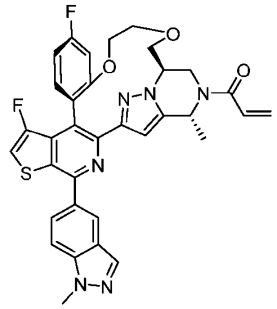
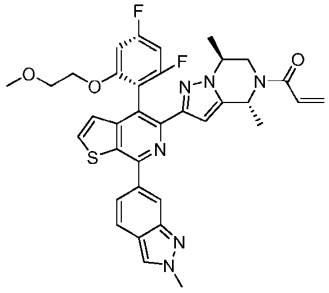
634		LCMS m/z [M+1]: 659.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (d, J = 8.8 Hz, 2H), 7.99 – 7.93 (m, 1H), 7.81 (dd, J = 8.7, 1.7 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.67 – 7.52 (m, 1H), 6.89 – 6.77 (m, 2H), 6.68 (td, J = 9.3, 2.4 Hz, 1H), 6.3 - 6.21 (m, 1H), 6.10 (s, 1H), 5.82 (dd, J = 10.7, 1.9 Hz, 1H), 5.74 - 5.53 (m, 1H), 4.30 (s, 3H), 4.23 (dd, J = 12.9, 2.8 Hz, 1H), 4.16 - 3.98 (m, 2H), 3.88 – 3.68 (m, 4H), 1.50 - 1.37 (m, 3H), 0.97 – 0.89 (m, 3H).
635		LCMS m/z [M+1]: 621.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51- 8.38 (m, 1H), 8.28 - 8.20 (m, 1H), 8.14 (d, J = 6.0 Hz, 0.65H), 8.04 (d, J = 1.6 Hz, 8.8 Hz, 1H), 7.93 - 7.71 (m, 3H), 7.32 - 7.25 (m, 0.32H), 7.20 - 7.12 (m, 0.32H), 7.10 - 6.75 (m, 3H), 6.40 - 6.20 (m, 1H), 5.95 - 5.80 (m, 2H), 5.80 - 5.35 (m, 1H), 4.75 - 4.65 (m, 1H), 4.60 - 4.30 (m, 0.61H), 4.21 - 4.18 (m, 3H), 4.15 - 4.00 (m, 0.61H), 4.00 - 3.80 (m, 3H), 3.80 - 3.40 (m, 2H), 3.25 - 3.05 (m, 0.42H), 1.60 - 1.25 (m, 3H).
636		LCMS m/z [M+1]: 671.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (d, J = 2.1 Hz, 1H), 8.25 (dd, J = 8.6, 1.6 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.94 – 6.79 (m, 2H), 6.73 (td, J = 9.0, 2.1 Hz, 1H), 6.33 - 6.21 (m, 1H), 6.17 - 6.10 (m, 1H), 5.82 (dd, J = 10.7, 1.9 Hz, 1H), 5.70 - 5.48 (m, 1H), 5.19 (s, 2H), 4.55 - 4.31 (m, 1H), 4.23 (dd, J = 12.5, 3.0 Hz, 1H), 4.18 – 3.97 (m, 6H), 3.82 - 3.67 (m, 1H), 3.44 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 1.50 - 1.34 (m, 3H).

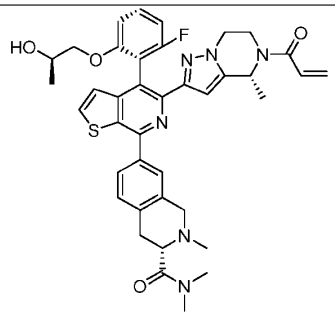
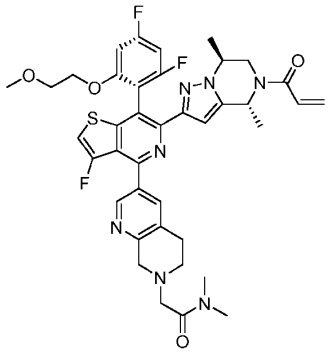
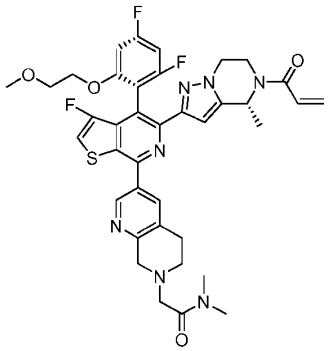
637		LCMS m/z [M+1]: 659.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (s, 1H), 8.59 (s, 1H), 8.44 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 6.90 – 6.75 (m, 2H), 6.70 - 6.60 (m, 1H), 6.29 (d, J = 15.2 Hz, 1H), 6.11 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.73 - 5.59 (m, 1H), 5.54 - 5.41 (m, 1H), 4.46 - 4.37 (m, 1H), 4.21 (s, 3H), 4.13 - 3.96 (m, 2H), 3.88 – 3.67 (m, 4H), 1.50 - 1.38 (m, 3H), 0.92 (d, J = 6.2 Hz, 3H).
638		LCMS m/z [M+1]: 623.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 3H), 8.06 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 7.1 Hz, 1H), 7.60 (dd, J = 15.2, 8.3 Hz, 1H), 7.31 (s, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.99 (t, J = 8.7 Hz, 1H), 6.85 (s, 1H), 6.31 (d, J = 16.4 Hz, 1H), 5.92 (d, J = 4.1 Hz, 1H), 5.88 – 5.82 (m, 1H), 5.59 (d, J = 77.8 Hz, 1H), 4.65 – 4.25 (m, 5H), 4.17 (s, 1H), 3.94 – 3.67 (m, 4H), 1.41 (s, 3H), 0.95 (d, J = 6.2 Hz, 3H).
639		LCMS m/z [M+1]: 623.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.21 (s, 1H), 7.85 – 7.79 (m, 3H), 7.36 (dd, J = 15.1, 8.1 Hz, 1H), 6.96 (d, J = 5.5 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.73 (t, J = 8.6 Hz, 2H), 6.20 (s, 1H), 5.92 (s, 1H), 5.71 (d, J = 10.5 Hz, 1H), 5.45 (d, J = 79.1 Hz, 1H), 4.37 – 4.09 (m, 5H), 3.91 (s, 1H), 3.69 (ddd, J = 17.6, 10.1, 4.0 Hz, 4H), 1.30 (s, 3H), 0.81 (d, J = 5.9 Hz, 3H).

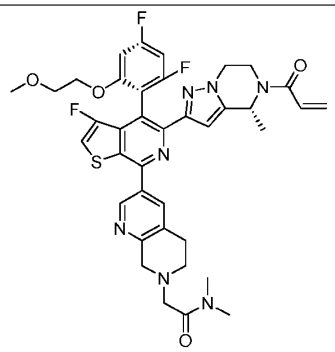
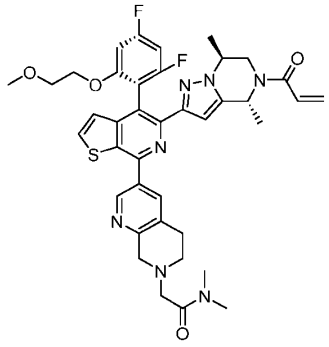
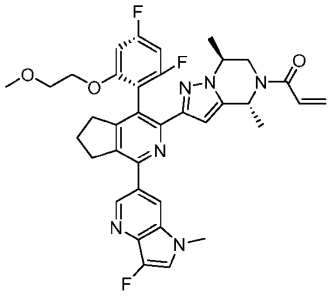
640		LCMS m/z [M+1]: 741.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 8.02 (d, J = 5.5 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 6.95 – 6.79 (m, 2H), 6.72 – 6.60 (m, 1H), 6.33 (d, J = 16.7 Hz, 1H), 6.21 (s, 1H), 5.89 – 5.81 (m, 1H), 5.75-5.45 (m, 1H), 4.96 – 4.89 (m, 1H), 4.80 (d, J = 15.6 Hz, 1H), 4.63 (d, J = 15.3 Hz, 1H), 4.52 – 4.34 (m, 1H), 3.94-3.72 (m, 2H), 3.78-3.66 (m, 1H), 3.66 – 3.55 (m, 1H), 3.24 (s, 3H), 3.10 (s, 6H), 1.57 – 1.37 (m, 3H), 1.34 – 1.18 (m, 3H), 0.91 (d, J = 6.3 Hz, 3H).
641		LCMS m/z [M+1]: 681.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.22 (dd, J = 8.6, 1.3 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.90 (t, J = 3.0 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.94 (d, J = 10.9 Hz, 1H), 6.89 - 6.79 (m, 1H), 6.77 (td, J = 9.2, 2.1 Hz, 1H), 6.30 (d, J = 16.8 Hz, 1H), 6.12 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.77 - 5.44 (m, 1H), 4.26 (dd, J = 12.4, 3.0 Hz, 1H), 4.20 (s, 3H), 4.15 - 4.00 (m, 3H), 3.45 (t, J = 4.6 Hz, 2H), 3.05 (s, 3H), 2.66 - 2.55 (m, 1H), 1.62 - 1.54 (m, 2H), 1.49 - 1.36 (m, 5H).
642		LCMS m/z [M+1]: 727.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 8.0 Hz, 1H), 8.10 - 8.03 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 5.4 Hz, 1H), 6.89 - 6.78 (m, 2H), 6.72 (td, J = 9.2, 2.1 Hz, 1H), 6.31 (d, J = 16.2 Hz, 1H), 6.11 (s, 1H), 5.84 (dd, J = 10.6, 1.4 Hz, 1H), 5.76 - 5.41 (m, 1H), 4.96 - 4.89 (m, 1H), 4.83 - 4.59 (m, 3H), 4.26 (dd, J = 12.8, 2.9 Hz, 1H), 4.08 (s, 1H), 3.86 - 3.56 (m, 5H), 3.37 - 3.32 (m, 1H), 3.24 (s, 3H), 3.09 (d, J = 1.1 Hz, 6H), 1.51 - 1.38 (m, 3H), 0.91 (d, J = 6.2 Hz, 3H).

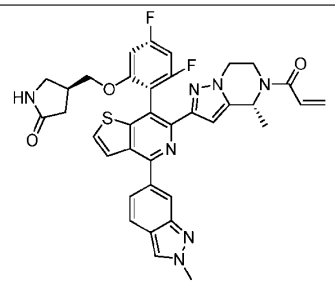
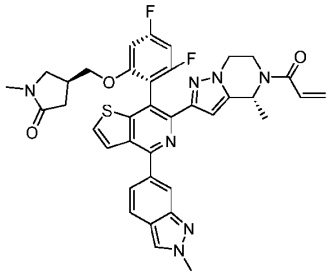
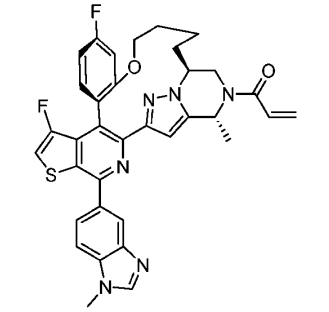
643		LCMS m/z [M+1]: 709.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 8.0 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.68 (d, J = 5.6 Hz, 1H), 7.49 (dd, J = 15.2, 8.3 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.93 – 6.79 (m, 2H), 6.30 (d, J = 13.9 Hz, 1H), 6.06 (s, 1H), 5.83 (d, J = 12.0 Hz, 1H), 5.57 (d, J = 79.3 Hz, 1H), 4.20 (d, J = 15.5 Hz, 2H), 4.00 – 3.70 (m, 6H), 3.31 – 3.21 (m, 5H), 3.13 – 2.99 (m, 5H), 2.48 (d, J = 12.5 Hz, 3H), 1.41 (s, 3H), 0.90 (d, J = 5.9 Hz, 3H).
644		LCMS m/z [M+1]: 716.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.91 (s, 1H), 8.23 (s, 1H), 7.38 (d, J = 2.8 Hz, 1H), 6.92 - 6.79 (m, 2H), 6.74 - 6.65 (m, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.26 (s, 1H), 5.88 - 5.81 (m, 1H), 5.77 - 5.48 (m, 1H), 4.71 (s, 2H), 4.52 (s, 2H), 4.38 (s, 1H), 3.89 - 3.73 (m, 2H), 3.71 (s, 3H), 3.41 (t, J = 6.0 Hz, 2H), 3.06 (d, J = 2.4 Hz, 6H), 1.55 - 1.36 (m, 3H), 1.31 - 1.18 (m, 3H).
645		LCMS m/z [M+1]: 760.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (d, J = 2.1 Hz, 1H), 8.29 (d, J = 2.0 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 6.95 – 6.75 (m, 2H), 6.62 – 6.53 (m, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.27 – 6.20 (m, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.77 – 5.45 (m, 1H), 4.45 – 4.35 (m, 1H), 4.27 – 4.15 (m, 0.5H), 4.00 (s, 2H), 3.92 – 3.70 (m, 4H), 3.61 (s, 2H), 3.50 – 3.40 (m, 0.5H), 3.23 – 3.15 (m, 2H), 3.15 – 3.08 (m, 5H), 2.99 (s, 3H), 1.55 – 1.37 (m, 3H), 1.30 – 1.18 (m, 3H).

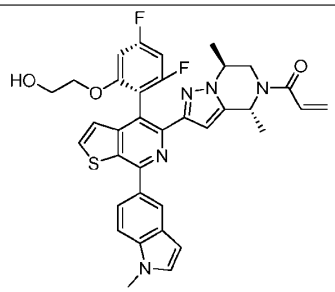
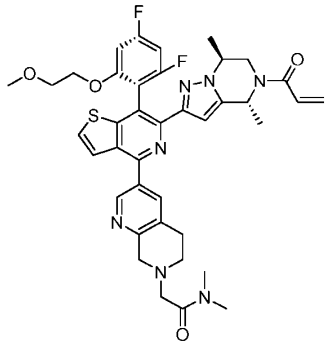
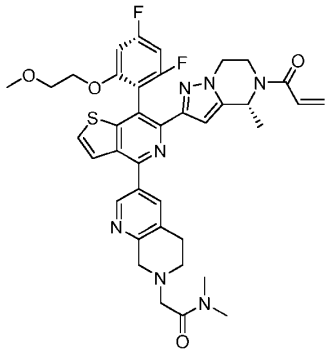
646		LCMS m/z [M+1]: 669.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (d, J = 0.8 Hz, 1H), 8.45 (dd, J = 8.7, 1.4 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 5.5 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 6.89 – 6.64 (m, 3H), 6.28 (s, 2H), 5.81 (d, J = 10.7 Hz, 1H), 5.49 (s, 1H), 4.18 – 4.13 (m, 2H), 4.09 (s, 3H), 3.88 – 3.76 (m, 3H), 2.94 (s, 3H), 1.53 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 5.9 Hz, 3H).
647		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.38 (s, 1H), 8.63 (s, 1H), 8.49 (dd, J = 8.7, 1.4 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 5.5 Hz, 1H), 7.19 (d, J = 5.5 Hz, 1H), 6.89 – 6.65 (m, 3H), 6.28 (s, 2H), 5.81 (d, J = 10.4 Hz, 1H), 5.48 (s, 1H), 4.22 (s, 3H), 4.18 – 4.12 (m, 2H), 1.53 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 5.9 Hz, 3H).
648		LCMS m/z [M+1]: 658.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (d, J = 1.6 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H), 7.91 (d, J = 8.4, 1.6 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 6.88 – 6.83 (m, 2H), 6.71 – 6.66 (m, 2H), 6.33 (d, J = 16.8 Hz, 1H), 6.09 (s, 1H), 5.86 – 5.83 (m, 1H), 5.79 – 5.51 (m, 1H), 4.55 (s, 1H), 4.31 – 4.23 (m, 1H), 4.05 – 4.00 (m, 2H), 3.94 (s, 3H), 3.94 – 3.83 (m, 1H), 3.64 – 3.60 (m, 2H), 1.42 (s, 3H), 1.34 (s, 3H).
649		LCMS m/z [M+1]: 709 ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 9.3 Hz, 1H), 7.73 (d, J = 5.7 Hz, 2H), 7.68 (d, J = 5.6 Hz, 1H), 7.49 (dd, J = 15.1, 8.2 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.85 (t, J = 8.5 Hz, 2H), 6.18 (d, J = 107.5 Hz, 2H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.57 (d, J = 78.9 Hz, 1H), 4.48 – 4.01 (m, 2H), 3.98 – 3.87 (m, 4H), 3.75 (dt, J = 10.0, 5.2 Hz, 2H), 3.32 – 3.21 (m, 5H),

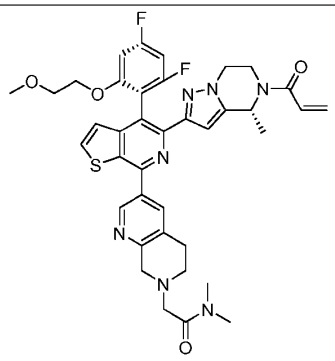
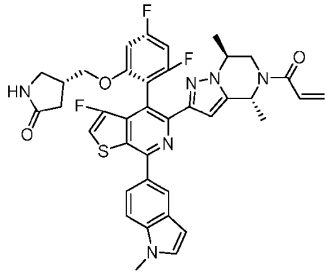
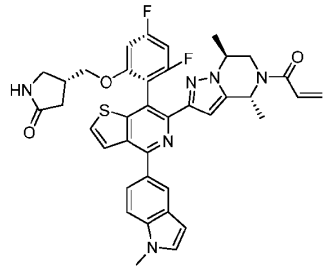
		3.15 – 2.96 (m, 5H), 2.52 – 2.43 (m, 3H), 1.41 (s, 3H), 0.91 (d, J = 6.1 Hz, 3H).
650		LCMS m/z [M+1]: 676.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.14 (d, J = 2.3 Hz, 1H), 8.53 (d, J = 2.6 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 6.88-6.77 (m, 2H), 6.59 (td, J = 9.3, 2.3 Hz, 1H), 6.32 (d, J = 15.9 Hz, 1H), 6.21-6.14 (m, 1H), 5.84 (dd, J = 10.5, 2.0 Hz, 1H), 5.74-5.58 (m, 1H), 5.36 (t, J = 6.5 Hz, 1H), 4.74-4.54 (m, 1H), 4.43-4.38 (m, 1H), 4.32- 4.16 (m, 1H), 4.11- 4.04 (m, 1H), 4.03-3.96 (m, 1H), 3.92- 3.76 (m, 1H), 3.46 (t, J = 4.6 Hz, 2H), 3.26-3.19 (m, 1H), 3.07 (s, 3H), 3.06- 2.99 (m, 1H), 2.70-2.58 (m, 1H), 2.14-2.03 (m, 1H), 1.50- 1.38 (m, 3H), 1.30- 1.23 (m, 3H).
651		LCMS m/z [M+1]: 639.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.24 (s, 1H), 8.15 (dd, J = 1.6 Hz, 8.8 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.47 - 7.42 (m, 1H), 6.92 - 6.80 (m, 2H), 6.69 (d, J = 11.2 Hz, 1H), 6.40 - 6.20 (m, 1H), 5.90 - 5.35 (m, 3H), 4.72 - 4.60 (m, 1H), 4.50 - 4.35 (m, 0.5H), 4.18 (s, 3H), 4.15 - 4.00 (m, 0.5H), 4.00 - 3.85 (m, 3H), 3.75 - 3.40 (m, 3H), 1.55 - 1.25 (m, 4H).
652		LCMS m/z [M+1]: 655.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.30 (s, 1H), 7.93 (d, J = 5.5 Hz, 1H), 7.90 (d, J = 1.2 Hz, 2H), 7.11 (d, J = 5.5 Hz, 1H), 6.90 - 6.81 (m, 2H), 6.65 (td, J = 9.2, 2.4 Hz, 1H), 6.32 (d, J = 15.9 Hz, 1H), 6.25 - 6.18 (m, 1H), 5.83 (dd, J = 10.7, 1.9 Hz, 1H), 5.73 - 5.49 (m, 1H), 4.77 - 4.61 (m, 1H), 4.43 - 4.37 (m, 1H), 4.28 (s, 3H), 4.13 - 4.06 (m, 1H), 4.01 - 3.93 (m, 1H), 3.91 - 3.75 (m, 1H), 3.44 (t, J = 4.7 Hz, 2H), 3.05 (s, 3H), 1.50 - 1.39 (m, 3H), 1.31 – 1.26 (m, 3H).

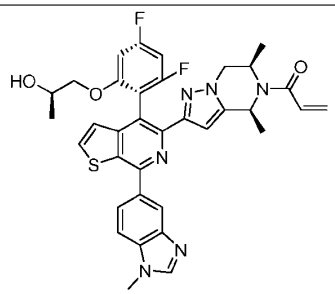
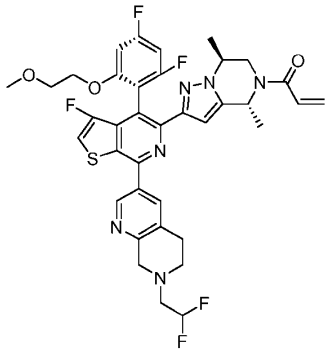
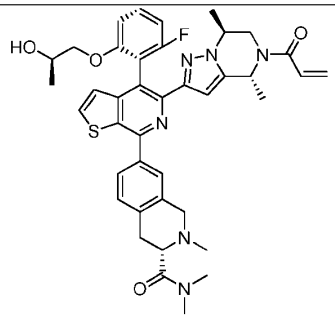
653		LCMS m/z [M+1]: 709.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 8.1 Hz, 1H), 8.07 (s, 2H), 7.56 (d, J = 7.9 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.10 (s, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.84 (t, J = 8.5 Hz, 2H), 6.27 (d, J = 15.4 Hz, 1H), 5.94 (s, 1H), 5.80 (dd, J = 10.6, 1.8 Hz, 1H), 5.42 (s, 1H), 4.92 (d, J = 5.2 Hz, 1H), 4.78 (d, J = 15.6 Hz, 1H), 4.62 (d, J = 15.6 Hz, 1H), 4.40 (s, 1H), 4.24 (d, J = 12.6 Hz, 1H), 4.09 (s, 1H), 3.77 (m, J = 24.1, 11.3, 6.3 Hz, 4H), 3.59 (dd, J = 17.7, 5.3 Hz, 1H), 3.33 (d, J = 11.1 Hz, 1H), 3.23 (s, 3H), 3.08 (s, 6H), 1.37 (s, 3H), 0.88 (d, J = 6.2 Hz, 3H).
654		LCMS m/z [M+1]: 760.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 8.23 (s, 1H), 7.38 (d, J = 2.6 Hz, 1H), 6.94 - 6.80 (m, 2H), 6.73 (td, J = 9.2, 2.2 Hz, 1H), 6.37 - 6.23 (m, 2H), 5.85 (dd, J = 10.5, 1.5 Hz, 1H), 5.78 - 5.43 (m, 1H), 4.70 (s, 2H), 4.51 (s, 2H), 4.39 (s, 1H), 4.15 - 4.00 (m, 2H), 3.83 - 3.68 (m, 2H), 3.49 - 3.37 (m, 4H), 3.09 - 3.03 (m, 9H), 1.51 - 1.38 (m, 3H), 1.28 (d, J = 3.9 Hz, 3H).
655		LCMS m/z [M+1]: 716.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.05 (d, J = 1.9 Hz, 1H), 8.34 (d, J = 1.7 Hz, 1H), 7.56 (d, J = 2.3 Hz, 1H), 6.86 (s, 1H), 6.76 (d, J = 11.0 Hz, 1H), 6.60 (td, J = 9.1, 1.9 Hz, 1H), 6.34 (d, J = 17.0 Hz, 1H), 6.12 (s, 1H), 5.85 (dd, J = 10.5, 1.4 Hz, 1H), 5.78 - 5.45 (m, 1H), 4.45 - 4.37 (m, 1H), 3.95 (s, 2H), 3.68 (s, 3H), 3.58 (s, 2H), 3.14 (s, 3H), 3.13 - 3.09 (m, 2H), 2.98 (s, 3H), 2.98 - 2.94 (m, 2H), 1.52 - 1.38 (m, 3H), 1.33 - 1.22 (m, 3H).

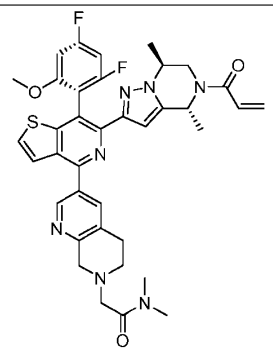
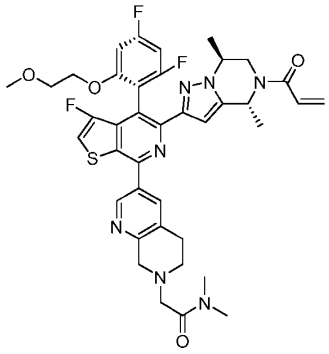
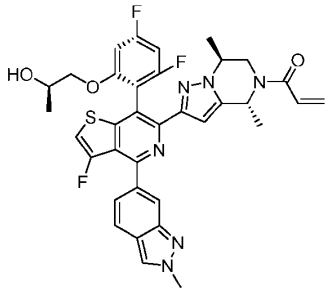
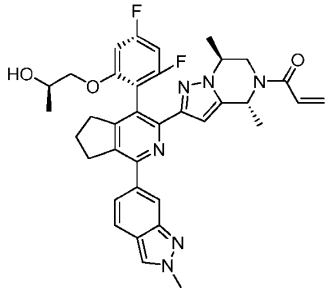
656		LCMS m/z [M+1]: 746.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.25 (d, J = 1.8 Hz, 1H), 8.52 (d, J = 1.6 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 6.89 - 6.78 (m, 2H), 6.66 (td, J = 9.2, 2.2 Hz, 1H), 6.30 (d, J = 16.0 Hz, 1H), 6.05 (s, 1H), 5.83 (dd, J = 10.5, 1.6 Hz, 1H), 5.73 - 5.42 (m, 1H), 4.70 (s, 2H), 4.51 (s, 2H), 4.24 (dd, J = 12.5, 2.8 Hz, 3H), 4.16 - 3.97 (m, 3H), 3.76 (s, 3H), 3.48 - 3.39 (m, 4H), 3.09 - 3.04 (m, 10H), 1.50 - 1.36 (m, 3H).
657		LCMS m/z [M+1]: 742.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (s, 1H), 8.39 (s, 1H), 7.96 (d, J = 5.4 Hz, 1H), 7.12 (d, J = 5.4 Hz, 1H), 6.86 (d, J = 10.9 Hz, 2H), 6.68 (td, J = 9.1, 2.0 Hz, 1H), 6.34 (d, J = 16.7 Hz, 1H), 6.18 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.76 - 5.48 (m, 1H), 4.46 - 4.37 (m, 1H), 4.13 - 4.06 (m, 1H), 4.02 - 3.91 (m, 3H), 3.86 (s, 1H), 3.59 (s, 2H), 3.43 (t, J = 4.5 Hz, 2H), 3.14 (s, 5H), 3.04 (s, 3H), 2.99 (s, 5H), 1.53 - 1.37 (m, 3H), 1.34 - 1.24 (m, 3H).
658		LCMS m/z [M+1]: 657.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1H), 8.43 (s, 1H), 7.54 (dd, J = 2.3, 0.8 Hz, 1H), 6.80 (dd, J = 31.5, 11.8 Hz, 2H), 6.56 (t, J = 9.4 Hz, 1H), 6.29 (d, J = 16.0 Hz, 1H), 6.05 (s, 1H), 5.81 (dd, J = 10.6, 1.6 Hz, 1H), 5.75 – 5.39 (m, 1H), 4.47 – 4.35 (m, 1H), 4.29 – 4.07 (m, 2H), 3.97 (dt, J = 10.9, 4.0 Hz, 1H), 3.90 – 3.73 (m, 4H), 3.53 (t, J = 4.6 Hz, 2H), 3.25 (dd, J = 7.5, 3.7 Hz, 2H), 3.21 (s, 3H), 2.96 – 2.85 (m, 1H), 2.76 – 2.66 (m, 1H), 2.13 (dt, J = 11.4, 7.5 Hz, 2H), 1.41 (d, J = 22.7 Hz, 3H), 1.27 (d, J = 9.7 Hz, 3H).

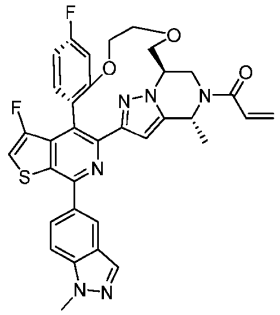
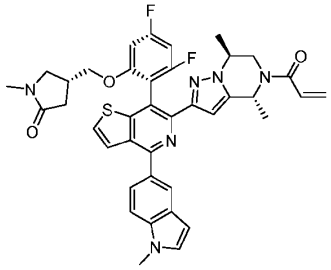
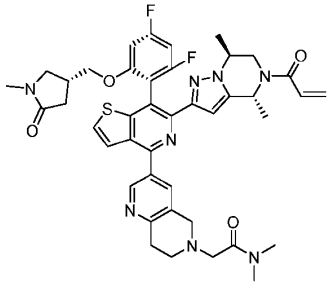
659		LCMS m/z [M+1]: 680.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 8.38 (s, 1H), 8.10 (d, J = 5.6 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.72 (dd, J = 8.6, 1.4 Hz, 1H), 6.98 (d, J = 10.5 Hz, 1H), 6.90 – 6.78 (m, 2H), 6.29 (d, J = 15.9 Hz, 1H), 6.07 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.77 – 5.52 (m, 1H), 4.53 – 4.26 (m, 5H), 4.26 – 4.04 (m, 2H), 4.03 – 3.65 (m, 2H), 3.28 (s, 1H), 2.83 (dd, J = 10.1, 4.2 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.21 (dd, J = 17.1, 9.8 Hz, 1H), 1.81 (dd, J = 17.1, 5.0 Hz, 1H), 1.52 - 1.35 (m, 3H).
660		LCMS m/z [M+1]: 694.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.43 (s, 1H), 8.14 (d, J = 5.6 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.75 (dd, J = 8.6, 1.3 Hz, 1H), 6.97 (d, J = 10.6 Hz, 1H), 6.92 – 6.77 (m, 2H), 6.29 (d, J = 16.0 Hz, 1H), 6.09 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.78 – 5.50 (m, 1H), 4.54 – 4.38 (m, 1H), 4.37 – 4.29 (m, 4H), 4.25 – 4.06 (m, 2H), 3.94 (dd, J = 9.1, 3.9 Hz, 1H), 3.77 (s, 1H), 3.44 – 3.34 (m, 1H), 2.85 (dd, J = 10.2, 3.4 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.33 (dd, J = 16.9, 10.2 Hz, 1H), 2.16 (s, 3H), 1.88 (dd, J = 17.0, 3.7 Hz, 1H), 1.52 - 1.38 (m, 3H).
661		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1H), 8.56 (s, 1H), 8.41 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.62 (s, 1H), 7.37 (t, J = 7.4 Hz, 1H), 6.94 – 6.94 (m, 3H), 6.41 – 6.28 (m, 1H), 5.90 – 5.81 (m, 1H), 5.68 (d, J = 19.7 Hz, 1H), 5.61 – 5.37 (m, 2H), 4.85 - 4.79 (m, 1H), 4.56 – 4.47 (m, 1H), 4.33 – 4.26 (m, 1H), 4.20 (s, 3H), 4.16 – 4.07 (m, 1H), 3.71 - 3.65 (m, 1H), 2.03 – 1.92 (m, 2H), 1.76 – 1.66 (m, 1H), 1.47 – 1.31 (m, 5H).

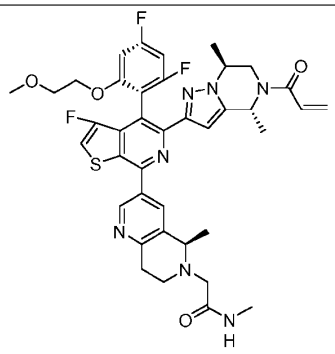
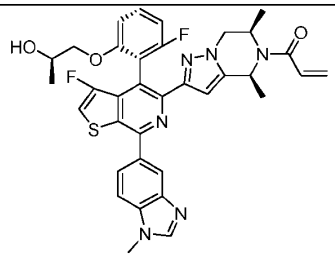
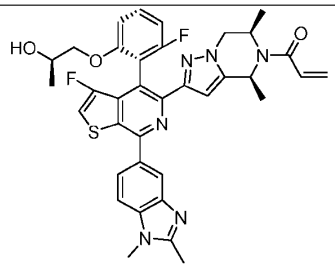
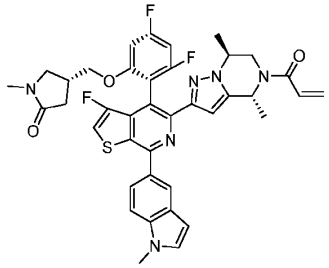
662		LCMS m/z [M+1]: 640.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 8.6, 1.8 Hz, 1H), 7.92 (d, J = 5.5 Hz, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 3.2 Hz, 1H), 7.08 (d, J = 5.5 Hz, 1H), 6.91 - 6.81 (m, 2H), 6.66 – 6.58 (m, 2H), 6.35 - 6.21 (m, 2H), 5.84 (d, J = 11.2 Hz, 1H), 5.72 - 5.57 (m, 1H), 4.77 - 4.65 (m, 1H), 4.45 - 4.38 (m, 1H), 4.27 - 4.17 (m, 1H), 4.05 – 3.99 (m, 2H), 3.90 (s, 3H), 3.87 - 3.76 (m, 1H), 3.68 – 3.62 (m, 1H), 3.60 – 3.54 (m, 1H), 3.49 – 3.40 (m, 1H), 1.53 - 1.42 (m, 3H), 1.29 - 1.21 (m, 3H).
663		LCMS m/z [M+1]: 742.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (d, J = 1.8 Hz, 1H), 8.40 (s, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.97 – 6.83 (m, 2H), 6.72 (t, J = 9.2 Hz, 1H), 6.35 (d, J = 16.8 Hz, 1H), 6.24 (s, 1H), 5.87 (d, J = 10.6 Hz, 1H), 5.64 (d, J = 86.6 Hz, 1H), 4.73 (s, 2H), 4.55 (s, 2H), 4.45 (s, 1H), 4.26 (d, J = 14.8 Hz, 1H), 4.17 – 4.01 (m, 2H), 3.99 – 3.62 (m, 3H), 3.46 (t, J = 4.7 Hz, 4H), 3.15 – 2.96 (m, 9H), 1.45 (s, 3H), 1.33 (s, 3H).
664		LCMS m/z [M+1]: 728.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (d, J = 1.6 Hz, 1H), 8.41 (s, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.99 – 6.81 (m, 2H), 6.75 (td, J = 9.2, 2.2 Hz, 1H), 6.31 (d, J = 16.1 Hz, 1H), 6.17 (s, 1H), 5.91 – 5.80 (m, 1H), 5.62 (d, J = 83.6 Hz, 1H), 4.73 (s, 2H), 4.55 (s, 2H), 4.45 (s, 1H), 4.30 – 4.20 (m, 1H), 4.18 – 3.98 (m, 3H), 3.79 (s, 3H), 3.51 – 3.37 (m, 4H), 3.16 – 2.88 (m, 9H), 1.45 (s, 3H).

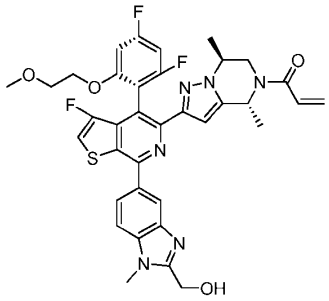
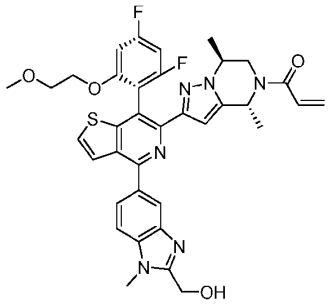
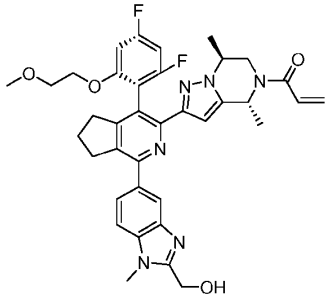
665		LCMS m/z [M+1]: 728.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1H), 8.58 (s, 1H), 8.04 (d, J = 5.5 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 6.94 – 6.80 (m, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.31 (d, J = 16.5 Hz, 1H), 6.11 (s, 1H), 5.85 (d, J = 10.7 Hz, 1H), 5.62 (d, J = 85.7 Hz, 1H), 4.74 (s, 2H), 4.55 (s, 2H), 4.46 (s, 1H), 4.31 – 4.20 (m, 1H), 4.18 – 3.97 (m, 3H), 3.80 (s, 3H), 3.53 – 3.40 (m, 4H), 3.16 – 2.96 (m, 9H), 1.45 (s, 3H).
666		LCMS m/z [M+1]: 711.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 (d, J = 0.9 Hz, 1H), 8.04 – 8.00 (m, 1H), 7.95 (dd, J = 8.5, 1.4 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 3.1 Hz, 1H), 6.91 – 6.81 (m, 2H), 6.78 – 6.68 (m, 2H), 6.33 (d, J = 16.3 Hz, 1H), 6.04 (s, 1H), 5.85 (dd, J = 10.6, 1.1 Hz, 1H), 5.78 – 5.46 (m, 1H), 4.60 – 4.50 (m, 1H), 4.32 – 4.20 (m, 0.5H), 4.04 – 3.78 (m, 5.5H), 3.28 – 3.22 (m, 1H), 2.84 (dd, J = 10.1, 4.5 Hz, 1H), 2.74 – 2.62 (m, 1H), 2.25 (dd, J = 17.1, 9.6 Hz, 1H), 1.82 (dd, J = 17.1, 5.3 Hz, 1H), 1.52 – 1.26 (m, 6H).
667		LCMS m/z [M+1]: 693.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.14 (d, J = 5.6 Hz, 1H), 7.94 (d, J = 5.6 Hz, 1H), 7.87 (dd, J = 1.6 Hz, 8.8 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 3.2 Hz, 1H), 7.00 - 6.83 (m, 3H), 6.74 (d, J = 3.2 Hz, 1H), 6.36 - 6.30 (m, 1H), 6.01 (s, 1H), 5.85 (dd, J = 1.6 Hz, 10.8 Hz, 1H), 5.80 - 5.50 (m, 1H), 4.72 - 4.60 (m, 1H), 4.40 - 4.25 (m, 0.5H), 4.01 (d, J = 4.4 Hz, 2H), 3.96 (s, 3H), 3.90 - 3.80 (m, 0.5H), 3.26 (s, 1H), 2.80 - 2.75 (m, 1H), 2.75 - 2.60 (m, 1H), 2.26 - 2.19 (m, 1H), 1.72 - 1.65 (m, 1H), 1.55 - 1.30 (m, 6H).

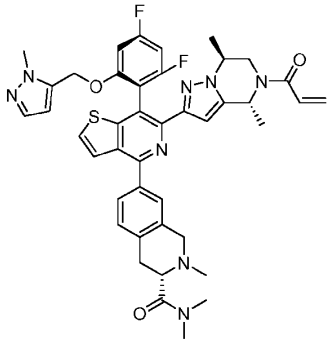
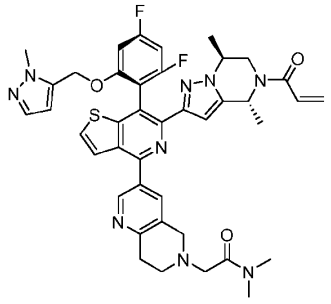
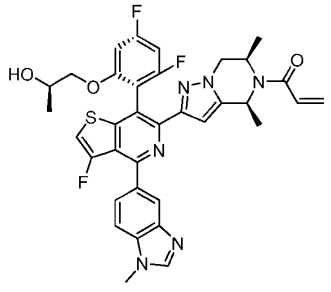
668		LCMS m/z [M+1]: 655.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.39 (s, 1H), 8.63 (s, 1H), 8.49 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 6.89 – 6.67 (m, 3H), 6.28 (s, 1H), 6.18 (s, 1H), 5.81 (d, J = 11.0 Hz, 1H), 5.56 – 5.43 (m, 1H), 4.22 (s, 3H), 4.21 – 4.15 (m, 2H), 3.83 – 3.70 (m, 3H), 1.51 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 5.6 Hz, 3H).
669		LCMS m/z [M+1]: 739.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.26 (s, 1H), 8.59 (s, 1H), 7.62 (d, J = 2.2 Hz, 1H), 6.85 (t, J = 11.6 Hz, 2H), 6.69 – 6.60 (m, 1H), 6.36 (dd, J = 35.4, 19.0 Hz, 2H), 6.15 (s, 1H), 5.89 – 5.84 (m, 1H), 5.71 (d, J = 25.6 Hz, 1H), 4.74 (s, 1H), 4.50 (d, J = 33.2 Hz, 3H), 4.32 – 3.86 (m, 4H), 3.74 – 3.55 (m, 3H), 3.47 (t, J = 4.6 Hz, 2H), 3.36 (d, J = 5.8 Hz, 2H), 3.10 (s, 3H), 1.46 (d, J = 16.8 Hz, 3H), 1.33 (s, 3H).
670		LCMS m/z [M+1]: 723 ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 5.6 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 15.2, 8.2 Hz, 1H), 7.16 (d, J = 5.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.94 – 6.81 (m, 2H), 6.35 (d, J = 16.4 Hz, 1H), 6.08 (s, 1H), 5.87 (d, J = 10.6 Hz, 1H), 5.78 – 5.43 (m, 1H), 4.99 – 4.93 (m, 1H), 4.83 (d, J = 15.4 Hz, 1H), 4.66 (d, J = 15.6 Hz, 1H), 4.50 (s, 1H), 4.00 – 3.57 (m, 5H), 3.54 – 3.36 (m, 2H), 3.27 (s, 3H), 3.13 (d, J = 1.0 Hz, 6H), 1.44 (d, J = 21.8 Hz, 3H), 1.31 (s, 3H), 0.94 (d, J = 6.2 Hz, 3H).

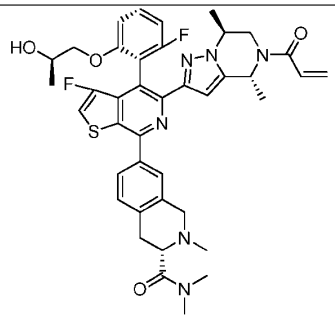
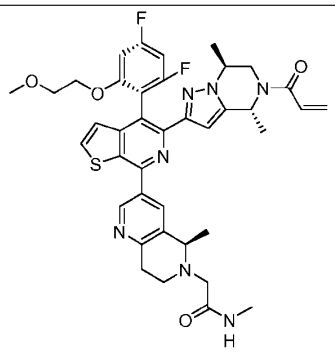
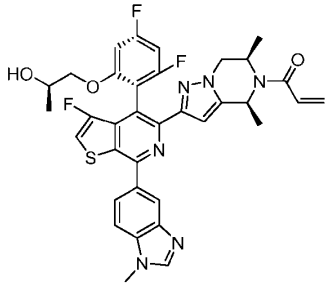
671		LCMS m/z [M+1]: 698.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.07 (d, J = 1.8 Hz, 1H), 8.35 (s, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 6.84 (d, J = 10.7 Hz, 2H), 6.67 (m, J = 9.2, 2.2 Hz, 1H), 6.31 (d, J = 16.4 Hz, 1H), 6.17 (s, 1H), 5.85 – 5.80 (m, 1H), 5.71 (s, 1H), 4.69 (s, 2H), 4.51 (s, 2H), 4.41 (s, 1H), 4.21 (s, 1H), 3.99 – 3.60 (m, 6H), 3.42 (s, 2H), 3.05 (d, J = 1.8 Hz, 6H), 1.41 (s, 3H), 1.27 (s, 3H).
672		LCMS m/z [M+1]: 760.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.25 (s, 1H), 8.51 (s, 1H), 7.60 (d, J = 2.0 Hz, 1H), 6.84 (t, J = 12.4 Hz, 2H), 6.62 (dd, J = 10.1, 8.3 Hz, 1H), 6.34 (d, J = 16.5 Hz, 1H), 6.15 (s, 1H), 5.85 (d, J = 11.5 Hz, 1H), 5.62 (d, J = 87.8 Hz, 1H), 4.71 (s, 2H), 4.52 (s, 2H), 4.44 (s, 1H), 4.39 – 4.17 (m, 1H), 4.09 (t, J = 4.9 Hz, 1H), 4.03 (d, J = 4.5 Hz, 1H), 3.79 (d, J = 16.8 Hz, 3H), 3.46 (t, J = 4.6 Hz, 4H), 3.10 – 3.05 (m, 9H), 1.43 (s, 3H), 1.31 (s, 3H).
673		LCMS m/z [M+1]: 673.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 – 8.34 (m, 1H), 8.10 (s, 1H), 7.97 – 7.89 (m, 1H), 7.64 – 7.55 (m, 1H), 7.49 (s, 1H), 7.00 – 6.66 (m, 3H), 6.42 – 6.24 (m, 2H), 5.85 (d, J = 9.4 Hz, 1H), 5.77 – 5.43 (m, 1H), 4.54 – 4.43 (m, 1H), 4.39 – 4.19 (m, 4H), 3.99 – 3.75 (m, 4H), 1.55 – 1.39 (m, 3H), 1.37 – 1.20 (m, 3H), 1.06 – 0.89 (m, 3H).
674		LCMS m/z [M+1]: 639.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 8.15 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.51 (dd, J = 8.6, 1.2 Hz, 1H), 6.95 - 6.73 (m, 3H), 6.35 (d, J = 16.6 Hz, 1H), 6.0 (s, 1H), 5.86 (dd, J = 10.5, 1.6 Hz, 1H), 5.78 - 5.44 (m, 1H), 4.65 - 4.54 (m, 1H), 4.31 (s, 3H), 4.00 - 3.95 (m, 1H), 3.95 - 3.87 (m, 1H), 3.86 - 3.79 (m, 1H), 3.37 -

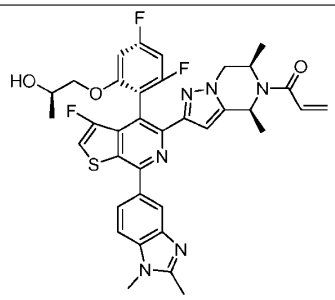
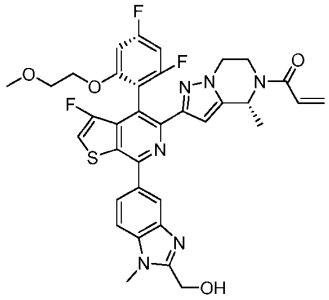
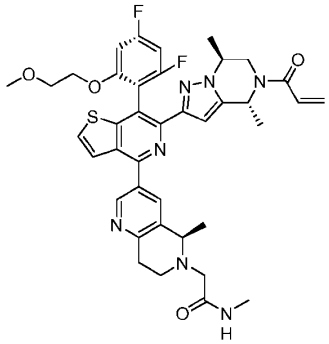
		3.31 (m, 2H), 3.17 - 2.95 (m, 2H), 2.33 - 2.21 (m, 2H), 1.49 - 1.30 (m, 6H), 1.06 (d, J = 6.2 Hz, 3H).
675		LCMS m/z [M+1]: 639.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 - 8.50 (m, 1H), 8.25 - 8.18 (m, 2H), 7.79 (dd, J = 3.6 Hz, 8.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.10 - 7.00 (m, 2H), 7.00 - 6.75 (m, 2H), 6.65 (t, J = 8.0 Hz, 1H), 6.35 - 6.25 (m, 1H), 5.92 - 5.50 (m, 2H), 4.70 - 4.60 (m, 1.5H), 4.42 - 4.30 (m, 1H), 4.17 (s, 3H), 3.95 - 3.80 (m, 3.5H), 3.52 - 3.45 (m, 0.5H), 3.20 - 3.05 (m, 1H), 2.80 - 2.65 (m, 1H), 1.57 - 1.47 (m, 3H).
676		LCMS m/z [M+1]: 707.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.12 (d, J = 5.6 Hz, 1H), 7.94 - 7.88 (m, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 3.2 Hz, 1H), 7.00 (d, J = 10.4 Hz, 1H), 6.90 - 6.83 (m, 2H), 6.74 (d, J = 3.2 Hz, 1H), 6.36 - 6.31 (m, 1H), 6.08 (s, 1H), 5.85 (dd, J = 1.6 Hz, 10.4 Hz, 1H), 5.80 - 5.50 (m, 1H), 4.72 - 4.60 (m, 1H), 4.40 - 4.25 (m, 0.5H), 4.15 - 4.05 (m, 2H), 3.96 (s, 3H), 3.95 - 3.85 (m, 0.5H), 3.39 (t, J = 9.6 Hz, 1H), 2.98 (d, J = 3.6 Hz, 1H), 2.65 - 2.55 (m, 1H), 2.45 (s, 3H), 2.35 - 2.28 (m, 1H), 1.75 (dd, J = 1.6 Hz, 10 Hz, 1H), 1.55 - 1.30 (m, 6H).
677		LCMS m/z [M+1]: 795.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.21 (s, 1H), 8.39 (s, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.95 - 6.85 (m, 2H), 6.72 (td, J = 2.0 Hz, 9.2 Hz, 1H), 6.40 - 6.31 (m, 2H), 5.86 (dd, J = 1.6 Hz, 10.8 Hz, 1H), 5.83 - 5.50 (m, 1H), 4.79 (s, 2H), 4.51 (s, 2H), 4.48 - 4.40 (m, 1H), 4.30 - 4.20 (m, 0.5H), 4.05 - 3.85 (m, 4.5H), 3.52 (t, J = 6.4 Hz, 2H), 3.28 (t, J = 6.4 Hz, 1H), 3.08 (s, 6H), 2.95 - 2.90 (m, 1H), 2.65 - 2.55 (m, 1H), 2.41 (s, 3H), 2.32 - 2.20 (m, 1H), 1.90 - 1.80 (m, 1H), 1.60 - 1.40 (m, 3H), 1.35 - 1.20 (m, 3H).

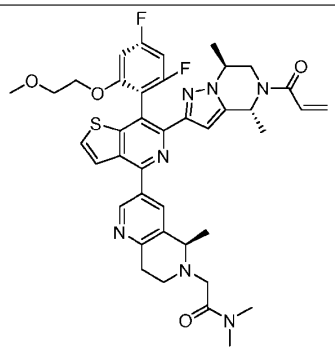
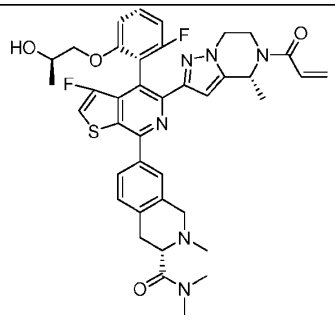
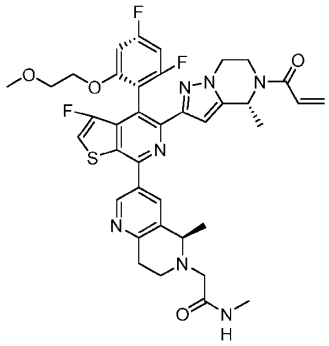
678		LCMS m/z [M+1]: 760.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (d, J = 2.0 Hz, 1H), 8.58 (s, 1H), 7.63 (d, J = 2.3 Hz, 1H), 6.97 – 6.78 (m, 2H), 6.72 – 6.58 (m, 1H), 6.35 (d, J = 16.7 Hz, 1H), 6.12 (s, 1H), 5.87 (d, J = 10.6, 1.7 Hz, 1H), 5.63 (d, J = 88.8 Hz, 1H), 5.02 – 4.95 (m, 1H), 4.47 (s, 1H), 4.38 – 4.07 (m, 4H), 4.07 – 3.83 (m, 3H), 3.81 – 3.71 (m, 1H), 3.50 – 3.43 (m, 4H), 3.10 (s, 3H), 2.87 (s, 3H), 1.88 (d, J = 6.9 Hz, 3H), 1.46 (d, J = 20.7 Hz, 3H), 1.34 (s, 3H).
679		LCMS m/z [M+1]: 655.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.45 (s, 1H), 8.60 (s, 1H), 8.47 (dd, J = 8.7, 1.4 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 7.45 (dd, J = 15.2, 8.4 Hz, 1H), 6.96 – 6.70 (m, 3H), 6.42 – 6.16 (m, 1H), 5.95 (s, 1H), 5.81 (d, J = 10.5 Hz, 1H), 5.51 – 5.28 (m, 1H), 4.23 (s, 3H), 4.20 – 4.13 (m, 2H), 3.81 – 3.72 (m, 3H), 1.43 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 5.9 Hz, 3H).
680		LCMS m/z [M+1]: 669.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.41 (dd, J = 8.7, 1.4 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.44 (dd, J = 15.2, 8.4 Hz, 1H), 6.92 – 6.75 (m, 3H), 6.39 – 6.12 (m, 1H), 5.95 (s, 1H), 5.80 (d, J = 10.5 Hz, 1H), 5.52 – 5.31 (m, 1H), 4.24 – 4.13 (m, 2H), 4.09 (s, 3H), 3.83 – 3.69 (m, 3H), 2.94 (s, 3H), 1.43 (d, J = 6.4 Hz, 3H), 1.22 – 1.12 (m, 3H), 0.96 (d, J = 5.8 Hz, 3H).
681		LCMS m/z [M+1]: 725.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 – 8.35 (m, 1H), 7.97 (dd, J = 8.6, 1.4 Hz, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 6.93 – 6.81 (m, 1H), 6.80 – 6.74 (m, 1H), 6.63 – 6.53 (m, 2H), 6.36 – 6.17 (m, 2H), 5.87 – 5.81 (m, 1H), 5.77 – 5.48 (m, 1H), 4.43 – 4.35 (m, 1H), 4.25 – 4.17 (m,

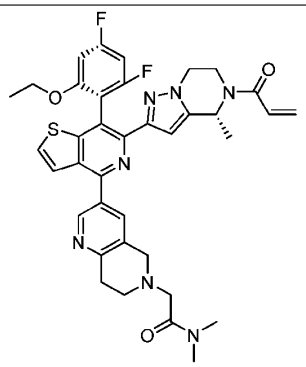
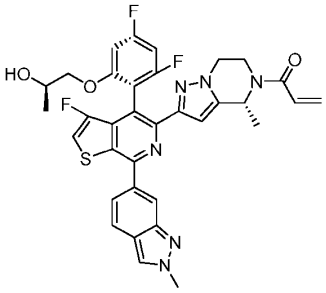
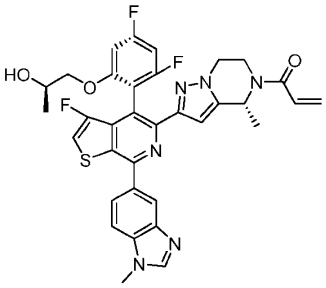
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682		LCMS m/z [M+1]: 703.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.42 (dd, J = 1.6 Hz, 8.8 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.95 - 7.80 (m, 2H), 6.61 (td, J = 2.0 Hz, 9.2 Hz, 1H), 6.35 - 6.30 (m, 1H), 6.13 (s, 1H), 5.84 (dd, J = 1.6 Hz, 10.8 Hz, 1H), 5.80 - 5.45 (m, 1H), 5.21 (s, 2H), 4.80 - 4.70 (m, 1H), 4.50 - 4.40 (m, 1H), 4.30 - 4.20 (m, 0.5H), 4.15 - 4.00 (m, 5H), 3.90 - 3.80 (m, 0.5H), 3.47 (t, J = 4.8 Hz, 2H), 3.09 (s, 3H), 1.55 - 1.25 (m, 6H).
683		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 7.97 (dd, J = 8.4, 1.3 Hz, 1H), 7.76 – 7.64 (m, 3H), 6.94 – 6.80 (m, 2H), 6.70 – 6.63 (m, 1H), 6.36 – 6.23 (m, 2H), 5.83 (dd, J = 10.6, 1.2 Hz, 1H), 5.77 – 5.46 (m, 1H), 4.94 (s, 2H), 4.44 – 4.35 (m, 1H), 4.27 – 4.17 (m, 0.5H), 4.14 – 3.96 (m, 5H), 3.89 – 3.79 (m, 0.5H), 3.45 (t, J = 4.7 Hz, 2H), 3.05 (s, 3H), 1.54 – 1.38 (m, 3H), 1.34 – 1.20 (m, 3H).
684		LCMS m/z [M+1]: 669.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 7.91 (dd, J = 8.5, 1.2 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 6.92 – 6.73 (m, 2H), 6.60 – 6.52 (m, 1H), 6.31 (d, J = 16.5 Hz, 1H), 6.20 – 6.10 (m, 1H), 5.86 – 5.80 (m, 1H), 5.75 – 5.42 (m, 1H), 4.92 (s, 2H), 4.42 – 4.32 (m, 1H), 4.25 – 4.09 (m, 1.5H), 4.03 – 3.93 (m, 4H), 3.87 – 3.78 (m, 1H), 3.56 (t, J = 4.6 Hz, 2H), 3.48 – 3.38 (m, 0.5H), 3.28 – 3.16 (m, 5H), 2.97 – 2.87 (m, 1H), 2.76 – 2.65 (m,

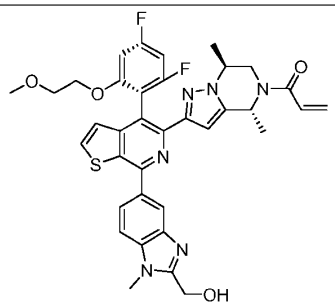
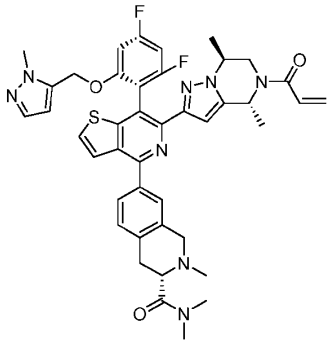
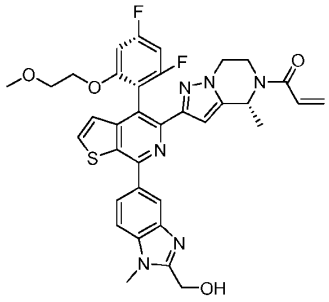
		1H), 2.18 – 2.05 (m, 2H), 1.51 – 1.35 (m, 3H), 1.31 – 1.20 (m, 3H).
685		LCMS m/z [M+1]: 777.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (d, J = 8.1 Hz, 1H), 7.79 (s, 1H), 7.66 (d, J = 5.5 Hz, 1H), 7.56 (d, J = 5.6 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 1.8 Hz, 1H), 6.93 (d, J = 10.5 Hz, 1H), 6.85 – 6.65 (m, 2H), 6.24 (d, J = 16.7 Hz, 1H), 6.08 (d, J = 22.4 Hz, 2H), 5.75 (d, J = 10.6 Hz, 1H), 5.52 (d, J = 88.0 Hz, 1H), 4.95 (s, 2H), 4.87 – 4.79 (m, 1H), 4.68 (d, J = 15.5 Hz, 1H), 4.52 (d, J = 15.4 Hz, 1H), 4.21 (d, J = 45.2 Hz, 2H), 3.82 – 3.65 (m, 1H), 3.55 – 3.44 (m, 1H), 3.28 – 3.23 (m, 1H), 3.18 (s, 3H), 3.15 (s, 3H), 3.00 (d, J = 1.6 Hz, 6H), 1.33 (s, 3H), 1.13 (d, J = 5.6 Hz, 3H).
686		LCMS m/z [M+1]: 778.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.04 (d, J = 1.5 Hz, 1H), 8.23 (s, 1H), 7.71 (d, J = 5.6 Hz, 1H), 7.61 (d, J = 5.6 Hz, 1H), 7.15 (d, J = 1.8 Hz, 1H), 6.93 (d, J = 10.7 Hz, 1H), 6.85 – 6.62 (m, 2H), 6.24 (d, J = 16.7 Hz, 1H), 6.15 (s, 1H), 6.05 (d, J = 1.3 Hz, 1H), 5.75 (d, J = 10.8 Hz, 1H), 5.51 (d, J = 96.3 Hz, 1H), 4.95 (s, 2H), 4.65 (s, 2H), 4.38 (s, 2H), 4.18 (d, J = 61.5 Hz, 2H), 3.75 (s, 3H), 3.39 (t, J = 6.2 Hz, 2H), 3.18 (s, 3H), 2.96 (s, 6H), 1.33 (s, 3H), 1.13 (d, J = 5.6 Hz, 3H).
687		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.28 (s, 1H), 8.17 – 8.11 (m, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 2.7 Hz, 1H), 6.89 – 6.80 (m, 2H), 6.78 – 6.71 (m, 1H), 6.32 - 6.18 (m, 2H), 5.80 (d, J = 10.0 Hz, 1H), 5.51 - 5.41 (m, 1H), 4.21 (s, 3H), 4.10 (t, J = 13.0 Hz, 2H), 3.83 – 3.70 (m, 3H), 3.51 - 3.42 (s, 1H), 3.15 - 3.08 (s, 1H), 1.51 (d, J = 6.5 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H).

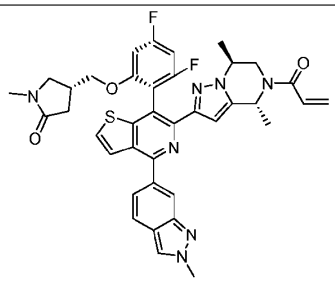
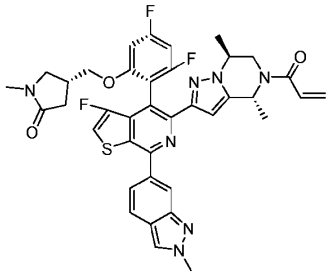
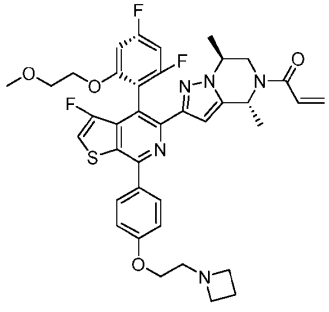
688		LCMS m/z [M+1]: 741.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (dd, J = 8.0, 1.4 Hz, 1H), 8.06 (s, 1H), 7.58 (dd, J = 5.0, 2.8 Hz, 2H), 7.43 (dd, J = 15.2, 8.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.87 (dd, J = 16.4, 10.6 Hz, 1H), 6.76 (t, J = 8.6 Hz, 1H), 6.34 (d, J = 16.6 Hz, 1H), 6.05 (s, 1H), 5.86 (dd, J = 10.6, 1.8 Hz, 1H), 5.75 – 5.45 (m, 1H), 4.98 – 4.93 (m, 1H), 4.81 (d, J = 15.4 Hz, 1H), 4.65 (d, J = 15.4 Hz, 1H), 4.47 (s, 1H), 4.36 – 3.99 (m, 1H), 3.97 – 3.77 (m, 4H), 3.62 (dd, J = 17.6, 5.2 Hz, 1H), 3.50 – 3.34 (m, 1H), 3.26 (s, 3H), 3.12 (s, 6H), 1.43 (d, J = 21.2 Hz, 3H), 1.29 (s, 3H), 0.96 (d, J = 6.0 Hz, 3H).
689		LCMS m/z [M+1]: 742.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.38 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 1.8 Hz, 1H), 8.04 (d, J = 5.4 Hz, 1H), 7.18 (d, J = 5.4 Hz, 1H), 6.89 (t, J = 11.4 Hz, 2H), 6.70 (td, J = 9.2, 2.2 Hz, 1H), 6.35 (d, J = 16.6 Hz, 1H), 6.14 (d, J = 8.8 Hz, 1H), 5.87 (dd, J = 10.6, 1.8 Hz, 1H), 5.79 – 5.44 (m, 1H), 5.00 – 4.93 (m, 1H), 4.76 – 4.24 (m, 2H), 4.18 – 4.09 (m, 3H), 4.08 – 3.81 (m, 3H), 3.79 – 3.72 (m, 1H), 3.58 – 3.34 (m, 4H), 3.08 (s, 3H), 2.87 (s, 3H), 1.88 (d, J = 6.8 Hz, 3H), 1.47 (d, J = 21.4 Hz, 3H), 1.35 (s, 3H).
690		LCMS m/z [M+1]: 673.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.19 (s, 1H), 8.56 (d, J = 1.2 Hz, 1H), 8.39 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 6.87 – 6.64 (m, 3H), 6.27 - 6.16 (m, 2H), 5.81 (d, J = 10.5 Hz, 1H), 5.52 - 5.41 (m, 1H), 4.21 - 4.13 (m, 4H), 3.81 – 3.72 (m, 3H), 3.48 (s, 1H), 3.12 (s, 1H), 1.50 (d, J = 6.5 Hz, 3H), 1.19 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 6.2 Hz, 3H).

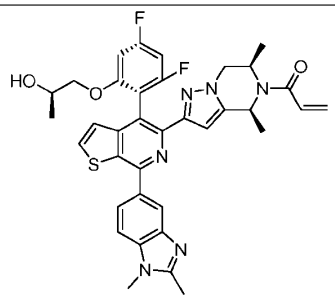
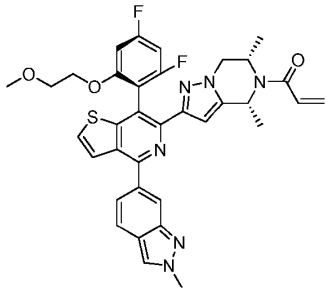
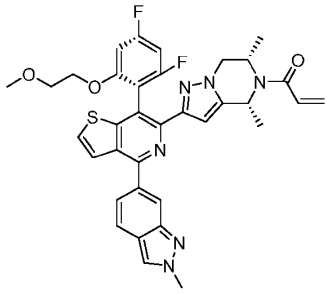
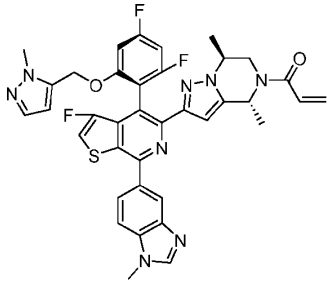
691		LCMS m/z [M+1]: 687.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 – 8.47 (m, 1H), 8.43 – 8.38 (m, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.87 – 6.74 (m, 2H), 6.67 (t, J = 9.1 Hz, 1H), 6.32 - 6.22 (m, 1H), 6.14 (s, 1H), 5.81 (d, J = 10.0 Hz, 1H), 5.49 - 5.42 (m, 1H), 4.21 - 4.11 (m, 2H), 4.09 (s, 3H), 3.80 - 3.70 (m, 3H), 3.48 (s, 1H), 3.13 (d, J = 1.6 Hz, 1H), 2.93 (s, 3H), 1.49 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.2 Hz, 3H).
692		LCMS m/z [M+1]: 689.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.42 (dd, J = 8.7, 1.3 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 2.3 Hz, 1H), 6.91 - 6.77 (m, 2H), 6.69 - 6.58 (m, 1H), 6.36 - 6.22 (m, 1H), 6.05 (s, 1H), 5.82 (dd, J = 10.6, 1.5 Hz, 1H), 5.76 - 5.38 (m, 1H), 5.19 (s, 2H), 4.50 - 4.35 (m, 1H), 4.28 - 4.18 (m, 1H), 4.16 - 3.98 (m, 6H), 3.84 - 3.68 (m, 1H), 3.45 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 1.55 - 1.32 (m, 3H).
693		LCMS m/z [M+1]: 742.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.14 (d, J = 1.8 Hz, 1H), 8.43 (s, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 5.6 Hz, 1H), 6.89 (d, J = 10.8 Hz, 2H), 6.71 – 6.65 (m, 1H), 6.31 (d, J = 16.8 Hz, 1H), 6.17 (s, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.60 (d, J = 85.6 Hz, 1H), 4.91 (s, 1H), 4.43 (s, 2H), 4.15 – 3.75 (m, 6H), 3.70 (s, 1H), 3.44 – 3.37 (m, 4H), 3.04 (s, 3H), 2.83 (s, 3H), 1.81 (d, J = 6.9 Hz, 3H), 1.42 (d, J = 19.1 Hz, 3H), 1.29 (s, 3H).

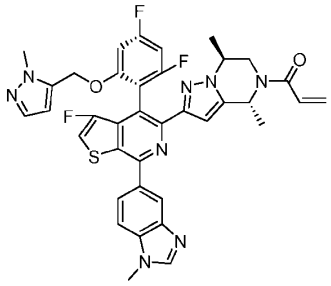
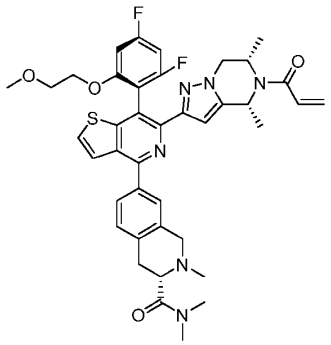
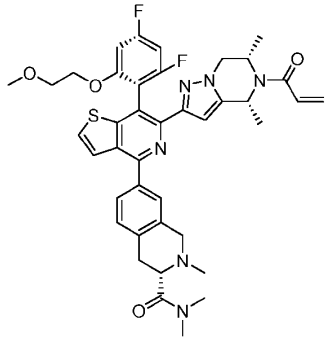
694		LCMS m/z [M+1]: 756.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.90 (d, J = 1.7 Hz, 1H), 8.21 (s, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 10.9 Hz, 2H), 6.67 (t, J = 9.1 Hz, 1H), 6.39 – 6.16 (m, 2H), 5.83 (d, J = 10.4 Hz, 1H), 5.60 (d, J = 93.9 Hz, 1H), 4.40 (s, 1H), 4.26 – 3.81 (m, 4H), 3.59 (s, 2H), 3.42 (t, J = 4.6 Hz, 2H), 3.13 (s, 4H), 3.04 (s, 5H), 2.97 (s, 3H), 2.94 (s, 2H), 1.47 (t, J = 19.0 Hz, 6H), 1.27 (s, 3H).
695		LCMS m/z [M+1]: 727.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 7.9 Hz, 1H), 8.03 (s, 1H), 7.57 – 7.50 (m, 2H), 7.41 (dd, J = 15.1, 8.3 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.76 (dd, J = 19.3, 10.6 Hz, 2H), 6.26 (d, J = 15.6 Hz, 1H), 5.87 (s, 1H), 5.79 (dd, J = 10.6, 1.7 Hz, 1H), 5.60 (s, 1H), 4.90 (d, J = 5.3 Hz, 1H), 4.76 (d, J = 15.5 Hz, 1H), 4.60 (d, J = 15.5 Hz, 1H), 4.38 (s, 1H), 4.22 (dd, J = 12.6, 2.9 Hz, 1H), 4.07 (s, 1H), 3.77 (m, J = 10.9, 4.1 Hz, 4H), 3.57 (dd, J = 17.7, 5.2 Hz, 1H), 3.33 (s, 1H), 3.22 (s, 3H), 3.07 (s, 6H), 1.34 (s, 3H), 0.90 (d, J = 5.9 Hz, 3H).
696		LCMS m/z [M+1]: 746.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (d, J = 1.9 Hz, 1H), 8.55 (d, J = 1.9 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 6.82 (d, J = 10.9 Hz, 2H), 6.66 – 6.60 (m, 1H), 6.28 (d, J = 14.1 Hz, 1H), 6.00 (s, 1H), 5.81 (dd, J = 10.6, 1.6 Hz, 1H), 5.56 (d, J = 87.0 Hz, 1H), 4.91 (d, J = 6.7 Hz, 1H), 4.27 – 4.21 (m, 1H), 4.16 – 3.82 (m, 7H), 3.71 (d, J = 13.2 Hz, 1H), 3.51 – 3.32 (m, 5H), 3.07 (s, 3H), 2.83 (s, 3H), 1.84 (d, J = 6.9 Hz, 3H), 1.41 (s, 3H).

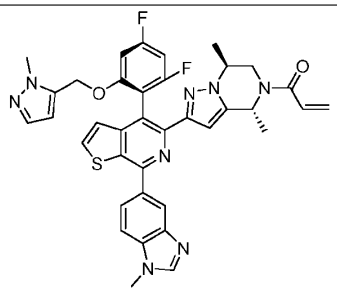
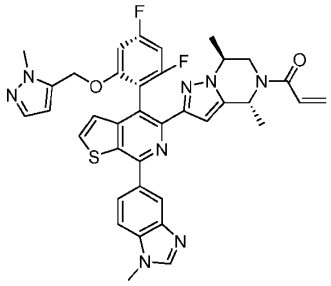
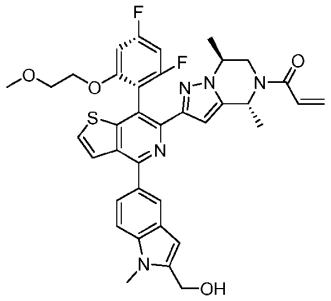
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698		LCMS m/z [M+1]: 659.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.31 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.84 (dd, J = 8.7, 1.3 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 16.7, 10.6 Hz, 1H), 6.76 (d, J = 10.9 Hz, 1H), 6.61 (td, J = 9.3, 2.2 Hz, 1H), 6.28 (d, J = 14.7 Hz, 1H), 6.16 (s, 1H), 5.81 (d, J = 10.7 Hz, 1H), 5.73 - 5.45 (m, 1H), 4.39 (s, 1H), 4.29 (s, 3H), 4.20 (dd, J = 12.6, 2.9 Hz, 1H), 4.05 (s, 1H), 3.89 – 3.71 (m, 4H), 1.50 - 1.36 (m, 3H), 0.94 (d, J = 6.0 Hz, 3H).
699		LCMS m/z [M+1]: 659.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.47 (s, 1H), 8.60 (d, J = 8.5 Hz, 1H), 8.47 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 6.91 – 6.76 (m, 2H), 6.67 – 6.62 (m, 1H), 6.29 (d, J = 16.3 Hz, 1H), 6.11 (s, 1H), 5.86 – 5.78 (m, 1H), 5.73 - 5.40 (m, 1H), 4.41 (s, 1H), 4.28 – 4.16 (m, 4H), 4.14 – 3.99 (m, 1H), 3.91 – 3.70 (m, 4H), 1.52 - 1.36 (m, 3H), 0.94 (d, J = 6.1 Hz, 3H).

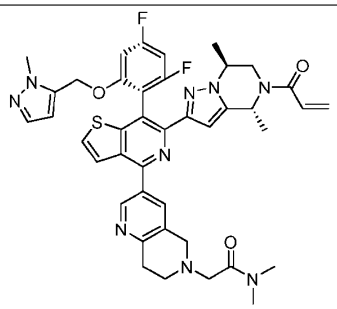
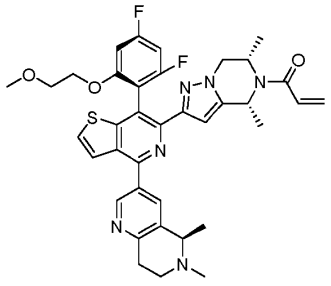
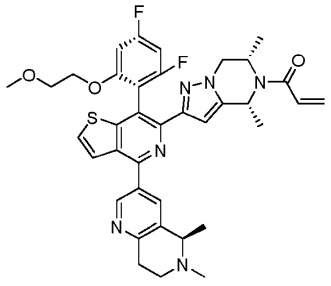
700		LCMS m/z [M+1]: 685.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.47 (dd, J = 8.6, 1.2 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 5.5 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 6.92 - 6.81 (m, 2H), 6.72 - 6.64 (m, 1H), 6.35 (d, J = 16.4 Hz, 1H), 6.15 (s, 1H), 5.85 (dd, J = 10.5, 1.4 Hz, 1H), 5.77 - 5.46 (m, 1H), 5.20 (s, 2H), 4.51 - 4.40 (m, 1H), 4.17 - 4.09 (m, 1H), 4.06 (s, 3H), 4.04 - 3.97 (m, 1H), 3.44 (t, J = 4.6 Hz, 2H), 3.06 (s, 3H), 1.52 - 1.38 (m, 3H), 1.36 - 1.27 (m, 3H).
701		LCMS m/z [M+1]: 777.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.81 (dd, J = 9.0, 4.6 Hz, 1H), 7.70 (dd, J = 5.1, 3.4 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 1.9 Hz, 1H), 7.13 (d, J = 10.8 Hz, 1H), 6.88 (s, 1H), 6.81 – 6.72 (m, 1H), 6.35 (d, J = 16.4 Hz, 1H), 6.28 (d, J = 1.9 Hz, 1H), 6.20 (s, 1H), 5.87 (d, J = 10.7 Hz, 1H), 5.62 (d, J = 94.2 Hz, 1H), 5.28 – 5.10 (m, 2H), 4.98 – 4.91 (m, 1H), 4.81 (d, J = 15.5 Hz, 1H), 4.64 (d, J = 15.6 Hz, 1H), 4.43 – 4.14 (m, 2H), 3.99 – 3.74 (m, 1H), 3.68 – 3.57 (m, 1H), 3.44 – 3.34 (m, 4H), 3.27 (s, 3H), 3.12 (s, 6H), 1.46 (s, 3H), 1.25 (s, 3H).
702		LCMS m/z [M+1]: 671.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.46 (dd, J = 8.7, 1.3 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 8.04 (d, J = 5.5 Hz, 1H), 7.16 (d, J = 5.5 Hz, 1H), 6.93 – 6.79 (m, 2H), 6.71 (td, J = 9.2, 2.0 Hz, 1H), 6.29 (d, J = 15.9 Hz, 1H), 6.09 (s, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.71 – 5.42 (m, 1H), 5.20 (s, 2H), 4.24 (dd, J = 12.7, 2.7 Hz, 1H), 4.16 – 3.97 (m, 6H), 3.43 (t, J = 4.6 Hz, 2H), 3.06 (s, 3H), 1.52 -1.35 (m, 3H).

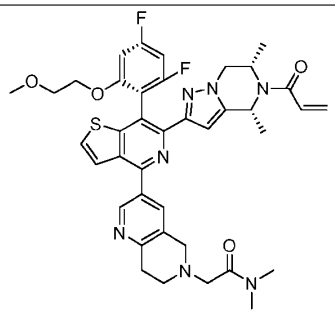
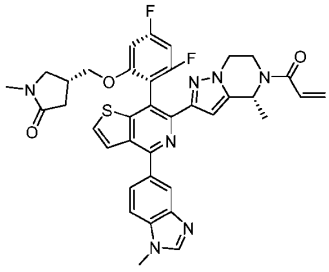
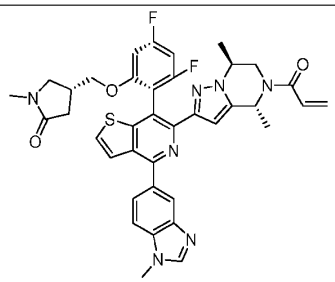
703		LCMS m/z [M+1]: 708.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 8.36 (s, 1H), 8.10 - 8.00 (m, 2H), 7.82 (d, J = 5.6 Hz, 1H), 7.73 (dd, J = 1.2 Hz, 8.4 Hz, 1H), 6.97 (d, J = 10.4 Hz, 1H), 6.90 - 6.80 (m, 2H), 6.36 - 6.31 (m, 1H), 6.16 (s, 1H), 5.90 - 5.50 (m, 2H), 4.60 - 4.50 (m, 1H), 4.33 (s, 3H), 4.30 - 4.20 (m, 0.5H), 4.12 - 4.00 (m, 2H), 3.96 (s, 3H), 3.95 - 3.85 (m, 0.5H), 3.65 (s, 1H), 3.35 (t, J = 9.2 Hz, 1H), 2.96 (dd, J = 3.6 Hz, 10.4 Hz, 1H), 2.65 - 2.55 (m, 1H), 2.47 (s, 3H), 2.40 - 2.28 (m, 1H), 1.80 - 1.75 (m, 1H), 1.55 - 1.25 (m, 6H).
704		LCMS m/z [M+1]: 726.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1H), 8.36 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 8.4, 0.8 Hz, 1H), 7.75 (s, 1H), 6.92 - 6.78 (m, 2H), 6.68 - 6.58 (m, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.21 (s, 1H), 5.87 - 5.80 (m, 1H), 5.78 - 5.51 (m, 1H), 4.49 - 4.40 (m, 1H), 4.31 (s, 3H), 4.04 - 3.95 (m, 2H), 3.00 - 2.93 (m, 1H), 2.65 – 2.55 (m, 1H), 2.47 (s, 3H), 2.39 - 2.28 (m, 1H), 1.92 (dd, J = 17.2, 5.2 Hz, 1H), 1.52 - 1.38 (m, 3H), 1.32 - 1.23 (m, 3H).
705		LCMS m/z [M+1]: 718.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 – 8.10 (m, 2H), 7.52 (d, J = 2.6 Hz, 1H), 7.26 – 7.20 (m, 2H), 6.90 - 6.73 (m, 2H), 6.63 – 6.54 (m, 1H), 6.32 (d, J = 16.0 Hz, 1H), 6.12 (s, 1H), 5.89 – 5.81 (m, 1H), 5.75 - 5.52 (m, 1H), 4.45 – 4.22 (m, 7H), 4.11 – 3.97 (m, 2H), 3.91 - 3.76 (m, 1H), 3.73 – 3.67 (m, 2H), 3.46 (t, J = 4.6 Hz, 3H), 3.07 (s, 3H), 2.72 - 2.59 (m, 1H), 2.52 - 2.40 (s, 1H), 1.48 - 1.36 (m, 3H), 1.31 - 1.23 (m, 3H).

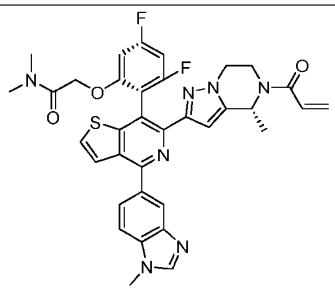
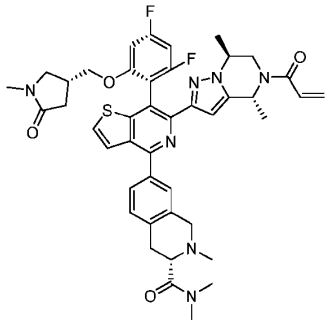
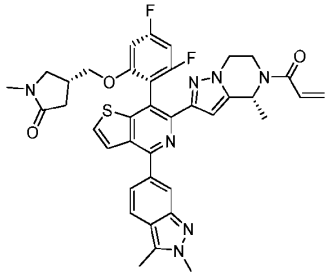
706		LCMS m/z [M+1]: 669.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.44 (d, J = 8.8 Hz, 1H), 8.07 – 8.01 (m, 2H), 7.17 (d, J = 5.2 Hz, 1H), 6.84 (dd, J =16.4, 10.8 Hz, 2H), 6.75 – 6.70 (m, 1H), 6.23 (s, 1H), 6.18 (s, 1H), 5.81 (d, J = 10.4 Hz, 1H), 5.47 (s, 1H), 4.16 (s, 2H), 4.08 (s, 3H), 3.76 (dd, J =11.2, 6.4 Hz, 3H), 2.92 (s, 3H), 1.51 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 5.2 Hz, 3H).
707		LCMS m/z [M+1]: 655 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.30 (s, 1H), 8.07 (dd, J = 10.8, 7.0 Hz, 2H), 7.86 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 11.0 Hz, 1H), 6.93 – 6.82 (m, 2H), 6.31 (s, 1H), 6.19 (s, 1H), 5.84 (d, J = 10.4 Hz, 1H), 5.51 (s, 1H), 4.98 (s, 1H), 4.35 (s, 3H), 4.28 (s, 2H), 4.21 – 4.12 (m, 1H), 4.09 – 4.00 (m, 1H), 3.48 (t, J = 4.4 Hz, 2H), 3.13 (s, 3H), 1.53 (d, J = 6.0 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H).
708		LCMS m/z [M+1]: 655.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 8.05 (s, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.67 – 7.58 (m, 3H), 6.79 – 6.69 (m, 2H), 6.60 (td, J = 9.2, 2.2 Hz, 1H), 6.24 (s, 1H), 6.15 (s, 1H), 5.70 (d, J = 10.6 Hz, 1H), 5.38 (s, 1H), 4.18 (s, 3H), 4.14 – 3.80 (m, 5H), 3.35 (t, J = 4.6 Hz, 2H), 2.96 (s, 3H), 1.42 (d, J = 4.0 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H).
709		LCMS m/z [M+1]: 709.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.52 (s, 1H), 8.62 (d, J = 0.8 Hz, 1H), 8.48 (dd, J = 8.6, 1.4 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 1.8 Hz, 1H), 6.98 (d, J = 10.8 Hz, 1H), 6.89 (s, 1H), 6.77 (td, J = 9.2, 2.2 Hz, 1H), 6.36 (d, J = 16.4 Hz, 1H), 6.18 (d, J = 5.2 Hz, 2H), 5.87 (d, J = 11.0 Hz, 1H), 5.76 –

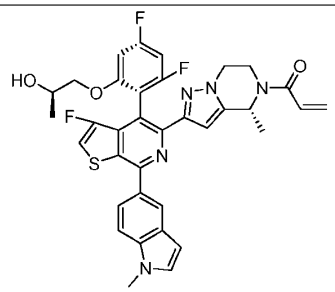
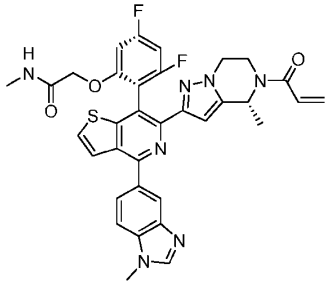
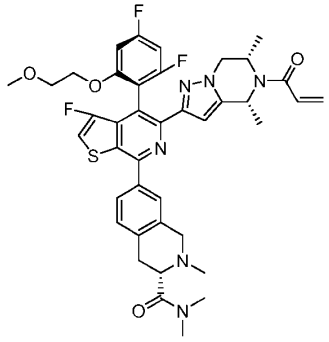
		5.40 (m, 1H), 5.12 – 5.04 (m, 2H), 4.90 – 4.64 (m, 1H), 4.40 (s, 1H), 4.26 (s, 3H), 4.20 – 3.49 (m, 1H), 3.40 (s, 3H), 1.45 (s, 3H), 1.27 (d, J = 5.4 Hz, 3H).
710		LCMS m/z [M+1]: 709.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.46 (s, 1H), 8.62 (s, 1H), 8.48 (d, J = 8.6 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 10.8 Hz, 1H), 6.89 (s, 1H), 6.68 (td, J = 9.2, 2.2 Hz, 1H), 6.35 (d, J = 15.8 Hz, 1H), 6.29 (d, J = 1.8 Hz, 1H), 6.17 (s, 1H), 5.87 (d, J = 10.2 Hz, 1H), 5.74 (s, 1H), 5.19 (q, J = 12.8 Hz, 2H), 4.96 (s, 1H), 4.76 (s, 1H), 4.31 (s, 1H), 4.25 (s, 3H), 3.90 (s, 1H), 3.42 (s, 2H), 1.48 (d, J = 24.6 Hz, 3H), 1.25 (s, 3H).
711		LCMS m/z [M+1]: 741.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 5.2 Hz, 2H), 7.73 – 7.67 (m, 1H), 7.57 (d, J = 6.0 Hz, 1H), 6.93 – 6.71 (m, 3H), 6.19 (s, 2H), 5.81 (d, J = 10.8 Hz, 1H), 5.46 (s, 1H), 4.95 – 4.88 (m, 2H), 4.78 (d, J = 15.5 Hz, 1H), 4.63 (d, J = 15.3 Hz, 1H), 4.11 (dd, J = 22.6, 17.9 Hz, 3H), 4.02 – 3.94 (m, 1H), 3.59 (d, J = 5.3 Hz, 1H), 3.43 (t, J = 4.6 Hz, 2H), 3.35 (d, J = 11.0 Hz, 1H), 3.24 (s, 3H), 3.14 – 3.00 (m, 9H), 1.51 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).
712		LCMS m/z [M+1]: 741.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 7.9 Hz, 1H), 7.93 (s, 2H), 7.73 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 6.95 – 6.82 (m, 2H), 6.75 (d, J = 6.9 Hz, 1H), 6.25 (s, 2H), 5.83 (d, J = 10.2 Hz, 1H), 5.49 (s, 1H), 4.95 (dd, J = 10.0, 5.2 Hz, 2H), 4.81 (d, J = 15.4 Hz, 1H), 4.65 (d, J = 15.3 Hz, 1H), 4.26 – 4.10 (m, 3H), 4.06 (dd, J = 9.8, 5.5 Hz, 1H), 3.63 (dd, J = 17.7, 5.2 Hz, 1H), 3.47 (t, J = 4.6 Hz, 2H), 3.38 (d, J = 10.4 Hz, 1H), 3.27 (s, 3H), 3.14 – 3.06 (m, 9H), 1.53 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).

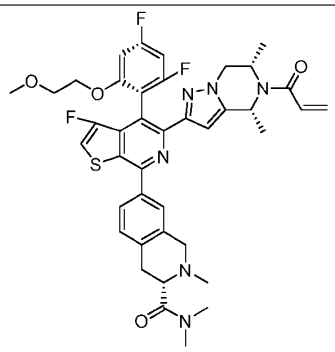
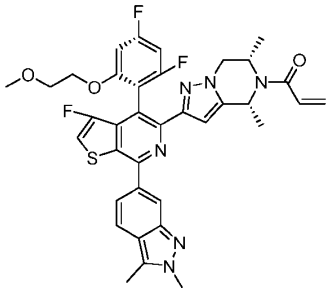
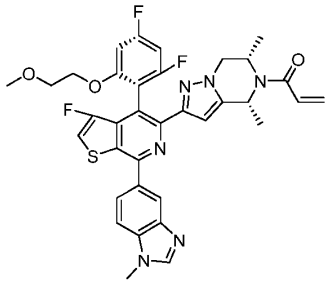
713		LCMS m/z [M+1]: 691.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (d, J = 3.7 Hz, 1H), 8.63 (d, J = 0.9 Hz, 1H), 8.50 (m, J = 8.7, 1.4 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 8.03 – 7.98 (m, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.06 (dd, J = 23.9, 8.0 Hz, 2H), 6.92 – 6.77 (m, 2H), 6.34 (d, J = 16.5 Hz, 1H), 6.16 (d, J = 4.6 Hz, 2H), 5.85 (d, J = 10.6 Hz, 1H), 5.61 (d, J = 96.8 Hz, 1H), 5.08 – 5.01 (m, 2H), 4.88 (s, 1H), 4.39 (s, 1H), 4.23 (s, 3H), 3.67 (d, J = 154.3 Hz, 1H), 3.31 (d, J = 1.6 Hz, 3H), 1.43 (s, 3H), 1.25 (d, J = 5.6 Hz, 3H).
714		LCMS m/z [M+1]: 691.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.46 (d, J = 3.6 Hz, 1H), 8.64 (d, J = 0.9 Hz, 1H), 8.51 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 8.01 (dd, J = 5.5, 2.4 Hz, 1H), 7.29 (d, J = 1.9 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.87 (s, 1H), 6.72 (m, J = 9.2, 2.2 Hz, 1H), 6.29 (dd, J = 33.4, 9.2 Hz, 2H), 6.15 (s, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.72 (s, 1H), 5.23 – 5.11 (m, 2H), 4.89 (s, 1H), 4.31 (s, 1H), 4.23 (s, 3H), 3.89 – 3.43 (m, 1H), 3.33 (s, 3H), 1.44 (s, 3H), 1.24 (s, 3H).
715		LCMS m/z [M+1]: 684.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 5.6 Hz, 1H), 7.84 - 7.75 (m, 2H), 7.03 (d, J = 10.4 Hz, 1H), 6.91 - 6.81 (m, 2H), 6.72 (s, 1H), 6.35 (d, J = 16.4 Hz, 1H), 6.07 - 6.00 (m, 1H), 5.86 (dd, J = 10.6, 1.6 Hz, 1H), 5.79 - 5.45 (m, 1H), 4.94 - 4.84 (m, 3H), 4.68 - 4.58 (m, 1H), 4.20 - 4.05 (m, 2H), 3.94 (s, 3H), 3.45 (t, J = 4.4 Hz, 2H), 3.09 (s, 3H), 1.50 - 1.33 (m, 6H).

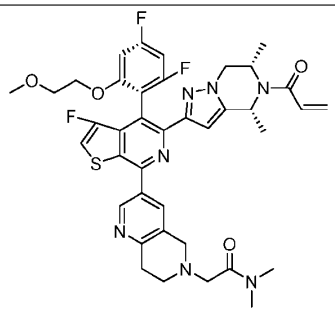
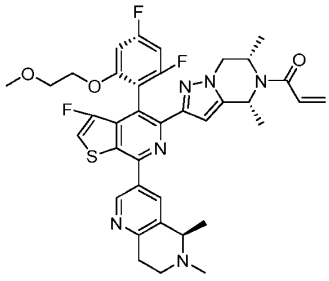
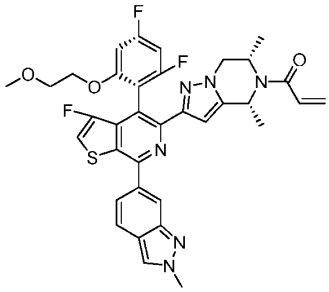
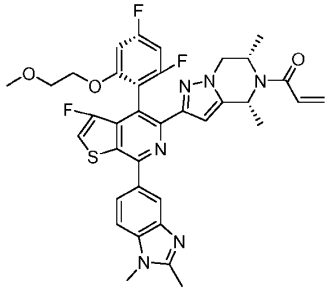
716		LCMS m/z [M+1]: 778.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (d, J = 1.8 Hz, 1H), 8.36 (s, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 7.31 (d, J = 1.9 Hz, 1H), 7.12 (d, J = 10.8 Hz, 1H), 6.88 (s, 1H), 6.80 – 6.72 (m, 1H), 6.35 (d, J = 16.8 Hz, 1H), 6.29 – 6.22 (m, 2H), 5.86 (d, J = 11.2 Hz, 1H), 5.62 (d, J = 91.0 Hz, 1H), 5.25 – 5.10 (m, 2H), 4.78 (s, 2H), 4.50 (s, 2H), 4.36 – 4.07 (m, 2H), 3.88 (s, 3H), 3.51 (t, J = 6.1 Hz, 2H), 3.31 (d, J = 6.1 Hz, 3H), 3.08 (s, 6H), 1.47 (s, 3H), 1.23 (s, 3H).
717		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (d, J = 1.8 Hz, 1H), 8.46 (s, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.96 – 6.81 (m, 2H), 6.80 – 6.72 (m, 1H), 6.39 – 6.16 (m, 2H), 5.83 (d, J = 10.8 Hz, 1H), 5.48 (s, 1H), 4.90 – 4.79 (m, 1H), 4.35 – 3.83 (m, 6H), 3.76 (s, 1H), 3.51 – 3.38 (m, 4H), 3.13 (s, 3H), 3.09 (s, 3H), 1.86 (d, J = 6.4 Hz, 3H), 1.53 (d, J = 6.5 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H).
718		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (d, J = 1.8 Hz, 1H), 8.45 (s, 1H), 7.88 (dd, J = 5.6, 1.1 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.95 – 6.80 (m, 2H), 6.74 (td, J = 9.2, 2.2 Hz, 1H), 6.45 – 6.17 (m, 2H), 5.83 (d, J = 10.1 Hz, 1H), 5.49 (s, 1H), 4.88 – 4.72 (m, 1H), 4.36 – 3.84 (m, 6H), 3.76 (s, 1H), 3.46 (t, J = 4.5 Hz, 4H), 3.13 (s, 3H), 3.08 (s, 3H), 1.86 (d, J = 6.6 Hz, 3H), 1.53 (d, J = 6.0 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).

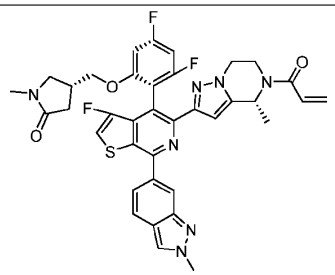
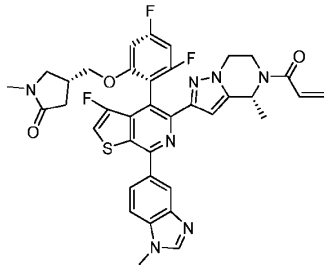
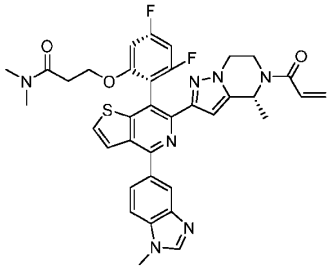
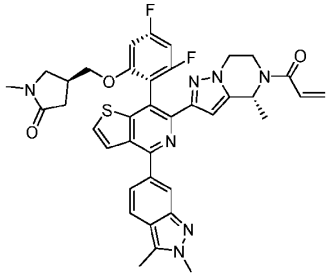
719		LCMS m/z [M+1]: 742.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (s, 1H), 8.37 (s, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 5.6 Hz, 1H), 6.96 – 6.81 (m, 2H), 6.79 – 6.66 (m, 1H), 6.45 – 6.16 (m, 2H), 5.83 (d, J = 10.1 Hz, 1H), 5.50 (s, 1H), 4.78 (s, 2H), 4.51 (s, 2H), 4.34 – 3.95 (m, 5H), 3.88 (s, 2H), 3.51 (t, J = 6.0 Hz, 2H), 3.45 (t, J = 4.5 Hz, 2H), 3.07 (s, 9H), 1.53 (d, J = 5.5 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H).
720		LCMS m/z [M+1]: 694.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (s, 1H), 8.48 (s, 1H), 8.32 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 6.97 – 6.69 (m, 3H), 6.29 (d, J = 14.9 Hz, 1H), 6.17 (s, 1H), 5.82 (d, J = 10.5 Hz, 1H), 5.75 - 5.45 (m, 1H), 4.40 (s, 1H), 4.22 (s, 4H), 4.16 – 3.92 (m, 3H), 3.79 (s, 1H), 3.26 (d, J = 9.4 Hz, 1H), 2.92 (dd, J = 10.0, 4.2 Hz, 1H), 2.63 – 2.52 (m, 1H), 2.42 (s, 3H), 2.27 (dd, J = 17.1, 9.8 Hz, 1H), 1.80 (dd, J = 17.2, 4.9 Hz, 1H), 1.52 - 1.32 (m, 3H).
721		LCMS m/z [M+1]: 708.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.46 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 5.2 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 6.92 - 6.80 (m, 2H), 6.71 (t, J = 5.6 Hz, 1H), 6.35 - 6.27 (m, 2H), 5.84 (dd, J = 1.6 Hz, 10.8 Hz, 1H), 5.75 - 5.50 (m, 1H), 4.80 - 4.60 (m, 0.5H), 4.50 - 4.40 (m, 1H), 4.22 (s, 3H), 4.05 - 3.95 (m, 2H), 3.95 - 3.80 (m, 0.5H), 3.25 - 3.20 (m, 1H), 2.95 - 2.90 (m, 1H), 2.65 - 2.55 (m, 1H), 2.41 (s, 3H), 2.30 - 2.20 (m, 1H), 1.90 - 1.80 (m, 1H), 1.55 - 1.20 (m, 6H).

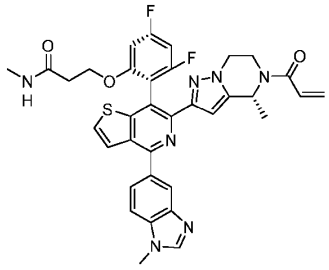
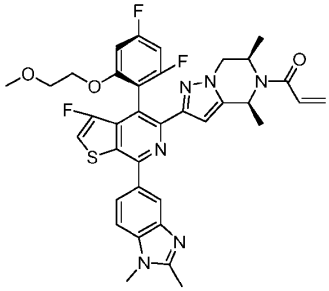
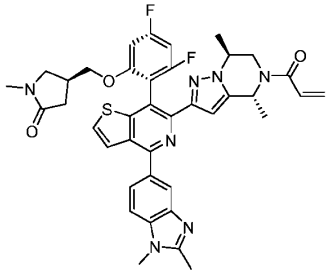
722		LCMS m/z [M+1]: 668.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (s, 1H), 8.43 (s, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.91 – 6.69 (m, 3H), 6.40 - 6.21 (m, 2H), 5.82 (d, J = 10.4 Hz, 1H), 5.75 - 5.45 (m, 1H), 4.82 – 4.73 (m, 2H), 4.42 (s, 1H), 4.31 – 4.16 (m, 4H), 4.10 (s, 1H), 3.77 (s, 1H), 2.86 (d, J = 8.8 Hz, 6H), 1.52 - 1.32 (m, 3H)
723		LCMS m/z [M+1]: 794.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, J = 8.3 Hz, 1H), 7.90 (s, 1H), 7.73 (d, J = 5.6 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 6.93 - 6.79 (m, 2H), 6.73 - 6.62 (m, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.26 (s, 1H), 5.87 - 5.80 (m, 1H), 5.79 - 5.41 (m, 1H), 4.96 - 4.87 (m, 1H), 4.80 - 4.74 (m, 1H), 4.66 - 4.57 (m, 1H), 4.44 - 4.33 (m, 1H), 4.29 - 4.12 (m, 1H), 4.04 - 3.93 (m, 2H), 3.92 - 3.74 (m, 1H), 3.65 - 3.55 (m, 1H), 3.50 - 3.32 (m, 1H), 3.27 - 3.19 (m, 4H), 3.10 (s, 6H), 2.96 - 2.89 (m, 1H), 2.63 - 2.51 (m, 1H), 2.40 (s, 3H), 2.31 - 2.20 (m, 1H), 1.93 - 1.82 (m, 1H), 1.55 - 1.37 (m, 3H), 1.33 - 1.18 (m, 3H).
724		LCMS m/z [M+1]: 708.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.12 (d, J = 5.6 Hz, 1H), 8.04 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 10.4 Hz, 1H), 6.92 – 6.77 (m, 2H), 6.36 – 6.21 (m, 1H), 6.03 (s, 1H), 5.88 – 5.79 (m, 1H), 5.78 – 5.43 (m, 1H), 4.44 – 4.31 (m, 1H), 4.22 (s, 3H), 4.14 – 3.98 (m, 2H), 3.38 (t, J = 9.4 Hz, 1H), 2.95 (d, J = 10.1 Hz, 1H), 2.78 (s, 3H), 2.67 – 2.53 (m, 1H), 2.46 (s, 3H), 2.37 – 2.24 (m, 1H), 1.71 (dd, J = 17.1, 3.4 Hz, 1H), 1.54 – 1.33 (m, 3H).

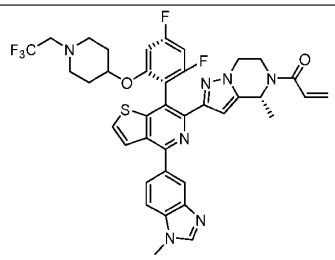
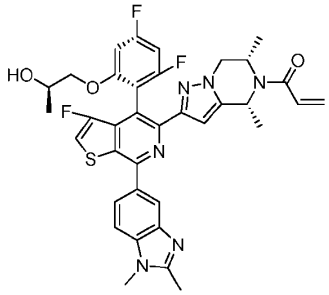
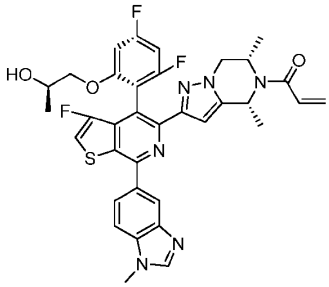
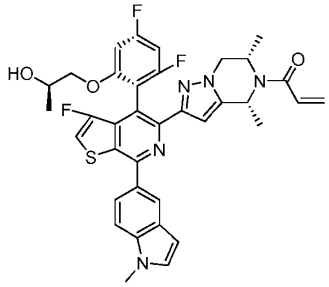
725		LCMS m/z [M+1]: 658.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (d, J = 1.2 Hz, 1H), 8.07 (d, J = 1.9 Hz, 1H), 7.91 (dd, J = 8.6, 1.6 Hz, 1H), 7.74 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 3.0Hz, 1H), 6.91 - 6.78 (m, 2H), 6.76 - 6.68 (m, 2H), 6.31 (d, J = 15.7 Hz, 1H), 5.98 (s, 1H), 5.84 (dd, J = 10.6, 1.5 Hz, 1H), 5.75 - 5.43 (m, 1H), 4.36 (dd, J = 12.9, 2.7 Hz, 1H), 4.24 - 4.05 (m, 1H), 3.94 (s, 3H), 3.89 - 3.72 (m, 4H), 1.50 - 1.36 (m, 3H), 0.99 (d, J = 6.1 Hz, 3H).
726		LCMS m/z [M+1]: 654.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.37 (s, 1H), 8.42 (s, 1H), 8.27 (d,J = 8.8 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.91 - 6.71 (m, 4H), 6.36 (s, 1H), 6.29 (d, J = 15.6 Hz, 1H), 5.82 (d, J = 10.2 Hz, 1H), 5.77 - 5.38 (m, 1H), 4.49（s, 2H), 4.22 (s, 3H), 4.19 - 4.13 (m, 1H), 4.11 - 3.90 (m, 1H), 2.62 (s, 3H), 1.57 - 1.36 (s, 3H).
727		LCMS m/z [M+1]: 759 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (dd, J = 8.0, 1.4 Hz, 1H), 8.07 (s, 1H), 7.60 – 7.57 (m, 2H), 6.91 – 6.78 (m, 2H), 6.67 (td, J = 9.2, 2.2 Hz, 1H), 6.31 (s, 1H), 6.15 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.47 (s, 1H), 4.96 – 4.92 (m, 1H), 4.81 (d, J = 15.4 Hz, 1H), 4.65 (d, J = 15.4 Hz, 1H), 4.23 – 4.07 (m, 3H), 3.99 – 3.94 (m, 1H), 3.62 (dd, J = 17.6, 5.2 Hz, 1H), 3.47 (t, J = 4.6 Hz, 2H), 3.38 – 3.33 (m, 1H), 3.32 – 3.28 (m, 1H), 3.26 (s, 3H), 3.11 (d, J = 4.2 Hz, 9H), 1.53 (d, J = 6.6 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H).

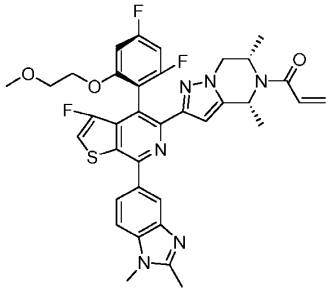
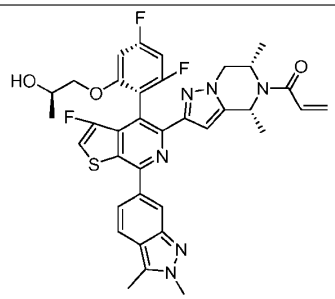
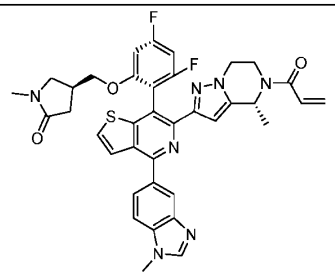
728		LCMS m/z [M+1]: 759 ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 8.0 Hz, 1H), 8.06 (s, 1H), 7.62 – 7.57 (m, 2H), 6.90 – 6.79 (m, 2H), 6.67 – 6.62 (m, 1H), 6.29 (s, 1H), 6.18 (s, 1H), 5.83 (d, J = 10.2 Hz, 1H), 5.48 (s, 1H), 4.98 – 4.91 (m, 1H), 4.81 (d, J = 15.4 Hz, 1H), 4.65 (d, J = 15.4 Hz, 1H), 4.20 – 4.08 (m, 3H), 4.06 – 4.01 (m, 1H), 3.62 (dd, J = 17.6, 5.2 Hz, 1H), 3.49 (t, J = 4.6 Hz, 2H), 3.40 – 3.34 (m, 1H), 3.31 – 3.28 (m, 1H), 3.26 (s, 3H), 3.11 (d, J = 4.6 Hz, 9H), 1.52 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H).
729		LCMS m/z [M+1]: 687.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.80 (dd, J = 8.6, 1.2 Hz, 1H), 7.70 (d, J = 2.2 Hz, 1H), 6.92 – 6.81 (m, 2H), 6.66 (td, J = 9.2, 2.2 Hz, 1H), 6.30 (s, 1H), 6.22 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.49 (s, 1H), 4.89 – 4.86 (m, 1H), 4.21 (s, 3H), 4.19 – 3.99 (m, 4H), 3.50 (t, J = 4.4 Hz, 2H), 3.13 (s, 3H), 2.76 (s, 3H), 1.52 (s, 3H), 1.20 (d, J = 6.8 Hz, 3H).
730		LCMS m/z [M+1]: 673 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (d, J = 1.0 Hz, 1H), 8.13 (s, 1H), 7.99 (dd, J = 8.4, 1.6 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 6.69 (dd, J = 16.6, 10.6 Hz, 1H), 6.62 (d, J = 10.8 Hz, 1H), 6.46 (td, J = 9.2, 2.2 Hz, 1H), 6.23 – 6.08 (m, 2H), 5.66 (d, J = 10.5 Hz, 1H), 5.33 (d, J = 11.0 Hz, 1H), 4.82 – 4.72 (m, 1H), 4.04 – 3.92 (m, 3H), 3.85 (s, 4H), 3.33 (t, J = 4.8 Hz, 2H), 2.95 (s, 3H), 1.36 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H).

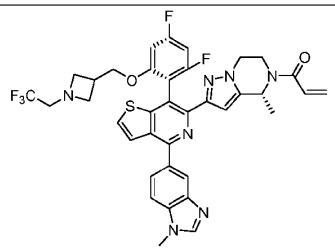
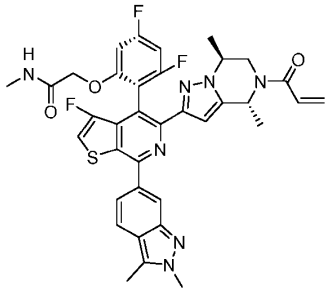
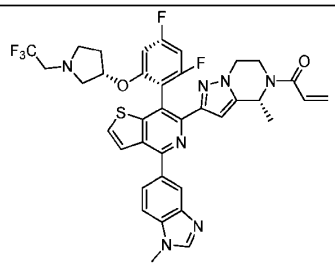
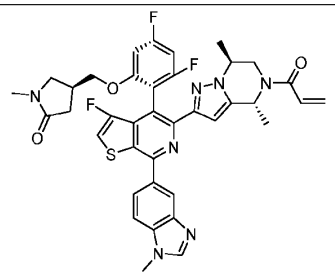
731		LCMS m/z [M+1]: 760.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (d, J = 2.0 Hz, 1H), 8.50 (s, 1H), 7.64 (d, J = 2.3 Hz, 1H), 6.93 – 6.78 (m, 2H), 6.66 (td, J = 9.3, 2.3 Hz, 1H), 6.30 (s, 1H), 6.18 (s, 1H), 5.84 (d, J = 10.3 Hz, 1H), 5.48 (s, 1H), 4.79 (s, 2H), 4.51 (s, 2H), 4.37 – 3.96 (m, 5H), 3.88 (s, 2H), 3.59 – 3.42 (m, 4H), 3.09 (d, J = 14.0 Hz, 9H), 1.52 (d, J = 6.0 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).
732		LCMS m/z [M+1]: 703.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 1.5 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 6.92 – 6.77 (m, 2H), 6.66 (td, J = 9.2, 2.3 Hz, 1H), 6.30 (s, 1H), 6.15 (s, 1H), 5.84 (d, J = 10.5 Hz, 1H), 5.48 (s, 1H), 4.94 (s, 1H), 4.41 – 3.54 (m, 7H), 3.53 – 3.40 (m, 4H), 3.12 (d, J = 8.0 Hz, 6H), 1.87 (d, J = 6.4 Hz, 3H), 1.51 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).
733		LCMS m/z [M+1]: 673.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.34 (s, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.87 (dd, J = 8.7, 1.4 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 6.89 – 6.77 (m, 2H), 6.64 (m, J = 9.2, 2.3 Hz, 1H), 6.26 (s, 2H), 5.83 (d, J = 10.4 Hz, 1H), 5.49 (s, 1H), 4.89 – 4.76 (m, 1H), 4.31 (s, 3H), 4.17 (s, 1H), 4.13 – 4.08 (m, 2H), 4.03 (t, J = 4.5 Hz, 1H), 3.50 (t, J = 4.6 Hz, 2H), 3.12 (s, 3H), 1.53 (d, J = 5.3 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H).
734		LCMS m/z [M+1]: 687.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 1.0 Hz, 1H), 8.43 (dd, J = 8.6, 1.4 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 6.90 – 6.81 (m, 2H), 6.66 (td, J = 9.2, 2.2 Hz, 1H), 6.31 (s, 1H), 6.19 (s, 1H), 5.84 (d, J = 10.6 Hz, 1H), 5.48 (s, 1H), 4.35 – 3.89 (m, 8H), 3.49 (t, J = 4.6 Hz, 2H), 3.12 (s, 3H), 2.96 (s, 3H), 1.52 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H).

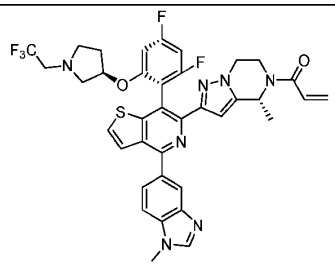
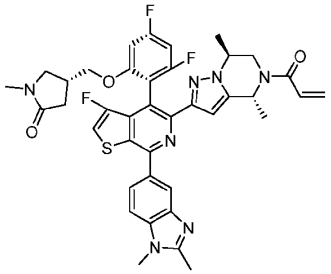
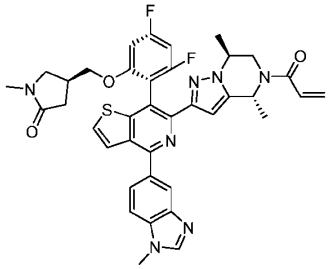
735		LCMS m/z [M+1]: 712.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.37 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.80 (s, 1H), 6.92 - 6.77 (m, 2H), 6.68 (t, J = 8.8 Hz, 1H), 6.37 - 6.22 (m, 1H), 6.08 (s, 1H), 5.82 (d, J = 10.4 Hz, 1H), 5.76 - 5.46 (m, 1H), 4.31 (s, 3H), 4.28 - 4.21 (m, 1H), 4.17 - 4.06 (m, 1H), 3.98 (d, J = 4.4 Hz, 2H), 3.28 (s, 1H), 2.99 - 2.89 (m, 1H), 2.68 - 2.55 (m, 1H), 2.47 (s, 3H), 2.39 - 2.28 (m, 1H), 1.91 - 1.81 (m, 1H), 1.56 - 1.36 (m, 3H).
736		LCMS m/z [M+1]: 712.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.28 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 6.91 – 6.74 (m, 2H), 6.62 (t, J = 9.2 Hz, 1H), 6.36 – 6.08 (m, 2H), 5.82 (d, J = 10.4 Hz, 1H), 5.73 - 5.47 (m, 1H), 4.18 (d, J = 10.4 Hz, 1H), 4.00 (s, 3H), 3.98 – 3.89 (m, 2H), 3.23 (t, J = 9.2 Hz, 2H), 2.99 - 2.85 (m, 1H), 2.65 - 2.54 (m, 1H), 2.48 (s, 3H), 2.37 - 2.24 (m, 1H), 2.01 - 1.86 (m, 1H), 1.54 - 1.33 (m, 3H).
737		LCMS m/z [M+1]: 682.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.37 (s, 1H), 8.44 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 5.6 Hz, 1H), 6.95 – 6.70 (m, 3H), 6.35 – 6.23 (m, 1H), 6.20 – 6.10 (m, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.77 – 5.45 (m, 1H), 4.33 – 4.18 (m, 5H), 4.15 – 3.95 (m, 1H), 2.63 – 2.52 (m, 4H), 2.49 (s, 3H), 1.50 – 1.37 (m, 3H).
738		LCMS m/z [M+1]: 708.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.13 (d, J = 5.2 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 10.8 Hz, 1H), 6.90 - 6.80 (m, 2H), 6.36 - 6.21 (m, 1H), 6.08 (s, 1H), 5.85 - 5.45 (m, 2H), 4.35 - 4.31 (m, 1H), 4.22 (s, 3H), 4.20 - 4.05 (m, 2H), 4.00 - 3.90 (m, 1H), 3.38

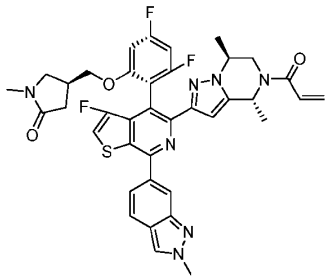
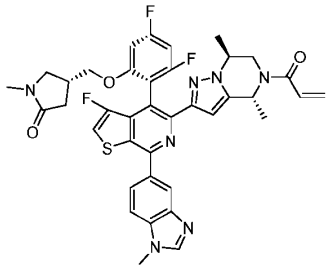
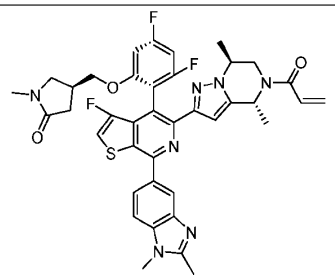
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739		LCMS m/z [M+1]: 668.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (s, 1H), 8.44 (s, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 5.5 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.95 – 6.68 (m, 3H), 6.35 – 6.20 (m, 1H), 6.11 (s, 1H), 5.82 (d, J = 10.7 Hz, 1H), 5.78 – 5.40 (m, 1H), 4.30 – 3.98 (m, 7H), 2.40 – 2.28 (m, 5H), 1.55 – 1.35 (m, 3H).
740		LCMS m/z [M+1]: 687.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.41 – 8.35 (m, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.88 – 6.77 (m, 2H), 6.63 (td, J = 9.1, 2.3 Hz, 1H), 6.32 - 6.12 (m, 2H), 5.81 (d, J = 10.6 Hz, 1H), 5.52 - 5.36 (m, 1H), 4.22 - 4.05 (m, 6H), 4.05 – 3.97 (m, 1H), 3.32 – 3.28 (m, 2H), 3.09 (s, 3H), 2.94 (s, 3H), 1.50 (d, J = 6.6 Hz, 3H), 1.18 (d, J = 7.1 Hz, 3H).
741		LCMS m/z [M+1]: 722.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.27 - 8.23 (m, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 5.5 Hz, 1H), 7.69 (d, J = 5.5 Hz, 1H), 6.93 - 6.80 (m, 2H), 6.75 - 6.67 (m, 1H), 6.36 - 6.26 (m, 2H), 5.86 - 5.81 (m, 1H), 5.79 - 5.48 (m, 1H), 4.45 - 4.33 (m, 1H), 4.10 (s, 3H), 4.07 - 4.01 (m, 1H), 3.98 - 3.92 (m, 1H), 3.28 - 3.19 (m, 1H), 2.94 (s, 3H), 2.90 - 2.84 (m, 1H), 2.64 - 2.52 (m, 1H), 2.30 (s, 3H), 2.28 - 2.18 (m, 1H), 2.04 - 1.92 (m, 1H), 1.56 - 1.37 (m, 3H), 1.32 - 1.20 (m, 3H).

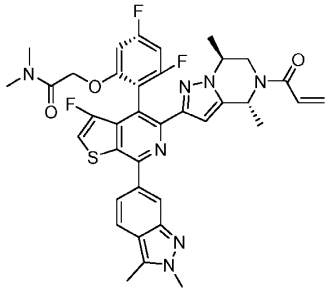
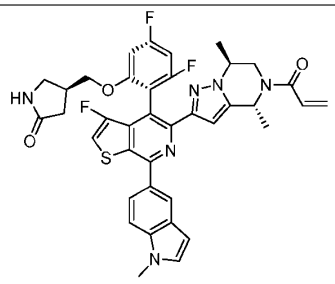
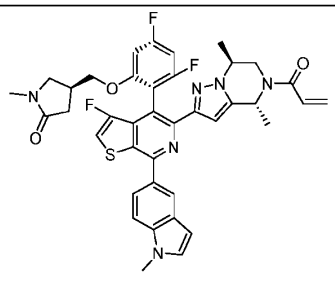
742		LCMS m/z [M+1]: 748.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.46 (s, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 5.6 Hz, 1H), 6.93 – 6.70 (m, 3H), 6.29 (d, J = 17.1 Hz, 1H), 6.15 (s, 1H), 5.83 (d, J = 9.9 Hz, 1H), 5.76 – 5.49 (m, 1H), 4.46 (s, 2H), 4.33 – 4.17 (m, 4H), 4.09 (s, 1H), 3.86 – 3.64 (m, 1H), 2.96 (q, J = 9.7 Hz, 2H), 2.57 – 2.35 (m, 4H), 1.90 – 1.71 (m, 2H), 1.62 – 1.53 (m, 1H), 1.50 – 1.38 (m, 3H), 1.37 – 1.24 (m, 1H).
743		LCMS m/z [M+1]: 687.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.42 (d, J = 8.6 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 6.91 – 6.75 (m, 2H), 6.65 (td, J = 9.2, 2.2 Hz, 1H), 6.42 – 6.16 (m, 2H), 5.83 (d, J = 10.7 Hz, 1H), 5.48 (s, 1H), 4.84 (s, 1H), 4.13 (d, J = 18.6 Hz, 5H), 3.92 – 3.71 (m, 3H), 2.96 (s, 3H), 1.53 (d, J = 6.4 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 5.9 Hz, 3H).
744		LCMS m/z [M+1]: 673.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (d, J = 1.1 Hz, 1H), 8.28 (s, 1H), 8.15 (dd, J = 8.5, 1.4 Hz, 1H), 7.83 – 7.77 (m, 1H), 7.55 (s, 1H), 6.88 – 6.75 (m, 2H), 6.62 (m, J = 9.2, 2.3 Hz, 1H), 6.29 (s, 2H), 5.81 (d, J = 10.4 Hz, 1H), 5.47 (s, 1H), 4.87 – 4.84 (m, 1H), 4.12 (s, 2H), 4.01 (d, J = 2.4 Hz, 3H), 3.79 (t, J = 4.8 Hz, 3H), 1.53 (d, J = 5.4 Hz, 3H), 1.21 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 5.8 Hz, 3H).
745		LCMS m/z [M+1]: 671.7 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (d, J = 1.4 Hz, 1H), 7.95 (dd, J = 8.6, 1.5 Hz, 1H), 7.87 (s, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 3.1 Hz, 1H), 6.86 (dd, J = 16.6, 10.7 Hz, 2H), 6.74 – 6.65 (m, 2H), 6.30 (s, 1H), 6.18 (s, 1H), 5.84 (d, J = 10.3 Hz, 1H), 5.48 (s, 1H), 4.88 – 4.83 (m, 1H), 4.23 (s, 2H), 3.95 (s, 3H), 3.87 – 3.80 (m, 3H),

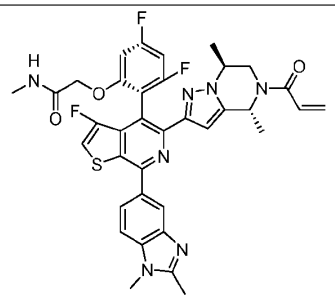
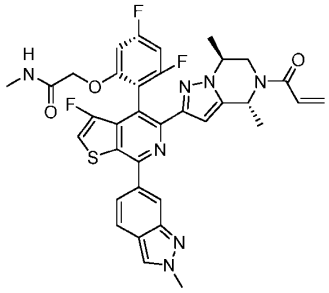
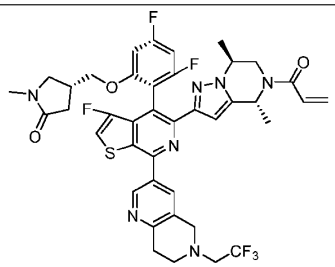
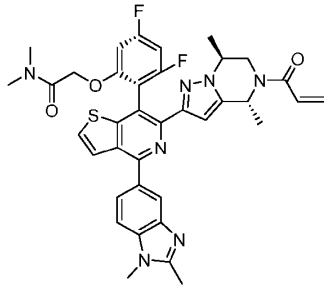
		1.52 (d, J = 6.1 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.0 Hz, 3H).
746		LCMS m/z [M+1]: 687.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (d, J = 1.0 Hz, 1H), 8.44 (dd, J = 8.6, 1.4 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 6.89 – 6.80 (m, 2H), 6.68 (td, J = 9.2, 2.2 Hz, 1H), 6.30 (s, 1H), 6.16 (s, 1H), 5.83 (d, J = 10.8 Hz, 1H), 5.48 (s, 1H), 4.30 – 4.03 (m, 7H), 4.01 – 3.96 (m, 1H), 3.48 (t, J = 4.6 Hz, 2H), 3.12 (s, 3H), 2.96 (s, 3H), 1.53 (d, J = 6.6 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H).
747		LCMS m/z [M+1]: 687.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 7.77 (dd, J = 8.6, 0.6 Hz, 1H), 7.68 (dd, J = 8.6, 1.4 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 6.73 (dd, J = 16.6, 10.6 Hz, 1H), 6.65 (d, J = 10.8 Hz, 1H), 6.50 (td, J = 9.2, 2.2 Hz, 1H), 6.17 (s, 2H), 5.70 (d, J = 10.4 Hz, 1H), 5.36 (s, 1H), 4.72 (s, 1H), 4.07 (s, 3H), 4.01 (t, J = 12.2 Hz, 2H), 3.75 – 3.66 (m, 3H), 2.62 (s, 3H), 1.42 (d, J = 5.2 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 5.8 Hz, 3H).
748		LCMS m/z [M+1]: 694.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.67 (s, 1H), 8.35 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.87 – 6.73 (m, 3H), 6.30 – 6.26 (m, 2H), 5.82 (d, J = 10.4 Hz, 1H), 5.80 – 5.48 (m, 1H), 4.17 – 3.94 (m, 7H), 3.31 – 3.22 (m, 1H), 2.84 – 2.81 (m, 1H), 2.57 (s, 1H), 2.40 (s, 3H), 2.26 – 2.19 (m, 1H), 1.97 – 1.92 (m, 1H), 1.54 – 1.35 (m, 3H)

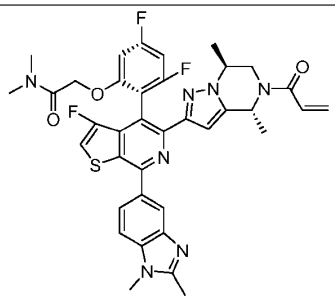
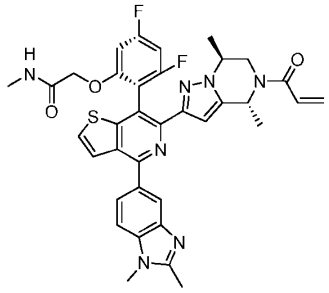
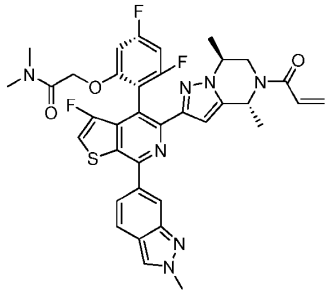
749		LCMS m/z [M+1]: 734.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.46 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.79 (d, J = 5.6 Hz, 1H), 6.93 - 6.65 (m, 3H), 6.35 - 6.25 (m, 2H), 5.85 - 5.45 (m, 2H), 4.22 (s, 3H), 4.19 - 4.17 (m, 1H), 4.10 - 4.00 (m, 3H), 3.93 (t, J = 9.2 Hz, 2H), 3.57 (t, J = 5.6 Hz, 1H), 3.35 - 3.33 (m, 1H), 3.28 - 3.25 (m, 1H), 3.15 - 3.00 (m, 2H), 1.54 - 1.35 (m, 3H).
750		LCMS m/z [M+1]: 700.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.80 - 7.74 (m, 2H), 6.95 - 6.69 (m, 3H), 6.35 - 6.30 (m, 2H), 5.86 - 5.48 (m, 2H), 4.50 - 4.40 (m, 3H), 4.20 (s, 3H), 2.76 (s, 3H), 2.65 (s, 3H), 1.55 - 1.40 (m, 3H), 1.40 - 1.15 (m, 3H).
751		LCMS m/z [M+1]: 734.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.27 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.71 (dd, J = 14.8, 5.2 Hz, 2H), 6.87 – 6.68 (m, 3H), 6.27 (d, J = 18.2 Hz, 2H), 5.81 (d, J = 10.5 Hz, 1H), 5.70 – 5.53 (m, 1H), 4.43 – 4.39 (m, 0.5H), 4.15 – 4.13 (m, 1H), 4.04 – 4.02 (m, 4H), 3.75 - 3.73 (m, 0.5 H), 3.15 – 3.11 (m, 1H), 2.92 – 2.85 (m, 2H), 2.72 – 2.67 (m, 1H), 2.55 – 2.52 (m, 1H), 2.37 – 2.31 (m, 1H), 1.61 – 1.58 (m, 1H), 1.59 – 1.35 (m, 3H).
752		LCMS m/z [M+1]: 726.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.47 (s, 1H), 8.61 (s, 1H), 8.47 (dd, J = 8.7, 1.3 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 2.3 Hz, 1H), 6.92 – 6.78 (m, 2H), 6.66 – 6.57 (m, 1H), 6.33 (d, J = 16.7 Hz, 1H), 6.24 (s, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.80 – 5.48 (m, 1H), 4.43 – 4.34 (m, 1H), 4.24 (s, 3H), 4.04 (dd, J = 9.2, 4.7

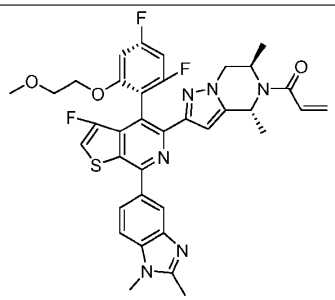
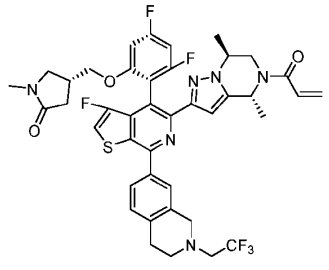
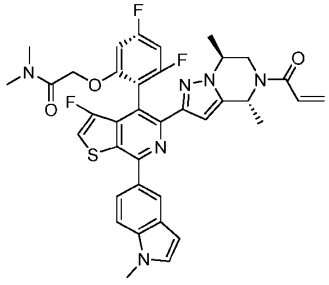
		Hz, 1H), 3.95 (dd, J = 9.2, 4.8 Hz, 1H), 3.91 – 3.78 (m, 1H), 2.94 (dd, J = 10.0, 5.1 Hz, 1H), 2.69 – 2.56 (m, 1H), 2.42 (s, 3H), 2.24 (dd, J = 16.8, 9.7 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.54 – 1.40 (m, 3H), 1.32 – 1.20 (m, 3H).
753		LCMS m/z [M+1]: 734.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.45 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 5.4 Hz, 1H), 7.75 (d, J = 5.5 Hz, 1H), 6.90 - 6.75 (m, 3H), 6.34 - 6.24 (m, 1H), 6.18 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.77 - 5.41 (m, 1H), 5.03 - 4.93 (m, 1H), 4.27 - 4.19 (m, 4H), 4.14 - 3.98 (m, 1H), 3.24 - 3.17 (m, 1H), 3.14 - 2.85 (m, 3H), 2.78 - 2.62 (m, 2H), 2.25 - 2.15 (m, 1H), 1.91 - 1.80 (m, 1H), 1.54 - 1.36 (m, 3H).
754		LCMS m/z [M+1]: 740.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 - 8.51 (m, 1H), 8.43 (dd, J = 8.6, 1.4 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 2.3 Hz, 1H), 6.92 - 6.76 (m, 2H), 6.65 - 6.57 (m, 1H), 6.38 - 6.28 (m, 1H), 6.19 (s, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.79 - 5.45 (m, 1H), 4.46 - 4.36 (m, 1H), 4.09 (s, 3H), 4.05 - 3.93 (m, 2H), 3.27 - 3.20 (m, 1H), 3.00 - 2.90 (m, 4H), 2.66 - 2.55 (m, 1H), 2.39 (s, 3H), 2.36 - 2.27 (m, 1H), 1.95 - 1.87 (m, 1H), 1.54 - 1.37 (m, 3H), 1.33 - 1.21 (m, 3H).
755		LCMS m/z [M+1]: 708.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.25 (s, 1H), 8.44 (s, 1H), 8.26 (dd, J = 8.6, 1.2 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.90 – 6.82 (m, 2H), 6.71 (td, J = 9.2, 1.9 Hz, 1H), 6.34 – 6.29 (m, 2H), 5.83 (dd, J = 10.6, 1.5 Hz, 1H), 5.74 – 5.42 (m, 1H), 4.40 – 4.37 (m, 1H), 4.23 – 4.20 (m, 4H), 4.06 – 4.02 (m, 1H), 3.97 – 3.93 (m, 1H), 2.89 – 2.86 (m, 1H), 2.62 – 2.55 (m, 1H), 2.31 (s, 3H), 2.23 (dd, J

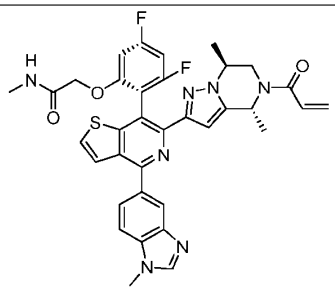
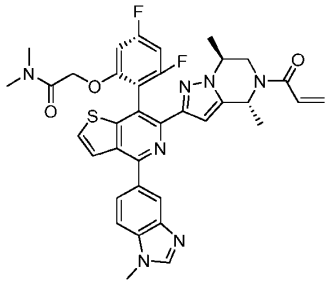
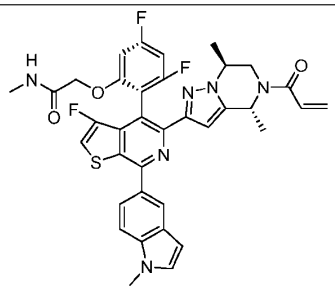
		= 17.0, 9.8 Hz, 1H), 1.96 (dd, J = 17.1, 5.4 Hz, 1H), 1.60 – 1.38 (m, 3H), 1.29 – 1.16 (m, 3H).
756		LCMS m/z [M+1]: 726.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 – 8.38 (m, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.85 (dd, J = 8.8, 1.2 Hz, 1H), 7.87 – 7.81 (m, 2H), 6.83 (d, J = 10.4 Hz, 2H), 6.69 – 6.65 (m, 1H), 6.33 (d, J =16.4 Hz, 1H), 6.22 (s, 1H), 5.86 – 5.83 (m, 1H), 5.79 – 5.52 (m, 1H), 4.46 (s, 1H), 4.31 (s, 3H), 4.08 – 4.05 (m, 1H), 3.93 – 3.90 (m, 1H), 3.35 (d, J = 10.0 Hz, 2H), 2.94 (dd, J = 10.0, 4.4 Hz, 1H), 2.69 – 2.63 (m, 1H), 2.45 (s, 3H), 2.33 – 2.27 (m, 1H), 2.03 – 1.97 (m, 1H), 1.54 – 1.35 (m, 3H), 1.34 – 1.18 (m, 3H).
757		LCMS m/z [M+1]: 726.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.28 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 6.87 (s, 1H), 6.78 (d, J = 10.9 Hz, 1H), 6.58 (t, J = 8.7 Hz, 1H), 6.38 – 6.21 (m, 2H), 5.84 (d, J = 10.7 Hz, 1H), 5.77 – 5.51 (m, 1H), 4.69 (s, 1H), 4.45 – 4.33 (m, 1H), 4.28 – 4.14 (m, 1H), 4.07 – 3.90 (m, 6H), 3.27 – 3.20 (m, 1H), 2.97 (dd, J = 10.1, 4.7 Hz, 1H), 2.67 – 2.54 (m, 1H), 2.46 (s, 3H), 2.40 - 2.22 (m, 1H), 1.98 (dd, J = 17.2, 5.4 Hz, 1H), 1.56 – 1.40 (m, 3H), 1.32 – 1.17 (m, 3H).
758		LCMS m/z [M+1]: 740.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.11 – 8.09 (m, 1H), 7.71 (d, J = 4.4 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 6.91 – 6.78 (m, 2H), 6.62 – 6.58 (m, 1H), 6.40 - 6.22 (m, 2H), 5.84 (d, J = 10.8 Hz, 1H), 5.81 – 5.48 (m, 1H), 4.79 – 4.61 (m, 1H), 4.41 – 4.39 (m, 1H), 4.09 – 3.98 (m, 1H), 3.95 – 3.93 (m, 1H), 3.92 (s, 3H), 3.28 – 3.25 (m, 1H), 2.94 (dd, J =5.2, 10.0 Hz, 1H), 2.72 (s, 3H), 2.69 –

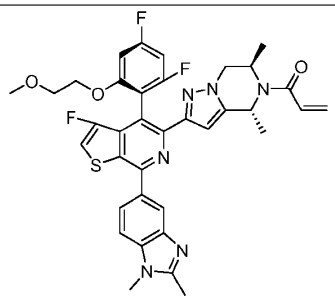
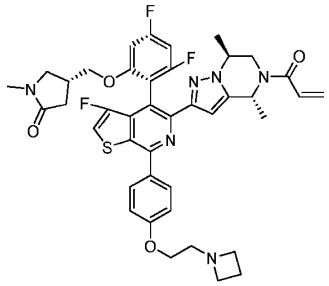
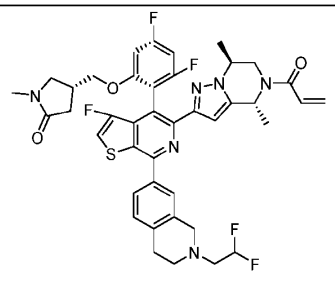
		2.58 (m, 1H), 2.50 (s, 3H), 2.29 – 2.23 (m, 1H), 2.04 – 1.98 (m, 1H), 1.54 – 1.35 (m, 3H), 1.34 – 1.18 (m, 3H).
759		LCMS m/z [M+1]: 714.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.62 (s, 1H), 6.92 - 6.74 (m, 2H), 6.40 (t, J = 9.2 Hz, 1H), 6.35 - 6.30 (m, 2H), 5.86 - 5.50 (m, 2H), 4.80 - 4.70 (m, 2H), 4.50 - 4.40 (m, 1H), 4.17 (s, 3H), 2.84 (s, 3H), 2.82 (s, 3H), 2.73 (s, 3H), 1.55 - 1.40 (m, 3H), 1.38 - 1.20 (m, 3H).
760		LCMS m/z [M+1]: 711.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (d, J = 1.2 Hz, 1H), 7.95 (dd, J = 8.5, 1.6 Hz, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 2.3 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 6.93 – 6.76(m, 2H), 6.63 – 6.55 (m, 2H), 6.37 – 6.17 (m, 2H), 5.84 (d, J = 10.8 Hz, 1H), 5.77 – 5.45 (m, 1H), 4.42 – 4.35 (m, 1H), , 4.02 (dd, J = 9.2, 6.1 Hz, 1H), 3.97 – 3.79 (m, 4H), 3.22 (dd, J = 10.0, 8.3 Hz, 1H), 2.95 (dd, J = 10.1, 5.7 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.18 (dd, J = 17.1, 9.2 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.55 – 1.37 (m, 3H), 1.35 – 1.20 (m, 3H).
761		LCMS m/z [M+1]: 725.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (d, J = 1.3 Hz, 1H), 7.96 (dd, J = 8.6, 1.6 Hz, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 6.93 – 6.81 (m, 1H), 6.81 – 6.75 (m, 1H), 6.63 – 6.53 (m, 2H), 6.36 – 6.21 (m, 2H), 5.83 (d, J = 10.4 Hz, 1H), 5.78 – 5.47 (m, 1H), 4.39 – 4.31 (m, 1H), 4.03 – 3.89 (m, 5H), 3.28 – 3.24 (m, 1H), 2.94 (dd, J = 10.0, 5.4 Hz, 1H), 2.66 – 2.57 (m, 1H), 2.51 (s, 3H), 2.26 (dd, J = 17.0, 9.6 Hz, 1H), 2.02 (dd, J = 17.2, 6.4 Hz, 1H), 1.55 – 1.39 (m, 3H), 1.30 – 1.18 (m, 3H).

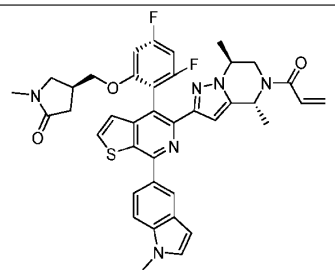
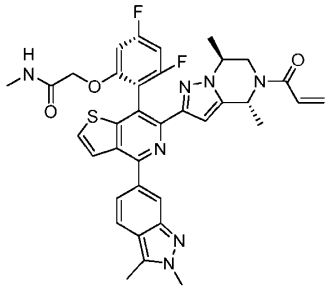
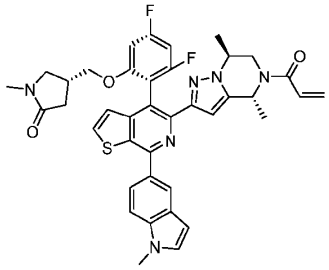
762		LCMS m/z [M+1]: 700.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 - 8.47 (m, 1H), 8.40 (dd, J = 8.6, 1.4 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 6.93 - 6.80 (m, 1H), 6.79 - 6.74 (m, 1H), 6.72 - 6.65 (m, 1H), 6.38 - 6.29 (m, 2H), 5.84 (dd, J = 10.6, 1.5 Hz, 1H), 5.80 - 5.50 (m, 1H), 4.52 - 4.32 (m, 3H), 4.09 (s, 3H), 2.93 (s, 3H), 2.64 (s, 3H), 1.56 - 1.38 (m, 3H), 1.26 - 1.18 (m, 3H).
763		LCMS m/z [M+1]: 686.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 – 8.35 (m, 2H), 7.98 (dd, J = 8.7, 0.9 Hz, 1H), 7.84 – 7.74 (m, 2H), 6.94 – 6.75 (m, 2H), 6.75 – 6.68 (m, 1H), 6.38 - 6.28 (m, 2H), 5.84 (dd, J = 10.5, 1.9 Hz, 1H), 5.76 - 5.45 (m, 1H), 4.79 - 4.56 (m, 1H), 4.46 (s, 3H), 4.31 (s, 3H), 3.96 - 3.71 (m, 1H), 2.65 (s, 3H), 1.53 - 1.39 (m, 3H), 1.26 - 1.15 (m, 3H).
764		LCMS m/z [M+1]: 810.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.35 (s, 1H), 8.88 (s, 1H), 7.64 (s, 1H), 6.92 - 6.80 (m, 2H), 6.62 (dt, J = 9.2 Hz, 2.0 Hz, 1H), 6.35 - 6.31 (m, 1H), 6.20 (s, 1H), 5.86 - 5.50 (m, 2H), 4.45 - 4.40 (m, 1H), 4.23 (s, 2H), 4.05 - 3.95 (m, 2H), 3.52 - 3.40 (m, 2H), 3.30 - 3.25 (m, 2H), 3.00 - 2.90 (m, 1H), 2.65 - 2.50 (m, 1H), 2.37 (s, 3H), 2.33 - 2.26 (m, 1H), 1.84 (dd, J = 16.8 Hz, 4.8 Hz, 1H), 1.55 - 1.40 (m, 3H), 1.38 - 1.20 (m, 3H).
765		LCMS m/z [M+1]: 696.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.22 (dd, J = 8.6, 1.3 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 6.93 – 6.68 (m, 3H), 6.41 - 6.25 (m, 2H), 5.84 (dd, J = 10.6, 1.2 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.81 – 4.65 (m, 2H), 4.49 – 4.42 (m, 1H), 4.09 (s, 3H), 2.94 (s, 3H), 2.86 (s, 3H), 2.83 (s, 3H), 1.51 – 1.36 (m, 3H), 1.35 – 1.25 (m, 3H).

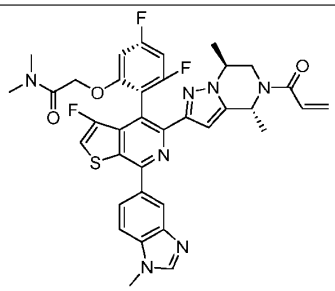
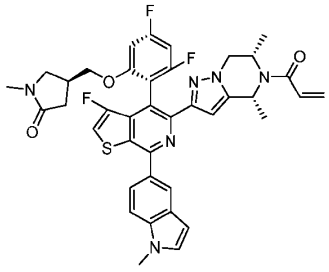
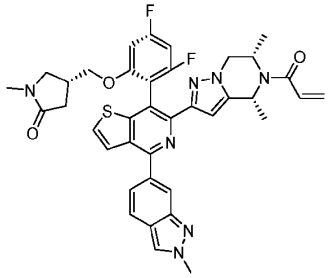
766		LCMS m/z [M+1]: 714.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.41 – 8.39 (m, 1H), 8.19 – 8.07 (m, 1H), 7.59 (d, J = 2.4 Hz, 1H), 6.93 – 6.87 (m, 1H), 6.86 – 6.74 (m, 1H), 6.66 – 6.61 (m, 1H), 6.35 – 6.30 (m, 2H), 5.90 – 5.85 (m, 1H), 5.84 – 5.47 (m, 1H), 4.81 – 4.75 (m, 2H), 4.46 (s, 1H), 4.09 (s, 3H), 2.94 (s, 3H), 2.86 (s, 6H), 1.58 - 1.22 (m, 6H).	
767		LCMS m/z [M+1]: 682.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J = 0.8 Hz, 1H), 8.23 (dd, J = 8.6, 1.4 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.93 – 6.73 (m, 3H), 6.44 (s, 1H), 6.33 (d, J = 16.5 Hz, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.78 – 4.64 (m, 1H), 4.55 – 4.44 (m, 2H), 4.41 – 4.34 (m, 1H), 4.10 (s, 3H), 2.94 (s, 3H), 2.62 (s, 3H), 1.55 – 1.42 (m, 3H), 1.22 (d, J = 5.9 Hz, 3H).	
768		LCMS m/z [M+1]: 700.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 – 8.29 (m, 2H), 7.95 (dd, J = 8.7, 1.0 Hz, 1H), 7.82 (dd, J = 8.7, 1.5 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 6.92 – 6.72 (m, 2H), 6.65 (td, J = 9.2, 2.2 Hz, 1H), 6.38 – 6.26 (m, 2H), 5.88 – 5.79 (m, 1H), 5.73 - 5.42 (m, 1H), 4.82 – 4.68 (m, 3H), 4.49 - 4.41 (m, 1H), 4.30 (s, 3H), 3.95 - 3.74 (m, 1H), 2.84 (d, J = 6.5 Hz, 6H), 1.51 - 1.37 (m, 3H), 1.33 - 1.29 (m, 3H).	

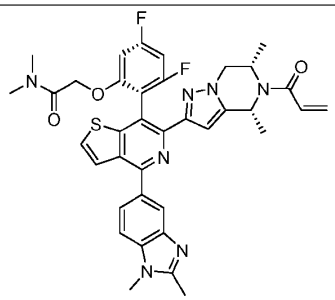
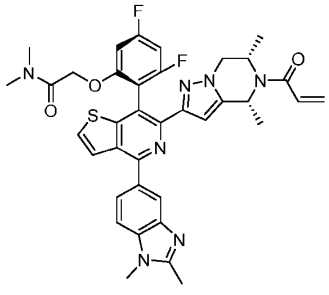
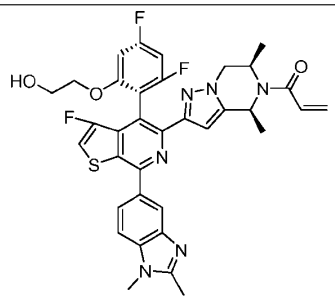
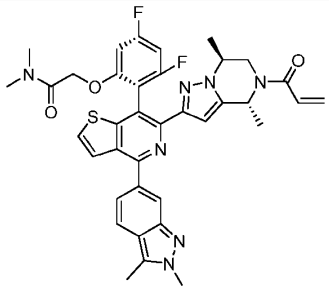
769		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.40 (dd, J = 8.6 Hz, 1.2 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 6.92 - 6.72 (m, 2H), 6.65 - 6.55 (m, 1H), 6.34 (dd, J = 16.6 Hz, 1.6 Hz, 1H), 6.23 (s, 1H), 5.81 (dd, J = 10.4 Hz, 1.6 Hz, 1H), 5.42 - 5.30 (m, 1H), 4.80 - 4.68 (m, 1H), 4.49 (dd, J = 13.6 Hz, 3.2 Hz, 1H), 4.16 (d, J = 13.6 Hz, 1H), 4.12 - 4.04 (m, 4H), 4.03 - 3.95 (m, 1H), 3.46 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 2.94 (s, 3H), 1.44 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H).
770		LCMS m/z [M+1]: 809.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 - 7.98 (m, 1H), 7.92 - 7.89 (m, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 6.92 - 6.76 (m, 2H), 6.65 - 6.57 (m, 1H), 6.38 - 6.28 (m, 1H), 6.16 (s, 1H), 5.87 - 5.81 (m, 1H), 5.79 - 5.45 (m, 1H), 4.47 - 4.36 (m, 1H), 4.30 - 4.17 (m, 2H), 4.03 - 3.92 (m, 2H), 3.74 - 3.58 (m, 2H), 3.28- 3.24 (m, 1H), 3.19 - 3.12 (m, 2H), 2.99 - 2.93 (m, 1H), 2.65 - 2.54 (m, 1H), 2.42 (s, 3H), 2.39 - 2.28 (m, 1H), 1.95 - 1.86 (m, 1H), 1.54 - 1.37 (m, 3H), 1.36 - 1.18 (m, 7H).
771		LCMS m/z [M+1]: 699.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (d, J = 1.3 Hz, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.92 (dd, J = 8.5, 1.6 Hz, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 3.1 Hz, 1H), 6.93 - 6.78 (m, 2H), 6.74 - 6.67 (m, 2H), 6.35 (d, J = 16.3 Hz, 1H), 6.23 (s, 1H), 5.83 (dd, J = 10.5, 1.4 Hz, 1H), 5.80 - 5.49 (m, 1H), 4.83 - 4.68 (m, 3H), 4.62 - 4.52 (m, 1H), 3.93 (s, 3H), 2.90 (s, 3H), 2.88 (s, 3H), 1.50 - 1.32 (m, 6H).

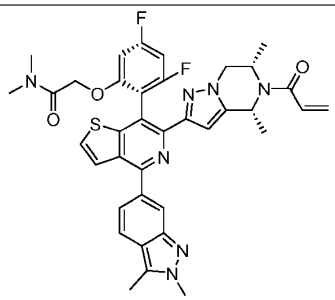
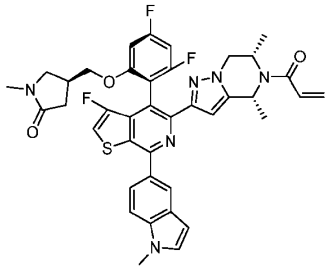
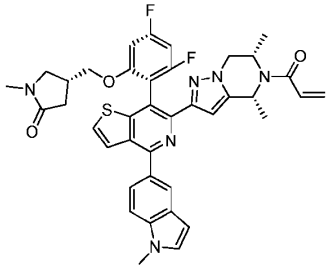
772		LCMS m/z [M+1]: 668.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.42 (s, 1H), 8.43 (s, 1H), 8.30 (dd, J = 8.6, 1.2 Hz, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.93 - 6.74 (m, 3H), 6.43 (s, 1H), 6.34 (d, J = 16.3 Hz, 1H), 5.85 (dd, J = 10.5, 1.4 Hz, 1H), 5.81 - 5.50 (m, 1H), 4.56 - 4.36 (m, 3H), 4.23 (s, 3H), 2.63 (s, 3H), 1.55 - 1.42 (m, 3H), 1.26 - 1.19 (m, 3H).
773		LCMS m/z [M+1]: 682.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.37 (s, 1H), 8.44 (s, 1H), 8.27 (dd, J = 8.6, 1.2 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.92 - 6.81 (m, 2H), 6.77 - 6.70 (m, 1H), 6.39 - 6.28 (m, 2H), 5.85 (dd, J = 10.5, 1.4 Hz, 1H), 5.80 - 5.49 (m, 1H), 4.81 - 4.74 (m, 2H), 4.52 - 4.42 (m, 1H), 4.21 (s, 3H), 2.86 (s, 3H), 2.84 (s, 3H), 1.50 - 1.38 (m, 3H), 1.35 - 1.29 (m, 3H).
774		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (d, J = 1.4 Hz, 1H), 7.92 (dd, J = 8.6, 1.7 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 3.1 Hz, 1H), 6.92 – 6.82 (m, 1H), 6.79 (d, J = 10.4 Hz, 1H), 6.77 – 6.69 (m, 1H), 6.67 (d, J = 3.0 Hz, 1H), 6.33 (d, J = 16.8 Hz, 1H), 6.28 (s, 1H), 5.85 (dd, J = 10.6, 1.2 Hz, 1H), 5.78 – 5.52 (m, 1H), 4.46 (s, 3H), 4.33 – 4.17 (m, 1H), 4.00 – 3.76 (m, 4H), 2.66 (s, 3H), 1.47 – 1.42 (m, 3H), 1.31 – 1.23 (m, 3H).

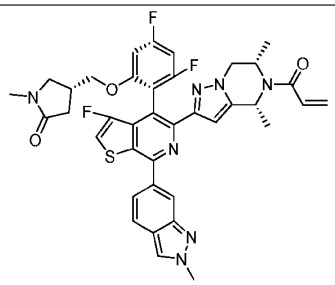
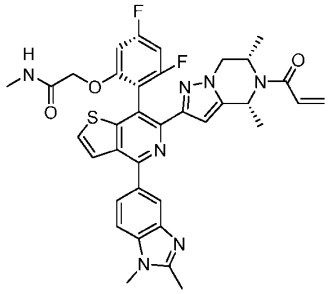
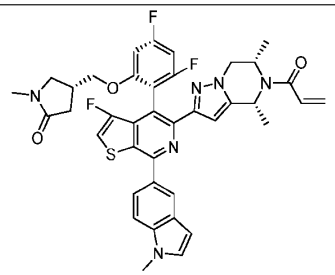
775		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (d, J = 0.8 Hz, 1H),8.40 (dd, J = 8.6 Hz, 1.4 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.60 (d,J = 2.4 Hz, 1H), 6.94 - 6.71 (m, 2H), 6.69 - 6.54 (m, 1H), 6.34 (dd, J = 16.6 Hz, 1.8 Hz, 1H), 6.19 (s, 1H), 5.81 (dd, J = 10.4 Hz, 1.8 Hz, 1H), 5.40 - 5.29 (m, 1H), 4.79 - 4.66 (m, 1H), 4.51 (dd, J = 13.6 Hz, 3.0 Hz, 1H), 4.23 - 4.15 (m, 1H), 4.09 (s, 3H), 4.08 - 4.03 (m, 1H), 4.01 - 3.92 (m, 1H), 3.46 (t, J = 4.4 Hz, 1H), 3.09 (s, 3H), 2.94 (s, 3H), 1.45 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H).
776		LCMS m/z [M+1]: 771.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 2.3 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.94 – 6.74 (m, 2H), 6.62 – 6.52 (m, 1H), 6.32 (d, J = 16.0 Hz, 1H), 6.26 – 6.18 (m, 1H), 5.88 – 5.80 (m, 1H), 5.78 – 5.46 (m, 1H), 4.42 – 4.34 (m, 1H), 4.19 (t, J = 5.1 Hz, 2H), 4.02 – 3.90 (m, 2H), 3.72 – 3.62 (m, 3H), 3.28 – 3.20 (m, 1H), 3.16 – 3.10 (m, 2H), 2.95 (dd, J = 10.2, 4.6 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.43 (s, 3H), 2.38 – 2.22 (m, 3H), 1.95 (dd, J = 16.8, 5.5 Hz, 1H), 1.54 – 1.38 (m, 3H), 1.30 – 1.18 (m, 3H).
777		LCMS m/z [M+1]: 791.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (dd, J = 7.9, 1.5 Hz, 1H), 7.84 (s, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 6.92 – 6.74 (m, 2H), 6.61 – 6.53 (m, 1H), 6.32 (d, J = 16.7 Hz, 1H), 6.27 – 6.08 (m, 2H), 5.83 (dd, J = 10.6, 1.4 Hz, 1H), 5.77 – 5.47 (m, 1H), 4.41 – 4.34 (m, 1H), 4.26 – 4.16 (m, 0.5H), 4.01 – 3.80 (m, 4.5H), 3.34 (s, 1H), 3.26 – 3.20 (m, 1H), 3.06 – 2.93 (m, 6H), 2.62 – 2.53 (m, 1H), 2.43 (s, 3H), 2.32 (dd, J = 17.1, 9.8 Hz, 1H), 1.95 (dd, J = 17.8, 4.8 Hz, 1H), 1.53 – 1.39 (m, 3H), 1.31 – 1.20 (m, 3H).

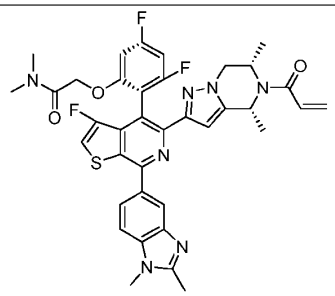
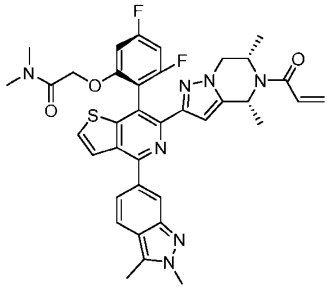
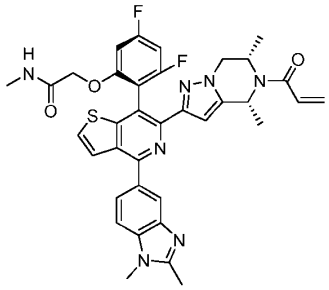
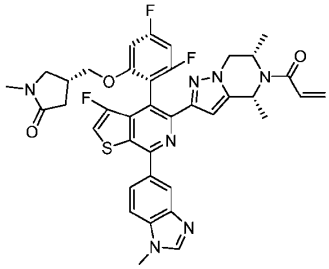
778		LCMS m/z [M+1]: 707.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (d, J = 5.6 Hz, 1H), 8.49 (d, J = 2.0 Hz, 1H), 8.01 (dd, J = 8.6, 2.0 Hz, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 3.2 Hz, 1H), 7.39 (d, J = 5.4 Hz, 1H), 6.95 – 6.80 (m, 3H), 6.75 (d, J = 3.2 Hz, 1H), 6.38 – 6.30 (m, 1H), 6.04 (s, 1H), 5.86 (dd, J = 10.6, 2.0 Hz, 1H), 5.77 - 5.45 (m, 1H), 4.63 - 4.54 (m, 1H), 4.16 - 4.06 (m, 1H), 3.96 (s, 3H), 3.93 - 3.85 (m, 1H), 3.40 – 3.34 (m, 1H), 2.83 (dd, J = 10.2, 3.6 Hz, 1H), 2.60 - 2.52 (m, 1H), 2.38 - 2.25 (m, 1H), 2.14 (s, 3H), 2.06 – 1.88 (m, 2H), 1.49 - 1.19 (m, 6H).
779		LCMS m/z [M+1]: 682.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 8.14 (d, J = 5.6 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.62 (dd, J = 1.2, 8.4 Hz, 1H), 6.94 – 6.83 (m, 3H), 6.36 – 6.32 (m, 1H), 6.27 (s, 1H), 5.91 – 5.84 (m, 1H), 5.82 - 5.51 (m, 1H), 4.55 (s, 1H), 4.51 (d, J = 3.2 Hz, 2H), 4.23 (s, 3H), 3.98 – 3.46 (m, 1H), 2.77 (s, 3H), 2.67 (s, 3H), 1.54 – 1.35 (m, 3H), 1.34 – 1.16 (m, 3H).
780		LCMS m/z [M+1]: 707.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (d, J = 5.4 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 7.98 (dd, J = 8.6, 1.8 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 3.1 Hz, 1H), 7.33 (d, J = 5.4 Hz, 1H), 6.96 (d, J = 10.3 Hz, 1H), 6.91 – 6.77 (m, 2H), 6.74 (d, J = 3.1 Hz, 1H), 6.34 (d, J = 17.0 Hz, 1H), 6.05 (s, 1H), 5.86 (dd, J = 10.6, 1.8 Hz, 1H), 5.79 – 5.46 (m, 1H), 4.66 – 4.57 (m, 1H), 4.03 (d, J = 3.9 Hz, 2H), 3.96 (s, 3H), 3.92 – 3.83 (m, 1H), 3.39 – 3.32 (m, 1H), 2.96 (dd, J = 10.1, 3.7 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.45 (s, 3H), 2.31 (dd, J = 17.0, 10.1 Hz, 1H), 1.85 – 1.71 (m, 1H), 1.52 – 1.30 (m, 6H).

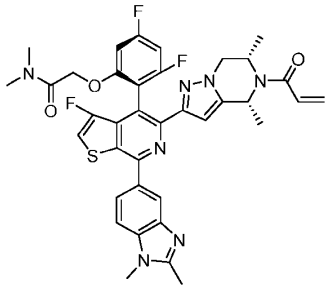
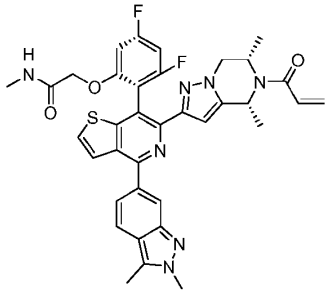
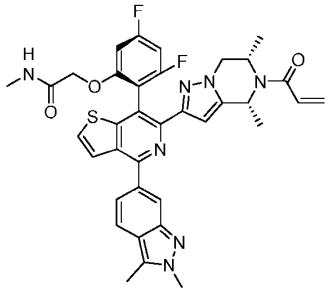
781		LCMS m/z [M+1]: 700.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (s, 1H), 8.60 (s, 1H), 8.46 (dd, J = 8.7, 1.4 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 6.95 – 6.80 (m, 1H), 6.76 (d, J = 10.7 Hz, 1H), 6.70 – 6.60 (m, 1H), 6.38 – 6.26 (m, 2H), 5.88 – 5.81 (m, 1H), 5.80 – 5.45 (m, 1H), 4.81 – 4.70 (m, 2H), 4.53 – 4.40 (m, 1H), 4.22 (s, 3H), 2.85 (s, 6H), 1.52 – 1.35 (m, 3H), 1.35 – 1.27 (m, 3H).
782		LCMS m/z [M+1]: 725.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (d, J = 1.3 Hz, 1H), 7.88 (dd, J = 8.6, 1.7 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.20 (d, J = 3.1 Hz, 1H), 6.79 – 6.62 (m, 2H), 6.58 – 6.46 (m, 2H), 6.15 (s, 2H), 5.70 (d, J = 10.5 Hz, 1H), 5.36 (s, 1H), 4.71 (s, 1H), 4.13 – 3.92 (m, 2H), 3.90 – 3.83 (m, 1H), 3.81 – 3.71 (m, 4H), 3.19 – 3.11 (m, 1H), 2.83 – 2.72 (m, 1H), 2.56 – 2.44 (m, 1H), 2.39 (s, 3H), 2.24 – 2.10 (m, 1H), 1.95 – 1.81 (m, 1H), 1.42 (d, J = 5.6 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H).
783		LCMS m/z [M+1]: 707.7 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.28 (s, 1H), 8.01 – 7.93 (m, 2H), 7.75 (d, J = 5.6 Hz, 1H), 7.65 (dd, J = 8.7, 0.9 Hz, 1H), 6.89 (d, J = 10.6 Hz, 1H), 6.80 – 6.69 (m, 2H), 6.20 (s, 1H), 6.04 (s, 1H), 5.72 (d, J = 10.8 Hz, 1H), 5.39 (s, 1H), 4.73 (s, 1H), 4.23 (s, 3H), 4.19 (s, 2H), 4.03 – 3.88 (m, 2H), 3.31 – 3.24 (m, 1H), 2.91 – 2.83 (m, 1H), 2.55 – 2.45 (m, 1H), 2.38 (s, 3H), 2.28 – 2.16 (m, 1H), 1.71 – 1.61 (m, 1H), 1.40 (d, J = 5.8 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H).

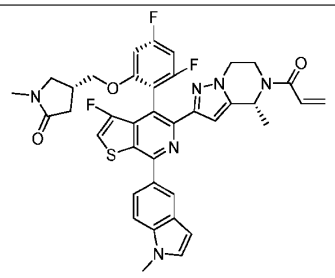
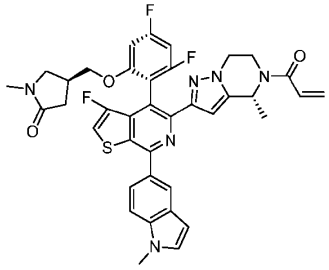
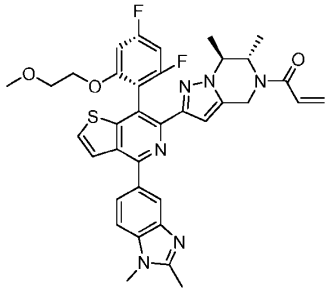
784		LCMS m/z [M+1]: 695.8 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.23 (dd, J = 8.6, 1.4 Hz, 1H), 8.06 (dd, J = 8.6, 1.8 Hz, 1H), 7.87 (t, J = 4.6 Hz, 1H), 7.71 (dd, J = 5.6, 1.5 Hz, 1H), 6.84 (dd, J = 16.7, 10.7 Hz, 2H), 6.73 (t, J = 9.2 Hz, 1H), 6.34 (d, J = 63.0 Hz, 2H), 5.81 (d, J = 10.5 Hz, 1H), 5.48 (s, 1H), 4.78 (t, J = 14.4 Hz, 3H), 4.17 (s, 2H), 4.09 (s, 3H), 2.94 (s, 3H), 2.88 – 2.82 (m, 6H), 1.51 (t, J = 13.7 Hz, 3H), 1.21 (t, J = 9.0 Hz, 3H).
785		LCMS m/z [M+1]: 695.8 ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 1.0 Hz, 1H), 7.85 – 7.77 (m, 1H), 7.64 – 7.52 (m, 3H), 6.78 – 6.57 (m, 3H), 6.47 (s, 1H), 6.17 (s, 1H), 5.70 (d, J = 10.1 Hz, 1H), 5.37 (s, 1H), 4.63 (m, J = 14.5 Hz, 3H), 4.01 (t, J = 10.1 Hz, 2H), 3.82 – 3.72 (m, 3H), 2.70 (d, J = 22.8 Hz, 6H), 2.59 – 2.52 (m, 3H), 1.47 (d, J = 6.0 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H).
786		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J = 1.1 Hz, 1H), 8.05 (dd, J = 8.4, 1.6 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 6.89 – 6.57 (m, 3H), 6.36 – 6.18 (m, 2H), 5.84 (dd, J = 10.6, 1.2 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.21 – 4.08 (m, 2H), 4.02 – 3.96 (m, 1H), 3.94 – 3.82 (m, 4H), 3.65 – 3.55 (m, 2H), 2.66 (s, 3H), 1.50 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H).
787		LCMS m/z [M+1]: 696.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 8.11 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.61 (dd, J = 8.8, 1.2 Hz, 1H), 6.91 – 6.79 (m, 3H), 6.35 – 6.29 (m, 2H), 5.86 – 5.83 (m, 1H), 5.82 - 5.53 (m, 1H), 4.89 (s, 1H), 4.59 (s, 1H), 4.22 (s, 3H), 2.90 (s, 3H), 2.88 (s, 3H), 2.77 (s, 3H), 1.58 - 1.22 (m, 6H).

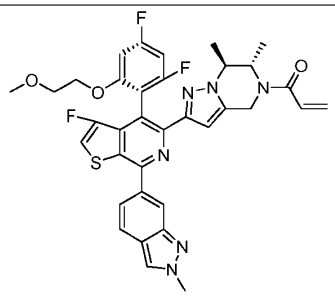
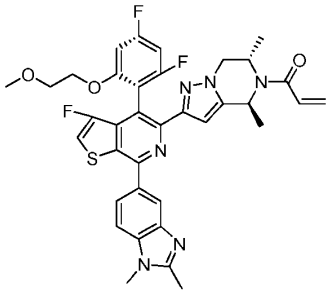
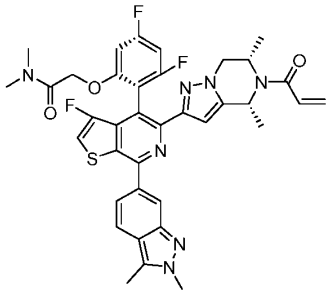
788		LCMS m/z [M+1]: 696.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.71 (m, J = 18.8, 9.4, 5.5 Hz, 3H), 6.88 – 6.68 (m, 3H), 6.36 (d, J = 78.5 Hz, 2H), 5.80 (d, J = 10.1 Hz, 1H), 5.48 (s, 1H), 4.75 (q, J = 14.6 Hz, 3H), 4.17 (s, 5H), 2.85 (s, 3H), 2.79 (d, J = 1.7 Hz, 3H), 2.73 (s, 3H), 1.52 (d, J = 6.0 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H).
789		LCMS m/z [M+1]: 725.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 2.2 Hz, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 3.1 Hz, 1H), 6.78 – 6.68 (m, 2H), 6.64 – 6.54 (m, 2H), 6.17 (s, 1H), 6.03 (s, 1H), 5.72 (d, J = 10.6 Hz, 1H), 5.37 (s, 1H), 4.76 – 4.71 (m, 1H), 4.11 (s, 2H), 3.92 – 3.84 (m, 1H), 3.83 – 3.77 (m, 4H), 3.24 (d, J = 9.9 Hz, 1H), 2.93 – 2.84 (m, 1H), 2.56 – 2.45 (m, 1H), 2.41 (s, 3H), 2.32 – 2.21 (m, 1H), 1.88 – 1.78 (m, 1H), 1.41 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H).
790		LCMS m/z [M+1]: 706.8 ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.65 – 7.54 (m, 2H), 7.48 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 2.8 Hz, 1H), 6.80 – 6.68 (m, 2H), 6.60 (t, J = 8.8 Hz, 1H), 6.50 (d, J = 2.7 Hz, 1H), 6.20 (s, 2H), 5.70 (d, J = 10.2 Hz, 1H), 5.37 (s, 1H), 4.72 (s, 1H), 4.16 – 3.94 (m, 2H), 3.89 – 3.76 (m, 5H), 3.10 (t, J = 9.1 Hz, 1H), 2.83 – 2.73 (m, 1H), 2.47 (s, 1H), 2.38 (s, 3H), 2.20 (dd, J = 16.9, 10.0 Hz, 1H), 1.82 (dd, J = 16.9, 5.3 Hz, 1H), 1.43 (s, 3H), 1.09 (d, J = 6.5 Hz, 3H).

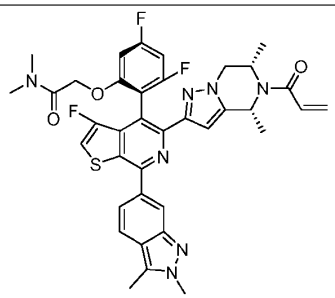
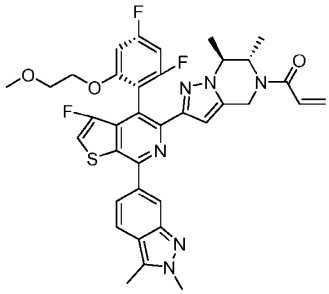
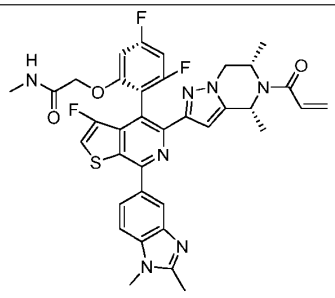
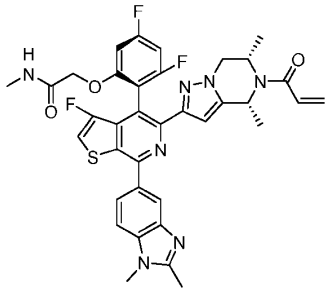
791		LCMS m/z [M+1]: 726.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.22 (s, 1H), 7.86 – 7.75 (m, 2H), 7.45 (d, J = 1.4 Hz, 1H), 6.78 – 6.64 (m, 2H), 6.58 – 6.46 (m, 1H), 6.15 (s, 2H), 5.71 (d, J = 10.4 Hz, 1H), 5.37 (s, 1H), 4.74 (s, 1H), 4.19 (s, 3H), 4.13 – 3.96 (m, 2H), 3.92 – 3.76 (m, 2H), 3.15 (t, J = 9.3 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.56 – 2.43 (m, 1H), 2.40 (s, 3H), 2.31 – 2.16 (m, 1H), 1.90 – 1.78 (m, 1H), 1.42 (d, J = 4.8 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H).
792		LCMS m/z [M+1]: 682.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.14 (dd, J = 8.6, 1.2 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 5.6 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 6.77 – 6.68 (m, 3H), 6.37 (s, 1H), 6.17 (s, 1H), 5.71 (d, J = 10.4 Hz, 1H), 5.40 (s, 1H), 4.78 – 4.76 (m, 1H), 4.35 (s, 2H), 4.09 – 3.97 (m, 5H), 2.85 (s, 3H), 2.53 (s, 3H), 1.45 (d, J = 6.4 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H).
793		LCMS m/z [M+1]: 725.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.89 (dd, J = 8.5, 1.6 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 3.1 Hz, 1H), 6.80 – 6.64 (m, 2H), 6.58 – 6.47 (m, 2H), 6.30 – 6.01 (m, J = 57.4 Hz, 2H), 5.70 (d, J = 10.4 Hz, 1H), 5.37 (s, 1H), 4.73 (s, 1H), 4.02 (t, J = 14.4 Hz, 2H), 3.91 – 3.85 (m, 1H), 3.83 – 3.72 (m, 4H), 3.14 (t, J = 9.3 Hz, 1H), 2.88 – 2.81 (m, 1H), 2.56 – 2.45 (m, 1H), 2.38 (s, 3H), 2.30 – 2.18 (m, 1H), 1.93 – 1.79 (m, 1H), 1.41 (d, J = 5.4 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H).

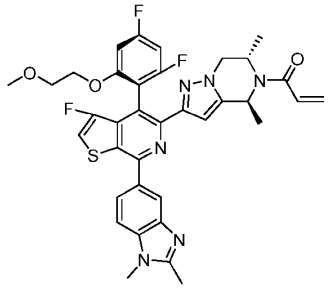
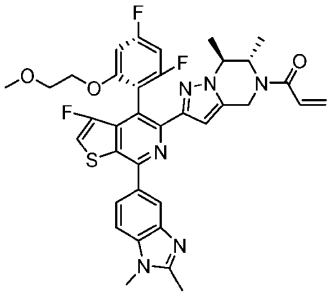
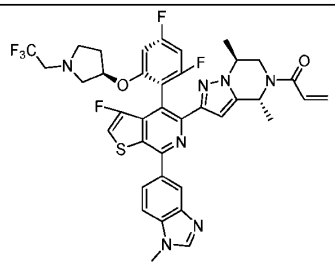
794		LCMS m/z [M+1]: 714.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.43 (dd, J = 8.7, 1.5 Hz, 1H), 8.10 (dd, J = 8.6, 3.0 Hz, 1H), 7.63 (d, J = 2.3 Hz, 1H), 6.86 (dd, J = 16.7, 10.7 Hz, 1H), 6.76 (d, J = 10.7 Hz, 1H), 6.67 (td, J = 9.2, 2.2 Hz, 1H), 6.42 – 6.19 (m, 2H), 5.83 (d, J = 10.6 Hz, 1H), 5.49 (s, 1H), 4.80 (dd, J = 30.7, 14.7 Hz, 3H), 4.19 (t, J = 10.6 Hz, 2H), 4.11 (s, 3H), 2.96 (s, 3H), 2.90 (d, J = 1.8 Hz, 6H), 1.50 (d, J = 6.5 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H).
795		LCMS m/z [M+1]: 696.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 7.85 (dd, J = 8.6, 1.0 Hz, 1H), 7.76 – 7.64 (m, 3H), 6.88 – 6.68 (m, 3H), 6.52 (d, J = 45.0 Hz, 1H), 6.27 (s, 1H), 5.80 (d, J = 10.4 Hz, 1H), 5.48 (s, 1H), 4.74 (q, J = 14.6 Hz, 3H), 4.23 – 4.06 (m, 5H), 2.77 (dd, J = 33.3, 11.8 Hz, 9H), 1.57 (d, J = 6.2 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H).
796		LCMS m/z [M+1]: 682.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.14 (dd, J = 8.6, 1.4 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 5.6 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 6.77 – 6.68 (m, 3H), 6.36 (s, 1H), 6.17 (s, 1H), 5.72 (d, J = 10.4 Hz, 1H), 5.39 (s, 1H), 4.76 – 4.64 (m, 1H), 4.34 (t, J = 10.4 Hz, 2H), 4.08 (s, 1H), 4.00 (s, 3H), 3.95 (d, J = 12.8 Hz, 1H), 2.85 (s, 3H), 2.55 (s, 3H), 1.45 (d, J = 6.4 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H).
797		LCMS m/z [M+1]: 726.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (d, J = 1.1 Hz, 1H), 8.17 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 6.79 – 6.66 (m, 2H), 6.53 (td, J = 9.2, 2.2 Hz, 1H), 6.15 (s, 2H), 5.70 (d, J = 10.4 Hz, 1H), 5.37 (s, 1H), 4.73 (d, J = 10.5 Hz, 1H), 4.01 (t, J = 16.1 Hz, 2H), 3.92 – 3.84 (m, 4H), 3.80 (dd, J = 9.1, 4.8 Hz, 1H), 3.14 (t, J = 9.3 Hz, 1H), 2.84 (dd, J = 10.0, 4.8 Hz, 1H), 2.58 – 2.44 (m, 1H), 2.39 (s, 3H),

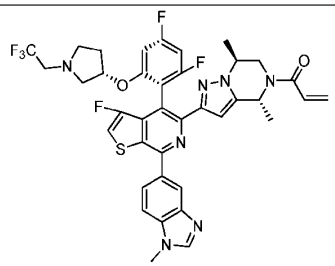
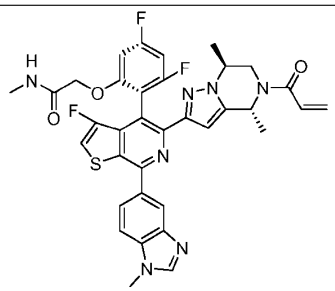
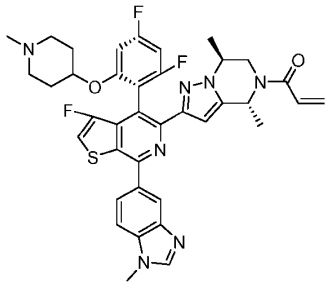
		2.23 (dd, J = 17.1, 9.8 Hz, 1H), 1.85 (dd, J = 17.1, 5.6 Hz, 1H), 1.42 (d, J = 4.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H).
798		LCMS m/z [M+1]: 714.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, J = 0.9 Hz, 1H), 8.41 (dd, J = 8.7, 1.5 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 16.7, 10.7 Hz, 1H), 6.75 – 6.63 (m, 2H), 6.48 (s, 1H), 6.32 (d, J = 38.5 Hz, 1H), 5.82 (d, J = 10.5 Hz, 1H), 5.48 (s, 1H), 4.75 (dd, J = 29.1, 14.8 Hz, 3H), 4.18 (d, J = 7.3 Hz, 2H), 4.09 (s, 3H), 2.94 (s, 3H), 2.87 (s, 6H), 1.56 (d, J = 6.3 Hz, 3H), 1.24 (d, J = 6.9 Hz, 3H).
799		LCMS m/z [M+1]: 682.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 8.01 (d, J = 5.6 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 5.6 Hz, 1H), 7.52 (dd, J = 8.6, 1.2 Hz, 1H), 6.86 – 6.70 (m, 3H), 6.25 (s, 1H), 6.20 (s, 1H), 5.72 (d, J = 10.8 Hz, 1H), 5.39 (s, 1H), 4.78 – 4.73 (m, 1H), 4.40 (t, J = 11.0 Hz, 2H), 4.12 (s, 5H), 2.67 (s, 3H), 2.59 (s, 3H), 1.43 (d, J = 6.2 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H).
800		LCMS m/z [M+1]: 682.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 8.01 (d, J = 5.6 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 5.6 Hz, 1H), 7.52 (dd, J = 8.6, 1.2 Hz, 1H), 6.86 – 6.70 (m, 3H), 6.25 (s, 1H), 6.20 (s, 1H), 5.72 (d, J = 10.8 Hz, 1H), 5.39 (s, 1H), 4.78 – 4.73 (m, 1H), 4.40 (t, J = 11.0 Hz, 2H), 4.12 (s, 5H), 2.67 (s, 3H), 2.59 (s, 3H), 1.43 (d, J = 6.2 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H).

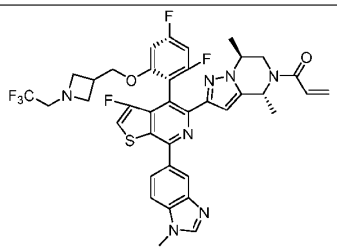
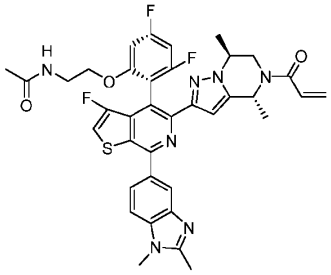
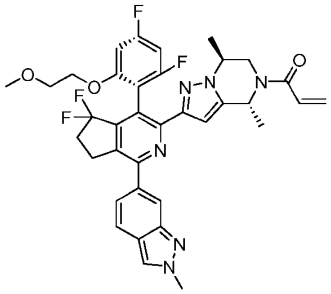
801		LCMS m/z [M+1]: 711.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (d, J = 1.2 Hz, 1H), 8.03 – 7.94 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 3.2 Hz, 1H), 6.94 - 6.78 (m, 2H), 6.76 – 6.66 (m, 2H), 6.35 - 6.22 (m, 1H), 5.98 (s, 1H), 5.83 (dd, J = 10.4, 1.6 Hz, 1H), 5.75 - 5.49 (m, 1H), 4.38 – 4.27 (m, 1H), 4.10 – 3.96 (m, 2H), 3.94 (s, 3H), 3.40 - 3.28 (m, 1H), 3.03 - 2.89 (m, 1H), 2.68 – 2.56 (m, 1H), 2.45 (s, 3H), 2.42 - 2.31(m, 1H), 1.90 - 1.79(m, 1H), 1.53 - 1.34 (m, 3H).
802		LCMS m/z [M+1]: 711.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, J = 1.4 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.4, 1.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 3.2 Hz, 1H), 6.94 – 6.68 (m, 4H), 6.30 (d, J = 15.2 Hz, 1H), 5.97 (s, 1H), 5.83 (dd, J = 10.4, 1.6 Hz, 1H), 5.75 - 5.57 (m, 1H), 4.34 (dd, J = 13.2, 2.8 Hz, 1H), 4.09 (dd, J = 9.2, 4.0 Hz, 1H), 3.95 (s, 3H), 3.40 - 3.89 (m, 1H), 3.45 – 3.36 (m, 1H), 2.90 (dd, J = 10.4, 4.0 Hz, 1H), 2.65 - 2.57 (m, 1H), 2.40 – 2.31 (m, 1H), 2.29 (s, 3H), 1.92 (dd, J = 17.2, 4.2 Hz, 1H), 1.53 - 1.34 (m, 3H).
803		LCMS m/z [M+1]: 669.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.86 (dd, J = 5.6, 1.2 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.95 – 6.81 (m, J = 21.4, 11.0 Hz, 2H), 6.74 (td, J = 9.2, 2.1 Hz, 1H), 6.32 (dd, J = 16.7, 1.7 Hz, 1H), 6.26 (d, J = 15.7 Hz, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.22 (dd, J = 53.3, 16.9 Hz, 1H), 4.66 (d, J = 15.2 Hz, 1H), 4.42 – 4.25 (m, 2H), 4.17 – 4.09 (m, 4H), 4.08 – 3.98 (m, 1H), 3.46 (t, J = 4.6 Hz, 2H), 3.08 (s, 3H), 2.96 (s, 3H), 1.35 (s, 3H), 1.26 – 1.15 (m, 3H).

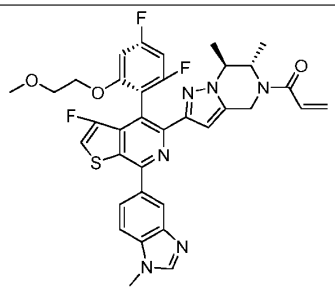
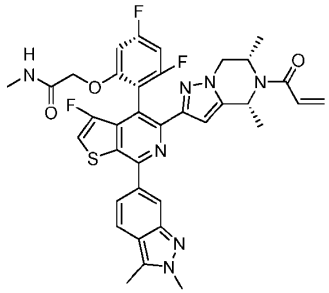
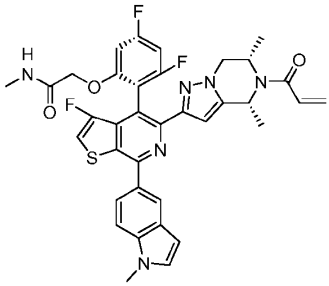
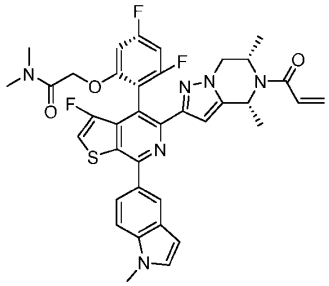
804		LCMS m/z [M+1]: 673.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 8.23 (s, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.73 (dd, J = 8.7, 1.2 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 6.82 – 6.65 (m, 2H), 6.52 (dd, J = 12.9, 5.5 Hz, 1H), 6.20 (dd, J = 16.7, 1.8 Hz, 1H), 6.15 (s, 1H), 5.73 (dd, J = 10.6, 1.8 Hz, 1H), 5.10 (dd, J = 49.7, 17.5 Hz, 1H), 4.54 (d, J = 19.9 Hz, 1H), 4.27 – 4.14 (m, 5H), 4.02 – 3.95 (m, 1H), 3.92 – 3.82 (m, 1H), 3.37 (t, J = 4.6 Hz, 2H), 2.99 (s, 3H), 1.20 (d, J = 11.1 Hz, 3H), 1.14 – 1.03 (m, 3H).
805		LCMS m/z [M+1]: 687 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (d, J = 1.3 Hz, 1H), 8.08 (dd, J = 8.4, 1.6 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 6.93 – 6.75 (m, 2H), 6.63 (td, J = 9.2, 2.3 Hz, 1H), 6.25 (s, 2H), 5.83 (d, J = 10.4 Hz, 1H), 5.48 (s, 1H), 4.85 (s, 1H), 4.25 – 4.07 (m, 3H), 4.04 – 3.97 (m, 1H), 3.90 (s, 3H), 3.54 – 3.45 (m, 2H), 3.10 (d, J = 10.6 Hz, 3H), 2.69 (s, 3H), 1.53 (d, J = 5.6 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H).
806		LCMS m/z [M+1]: 714.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 6.90 – 6.83 (m, 1H), 6.77 (d, J = 10.8 Hz, 1H), 6.67 (t, J = 9.0 Hz, 1H), 6.40 (s, 1H), 6.31 (s, 1H), 5.83 (d, J = 9.8 Hz, 1H), 5.51 (s, 1H), 4.88 – 4.74 (m, 3H), 4.28 – 4.15 (m, 5H), 2.88 (s, 6H), 2.76 (s, 3H), 1.51 (d, J = 6.0 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H).

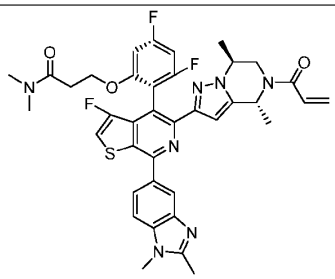
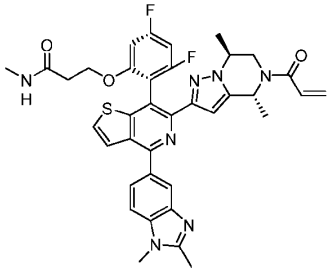
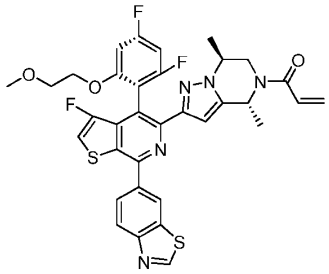
807		LCMS m/z [M+1]: 714.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.81 (dd, J = 8.7, 1.3 Hz, 1H), 7.55 (d, J = 2.5 Hz, 1H), 6.85 (dd, J = 16.7, 10.7 Hz, 1H), 6.73 – 6.62 (m, 2H), 6.50 (s, 1H), 6.28 (s, 1H), 5.82 (d, J = 10.7 Hz, 1H), 5.50 (s, 1H), 4.73 (q, J = 14.5 Hz, 3H), 4.16 (d, J = 14.2 Hz, 5H), 2.84 (d, J = 10.4 Hz, 6H), 2.74 (s, 3H), 1.57 (d, J = 6.3 Hz, 3H), 1.25 – 1.21 (m, 3H).
808		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 7.95 – 7.91 (m, 1H), 7.80 (dd, J = 8.6, 1.4 Hz, 1H), 7.65 (d, J = 2.2 Hz, 1H), 6.81 (d, J = 10.6 Hz, 2H), 6.68 – 6.61 (m, 1H), 6.32 (dd, J = 16.6, 1.8 Hz, 1H), 6.25 (s, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.32 – 5.14 (m, 1H), 4.66 (d, J = 17.6 Hz, 1H), 4.39 – 4.21 (m, 2H), 4.21 – 3.98 (m, 5H), 3.49 (s, 2H), 3.11 (s, 3H), 2.76 (s, 3H), 1.34 (s, 3H), 1.21 (d, J = 14.6 Hz, 3H).
809		LCMS m/z [M+1]: 700.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (d, J = 0.9 Hz, 1H), 8.40 (dd, J = 8.7, 1.5 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 16.7, 10.7 Hz, 1H), 6.78 – 6.70 (m, 2H), 6.33 (d, J = 38.3 Hz, 2H), 5.81 (d, J = 10.7 Hz, 1H), 5.49 (s, 1H), 4.86 – 4.78 (m, 1H), 4.41 (d, J = 2.7 Hz, 2H), 4.15 (s, 1H), 4.10 (d, J = 6.2 Hz, 4H), 2.93 (s, 3H), 2.65 (s, 3H), 1.54 (d, J = 6.5 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H).
810		LCMS m/z [M+1]: 700.0 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.41 (d, J = 8.7 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 6.84 (dd, J = 16.7, 10.7 Hz, 1H), 6.75 (dd, J = 12.0, 5.6 Hz, 2H), 6.33 (d, J = 36.4 Hz, 2H), 5.82 (d, J = 10.4 Hz, 1H), 5.49 (s, 1H), 4.87 – 4.82 (m, 1H), 4.41 (s, 2H), 4.19 (s, 1H), 4.11 – 4.03 (m, 4H), 2.94 (s, 3H),

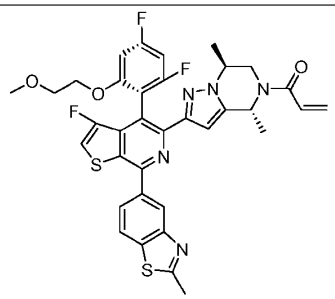
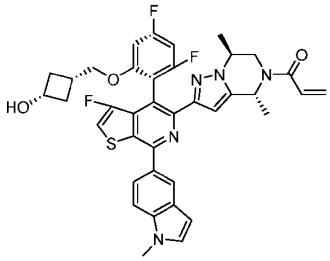
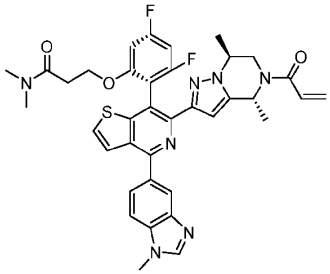
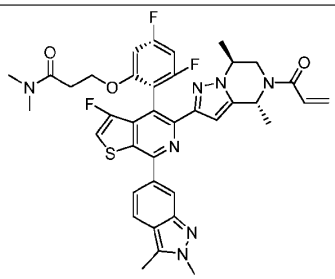
		2.67 (s, 3H), 1.55 (d, J = 6.5 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H).
811		LCMS m/z [M+1]: 687 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.43 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 16.4, 10.4 Hz, 2H), 6.69 (t, J = 9.2 Hz, 1H), 6.31 (s, 1H), 6.16 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.48 (s, 1H), 4.28 – 4.07 (m, 7H), 4.00 – 3.95 (m, 1H), 3.48 (t, J = 4.4 Hz, 2H), 3.12 (s, 3H), 2.96 (s, 3H), 1.53 (d, J = 6.4 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H).
812		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (d, J = 0.8 Hz, 1H), 8.42 (dd, J = 8.6, 1.4 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.83 (t, J = 14.0 Hz, 2H), 6.65 (td, J = 9.2, 2.2 Hz, 1H), 6.32 (dd, J = 16.6, 1.6 Hz, 1H), 6.21 (d, J = 14.6 Hz, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.31 – 5.14 (m, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.39 – 4.13 (m, 2H), 4.12 – 3.97 (m, 5H), 3.48 (t, J = 4.6 Hz, 2H), 3.11 (s, 3H), 2.96 (s, 3H), 1.35 (d, J = 4.6 Hz, 3H), 1.21 (dd, J = 21.0, 5.2 Hz, 3H).
813		LCMS m/z [M+1]: 766.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.48 (s, 1H), 8.62 (d, J = 0.7 Hz, 1H), 8.49 (dd, J = 8.7, 1.4 Hz, 1H), 8.19 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 2.3 Hz, 1H), 6.94 - 6.84 (m, 1H), 6.82 (d, J = 10.7 Hz, 1H), 6.70 - 6.62 (m, 1H), 6.37 (d, J = 16.4 Hz, 1H), 6.28 (s, 1H), 5.88 (dd, J = 10.5, 1.4 Hz, 1H), 5.82 - 5.48 (m, 1H), 5.01 - 4.95 (m, 1H), 4.47 - 4.36 (m, 1H), 4.25 (s, 3H), 3.29 - 3.21 (m, 1H), 3.20 - 3.02 (m, 2H), 2.98 - 2.84 (m, 2H), 2.80 - 2.70 (m, 1H), 2.30 - 2.20 (m, 1H), 1.95 - 1.85 (m, 1H), 1.54 - 1.40 (m, 3H), 1.34 - 1.23 (m, 3H).

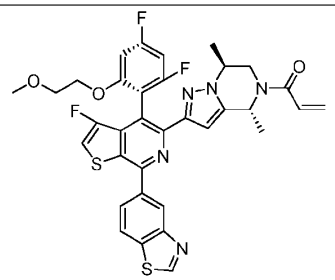
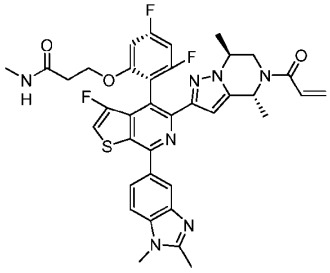
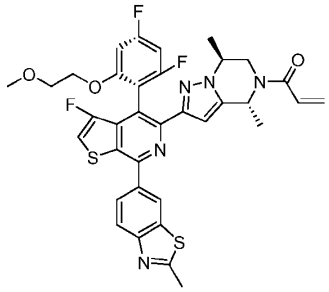
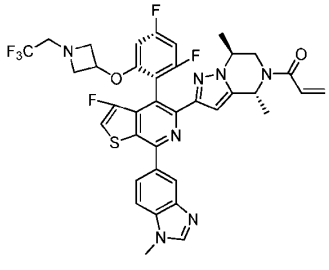
814		LCMS m/z [M+1]: 766.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.45 (s, 1H), 8.60 (s, 1H), 8.46 (dd, J = 8.6 Hz, 1.2 Hz, 1H), 8.61 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 2.2 Hz, 1H), 6.93 - 6.81 (m, 1H), 6.77 (d, J = 11.2 Hz, 1H), 6.68 - 6.59 (m, 1H), 6.33 (d, J = 16.2 Hz, 1H), 6.25 (s, 1H), 5.84 (dd, J = 10.6 Hz, 1.4 Hz, 1H), 5.79 - 5.43 (m, 1H), 5.02 - 4.94 (m, 1H), 4.44 - 4.32 (m, 1H), 4.23 (s, 3H), 3.27 - 3.21 (m, 1H), 3.19 - 3.00 (m, 2H), 2.93 - 2.85 (m, 1H), 2.81 (d, J = 11.6 Hz, 1H), 2.72 - 2.56 (m, 1H), 2.24 - 2.06 (m, 1H), 1.89 - 1.75 (m, 1H), 1.57 - 1.37 (m, 3H), 1.35 - 1.20 (m, 3H).
815		LCMS m/z [M+1]: 686.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (s, 1H), 8.59 (s, 1H), 8.44 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.64 - 6.60 (m, 1H), 6.95 - 6.74 (m, 2H), 7.74 - 6.63 (m, 1H), 6.39 (s, 1H), 6.33 (d, J = 16.7 Hz, 1H), 5.88 - 5.81 (m, 1H), 5.80 - 5.45 (m, 1H), 4.54 - 4.34 (m, 3H), 4.22 (s, 3H), 2.64 (s, 1H), 1.60 - 1.38 (m, 3H), 1.29 - 1.15 (s, 3H).
816		LCMS m/z [M+1]: 712.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.39 (d, J = 10.1 Hz, 1H), 8.64 (d, J = 10.2 Hz, 1H), 8.48 (t, J = 8.5 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 7.72 - 7.60 (m, 1H), 7.01 - 6.80 (m, 2H), 6.74 - 6.64 (m, 1H), 6.52 - 6.19 (m, 2H), 5.91 - 5.84 (m, 1H), 5.82 - 5.46 (m, 1H), 4.84 - 4.58 (m, 2H), 4.47 - 4.31 (m, 1H), 4.24 (s, 3H), 3.52 - 3.38 (m, 1H), 3.25 - 3.04 (m, 2H), 2.84 (s, 1H), 2.52 (s, 2H), 2.47 - 1.88 (m, 4H), 1.70 - 1.40 (m, 4H), 1.34 - 1.19 (m, 3H).

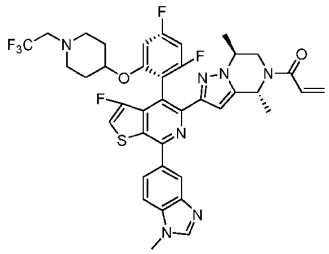
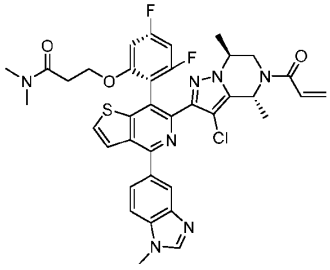
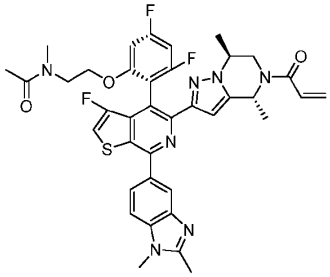
817		LCMS m/z [M+1]: 766.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.63 (d, J = 1.8 Hz, 1H), 8.47 (dd, J = 8.8, 1.6 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 6.91 – 6.79 (m, 2H), 6.67 (td, J = 9.0, 2.2 Hz, 1H), 6.39 – 6.28 (m, 2H), 5.85 (dd, J = 10.6, 2.0 Hz, 1H), 5.77 - 5.45(m, 1H), 4.80 - 4.56 (m, 1H), 4.42 - 4.36 (m, 1H), 4.22 (s, 3H), 4.15 – 3.94 (m, 4H), 3.90 - 3.77 (m, 1H), 3.73 – 3.63 (m, 1H), 3.49 (t, J = 9.0 Hz, 1H), 3.40 – 3.32 (m, 1H), 3.28 – 3.07 (m, 2H), 1.54 - 1.40 (m, 3H), 1.27 - 1.16 (m, 3H).
818		LCMS m/z [M+1]: 714.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.38 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 6.92 - 6.80 (m, 2H), 6.60 (dt, J = 9.2 Hz, 2.4 Hz, 1H), 6.35 - 6.22 (m, 2H), 5.84 (d, J = 10.8 Hz, 1H), 5.80 - 5.45 (m, 1H), 4.50 - 4.40 (m, 1H), 4.10 - 4.00 (m, 5H), 2.92 (s, 3H), 1.68 (s, 3H), 1.55 - 1.40 (m, 3H), 1.38 - 1.20 (m, 3H).
819		LCMS m/z [M+1]: 675.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.12 (s, 1H), 7.89 (dd, J = 8.7, 0.6 Hz, 1H), 7.72 (dd, J = 8.7, 1.3 Hz, 1H), 6.93 – 6.82 (m, 1H), 6.78 (d, J = 10.9 Hz, 1H), 6.65 – 6.56 (m, 1H), 6.34 (d, J = 16.8 Hz, 1H), 6.22 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.74 – 5.50 (m, 1H), 4.47 – 4.38 (m, 1H), 4.30 (s, 3H), 4.27 – 4.17 (m, 1H), 4.12 – 4.05 (m, 2H), 3.91 – 3.77 (m, 1H), 3.54 (t, J = 4.8 Hz, 2H), 3.39 – 3.35 (m, 2H), 3.19 (s, 3H), 2.72 – 2.59 (m, 2H), 1.54 – 1.40 (m, 3H), 1.34 – 1.28 (m, 3H).

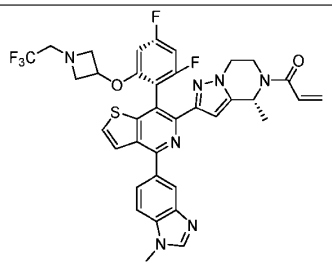
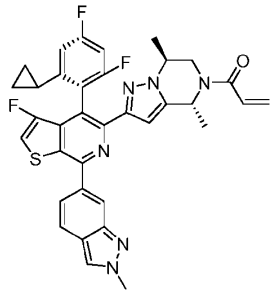
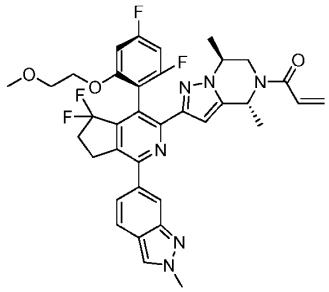
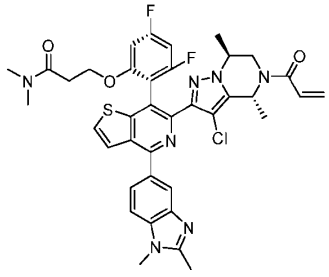
820		LCMS m/z [M+1]: 673.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (s, 1H), 8.61 (s, 1H), 8.47 (d, J = 8.6 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 6.83 (t, J = 13.6 Hz, 2H), 6.65 (td, J = 9.2, 2.2 Hz, 1H), 6.32 (dd, J = 16.6, 1.6 Hz, 1H), 6.23 (d, J = 12.4 Hz, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.19 (d, J = 52.2 Hz, 1H), 4.66 (d, J = 15.8 Hz, 1H), 4.39 – 4.19 (m, 5H), 4.15 – 3.99 (m, 2H), 3.48 (t, J = 4.6 Hz, 2H), 3.11 (s, 3H), 1.34 (s, 3H), 1.25 – 1.16 (m, 3H).
821		LCMS m/z [M+1]: 700.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.80 (dd, J = 8.7, 1.2 Hz, 1H), 7.66 (s, 1H), 6.85 (dd, J = 16.7, 10.7 Hz, 1H), 6.78 – 6.71 (m, 2H), 6.42 (s, 1H), 6.29 (s, 1H), 5.82 (d, J = 11.0 Hz, 1H), 5.50 (s, 1H), 4.84 (s, 1H), 4.41 (d, J = 6.7 Hz, 2H), 4.19 (s, 4H), 4.11 (s, 1H), 2.75 (s, 3H), 2.66 (s, 3H), 1.58 – 1.53 (m, 3H), 1.22 (d, J = 6.8 Hz, 3H).
822		LCMS m/z [M+1]: 685.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 7.96 (d, J = 7.3 Hz, 1H), 7.78 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 2.9 Hz, 1H), 6.91 – 6.74 (m, 3H), 6.67 (d, J = 2.5 Hz, 1H), 6.36 (s, 1H), 6.33 – 6.18 (d, 1H), 5.83 (d, J = 10.3 Hz, 1H), 5.52 (s, 1H), 4.87 – 4.82 (m, 1H), 4.44 (d, J = 3.5 Hz, 2H), 4.17 (s, 2H), 3.94 (s, 3H), 2.68 (s, 3H), 1.55 (d, J = 5.5 Hz, 3H), 1.24 (d, J = 6.7 Hz, 3H).
823		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 7.94 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 3.0 Hz, 1H), 6.90 – 6.79 (m, 2H), 6.71 (t, J = 8.5 Hz, 2H), 6.37 (s, 1H), 6.30 (s, 1H), 5.84 (d, J = 10.5 Hz, 1H), 5.50 (s, 1H), 4.80 (d, J = 15.0 Hz, 2H), 4.26 (s, 2H), 3.95 (s, 3H), 2.92 (d, J = 8.3 Hz, 6H), 1.49 (d, J = 6.3 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H).

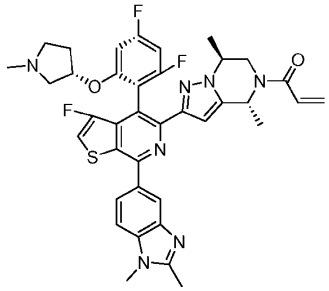
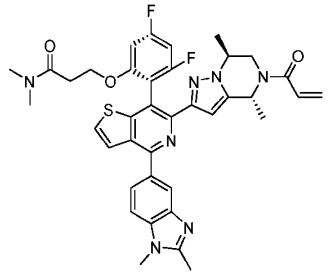
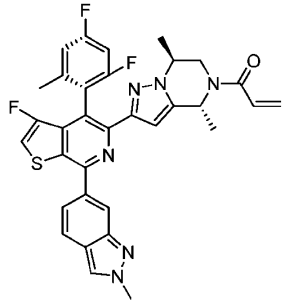
824		LCMS m/z [M+1]: 728.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.40 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 2.2 Hz, 1H), 6.92 - 6.79 (m, 2H), 6.65 - 6.57 (m, 1H), 6.32 (d, J = 17.0 Hz, 1H), 6.21 - 6.07 (m, 1H), 5.84 (d, J = 10.9 Hz, 1H), 5.78 - 5.44 (m, 1H), 4.51 - 4.37 (m, 1H), 4.33 - 4.11 (m, 3H), 4.08 (s, 3H), 2.92 (s, 3H), 2.62 (s, 3H), 2.61 - 2.55 (m, 2H), 2.54 (s, 3H), 1.52 - 1.37 (m, 3H), 1.32 - 1.24 (m, 3H).
825		LCMS m/z [M+1]: 696.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.96 - 6.84 (m, 2H), 6.72 (td, J = 9.2, 2.2 Hz, 1H), 6.35 (d, J = 16.6 Hz, 1H), 6.23 (s, 1H), 5.90 – 5.83 (m, 1H), 5.80 – 5.45 (m, 1H), 4.80 - 4.62 (m, 1H), 4.51 - 4.41 (m, 1H), 4.32 - 4.25 (m, 1H), 4.23 - 4.16 (m, 1H), 4.12 (s, 3H), 3.94 - 3.83 (m, 1H), 3.57 - 3.42 (m, 1H), 2.97 (s, 3H), 2.40 - 2.32 (m, 5H), 1.50 - 1.40 (s, 3H), 1.33 – 1.28 (m, 3H).
826		LCMS m/z [M+1]: 676.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (d, J = 2.4 Hz, 1H), 8.87 (s, 1H), 8.33 (d, J = 1.3 Hz, 2H), 7.72 - 7.66 (m, 1H), 6.92 - 6.81 (m, 2H), 6.70 – 6.61 (m, 1H), 6.35 (d, J = 17.0 Hz, 1H), 6.17 (s, 1H), 5.86 (d, J = 10.4 Hz, 1H), 5.76 - 5.47 (m, 1H), 4.52 – 4.43 (m, 1H), 4.32 - 4.18 (m, 1H), 4.14 - 4.09 (m, 1H), 4.07 – 4.01 (m, 1H), 3.91 - 3.79 (m, 1H), 3.48 (dt, J = 4.4, 2.6 Hz, 2H), 3.11 (d, J = 2.4 Hz, 3H), 1.48 - 1.38 (m, 3H), 1.38 – 1.32 (m, 3H).

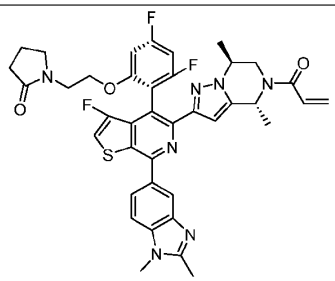
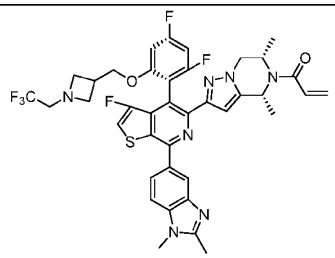
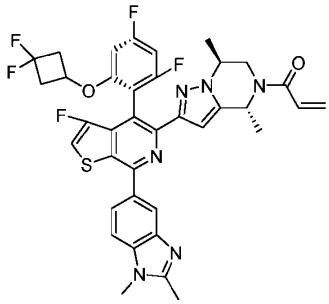
827		LCMS m/z [M+1]: 690.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.67 - 8.63 (m, 1H), 8.21 - 8.12 (m, 2H), 7.54 (d, J = 2.3 Hz, 1H), 6.96 - 6.76 (m, 2H), 6.66 - 6.57 (m, 1H), 6.34 (d, J = 16.5 Hz, 1H), 6.28 - 6.18 (m, 1H), 5.89 - 5.81 (m, 1H), 5.80 - 5.46 (m, 1H), 4.46 - 4.37 (m, 1H), 4.31 - 3.79 (m, 3H), 3.48 (t, J = 4.9 Hz, 2H), 3.09 (s, 3H), 2.90 (s, 3H), 1.55- 1.38 (m, 3H), 1.37 - 1.21 (m, 3H).
828		LCMS m/z [M+1]: 698.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (d, J = 1.4 Hz, 1H), 7.97 – 7.90 (m, 2H), 7.70 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 3.1 Hz, 1H), 6.94 – 6.78 (m, 2H), 6.71 – 6.62 (m, 2H), 6.33 (d, J = 16.6 Hz, 1H), 6.02 (s, 1H), 5.88 – 5.82 (m, 1H), 5.79 – 5.45 (m, 1H), 4.62 – 4.48 (m, 1H), 4.00 – 3.82 (m, 6H), 2.17 – 1.89 (m, 3H), 1.53 – 1.24 (m, 8H).
829		LCMS m/z [M+1]: 696.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.36 (s, 1H), 8.42 (s, 1H), 8.29 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 5.5 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.95 - 6.81 (m, 2H), 6.73 - 6.65 (m, 1H), 6.34 (d, J = 16.6 Hz, 1H), 6.27 - 6.17 (m, 1H), 5.85 (d, J = 11.5 Hz, 1H), 5.79 - 5.45 (m, 1H), 4.49 - 4.36 (m, 1H), 4.34 - 4.26 (m, 1H), 4.24 - 4.19 (m, 4H), 2.60 - 2.54 (m, 5H), 2.46 (s, 3H), 1.51 - 1.38 (m, 3H), 1.32 - 1.23 (m, 3H).
830		LCMS m/z [M+1]: 728.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.73 - 7.69 (m, 1H), 6.95 - 6.81 (m, 2H), 6.70 - 6.60 (m, 1H), 6.35 (d, J = 16.0 Hz, 1H), 6.20 (s, 1H), 5.86 (d, J = 10.7 Hz, 1H), 5.80 - 5.46 (m, 1H), 4.53 - 4.42 (m, 1H), 4.35 - 4.26 (m, 1H), 4.22 (s, 3H), 4.20 - 4.14 (m, 1H), 3.94 - 3.80 (m, 1H), 2.78 (s, 3H), 2.67 - 2.54 (m, 8H), 1.55 - 1.40 (m, 3H), 1.35 - 1.25 (m, 3H).

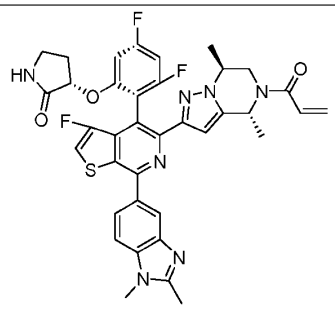
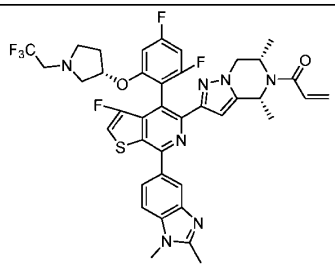
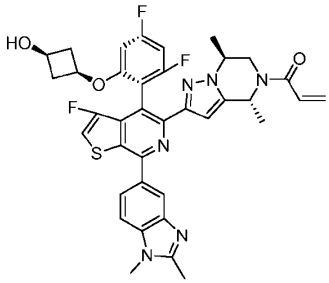
831		LCMS m/z [M+1]: 676.1 ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 8.84 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.68 - 7.64 (m, 1H), 6.96 - 6.78 (m, 2H), 6.70 - 6.60 (m, 1H), 6.34 (d, J = 16.3 Hz, 1H), 6.21 (s, 1H), 5.86 (d, J = 10.7 Hz, 1H), 5.80 - 5.46 (m, 1H), 4.52 - 4.40 (m, 1H), 4.31 - 4.20 (m, 1H), 4.16 - 4.00 (m, 2H), 3.94 - 3.80 (m, 1H), 3.49 (t, J = 4.6 Hz, 2H), 3.11 (s, 3H), 1.57 - 1.40 (m, 3H), 1.38 - 1.26 (m, 3H).
832		LCMS m/z [M+1]: 714.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.96 (dd, J = 8.4, 1.5 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 6.84 - 6.71 (m, 1H), 6.67 (d, J = 10.8 Hz, 1H), 6.53 - 6.43 (m, 1H), 6.22 (d, J = 17.0 Hz, 1H), 6.08 (s, 1H), 5.73 (d, J = 10.9 Hz, 1H), 5.69 - 5.35 (m, 1H), 4.68 - 4.45 (m, 1H), 4.37 - 4.26 (m, 1H), 4.19 - 4.10 (m, 1H), 4.06 - 3.98 (m, 1H), 3.78 (s, 3H), 2.57 (s, 3H), 2.30 - 2.24 (m, 5H), 1.44 - 1.28 (m, 3H), 1.21 - 1.16 (m, 3H).
833		LCMS m/z [M+1]: 690.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.73 (d, J = 1.4 Hz, 1H), 8.26 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 6.84 (d, J = 10.8 Hz, 2H), 6.71 - 6.58 (m, 1H), 6.34 (d, J = 16.8 Hz, 1H), 6.16 (s, 1H), 5.86 (dd, J = 10.6 Hz, 1.4 Hz, 1H), 5.80 - 5.43 (m, 1H), 4.55 - 4.38 (m, 1H), 4.16 - 4.08 (m, 1H), 4.07 - 3.99 (m, 1H), 3.48 (t, J = 4.4 Hz, 2H), 3.11 (s, 3H), 2.93 (s, 3H), 1.53 - 1.39 (m, 3H), 1.38 - 1.24 (m, 3H).
834		LCMS m/z [M+1]: 752.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.49 (s, 1H), 8.64 (s, 1H), 8.50 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 2.2 Hz, 1H), 6.99 – 6.81 (m, 1H), 6.70 (t, J = 8.7 Hz, 1H), 6.60 (d, J = 10.2 Hz, 1H), 6.36 (d, J = 16.0 Hz, 1H), 6.30 (s, 1H), 5.87 (d, J = 10.1 Hz, 1H), 5.81 – 5.53 (m, 1H), 4.42 (s, 1H), 4.36 – 4.13 (m, 4H), 4.11 –

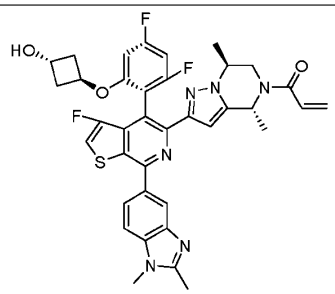
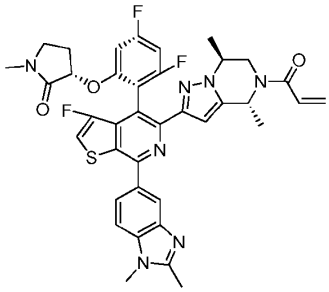
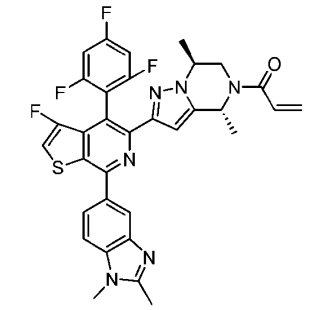
		3.97 (m, 2H), 3.90 (s, 1H), 3.46 – 3.35 (m, 2H), 3.32 – 3.19 (m, 3H), 1.57 – 1.41 (m, 3H), 1.35 – 1.21 (m, 3H).
835		LCMS m/z [M+1]: 780.3 ^{1}H NMR (400 MHz, CD_3OD) δ 9.44 (s, 1H), 8.64 - 8.61 (m, 1H), 8.48 (dd, J = 8.6, 1.2 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 2.2 Hz, 1H), 6.93 - 6.79 (m, 2H), 6.68 - 6.59 (m, 1H), 6.37 - 6.28 (m, 1H), 6.13 (s, 1H), 5.84 (dd, J = 10.6, 1.5 Hz, 1H), 5.78 - 5.42 (m, 1H), 4.53 - 4.37 (m, 2H), 4.31 - 4.15 (m, 4H), 3.13 - 2.99 (m, 2H), 2.65 - 2.47 (m, 4H), 1.94 - 1.76 (m, 2H), 1.68 - 1.57 (m, 1H), 1.55 - 1.20 (m, 8H).
836		LCMS m/z [M+1]: 730.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.40 (s, 1H), 8.45 (s, 1H), 8.32 (d, J = 8.6 Hz, 1H), 8.14 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 5.6 Hz, 1H), 7.80 (d, J = 5.5 Hz, 1H), 6.97 - 6.73 (m, 2H), 6.66 - 6.57 (m, 1H), 6.36 (dd, J = 16.6 Hz, 1.6 Hz, 1H), 5.89 - 5.82 (m, 1H), 5.80 - 5.38 (m, 1H), 4.39 - 4.28 (m, 2H), 4.27 - 4.12 (m, 5H), 2.73 - 2.63 (m, 1H), 2.60 (s, 3H), 2.59 - 2.53 (m, 1H), 2.50 (s, 3H), 1.61 - 1.49 (m, 3H), 1.32 - 1.23 (m, 3H).
837		LCMS m/z [M+1]: 728.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (d, J = 10.8 Hz, 1H), 8.44 – 8.34 (m, 1H), 8.10 – 8.03 (m, 1H), 7.59 (d, J = 17.6 Hz, 1H), 6.93 – 6.76 (m, 2H), 6.68 – 6.56 (m, 1H), 6.37 – 6.21(m, 2H), 5.84 (d, J = 10.8 Hz, 1H), 5.78 – 5.49 (m, 1H), 4.39 (s, 1H), 4.27 – 4.10 (m, 2H), 4.10 – 4.03 (m, 3H), 3.62 – 3.42 (m, 2H), 2.98 – 2.85 (m,3H), 2.62 (s, 1.68H), 2.43 (s, 1.24H), 1.56 – 1.39 (m, 3H), 1.31 – 1.21 (m, 3H).

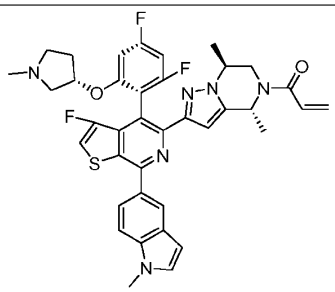
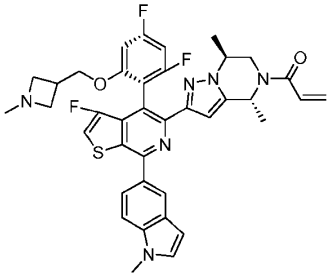
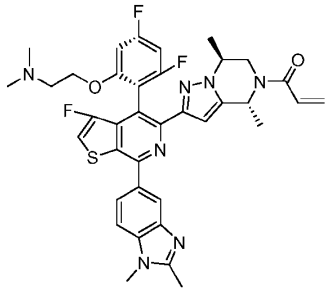
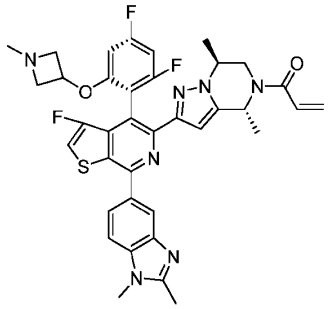
838		LCMS m/z [M+1]: 720.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.39 (s, 1H), 8.46 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 5.5 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.91 – 6.74 (m, 2H), 6.64 (d, J = 9.9 Hz, 1H), 6.29 (d, J = 16.6 Hz, 1H), 6.20 (s, 1H), 5.83 (d, J = 10.7 Hz, 1H), 5.76 – 5.41 (m, 1H), 4.29 – 3.99 (m, 5H), 3.96 – 3.81 (m, 2H), 3.29 – 2.96 (m, 6H), 1.54 – 1.36 (m, 3H).
839		LCMS m/z [M+1]: 639.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (d, J = 14.2 Hz, 2H), 7.98 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.77 (s, 1H), 6.87 (t, J = 8.8 Hz, 2H), 6.61 (d, J = 9.9 Hz, 1H), 6.33 (d, J = 16.9 Hz, 1H), 6.00 (s, 1H), 5.84 (d, J = 10.7 Hz, 1H), 5.75 - 5.44 (m, 1H), 4.52 - 4.43 (m, 1H), 4.31 (s, 3H), 1.55 - 1.37 (m, 4H), 1.36 - 1.22 (m, 3H), 0.73 - 0.60 (m, 3H), 0.57 - 0.48 (m, 1H).
840		LCMS m/z [M+1]: 675.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.10 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 6.88 (s, 1H), 6.70 (d, J = 10.2 Hz, 1H), 6.64 (t, J = 9.4 Hz, 1H), 6.39 – 6.29 (m, 2H), 5.85 (d, J = 10.7 Hz, 1H), 5.76 – 5.57 (m, 1H), 4.62 (s, 3H), 4.44 – 4.34 (m, 1H), 4.29 (s, 3H), 4.25 – 4.16 (m, 1H), 4.07 – 3.98 (m, 1H), 3.98 – 3.90 (m, 1H), 3.88 – 3.77 (m, 1H), 3.54 – 3.40 (m, 4H), 3.14 (s, 3H), 2.73 – 2.57 (m, 2H), 1.55 – 1.44 (m, 3H), 1.27 – 1.19 (m, 3H).
841		LCMS m/z [M+1]: 744.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.28 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.92 (dd, J = 5.6, 0.9 Hz, 1H), 7.81 (d, J = 5.3 Hz, 1H), 6.97 – 6.84 (m, 2H), 6.63 (t, J = 9.0 Hz, 1H), 6.36 (d, J = 16.7 Hz, 1H), 5.89 – 5.77 (m, 2H), 4.35 – 4.20 (m, 3H), 4.11 (s, 3H), 2.95 (s, 3H), 2.73 – 2.66 (m, 1H), 2.62 (s, 3H), 2.60

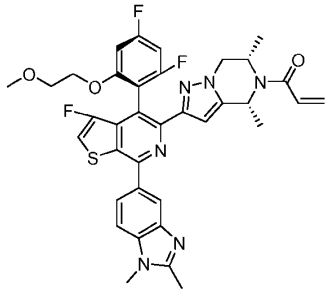
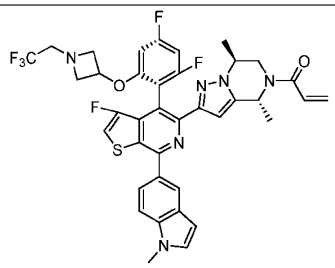
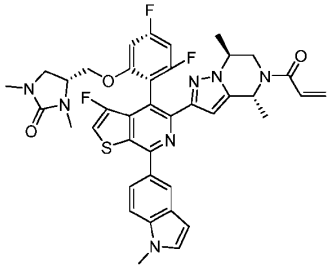
		– 2.56 (m, 1H), 2.52 (s, 3H), 1.59 – 1.50 (m, 3H), 1.19 – 1.14 (m, 3H)
842		LCMS m/z [M+1]: 712.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.39 (d, J = 8.7 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.64 (s, 1H), 6.94 - 6.79 (m, 2H), 6.72 (t, J = 8.9 Hz, 1H), 6.50 - 6.27 (m, 2H), 5.85 (d, J = 10.6 Hz, 1H), 5.80 - 5.47 (m, 1H), 5.28 - 5.14 (m, 1H), 4.41 - 4.30 (m, 1H), 4.09 (s, 3H), 3.93 - 3.77 (m, 1H), 3.68 - 3.54 (m, 1H), 3.18 - 3.03 (m, 1H), 2.94 (s, 3H), 2.87 - 2.68 (m, 2H), 2.61 - 2.44 (m, 2H), 2.34 - 2.16 (m, 1H), 1.59 - 1.41 (m, 3H), 1.28 - 1.13 (m, 3H).
843		LCMS m/z [M+1]: 710.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.26 (dd, J = 8.6, 1.3 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 6.93 – 6.85 (m, 2H), 6.70 (td, J = 9.2, 2.2 Hz, 1H), 6.34 (d, J = 16.6 Hz, 1H), 6.26 (s, 1H), 5.86 (dd, J = 10.6, 1.6 Hz, 1H), 5.76 – 5.54 (m, 1H), 4.44 (s, 1H), 4.33 – 4.22 (m, 2H), 4.12 (s, 3H), 2.96 (s, 3H), 2.60 – 2.57 (m, 5H), 2.48 (s, 3H), 1.51 – 1.42 (m, 3H), 1.29 (d, J = 6.4 Hz, 3H).
844		LCMS m/z [M+1]: 613.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (s, 1H), 8.35 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 8.84 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 6.96 (d, J = 9.4 Hz, 1H), 6.91 – 6.80 (m, 2H), 6.32 (d, J = 16.2 Hz, 1H), 6.08 (s, 1H), 5.88 – 5.80 (m, 1H), 5.78 – 5.44 (m, 1H), 4.49 – 4.39 (m, 1H), 4.30 (s, 3H), 2.06 (s, 3H), 1.52 – 1.38 (m, 3H), 1.36 – 1.21 (m, 3H).

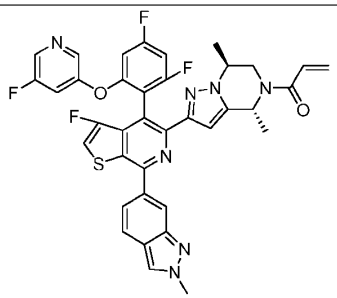
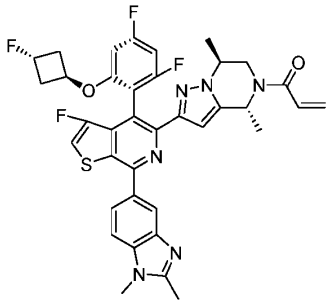
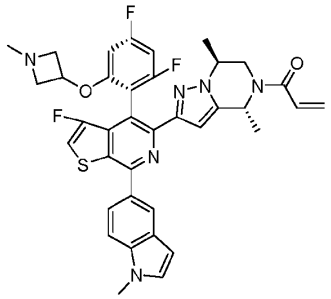
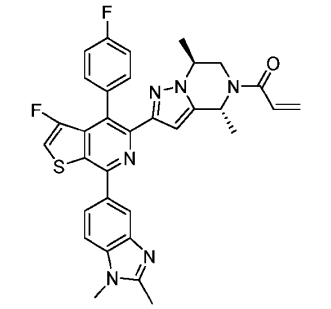
845		LCMS m/z [M+1]: 740.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.43 (d, J = 8.7 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 6.96 – 6.80 (m, 2H), 6.64 (t, J = 9.3 Hz, 1H), 6.40 – 6.27 (m, 2H), 5.86 (d, J = 10.7 Hz, 1H), 5.79 – 5.58 (m, 1H), 4.45 – 4.34 (m, 2H), 4.25 – 4.15 (m, 2H), 4.12 (s, 3H), 3.95 – 3.83 (m, 1H), 3.47 – 3.38 (m, 2H), 2.96 (s, 3H), 2.89 (t, J = 7.0 Hz, 2H), 2.09 – 1.91 (m, 2H), 1.68 – 1.55 (m, 2H), 1.53 – 1.40 (m, 3H), 1.32 – 1.20 (m, 3H).
846		LCMS m/z [M+1]: 780.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 6.88 - 6.78 (m, 1H), 6.75 (m, 1H), 6.67 - 6.59 (m, 1H), 6.32 - 6.19 (m, 2H), 5.80 (d, J = 10.0 Hz, 1H), 5.52 - 5.40 (m, 1H), 4.19 - 4.03 (m, 2H), 3.99 - 3.92 (m, 1H), 3.91 - 3.83 (m, 4H), 2.93 - 2.84 (m, 1H), 2.80 - 2.71 (m, 2H), 2.66 (s, 3H), 2.63 - 2.52 (m, 1H), 2.49 - 2.37 (m, 1H), 1.56 - 1.47 (m, 3H), 1.18 (d, J = 6.9 Hz, 3H).
847		LCMS m/z [M+1]: 719.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (d, J = 1.3 Hz, 1H), 8.42 (dd, J = 8.6, 1.5 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.86 (s, 1H), 6.66 (d, J = 9.8 Hz, 2H), 6.33 (d, J = 16.2 Hz, 1H), 6.22 (s, 1H), 5.85 (d, J = 11.6 Hz, 1H), 5.75 – 5.46 (m, 1H), 4.72 (s, 2H), 4.39 (s, 1H), 4.09 (s, 3H), 3.48 (s, 1H), 3.01 (dd, J = 13.8, 7.2 Hz, 2H), 2.94 (s, 3H), 2.46 (d, J = 14.9 Hz, 1H), 2.26 (d, J = 14.8 Hz, 1H), 1.45 (s, 3H), 1.28 (d, J = 7.3 Hz, 3H).

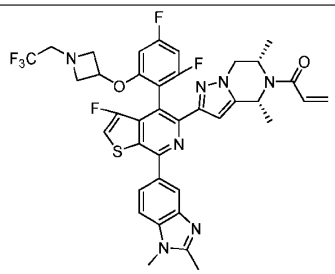
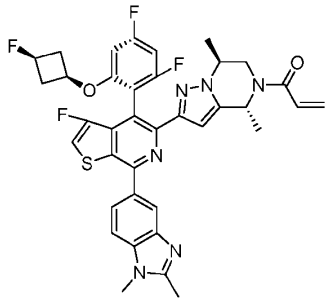
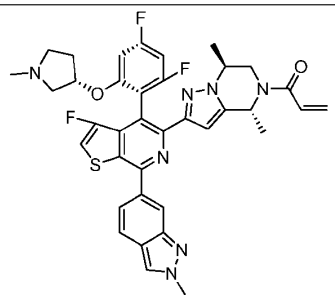
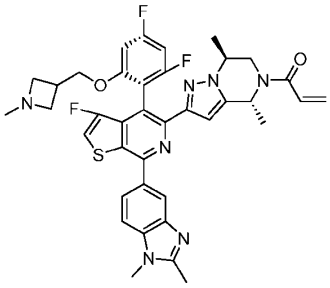
848		LCMS m/z [M+1]: 712.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.14 – 8.03 (m, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 10.7 Hz, 1H), 6.87 (s, 1H), 6.67 (t, J = 9.3 Hz, 1H), 6.40 -6.19 (m, 2H), 5.84 (d, J = 10.7 Hz, 1H), 5.75 – 5.46 (m, 1H), 5.34 (t, J = 4.8 Hz, 1H), 4.55 (s, 1H), 3.88 (s, 3H), 3.09 (dd, J = 10.0, 4.3 Hz, 1H), 2.67 (s, 3H), 2.38 – 2.29 (m, 1H), 2.19 (t, J = 7.6 Hz, 2H), 2.03 (d, J = 5.7 Hz, 3H), 1.60 (s, 3H), 1.46 (s, 3H).
849		LCMS m/z [M+1]: 780.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.43 - 8.37 (dd, J = 8.6 Hz, 1.4 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.61 (t, J = 2.6 Hz, 1H), 6.88 - 6.78 (m, 1H), 6.76 - 6.60 (m, 2H), 6.32 - 6.18 (m, 2H), 5.81 (d, J = 10.1 Hz, 1H), 5.53 - 5.43 (m, 1H), 4.22 - 4.13 (m, 1H), 4.12 - 4.05 (m, 4H), 3.18 - 3.04 (m, 1H), 3.03 - 2.84 (m, 5H), 2.80 - 2.70 (m, 1H), 2.70 - 2.50 (m, 2H), 2.22 - 2.04 (m, 1H), 1.83 - 1.63 (m, 1H), 1.57 - 1.46 (m, 3H), 1.23 - 1.17 (m, 3H).
850		LCMS m/z [M+1]: 699.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.51 (s, 1H), 6.92 - 6.80 (m, 1H), 6.60 - 6.50 (m, 2H), 6.40 - 6.10 (m, 2H), 5.86 - 5.50 (m, 2H), 4.75 - 4.50 (m, 1H), 4.45 - 4.35 (m, 1H), 4.30 - 4.20 (m, 1H), 3.90 - 3.80 (m, 5H), 2.85 - 2.70 (m, 2H), 2.66 (s, 3H), 2.90 - 2.65 (m, 2H), 1.55 - 1.35 (m, 3H), 1.35 – 1.20 (m, 3H)

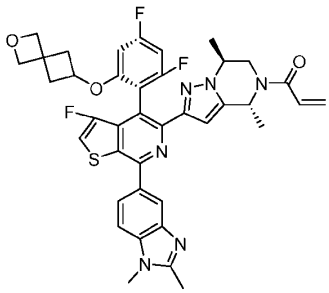
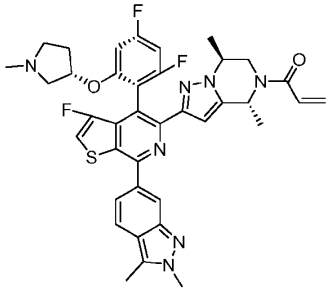
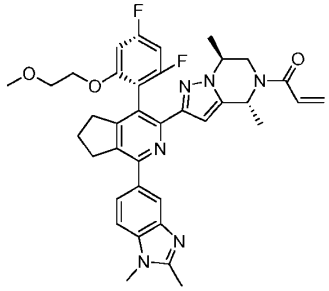
851		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.2 Hz, 1H), 6.94 – 6.81 (m, 1H), 6.58 (t, J = 8.4 Hz, 1H), 6.48 (d, J = 10.8 Hz, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.25 – 6.13 (m, 1H), 5.84 (d, J = 10.8 Hz, 1H), 5.78 – 5.44 (m, 1H), 4.80 – 4.70 (m, 2H), 4.56 (s, 1H), 4.45 – 4.35 (m , 1H), 4.21 – 4.12 (m, 1H), 3.88 (s, 3H), 2.67 (s, 3H), 2.28 – 2.16 (m, 3H), 2.07-1.99 (m, 1H), 1.52 – 1.38 (m, 3H), 1.34 – 1.20 (m, 3H).
852		LCMS m/z [M+1]: 726.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 – 8.29 (m, 1H), 8.08 (dd, J = 8.3, 1.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.60 – 7.46 (m, 1H), 7.12 – 6.98 (m, 1H), 6.87 (s, 1H), 6.67 (t, J = 9.0 Hz, 1H), 6.26 (dd, J = 47.7, 19.6 Hz, 2H), 5.92 – 5.79 (m, 1H), 5.75 – 5.46 (m, 1H), 4.98 – 4.88 (m, 1H), 4.54 (s, 1H), 4.38 (s, 1H), 3.89 (s, 3H), 3.48 (s, 1H), 3.28 – 3.06 (m, 3H), 2.76 (s, 3H), 2.67 (s, 3H), 2.35 – 2.24 (m, 1H), 1.60 (s, 1H), 1.46 (s, 3H), 1.29 (s, 3H).
853		LCMS m/z [M+1]: 631.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.40 (dd, J = 8.6, 1.5 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 7.00 – 6.82 (m, 3H), 6.46 (s, 1H), 6.32 (d, J = 16.4 Hz, 1H), 5.84 (d, J = 10.54 Hz, 1H), 5.76 – 5.53 (m, 1H), 4.34 – 3.84 (m, 2H), 4.09 (s, 3H), 2.93 (s, 3H), 1.54 – 1.42 (m, 3H), 1.23 (d, J = 5.4 Hz, 3H).

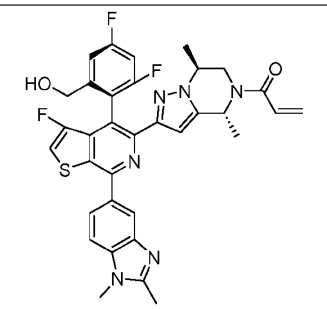
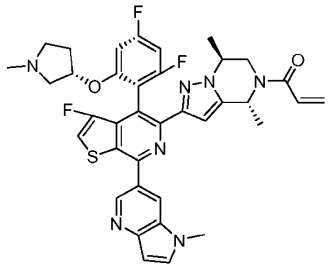
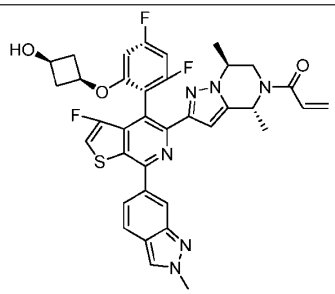
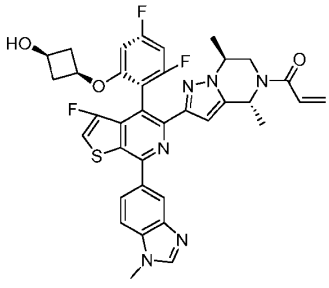
854		LCMS m/z [M+1]: 697.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.63 - 7.60 (m, 2H), 7.32 (s, 1H), 6.95 - 6.80 (m, 2H), 6.80 - 6.70 (m, 1H), 6.62 (d, J = 3.2 Hz, 1H), 6.50 - 6.20 (m, 2H), 5.90 - 5.47 (m, 2H), 5.25 - 5.14 (m, 1H), 4.45 - 4.15 (m, 1H), 3.91 (s, 3H), 3.90 - 3.77 (m, 1H), 3.70 - 3.54 (m, 2H), 3.18 - 3.03 (m, 1H), 2.90 - 2.75 (m, 2H), 2.65 - 2.45 (m, 2H), 2.40 - 1.90 (m, 2H), 1.59 - 1.41 (m, 3H), 1.40 - 1.10 (m, 3H).
855		LCMS m/z [M+1]: 697.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (d, J = 6.4 Hz, 1H), 7.94 (d, J = 6.4 Hz, 1H), 7.63 - 7.60 (m, 2H), 7.32 (d, J = 3.2 Hz, 1H), 6.95 - 6.80 (m, 2H), 6.80 - 6.60 (m, 2H), 6.40 - 6.20 (m, 2H), 5.90 - 5.47 (m, 2H), 4.50 - 4.40 (m, 1H), 4.30 - 4.00 (m, 4H), 4.00 - 3.70 (m, 6H), 3.70 - 3.45 (m, 2H), 3.20 - 3.10 (m, 1H), 2.63 (t, J = 5.6 Hz, 1H), 2.20 - 2.00 (m, 3H), 1.59 - 1.41 (m, 3H), 1.40 - 1.10 (m, 5H).
856		LCMS m/z [M+1]: 700.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.35 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 6.96 – 6.80 (m, 2H), 6.77 – 6.68 (m, 1H), 6.39 – 6.28 (m, 2H), 5.85 (d, J = 11.5 Hz, 1H), 5.79 – 5.44 (m, 1H), 4.46 – 4.17 (m, 3H), 4.06 (s, 3H), 3.51 – 3.33 (m, 2H), 2.90 (s, 3H), 2.61 (s, 6H), 1.58 – 1.39 (m, 3H), 1.30 – 1.14 (m, 3H).
857		LCMS m/z [M+1]: 698.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.37 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.64 (s, 1H), 6.95 – 6.80 (m, 1H), 6.73 (t, J = 8.2 Hz, 1H), 6.64 (d, J = 10.0 Hz, 1H), 6.52 – 6.38 (m, 1H), 6.33 (d, J = 16.4 Hz, 1H), 5.85 (d, J = 10.4 Hz, 1H), 5.85 – 5.45 (m, 1H), 5.25 – 5.05 (m, 1H), 4.45 – 4.32 (m, 1H), 4.28 – 4.13

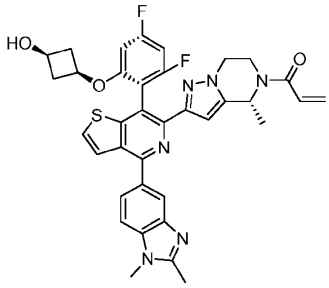
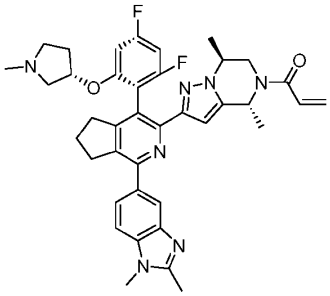
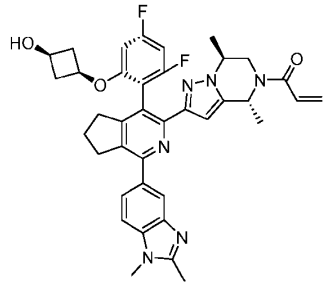
		(m, 1H), 4.07 (s, 3H), 3.92 – 3.75 (m, 1H), 2.95 – 2.70 (m, 6H), 1.58 – 1.40 (m, 3H), 1.25 - 1.10 (m, 3H).
858		LCMS m/z [M+1]: 687.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32(s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.52 (s, 1H), 6.83 (dd, J = 16.4, 10.6 Hz, 1H), 6.75 (d, J = 10.8 Hz, 1H), 6.63(t, J = 9.2 Hz, 1H), 6.40 - 6.16(m, 2H), 5.80 (d, J = 10.6 Hz, 1H), 5.54 - 5.35(m, 1H), 4.21 - 4.01 (m, 3H), 3.98 - 3.90 (m, 1H), 3.88 (s, 3H), 3.46 (t, J = 4.4 Hz, 2H), 3.09 (s, 3H), 2.66 (s, 3H), 1.52 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.0 Hz, 3H)
859		LCMS m/z [M+1]: 751.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 7.95 - 7.92 (m, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 1.6 Hz, 1H), 6.90 - 6.80 (m, 1H), 6.80 - 6.60 (m, 3H), 6.40 - 6.10 (m, 2H), 5.90 - 5.47 (m, 2H), 5.00 - 4.90 (m, 1H), 4.55 - 4.45 (m, 1H), 4.20 - 4.05 (m, 2H), 3.93 (s, 3H), 3.60 - 3.35 (m, 5H), 1.55 - 1.41 (m, 3H), 1.40 - 1.20 (m, 3H).
860		LCMS m/z [M+1]: 740.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 (d, J = 1.2 Hz, 1H), 8.05 – 7.86 (m, 2H), 7.71 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 3.2 Hz, 1H), 6.98 – 6.79 (m, 2H), 6.76 – 6.59 (m, 2H), 6.33 (d, J = 16.4 Hz, 1H), 6.11 (s, 1H), 5.85 (dd, J = 10.4, 1.6Hz, 1H), 5.78 – 5.48 (m, 1H), 4.58 – 4.46 (m, 1H), 4.25 (dd, J =10.0, 2.8Hz, 1H), 3.97 (d, J = 12.0 Hz, 1H), 3.93 (s, 3H), 3.70 – 3.64 (m, 1H), 3.29 – 3.22 (m, 2H), 2.96 – 2.86 (m, 1H), 2.46 (s, 3H), 2.35 (s, 3H), 1.59 –1.37 (m, 3H), 1.36 – 1.24 (m, 3H).

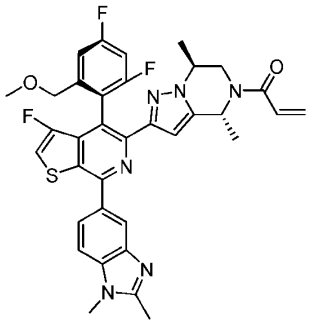
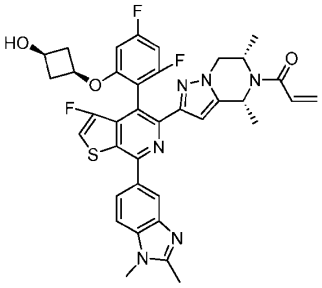
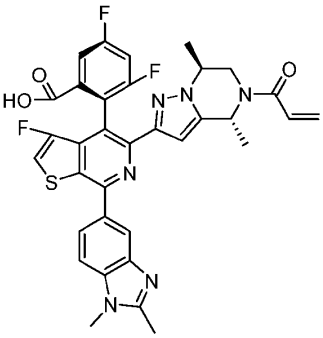
861		LCMS m/z [M+1]: 710.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J = 5.2 Hz, 2H), 8.10 (d, J = 2.4 Hz, 1H), 8.00 – 7.90 (m, 2H), 7.80 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.20 – 7.15 (m, 1H), 6.98 (t, J = 9.1 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.53 (s, 1H), 6.34 (d, J = 16.6 Hz, 1H), 5.85 (d, J = 10.6 Hz, 1H), 5.75 – 5.46 (m, 1H), 4.39 (s, 1H), 4.29 (s, 3H), 3.48 (s, 1H), 3.13 (s, 1H), 1.61 -1.40 (m, 3H), 1.27 (d, J = 13.2 Hz, 3H).
862		LCMS m/z [M+1]: 701.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 6.95 - 6.80 (m, 1H), 6.65 - 6.50 (m, 2H), 6.40 - 6.15 (m, 2H), 5.86 - 5.50 (m, 2H), 5.05 - 5.00 (m, 1H), 4.57 (s, 1H), 4.45 - 4.35 (m, 1H), 3.89 (3H), 2.66 (s, 3H), 2.60 - 2.50 (m, 2H), 2.40 - 2.25 (m, 1H), 2.20 - 2.00 (m, 2H), 1.55 - 1.40 (m, 3H), 1.35 – 1.20 (m, 3H).
863		LCMS m/z [M+1]: 683.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.63 - 7.59 (m, 2H), 7.32 (d, J = 3.2 Hz, 1H), 6.95 - 6.55 (m, 4H), 6.55 - 6.25 (m, 2H), 5.90 - 5.47 (m, 2H), 5.20 - 5.05 (m, 1H), 4.80 - 4.60 (m, 2H), 4.45 - 4.10 (m, 3H), 3.91 (s, 3H), 3.90 - 3.80 (m, 1H), 2.95 - 2.75 (m, 3H), 1.65 - 1.45 (m, 3H), 1.30 - 1.10 (m, 3H).
864		LCMS m/z [M+1]: 595.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.38 (s, 1H), 7.24 (s, 1H), 7.12 (s, 2H), 6.85 (dd, J = 16.3, 10.9 Hz, 1H), 6.32 (d, J = 16.6 Hz, 1H), 5.95 – 5.75 (m, 2H), 5.75 – 5.46 (m, 1H), 4.45 (s, 1H), 3.85 (d, J = 15.5 Hz, 3H), 2.68 (s, 3H), 1.38 (s, 3H), 1.34 – 1.21 (m, 5H), 1.20 (s, 1H).

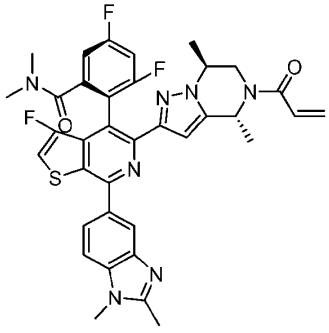
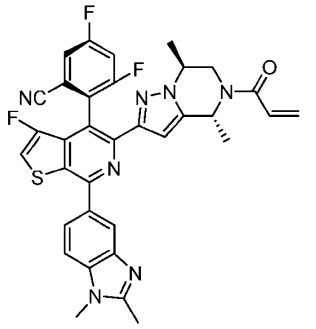
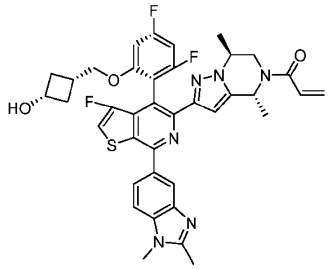
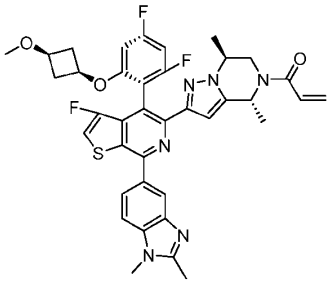
865		LCMS m/z [M+1]: 766.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.43 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.63 (s, 1H), 6.88 - 6.79 (m, 1H), 6.75 - 6.66 (m, 1H), 6.53 (d, J = 10.5 Hz, 1H), 6.33 - 6.16 (m, 2H), 5.82 (d, J = 10.3 Hz, 1H), 5.53 - 5.41 (m, 1H), 4.22 - 4.07 (m, 5H), 3.90 - 3.78 (m, 2H), 3.23 - 2.98 (m, 6H), 2.94 (s, 3H), 1.56 - 1.49 (m, 3H), 1.24 - 1.18 (m, 3H).
866		LCMS m/z [M+1]: 701.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.61(d, J = 2.4 Hz, 1H), 7.01 – 6.77 (m, 1H), 6.72 – 6.55 (m, 2H), 6.33 (d, J = 16.8 Hz, 1H), 6.14 (s, 1H), 5.84 (d, J = 12.0 Hz, 1H), 5.78 – 5.46 (m, 1H), 4.82 – 4.72 (m, 1H), 4.42 (s, 1H), 4.35 – 4.25 (m, 1H), 4.09 (s, 3H), 2.94 (s, 3H), 2.90 – 2.77 (m, 2H), 2.09 – 2.00 (m, 1H), 1.87 – 1.70 (m, 1H), 1.60 –1.40 (m, 3H), 1.39 – 1.21 (m, 3H).
867		LCMS m/z [M+1]: 698.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 – 8.30 (m, 2H), 7.98 – 7.89 (m, 1H), 7.84 (dd, J = 8.8, 1.5 Hz, 1H), 7.66 – 7.56 (m, 1H), 6.87 (d, J = 12.1 Hz, 2H), 6.70 (d, J = 9.1 Hz, 1H), 6.53 – 6.29 (m, 2H), 5.88 – 5.81 (m, 1H), 5.76 (s, 1H), 5.24 (s, 1H), 5.75 – 5.46 (m, 1H), 4.32 - 4.29 (m, 4H), 3.91 – 3.42 (m, 4H), 3.06 (s, 1H), 2.83 (s, 1H), 2.79 – 2.62 (m, 1H), 2.38 (d, J = 79.0 Hz, 3H), 1.49 (s, 3H), 1.20 (s, 3H)
868		LCMS m/z [M+1]: 712.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (s, 1H), 8.33 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.72 - 7.57 (m, 1H), 6.93 - 6.79 (m, 2H), 6.70 (t, J = 8.6 Hz, 1H), 6.33 (d, J = 16.0 Hz, 2H), 5.84 (d, J = 10.4 Hz, 1H), 5.79 - 5.45 (m, 1H), 4.45 - 4.33 (m, 1H), 4.26 - 4.11 (m, 2H), 4.05 (s, 3H), 4.02 - 3.95 (m, 1H), 3.91 - 3.73 (m, 1H),

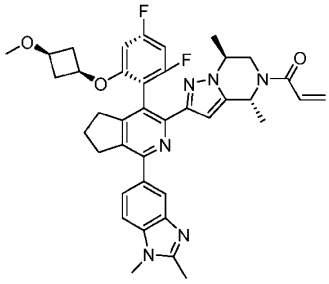
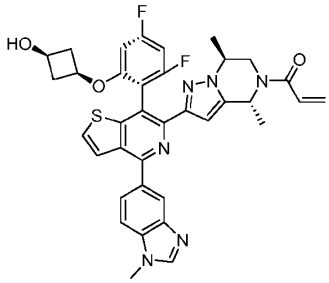
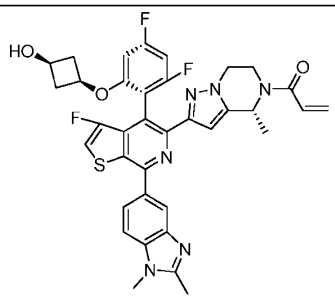
		3.65 - 3.54 (m, 1H), 3.21 - 3.08 (m, 1H), 2.90 (s, 3H), 2.07 (s, 2H), 1.57 - 1.36 (m, 3H), 1.30 - 1.12 (m, 3H).
869		LCMS m/z [M+1]: 725.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.42 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.60 (s, 1H), 6.98 – 6.80 (m, 1H), 6.68 – 6.52 (m, 2H), 6.33 (d, J = 16.4 Hz, 1H), 6.25 – 6.06 (m, 1H), 5.85 (d, J = 10.5 Hz, 1H), 5.79 – 5.36 (m, 1H), 4.78 – 4.53 (m, 2H), 4.50 – 4.35 (m, 3H), 4.32 – 4.14 (m, 1H), 4.10 (s, 3H), 3.94 – 3.77 (m, 1H), 2.94 (s, 3H), 2.78 – 2.23 (m, 2H), 2.12 – 1.67 (m, 2H), 1.55 – 1.12 (m, 6H).
870		LCMS m/z [M+1]: 712.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.89 (d, J = 8.9 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.64 – 7.55 (m, 1H), 6.95 – 6.78 (m, 2H), 6.78 – 6.66 (m, 1H), 6.60 – 6.35 (m, 1H), 6.33 (d, J = 15.8 Hz, 1H), 5.85 (d, J = 10.3 Hz, 1H), 5.81 – 5.48 (m, 1H), 5.25 – 5.14 (m, 1H), 4.42 – 4.28 (m, 1H), 4.18 (s, 3H), 3.93 – 3.78 (m, 1H), 3.65 – 3.55 (m, 1H), 3.55 – 3.40 (m, 1H), 3.20 – 3.02 (m, 1H), 2.82 (s, 1H), 2.73 (s, 3H), 2.64 – 2.42 (m, 2H), 2.38 – 1.95 (m, 1H), 1.61 – 1.39 (m, 3H), 1.28 – 1.08 (m, 3H).
871		LCMS m/z [M+1]: 653.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 0.8 Hz, 1H), 7.83 (dd, J = 8.4, 1.3 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 6.94 – 6.72 (m, 2H), 6.60 – 6.51 (m, 1H), 6.31 (d, J = 16.8 Hz, 1H), 6.20 – 6.10 (m, 1H), 5.87 – 5.79 (m, 1H), 5.75 – 5.45 (m, 1H), 4.75 – 4.64 (m, 0.5H), 4.41 – 4.33 (m, 1H), 4.25 – 4.09 (m, 1.5H), 4.03 – 3.95 (m, 1H), 3.84 (s, 3H), 3.56 (t, J = 4.6 Hz, 2H), 3.25 – 3.18 (m, 4H), 2.97 – 2.86 (m, 1H), 2.75 – 2.60 (m, 4H), 2.17 – 2.04 (m, 2H), 1.52 – 1.38 (m, 3H), 1.32 – 1.19 (m, 3H).

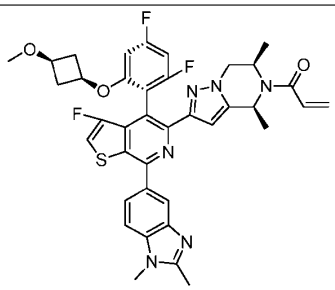
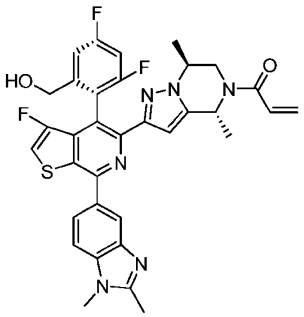
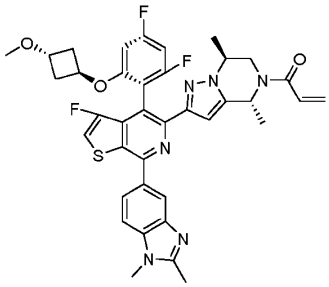
872		LCMS m/z [M+1]: 643.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.08 (d J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 10.4 Hz, 1H), 6.95 - 6.76 (m, 2H), 6.33 - 6.31 (m, 2H), 5.83 (d, J = 10.4 Hz, 1H), 5.57 - 5.55 (m, 1H), 4.58 (s, 2H), 4.34 (s, 1H), 4.21 - 4.12 (m, 3H), 3.89 (s, 3H), 2.68 (s, 3H), 1.47 - 1.43 (m, 3H), 1.25 - 1.19 (m, 3H).
873		LCMS m/z [M+1]: 698.4 ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (s, 1H), 9.22 (s, 1H), 8.15 (d, J = 3.0 Hz, 1H), 7.71 (s, 1H), 7.02 – 6.80 (m, 3H), 6.75 (t, J = 9.0 Hz, 1H), 6.52 – 6.25 (m, 2H), 5.86 (d, J = 10.6 Hz, 1H), 5.81 – 5.45 (m, 1H), 5.29 – 5.13 (m, 1H), 4.48 – 4.26 (m, 1H), 4.15 (s, 3H), 3.98 – 3.79 (m, 1H), 3.70 – 3.48 (m, 1H), 3.18 – 3.00 (m, 1H), 2.96 – 2.63 (m, 2H), 2.67 – 2.43 (m, 2H), 2.32-2.16 (m, 1H), 1.62-1.39 (m, 3H), 1.31-1.15 (m, 3H).
874		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (d, J = 1.3 Hz, 1H), 8.36 (s, 1H), 7.97 (dd, J = 8.7, 0.9 Hz, 1H), 7.83 (dd, J = 8.7, 1.5 Hz, 1H), 7.74 (s, 1H), 6.86 (s, 1H), 6.61 (dd, J = 9.4, 6.7 Hz, 2H), 6.33 (d, J = 16.6 Hz, 1H), 6.15 (s, 1H), 5.84 (dd, J = 10.6, 1.9 Hz, 1H), 5.78 – 5.46 (m, 1H), 4.71 (s, 1H), 4.45 (d, J = 4.7 Hz, 1H), 4.33 - 4.29 (m, 4H), 3.89 (p, J = 7.3 Hz, 2H), 2.76 (ddt, J = 18.0, 12.1, 6.1 Hz, 2H), 1.82 (dt, J = 11.4, 7.5 Hz, 1H), 1.68 (q, J = 8.9, 8.4 Hz, 1H), 1.43 (s, 3H), 1.31 (s, 3H).
875		LCMS m/z [M+1]: 685.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (s, 1H), 8.29 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 6.87 (s, 1H), 6.60 – 6.52 (m, 2H), 6.32 (d, J = 16.5 Hz, 1H), 6.18 (s, 1H), 5.84 (dd, J = 10.7, 1.4 Hz, 1H), 5.75 – 5.46 (m, 1H), 4.44 – 4.36 (m, 1H), 4.32 – 4.17 (m, 2H), 4.01 (s, 3H), 3.92 –

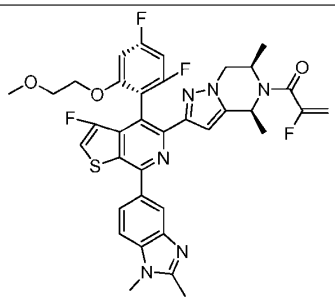
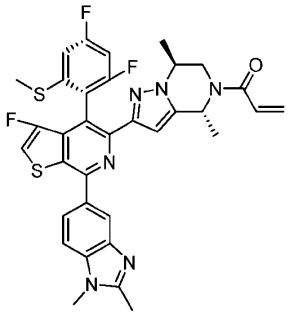
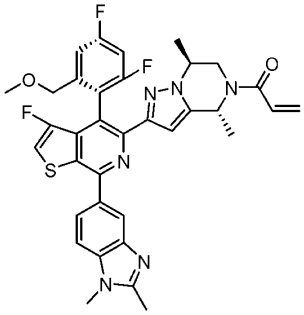
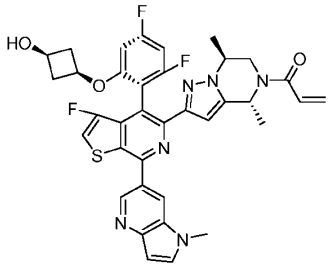
		3.80 (m, 2H), 2.81 – 2.70 (m, 2H), 1.87 – 1.78 (m, 1H), 1.73 – 1.66 (m, 1H), 1.54 – 1.41 (m, 3H), 1.30 – 1.24 (m, 3H).
876		LCMS m/z [M+1]: 667.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.25 (dd, J = 8.6, 1.3 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.84 (dd, J = 16.7, 10.6 Hz, 1H), 6.76 – 6.70 (m, 1H), 6.67 (d, J = 10.7 Hz, 1H), 6.28 (d, J = 17.0 Hz, 1H), 6.07 (s, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.75 – 5.49 (m, 1H), 4.51 – 4.34 (m, 1H), 4.31 – 4.13 (m, 3H), 4.10 (s, 3H), 3.92 – 3.82 (m, 1H), 3.81 – 3.66 (m, 1H), 2.94 (s, 3H), 2.77 – 2.63 (m, 2H), 1.86 – 1.75 (m, 1H), 1.50 – 1.39 (m, 3H).
877		LCMS m/z [M+1]: 678.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (s, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 6.93 – 6.75 (m, 2H), 6.69 – 6.59 (m, 1H), 6.38 – 6.22 (m, 2H), 5.84 (d, J = 10.2 Hz, 1H), 5.78 – 5.47 (m, 1H), 5.12 – 5.04 (m, 1H), 4.37 – 4.09 (m, 2H), 3.85 (s, 3H), 3.24 (t, J = 7.2 Hz, 2H), 3.17 – 3.09 (m, 1H), 3.06 – 2.97 (m, 1H), 2.96 – 2.71 (m, 3H), 2.65 (s, 3H), 2.51 (s, 3H), 2.34 – 2.23 (m, 1H), 2.17 – 1.99 (m, 3H), 1.54 – 1.40 (m, 3H), 1.24 – 1.13 (m, 3H).
878		LCMS m/z [M+1]: 665.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 – 8.06 (m, 1H), 7.94 – 7.88 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 6.94 – 6.79 (m, 1H), 6.61 – 6.48 (m, 2H), 6.31 (d, J = 16.2 Hz, 1H), 6.18 – 6.08 (m, 1H), 5.83 (dd, J = 10.5, 1.2 Hz, 1H), 5.75 – 5.43 (m, 1H), 4.74 – 4.63 (m, 0.5H), 4.41 – 4.32 (m, 1H), 4.31 – 4.15 (m, 1.5H), 3.96 – 3.78 (m, 4H), 3.28 – 3.16 (m, 2H), 2.90 – 2.73 (m, 3H), 2.69 (s, 3H), 2.20 – 2.05 (m, 2H), 1.93 – 1.83 (m, 1H), 1.82

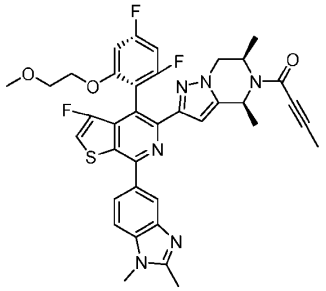
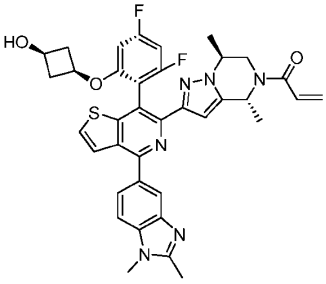
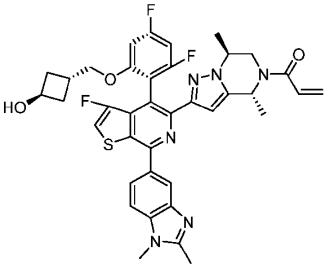
		– 1.72 (m, 1H), 1.52 – 1.37 (m, 3H), 1.33 – 1.20 (m, 3H).
879		LCMS m/z [M+1]: 657.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.42 (d J = 8.8 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.09 - 6.75 (m, 3H), 6.34 - 6.18 (m, 2H), 5.83 (d, J = 12.4 Hz, 1H), 5.73 - 5.46 (m, 1H), 4.75 - 4.60 (m, 1H), 4.38 (s, 2H), 4.09 (s, 3H), 4.02 (dd, J = 13.6, 13.2 Hz, 2H), 3.82 - 3.75 (m, 1H), 3.06 (s, 3H), 2.94 (s, 3H), 1.45 - 1.41 (m, 3H), 1.22 (d, J = 6.8 Hz, 3H).
880		LCMS m/z [M+1]: 699.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.41 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.61 (t, J = 2.0 Hz, 1H), 7.90 - 7.80 (m, 1H), 7.70 - 7.55 (m, 2H), 6.35 - 6.05 (m, 2H), 5.82 (d, J = 10.4 Hz, 1H), 5.70 - 5.40 (m, 1H), 4.40 - 4.21 (m, 3H), 4.20 (s, 3H), 3.95 - 3.85 (m, 1H), 2.92 (s, 3H), 2.80 - 2.70 (m, 2H), 1.85 - 1.75 (m, 1H), 1.60 - 1.45 (m, 4H), 1.30 - 1.20 (m, 3H).
881		LCMS m/z [M+1]: 657.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.39 (dd, J = 8.6, 1.3 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H), 7.30 (dd, J = 8.9, 2.6 Hz, 1H), 6.88 – 6.81 (m, 1H), 6.33 – 6.29 (m, 2H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.72 – 5.48 (m, 1H), 4.29 – 4.18 (m, 2H), 4.08 (s, 3H), 2.92 (s, 3H), 1.52 – 1.42 (m, 3H), 1.20 (d, J = 6.4 Hz, 3H).

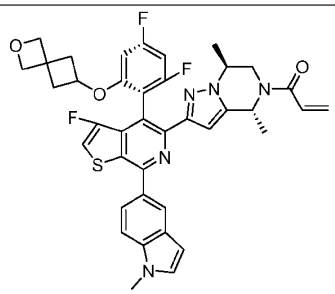
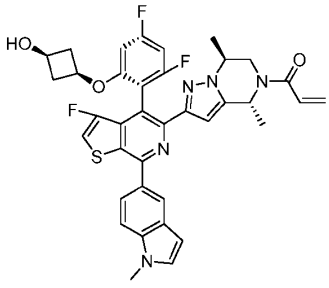
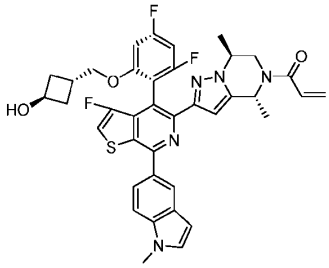
882		LCMS m/z [M+1]: 684.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.38 (dd, J = 8.6, 1.2 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.23 (td, J = 9.0, 2.3 Hz, 1H), 7.03 (dd, J = 7.2, 1.4 Hz, 1H), 6.88 – 6.81 (m, 1H), 6.45 (s, 1H), 6.32 (d, J = 16.4 Hz, 1H), 5.84 (d, J = 10.7 Hz, 1H), 5.76 – 5.55 (m, 1H), 4.39 – 3.82 (m, 2H), 4.08 (s, 3H), 2.92 (s, 3H), 2.69 (s, 3H), 2.41 (s, 3H), 1.49 – 1.42 (m, 3H), 1.17 (d, J = 6.3 Hz, 3H)
883		LCMS m/z [M+1]: 638.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.43 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.60 - 7.50 (m, 2H), 6.95 - 6.80 (m, 1H), 6.71 (s, 1H), 6.35 - 6.30 (m, 1H), 5.90 - 5.50 (m, 2H), 4.30 - 4.20 (m, 1H), 4.09 (s, 3H), 2.94 (s, 3H), 1.60 - 1.45 (m, 3H), 1.25 - 1.10 (m, 3H).
884		LCMS m/z [M+1]: 713.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J= 4.8 Hz, 1H), 8.10 – 8.03 (m, 1H), 7.70 – 7.65 (m, 1H), 7.50 (d, J = 2.4Hz, 1H), 6.94 – 6.81 (m, 1H), 6.73 (d, J = 10.8 Hz, 1H), 6.62 – 6.51 (m, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.23 – 6.12 (m, 1H), 5.84 (d, J =11.6 Hz, 1H), 5.78 – 5.53 (m, 1H), 4.60 (s, 1H), 4.45 – 4.38 (m, 1H), 4.00 – 3.75 (m, 7H), 2.67 (s, 3H), 2.11 – 1.91 (m, 3H), 1.55 – 1.37 (m, 5H), 1.34 –1.21 (m, 4H).
885		LCMS m/z [M+1]: 713.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 0.9 Hz, 1H), 8.42 (dd, J = 8.7, 1.3 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 6.93 - 6.81 (m, 1H), 6.66 - 6.57 (m, 2H), 6.33 (d, J = 16.2 Hz, 1H), 6.10 (s, 1H), 5.85 (dd, J = 10.6, 1.6 Hz, 1H), 5.77 - 5.44 (m, 1H), 4.43 (s, 1H), 4.37 - 4.29 (m, 1H), 4.09 (s, 3H), 3.61 - 3.52 (m,

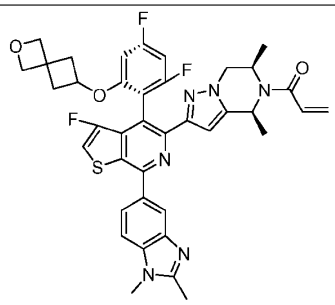
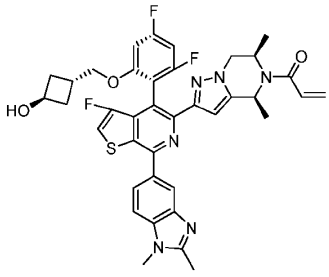
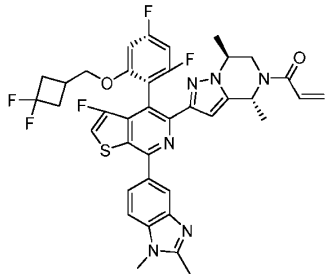
		1H), 3.14 (s, 3H), 2.94 (s, 3H), 2.80 - 2.70 (m, 2H), 1.80 - 1.70 (m, 1H), 1.58 - 1.39 (m, 4H), 1.37 - 1.26 (m, 3H).
886		LCMS m/z [M+1]: 679.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 6.86 (dd, J = 16.4, 10.5 Hz, 1H), 6.73 - 6.59 (m, 2H), 6.33 (d, J = 16.6 Hz, 1H), 6.01 (s, 1H), 5.85 (dd, J = 10.6, 1.5 Hz, 1H), 5.74 - 5.43 (m, 1H), 4.53 - 4.43 (m, 1H), 4.38 - 4.29 (m, 1H), 4.06 (s, 3H), 3.65 - 3.54 (m, 1H), 3.28 - 3.21 (m, 2H), 3.16 (s, 3H), 2.96 - 2.87 (m, 5H), 2.84 - 2.73 (m, 2H), 2.26 - 2.14 (m, 2H), 1.84 - 1.74 (m, 1H), 1.61 - 1.51 (m, 1H), 1.50 - 1.38 (m, 3H), 1.38 - 1.24 (m, 3H).
887		LCMS m/z [M+1]: 667.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.30 (s, 1H), 8.43 (s, 1H), 8.28 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.89 - 7.80 (m, 1H), 7.72 (d, J = 5.6 Hz, 1H), 6.95 - 6.78 (m, 1H), 6.74 - 6.55 (m, 2H), 6.32 (d, J = 16.8 Hz, 1H), 6.23 - 6.12 (m, 1H), 5.84 (d, J = 10.8 Hz, 1H), 5.79 - 5.46 (m, 1H), 4.49 - 4.36 (m, 1H), 4.35 - 4.26 (m, 1H), 4.21 (s, 3H), 3.96 - 3.80 (m, 1H), 2.84 - 2.59 (m, 2H), 1.87 - 1.74 (m, 1H), 1.72 - 1.60 (m, 1H), 1.55 - 1.37 (m, 3H), 1.35 - 1.22 (m, 3H).
888		LCMS m/z [M+1]: 685.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (d, J = 0.8 Hz, 1H), 8.43 (dd, J = 8.8, 1.6 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 6.90 – 6.79 (m, 1H), 6.65 (td, J = 9.2, 2.0 Hz, 1H), 6.58 (d, J = 10.8 Hz, 1H), 6.36 – 6.22 (m, 1H), 5.98 (s, 1H), 5.82 (d, J = 10.4 Hz, 1H), 5.73 –5.49 (m, 1H), 4.28 – 4.18 (m, 2H), 4.09 (s, 3H), 3.87 (dt, J = 14.4, 7.2Hz, 1H), 3.37 – 3.32 (m, 1H), 2.94 (s, 3H), 2.77 – 2.65 (m, 2H), 1.86 – 1.76(m, 1H), 1.53 – 1.34 (m, 3H)

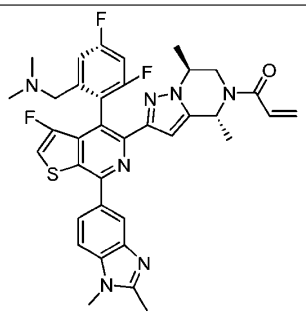
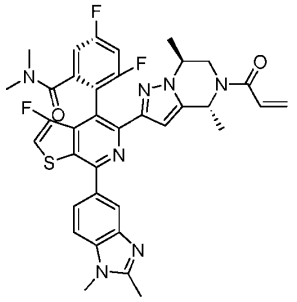
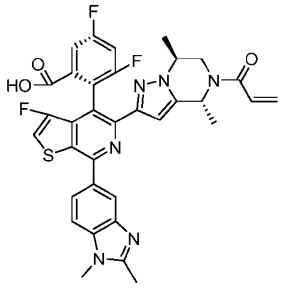
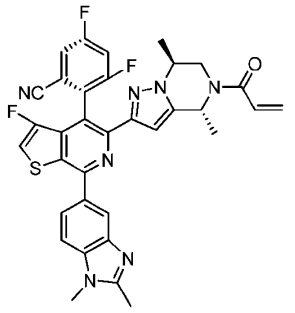
889		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.09 (dd, J = 8.6, 1.2 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.53 (d, J = 2.3 Hz, 1H), 6.84 (dd, J = 16.5, 10.7 Hz, 1H), 6.68 – 6.58 (m, 1H), 6.51 (d, J = 11.0 Hz, 1H), 6.32 – 6.20 (m, 2H), 5.85 – 5.75 (m, 1H), 5.57 – 5.44 (m, 1H), 4.30 – 4.21 (m, 1H), 4.17 – 4.05 (m, 2H), 3.88 (s, 3H), 3.59 – 3.49 (m, 1H), 3.18 – 3.08 (m, 4H), 2.75 – 2.61 (m, 5H), 1.83 – 1.73 (m, 1H), 1.55 (d, J = 6.5 Hz, 3H), 1.45 – 1.34 (m, 1H), 1.23 (d, J = 6.7 Hz, 3H).
890		LCMS m/z [M+1]: 643.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.41 (dd, J = 8.6, 1.2 Hz, 1H), 8.09 (dd, J = 8.5, 1.8 Hz, 1H), 7.63 (s, 1H), 7.23 (d, J = 9.4 Hz, 1H), 6.94 – 6.82 (m, 2H), 6.32 (d, J = 16.4 Hz, 1H), 6.19 (s, 1H), 5.84 (d, J = 10.8 Hz, 1H), 5.71 – 5.49 (m, 1H), 4.39 – 4.21 (m, 4H), 4.09 (s, 3H), 2.94 (s, 3H), 1.50 – 1.40 (m, 3H), 1.25 – 1.20 (m, 3H).
891		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.08 (dd, J = 8.4, 1.5 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 6.95 – 6.81 (m, 1H), 6.59 (t, J = 8.4 Hz, 1H), 6.50 (d, J = 10.7 Hz, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.18 (s, 1H), 5.84 (d, J = 11.5 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.81 – 4.73 (m, 1H), 4.42-4.35 (m, 1H), 3.90 – 3.78 (m, 5H), 3.15 (s, 3H), 2.67 (s, 3H), 2.35 – 2.25 (m, 2H), 2.23 – 2.11 (m, 2H), 2.08 – 1.91 (m, 2H), 1.51 – 1.36 (m, 3H), 1.35 – 1.25 (m, 3H).

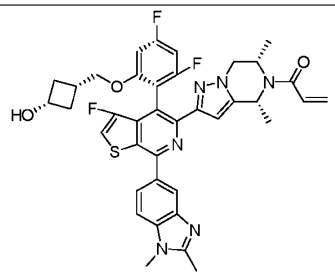
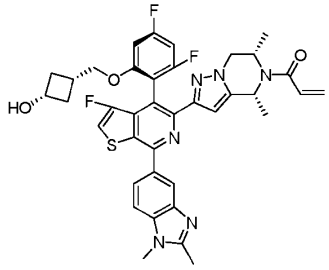
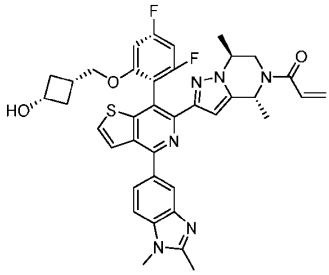
892		LCMS m/z [M+1]: 705.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.40 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 6.79 (d, J = 10.8 Hz, 1H), 6.65 (t, J = 8.4 Hz, 1H), 6.19 (s, 1H), 5.50 - 5.40 (m, 1H), 5.40 - 5.20 (m, 2H), 4.30 - 4.10 (m, 2H), 4.09 (s, 3H), 4.08 - 3.90 (m, 2H), 3.45 (t, J = 5.2 Hz, 2H), 3.09 (s, 3H), 2.94 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 7.2 Hz, 3H).
893		LCMS m/z [M+1]: 659.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 – 8.26 (m, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.48 (s, 1H), 6.97 (d, J = 9.2 Hz, 1H), 6.91 – 6.74 (m, 2H), 6.31 (d, J = 16.6 Hz, 1H), 6.24 – 6.14 (m, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.76 – 5.42 (m, 1H), 4.74 – 4.62 (m, 0.5H), 4.44 – 4.32 (m, 1H), 4.24 – 4.14 (m, 0.5H), 3.84 (s, 3H), 2.66 (s, 3H), 2.36 (s, 3H), 1.48 – 1.36 (m, 3H), 1.32 – 1.22 (m, 3H).
894		LCMS m/z [M+1]: 657.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.42 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.09 - 6.81 (m, 3H), 6.34 - 6.30 (m, 2H), 5.83 (d, J = 12.4 Hz, 1H), 5.73 - 5.50 (m, 1H), 4.75 - 4.60 (m, 1H), 4.38 (s,2H), 4.09 (s, 3H), 4.02 (dd, J = 13.6, 13.2 Hz, 2H), 3.82 - 3.75 (m, 1H), 3.13 (s, 3H), 2.94 (s, 3H), 1.45 - 1.41 (m, 3H), 1.22 (d, J = 6.8 Hz, 3H).
895		LCMS m/z [M+1]: 685.2 ^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (d, J = 1.7 Hz, 1H), 8.68 (s, 1H), 7.72 (d, J = 3.2 Hz, 1H), 7.58 (d, J = 2.3 Hz, 1H), 6.94 – 6.78 (m, 1H), 6.72 (d, J = 2.6 Hz, 1H), 6.60 (d, J = 10.7 Hz, 2H), 6.33 (d, J = 16.3 Hz, 1H), 6.19 – 6.06 (m, 1H), 5.84 (d, J = 11.5 Hz, 1H), 5.75 – 5.41 (m, 1H), 4.49 – 4.36 (m, 1H), 4.31 – 4.14 (m, 1H), 4.00 (s, 3H), 3.92 – 3.76 (m, 1H), 2.85 – 2.69 (m, 2H), 1.86

		– 1.73 (m, 1H), 1.73 – 1.59 (m, 1H), 1.54 – 1.39 (m, 3H), 1.37 – 1.20 (m, 3H).
896		LCMS m/z [M+1]: 699.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.41 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.81 - 6.63 (m, 2H), 6.35 - 6.20 (m, 1H), 6.20 - 6.10 (m, 1H), 5.50 - 5.40 (m, 1H), 5.28 (d, J = 6.4 Hz, 2H), 4.25 - 4.00 (m, 6H), 4.00 - 3.90 (m, 1H), 3.46 (t, J = 4.8 Hz, 2H), 3.09 (s, 3H), 2.94 (s, 3H), 1.55 - 1.40 (m, 3H), 1.21 (d, J = 6.8 Hz, 3H).
897		LCMS m/z [M+1]: 681.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 – 8.34 (m, 1H), 8.25 (dd, J = 8.6, 1.3 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.85 (dd, J = 5.6, 2.9 Hz, 1H), 7.71 (d, J = 5.6 Hz, 1H), 6.92 – 6.81 (m, 1H), 6.78 – 6.55 (m, 2H), 6.33 (d, J = 16.7 Hz, 1H), 6.26 – 6.06 (m, 1H), 5.84 (d, J = 10.7 Hz, 1H), 5.79 – 5.45 (m, 1H), 4.50 – 4.39 (m, 1H), 4.36 – 4.18 (m, 1H), 4.18 – 4.06 (m, 3H), 3.97 – 3.82 (m, 1H), 2.94 (s, 3H), 2.85 – 2.66 (m, 2H), 1.87 – 1.74 (m, 1H), 1.71 – 1.59 (m, 1H), 1.54 – 1.38 (m, 3H), 1.36 – 1.21 (m, 3H).
898		LCMS m/z [M+1]: 713.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.42 – 8.40 (m, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.90 – 6.78 (m, 2H), 6.66 – 6.58 (m, 1H), 6.35 – 6.31 (m, 1H), 6.11 (s, 1H), 5.84 (dd, J = 10.8, 1.6 Hz, 1H), 5.73 – 5.51 (m, 1H), 4.75 – 4.74 (m, 1H), 4.44 (s, 1H), 4.09 (s, 3H), 3.94 – 3.89 (m, 2H), 3.69 – 3.65 (m, 1H), 2.94 (s, 3H), 2.38 – 2.34 (m, 1H), 1.88 – 1.79 (m, 4H), 1.48 – 1.36 (m, 3H), 1.32 – 1.22 (m, 3H)

899		LCMS m/z [M+1]: 710.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 – 8.36 (m, 1H), 7.99 (s, 1H), 7.92 (dd, J = 8.5, 1.2 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 2.9 Hz, 1H), 6.94 – 6.81 (m, 1H), 6.74 – 6.60 (m, 3H), 6.34 (d, J = 16.4 Hz, 1H), 6.02 (s, 1H), 5.86 (dd, J = 10.6, 1.0 Hz, 1H), 5.78 – 5.47 (m, 1H), 4.79 – 4.63 (m, 2H), 4.61 – 4.50 (m, 2H), 4.49 – 4.40 (m, 2H), 4.32 – 4.22 (m, 0.5H), 3.98 – 3.82 (m, 3.5H), 2.75 – 2.63 (m, 2H), 2.13 – 1.90 (m, 2H), 1.52 – 1.26 (m, 6H).
900		LCMS m/z [M+1]: 684.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (d, J = 1.4 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.70 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 3.1 Hz, 1H), 6.94 – 6.80 (m, 1H), 6.72 – 6.62 (m, 3H), 6.33 (d, J = 16.5 Hz, 1H), 6.10 – 6.02 (m, 1H), 5.85 (dd, J = 10.5, 1.6 Hz, 1H), 5.78 – 5.46 (m, 1H), 4.57 – 4.48 (m, 1H), 4.34 – 4.22 (m, 1H), 3.97 – 3.81 (m, 4H), 2.84 – 2.70 (m, 2H), 1.86 – 1.76 (m, 1H), 1.71 – 1.62 (m, 1H), 1.54 – 1.28 (m, 6H).
901		LCMS m/z [M+1]: 698.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 - 8.35 (m, 1H), 7.98 - 7.94 (m, 1H), 7.92 (dd, J = 8.5, 1.7 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 3.1 Hz, 1H), 6.92 - 6.80 (m, 2H), 6.73 - 6.65 (m, 2H), 6.37 - 6.29 (m, 1H), 6.02 (s, 1H), 5.84 (dd, J = 10.5, 1.7 Hz, 1H), 5.78 - 5.44 (m, 1H), 4.60 - 4.50 (m, 1H), 4.01 - 3.70 (m, 7H), 2.43 - 2.30 (m, 1H), 1.94 - 1.77 (m, 4H), 1.52 - 1.24 (m, 7H).

902		LCMS m/z [M+1]: 725.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34(s, 1H), 8.08 (dd, J = 8.4, 1.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 16.7, 10.7 Hz, 1H), 6.68 - 6.58(m, 1H), 6.52 (d, J = 11.1 Hz, 1H), 6.35 - 6.10 (m, 2H), 5.81 (d, J = 9.8 Hz, 1H), 5.55 - 5.40 (m, 1H), 4.67 - 4.60(m, 2H), 4.53 - 4.37 (m, 3H), 4.21 - 4.05(m, 2H), 3.88 (s, 3H), 2.70 - 2.59(m, 5H), 2.13 - 2.04 (m, 1H), 1.89 - 1.80(m, 1H), 1.52 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H)
903		LCMS m/z [M+1]: 713.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.41 (dd, J = 8.6 Hz, 1.4 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 6.89 – 6.74 (m, 2H), 6.71 – 6.62 (m, 1H), 6.40 – 6.38 (m, 1H), 6.09 (s, 1H), 5.81 (d, J = 10.6 Hz, 1H), 5.52 – 5.40 (m, 1H), 4.24 – 4.11 (m, 2H), 4.09 (s, 3H), 3.96 – 3.88 (m, 1H), 3.86 – 3.79 (m, 1H), 3.74 – 3.65 (m, 1H), 2.93 (s, 3H), 2.41 – 2.28 (m, 1H), 1.94 – 1.76 (m, 4H), 1.50 (d, J = 6.4 Hz, 3H), 1.20 (d, J = 6.7 Hz, 3H).
904		LCMS m/z [M+1]: 733.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (s, 1H), 8.46 – 8.37 (m, 1H), 8.09(d, J = 8.4 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.93 – 6.78 (m, 2H), 6.66 – 6.61 (m, 1H), 6.35 – 6.31 (m, 1H), 6.16 (s, 1H), 5.84 (dd, J = 10.4, 1.6 Hz, 1H), 5.81 – 5.42 (m, 1H), 4.84 – 4.72 (m, 1H), 4.42 (s, 1H), 4.09 (s, 3H), 4.08 – 3.92 (m, 2H), 3.89 – 3.44 (m, 1H), 2.94 (s, 3H), 2.39 – 2.28 (m, 3H), 2.19 – 1.98 (m, 2H), 1.48 – 1.36 (m, 3H), 1.32 – 1.22 (m, 3H).

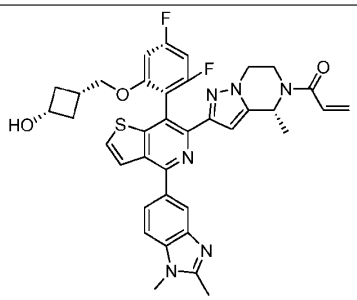
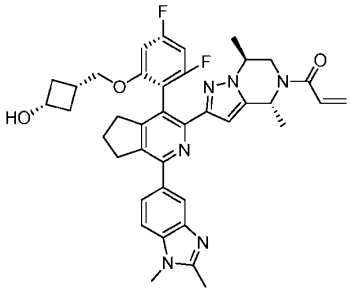
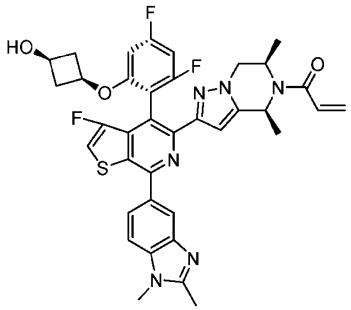
905		LCMS m/z [M+1]: 670.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.41 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.22 - 7.18 (m, 1H), 6.91-6.75 (m, 1H), 6.67 (s, 1H), 6.33 (d, J = 16.8 Hz, 1H), 5.86 - 5.51 (m, 2H), 4.79 - 4.70 (m, 3H), 4.32 - 4.24 (m, 4H), 4.08 (s, 3H), 3.80 - 3.76 (m, 1H), 2.92 (s, 3H), 2.78 (s, 6H), 1.61 - 1.36 (m, 3H), 1.21 - 1.05 (m, 3H).
906		LCMS m/z [M+1]: 684.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 - 8.31 (m, 1H), 8.07 (dd, J = 8.4, 1.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.22 - 7.14 (m, 1H), 7.09 - 7.03 (m, 1H), 6.96 - 6.76 (m, 1H), 6.49 (s, 1H), 6.36 - 6.27 (m, 1H), 5.86 - 5.80 (m, 1H), 5.79 - 5.46 (m, 1H), 4.75 - 4.52 (m, 1H), 4.32 - 4.23 (m, 1H), 3.87 (s, 3H), 2.70 (s, 3H), 2.66 (s, 3H), 2.59 (s, 3H), 1.59 - 1.38 (m, 3H), 1.35 - 1.20 (m, 3H).
907		LCMS m/z [M+1]: 657.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 - 8.30 (m, 1H), 8.09 - 8.04 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.66 - 7.61 (m, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.22 - 7.14 (m, 1H), 6.94 - 6.76 (m, 1H), 6.36 - 6.26 (m, 2H), 5.87 - 5.78 (m, 1H), 5.76 - 5.41 (m, 1H), 4.37 - 4.25 (m, 1H), 3.88 (s, 3H), 2.67 (s, 3H), 1.53 - 1.35 (m, 3H), 1.26 - 1.11 (m, 3H).
908		LCMS m/z [M+1]: 638.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (d, J = 1.7 Hz, 1H), 8.13 (dd, J = 8.5, 1.7 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.44 (td, J = 9.0, 2.6 Hz, 1H), 6.85 (s, 1H), 6.71 (s, 1H), 6.32 (d, J = 16.6 Hz, 1H), 5.83 (d, J = 10.7 Hz, 2H), 4.65 (s, 1H), 4.23-3.83 (m, 5H), 2.68 (s, 3H), 1.55 - 1.47 (m, 3H), 1.18 - 1.12 (m, 3H).

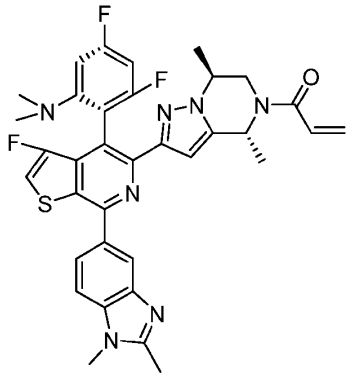
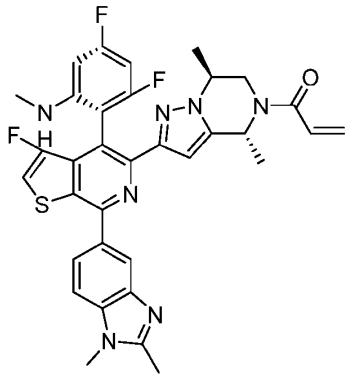
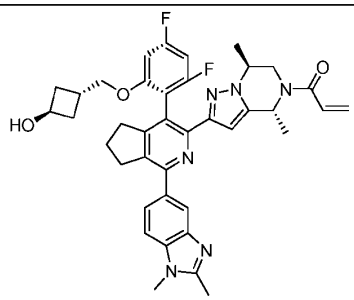
909		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 1.6 Hz, 1H), 6.87 - 6.73 (m, 2H), 6.62 (t, J = 6.4 Hz, 1H), 6.40 - 6.05 (m, 2H), 5.81 (d, J = 10.4 Hz, 1H), 5.55 - 5.40 (m, 1H), 4.25 - 4.10 (m, 2H), 4.08 (s, 3H), 3.97 - 3.80 (m, 3H), 2.92 (s, 3H), 2.20 - 1.85 (m, 3H), 1.65 (d, J = 7.2 Hz, 1H), 1.55 - 1.25 (m, 6H), 1.20 (d, J = 6.8 Hz, 3H).
910		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.40 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 6.87 - 6.80 (m, 1H), 6.73 (d, J = 10.8 Hz, 1H), 6.65 (t, J = 6.4 Hz, 1H), 6.40 - 6.00 (m, 2H), 5.81 (d, J = 10.8 Hz, 1H), 5.50 - 5.40 (m, 1H), 4.25 - 4.10 (m, 2H), 4.08 (s, 3H), 3.97 - 3.80 (m, 3H), 2.92 (s, 3H), 2.20 - 1.85 (m, 3H), 1.55 - 1.30 (m, 6H), 1.21 (d, J = 6.8 Hz, 3H).
911		LCMS m/z [M+1]: 695.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.23 (dd, J = 8.5, 1.3 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 6.89 – 6.82 (m, 2H), 6.68 (dd, J = 9.2, 2.2 Hz, 1H), 6.32 (d, J = 16.0 Hz, 1H), 6.16 (s, 1H), 5.84 (dd, J = 10.5, 1.7 Hz, 1H), 5.72 – 5.51 (m, 1H), 4.43 (s, 1H), 4.26 – 3.85 (m, 4H), 4.09 (s, 3H), 2.93 (s, 3H), 2.07 – 1.86 (m, 3H), 1.45 – 1.38 (m, 4H), 1.35 – 1.28 (m, 4H).

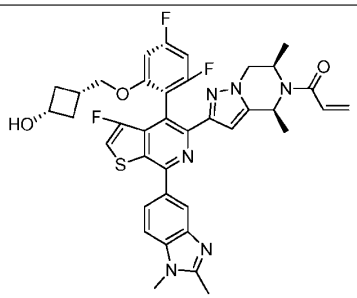
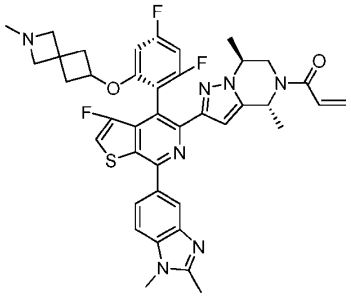
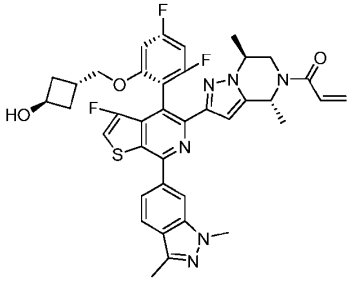
[000781] Table 3 includes additional selected compounds of the present disclosure.

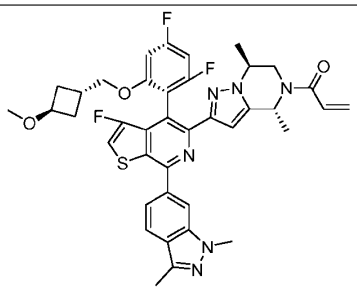
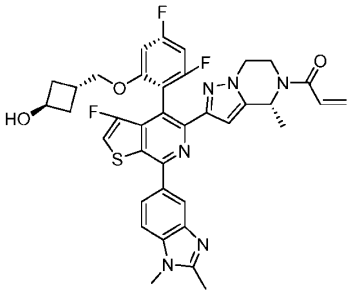
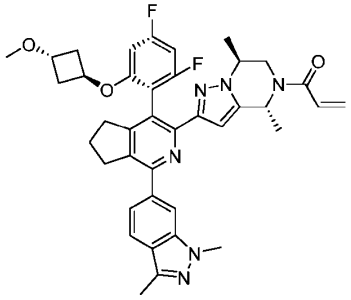
Table 3. Selected compounds of the present disclosure.

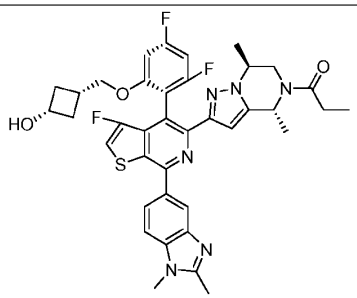
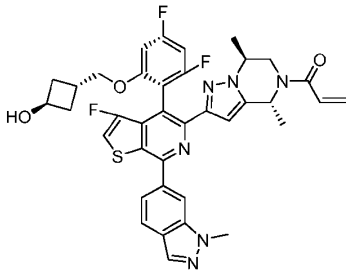
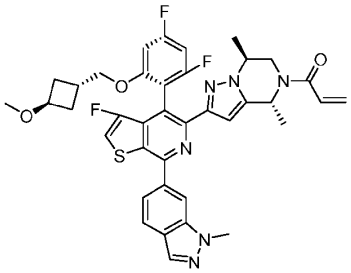
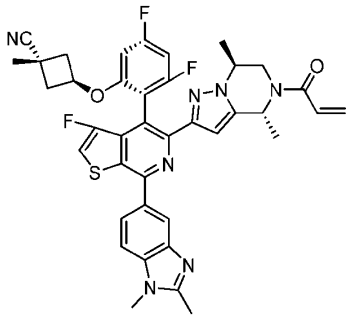
Cmpd. No.	Structure	Analytical data

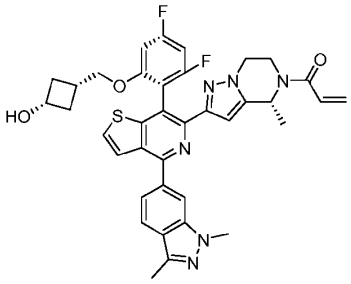
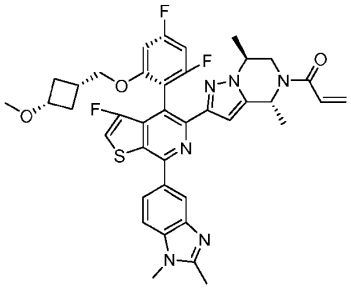
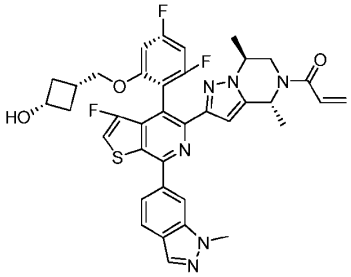
912		LCMS m/z [M+1]: 681.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.23 (dd, J = 8.6 Hz, 1.2 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 5.8 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 6.90 - 6.78 (m, 2H), 6.77 - 6.67 (m, 1H), 6.36 - 6.19 (m, 1H), 6.10 (s, 1H), 5.82 (dd, J = 10.6 Hz, 1.4 Hz, 1H), 5.76 - 5.43 (m, 1H), 4.24 (dd, J = 12.6 Hz, 2.8 Hz, 1H), 4.09 (s, 3H), 3.94 - 3.82 (m, 3H), 2.93 (s, 3H), 2.09 - 1.94 (m, 2H), 1.93 - 1.83 (m, 1H), 1.50 - 1.40 (m, 3H), 1.39 - 1.34 (m, 1H), 1.32 - 1.19 (m, 1H).
913		LCMS m/z [M+1]: 679.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 6.89 - 6.77 (m, 2H), 6.65 (t, J = 9.2 Hz, 1H), 6.32 (d, J = 17.2 Hz, 1H), 6.00 (s, 1H), 5.84 (d, J = 12.0 Hz, 1H), 5.69 - 5.45 (m, 1H), 4.47 (s, 1H), 4.05 - 3.87 (m, 6H), 3.30 - 3.26 (m, 2H), 2.90 - 2.85 (m, 5H), 2.20 - 2.16 (m, 4H), 2.01 (s, 1H), 1.57 - 1.32 (m, 8H).
914		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41(s, 1H), 8.21 (dd, J = 8.5, 1.2 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 16.7, 10.6 Hz, 1H), 6.68 - 6.58 (m, 1H), 6.54 (d, J = 11.0 Hz, 1H), 6.40 - 6.18(m, 1H), 6.18 (s, 1H), 5.80 (d, J = 10.0 Hz, 1H), 5.55 - 5.41 (m, 1H), 4.25 - 4.10 (m, 3H), 3.96 (s, 3H), 3.91 - 3.80 (m, 1H), 2.81 - 2.65(m, 5H), 1.88 - 1.75 (m, 1H), 1.52 (d, J = 6.0 Hz, 3H), 1.42 - 1.32 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H).

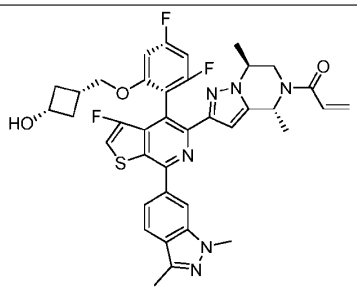
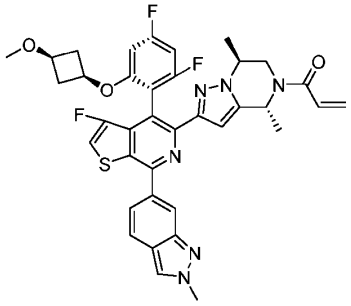
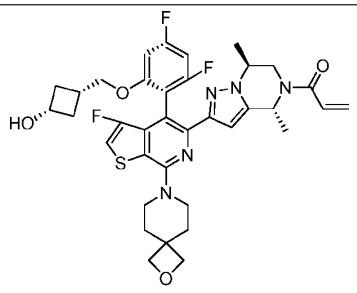
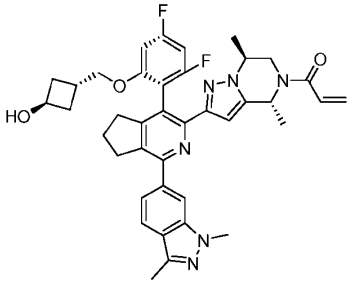
915		LCMS m/z [M+1]: 656.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (s, 1H), 8.20 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 6.94 – 6.80 (m, 1H), 6.64 – 6.53 (m, 2H), 6.33 (d, J = 16.3 Hz, 1H), 6.00 (s, 1H), 5.85 (d, J = 9.8 Hz, 1H), 5.72 – 5.47 (m, 2H), 4.47 – 4.41 (m, 1H), 4.31 – 4.19 (m, 1H), 3.95 (s, 3H), 3.90 – 3.80 (m, 1H), 2.76 (s, 3H), 2.42 (s, 6H), 1.52 – 1.38 (m, 3H), 1.35 – 1.27 (m, 3H).
916		LCMS m/z [M+1]: 642.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.41 (d, J = 7.7 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 6.93 – 6.81 (m, 1H), 6.40 – 6.15 (m, 3H), 6.00 (s, 1H), 5.84 (d, J = 12.1 Hz, 1H), 5.71 – 5.48 (m, 1H), 4.58 – 4.46 (m, 1H), 4.34 – 4.17 (m, 1H), 4.09 (s, 3H), 3.96 – 3.80 (m, 1H), 2.93 (s, 3H), 2.68 (s, 3H), 1.49 – 1.23 (m, 6H).
917		LCMS m/z [M+1]: 679.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 6.95 - 6.80 (m, 1H), 6.74 (d, J = 11.6 Hz, 1H), 6.60 – 6.55 (m, 1H), 6.31 (d, J = 16.0 Hz, 1H), 6.20 - 6.02 (m, 1H), 5.83 (d, J = 10.8 Hz, 1H), 5.69 – 5.40 (m, 1H), 4.42 - 4.36 (m, 1H), 3.98 – 3.90 (m, 6H), 3.22 -3.17 (m, 2H), 2.85 – 2.70 (m, 2H), 2.64 (s, 3H), 2.50 - 2.36(m, 1H), 2.17 – 2.05 (m, 2H), 2.05 – 1.83 (m, 4H), 1.55 - 1.34 (m, 3H), 1.33 - 1.18 (m, 3H).

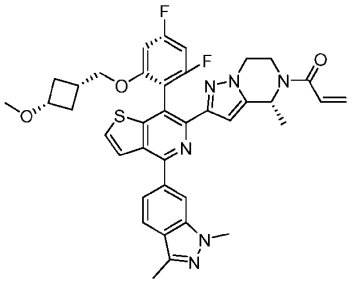
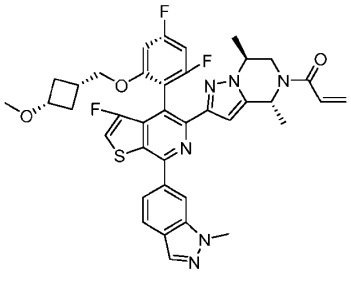
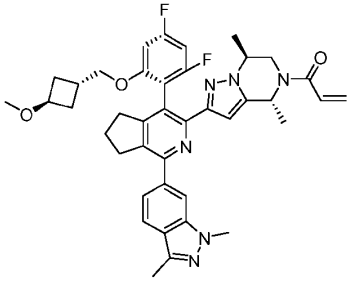
918		LCMS m/z [M+1]: 713.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.42 (dd, J = 8.7, 1.3 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 6.88 - 6.78 (m, 1H), 6.74 (d, J = 10.8 Hz, 1H), 6.65 (td, J = 9.2, 2.1 Hz, 1H), 6.37 - 6.19 (m, 1H), 6.11 - 6.04 (m, 1H), 5.81 (d, J = 10.8 Hz, 1H), 5.51 - 5.40 (m, 1H), 4.23 - 4.12 (m, 2H), 4.09 (s, 3H), 3.96 - 3.78 (m, 3H), 2.94 (s, 3H), 2.14 - 1.99 (m, 2H), 1.97 - 1.86 (m, 1H), 1.54 - 1.47 (m, 3H), 1.48 - 1.32 (m, 2H), 1.24 - 1.17 (m, 3H).
919		LCMS m/z [M+1]: 738.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.39 (dd, J = 8.6, 1.4 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 6.90 – 6.83 (m, 1H), 6.64 – 6.58 (m, 2H), 6.33 (d, J = 17.0 Hz, 1H), 6.19 – 6.14 (m, 1H), 5.85 (dd, J = 10.7, 1.3 Hz, 1H), 5.72 – 5.51 (m, 1H), 4.68 – 4.61 (m, 1H), 4.45 – 4.39 (m, 1H), 4.33 – 4.23 (m, 2H), 4.08 (s, 3H), 4.03 – 3.83 (m, 4H), 2.92 (s, 3H), 2.82 (s, 3H), 2.78 – 2.68 (m, 2H), 2.25 – 2.06 (m, 2H), 1.48 – 1.42 (m, 3H), 1.30 – 1.24 (m, 3H).
920		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 7.95 – 7.85 (m, 2H), 7.54 (d, J = 2.4 Hz, 1H), 6.93 – 6.73 (m, 2H), 6.64 – 6.55 (m, 1H), 6.32 (d, J = 17.0 Hz, 1H), 6.12 (s, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.81 – 4.65 (m, 1H), 4.58 (s, 1H), 4.48 – 4.41 (m, 1H), 4.09 (s, 3H), 3.97 – 3.78 (m, 2H), 3.76 – 3.65 (m, 1H), 2.62 (s, 3H), 2.43 – 2.32 (m, 1H), 1.96 – 1.71 (m, 4H), 1.51 – 1.36 (m, 3H), 1.35 – 1.25 (m, 3H).

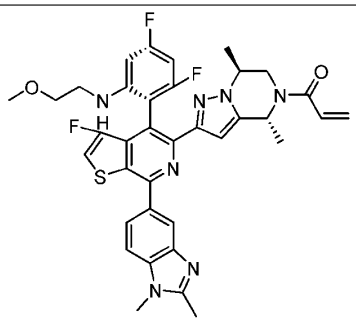
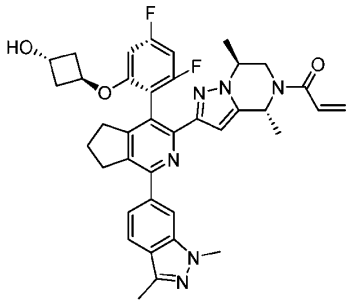
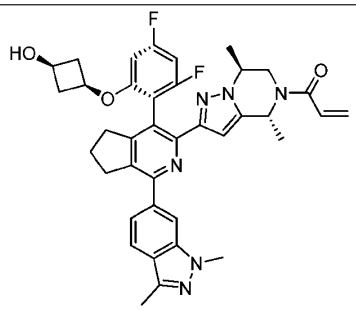
921		LCMS m/z [M+1]: 727.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 8.4, 1.3 Hz, 1H), 7.71 (d, J = 2.2 Hz, 1H), 6.93 – 6.78 (m, 2H), 6.64 (td, J = 9.3, 2.1 Hz, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.13 (s, 1H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.75 - 4.25 (m, 1H), 4.51 – 4.40 (m, 1H), 4.01 (s, 3H), 3.96 – 3.90 (m, 2H), 3.85 - 3.55 (m, 1H), 3.19 -3.11 (m, 1H), 2.87 (s, 3H), 2.62 (s, 3H), 2.44 – 2.32 (m, 1H), 1.92 – 1.81 (m, 3H), 1.77 – 1.67 (m, 1H), 1.51 – 1.36 (m, 3H), 1.35 – 1.25 (m, 3H).
922		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.07 (dd, J = 8.4, 1.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 6.91 – 6.80 (m, 1H), 6.76 (d, J = 10.8 Hz, 1H), 6.67 – 6.55 (m, 1H), 6.37 – 6.22 (m, 1H), 6.09 (s, 1H), 5.81 (d, J = 10.8 Hz, 1H), 5.72 – 5.46 (m, 1H), 4.19 (dd, J = 12.4, 2.8 Hz, 1H), 4.12 – 3.99 (m, 1H), 3.95 – 3.88 (m, 2H), 3.87 (s, 3H), 3.81 – 3.70 (m, 1H), 2.66 (s, 3H), 2.42 – 2.30 (m, 1H), 1.93 – 1.73 (m, 4H), 1.51 – 1.37 (m, 3H), 1.35 – 1.20 (m, 3H).
923		LCMS m/z [M+1]: 679.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.58 (dd, J = 8.4, 1.2 Hz, 1H), 6.92 – 6.73 (m, 2H), 6.65 (d, J = 10.5 Hz, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.01 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.83 – 4.78 (m, 1H), 4.65 – 4.55 (m, 1H), 4.12 (s, 3H), 3.90 – 3.84 (m, 2H), 3.38 – 3.32 (m, 2H), 3.19 (s, 3H), 3.12 – 2.94 (m, 2H), 2.63 (s, 3H), 2.48 – 2.21 (m, 5H), 2.00 – 1.87 (m, 1H), 1.51 – 1.32 (m, 6H).

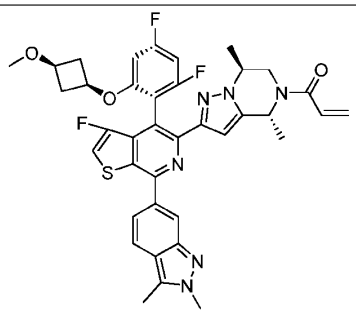
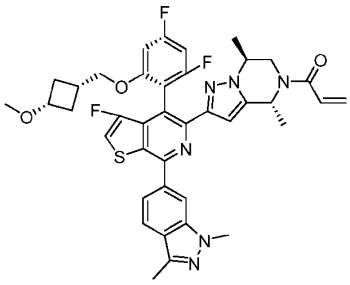
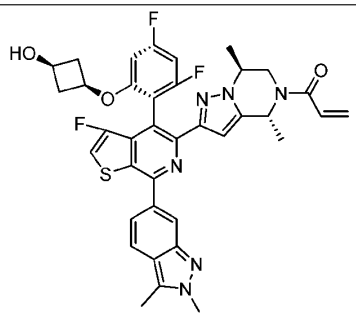
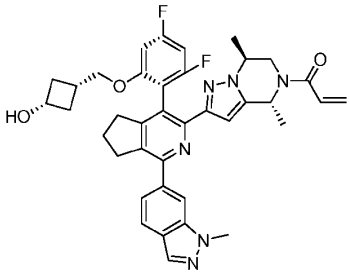
924		LCMS m/z [M+1]: 715.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.41 (dd, J = 8.7, 1.4 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.3 Hz, 1H), 6.81 – 6.50 (m, 2H), 6.08 (s, 1H), 5.69 – 5.35 (m, 1H), 4.49 – 4.36 (m, 1H), 4.09 (s, 3H), 3.95 – 3.76 (m, 4H), 2.94 (s, 3H), 2.65 – 2.41 (m, 2H), 2.16 – 1.85 (m, 3H), 1.52 – 1.25 (m, 6H), 1.14 (d, J = 7.4 Hz, 3H).
925		LCMS m/z [M+1]: 699.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.12 (s, 1H), 7.99 - 7.91 (m, 2H), 7.55 (d, J = 2.4 Hz, 1H), 6.79 - 6.76 (m, 2H), 6.60 (t, J = 8.0 Hz, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.12 (s, 1H), 5.84 (d, J = 12.4 Hz, 1H), 5.72 - 5.49 (m, 1H), 4.44 (s, 1H), 4.18 (s, 3H), 3.93 - 3.88 (m, 2H), 3.71 - 3.69 (m, 1H), 2.38 (s, 1H), 1.89 - 1.78 (m, 4H), 1.40-1.30 (m, 6H).
926		LCMS m/z [M+1]: 713.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.13 (s, 1H), 7.99 - 7.91 (m, 2H), 7.57 (s, 1H), 6.86 (s, 1H), 6.78 (d, J = 10.4 Hz, 1H), 6.63 - 6.59 (m, 1H), 6.32 (d, J = 12.8 Hz, 1H), 6.16 (s, 1H), 5.84 (d, J = 12.4 Hz, 1H), 5.72 - 5.52 (m, 1H), 4.43 (s, 1H), 4.18 (s, 3H), 3.96 - 3.94 (m, 3H), 3.11 - 3.08 (m, 1H), 2.85 (s, 3H), 2.40 (s, 1H), 1.86 - 1.76 (m, 4H), 1.42 - 1.29 (m, 6H).
927		LCMS m/z [M+1]: 722.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (d, J = 1.5 Hz, 1H), 8.42 (dd, J = 8.6, 1.6 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 6.87 (s, 1H), 6.77 – 6.59 (m, 2H), 6.33 (d, J = 16.7 Hz, 1H), 6.26 (s, 1H), 5.85 (dd, J = 10.5, 1.9 Hz, 1H), 5.76 – 5.39 (m, 1H), 4.86 – 4.65 (m, 2H), 4.39 (s, 1H), 4.23-3.86 (m, 1H), 4.10 (s, 3H), 3.04 – 2.88 (m, 5H), 2.03 (dd, J = 12.7, 5.9 Hz, 1H), 1.96 (dd, J =

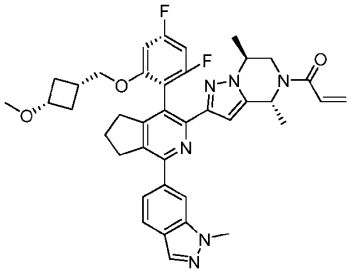
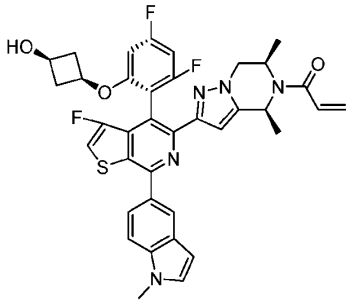
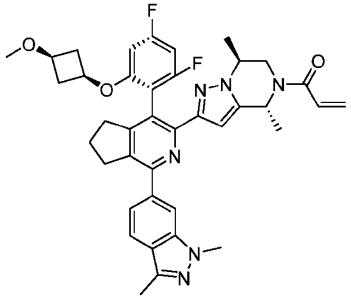
		12.4, 5.9 Hz, 1H), 1.57 - 1.40 (m, 3H), 1.33 (s, 3H), 1.30 - 1.23 (m, 3H).
928		LCMS m/z [M+1]: 681.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 8.01- 7.98 (m, 2H), 7.81 (d, J = 5.6 Hz, 1H), 7.71 (dd, J = 8.3, 1.1 Hz, 1H), 6.92 – 6.77 (m, 3H), 6.29 (d, J = 17.3 Hz, 1H), 6.04 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.72 – 5.55 (m, 1H), 4.44 – 3.87 (m, 2H), 4.15 – 4.07 (m, 4H), 3.94 – 3.87 (m, 3H), 2.63 (s, 3H), 2.06 – 1.90 (m, 3H), 1.46 – 1.38 (m, 4H), 1.28 – 1.21 (m, 1H).
929		LCMS m/z [M+1]: 727.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 2.3 Hz, 1H), 6.94 – 6.68 (m, 2H), 6.58 – 6.52 (m, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.18 (s, 1H), 5.84 (d, J = 11.8 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.44 – 4.36 (m, 1H), 3.88 – 3.82 (m, 5H), 3.62 – 3.54 (m, 1H), 2.98 (s, 3H), 2.67 (s, 3H), 2.09 – 1.92 (m, 4H), 1.50 – 1.30 (m, 7H).
930		LCMS m/z [M+1]: 699.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.14 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.89 (dd, J = 8.4, 1.3 Hz, 1H), 7.69 (d, J = 2.1 Hz, 1H), 6.93 - 6.80 (m, 1H), 6.77 (d, J = 10.8 Hz, 1H), 6.62 (td, J = 9.3, 2.1 Hz, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.10 (s, 1H), 5.84 (dd, J = 10.6, 1.2 Hz, 1H), 5.77 - 5.46 (m, 1H), 4.52 - 4.44 (m, 1H), 4.19 (s, 3H), 3.98 - 3.75 (m, 4H), 2.16 - 1.87 (m, 3H), 1.53 - 1.40 (m, 5H), 1.38 - 1.24 (m, 3H).

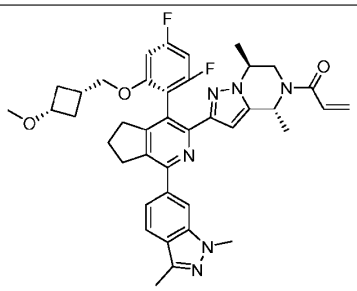
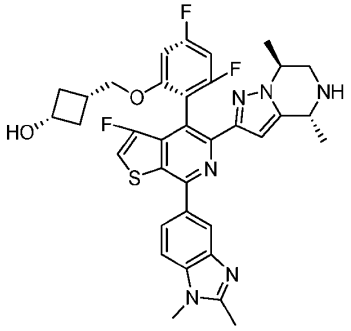
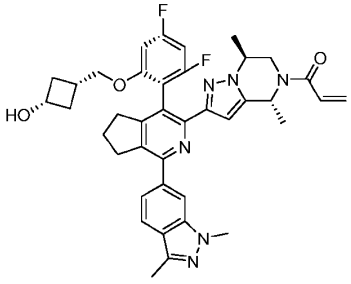
931		LCMS m/z [M+1]: 713.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 – 8.20 (m, 1H), 7.99 – 7.92 (m, 1H), 7.89 – 7.84 (m, 1H), 7.71 – 7.60 (m, 1H), 6.93 – 6.72 (m, 2H), 6.67 – 6.56 (m, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.09 (s, 1H), 5.89 – 5.80 (m, 1H), 5.76 – 5.46 (m, 1H), 4.56 – 4.40 (m, 1H), 4.11 (s, 3H), 3.97 – 3.81 (m, 3H), 2.63 (s, 3H), 2.16 – 1.88 (m, 3H), 1.56 – 1.22 (m, 8H).
932		LCMS m/z [M+1]: 699.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (s, 1H), 8.33 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.85 (dd, J = 8.7, 1.3 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 6.97 – 6.79 (m, 1H), 6.71 – 6.54 (m, 2H), 6.32 (d, J = 16.6 Hz, 1H), 6.22 – 6.09 (m, 1H), 5.89 – 5.79 (m, 1H), 5.76 – 5.46 (m, 1H), 4.49 – 4.38 (m, 1H), 4.37 – 4.27 (m, 4H), 3.62 – 3.50 (m, 1H), 3.14 (s, 3H), 2.82 – 2.69 (m, 2H), 1.84 – 1.69 (m, 1H), 1.65 – 1.38 (m, 4H), 1.37 – 1.23 (m, 3H).
933		LCMS m/z [M+1]: 694.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.27 (d, J = 2.4 Hz, 1H), 6.94 – 6.79 (m, 1H), 6.64 (d, J = 10.8 Hz, 1H), 6.52 – 6.45 (m, 1H), 6.32 (d, J = 16.4 Hz, 1H), 6.06 (s, 1H), 5.83 (d, J = 11.9 Hz, 1H), 5.72 – 5.45 (m, 1H), 4.75 – 4.47 (m, 8H), 4.42 – 4.30 (m, 1H), 3.95 – 3.77 (m, 3H), 3.74 – 3.59 (m, 4H), 2.19 – 2.06 (m, 4H), 2.04 – 1.94 (m, 1H), 1.93 – 1.82 (m, 1H), 1.52 – 1.31 (m, 5H), 1.30 – 1.21 (m, 3H).
934		LCMS m/z [M+1]: 679.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 6.93 – 6.75 (m, 3H), 6.33 (d, J = 17.2 Hz, 1H), 5.98 (s, 1H), 5.85 (dd, J = 10.6, 1.5 Hz, 1H), 5.76 – 5.39 (m, 1H), 4.64 – 4.52 (m, 1H), 4.36 – 4.21 (m, 1H), 4.11 (s, 3H), 4.07 – 3.99 (m, 1H), 3.91 – 3.80 (m, 2H), 3.44 – 3.32 (m, 2H), 3.28 – 3.21 (m, 1H), 3.12 – 2.93 (m, 2H), 2.62 (s, 3H), 2.48 – 2.36 (m,

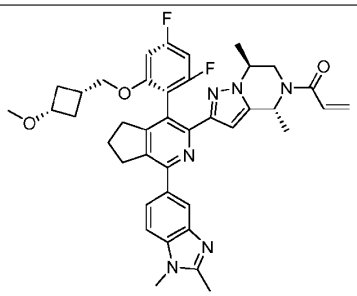
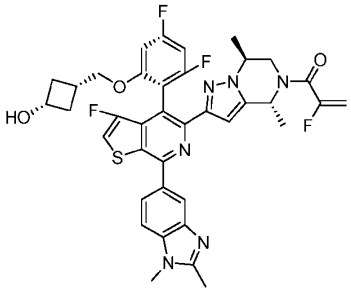
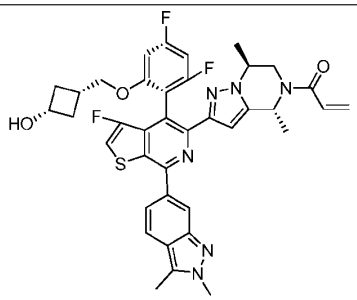
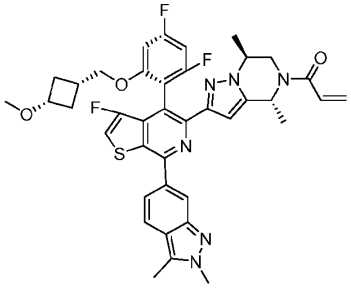
		1H), 2.36 – 2.19 (m, 2H), 2.04 – 1.89 (m, 4H), 1.46 – 1.31 (m, 6H).
935		LCMS m/z [M+1]: 695.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 8.05 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.71 (dd, J = 8.3, 1.1 Hz, 1H), 6.92 (d, J = 10.6 Hz, 1H), 6.87 – 6.79 (m, 2H), 6.29 (d, J = 16.3 Hz, 1H), 6.03 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 – 5.51 (m, 1H), 4.47 – 3.78 (m, 2H), 4.18 – 4.12 (m, 4H), 3.90 (d, J = 3.7 Hz, 2H), 3.59 – 3.52 (m, 1H), 2.94 (s, 3H), 2.64 (s, 3H), 2.02 – 1.95 (m, 3H), 1.44 – 1.39 (m, 4H), 1.19 – 1.13 (m, 1H).
936		LCMS m/z [M+1]: 713.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.15 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 6.92 - 6.81 (m, 1H), 6.77 (d, J = 10.7 Hz, 1H), 6.62 (td, J = 9.3, 2.2 Hz, 1H), 6.33 (d, J = 16.9 Hz, 1H), 6.10 (s, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.79 - 5.43 (m, 1H), 4.52 - 4.43 (m, 1H), 4.18 (d, J = 1.2 Hz, 3H), 3.88 (d, J = 4.0 Hz, 2H), 3.63 - 3.53 (m, 1H), 2.97 (s, 3H), 2.10 - 1.93 (m, 3H), 1.52 - 1.23 (m, 8H).
937		LCMS m/z [M+1]: 693.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 6.94 – 6.74 (m, 3H), 6.33 (d, J = 16.6 Hz, 1H), 5.99 (s, 1H), 5.85 (d, J = 10.5 Hz, 1H), 5.76 – 5.49 (m, 1H), 4.59 (s, 1H), 4.38 – 4.20 (m, 1H), 4.11 (s, 3H), 4.08 – 4.00 (m, 1H), 3.95 – 3.79 (m, 2H), 3.56 – 3.45 (m, 1H), 3.43 – 3.33 (m, 2H), 3.15 – 2.93 (m, 5H), 2.62 (s, 3H), 2.51 – 2.39 (m, 1H), 2.36 – 2.16 (m, 2H), 2.06 – 1.84 (m, 4H), 1.50 – 1.31 (m, 6H).

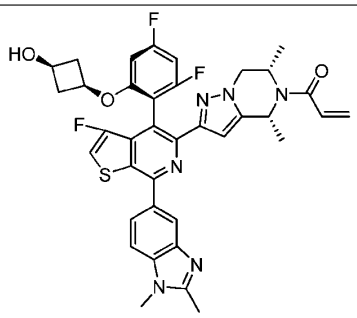
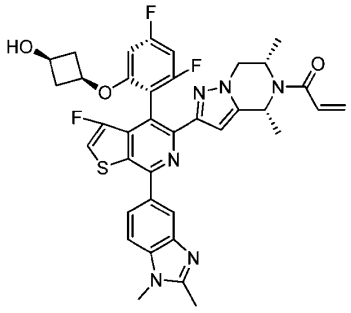
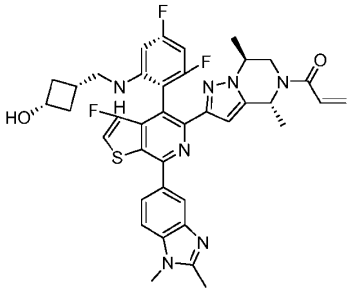
938		LCMS m/z [M+1]: 686.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.44 (d, J = 8.7 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 6.95 – 6.82 (m, 1H), 6.38 (dd, J = 26.0, 14.5 Hz, 2H), 6.25 (t, J = 9.3 Hz, 1H), 6.09 (s, 1H), 5.86 (d, J = 10.5 Hz, 1H), 5.78 – 5.48 (m, 1H), 4.57 – 4.51 (m, 1H), 4.11 (s, 3H), 3.42 – 3.38 (m, 2H), 3.27 – 3.23 (m, 2H), 3.21 (s, 3H), 2.96 (s, 3H), 1.49 – 1.34 (m, 6H).
939		LCMS m/z [M+1]: 665.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 6.78 (s, 1H), 6.53 (t, J = 8.7 Hz, 1H), 6.40 (d, J = 10.3 Hz, 1H), 6.28 (s, 1H), 6.05 – 5.93 (m, 1H), 5.76 (d, J = 10.4 Hz, 1H), 5.67 – 5.40 (m, 1H), 4.73 – 4.58 (m, 2H), 4.37 – 4.28 (m, 1H), 4.19 – 4.11 (m, 1H), 4.00 (s, 3H), 3.21 – 3.16 (m, 2H), 2.76 – 2.65 (m, 2H), 2.52 (s, 3H), 2.25 – 2.13 (m, 3H), 2.11 – 1.93 (m, 3H), 1.44 – 1.31 (m, 3H), 1.26 – 1.17 (m, 3H).
940		LCMS m/z [M+1]: 665.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.66 (dd, J = 8.4, 1.2 Hz, 1H), 6.93 – 6.79 (m, 1H), 6.62 – 6.51 (m, 2H), 6.31 (d, J = 16.4 Hz, 1H), 6.15 – 6.00 (m, 1H), 5.83 (d, J = 10.4 Hz, 1H), 5.71 – 5.47 (m, 1H), 4.75 – 4.55 (m, 1H), 4.44 – 4.36 (m, 1H), 4.29 – 4.22 (m, 1H), 4.07 (s, 3H), 3.97 – 3.87 (m, 1H), 3.28 – 3.20 (m, 1H), 2.90 – 2.73 (m, 4H), 2.59 (s, 3H), 2.21 – 2.06 (m, 2H), 1.94 – 1.84 (m, 1H), 1.81 – 1.71 (m, 1H), 1.50 – 1.38 (m, 3H), 1.31 – 1.26 (m, 3H)

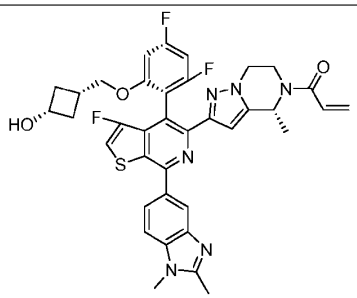
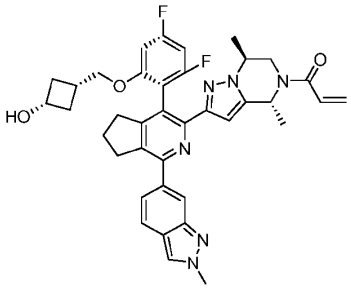
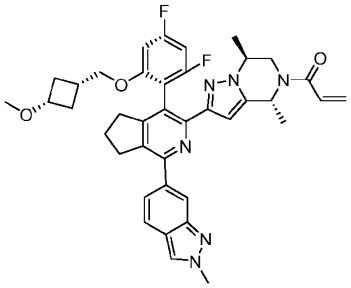
941		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.6 Hz, 1H), 7.74 (s, 1H), 6.97 – 6.79 (m, 1H), 6.72 – 6.58 (m, 2H), 6.33 (d, J = 16.5 Hz, 1H), 6.11 (s, 1H), 5.84 (d, J = 10.6 Hz, 1H), 5.80 – 5.41 (m, 1H), 4.45 (s, 1H), 4.37 – 4.27 (m, 1H), 4.20 (s, 3H), 3.61 – 3.51 (m, 1H), 3.14 (s, 3H), 2.82 – 2.69 (m, 5H), 1.82 – 1.71 (m, 1H), 1.62 – 1.24 (m, 7H).
942		LCMS m/z [M+1]: 727.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.86 (dd, J = 8.4, 1.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 6.94 – 6.81 (m, 1H), 6.77 (d, J = 10.8 Hz, 1H), 6.62 (td, J = 9.2, 2.1 Hz, 1H), 6.33 (d, J = 16.3 Hz, 1H), 6.10 (s, 1H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.77 – 5.42 (m, 1H), 4.53 – 4.41 (m, 3H), 3.88 (d, J = 4.1 Hz, 2H), 3.65 – 3.54 (m, 1H), 2.98 (s, 3H), 2.63 (s, 3H), 2.10 – 1.91 (m, 3H), 1.53 – 1.38 (m, 5H), 1.35 – 1.28 (m, 3H).
943		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.86 (d, J = 6.6 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.52 (s, 1H), 6.95 – 6.75 (m, 1H), 6.63 – 6.52 (m, 2H), 6.32 (d, J = 16.5 Hz, 1H), 6.26 – 6.13 (m, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.78 - 5.42 (m, 1H), 4.58 (s, 1H), 4.44 – 4.35 (m, 1H), 4.28 – 4.22 (m, 1H), 4.16 (s, 3H), 3.91 – 3.80 (m, 1H), 2.80 – 2.68 (m, 5H), 1.87 – 1.78 (m, 1H), 1.74 – 1.65 (m, 1H), 1.55 – 1.35 (m, 3H), 1.35 – 1.20 (m, 3H).
944		LCMS m/z [M+1]: 665.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 2H), 7.86 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 6.92 – 6.79 (m, 1H), 6.73 (d, J = 10.8 Hz, 1H), 6.58 (t, J = 8.9 Hz, 1H), 6.31 (d, J = 16.5 Hz, 1H), 6.12 – 5.99 (m, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.74 – 5.41 (m, 1H), 4.76 – 4.52 (m, 1H), 4.46 – 4.37 (m, 1H), 4.15 (s, 3H), 4.05 – 3.95 (m, 1H), 3.94 – 3.83 (m, 2H), 3.29 – 3.17 (m, 2H), 2.88 – 2.68 (m, 2H),

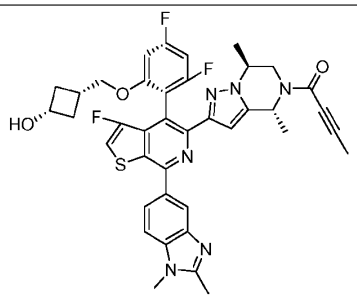
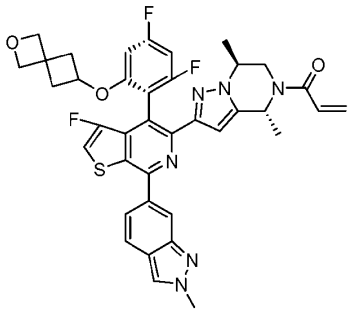
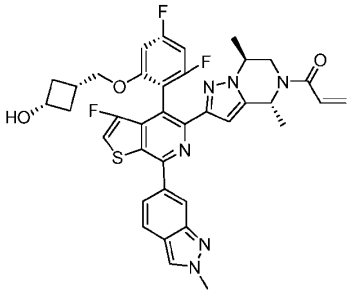
		2.26 – 1.94 (m, 5H), 1.61 – 1.35 (m, 5H), 1.34 – 1.19 (m, 3H).
945		LCMS m/z [M+1]: 679.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 2H), 7.86 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 6.93 – 6.77 (m, 1H), 6.72 (d, J = 10.7 Hz, 1H), 6.57 (t, J = 9.2 Hz, 1H), 6.31 (d, J = 16.5 Hz, 1H), 6.13 – 6.02 (m, 1H), 5.82 (d, J = 10.6 Hz, 1H), 5.75 – 5.41 (m, 1H), 4.44 – 4.34 (m, 0H), 4.14 (s, 3H), 3.97 – 3.90 (m, 1H), 3.87 – 3.80 (m, 1H), 3.72 – 3.60 (m, 1H), 3.28 – 3.19 (m, 2H), 3.06 (s, 3H), 2.89 – 2.65 (m, 2H), 2.22 – 2.04 (m, 5H), 1.61 – 1.51 (m, 2H), 1.49 – 1.34 (m, 3H), 1.32 – 1.20 (m, 3H).
946		LCMS m/z [M+1]: 684.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.29 – 7.28 (m, 1H), 6.87 – 6.79 (m, 1H), 6.64 – 6.51 (m, 2H), 6.52 (d, J = 10.8 Hz, 1H), 6.25 (s, 1H), 6.16 (s, 1H), 5.79 (d, J = 5.6 Hz, 1H), 5.54 – 5.43 (m, 1H), 4.18 – 4.14 (m, 3H), 3.89 – 3.83 (m, 4H), 2.74 – 2.70 (m, 2H), 1.85 – 1.82 (m, 1H), 1.51 (d, J = 4.8 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H).
947		LCMS m/z [M+1]: 679.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 6.86 (s, 1H), 6.67 – 6.51 (m, 2H), 6.32 (d, J = 16.6 Hz, 1H), 6.17 – 5.96 (m, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.73 – 5.37 (m, 1H), 4.47 – 4.36 (m, 1H), 4.36 – 4.25 (m, 1H), 3.63 – 3.53 (m, 1H), 3.25 (t, J = 7.2 Hz, 2H), 3.17 (s, 3H), 2.88 – 2.72 (m, 4H), 2.59 (s, 3H), 2.17 – 2.07 (m, 2H), 1.88 – 1.76 (m, 1H), 1.67 – 1.55 (m, 1H), 1.51 – 1.36 (m, 3H), 1.35 – 1.24 (m, 3H).

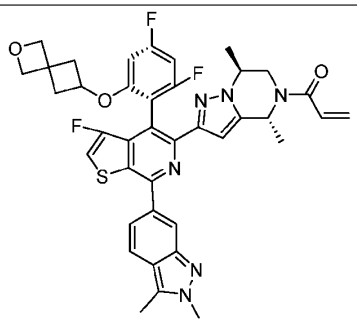
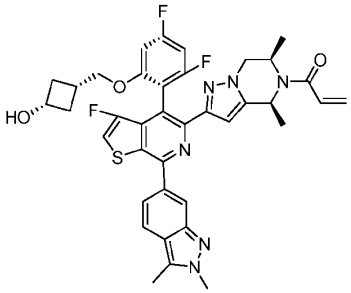
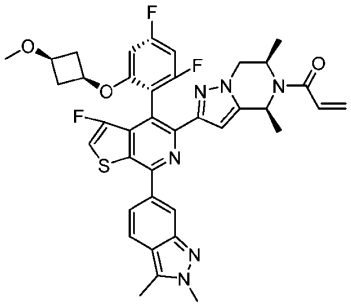
948		LCMS m/z [M+1]: 693.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 6.93 – 6.80 (m, 1H), 6.74 (d, J = 10.7 Hz, 1H), 6.59 (t, J = 9.2 Hz, 1H), 6.32 (d, J = 16.5 Hz, 1H), 6.05 (s, 1H), 5.83 (d, J = 10.6 Hz, 1H), 5.76 – 5.41 (m, 1H), 4.49 – 4.36 (m, 1H), 4.07 (s, 3H), 4.00 – 3.75 (m, 2H), 3.74 – 3.62 (m, 1H), 3.25 (t, J = 7.3 Hz, 2H), 3.06 (s, 3H), 2.91 – 2.72 (m, 2H), 2.59 (s, 3H), 2.24 – 2.04 (m, 5H), 1.62 – 1.49 (m, 2H), 1.49 – 1.35 (m, 3H), 1.34 – 1.21 (m, 3H).
949		LCMS m/z [M+1]: 659.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.48 (s, 1H), 6.71 (d, J = 11.5 Hz, 1H), 6.53 (t, J = 8.8 Hz, 1H), 6.30 (s, 1H), 4.14 – 3.97 (m, 2H), 3.96 – 3.83 (m, 5H), 3.43 – 3.35 (m, 1H), 2.86 – 2.76 (m, 1H), 2.67 (s, 3H), 2.19 – 1.85 (m, 4H), 1.52 – 1.43 (m, 1H), 1.40 (d, J = 6.5 Hz, 3H), 1.35 (d, J = 6.6 Hz, 3H).
950		LCMS m/z [M+1]: 679.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (s, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 6.93 – 6.78 (m, 1H), 6.72 (d, J = 10.7 Hz, 1H), 6.57 (t, J = 9.2 Hz, 1H), 6.31 (d, J = 16.5 Hz, 1H), 6.11 – 5.98 (m, 1H), 5.83 (d, J = 10.4 Hz, 1H), 5.75 - 5.42 (m, 1H), 4.46 – 4.35 (m, 1H), 4.06 (s, 3H), 4.04 – 3.95 (m, 1H), 3.95 – 3.78 (m, 2H), 3.28 – 3.20 (m, 2H), 2.86 – 2.68 (m, 2H), 2.58 (s, 3H), 2.25 – 1.95 (m, 5H), 1.63 – 1.35 (m, 5H), 1.35 – 1.20 (m, 3H).

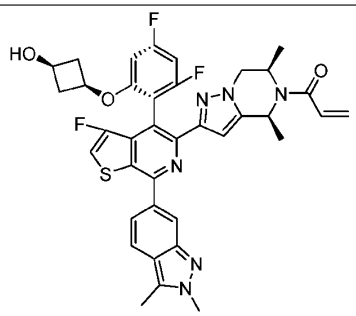
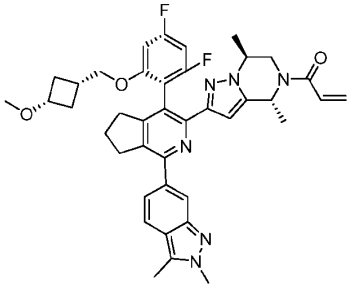
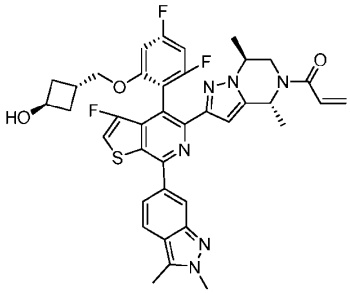
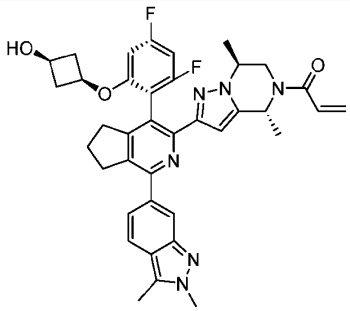
951		LCMS m/z [M+1]: 693.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 6.88 – 6.79 (m, 2H), 6.68 (t, J = 9.1 Hz, 1H), 6.32 (d, J = 16.5 Hz, 1H), 6.00 (s, 1H), 5.84 (d, J = 10.4 Hz, 1H), 5.70 – 5.49 (m, 1H), 4.50 (s, 1H), 4.26 – 4.24 (m, 1H), 4.06 (s, 3H), 3.96 – 3.82 (m, 3H), 3.68 – 3.63 (m, 1H), 3.30 – 3.24 (m, 2H), 3.04 (s, 3H), 2.94 – 2.92 (m, 5H), 2.23 – 2.10 (m, 5H), 1.54 – 1.32 (m, 8H).
952		LCMS m/z [M+1]: 731.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.07 (dd, J = 8.4, 1.5 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 6.72 (d, J = 10.6 Hz, 1H), 6.61 – 6.52 (m, 1H), 6.20 (s, 1H), 5.59 – 5.49 (m, 1H), 5.38 (d, J = 3.9 Hz, 1H), 5.31 (d, J = 4.0 Hz, 1H), 5.26 (s, 1H), 4.47 – 4.34 (m, 1H), 3.97 – 3.83 (m, 5H), 3.37 - 3.33 (m, 1H), 2.67 (s, 3H), 2.19 – 1.83 (m, 4H), 1.51 – 1.37 (m, 4H), 1.34 – 1.26 (m, 3H).
953		LCMS m/z [M+1]: 713.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.81 – 7.76 (m, 2H), 6.93 – 6.75 (m, 2H), 6.68 – 6.59 (m, 1H), 6.33 (d, J = 16.7 Hz, 1H), 6.10 (s, 1H), 5.84 (dd, J = 10.6, 1.7 Hz, 1H), 5.79 – 5.45 (m, 1H), 4.53 - 4.43 (m, 1H), 4.20 (s, 3H), 3.97 – 3.80 (m, 3H), 2.75 (s, 3H), 2.17 – 1.87 (m, 3H), 1.53 – 1.25 (m, 8H).
954		LCMS m/z [M+1]: 727.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.82 – 7.76 (m, 2H), 6.92 – 6.80 (m, 1H), 6.77 (d, J = 10.8 Hz, 1H), 6.68 – 6.59 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.11 (s, 1H), 5.84 (dd, J = 10.5, 1.7 Hz, 1H), 5.79 – 5.44 (m, 1H), 4.52 – 4.42 (m, 1H), 4.20 (s, 3H), 3.90 – 3.84 (m, 2H), 3.62 – 3.52 (m, 1H), 2.97 (s, 3H), 2.75 (s, 3H), 2.10 – 1.92 (m, 3H), 1.52 – 1.38 (m, 4H), 1.36 – 1.24 (m, 4H).

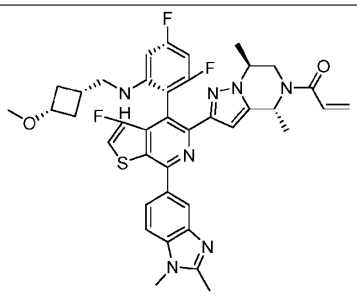
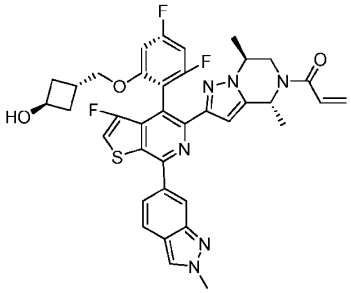
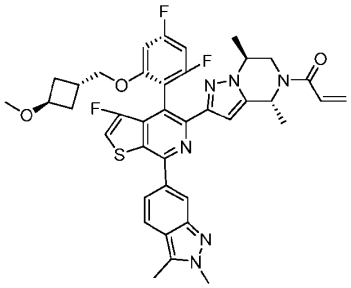
955		LCMS m/z [M+1]: 699.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 1.9 Hz, 1H), 6.83 (dd, J = 16.7, 10.7 Hz, 1H), 6.67 - 6.58 (m, 1H), 6.53 (d, J = 10.7 Hz, 1H), 6.35 - 6.16 (m, 2H), 5.80 (d, J = 10.5 Hz, 1H), 5.55 - 5.44 (m, 1H), 4.24 - 4.07 (m, 3H), 3.94 - 3.78 (m, 4H), 2.79 - 2.68 (m, 2H), 2.67 (s, 3H), 1.87 - 1.74 (m, 1H), 1.57 - 1.47 (m, 4H), 1.30 - 1.26 (m, 1H), 1.21 (d, J = 6.9 Hz, 3H).
956		LCMS m/z [M+1]: 699.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 1.9 Hz, 1H), 6.83 (dd, J = 16.7, 10.7 Hz, 1H), 6.71 - 6.49 (m, 2H), 6.39 - 6.06 (m, 2H), 5.80 (d, J = 10.2 Hz, 1H), 5.53 - 5.38 (m, 1H), 4.31 - 4.06 (m, 3H), 3.93 - 3.80 (m, 4H), 2.80 - 2.69 (m, 2H), 2.66 (s, 3H), 1.89 - 1.76 (m, 1H), 1.58 - 1.46 (m, 4H), 1.32 - 1.26 (m, 1H), 1.20 (d, J = 6.8 Hz, 3H).
957		LCMS m/z [M+1]: 712.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (d, J = 1.2 Hz, 1H), 8.08 (dd, J = 8.4, 1.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 6.91 – 6.81 (m, 1H), 6.29 (dd, J = 22.6, 13.8 Hz, 2H), 6.21 – 6.14 (m, 1H), 6.08 (s, 1H), 5.84 (dd, J = 10.6, 1.8 Hz, 1H), 5.72 – 5.48 (m, 1H), 4.54 – 4.45 (m, 1H), 3.98 – 3.90 (m, 1H), 3.88 (s, 3H), 3.06 (dd, J = 6.8, 2.6 Hz, 2H), 2.67 (s, 3H), 2.26 – 2.10 (m, 2H), 1.94 – 1.83 (m, 1H), 1.53 – 1.37 (m, 5H), 1.37 – 1.29 (m, 3H).

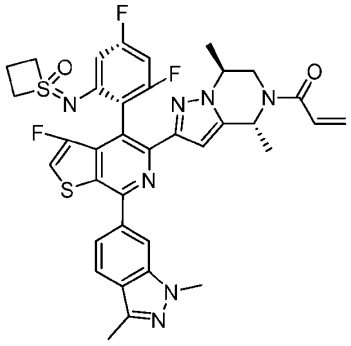
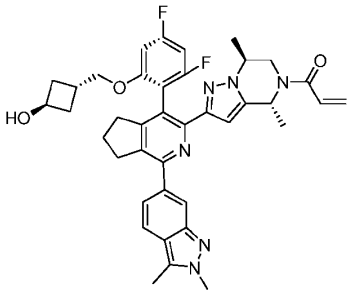
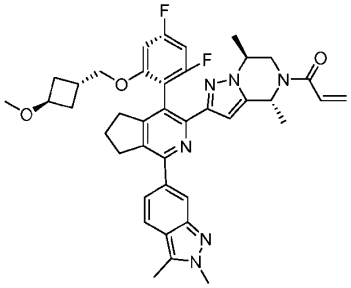
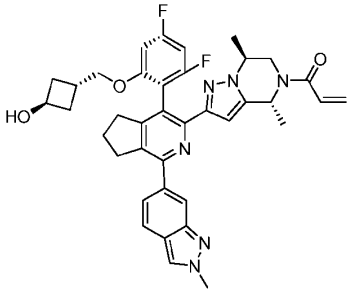
958		LCMS m/z [M+1]: 699.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.07 (dd, J = 8.4, 1.6 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 6.91 – 6.78 (m, 1H), 6.72 (d, J = 10.8 Hz, 1H), 6.65 – 6.54 (m, 1H), 6.37 – 6.22 (m, 1H), 6.06 (s, 1H), 5.81 (d, J = 12.0 Hz, 1H), 5.73 – 5.49 (m, 1H), 4.26 – 4.16 (m, 1H), 4.13 – 4.00 (m, 1H), 3.94 – 3.84 (m, 5H), 2.66 (s, 3H), 2.17 – 2.07 (m, 1H), 2.07 – 1.97 (m, 1H), 1.97 – 1.87 (m, 1H), 1.51 – 1.33 (m, 5H).
959		LCMS m/z [M+1]: 665.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 8.19 – 8.12 (m, 1H), 8.05 – 7.97 (m, 1H), 7.51 (dd, J = 8.6, 1.5 Hz, 1H), 6.95 – 6.74 (m, 3H), 6.33 (dd, J = 16.6, 1.9 Hz, 1H), 5.94 (s, 1H), 5.85 (dd, J = 10.6, 1.9 Hz, 1H), 5.76 – 5.40 (m, 1H), 4.67 - 4.55 (m, 1H), 4.32 (s, 3H), 4.12 – 3.91 (m, 1H), 3.85 (dd, J = 9.6, 5.0 Hz, 1H), 3.54 – 3.32 (m, 2H), 3.10 – 2.94 (m, 2H), 2.29 - 2.16 (m, 4H), 2.10 – 1.97 (m, 1H), 1.57 – 1.45 (m, 2H), 1.44 – 1.30 (m, 6H).
960		LCMS m/z [M+1]: 679.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 (s, 1H), 8.17 (s, 1H), 8.02 (dd, J = 8.7, 0.9 Hz, 1H), 7.51 (dd, J = 8.7, 1.6 Hz, 1H), 6.91 – 6.76 (m, 3H), 6.33 (d, J = 16.6 Hz, 1H), 5.93 (s, 1H), 5.85 (dd, J = 10.6, 1.9 Hz, 1H), 5.76 – 5.40 (m, 1H), 4.69 - 4.55(m, 1H), 4.32 (s, 3H), 3.95 (dd, J = 9.7 Hz, 3.2 Hz, 1H), 3.82 (dd, J = 9.7, 3.2 Hz, 2H), 3.72 – 3.60 (m, 1H), 3.45 - 3.35 (m, 1H), 3.29 – 3.23 (m, 1H), 3.15- 2.95 (m, 5H), 2.39 – 2.20 (m, 2H), 2.17 - 2.05 (m, 3H), 1.58 – 1.34 (m, 8H).

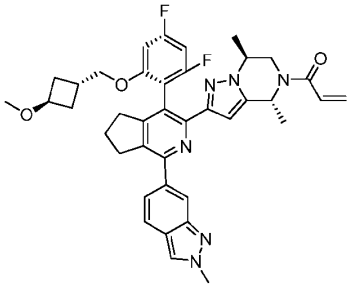
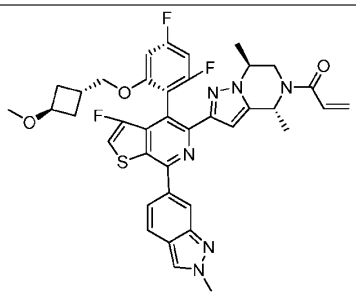
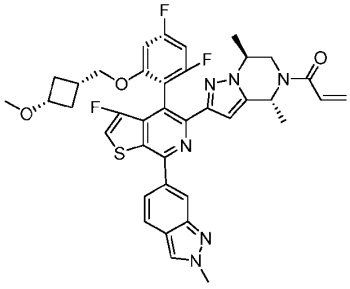
961		LCMS m/z [M+1]: 725.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, J = 1.2 Hz, 1H), 8.07 (dd, J = 8.4, 1.5 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 6.72 (d, J = 11.0 Hz, 1H), 6.59 - 6.51 (m, 1H), 6.20 (d, J = 27.2 Hz, 1H), 5.72 - 5.56 (m, 1H), 4.60 - 4.39 (m, 2H), 3.97 - 3.82 (m, 7H), 2.67 (s, 3H), 2.16 - 1.99 (m, 5H), 1.98 - 1.88 (m, 1H), 1.53 - 1.36 (m, 5H), 1.33 (d, J = 6.6 Hz, 2H), 1.22 (d, J = 6.6 Hz, 1H).
962		LCMS m/z [M+1]: 711.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (d, J = 0.9 Hz, 1H), 8.31 (s, 1H), 7.92 (dd, J = 8.7, 0.7 Hz, 1H), 7.85 (dd, J = 8.7, 1.4 Hz, 1H), 7.54 (d, J = 2.5 Hz, 1H), 6.95 – 6.81 (m, 1H), 6.62 – 6.54 (m, 2H), 6.37 – 6.15 (m, 2H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.69 – 4.62 (m, 2H), 4.58 – 4.52 (m, 1H), 4.46 (d, J = 6.5 Hz, 1H), 4.44 – 4.35 (m, 2H), 4.29 (s, 3H), 2.77 – 2.60 (m, 2H), 2.16 – 2.04 (m, 1H), 2.01 – 1.91 (m, 1H), 1.51 – 1.36 (m, 3H), 1.35 – 1.25 (m, 3H).
963		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (d, J = 1.2 Hz, 1H), 8.31 (s, 1H), 7.93 – 7.84 (m, 2H), 7.51 (d, J = 2.4 Hz, 1H), 6.98 – 6.79 (m, 1H), 6.73 (d, J = 10.9 Hz, 1H), 6.60 - 6.52 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.25 - 6.11(m, 1H), 5.84 (dd, J = 10.8, 1.6 Hz, 1H), 5.78 – 5.49 (m, 1H), 4.47 – 4.39 (m, 1H), 4.29 (s, 3H), 3.94 – 3.84 (m, 4H), 2.19 – 1.92 (m, 3H), 1.49 – 1.36 (m, 5H), 1.35 - 1.20 (m, 3H).

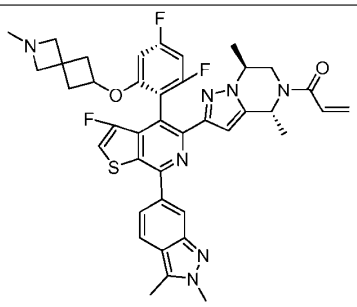
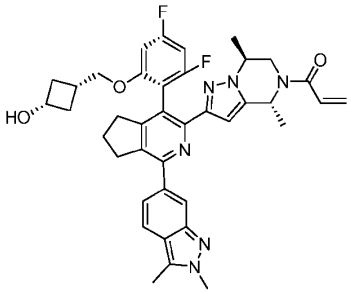
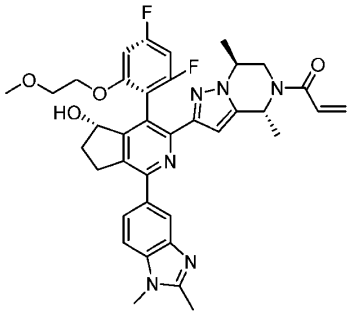
964		LCMS m/z [M+1]: 725.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), 7.54 (s, 1H), 6.92 – 6.82 (m, 1H), 6.61 – 6.52 (m, 2H), 6.33 (d, J = 16.0 Hz, 1H), 6.24 – 6.14 (m, 1H), 5.84 (d, J = 10.6 Hz, 1H), 5.75 – 5.52 (m, 1H), 4.66 (s, 2H), 4.61 – 4.51 (m, 3H), 4.47 (d, J = 6.3 Hz, 1H), 4.44 – 4.36 (m, 2H), 4.17 (s, 3H), 2.73 (s, 3H), 2.71 – 2.63 (m, 2H), 2.13 – 2.06 (m, 1H), 2.02 – 1.95 (m, 1H), 1.53 – 1.42 (m, 3H), 1.31 – 1.24 (m, 3H).
965		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.80 (dd, J = 8.7, 1.2 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 6.88 – 6.58 (m, 3H), 6.26 (s, 1H), 6.15 (s, 1H), 5.80 (d, J = 10.3 Hz, 1H), 5.45 (s, 1H), 4.58 (s, 2H), 4.24 – 4.10 (m, 5H), 3.97 – 3.87 (m, 1H), 3.86 – 3.78 (m, 2H), 2.72 (s, 3H), 2.16 – 2.00 (m, 2H), 1.98 – 1.87 (m, 1H), 1.50 (t, J = 7.5 Hz, 3H), 1.48 – 1.33 (m, 2H), 1.21 (d, J = 6.9 Hz, 3H).
966		LCMS m/z [M+1]: 713.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.93 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 7.82 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 6.87 - 6.80 (m, 1H), 6.67 (td, J = 9.2 Hz, 2.0 Hz, 1H), 6.56 (d, J = 10.8 Hz, 1H), 6.40 - 6.20 (m, 2H), 5.81 (d, J = 9.6 Hz, 1H), 5.55 - 5.48 (m, 1H), 4.32 - 4.25 (m, 1H), 4.20 (s, 3H), 4.16 (s, 2H), 3.60 - 3.50 (m, 1H), 3.16 (s, 3H), 2.80 - 2.68 (m, 5H), 1.85 - 1.75 (m, 1H), 1.53 (d, J = 6.8 Hz, 3H), 1.50 - 1.25 (m, 2H), 1.23 (d, J = 7.2 Hz, 3H).

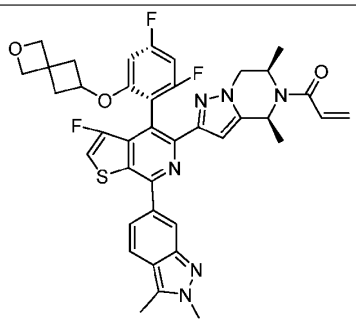
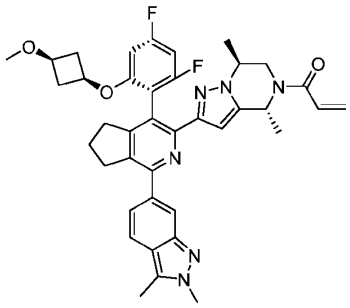
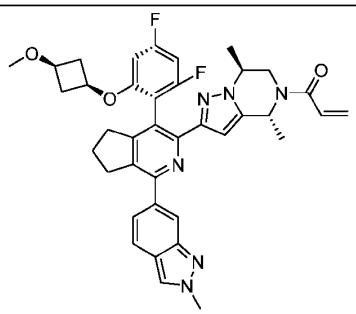
967		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.80 (dd, J = 8.7, 1.3 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 16.7, 10.7 Hz, 1H), 6.66 – 6.47 (m, 2H), 6.35 – 6.18 (m, 2H), 5.80 (d, J = 10.6 Hz, 1H), 5.49 (d, J = 6.4 Hz, 1H), 4.25 – 4.08 (m, 6H), 3.90 – 3.81 (m, 1H), 2.79 – 2.66 (m, 5H), 1.88 – 1.76 (m, 1H), 1.58 – 1.46 (m, 4H), 1.21 (d, J = 6.9 Hz, 3H).
968		LCMS m/z [M+1]: 693.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 6.91 – 6.75 (m, 3H), 6.33 (d, J = 17.2 Hz, 1H), 5.95 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.59 (s, 1H), 4.19 (s, 3H), 3.99 – 3.93 (m, 1H), 3.84 – 3.80 (m, 1H), 3.71 – 3.61 (m, 1H), 3.41 – 3.25 (m, 2H), 3.08 – 2.94 (m, 5H), 2.74 (s, 3H), 2.33 – 2.07 (m, 5H), 1.46 – 1.36 (m, 8H).
969		LCMS m/z [M+1]: 713.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.81 (dd, J = 8.7, 1.3 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H), 6.93 – 6.76 (m, 2H), 6.63 (td, J = 9.2, 2.0 Hz, 1H), 6.33 (d, J = 16.5 Hz, 1H), 6.13 (s, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.77 – 5.46 (m, 1H), 4.50 – 4.41 (m, 1H), 4.20 (s, 3H), 4.05 – 3.80 (m, 3H), 3.79 – 3.69 (m, 1H), 2.75 (s, 3H), 2.42 – 2.32 (m, 1H), 1.90 – 1.76 (m, 4H), 1.53 – 1.40 (m, 3H), 1.35 – 1.25 (m, 3H).
970		LCMS m/z [M+1]: 665.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (s, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 6.93 - 6.79 (m, 1H), 6.60 - 6.50 (m, 2H), 6.31 (d, J = 16.6 Hz, 1H), 6.21 - 6.10 (m, 1H), 5.83 (d, J = 9.6 Hz, 1H), 5.74 - 5.44 (m, 2H), 4.40 - 4.32 (m, 1H), 4.30 - 4.21 (m, 1H), 4.13 (s, 3H), 3.96 - 3.87 (m, 1H), 3.28 - 3.20 (m, 2H), 2.91 - 2.72 (m, 4H), 2.69 (s, 3H), 2.19 - 2.06 (m, 2H), 1.92 - 1.84 (m, 1H), 1.82 - 1.72 (m, 1H), 1.53 - 1.38 (m, 3H), 1.33-1.18 (m, 4H).

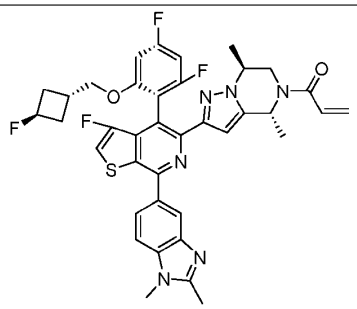
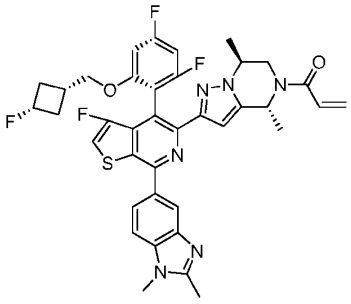
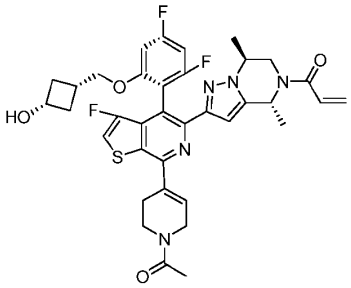
971		LCMS m/z [M+1]: 726.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.08 (dd, J = 8.4, 1.5 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.2 Hz, 1H), 6.93 – 6.81 (m, 1H), 6.36 – 6.23 (m, 2H), 6.22 – 6.14 (m, 1H), 6.12 – 6.03 (m, 1H), 5.84 (dd, J = 10.6, 1.6 Hz, 1H), 5.78 – 5.42 (m, 1H), 4.53 – 4.46 (m, 1H), 3.89 (s, 3H), 3.66 – 3.59 (m, 1H), 3.15 – 3.01 (m, 5H), 2.67 (s, 3H), 2.22 – 2.08 (m, 2H), 2.02 – 1.93 (m, 1H), 1.50 – 1.25 (m, 9H).
972		LCMS m/z [M+1]: 699.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.31 (s, 1H), 7.92 (dd, J = 8.7, 0.8 Hz, 1H), 7.85 (dd, J = 8.7, 1.4 Hz, 1H), 7.53 (d, J = 2.5 Hz, 1H), 6.94 – 6.79 (m, 1H), 6.80 – 6.71 (m, 1H), 6.62 – 6.49 (m, 1H), 6.38 – 6.26 (m, 1H), 6.26 – 6.11 (m, 1H), 5.84 (dd, J = 10.7, 1.5 Hz, 1H), 5.78 – 5.40 (m, 1H), 4.43 – 4.35 (m, 1H), 4.29 (s, 3H), 3.97 – 3.84 (m, 2H), 3.79 – 3.71 (m, 1H), 2.45 – 2.31 (m, 1H), 1.96 – 1.71 (m, 4H), 1.55 – 1.37 (m, 3H), 1.35 – 1.20 (m, 3H).
973		LCMS m/z [M+1]: 727.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H), 6.93 – 6.77 (m, 2H), 6.63 (td, J = 9.3, 1.8 Hz, 1H), 6.33 (d, J = 16.3 Hz, 1H), 6.16 (s, 1H), 5.84 (dd, J = 10.6, 1.1 Hz, 1H), 5.78 – 5.49 (m, 1H), 4.50 – 4.41 (m, 1H), 4.33 – 4.23 (m, 1H), 4.20 (s, 3H), 3.99 – 3.79 (m, 3H), 3.16 – 3.07 (m, 1H), 2.87 (s, 3H), 2.75 (s, 3H), 2.45 – 2.33 (m, 1H), 1.90 – 1.80 (m, 3H), 1.79 – 1.69 (m, 1H), 1.51 – 1.38 (m, 3H), 1.34 – 1.25 (m, 3H).

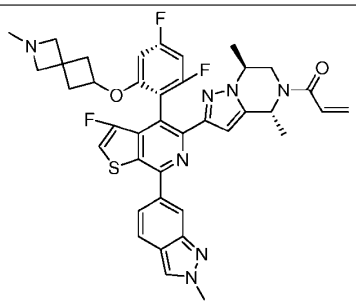
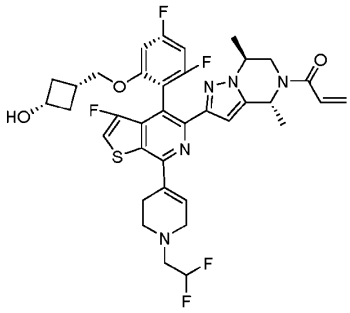
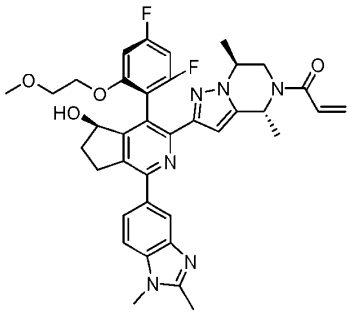
974		LCMS m/z [M+1]: 716.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.94 - 7.85 (m, 2H), 7.52 (d, J = 2.5 Hz, 1H), 6.93 - 6.79 (m, 1H), 6.77 (d, J = 10.6 Hz, 1H), 6.61 - 6.52 (m, 1H), 6.31 (d, J = 16.4 Hz, 1H), 6.14 (s, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.76 - 5.40 (m, 1H), 4.48 - 4.15 (m, 1H), 4.15 - 4.00 (m, 5H), 3.95 - 3.76 (m, 1H), 3.75 - 3.60 (m, 1H), 2.60 (s, 3H), 2.20 - 2.09 (m, 1H), 1.86 - 1.73 (m, 1H), 1.36 - 1.25 (m, 6H)
975		LCMS m/z [M+1]: 679.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (s, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.44 (dd, J = 8.7, 1.4 Hz, 1H), 6.93 – 6.75 (m, 3H), 6.34 (d, J = 16.8 Hz, 1H), 5.94 (s, 1H), 5.85 (dd, J = 10.6, 1.7 Hz, 1H), 5.75 – 5.41 (m, 1H), 4.61 (s, 1H), 4.20 (s, 3H), 4.03 (dd, J = 9.5, 5.8 Hz, 1H), 3.93 – 3.80 (m, 2H), 3.52 – 3.33 (m, 1H), 3.15 – 2.92 (m, 2H), 2.74 (s, 3H), 2.48 – 2.17 (m, 3H), 2.02 – 1.87 (m, 4H), 1.49 – 1.30 (m, 6H).
976		LCMS m/z [M+1]: 693.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.43 (dd, J = 8.7, 1.4 Hz, 1H), 6.99 – 6.77 (m, 3H), 6.34 (d, J = 16.5 Hz, 1H), 5.95 (s, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.77 – 5.45 (m, 1H), 4.62 (s, 1H), 4.20 (s, 3H), 4.04 (dd, J = 9.4, 5.3 Hz, 1H), 3.94 – 3.82 (m, 1H), 3.54 – 3.33 (m, 3H), 3.29 – 3.19 (m, 1H), 3.16 – 2.92 (m, 5H), 2.75 (s, 3H), 2.54 – 2.15 (m, 3H), 2.06 – 1.79 (m, 4H), 1.51 – 1.29 (m, 6H).
977		LCMS m/z [M+1]: 665.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 8.16 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.50 (dd, J = 8.7, 1.5 Hz, 1H), 6.94 – 6.74 (m, 3H), 6.34 (d, J = 16.3 Hz, 1H), 5.94 (s, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.61 (s, 1H), 4.32 (s, 3H), 4.08 – 4.01 (m, 1H), 3.91 – 3.82

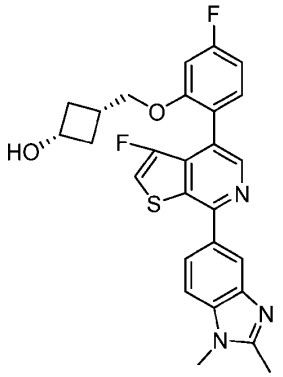
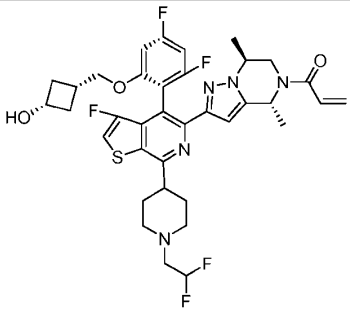
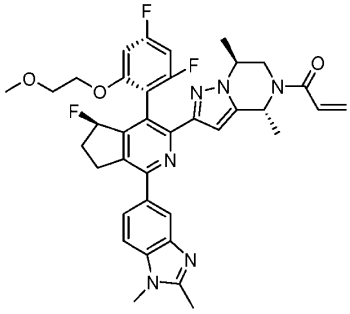
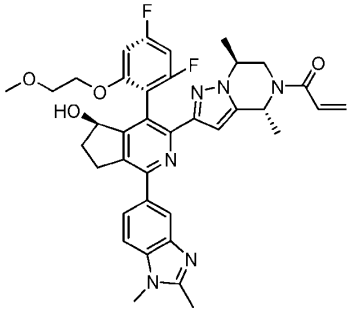
		(m, 2H), 3.49 – 3.25 (m, 2H), 3.15 – 2.92 (m, 2H), 2.48 – 2.18 (m, 3H), 2.02 – 1.88 (m, 4H), 1.51 – 2.28 (m, 6H).
978		LCMS m/z [M+1]: 679.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 8.14 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.49 (dd, J = 8.7, 1.4 Hz, 1H), 6.96 – 6.76 (m, 3H), 6.33 (d, J = 16.4 Hz, 1H), 5.96 (s, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.71 – 5.42 (m, 1H), 4.61 (s, 1H), 4.32 (s, 3H), 4.07 – 4.02 (m, 1H), 3.91 – 3.86 (m, 2H), 3.53 – 3.25 (m, 2H), 3.15 – 2.93 (m, 5H), 2.52 - 2.41 (m, 1H), 2.38 – 2.17 (m, 2H), 2.04 – 1.81 (m, 4H), 1.51 – 1.25 (m, 6H).
979		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.30 (s, 1H), 7.91 (dd, J = 8.7, 0.6 Hz, 1H), 7.85 (dd, J = 8.7, 1.3 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 6.95 – 6.79 (m, 1H), 6.80 – 6.70 (m, 1H), 6.65 – 6.53 (m, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.27 – 6.15 (m, 1H), 5.83 (dd, J = 10.6, 1.6 Hz, 1H), 5.77 – 5.40 (m, 1H), 4.44 – 4.34 (m, 1H), 4.28 (s, 3H), 3.98 – 3.90 (m, 2H), 3.89 – 3.39 (m, 1H), 3.11 – 3.01 (m, 1H), 2.84 (s, 3H), 2.46 – 2.32 (m, 1H), 1.91 – 1.69 (m, 4H), 1.55 – 1.36 (m, 3H), 1.35 – 1.17 (m, 3H).
980		LCMS m/z [M+1]: 713.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 - 8.35 (m, 2H), 7.97 (d, J = 8.4 Hz, 1H), 7.82 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 7.72 (d, J= 2.0 Hz, 1H), 6.92 - 6.75 (m, 2H), 6.61 (td, J = 9.2 Hz, 2.0 Hz, 1H), 6.35 - 6.30 (m, 1H), 6.14 (s, 1H), 5.85 - 5.40 (m, 2H), 4.50 - 4.40 (m, 1H), 4.30 (s, 3H), 3.88 (d, J = 4.0 Hz, 2H), 3.60 - 3.50 (m, 1H), 2.98 (s, 3H), 2.10 - 1.90 (m, 3H), 1.55 - 1.40 (m, 4H), 1.40 - 1.20 (m, 5H).

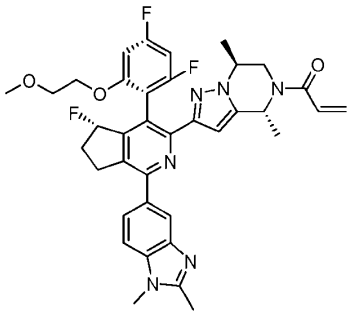
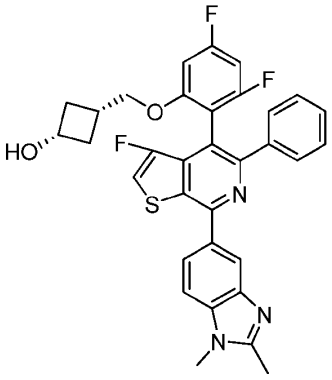
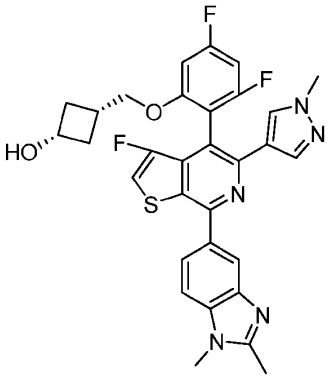
981		LCMS m/z [M+1]: 738.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.55 (s, 1H), 6.95 – 6.80 (m, 1H), 6.65 – 6.50 (m, 2H), 6.33 (d, J = 16.8 Hz, 1H), 6.25 – 6.10 (m, 1H), 5.85 (d, J = 11.9 Hz, 1H), 5.77 – 5.45 (m, 1H), 4.69 – 4.61 (m, 1H), 4.45 – 4.35 (m, 1H), 4.33 – 4.25 (m, 1H), 4.18 (s, 3H), 4.09 – 3.97 (m, 2H), 3.85 (t, J = 11.2 Hz, 2H), 2.84 – 2.64 (m, 8H), 2.25 – 2.06 (m, 2H), 1.55 – 1.40 (m, 3H), 1.35 – 1.15 (m, 3H).
982		LCMS m/z [M+1]: 679.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 6.78 (brs, 1H), 6.71 (d, J = 10.8 Hz, 1H), 6.55 (t, J = 9.2 Hz, 1H), 6.31 (d, J = 16.8 Hz, 1H), 6.02 (s, 1H), 5.82 (d, J = 11.6 Hz, 1H), 5.69 - 5.49 (m, 1H), 4.37 (s, 1H), 4.13 (s, 3H), 4.01 - 3.84 (m, 3H), 3.30 - 3.21 (m, 2H), 2.80 - 2.64 (m, 5H), 2.22 - 2.02 (m, 5H), 1.55 - 1.26 (m, 8H).
983		LCMS m/z [M+1]: 669.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 6.95 – 6.78 (m, 1H), 6.73 (d, J = 10.6 Hz, 1H), 6.68 – 6.57 (m, 1H), 6.31 (d, J = 17.2 Hz, 1H), 6.20-6.06 (m, 1H), 5.83 (d, J = 10.9 Hz, 1H), 5.75 - 5.40 (m, 1H), 5.03 – 4.95 (m, 1H), 4.42 – 4.35 (m, 1H), 4.15 – 4.08 (m, 1H), 3.92 – 3.80 (m, 5H), 3.56 – 3.40 (m, 5H), 3.23 (s, 3H), 3.10 – 2.98 (m, 1H), 2.64 (s, 3H), 2.38 – 2.28 (m, 1H), 2.12 – 2.03 (m, 1H), 1.54 – 1.37 (m, 4H) , 1.35 – 1.20 (m, 4H).

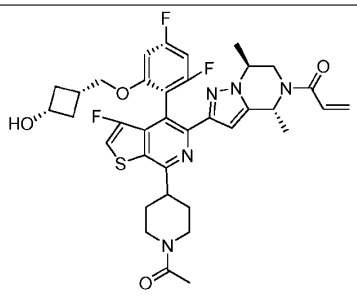
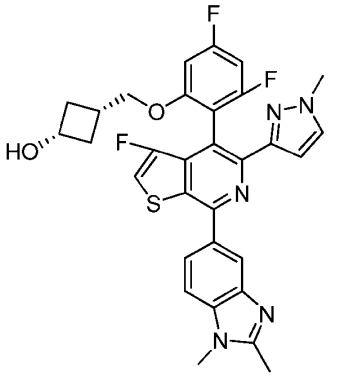
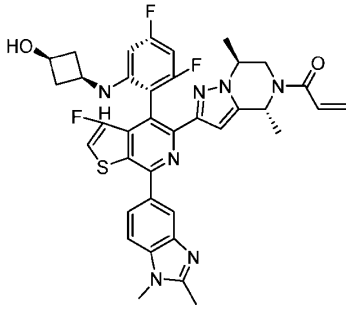
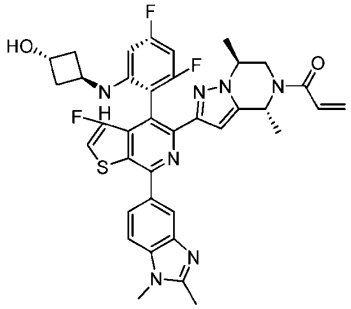
984		LCMS m/z [M+1]: 725.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.80 (dd, J = 8.7, 1.2 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 16.7, 10.7 Hz, 1H), 6.62 (td, J = 9.2, 2.2 Hz, 1H), 6.52 (d, J = 10.8 Hz, 1H), 6.34 – 6.15 (m, 2H), 5.81 (d, J = 10.7 Hz, 1H), 5.46 (s, 1H), 4.67-4.61 (m, 2H), 4.56 (s, 1H), 4.53 – 4.44 (m, 2H), 4.40 (d, J = 6.5 Hz, 1H), 4.17 (s, 3H), 4.10 (t, J = 14.0 Hz, 2H), 2.72 (s, 3H), 2.70 – 2.60 (m, 2H), 2.08 (dd, J = 11.3, 6.4 Hz, 1H), 1.85 (dd, J = 11.5, 6.1 Hz, 1H), 1.53 (d, J = 6.7 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H).
985		LCMS m/z [M+1]: 679.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.48 (dd, J = 8.6, 1.3 Hz, 1H), 6.86 (dd, J = 16.6, 10.6 Hz, 1H), 6.78 (td, J = 9.4, 2.2 Hz, 1H), 6.70 (d, J = 10.7 Hz, 1H), 6.33 (dd, J = 16.6, 1.6 Hz, 1H), 5.97 (s, 1H), 5.85 (dd, J = 10.6, 1.8 Hz, 1H), 5.77 - 5.46 (m, 1H), 4.62 - 4.53 (m, 1H), 4.40 - 4.31 (m, 1H), 4.20 (s, 3H), 3.63 - 3.53 (m, 1H), 3.41 - 3.32 (m, 1H), 3.28 - 3.22 (m, 1H), 3.16 (s, 3H), 3.12 - 2.93 (m, 2H), 2.87 - 2.76 (m, 2H), 2.74 (s, 3H), 2.37 - 2.18 (m, 2H), 1.83 - 1.74 (m, 1H), 1.56 - 1.47 (m, 1H), 1.46 - 1.33 (m, 6H).
986		LCMS m/z [M+1]: 665.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.04 (d, J = 0.8 Hz, 1H), 7.82 (dd, J = 8.8, 0.4 Hz, 1H), 7.70 (dd, J = 8.8, 1.2 Hz, 1H), 6.95 – 6.78 (m, 1H), 6.63 – 6.51 (m, 2H), 6.31 (d, J = 16.8 Hz, 1H), 6.21 – 6.04 (m, 1H), 5.83 (dd, J = 10.4, 1.2 Hz, 1H), 5.75 – 5.42 (m, 1H), 4.70 – 4.53 (m, 1H), 4.41 – 4.27 (m, 2H), 4.25 (s, 3H), 3.64 – 3.54 (m, 1H), 3.25 (t, J = 7.2 Hz, 2H), 3.17 (s, 3H), 2.88 – 2.68 (m, 4H), 2.17 – 2.06 (m, 2H), 1.88 – 1.77 (m, 1H), 1.69 – 1.59 (m, 1H), 1.52 – 1.36 (m, 3H), 1.33 – 1.25 (m, 3H).

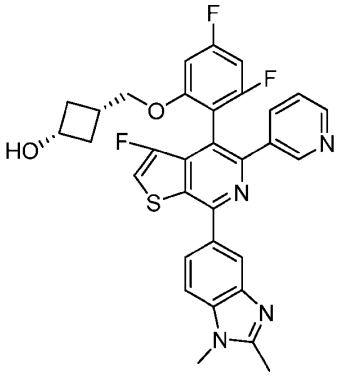
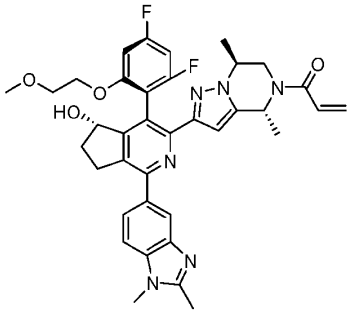
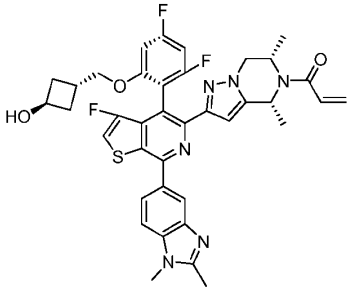
987		LCMS m/z [M+1]: 715.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (d, J = 1.2 Hz, 1H), 8.01 (dd, J = 8.4, 1.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 6.90 – 6.80 (m, 1H), 6.74 (d, J = 10.8 Hz, 1H), 6.59 (td, J = 6.6 , 2.2 Hz, 1H), 6.31 (d, J = 16.6 Hz, 1H), 6.24 – 6.20 (m, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.72 – 5.50 (m, 1H), 4.39 – 4.35 (m, 1H), 4.26 – 4.20 (m, 1H), 4.12 – 4.07 (m, 1H), 3.94 – 3.88 (m, 1H), 3.85 (s, 3H), 2.64 (s, 3H), 2.49 – 2.43 (m, 1H), 2.10 – 1.81 (m, 4H), 1.47 – 1.40 (m, 3H), 1.29 – 1.26 (m, 3H).
988		LCMS m/z [M+1]: 715.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, J = 0.9 Hz, 1H), 8.37 (dd, J = 8.6, 1.5 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 6.89 – 6.82 (m, 1H), 6.76 (d, J = 10.6 Hz, 1H), 6.60 (td, J = 9.2, 2.2 Hz, 1H), 6.32 (d, J = 16.9 Hz, 1H), 6.11 (s, 1H), 5.84 (dd, J = 10.6, 1.8 Hz, 1H), 5.72 – 5.50 (m, 1H), 4.74 – 4.53 (m, 1H), 4.43 (s, 1H), 4.26 – 3.86 (m, 3H), 4.08 (s, 3H), 2.93 (s, 3H), 2.13 – 1.93 (m, 3H), 1.74 – 1.42 (m, 5H), 1.36 – 1.25 (m, 4H).
989		LCMS m/z [M+1]: 692.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (t, J = 2.1 Hz, 1H), 6.94 – 6.80 (m, 1H), 6.79 – 6.64 (m, 2H), 6.53 (td, J = 9.3, 2.1 Hz, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.19 – 6.06 (m, 1H), 5.84 (d, J = 12.0 Hz, 1H), 5.77 – 5.36 (m, 1H), 4.46 – 4.32 (m, 3H), 3.95 – 3.76 (m, 6H), 3.08 – 2.82 (m, 2H), 2.22 (d, J = 6.7 Hz, 3H), 2.14 – 1.81 (m, 3H), 1.56 – 1.18 (m, 9H).

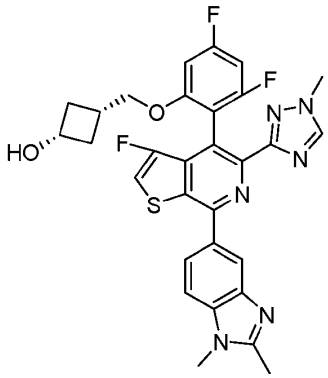
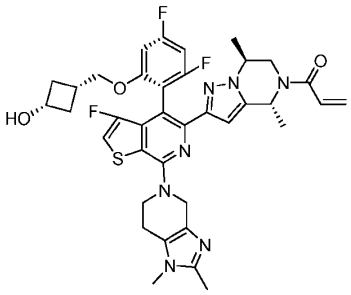
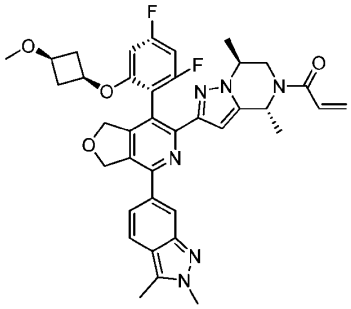
990		LCMS m/z [M+1]: 724.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.33 (s, 1H), 7.94 (d, J = 18.8 Hz, 1H),7.85 (dd, J = 8.6 Hz, 1.2 Hz, 1H), 7.58 - 7.54 (m, 1H), 6.95 - 6.78 (m, 1H), 6.65 - 6.51 (m, 2H), 6.39 - 6.12 (m, 2H), 5.84 (d, J = 12.0 Hz, 1H), 5.80 - 5.45 (m, 1H), 4.69 - 4.60 (m, 1H), 4.44 - 4.34 (m, 1H), 4.29 (s, 3H), 4.28 - 4.25 (m, 1H), 4.03 (t, J = 11.4 Hz, 2H), 3.85 (t, J = 11.2 Hz, 2H), 3.49 - 3.45 (m, 1H), 3.14 - 3.01 (m, 1H), 2.81 (d, J = 3.8 Hz, 3H), 2.78 - 2.63 (m, 2H), 2.25 - 2.07 (m, 2H), 1.56 - 1.36 (m, 3H), 1.32 - 1.19 (m, 3H).
991		LCMS m/z [M+1]: 714.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (d, J = 2.5 Hz, 1H), 6.93 – 6.78 (m, 1H), 6.72 – 6.66 (m, 2H), 6.59 – 6.48 (m, 1H), 6.32 (d, J = 16.8 Hz, 1H), 6.25 – 5.92 (m, 2H), 5.84 (dd, J = 10.5, 1.6 Hz, 1H), 5.77 – 5.42 (m, 1H), 4.44 – 4.31 (m, 1H), 3.95 – 3.74 (m, 4H), 3.47 (s, 2H), 3.05 – 2.84 (m, 5H), 2.14 – 1.79 (m, 3H), 1.55 – 1.12 (m, 9H).
992		LCMS m/z [M+1]: 669.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 1.0 Hz, 1H), 7.85 (dd, J = 8.4, 1.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 6.92 – 6.81 (m, 1H), 6.70 – 6.62 (m, 2H), 6.31 (d, J = 17.3 Hz, 1H), 6.21 (s, 1H), 5.87 – 5.81 (m, 1H), 5.77 – 5.42 (m, 1H), 5.10 – 5.05 (m, 1H), 4.41 – 4.31 (m, 1H), 4.07 – 3.96 (m, 1H), 3.85 (s, 3H), 3.77 – 3.68 (m, 1H), 3.49 – 3.35 (m, 4H), 3.20 (s, 3H), 3.15 – 3.02 (m, 2H), 2.64 (s, 3H), 2.43 – 2.33 (m, 1H), 2.09 – 1.98 (m, 1H), 1.54 – 1.37 (m, 3H), 1.27 – 1.15 (m, 3H).

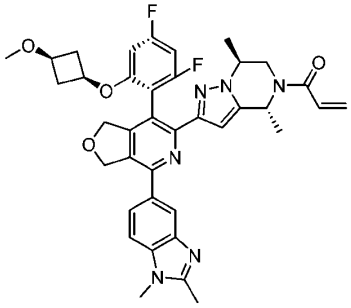
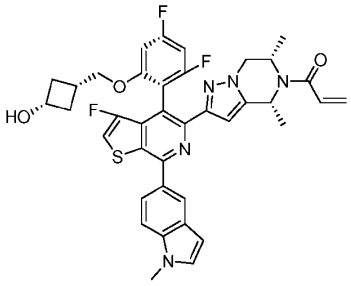
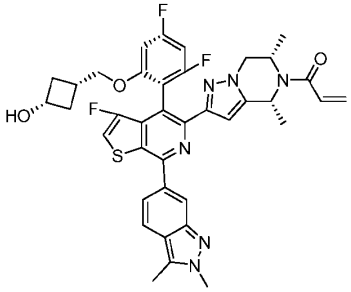
993		LCMS m/z [M+1]: 492.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.20 (d, J = 1.1 Hz, 1H), 7.90 (dd, J = 8.4, 1.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.42 – 7.35 (m, 1H), 6.89 (dd, J = 11.1, 2.3 Hz, 1H), 6.85 – 6.79 (m, 1H), 4.00 – 3.91 (m, 3H), 3.88 (s, 3H), 2.67 (s, 3H), 2.18 – 2.08 (m, 2H), 2.00 – 1.93 (m, 1H), 1.56 – 1.48 (m, 2H).
994		LCMS m/z [M+1]: 716.2 ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (d, J = 2.3 Hz, 1H), 6.97 – 6.77 (m, 1H), 6.67 (d, J = 10.8 Hz, 1H), 6.56 – 6.45 (m, 1H), 6.39 – 6.21 (m, 2H), 6.18 – 5.88 (m, 1H), 5.84 (d, J = 10.4 Hz, 1H), 5.78 – 5.45 (m, 1H), 4.39 – 4.28 (m, 1H), 3.94 – 3.77 (m, 3H), 3.22 – 3.06 (m, 3H), 2.85 (td, J = 15.3, 4.3 Hz, 2H), 2.49 (t, J = 11.0 Hz, 2H), 2.41 – 2.23 (m, 2H), 2.11 – 1.80 (m, 5H), 1.57 – 1.13 (m, 8H).
995		LCMS m/z [M+1]: 671.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.20 (dd, J = 8.7 Hz, 1.4 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 6.92 – 6.80 (m, 2H), 6.57 – 6.50 (m, 1H), 6.32 (d, J = 15.6 Hz, 1H), 6.15 (s, 1H), 6.00 - 5.80 (m, 2H), 5.78 - 5.45(m, 1H), 4.45 – 4.35 (m, 1H), 4.25 – 4.18 (m, 1H), 4.16 – 4.10 (m, 1H), 4.06 (s, 3H), 3.57 (t, J = 4.7 Hz, 2H), 3.54 – 3.43 (m, 2H), 3.23 (s, 3H), 3.22 – 3.10 (m, 1H), 2.91 (s, 3H), 2.55 – 2.25 (m, 2H), 1.52 – 1.35 (m, 3H) , 1.35 – 1.20 (m, 4H).
996		LCMS m/z [M+1]: 669.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (s, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 6.93 – 6.75 (m, 2H), 6.52 – 6.44 (m, 1H), 6.31 (d, J = 16.8 Hz, 1H), 6.12 (s, 1H), 5.83 (dd, J = 10.6 Hz, 1.6 Hz, 1H), 5.76 - 5.40(m, 1H), 5.20 – 5.14 (m, 1H), 4.42 – 4.35 (m, 1H), 4.25 – 4.16 (m, 1H), 4.16 – 4.08 (m, 1H), 3.87 (s, 3H), 3.63 – 3.56 (m,

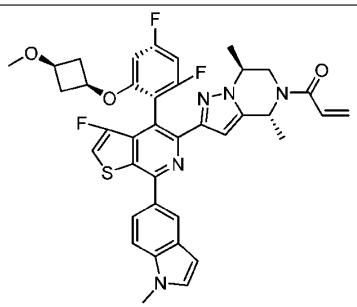
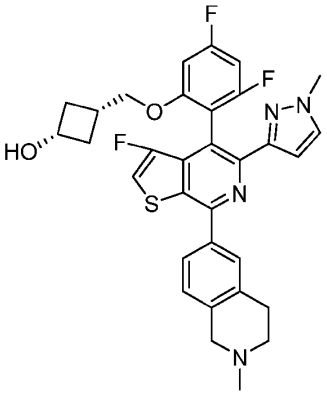
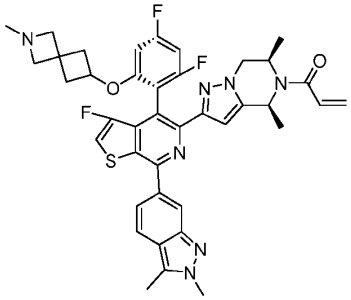
		2H), 3.44 – 3.34 (m, 1H), 3.23 (s, 3H), 3.11 – 3.00 (m, 1H), 2.67 (s, 3H) , 2.08 – 1.95 (m, 1H), 3.44 – 3.34 (m, 1H), 1.54 – 1.37 (m, 4H) , 1.35 – 1.20 (m, 4H).
997		LCMS m/z [M+1]: 671.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.20 (dd, J = 8.7 Hz, 1.5 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 6.92 – 6.80 (m, 2H), 6.57 – 6.50 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.15 (s, 1H), 6.00 - 5.80 (m, 2H), 5.78 - 5.45(m, 1H), 4.45 – 4.35 (m, 1H), 4.25 – 4.18 (m, 1H), 4.16 – 4.10 (m, 1H), 4.06 (s, 3H), 3.57 (t, J = 4.7 Hz, 2H), 3.54 – 3.43 (m, 2H), 3.23 (s, 3H), 3.22 – 3.10 (m, 1H), 2.91 (s, 3H), 2.55 – 2.28 (m, 2H), 1.52 – 1.35 (m, 3H) , 1.35 – 1.20 (m, 4H).
998		LCMS m/z [M+1]: 586.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.01 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.30 - 7.20 (m, 3H), 6.64 (d, J = 11.2 Hz, 1H), 6.47 (td, J = 9.2 Hz, 2.4 Hz, 1H), 4.65 - 4.55 (br, 1H), 4.02 - 3.90 (m, 1H), 3.90 - 3.80 (m, 5H), 2.66 (s, 3H), 2.25 - 1.90 (m, 3H), 1.55 - 1.40 (m, 2H)
999		LCMS m/z [M+1]: 590.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.06 (dd, J = 8.4, 1.3 Hz, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 2.5 Hz, 1H), 7.27 (s, 1H), 6.82 (d, J = 10.6 Hz, 1H), 6.71 (td, J = 9.2, 2.2 Hz, 1H), 3.97 - 3.86 (m, 6H), 3.85 (s, 3H), 2.67 (s, 3H), 2.15 - 1.85 (m, 3H), 1.46 - 1.27 (m, 2H).

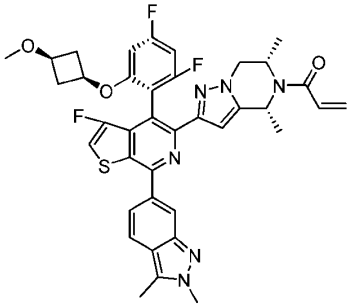
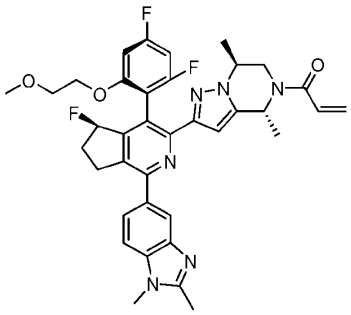
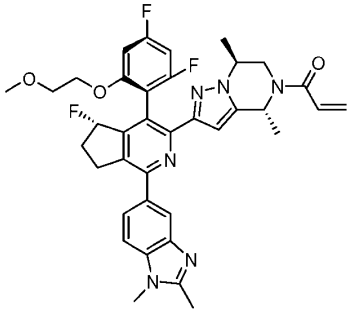
1000		LCMS m/z [M+1]: 694.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, J = 2.3 Hz, 1H), 6.94 – 6.79 (m, 1H), 6.68 (d, J = 11.0 Hz, 1H), 6.52 (t, J = 9.3 Hz, 1H), 6.32 (d, J = 16.2 Hz, 1H), 6.22 – 6.05 (m, 1H), 5.83 (d, J = 12.1 Hz, 1H), 5.74 – 5.41 (m, 1H), 4.72 (d, J = 12.8 Hz, 1H), 4.41 – 4.28 (m, 1H), 4.13 (d, J = 12.1 Hz, 1H), 3.95 – 3.75 (m, 4H), 3.51 – 3.32 (m, 2H), 2.97 – 2.82 (m, 1H), 2.31 – 1.81 (m, 10H), 1.58 – 1.19 (m, 9H).
1001		LCMS m/z [M+1]: 590.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (d, J = 1.6 Hz, 1H), 8.42 (dd, J = 8.6, 1.6 Hz, 1H), 8.07 (dd, J = 8.6, 0.7 Hz, 1H), 7.58 (d, J = 2.5 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 6.74 (dt, J = 10.6, 1.9 Hz, 1H), 6.62 (td, J = 9.3, 2.4 Hz, 1H), 6.03 (d, J = 2.3 Hz, 1H), 4.09 (s, 3H), 3.96 – 3.87 (m, 4H), 3.86 (d, J = 6.0 Hz, 2H), 2.93 (s, 3H), 2.15 – 1.86 (m, 3H), 1.50 - 1.25 (m, 2H).
1002		LCMS m/z [M+1]: 698.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (d, J = 1.2 Hz, 1H), 8.08 (dd, J = 8.4, 1.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 6.94 – 6.77 (m, 1H), 6.32 (d, J = 16.6 Hz, 1H), 6.26 – 6.17 (m, 2H), 6.16 – 6.03 (m, 1H), 5.83 (dd, J = 10.6, 1.7 Hz, 1H), 5.75 – 5.41 (m, 1H), 4.53 – 4.43 (m, 1H), 4.00 – 3.88 (m, 1H), 3.87 (s, 3H), , 3.43 – 3.33 (m, 1H), 2.74 – 2.58 (m, 5H), 1.69 – 1.57 (m, 1H), 1.55 – 1.21 (m, 8H).
1003		LCMS m/z [M+1]: 698.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.08 (dd, J = 8.4, 1.5 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.01 – 6.77 (m, 1H), 6.41 – 6.18 (m, 2H), 6.06 (d, J = 10.9 Hz, 2H), 5.83 (dd, J = 10.7, 1.4 Hz, 1H), 5.76 – 5.38 (m, 1H), 4.54 – 4.40 (m, 1H), 4.19 – 4.06 (m, 1H), 3.97 – 3.73 (m, 4H), 2.66 (s, 3H), 2.24 – 2.01 (m, 3H),

		1.98 – 1.80 (m, 1H), 1.54 – 1.36 (m, 3H), 1.34 – 1.20 (m, 3H).
1004		LCMS m/z [M+1]: 587.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (d, J = 1.7 Hz, 1H), 8.44 (dd, J = 4.9, 1.4 Hz, 1H), 8.32 (d, J = 1.2 Hz, 1H), 8.02 (dd, J = 8.4, 1.6 Hz, 1H), 7.94 – 7.91 (m, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.39 – 7.36 (m, 1H), 6.70 (d, J = 10.8 Hz, 1H), 6.53 (td, J = 9.2, 2.2 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.91 – 3.83 (m, 2H), 3.82 (s, 3H), 2.63 (s, 3H), 2.22 – 2.14 (m, 1H), 2.12 – 2.04 (m, 1H), 2.00 – 1.92 (m, 1H), 1.52 – 1.42 (m, 2H).
1005		LCMS m/z [M+1]: 669.4 ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 1.0 Hz, 1H), 7.85 (dd, J = 8.4, 1.5 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 6.95 – 6.79 (m, 1H), 6.73 (d, J = 10.9 Hz, 1H), 6.55 (td, J = 9.2, 2.3 Hz, 1H), 6.31 (d, J = 16.6 Hz, 1H), 6.10 (s, 1H), 5.83 (d, J = 12.0 Hz, 1H), 5.73 – 5.38 (m, 1H), 5.05 (dd, J = 6.5, 3.3 Hz, 1H), 4.44 – 4.35 (m, 1H), 4.16 – 4.09 (m, 1H), 4.08 – 3.98 (m, 1H), 3.54 (t, J = 4.5 Hz, 1H), 3.85 (s, 3H), 3.54 (t, J = 4.5 Hz, 2H), 3.49 – 3.38 (m, 1H), 3.19 (s, 3H), 3.07 – 2.96 (m, 1H), 2.64 (s, 3H), 2.42 – 2.26 (m, 1H), 2.09 – 1.96 (m, 1H), 1.53 – 1.35 (m, 3H), 1.30 – 1.20 (m, 3H).
1006		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.07 (dd, J = 8.4, 1.3 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 2.2 Hz, 1H), 6.88 – 6.53 (m, 3H), 6.39 – 6.18 (m, 2H), 5.80 (d, J = 10.9 Hz, 1H), 5.46 (s, 1H), 4.58 (s, 1H), 4.24 – 4.15 (m, 2H), 3.96 – 3.84 (m, 5H), 3.82 – 3.71 (m, 1H), 2.66 (s, 3H), 2.47 – 2.25 (m, 1H), 1.96 – 1.74 (m, 4H), 1.51 (d, J = 5.6 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H).

1007		LCMS m/z [M+1]: 591.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.45 (dd, J = 1.6, 1.6 Hz, 1H), 8.40 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 6.68 (d, J = 10.8 Hz, 1H), 6.61 – 6.55 (m, 1H), 4.08 (s, 3H), 3.91-3.83 (m, 6H), 2.94 (s, 3H), 2.09-1.90 (m, 3H), 1.44-1.33 (m, 2H).
1008		LCMS m/z [M+1]: 718.4 ^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (d, J = 2.4 Hz, 1H), 6.91 – 6.81 (m, 1H), 6.64 (d, J = 10.8 Hz, 1H), 6.47 (td, J = 9.5, 2.2 Hz, 1H), 6.32 (d, J = 15.9 Hz, 1H), 6.13 (s, 1H), 5.84 (d, J = 11.4 Hz, 1H), 5.74 – 5.49 (m, 1H), 4.76 (s, 2H), 4.38 – 4.30 (m, 1H), 4.26 – 4.11 (m, 3H), 3.95 – 3.75 (m, 4H), 3.51 (s, 3H), 2.91 (t, J = 5.0 Hz, 2H), 2.37 (s, 3H), 2.13 – 2.04 (m, 1H), 2.04 – 1.94 (m, 1H), 1.94 – 1.84 (m, 1H), 1.53 – 1.32 (m, 6H), 1.29 – 1.21 (m, 3H).
1009		LCMS m/z [M+1]: 681.3 ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 6.95 – 6.78 (m, 1H), 6.65 – 6.54 (m, 2H), 6.32 (d, J = 16.4 Hz, 2H), 5.83 (d, J = 10.4 Hz, 1H), 5.78 – 5.60 (m, 1H), 5.51 – 5.40 (m, 2H), 4.92 (d, J = 5.2 Hz,2H), 4.58 (s, 2H), 4.38 – 4.28 (m, 2H), 4.14 (s, 3H), 3.65 – 3.54 (m, 1H), 3.17 (s, 3H), 2.85 – 2.74 (m, 2H), 2.69 (s, 3H), 1.88 – 1.78 (m, 1H), 1.70 – 1.59 (m, 1H), 1.55 – 1.41 (m, 3H), 1.31 – 1.25 (m, 3H).

1010		LCMS m/z [M+1]: 681.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 6.97 – 6.78 (m, 1H), 6.65 – 6.52 (m, 2H), 6.32 (d, J = 16.0 Hz, 2H), 5.83 (d, J = 10.4 Hz, 1H), 5.79 – 5.53 (m, 1H), 5.50 – 5.39 (m, 2H), 4.91 (d, J = 5.2 Hz, 2H), 4.74 – 4.53 (m, 1H), 4.38 – 4.27 (m, 2H), 3.83 (s, 3H), 3.64 – 3.52 (m, 1H), 3.16 (s, 3H), 2.83 – 2.73 (m, 2H), 2.63 (s, 3H), 1.88 – 1.75 (m, 1H), 1.71 – 1.59 (m, 1H), 1.57 – 1.40 (m, 3H), 1.32 – 1.17 (m, 3H).
1011		LCMS m/z [M+1]: 698.1 ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (d, J = 1.4 Hz, 1H), 7.96 (dd, J = 8.5, 1.6 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 6.83 (dd, J = 16.7, 10.7 Hz, 1H), 6.71 (d, J = 11.0 Hz, 1H), 6.64 – 6.52 (m, 2H), 6.28 (s, 1H), 6.13 (s, 1H), 5.80 (d, J = 10.5 Hz, 1H), 5.46 (s, 1H), 4.20 – 4.06 (m, 2H), 3.97 – 3.82 (m, 6H), 2.19 – 2.09 (m, 1H), 2.07 – 1.99 (m, 1H), 1.98 – 1.87 (m, 1H), 1.54 – 1.32 (m, 6H), 1.19 (d, J = 6.9 Hz, 3H).
1012		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.82 - 7.77 (m, 1H), 7.52 (d, J = 2.5 Hz, 1H), 6.88 – 6.78 (m, 1H), 6.74 – 6.68 (m, 1H), 6.62 – 6.55 (m, 1H), 6.42 – 6.13 (m, 2H), 5.80 (d, J = 10.8 Hz, 1H), 5.53 – 5.40 (m, 1H), 4.21 – 4.06 (m, 5H), 3.97 – 3.89 (m, 1H), 3.86 (d, J = 6.2 Hz, 2H), 2.72 (s, 3H), 2.17 – 2.08 (m, 1H), 2.07 – 2.01 (m, 1H), 1.98 – 1.89 (m, 1H), 1.55 – 1.38 (m, 5H), 1.19 (d, J = 6.9 Hz, 3H).

1013		LCMS m/z [M+1]: 698.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (d, J = 1.2 Hz, 1H), 7.96 (dd, J = 8.6, 1.6 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.48 (d, J = 2.5 Hz, 1H), 7.27 (d, J = 3.1 Hz, 1H), 6.94 - 6.75 (m, 1H), 6.64 - 6.50 (m, 3H), 6.31 (d, J = 16.7 Hz, 1H), 6.24 - 6.05 (m, 1H), 5.82 (dd, J = 10.6, 1.6 Hz, 1H), 5.76 - 5.40 (m, 1H), 4.43 - 4.35 (m, 1H), 4.34 - 4.25 (m, 1H), 3.88 (s, 3H), 3.60 - 3.51 (m, 1H), 3.13 (s, 3H), 2.80 - 2.67 (m, 2H), 1.85 - 1.71 (m, 1H), 1.65 - 1.52 (m, 1H), 1.52 - 1.35 (m, 3H), 1.35 - 1.20 (m, 3H).
1014		LCMS m/z [M+1]: 591.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (d, J = 4.8 Hz, 2H), 7.53 (d, J = 2.5 Hz, 1H), 7.49 – 7.39 (m, 2H), 6.72 (d, J = 10.8 Hz, 1H), 6.60 (td, J = 9.2, 2.3 Hz, 1H), 6.01 (d, J = 2.3 Hz, 1H), 4.75 - 4.31 (m, 2H), 3.97 – 3.74 (m, 7H), 3.41 - 3.30 (m, 2H), 3.12 (s, 3H), 2.21 – 1.85 (m, 3H), 1.50-1.25 (m, 2H).
1015		LCMS m/z [M+1]: 738.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 6.88 - 6.79 (m, 1H), 6.68 - 6.60 (m, 1H), 6.51 (d, J = 10.6 Hz, 1H), 6.39 - 6.18 (m, 2H), 5.81 (d, J = 9.6 Hz, 1H), 5.55 - 5.42 (m, 1H), 4.65 - 4.40 (m, 1H), 4.38 - 4.26(m, 1H), 4.18 (s, 3H), 4.15 - 4.10 (m, 1H), 4.07 - 3.95 (m, 2H), 3.62 - 3.45 (m, 1H), 3.25 - 3.21 (m, 1H), 2.83 - 2.78 (m, 2H), 2.73 (s, 3H), 2.25 - 1.95 (m, 3H), 1.70 - 1.62 (m, 1H), 1.58 - 1.51 (m, 3H), 1.19 (d, J = 6.2 Hz, 3H).

1016		LCMS m/z [M+1]: 713.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.81 (dd, J = 8.6 Hz, 1.4 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 6.90 - 6.79 (m, 1H), 6.72 - 6.64 (m, 1H), 6.56 (d, J = 10.6 Hz, 1H), 6.34 - 6.19 (m, 1H), 6.06 (s, 1H), 5.81 (d, J =10.8 Hz, 1H), 5.53 - 5.36 (m, 1H), 4.34 - 4.24 (m, 2H), 4.19 (s, 3H), 4.17 - 4.14 (m, 1H), 3.58 - 3.49 (m, 1H), 3.34 (s, 1H), 3.13 (s, 3H), 2.74 (s, 3H), 2.72 - 2.65 (m, 1H), 1.84 - 1.75 (m, 1H), 1.51 (d, J = 6.2 Hz, 3H), 1.36 - 1.26 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H).
1017		LCMS m/z [M+1]: 671.3 ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.94 – 7.84 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 6.96 – 6.80 (m, 1H), 6.79 – 6.51 (m, 2H), 6.39 – 6.25 (m, 1H), 6.25 – 6.19 (m, 1H), 5.90 – 5.45 (m, 3H), 4.44 – 4.32 (m, 1H), 4.18 – 4.07 (m, 1H), 4.05 – 3.96 (m, 1H), 3.86 (s, 3H), 3.57 – 3.41 (m, 3H), 3.23 – 3.06 (m, 5H), 2.65 (s, 3H), 2.51 – 2.25 (m, 2H), 1.52 – 1.38 (m, 3H), 1.32 – 1.17 (m, 3H).
1018		LCMS m/z [M+1]: 671.2 ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (d, J = 1.1 Hz, 1H), 7.92 – 7.86 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 6.95 – 6.78 (m, 1H), 6.78 – 6.68 (m, 1H), 6.69 – 6.54 (m, 1H), 6.37 – 6.16 (m, 2H), 5.95 – 5.43 (m, 3H), 4.43 – 4.30 (m, 1H), 4.16 – 4.08 (m, 1H), 4.06 – 3.92 (m, 1H), 3.85 (s, 3H), 3.55 – 3.40 (m, 3H), 3.22 – 3.06 (m, 4H), 2.65 (s, 3H), 2.52 – 2.26 (m, 2H), 1.56 – 1.35 (m, 3H), 1.30 – 1.15 (m, 3H).

Biological Assays

Biological Example 1: Covalent modification assay using MALDI-TOF MS

[000782] Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) analysis of covalent modification of Cys242 in human PIK3CA (157-299) was performed using 3.33 μM protein target, and 1:7.5 protein to compound ratio.

[000783] Reaction: 3.33 μM of PIK3CA (157-299) protein (produced in-house by Protein Expression Laboratory, FNLCR/Leidos Biomed) in 20 mM HEPES buffer containing 150 mM NaCl, 2 mM $MgCl_2$, pH 7.3 was prepared freshly before assay. Twelve-μL aliquots of protein were dispensed onto low volume 384-well plate, then 470 nL DMSO and 30 nL of tested compounds from 10 mM DMSO stocks were added to appropriate wells using ECHO 555 acoustic liquid handler (Labcyte Inc.). For each reaction/assay, three blanks were prepared by mixing 12 μL of protein solution with 500 nL DMSO. The wells' content was carefully mixed by aspiration, and then the plate was sealed by an adhesive cover, centrifuged at 931 *g* for 1 minute, and kept in the dark at room temperature until 15 min, 30 min, 2 h, or 4 h collections.

[000784] Target pretreatment: Before each assay, MALDI target (Bruker MPT 384 ground steel BC) was pre-treated by pipetting on each spot 0.75 μL of saturated sinapinic acid in acetonitrile (ACN). This step significantly improves the uniformity of sample crystallization across the plate resulting in enhanced sensitivity.

[000785] Sample preparation: At collection time point, 2 μL of reaction mixtures were pipetted out into 20 μL MALDI matrix solution (saturated solution of sinapinic acid in 1:1 ACN:water solution containing 0.15% trifluoroacetic acid (TFA)) deposited on 384 well polypropylene plate. The resulting solution was mixed by aspiration, centrifuged at 931 *g* for 1 minute, then 1.5 μL aliquots were dispensed on a pre-treated MALDI target using Beckman Coulter Biomek FX^P 96/384-Span-8 Laboratory Automation Workstation. Finally, the MALDI target was dried under a mild vacuum to produce spots with a fine crystalline structure.

[000786] Measurements: MALDI-TOF measurements were performed on Bruker Daltonics rapifleX Tissuetyper TOF-TOF mass spectrometer using linear mode and mass ranging from 16.0 to 19.6 kDa. Detector gain was set to 0.64× (459 V), sample rate to 5 GS/s, real-time smoothing to medium (175 MHz), laser smart beam pattern was set to "Custom" single smartbeam beam scan with a scan range of 40 μm on both X and Y axis, and the laser frequency was 10000 Hz. Spectra were automatically collected using the custom AutoXecute method. Laser power was auto adjusted using fuzzy control. The peak selection range was set to be between 16.0 and 18.5 kDa. Peak evaluation uses a half-width parameter set to be smaller than 40 Da for processed spectrograms (centroid peak detection; smoothed by SavitzkyGolay algorithm using 7 m/z width and 2 cycles; baseline was subtracted using a median algorithm with flatness 1 and median level 0). Fuzzy control used Proteins/Oligonucleotides protocol with minimum half-width 1/10 times above threshold. Up to 40000 satisfactory shots were collected in 10000 short steps. Dynamic termination was implemented to finish data collection when the peak signal/noise ratio reached a value of 1000.

[000787] Spectra processing: Spectra were smoothed by SavitzkyGolay algorithm using 7 m/z width and three cycles. Centroid peak detection algorithm was used with signal to noise threshold set to 6, relative intensity threshold 3%, peak width 10 m/z, and median baseline subtraction using flatness of 1 and a median

level of 0.1. Peak intensity and area under the peak were evaluated and recorded for all peaks between 16.0 and 19.5 kDa.

[000788] Calculation of percent modification: Percent modification was calculated as a ratio of the peak height for protein modified by a compound to the sum of the peak height of the remaining protein plus the peak height for protein modified by a compound. If multiple modifications were observed, each was calculated as a ratio of peak height for a given modification versus the sum of peak heights for all observed protein species.

[000789] Data reported in Table 4 are from 4 h reaction time point. "A" means percent of modification of PIK3CA protein ≥ 75%; "B" means 50 ≤ percent of modification < 75%; "C" means 25% ≤ percent of modification < 50%; "D" means percent of modification < 25%. In Table 4, "Cmd" means "Compound" and "%mod" means "% of modification." Data for compounds 1-3 were collected using 3.33 μM protein target and 1:7.5 protein to compound ratio; data for compounds 4-911 were collected using 1 μM protein target with 1:5 protein to compound ratio.

Table 4. Covalent modification using MALDI-TOF MS of selected compounds.

Cmpd. No.	% mod	Cmpd. No.	% mod	Cmpd. No.	% mod
1	C	19	D	37	A
2	C	20	A	38	A
3	A	21	A	39	A
4	D	22	D	40	A
5	B	23	A	41	A
6	D	24	A	42	B
7	A	25	A	43	A
8	D	26	A	44	D
9	D	27	A	45	A
10	D	28	A	46	A
11	D	29	D	47	A
12	A	30	B	48	B
13	B	31	D	49	A
14	A	32	A	50	D
15	D	33	A	51	A
16	D	34	A	52	A
17	A	35	A	53	A
18	C	36	D	54	A

Cmpd. No.	% mod
55	B
56	D
57	A
58	D
59	A
60	A
61	D
62	A
63	D
64	A
65	A
66	D
67	A
68	A
69	A
70	A
71	A
72	A
73	D
74	A
75	A
76	A
77	A
78	C
79	D
80	D
81	D
82	D
83	B
84	B
85	A
86	A

Cmpd. No.	% mod
87	D
88	A
89	D
90	B
91	A
92	A
93	A
94	B
95	D
96	B
97	A
98	A
99	A
100	A
101	A
102	A
103	A
104	A
105	A
106	A
107	A
108	B
109	A
110	B
111	A
112	A
113	A
114	A
115	A
116	A
117	A
118	A

Cmpd. No.	% mod
119	A
120	D
121	D
122	D
123	A
124	A
125	A
126	D
127	A
128	A
129	D
130	A
131	A
132	A
133	A
134	D
135	A
136	A
137	A
138	D
139	A
140	C
141	A
142	A
143	C
144	C
145	D
146	A
147	A
148	B
149	A
150	D

Cmpd. No.	% mod
151	A
152	A
153	A
154	D
155	A
156	A
157	D
158	D
159	D
160	A
161	A
162	A
163	A
164	A
165	A
166	A
167	A
168	B
169	D
170	A
171	A
172	A
173	D
174	D
175	A
176	A
177	D
178	A
179	A
180	A
181	A
182	A

Cmpd. No.	% mod
183	A
184	D
185	A
186	A
187	A
188	A
189	A
190	A
191	A
192	A
193	A
194	A
195	A
196	A
197	A
198	A
199	A
200	A
201	A
202	A
203	A
204	A
205	A
206	C
207	A
208	A
209	A
210	A
211	A
212	A
213	A
214	A

Cmpd. No.	% mod
215	A
216	A
217	A
218	A
219	A
220	D
221	A
222	D
223	A
224	D
225	D
226	A
227	D
228	A
229	A
230	A
231	A
232	A
233	A
234	A
235	C
236	A
237	A
238	A
239	A
240	A
241	A
242	A
243	A
244	A
245	A
246	A

Cmpd. No.	% mod
247	A
248	A
249	A
250	A
251	A
252	A
253	A
254	A
255	A
256	A
257	A
258	A
259	A
260	A
261	A
262	A
263	A
264	A
265	A
266	A
267	A
268	A
269	A
270	A
271	A
272	A
273	A
274	A
275	A
276	A
277	A
278	A

Cmpd. No.	% mod
279	A
280	A
281	A
282	A
283	A
284	A
285	A
286	A
287	A
288	A
289	A
290	A
291	D
292	A
293	A
294	A
295	A
296	A
297	A
298	A
299	A
300	A
301	A
302	A
303	A
304	A
305	A
306	A
307	D
308	A
309	A
310	A

Cmpd. No.	% mod
311	D
312	D
313	D
314	D
315	A
316	A
317	A
318	A
319	A
320	A
321	A
322	A
323	A
324	A
325	A
326	A
327	A
328	A
329	A
330	A
331	A
332	A
333	A
334	A
335	A
336	A
337	A
338	A
339	A
340	A
341	A
342	A

Cmpd. No.	% mod
343	A
344	A
345	A
346	A
347	A
348	A
349	A
350	A
351	A
352	D
353	A
354	D
355	A
356	A
357	A
358	A
359	A
360	A
361	A
362	A
363	A
364	A
365	A
366	A
367	A
368	A
369	A
370	A
371	C
372	A
373	A
374	A

Cmpd. No.	% mod
375	A
376	A
377	A
378	A
379	A
380	A
381	A
382	A
383	A
384	A
385	A
386	A
387	A
388	A
389	A
390	A
391	A
392	A
393	A
394	A
395	A
396	C
397	A
398	D
399	A
400	B
401	A
402	A
403	A
404	A
405	A
406	A

Cmpd. No.	% mod
407	A
408	A
409	A
410	A
411	A
412	A
413	D
414	A
415	A
416	A
417	A
418	A
419	D
420	A
421	D
422	A
423	A
424	D
425	D
426	D
427	A
428	D
429	A
430	D
431	A
432	A
433	A
434	A
435	A
436	A
437	A
438	D

Cmpd. No.	% mod
439	A
440	A
441	A
442	A
443	A
444	A
445	A
446	A
447	A
448	A
449	D
450	A
451	A
452	A
453	A
454	A
455	A
456	A
457	A
458	A
459	A
460	A
461	A
462	A
463	A
464	A
465	A
466	A
467	A
468	A
469	A
470	A

Cmpd. No.	% mod
471	A
472	A
473	A
474	A
475	A
476	A
477	A
478	A
479	A
480	A
481	A
482	A
483	D
484	D
485	A
486	C
487	A
488	A
489	A
490	A
491	A
492	A
493	A
494	A
495	D
496	A
497	A
498	A
499	A
500	A
501	D
502	D

Cmpd. No.	% mod
503	A
504	A
505	A
506	D
507	A
508	A
509	A
510	A
511	A
512	A
513	A
514	A
515	A
516	A
517	A
518	A
519	A
520	A
521	A
522	A
523	D
524	A
525	A
526	A
527	D
528	A
529	A
530	A
531	A
532	A
533	A
534	A

Cmpd. No.	% mod
535	A
536	A
537	A
538	D
539	A
540	A
541	A
542	D
543	A
544	A
545	A
546	A
547	A
548	A
549	D
550	A
551	A
552	D
553	D
554	A
555	D
556	A
557	D
558	D
559	D
560	A
561	A
562	D
563	A
564	A
565	A
566	A

Cmpd. No.	% mod
567	A
568	A
569	A
570	A
571	A
572	A
573	A
574	A
575	A
576	A
577	A
578	A
579	A
580	A
581	A
582	A
583	A
584	A
585	A
586	A
587	A
588	A
589	A
590	A
591	A
592	A
593	A
594	A
595	A
596	A
597	A
598	A

Cmpd. No.	% mod
599	A
600	A
601	C
602	A
603	A
604	D
605	D
606	A
607	A
608	A
609	A
610	A
611	A
612	D
613	D
614	A
615	A
616	A
617	A
618	A
619	A
620	A
621	A
622	A
623	A
624	D
625	D
626	A
627	A
628	D
629	A
630	A

Cmpd. No.	% mod
631	A
632	D
633	A
634	D
635	A
636	A
637	C
638	D
639	A
640	A
641	A
642	A
643	D
644	A
645	A
646	D
647	D
648	A
649	A
650	A
651	A
652	A
653	A
654	A
655	A
656	A
657	A
658	A
659	A
660	A
661	A
662	A

Cmpd. No.	% mod
663	A
664	A
665	A
666	A
667	A
668	A
669	A
670	A
671	A
672	A
673	A
674	A
675	C
676	A
677	A
678	A
679	A
680	A
681	A
682	A
683	A
684	A
685	D
686	D
687	A
688	A
689	A
690	B
691	B
692	A
693	A
694	A

Cmpd. No.	% mod
695	A
696	A
697	A
698	A
699	A
700	A
701	A
702	A
703	A
704	A
705	A
706	A
707	D
708	A
709	D
710	A
711	D
712	A
713	D
714	A
715	A
716	A
717	D
718	A
719	A
720	A
721	A
722	A
723	A
724	A
725	A
726	A

Cmpd. No.	% mod
727	D
728	A
729	A
730	A
731	A
732	A
733	A
734	A
735	A
736	A
737	A
738	A
739	A
740	D
741	A
742	A
743	A
744	A
745	A
746	D
747	A
748	A
749	A
750	A
751	A
752	A
753	A
754	A
755	A
756	A
757	A
758	A

Cmpd. No.	% mod
759	A
760	A
761	A
762	A
763	A
764	A
765	A
766	A
767	A
768	A
769	A
770	A
771	A
772	A
773	A
774	A
775	C
776	A
777	A
778	A
779	A
780	A
781	A
782	A
783	A
784	A
785	D
786	A
787	A
788	A
789	D
790	A

Cmpd. No.	% mod
791	A
792	A
793	A
794	A
795	D
796	D
797	A
798	C
799	A
800	D
801	A
802	A
803	A
804	A
805	A
806	A
807	D
808	A
809	D
810	D
811	A
812	A
813	A
814	A
815	A
816	A
817	A
818	A
819	A
820	A
821	A
822	A

Cmpd. No.	% mod
823	A
824	A
825	A
826	A
827	A
828	A
829	A
830	A
831	A
832	A
833	A
834	A
835	A
836	A
837	A
838	A
839	A
840	D
841	A
842	A
843	A
844	A
845	A
846	A
847	A
848	A
849	A
850	A
851	A
852	A
853	A
854	A

Cmpd. No.	% mod
855	A
856	A
857	A
858	C
859	A
860	D
861	A
862	A
863	A
864	A
865	A
866	A
867	A
868	A
869	A
870	A
871	A
872	C
873	A
874	A
875	A
876	A
877	A
878	A
879	C
880	A
881	D
882	D
883	C
884	A
885	A
886	A

Cmpd. No.	% mod
887	A
888	A
889	A
890	A
891	A
892	A
893	A
894	A
895	A
896	A
897	A
898	A
899	A
900	A
901	A
902	A
903	A
904	A
905	A
906	A
907	C
908	A
909	A
910	D
911	A
912	A
913	A
914	A
915	A
916	A
917	A
918	A

Cmpd. No.	% mod
919	A
920	A
921	A
922	A
923	A
925	A
926	A
927	A
928	A
929	A
930	A
931	A
932	A
933	A
934	A
935	A
936	A
937	A
938	A
939	A
940	A
941	A
942	A
943	A
944	A
945	A
946	A
947	A

Cmpd. No.	% mod
948	A
950	A
951	A
952	D
953	A
954	A
955	D
956	A
957	A
958	A
959	A
960	A
961	B
962	A
963	A
964	A
965	A
966	A
967	A
968	A
969	A
970	A
971	A
972	A
973	A
974	A
975	A
976	A

Cmpd. No.	% mod
977	A
978	A
979	A
980	A
981	A
982	A
983	D
984	A
985	A
986	A
987	A
988	A
989	A
990	A
991	A
992	D
994	A
995	A
996	C
997	A
1000	A
1002	A
1003	A
1005	D
1006	A
1008	A
1009	A
1010	A

Biological Example 2: Cell-based pAKT HTRF assay in BT474 cells

[000790] On Day 1, cells were seeded into 96-well plates at 2.5 x 104 cells/well in complete growth media (DMEM, 10% FBS). 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 3 μM, with a 3-fold dilution between concentrations. 20 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 (75 μL per well). Plates were then placed on a plate shaker and incubated at 850 rpm for an additional 30 min. The antibody mixture solution was prepared by diluting aliquoted d2 and Eu Cryptate antibodies 1:20 in kit supplied detection buffer, then mixed 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). 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. The 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 1 min) and 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.

[000791] IC_{50} values of selected compounds measured using this assay are provided in Table 5. For pAKT inhibition IC_{50} values shown in Table 5, "A" means $IC_{50} < 0.1$ μM; "B" means $IC_{50} \geq 0.1$ μM and < 1 μM; and "C" means $IC_{50} \geq 1$ μM.

Table 5. pAKT inhibition IC_{50} of selected compounds in BT474 cells.

Cmpd. No.	pAKT IC_{50}	Cmpd. No.	pAKT IC_{50}	Cmpd. No.	pAKT IC_{50}
2	C	13	C	24	A
3	A	14	A	25	A
4	C	15	C	26	B
5	B	16	C	27	A
6	C	17	A	28	B
7	A	18	B	29	C
8	C	19	C	30	B
9	C	20	A	31	C
10	C	21	A	32	A
11	C	22	B	33	B
12	A	23	A	34	A

Cmpd. No.	pAKT IC_{50}
35	A
36	C
37	A
38	C
39	B
40	A
41	A
42	B
43	A
44	C
45	A
46	B
47	A
48	A
49	B
50	C
51	A
52	A
53	A
54	A
55	B
56	C
57	A
58	C
59	A
60	A
61	C
62	A
63	C
64	A
65	A
66	B

Cmpd. No.	pAKT IC_{50}
67	B
68	A
69	B
70	A
71	A
72	A
73	C
74	A
75	A
76	A
77	A
78	B
79	C
80	C
81	C
82	C
83	B
84	B
85	B
86	A
87	C
88	A
89	C
90	B
91	A
92	A
93	A
94	B
95	B
96	B
97	A
98	A

Cmpd. No.	pAKT IC_{50}
99	A
100	A
101	A
102	A
103	A
104	A
105	A
106	A
107	B
108	A
109	A
110	B
111	A
112	A
113	A
114	A
115	A
116	A
117	A
118	A
119	A
120	C
121	C
122	C
123	A
124	A
125	A
126	C
127	A
128	A
129	C
130	A

Cmpd. No.	pAKT IC_{50}
131	A
132	A
133	A
134	B
135	A
136	B
137	A
138	C
139	A
140	B
141	A
142	A

Cmpd. No.	pAKT IC_{50}
143	C
144	B
145	B
146	A
147	A
148	B
149	B
150	B
151	A
152	A
153	A
154	C

Cmpd. No.	pAKT IC_{50}
311	C
363	A
364	A
365	B
366	B
367	B
368	A
369	A
370	B
371	B
372	B

Biological Example 3: Cell-based pAKT HTRF assay in SKUT-1 cells

[000792] On Day 1, cells were seeded into 96-well plates at 2 x 104 cells/well in complete growth media (DMEM, 10% FBS). 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, with a half-log dilution between concentrations. 20 μL was transferred onto the cell plates (the 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. The antibody mixture solution was prepared by diluting aliquoted d2 and Eu Cryptate antibodies 1:20 in kit supplied detection buffer, then mixed 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). 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. The 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 1 min) and 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.

[000793] IC_{50} values of selected compounds measured using this assay are provided in Table 6. For pAKT inhibition IC_{50} values shown in Table 6, "A" means $IC_{50} < 0.1$ μM; "B" means $IC_{50} \geq 0.1$ μM and < 1 μM; and "C" means $IC_{50} \geq 1$ μM.

Table 6. pAKT inhibition IC_{50} of selected compounds in SKUT-1 cells.

Cmpd. No.	pAKT IC_{50}	Cmpd. No.	pAKT IC_{50}	Cmpd. No.	pAKT IC_{50}
155	A	183	A	211	A
156	A	184	A	212	A
157	C	185	A	213	A
158	C	186	A	214	A
159	C	187	A	215	A
160	C	188	A	216	A
161	A	189	A	217	A
162	A	190	A	218	A
163	A	191	A	219	B
164	A	192	A	220	B
165	A	193	A	221	C
166	A	194	A	222	C
167	C	195	A	223	A
168	B	196	A	224	C
169	B	197	A	225	C
170	B	198	A	226	A
171	A	199	A	227	C
172	A	200	A	228	A
173	B	201	A	229	A
174	B	202	A	230	A
175	C	203	A	231	A
176	A	204	A	232	A
177	B	205	A	233	A
178	A	206	B	234	C
179	A	207	A	235	C
180	A	208	A	236	A
181	A	209	A	237	A
182	A	210	A	238	B

Cmpd. No.	pAKT IC_{50}
239	A
240	A
241	A
242	C
243	A
244	A
245	A
246	A
247	A
248	C
249	A
250	A
251	A
252	A
253	A
254	A
255	A
256	A
257	A
258	A
259	A
260	A
261	A
262	A
263	A
264	A
265	A
266	A
267	A
268	A
269	A
270	A

Cmpd. No.	pAKT IC_{50}
271	A
272	A
273	A
274	A
275	A
276	A
277	A
278	A
279	A
280	A
281	A
282	A
283	A
284	C
285	A
286	A
287	A
288	C
289	A
290	A
291	B
292	A
293	A
294	A
295	A
296	A
297	A
298	A
299	A
300	A
301	A
302	A

Cmpd. No.	pAKT IC_{50}
303	A
304	A
305	A
306	A
307	C
308	A
309	A
310	A
312	C
313	C
314	C
315	A
316	A
317	A
318	A
319	A
320	A
321	A
322	A
323	A
324	A
325	A
326	A
327	A
328	A
329	A
330	A
331	A
332	A
333	A
334	A
335	A

Cmpd. No.	pAKT IC_{50}
336	A
337	A
338	A
339	A
340	A
341	A
342	A
343	A
344	A
345	A
346	A
347	C
348	C
349	A
350	A
351	A
352	C
353	A
354	B
355	A
356	B
357	A
358	A
359	C
360	A
361	A
362	C
373	A
374	A
375	C
376	A
377	A

Cmpd. No.	pAKT IC_{50}
378	A
379	A
380	A
381	A
382	C
383	A
384	A
385	A
386	A
387	A
388	B
389	C
390	A
391	A
392	A
393	A
394	A
395	A
396	A
397	A
398	A
399	A
400	A
401	A
402	A
403	B
404	A
405	B
406	C
407	A
408	A
409	A

Cmpd. No.	pAKT IC_{50}
410	A
411	A
412	A
413	C
414	A
415	A
416	A
417	C
418	A
419	B
420	A
421	A
422	A
423	A
424	C
425	C
426	A
427	A
428	B
429	C
430	C
431	A
432	A
433	A
434	A
435	B
436	A
437	A
438	C
439	A
440	A
441	A

Cmpd. No.	pAKT IC_{50}
442	A
443	A
444	C
445	C
446	C
447	A
448	A
449	C
450	A
451	A
452	A
453	A
454	A
455	A
456	A
457	A
458	A
459	A
460	A
461	A
462	A
463	A
464	A
465	A
466	A
467	A
468	A
469	A
470	A
471	A
472	A
473	A

Cmpd. No.	pAKT IC_{50}
474	A
475	A
476	A
477	A
478	A
479	A
480	A
481	A
482	A
483	B
484	A
485	A
486	A
487	A
488	A
489	A
490	A
491	A
492	A
493	A
494	A
495	B
496	A
497	A
498	A
499	A
500	A
501	B
502	A
503	A
504	A
505	A

Cmpd. No.	pAKT IC_{50}
506	B
507	A
508	A
509	A
510	A
511	A
512	A
513	A
514	A
515	A
516	A
517	A
518	A
519	A
520	A
521	A
522	A
523	C
524	A
525	A
526	A
527	A
528	A
529	A
530	A
531	A
532	A
533	A
534	A
535	A
536	A
537	A

Cmpd. No.	pAKT IC_{50}
538	A
539	A
540	A
541	C
542	A
543	A
544	A
545	A
546	A
547	A
548	B
549	C
550	A
551	A
552	B
553	B
554	B
555	C
556	A
557	B
558	C
559	B
560	A
561	A
562	A
563	A
564	A
565	C
566	A
567	A
568	A
569	A

Cmpd. No.	pAKT IC_{50}
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572	A
573	A
574	A
575	A
576	A
577	B
578	A
579	A
580	A
581	A
582	C
583	C
584	A
585	A
586	A
587	A
588	A
589	A
590	A
591	A
592	B
593	A
594	A
595	A
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597	A
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Cmpd. No.	pAKT IC_{50}
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607	A
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615	A
616	A
617	A
618	C
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620	A
621	A
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623	A
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632	C
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Cmpd. No.	pAKT IC_{50}
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Cmpd. No.	pAKT IC_{50}
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674	A
675	B
676	A
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Cmpd. No.	pAKT IC_{50}
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705	A
706	A
707	C
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721	A
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723	A
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726	A
727	B
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Cmpd. No.	pAKT IC_{50}
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731	A
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754	A
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756	A
757	A
758	A
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761	A

Cmpd. No.	pAKT IC_{50}
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763	A
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767	A
768	A
769	A
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772	A
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780	A
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784	A
785	A
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787	A
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791	A
792	A
793	A

Cmpd. No.	pAKT IC_{50}
794	A
795	A
796	A
797	A
798	A
799	A
800	B
801	A
802	A
803	A
804	A
805	A
806	A
807	A
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809	A
810	A
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812	A
813	A
814	A
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816	A
817	A
818	A
819	A
820	A
821	A
822	A
823	A
824	A
825	A

Cmpd. No.	pAKT IC_{50}
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833	A
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835	A
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845	A
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850	A
851	A
852	A
853	A
854	A
855	A
856	A
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Cmpd. No.	pAKT IC_{50}
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862	A
863	A
864	A
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866	A
867	A
868	A
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879	C
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881	C
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883	C
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885	A
886	A
887	A
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889	A

Cmpd. No.	pAKT IC_{50}
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896	A
897	A
898	A
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900	A
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912	A
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915	A
916	A
917	A
918	A
919	A
920	A
921	A

Cmpd. No.	pAKT IC_{50}
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923	A
925	A
926	A
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928	A
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930	A
931	A
932	A
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937	A
938	A
939	A
940	A
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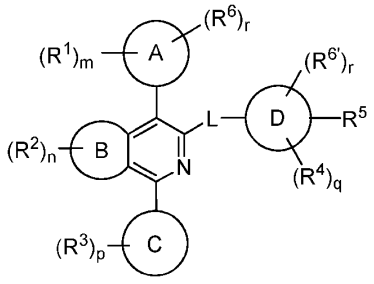
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976	A
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979	A
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981	A

Cmpd. No.	pAKT IC_{50}
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983	C
984	A
985	A
986	A
987	A
988	A
989	C
990	A
991	C
992	C
993	C
994	C
995	A
996	C
997	A
998	B
999	B
1000	C
1001	A
1002	A
1003	A
1004	B
1005	C
1006	A
1007	B
1008	C
1009	A
1010	A

[000794] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

1. A compound of Formula I'':



I''

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

Ring A is phenyl, pyridine, or a 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered carbocyclic ring; and phenyl;

Ring C is selected from phenyl; 9- to 10-membered bicyclic aryl ring, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is absent or selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; 5- to 10-membered bicyclic or polycyclic carbocyclic ring; 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is a covalent bond or a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-;

and when Ring D is absent, then L is absent;

each R^1 is independently selected from halogen, optionally substituted C_{1-6} alkyl, cycloalkyl, –CN, –C(O)OR, –C(O)NR_2, –CH_2NR_2, –$N(R^7)_2$, -N=S$(R^7)_2$, –SR^7, –(C_{1-4} alkylene)OR, and –OR^7, wherein a sulfur atom in R^1 can be oxidized;

each R^7 is independently selected from hydrogen, optionally substituted C_{1-6} aliphatic, –(C_{1-4} alkylene)OR, –(C_{1-4} alkylene)NR_2, optionally substituted 3- to 6-membered carbocyclic ring, optionally substituted 4- to 7-membered heteroaryl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

or two R^7 groups, together with the atom(s) to which they are attached, form a 4- to 6-membered hetserocyclic ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently selected from halogen and optionally substituted C_{1-6} aliphatic, and -OR;

each R^3 is independently selected from oxo, halogen, -CN, -OR, -C(O)R, -C(O)$N(R)_2$, -$(CH_2)_x$C(O)OR, -$(CH_2)_x$C(O)$N(R)_2$, -$(CH_2)_x$N(R)C(O)R, -$(CH_2)_x$Cy, -O$(CH_2)_x$Cy, -C(O)Cy, optionally substituted carbocyclic ring, and optionally substituted C_{1-6} aliphatic;

each R^4 is independently optionally substituted C_{1-6} aliphatic;

R^5 is absent, optionally substituted C_{1-6} aliphatic, -C(O)R^9, -$(CH_2)_x$N(R)C(O)R^9, or -CN;

R^9 is optionally substituted C_{2-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or a 4-membered bicyclic carbocyclic ring;

R^6 and $R^{6'}$ are connected with an optionally substituted C_{4-8} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2;

r is 0 or 1;

each x is independently 0, 1, or 2;

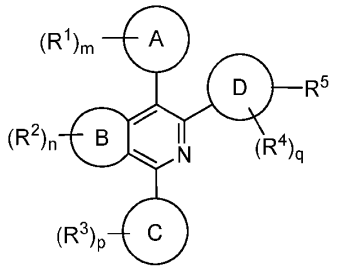
each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

each Cy is independently selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 4- to

7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8; and

each R^8 is independently selected from oxo, halogen, and optionally substituted C_{1-6} aliphatic.

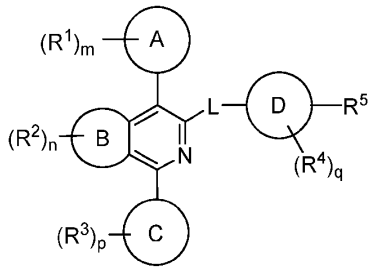
2. The compound of claim 1, wherein the compound is of Formula IC':



IC'

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

3. The compound of claim 1, wherein the compound is of Formula ID':

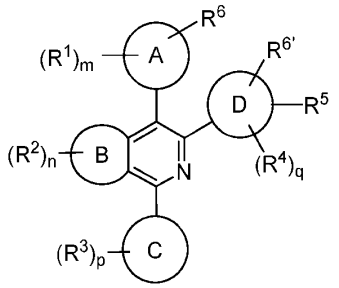


ID'

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

L is a bivalent straight or branched C_{1-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-.

4. The compound of claim 1, wherein the compound is of Formula IE':



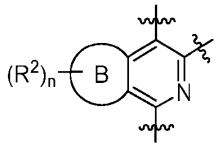
IE'

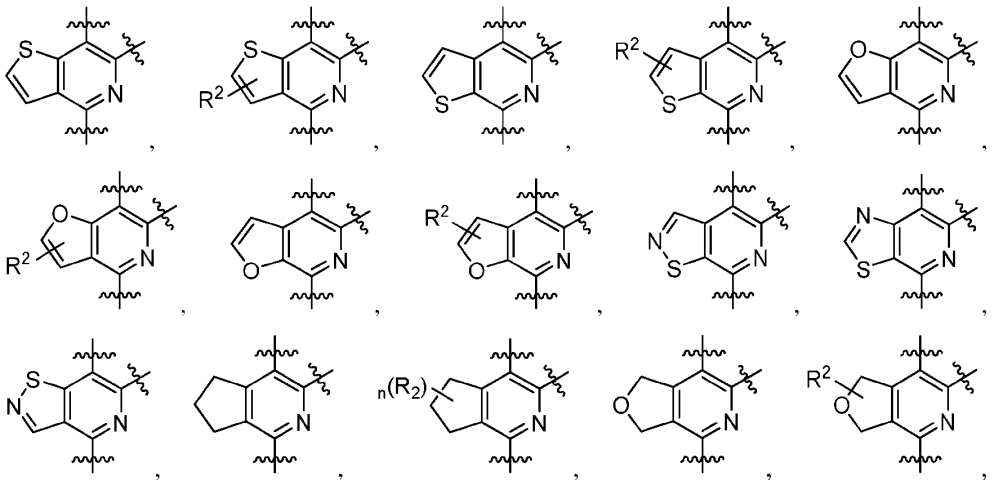
or a salt (e.g., a pharmaceutically acceptable salt) thereof.

5. The compound of any one of claims 1-4, wherein Ring B is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur and a 5-membered carbocyclic ring.

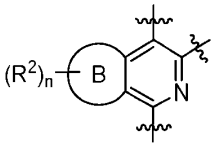
6. The compound of claim 5, wherein Ring B is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

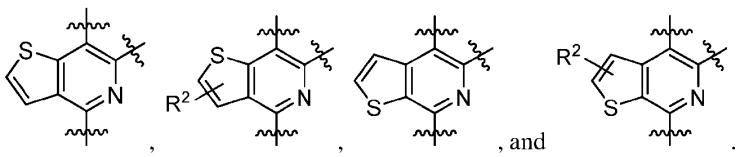
7. The compound of claim 5, wherein Ring B is a 5-membered carbocyclic ring.

8. The compound of any one of claims 1-4, wherein a moiety  is selected from:

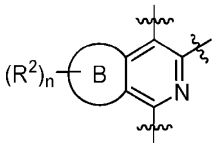
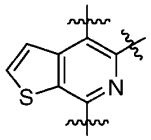


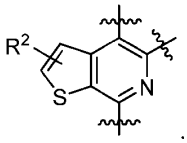
, and .

9. The compound of claim 8, wherein a moiety  is selected from:



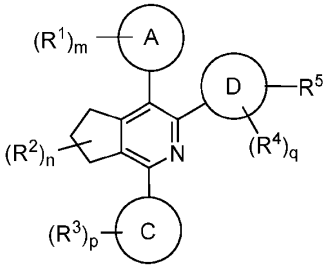
, and .

10. The compound of claim 9, wherein a moiety  is selected from: 

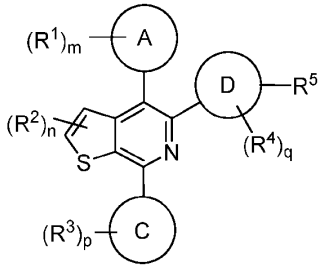


and .

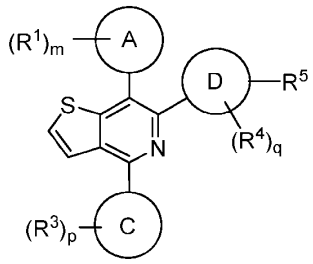
11. The compound of claim 1 or 2, wherein the compound is of Formula IC3'-a, IC3'-b, IC3'-c, IC3'-d, IC3'-e, IC3'-f, IC3'-g, IC3'-h, IC3'-i, IC3'-j, IC3'-k, IC3'-l, or IC3'-m:



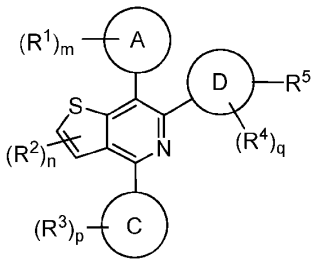
IC3'-a



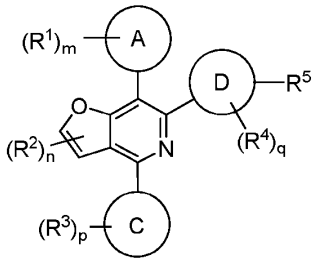
IC3'-b



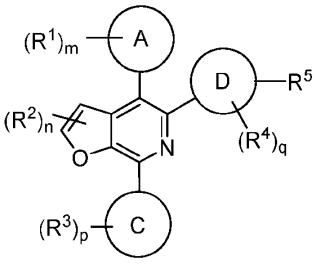
IC3'-c



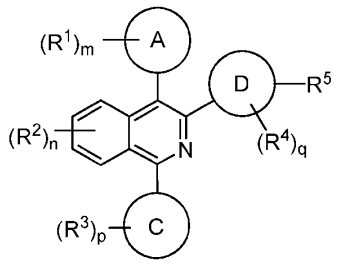
IC3'-d



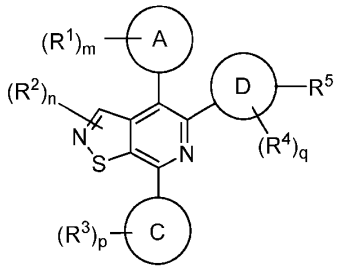
IC3'-e



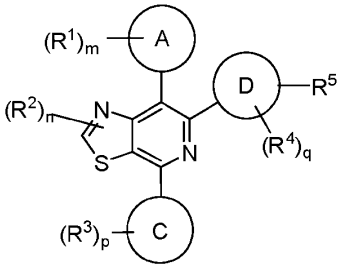
IC3'-f



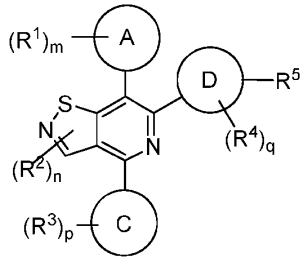
IC3'-g



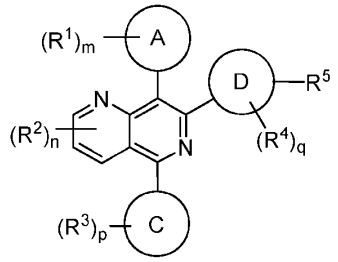
IC3'-h



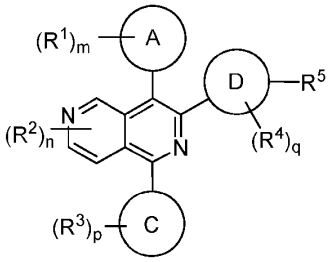
IC3'-i



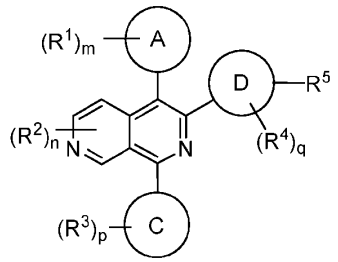
IC3'-j



IC3'-k



IC3'-l

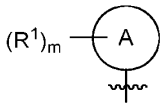
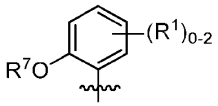


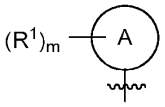
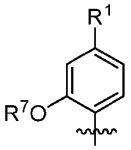
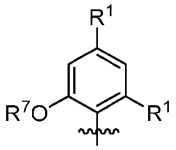
IC3'-m

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

12. The compound of claim 11, wherein the compound is of Formula IC3'-a, or a salt (e.g., a pharmaceutically acceptable salt) thereof, optionally wherein the compound is not a compound selected from Table P1.

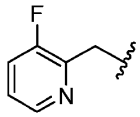
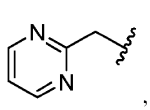
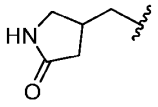
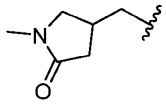
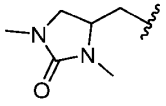
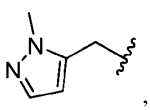
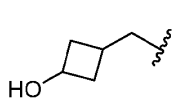
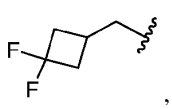
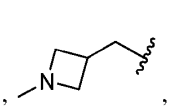
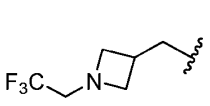
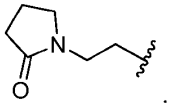
13. The compound of claim 11, wherein the compound is of Formula IC3'-b, or a salt (e.g., a pharmaceutically acceptable salt) thereof, optionally wherein the compound is not a compound selected from Table P2.
14. The compound of claim 11, wherein the compound is of Formula IC3'-c, or a salt (e.g., a pharmaceutically acceptable salt) thereof.
15. The compound of claim 11, wherein the compound is of Formula IC3'-d, or a salt (e.g., a pharmaceutically acceptable salt) thereof, optionally wherein the compound is not a compound selected from Table P3.
16. The compound of claim 11, wherein the compound is of Formula IC3'-e, or a salt (e.g., a pharmaceutically acceptable salt) thereof, optionally wherein the compound is not a compound selected from Table P4.
17. The compound of claim 11, wherein the compound is of Formula IC3'-f, or a salt (e.g., a pharmaceutically acceptable salt) thereof.
18. The compound of claim 11, wherein the compound is of Formula IC3'-g, or a salt (e.g., a pharmaceutically acceptable salt) thereof.
19. The compound of claim 11, wherein the compound is of Formula IC3'-h, or a salt (e.g., a pharmaceutically acceptable salt) thereof.
20. The compound of claim 11, wherein the compound is of Formula IC3'-i, or a salt (e.g., a pharmaceutically acceptable salt) thereof.
21. The compound of claim 11, wherein the compound is of Formula IC3'-j, or a salt (e.g., a pharmaceutically acceptable salt) thereof.
22. The compound of claim 11, wherein the compound is of Formula IC3'-k, or a salt (e.g., a pharmaceutically acceptable salt) thereof.
23. The compound of claim 11, wherein the compound is of Formula IC3'-l, or a salt (e.g., a pharmaceutically acceptable salt) thereof.
24. The compound of claim 11, wherein the compound is of Formula IC3'-m, or a salt (e.g., a pharmaceutically acceptable salt) thereof.
25. The compound of any one of claims 1-24, wherein each R^2 is independently selected from halogen and C_{1-6} alkyl.
26. The compound of claim 25, wherein each R^2 is F.
27. The compound of any one of claims 1-26, wherein n is 1.
28. The compound of any one of claims 1-27, wherein at least one R^1 is $-OR^7$.
29. The compound of claim 28, wherein one R^1 is $-OR^7$ and any other R^1 groups are halogen.

30. The compound of any one of claims 1-29, wherein a moiety  is .

31. The compound of claim 30, wherein a moiety  is  or .

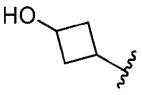
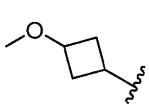
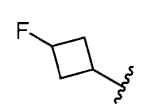
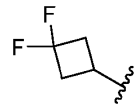
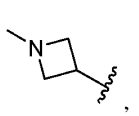
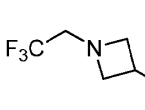
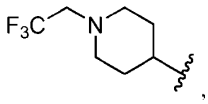
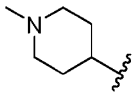
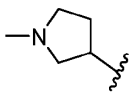
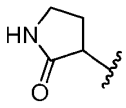
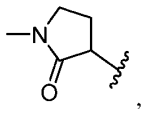
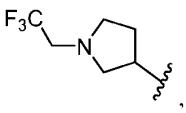
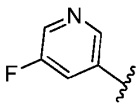
32. The compound of any one of claims 1-31, wherein each R^7 is independently selected from C_{1-6} alkyl and –(C_{1-4} alkylene)OR.

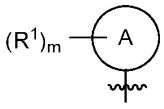
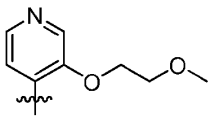
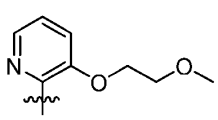
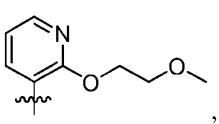
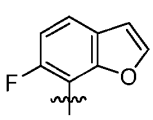
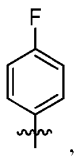
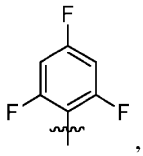
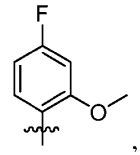
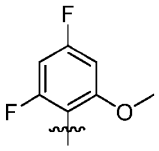
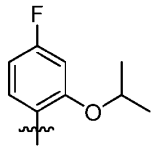
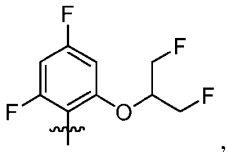
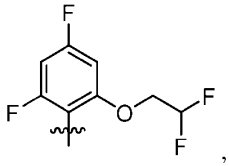
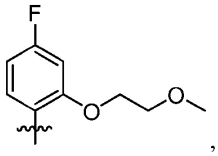
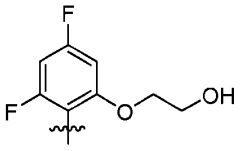
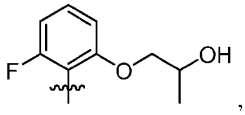
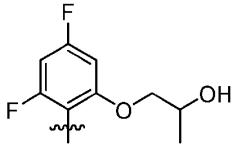
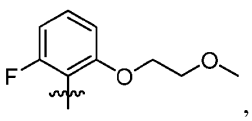
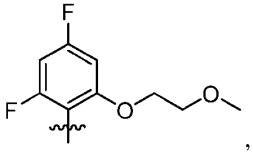
33. The compound of any one of claims 1-31, wherein each R^7 is independently selected from C_{1-6} aliphatic substituted with an optionally substituted 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; C_{1-6} aliphatic substituted with an optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and C_{1-6} aliphatic substituted with an optionally substituted 3-7 membered carbocyclic ring.

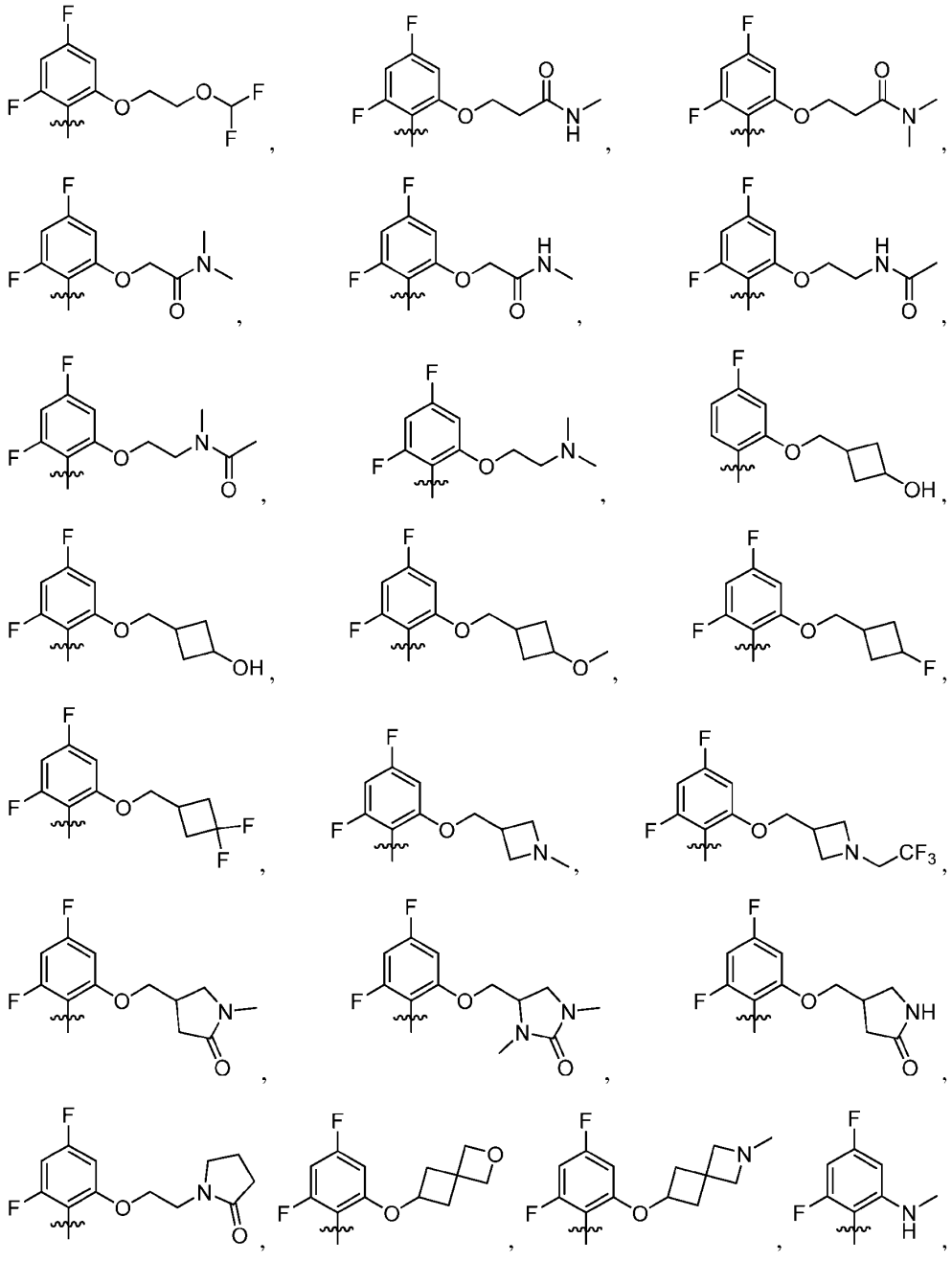
34. The compound of claim 33, wherein each R^7 is independently selected from , , , , , , , , , , and .

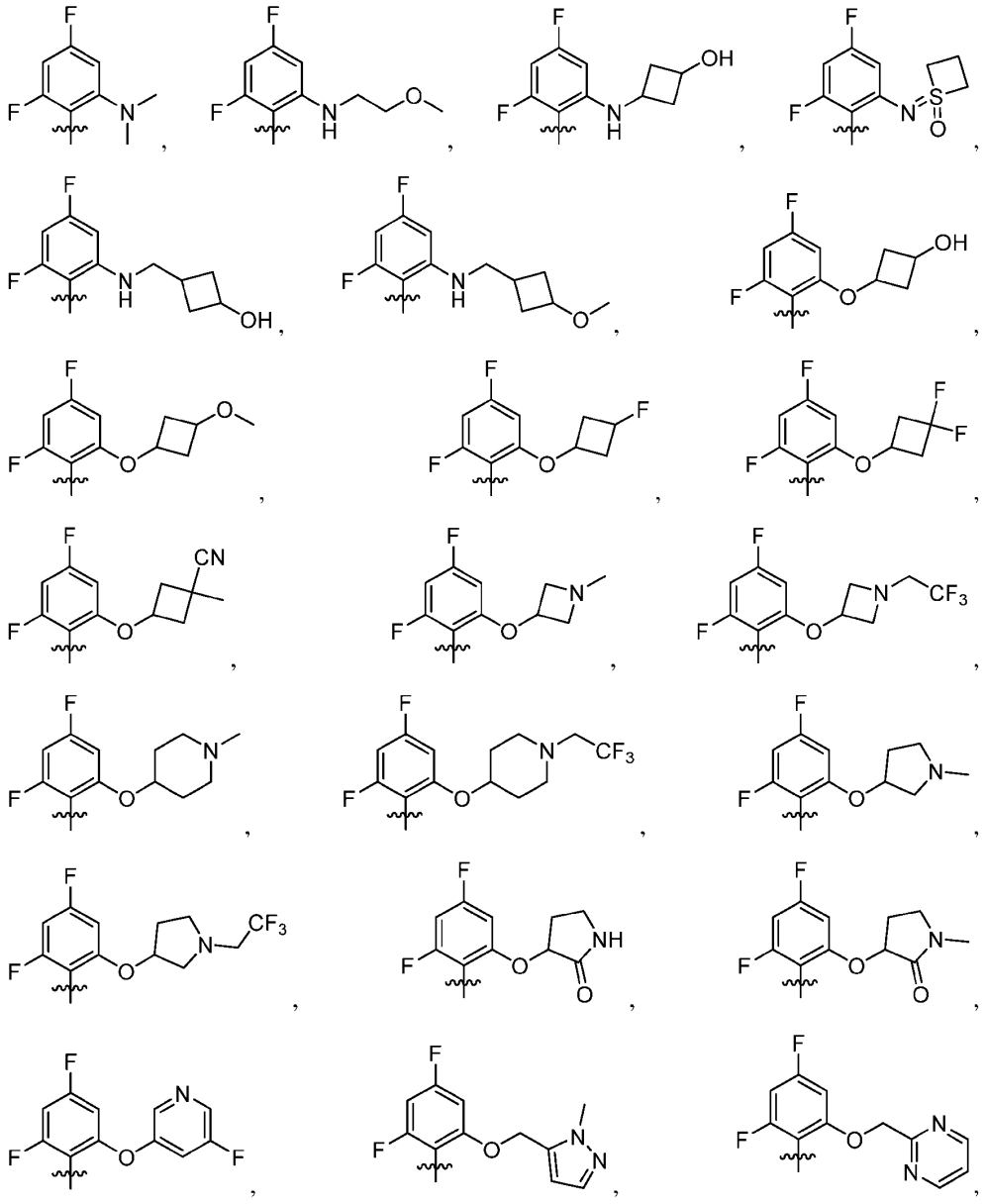
35. The compound of any one of claims 1-31, wherein each R^7 is independently selected from optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and optionally substituted 3- to 6-membered carbocyclic ring.

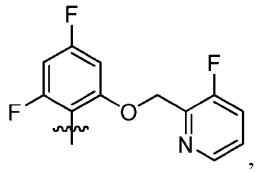
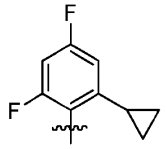
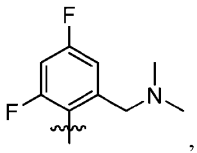
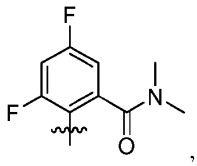
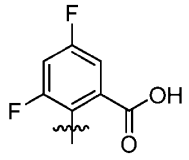
36. The compound of claim 35, wherein each R^7 is independently selected from optionally substituted pyrrolidinyl and piperidinyl.

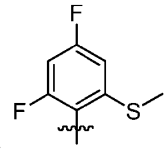
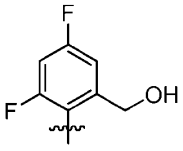
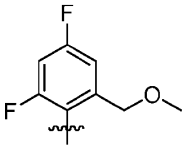
37. The compound of claim 35, wherein each R^7 is independently selected from: , , , , , , , , , , , , and .

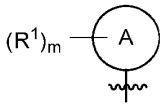
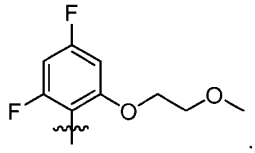
38. The compound of any one of claims 1-31, wherein a moiety  is selected from: , , , , , , , , , , , , , , , , .







, and

.

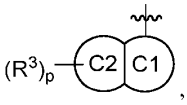
39. The compound of any one of claims 1-31, wherein a moiety  is .

40. The compound of any one of claims 1-37, wherein m is 2 or 3.

41. The compound of any one of claims 1-40, wherein Ring C is selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

42. The compound of any one of claims 1-40, wherein Ring C is selected from 9- to 10-membered bicyclic aryl ring; 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

43. The compound of claim 42, wherein Ring C is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

44. The compound of any one of claims 1-40, wherein Ring C substituted with p R^3 groups is , wherein:

Ring C1 is fused to Ring C2;

Ring C1 is selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

and

Ring C2 is selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

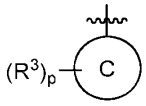
45. The compound of claim 44, wherein Ring C1 is a phenyl, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

46. The compound of claim 44, wherein Ring C1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

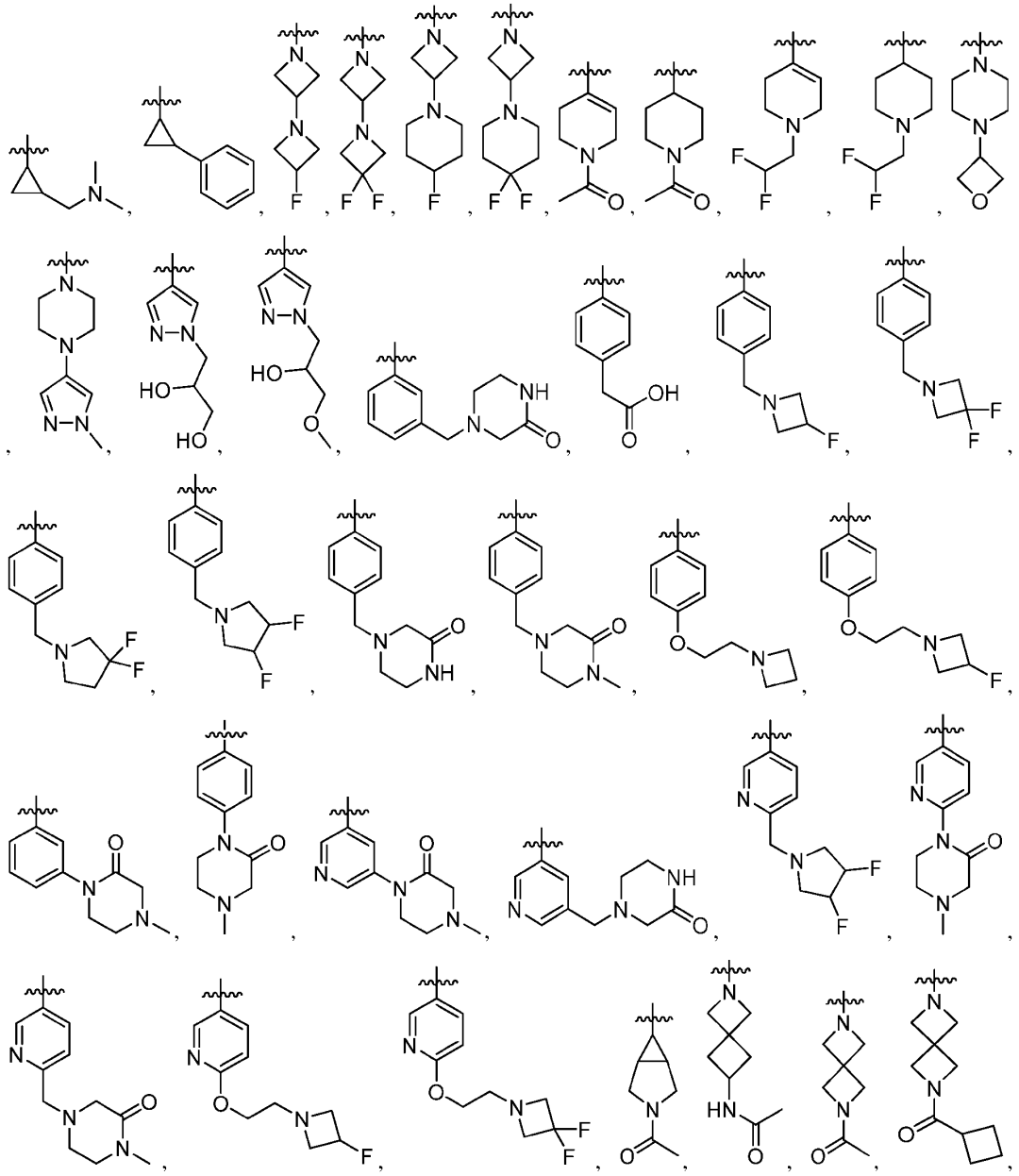
47. The compound of claim 44, wherein Ring C1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring C2 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, or 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

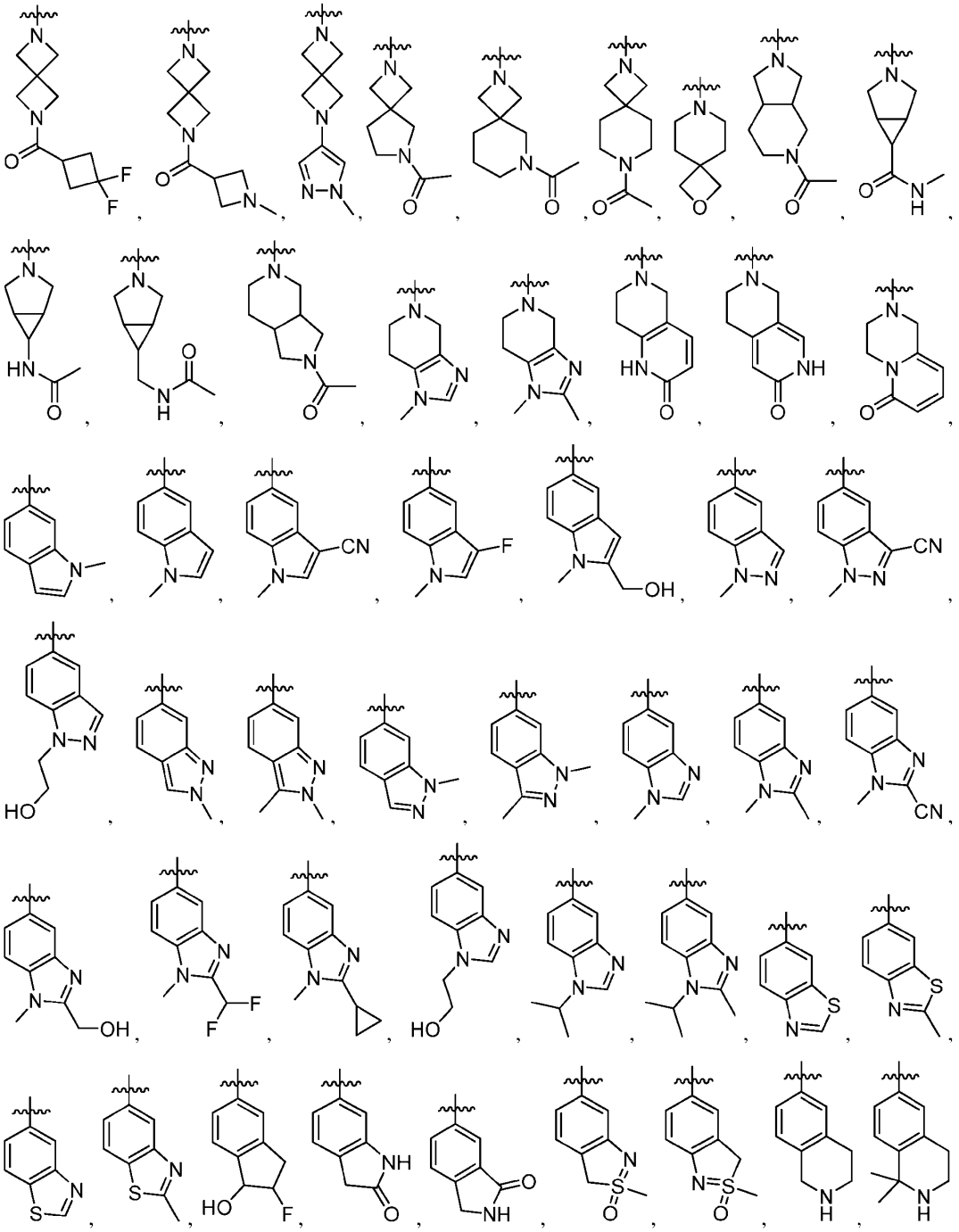
48. The compound of any one of claims 1-47, wherein each R^3 is independently selected from halogen, $-C(O)N(R)_2$, and optionally substituted C_{1-6} alkyl.

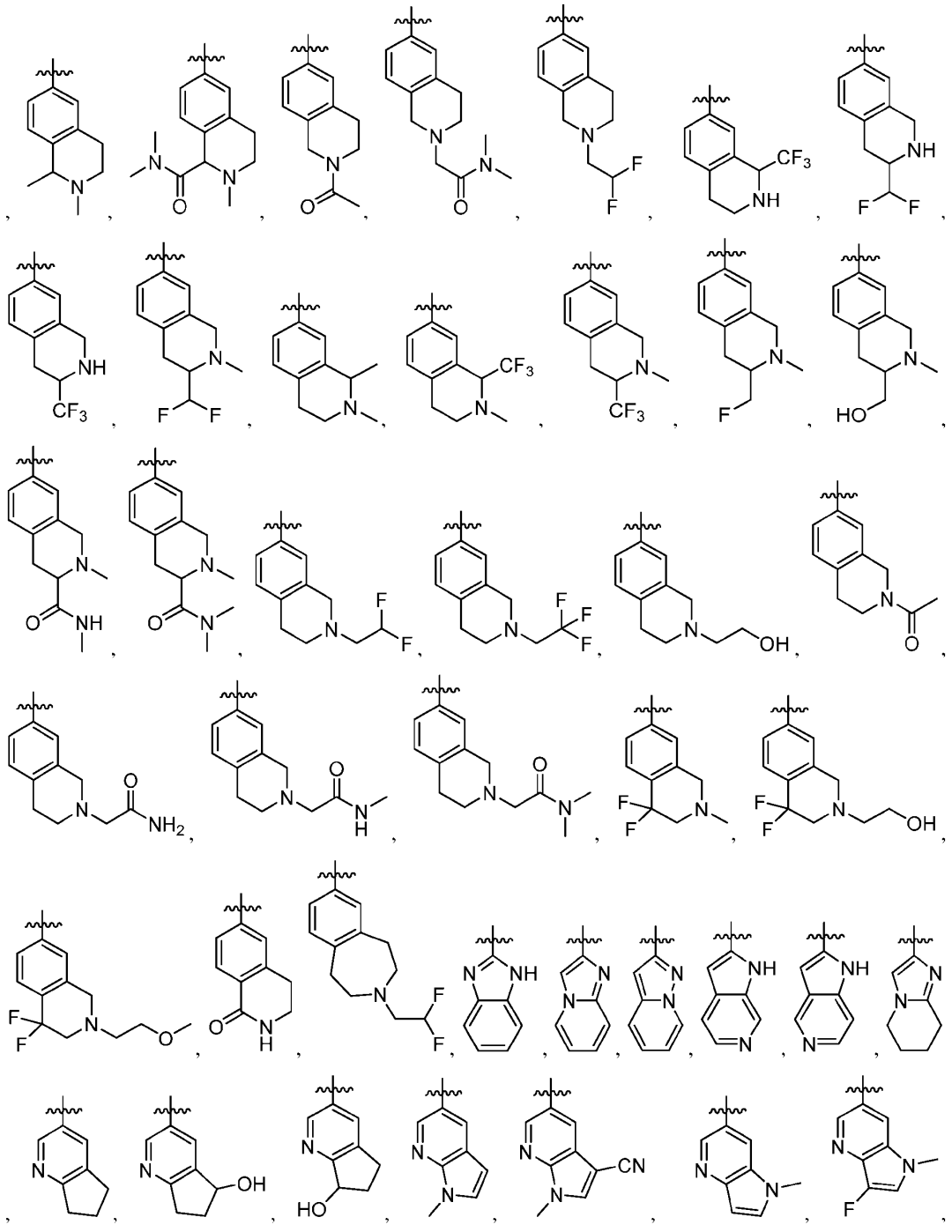
49. The compound of any one of claims 1-48, wherein p is 1, 2, or 3.

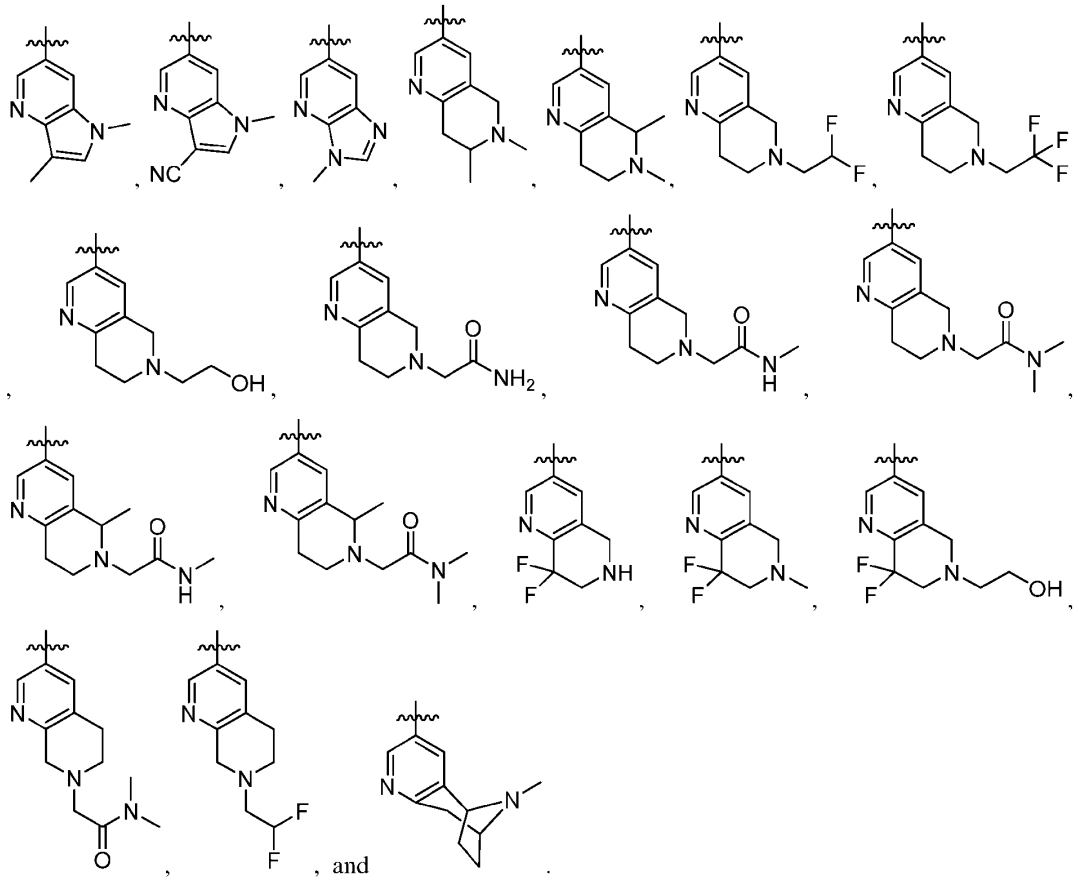
50. The compound of any one of claims 1-49, wherein a moiety 

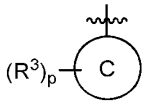
is selected from:

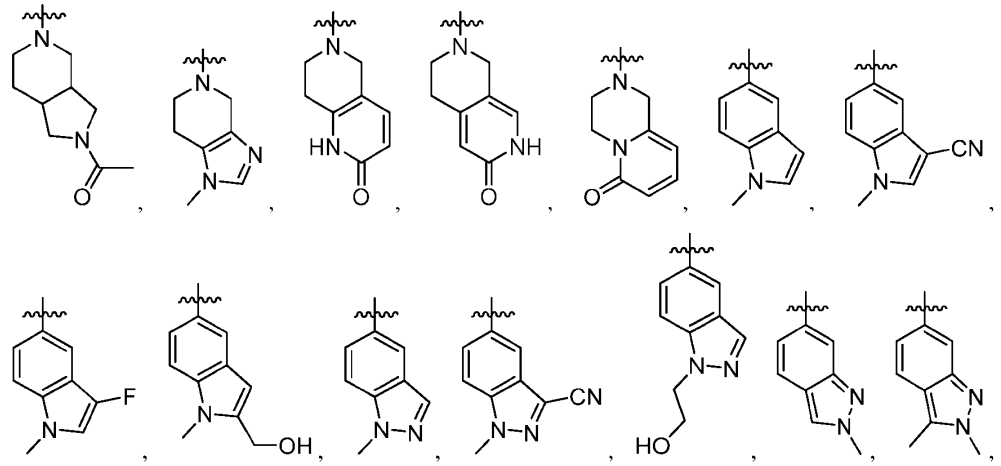


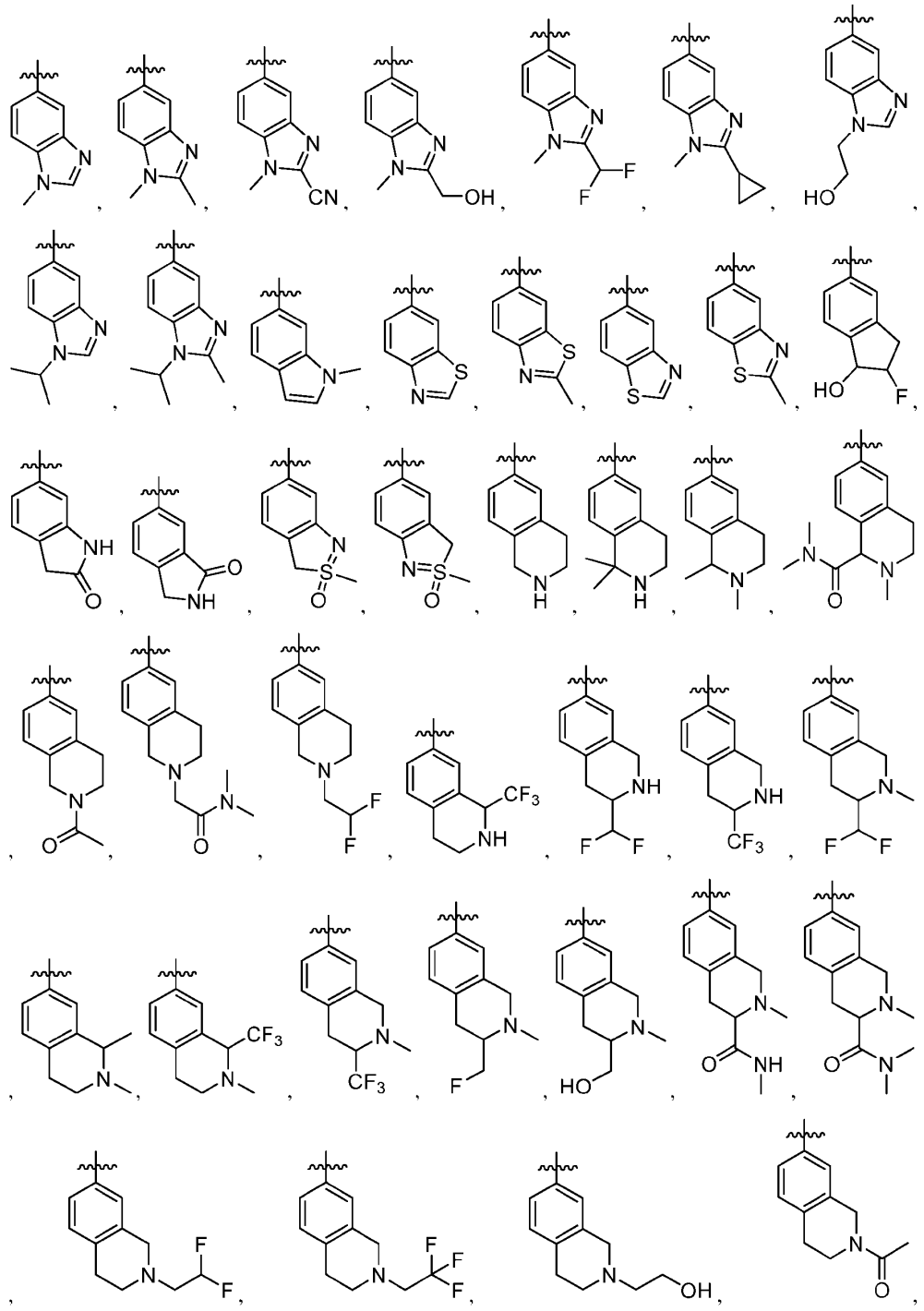


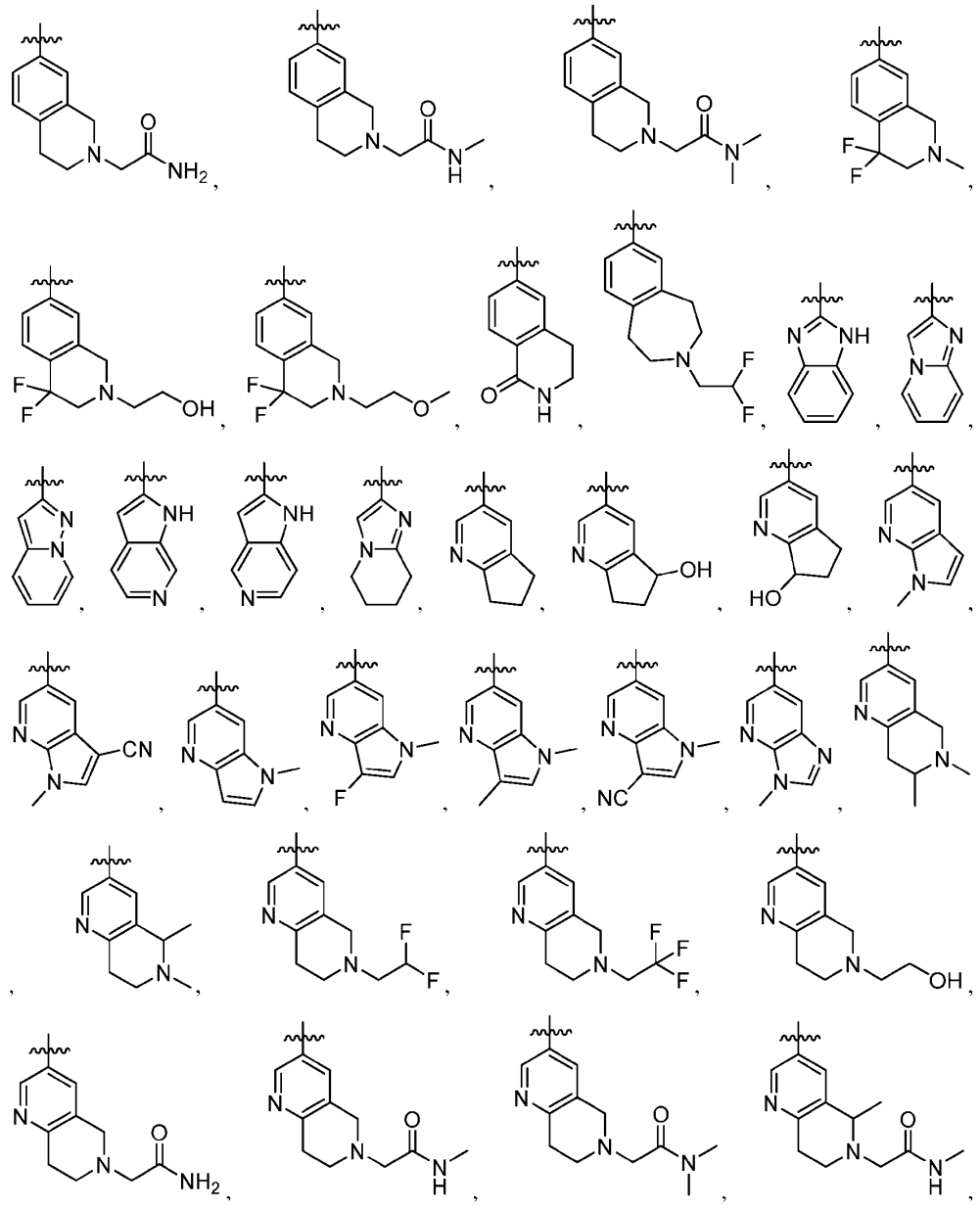


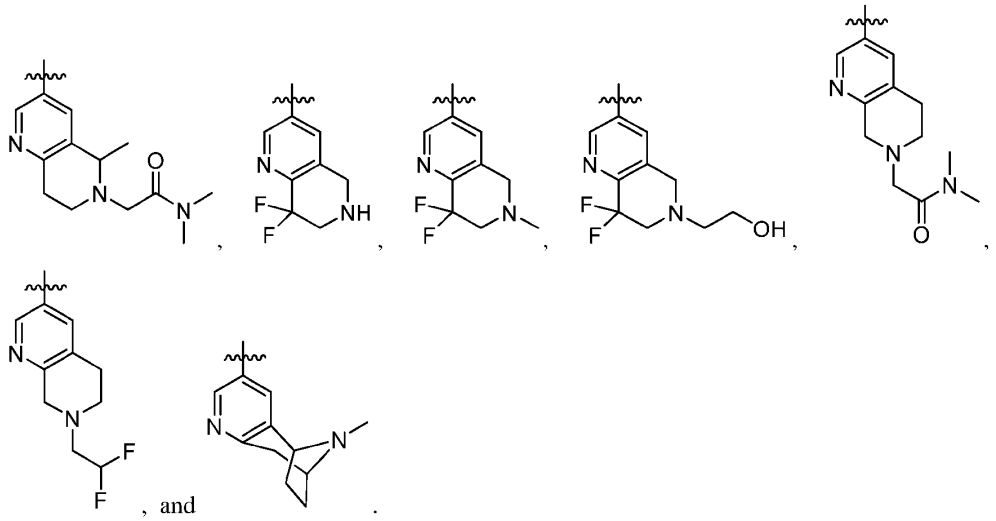


51. The compound of claim 50, wherein a moiety  is selected from:

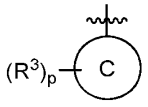


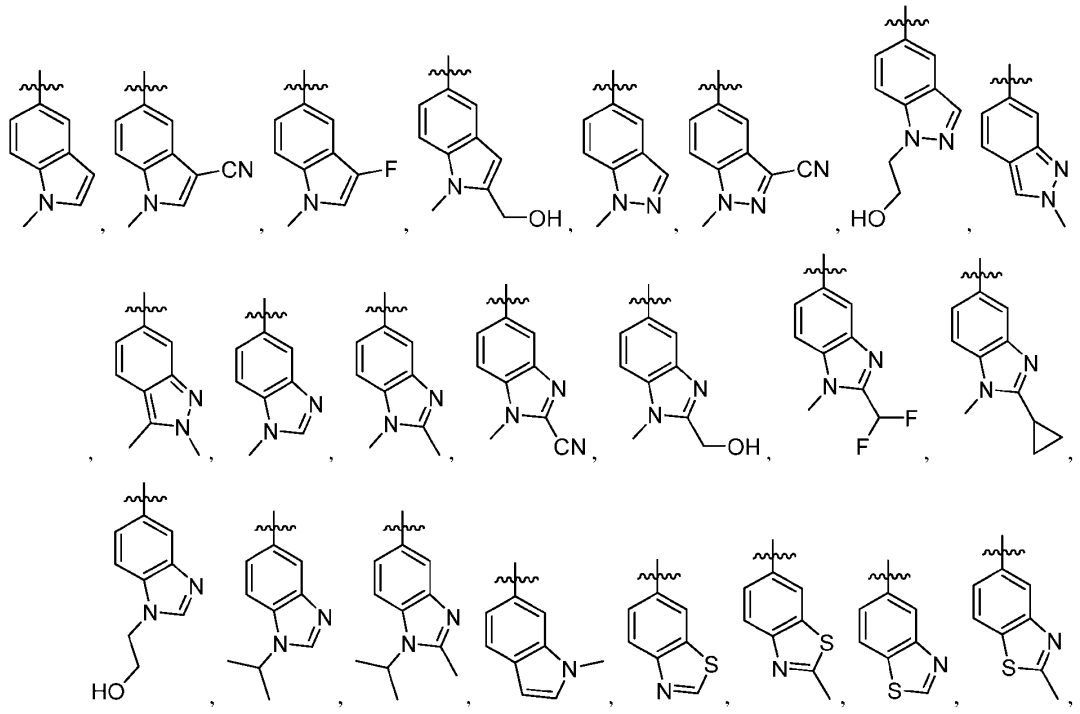


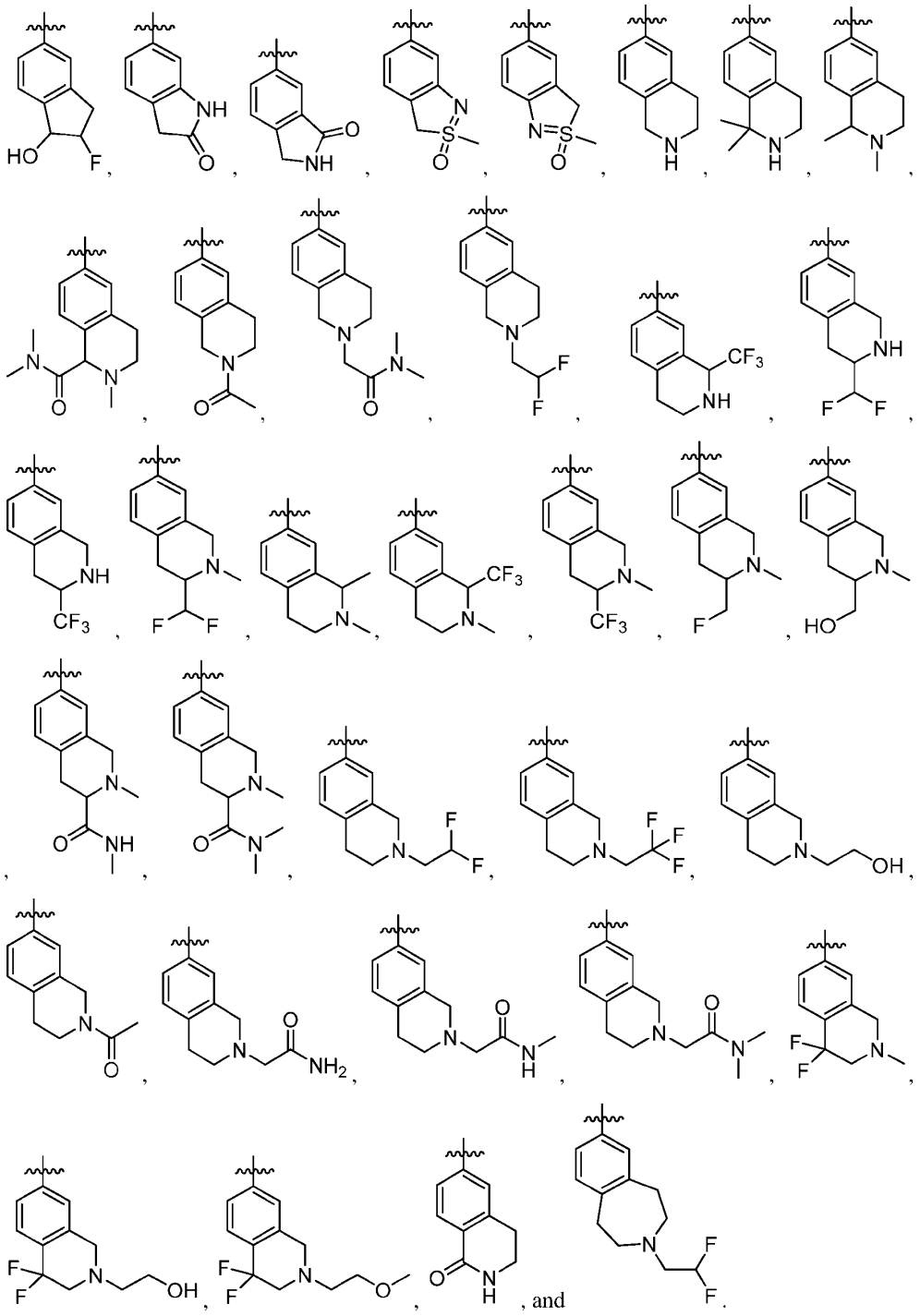




, and .

52. The compound of claim 51, wherein a moiety  is selected from:

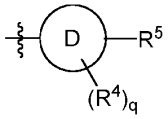


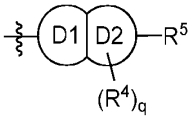


53. The compound of any one of claims 1-52, wherein Ring D is selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

54. The compound of any one of claims 1-52, wherein Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 5- to 10-membered bicyclic or polycyclic carbocyclic ring; and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

55. The compound of claim 54, wherein Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

56. The compound of any one of claims 1-52, wherein a moiety 

is 

, wherein:

Ring D1 is fused to Ring D2;

Ring D1 is selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

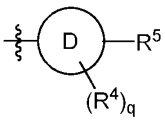
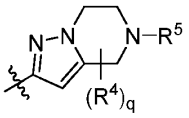
and

Ring D2 is selected from phenyl; 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

57. The compound of claim 56, wherein Ring D1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

58. The compound of claim 56, wherein Ring D1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-

membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

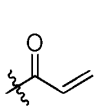
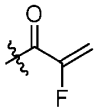
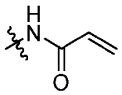
59. The compound of any one of claims 1-52, wherein a moiety  is .

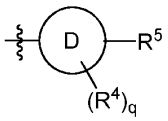
60. The compound of any one of claims 1-59, wherein each R^4 is independently C_{1-6} alkyl optionally substituted with one or more –OH.

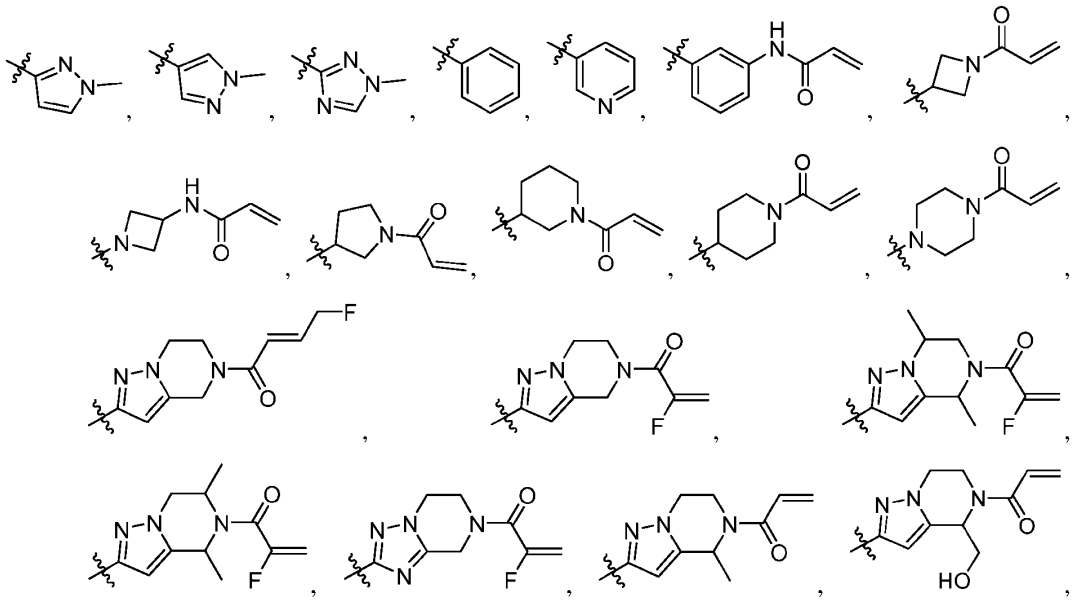
61. The compound of any one of claims 1-60, wherein q is 0 or 1.

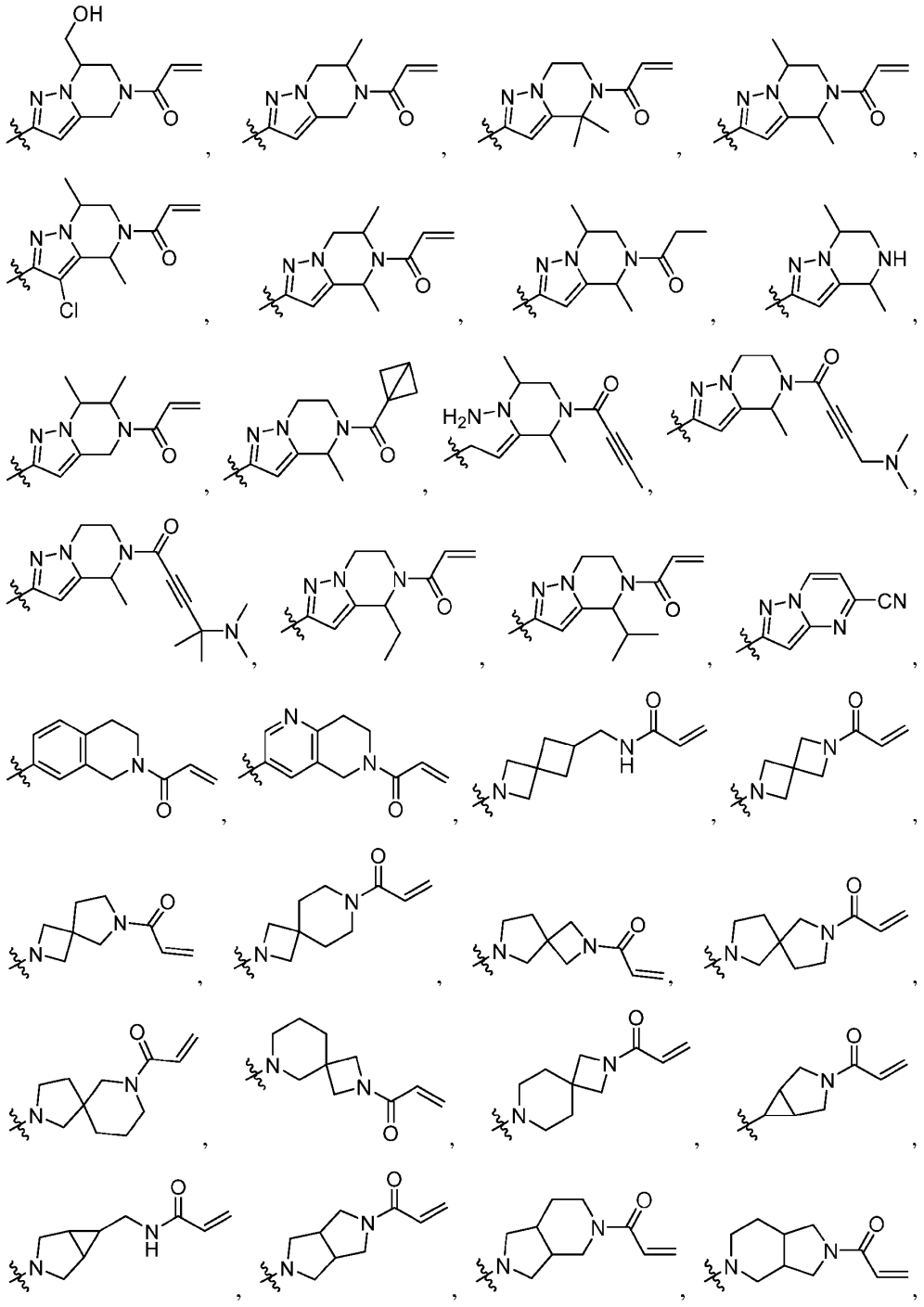
62. The compound of any one of claims 1-61, wherein R^5 is $-C(O)R^9$ or $-(CH_2)_xN(R)C(O)R^9$.

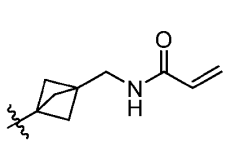
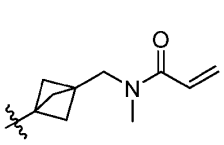
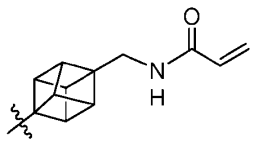
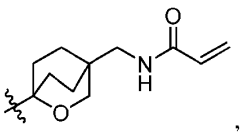
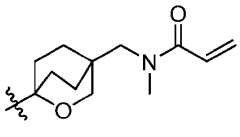
63. The compound of any one of claims 1-62, wherein R^9 is optionally substituted C_{2-6} alkenyl or optionally substituted C_{2-6} alkynyl.

64. The compound of any one of claims 1-63, wherein R^5 is , , or .

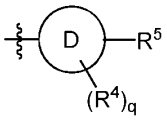
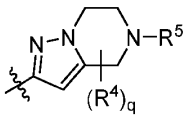
65. The compound of any one of claims 1-64, wherein a moiety  is selected from:

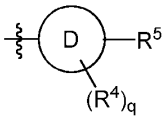


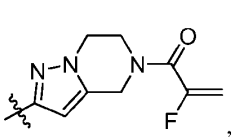
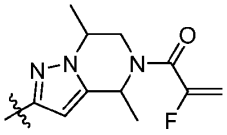
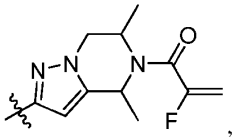
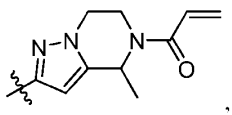
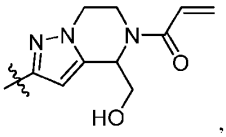
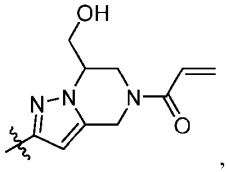
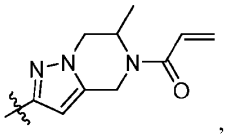
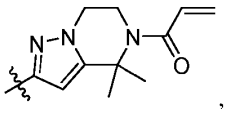
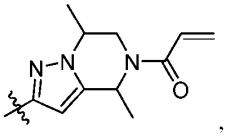
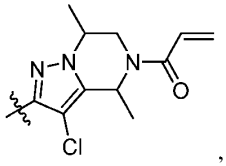
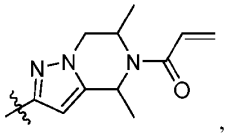
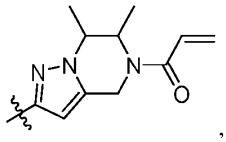
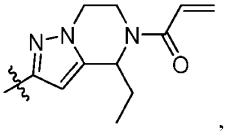
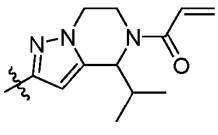


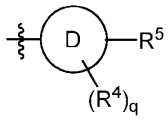






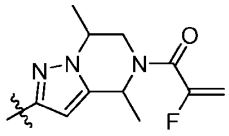
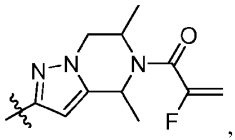
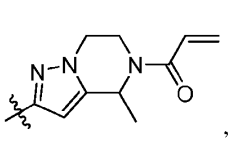
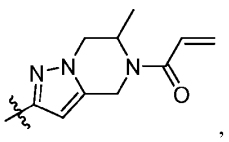
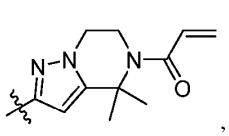
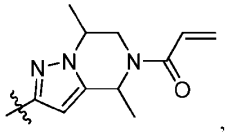
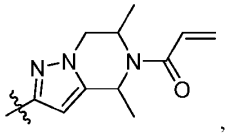
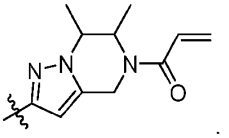
and .

66. The compound of claim 59, wherein a moiety  is , wherein each R^4 is independently methyl.

67. The compound of claim 59, wherein a moiety  is selected from:














, and .

68. The compound of claim 59, wherein a moiety  is selected from:

, , , , , , , and .

69. The compound of claim 1 or 3, wherein L is a bivalent straight or branched C_{2-6} hydrocarbon chain having at least one triple bond.

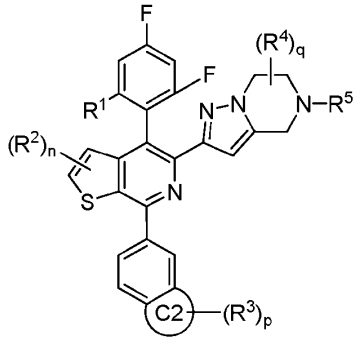
70. The compound of claim 1 or 3, wherein L is a bivalent straight or branched C_{1-2} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –N(R)-, -N(R)C(O)-, -C(O)N(R)-, or –C(O)-.

71. The compound of claim 1 or 4, wherein R^6 and $R^{6'}$ are connected with an optionally substituted C_{5-6} hydrocarbon chain, wherein one or more methylene units are optionally and independently replaced with –O- or –N(R)-.

72. The compound of claim 71, wherein R^6 and $R^{6'}$ are connected with: $-O(CH_2)_5-$, $-O(CH_2)_4-$, $-O(CH_2)_2OCH_2-$, or $-O(CH_2)_3OCH_2-$.

73. The compound of any one of claims 1-72, wherein each R is hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen.

74. The compound of claim 1, wherein the compound is a compound of Formula IF':

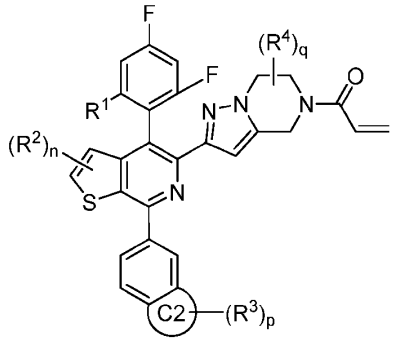


IF'

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

Ring C2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

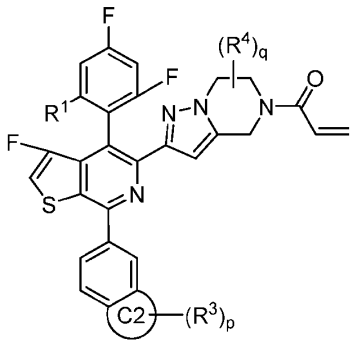
75. The compound of claim 74, wherein the compound is a compound of Formula IF1':



IF1'

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

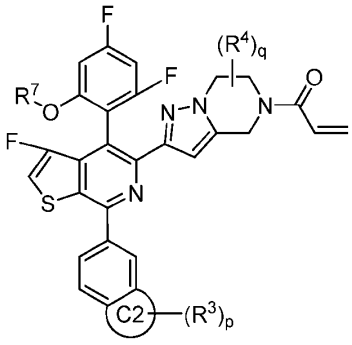
76. The compound of claim 74 or 75, wherein the compound is a compound of Formula IF2':



IF2'

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

77. The compound of any one of claims 74-76, wherein the compound is a compound of Formula IF3':



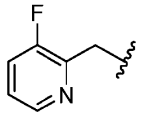
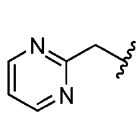
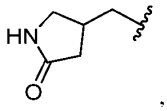
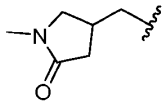
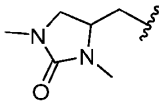
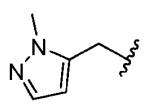
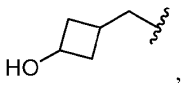
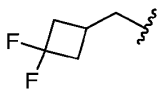
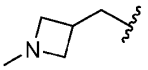
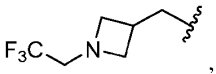
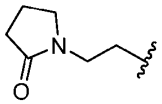
IF3'

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

78. The compound of any one of claims 74-76, wherein R^1 is $-OR^7$.

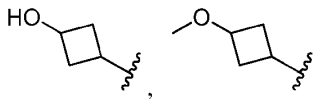
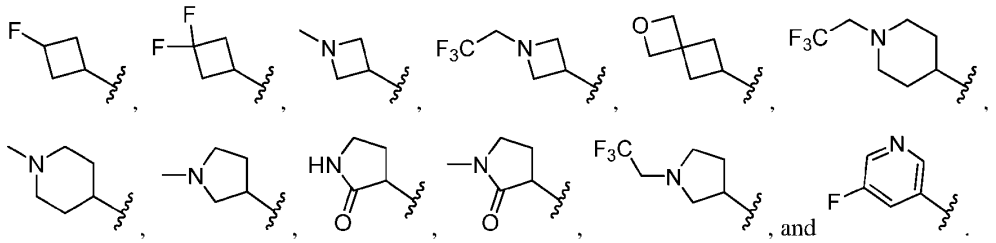
79. The compound of claim 77 or 78, wherein R^7 is selected from optionally substituted C_{1-6} aliphatic and $-(C_{1-4}$ alkylene)OR.

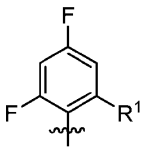
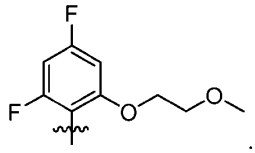
80. The compound of claim 77 or 78, wherein R^7 is selected from C_{1-6} aliphatic substituted with an optionally substituted 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; C_{1-6} aliphatic substituted with an optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and C_{1-6} aliphatic substituted with an optionally substituted 3-7 membered carbocyclic ring.

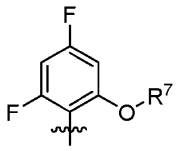
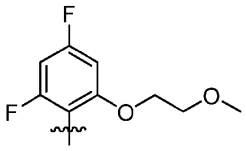
81. The compound of claim 78, wherein R^7 is selected from , , , , , , , , , , and .

82. The compound of claim 77 or 78, wherein R^7 is selected from optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and optionally substituted 3- to 6-membered carbocyclic ring.

83. The compound of claim 82, wherein R^7 is selected from optionally substituted pyrrolidinyl and piperidinyl.

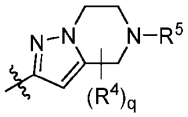
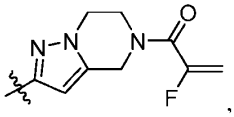
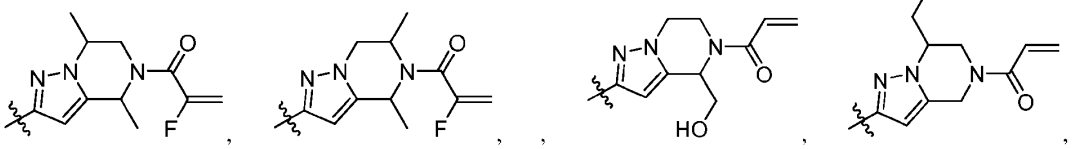
84. The compound of claim 83, wherein R^7 is selected from: , , and .

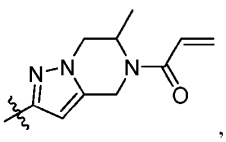
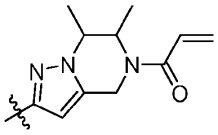
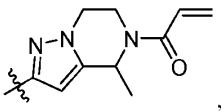
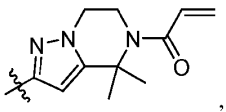
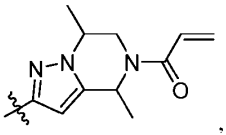
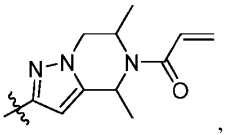
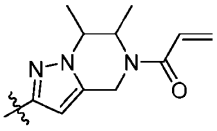
85. The compound of any one of claims 74-76, wherein a moiety  is .

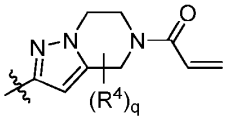
86. The compound of claim 77, wherein a moiety  is .

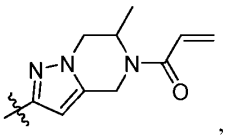
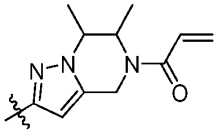
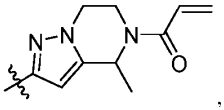
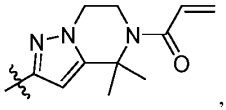
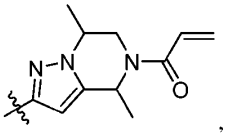
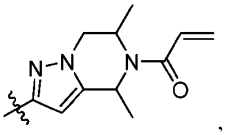
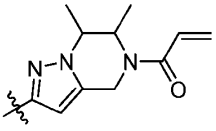
87. The compound of claim 74 or 75, wherein n is 0 or 1.

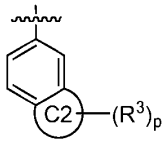
88 The compound of claim 74, 75, or 87, wherein R^2 is halogen.

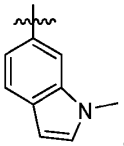
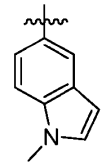
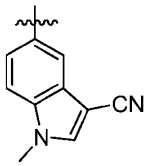
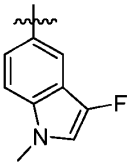
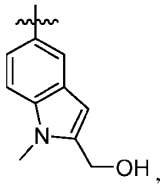
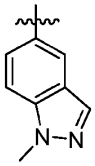
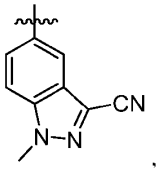
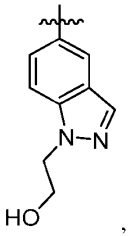
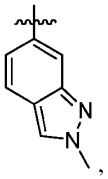
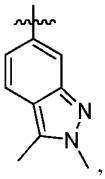
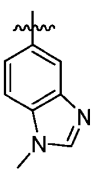
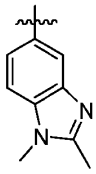
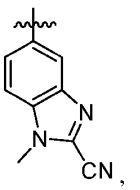
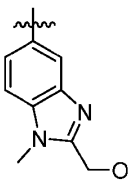
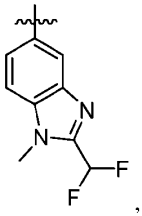
89. The compound of claim 74, wherein  is selected from: , .

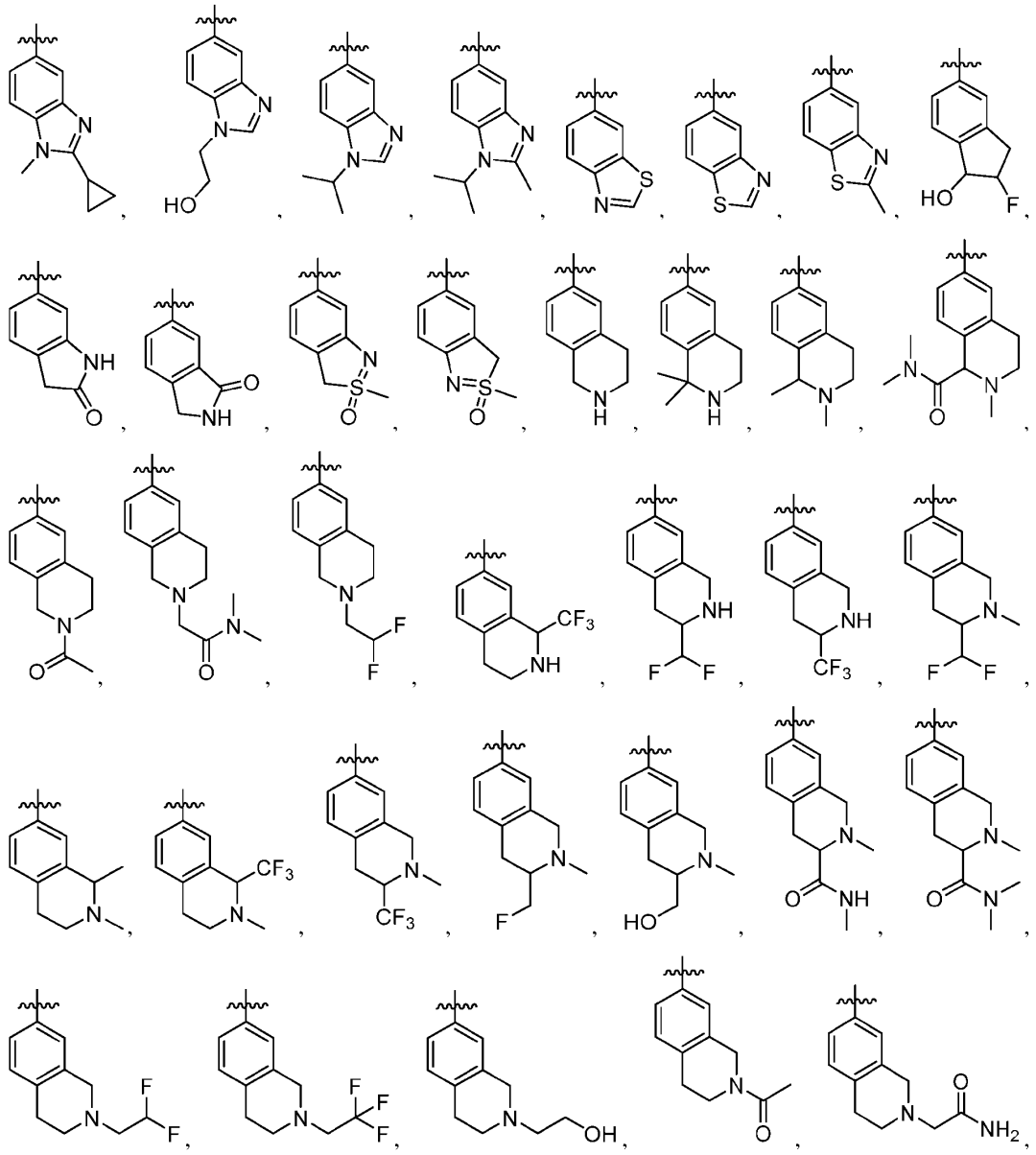

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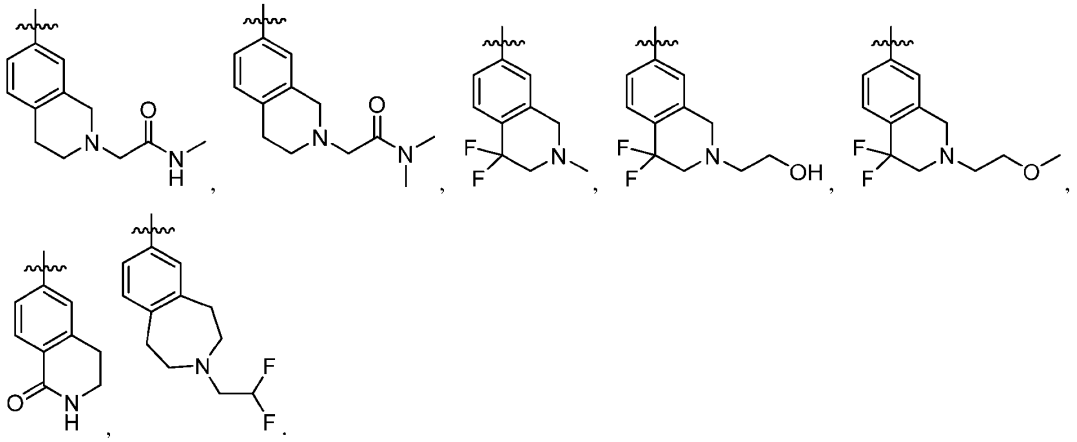
90. The compound of any one of claims 75-77, wherein  is selected from:

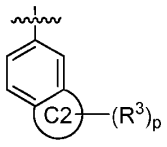
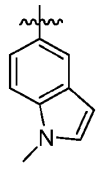

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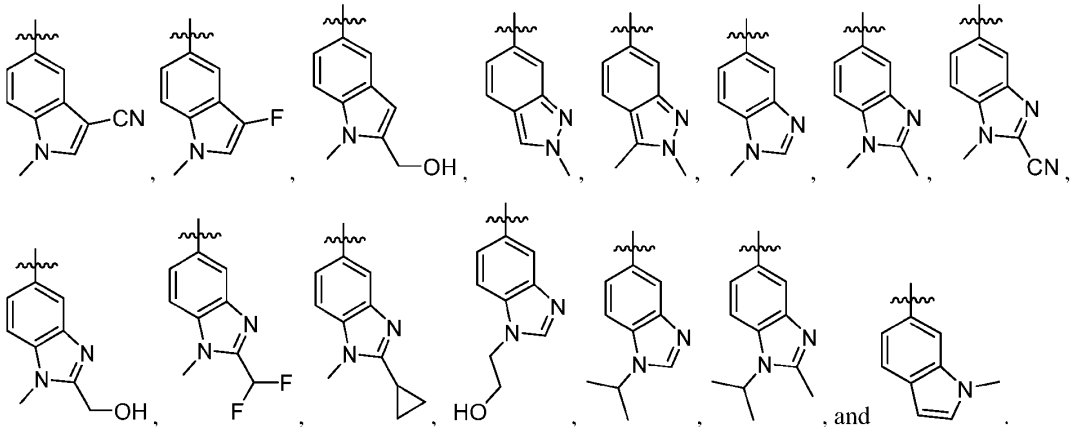
91. The compound of any one of claims 74-90, wherein a moiety  is selected from:


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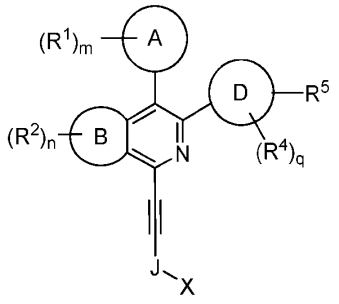




92. The compound of claim 91, wherein a moiety  is selected from: ,



93. A compound of Formula II:



II

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

Ring A is phenyl and a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring B is selected from a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5- to 6-membered carbocyclic ring, and phenyl;

Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

J is a covalent bond or a bivalent straight or branched C_{1-4} hydrocarbon chain;

X is –OR, $-N(R)_2$, $-C(O)N(R)_2$, or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 is independently selected from halogen and $–OR^7$;

each R^7 is independently selected from optionally substituted C_{1-6} aliphatic and $–(C_{1-4}$ alkylene$)OR$;

each R^2 is independently selected from halogen and optionally substituted C_{1-6} aliphatic;

each R^4 is independently selected from optionally substituted C_{1-6} aliphatic;

R^5 is $-C(O)R^9$, $-(CH_2)_xN(R)C(O)R^9$, or -CN;

R^9 is optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or a 4-membered bicyclic carbocyclic ring;

m is 0, 1, 2, or 3;

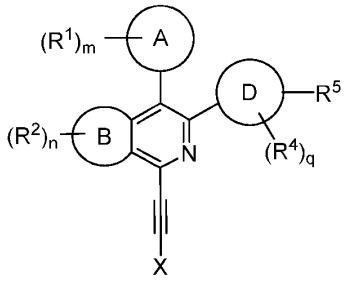
n is 0, 1, or 2;

q is 0, 1, or 2;

x is 0, 1, or 2;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic.

94. The compound of claim 93, wherein the compound is of Formula IIF:

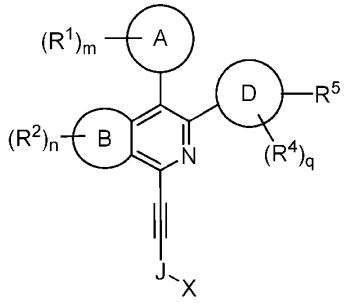


IIF

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

X is -C(O)N(R)$_2$ or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, 5- to 10-membered bicyclic carbocyclic ring, 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

95. The compound of claim 93, wherein the compound is of Formula IIG:



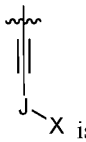
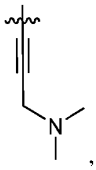
IIG

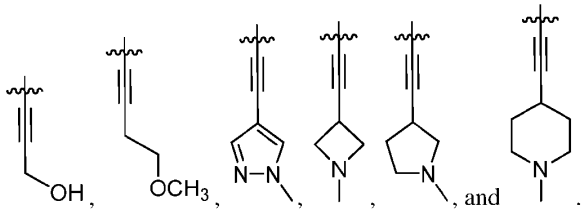
or a salt (e.g., a pharmaceutically acceptable salt) thereof, wherein:

J is a bivalent straight or branched C_{1-4} hydrocarbon chain; and

X is –OR or -N(R)$_2$.

96. The compound of claim 93 or 94, wherein X is a group selected from 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein any ring is optionally substituted with C_{1-6} alkyl.

97. The compound of any one of claims 93-96, wherein a moiety  is selected from: ,

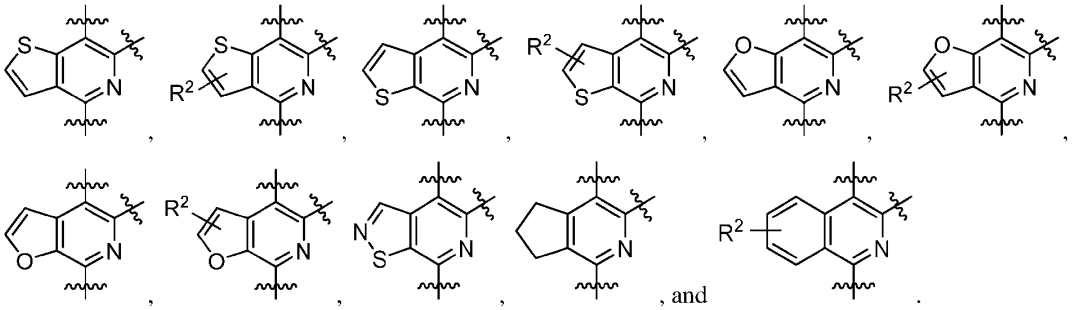


98. The compound of any one of claims 93-97, wherein Ring B is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur and a 5-membered carbocyclic ring.

99. The compound of claim 98, wherein Ring B is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

100. The compound of claim 98, wherein Ring B is a 5-membered carbocyclic ring.

101. The compound of any one of claims 93-100, wherein Ring B is selected from:



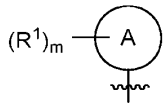
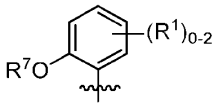
102. The compound of any one of claims 93-101, wherein each R^2 is independently selected from halogen and C_{1-6} alkyl.

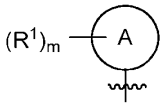
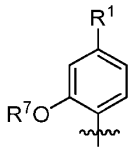
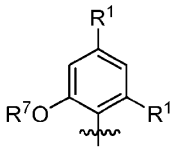
103. The compound of any one of claims 93-102, wherein n is 0 or 1.

104. The compound of any one of claims 93-103, wherein Ring A is phenyl.

105. The compound of any one of claims 93-104, wherein at least one R^1 is $-OR^7$.

106. The compound of claim 105, wherein one R^1 is $-OR^7$ and any other R^1 groups are halogen.

107. The compound of any one of claims 93-106, wherein a moiety  is .

108. The compound of claim 107, wherein a moiety  is  or .

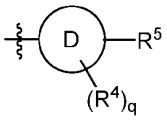
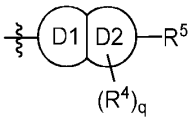
109. The compound of any one of claims 93-108, wherein each R^7 is independently selected from C_{1-6} alkyl and –(C_{1-4} alkylene)OR.

110. The compound of any one of claims 93-109, wherein m is 2 or 3.

111. The compound of any one of claims 93-110, wherein Ring D is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

112. The compound of any one of claims 93-110, wherein Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5- to 10-membered bicyclic or polycyclic carbocyclic ring, and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

113. The compound of claim 112, wherein Ring D is selected from 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

114. The compound of any one of claims 93-107, wherein a moiety  is , wherein:

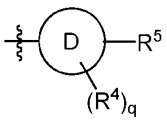
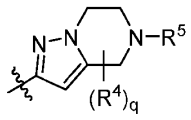
Ring D1 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

wherein Ring D1 is fused to Ring D2; and

Ring D2 is selected from phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

115. The compound of claim 114, wherein Ring D1 is a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

116. The compound of claim 114, wherein Ring D1 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and Ring D2 is a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

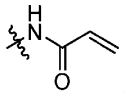
117. The compound of any one of claims 93-116, wherein a moiety  is .

118. The compound of any one of claims 93-117, wherein each R^4 is independently C_{1-6} alkyl optionally substituted with one or more –OH.

119. The compound of any one of claims 93-118, wherein q is 0 or 1.

120. The compound of any one of claims 93-119, wherein R^5 is $-C(O)R^9$ or $-(CH_2)_xN(R)C(O)R^9$.

121. The compound of any one of claims 93-119, wherein R^9 is optionally substituted C_{2-6} alkenyl or optionally substituted C_{2-6} alkynyl.

122. The compound of any one of claims 93-121, wherein R^5 is  or .

123. The compound of any one of claims 93-122, wherein each R is hydrogen or C_{1-6} alkyl optionally substituted with one or more halogen.

124. A compound selected from Table 1, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

125. A compound selected from Table 2, or a salt (e.g., a pharmaceutically acceptable salt) thereof.

126. A pharmaceutical composition comprising a compound according to any one of claims 1-125, or a salt (e.g., pharmaceutically acceptable salt) thereof, and a pharmaceutically acceptable carrier or excipient.

127. A method comprising administering a therapeutically effective amount of a compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof to a subject in need thereof.

128. The method of claim 127, wherein the subject has a disease, disorder, or condition ameliorated by disruption, inhibition, and/or prevention of an interaction between a small GTPase and a PI3Kα protein.

129. The method of claim 128, wherein the small GTPase is Rac1, CDC42, or a RAS protein.

130. The method of claim 129, wherein the small GTPase is a RAS protein.

131. The method of claim 130, wherein the RAS protein is KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, or RIT1.

132. The method of any one of claims 127-131, wherein the subject has a cancer.

133. A method of treating a cancer, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof.

134. The method of claim 132 or 133, wherein the cancer is associated with and/or characterized by aberrant activation of PI3Kα and/or a mutation in PI3Kα.

135. The method of claim 134, wherein the PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation.

136. The method of claim 135, wherein the PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation.

137. The method of any one of claims 132-136, wherein the cancer is characterized by a mutation in a RAS protein.

138. The method of claim 137, wherein the RAS protein comprises a mutation in codon 12, 13, or 61.

139. The method of claim 137 or 138, wherein the RAS protein is KRAS.

140. The method of claim 139, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

141. The method of claim 140, wherein the KRAS protein comprises a G12C or G12D mutation.

142. The method according to claim 137 or 138, wherein the RAS protein is HRAS.

143. The method according to claim 142, wherein the HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

144. The method according to claim 137 or 138, wherein the RAS protein is NRAS.

145. The method according to claim 144, wherein the NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

146. The method according to any one of claims 132-145, wherein the cancer is selected from pancreatic cancer; colon cancer; rectal cancer; colorectal cancer; bowel cancer; breast cancer; ovarian cancer; endometrial cancer; lung cancer; prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, liver and biliary passages, 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; cancers of the thyroid and other endocrine glands; 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.

147. The method according to claim 146, wherein the cancer is selected from breast cancer, lung cancer (e.g., non-small cell lung cancer), endometrial cancer, esophageal cancer, ovarian cancer, colorectal cancer, gastric cancer, squamous cell carcinoma, prostate cancer, and pancreatic cancer.

148. The method according to any one of claims 132-147, wherein the cancer is characterized by mutated, overexpressed, and/or amplified receptor tyrosine kinases (e.g., HER family, Met, FGFR, Alk, PDGF, EGFR, or ROS kinases).

149. The method according to any one of claims 132-148, wherein the cancer is characterized by a mutation in or a deletion of a PTEN protein.

150. The method according to any one of claims 127-149, wherein the subject has previously undergone a treatment regimen for cancer.

151. The method according to any one of claims 127-150, wherein the subject has previously entered remission from cancer.

152. A method of treating a metabolic disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof.

153. The method according to claim 152, wherein the metabolic disorder is selected from hyperinsulinemia and type 2 diabetes.

154. A method of treating a RASopathy, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof.

155. The method according to claim 154, wherein the RASopathy is selected from neurofibromatosis type 1 (NF1), capillary malformation-arteriovenous malformation syndrome, and Legius syndrome.

156. A method of treating a vascular disorder or condition, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof.

157. The method according to claim 156, wherein the vascular disorder or condition is selected from PIK3CA-related overgrowth syndrome (PROS) and vascular malformations (e.g., venous malformations; lymphatic malformations; congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies syndrome (CLOVES); Klippel-Trenaunay Syndrome; PTEN hamartoma tumor syndrome (PHTS); and fibro-adipose vascular anomaly (FAVA)).

158. A method of disrupting, inhibiting, and/or preventing an interaction between a small GTPase and a PI3Kα protein in a subject, comprising administering to the subject a compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof.

159. A method of disrupting, inhibiting, and/or preventing an interaction between a small GTPase and a PI3Kα protein, comprising contacting a cell containing the small GTPase and the PI3Kα protein

with a compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof.

160. A method comprising contacting a cell containing a small GTPase and a PI3Kα protein with a compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof.

161. The method of claim 159 or 160, wherein the cell is included in a subject.

162. The method of any one of claims 158-161, wherein the small GTPase is selected from Rac1, CDC42, and a RAS protein.

163. The method of claim 162, wherein the small GTPase is a RAS protein.

164. The method of claim 163, wherein the RAS protein is selected from HRAS, NRAS, KRAS, RRAS, RRAS2, MRAS, and RIT1.

165. The method of claim 164, wherein the RAS protein is KRAS.

166. The method of claim 165, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

167. The method of claim 166, wherein the KRAS protein comprises a G12C or G12D mutation.

168. The method according to claim 164, wherein the RAS protein is HRAS.

169. The method according to claim 168, wherein the HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

170. The method according to claim 164, wherein the RAS protein is NRAS.

171. The method according to claim 170, wherein the NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

172. A compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof for use as a medicament.

173. Use of a compound according to any one of claims 1-125 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament.

174. The compound or use according to claim 172 or 173, wherein the medicament is for treating a cancer.

175. The compound or use according to claim 174, wherein the cancer is associated with and/or characterized by aberrant activation of PI3Kα and/or a mutation in PI3Kα.

176. The compound or use according to claim 175, wherein the PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation.

177. The compound or use according to claim 176, wherein the PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation.

178. The compound or use according to any one of claims 174-177, wherein the cancer is characterized by a mutation in a RAS protein.

179. The compound or use according to claim 178, wherein the RAS protein comprises a mutation in codon 12, 13, or 61.

180. The compound or use according to claim 178 or 179, wherein the RAS protein is KRAS.

181. The compound or use according to claim 179, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

182. The compound or use according to claim 181, wherein the KRAS protein comprises a G12C or G12D mutation.

183. The compound or use according to claim 178 or 179, wherein the RAS protein is HRAS.

184. The compound according to claim 183, wherein the HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

185. The compound or use according to claim 178 or 179, wherein the RAS protein is NRAS.

186. The compound or use according to claim 184, wherein the NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

187. The compound or use according to any one of claims 174-186, wherein the cancer is selected from pancreatic cancer; colon cancer; rectal cancer; colorectal cancer; bowel cancer; breast cancer; ovarian cancer; endometrial cancer; lung cancer; prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, liver and biliary passages, 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; cancers of the thyroid and other endocrine glands; 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.

188. The compound or use according to claim 187, wherein the cancer is selected from breast cancer, lung cancer (e.g., non-small cell lung cancer), endometrial cancer, esophageal cancer, ovarian cancer, colorectal cancer, gastric cancer, squamous cell carcinoma, prostate cancer, and pancreatic cancer.

189. The compound or use according to any one of claims 174-186, wherein the cancer is characterized by mutated, overexpressed, and/or amplified receptor tyrosine kinases (e.g., HER family, Met, FGFR, Alk, PDGF, EGFR, or ROS kinases).

190. The compound or use according to any one of claims 174-186, wherein the cancer is characterized by a mutation in or a deletion of a PTEN protein.

191. The compound or use according to claim 172 or 173, wherein the medicament is for treating a metabolic disorder, a RASopathy, or a vascular disorder.

192. The compound or use according to claim 191, wherein: (i) the metabolic disorder is selected from hyperinsulinemia and type 2 diabetes; (ii) the RASopathy is selected from neurofibromatosis type 1 (NF1), capillary malformation-arteriovenous malformation syndrome, and Legius syndrome; and/or (iii) the vascular disorder or condition is selected from PIK3CA-related overgrowth syndrome (PROS) and vascular malformations (e.g., venous malformations; lymphatic malformations; congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies syndrome (CLOVES); Klippel-Trenaunay Syndrome; PTEN hamartoma tumor syndrome (PHTS); or fibro-adipose vascular anomaly (FAVA)).

193. A compound according to any one of claim 1-125 or a pharmaceutically acceptable salt thereof for use in treating a disease, disorder, or condition.

194. The compound for use according to claim 193 for use in treating a cancer.

195. The compound for use according to claim 192, wherein the cancer is associated with and/or characterized by aberrant activation of PI3Kα and/or a mutation in PI3Kα.

196. The compound for use according to claim 195, wherein the PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation.

197. The compound for use according to claim 196, wherein the PI3Kα protein comprises a E542K, E545K, H1047R, and/or H1047L mutation.

198. The compound for use according to any one of claims 194-197, wherein the cancer is characterized by a mutation in a RAS protein.

199. The compound for use according to claim 198, wherein the RAS protein comprises a mutation in codon 12, 13, or 61.

200. The compound for use according to claim 198 or 199, wherein the RAS protein is KRAS.

201. The compound for use according to claim 200, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.
202. The compound for use according to claim 201, wherein the KRAS protein comprises a G12C or G12D mutation.
203. The compound for use according to claim 198 or 199, wherein the RAS protein is HRAS.
204. The compound for use according to claim 203, wherein the HRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.
205. The compound for use according to claim 198 or 199, wherein the RAS protein is NRAS.
206. The compound for use according to claim 204, wherein the NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.
207. The compound for use according to any one of claims 194-206, wherein the cancer is selected from pancreatic cancer; colon cancer; rectal cancer; colorectal cancer; bowel cancer; breast cancer; ovarian cancer; endometrial cancer; lung cancer; prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, liver and biliary passages, 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; cancers of the thyroid and other endocrine glands; 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.
208. The compound for use according to claim 207, wherein the cancer is selected from breast cancer, lung cancer (e.g., non-small cell lung cancer), endometrial cancer, esophageal cancer, ovarian cancer, colorectal cancer, gastric cancer, squamous cell carcinoma, prostate cancer, and pancreatic cancer.
209. The compound for use according to any one of claims 194-208, wherein the cancer is characterized by mutated, overexpressed, and/or amplified receptor tyrosine kinases (e.g., HER family, Met, FGFR, Alk, PDGF, EGFR, or ROS kinases).

210. The compound for use according to any one of claims 194-209, wherein the cancer is characterized by a mutation in or a deletion of a PTEN protein.

211. The compound for use according to claim 193 for use in treating a metabolic disorder, a RASopathy, or a vascular disorder.

212. The compound for use according to claim 211, wherein: (i) the metabolic disorder is selected from hyperinsulinemia and type 2 diabetes; (ii) the RASopathy is selected from neurofibromatosis type 1 (NF1), capillary malformation-arteriovenous malformation syndrome, and Legius syndrome; and/or (iii) the vascular disorder or condition is selected from PIK3CA-related overgrowth syndrome (PROS) and vascular malformations (e.g., venous malformations; lymphatic malformations; congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies syndrome (CLOVES); Klippel-Trenaunay Syndrome; PTEN hamartoma tumor syndrome (PHTS); and fibro-adipose vascular anomaly (FAVA)).