HETEROBIFUNCTIONAL COMPOUNDS AND THEIR USE IN TREATING DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to United States Provisional Patent Application serial number 63/761,647, filed February 21, 2025, and United States Provisional Patent Application serial number 63/562,801, filed March 8, 2024; the contents of each of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The invention provides heterobifunctional compounds, pharmaceutical compositions, and their use in treating disease, such as cancer.

BACKGROUND

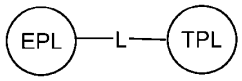
[0003] Cancer continues to be a significant health problem despite the substantial research efforts and scientific advances reported in the literature for treating this disease. Solid tumors, including prostate cancer, breast cancer, and lung cancer remain highly prevalent among the world population. The incidence of prostate cancer increases with age, and with increasing longevity of human subjects, there continues to be a corresponding rise in the number of patients suffering from prostate cancer. Breast cancer is one of the most common cancers among women and is a leading cause of death for women between ages 50-55. Lung cancer is a leading cause of death among cancer patients, where over 85% of lung cancers are non-small cell lung cancer (NSCLC). Many lung cancers are attributed to tobacco smoking. Current treatment options for these cancers are not effective for all patients and/or can have substantial adverse side effects.

[0004] New therapies are needed to address this unmet need in cancer therapy. In particular, new therapies are needed that achieve an anti-cancer effect through a different mechanism than commonly available therapies. Exemplary mechanisms for common anti-cancer therapies include (a) alkylation of DNA, which limits ability of the cell to reproduce, (b) topoisomerase inhibition, in which the therapeutic agent inhibits the activity of one or more topoisomerases, thereby limiting separation of strands of DNA, and (c) mitotic inhibition, where the therapeutic agent reduces ability of the cell to divide. New therapies that achieve an anti-cancer effect through a different mechanism present an opportunity to treat cancers more effectively and/or to treat cancers that have become resistant to currently available medicines.

[0005] The present invention addresses the foregoing needs and provides other related advantages.

SUMMARY

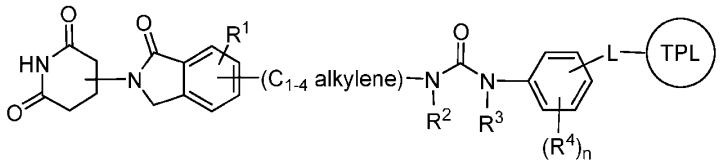
[0006] The invention provides heterobifunctional compounds, pharmaceutical compositions, and their use in treating disease, such as cancer. In particular, one aspect of the invention provides a collection of heterobifunctional compounds, such as a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. Further description of additional collections of heterobifunctional compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0007] Another aspect of the invention provides a collection of heterobifunctional compounds, such as a compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. Further description of additional collections of heterobifunctional compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0008] Another aspect of the invention provides a method of treating cancer. The method comprises administering to a patient in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I or II, to treat the cancer.

[0009] Another aspect of the invention provides a method of causing death of a cancer cell. The method comprises contacting a cancer cell with an effective amount of a compound described herein, such as a compound of Formula I or II, to cause death of the cancer cell.

DETAILED DESCRIPTION

[0010] The invention provides heterobifunctional compounds, pharmaceutical compositions, and their use in treating disease, such as cancer. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology. Such techniques are explained in the literature, such as in "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992); "Handbook of experimental immunology" (D.M. Weir & C.C. Blackwell, eds.); "Current protocols in molecular biology" (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and "Current protocols in immunology" (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety.

[0011] Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section. Further, when a variable is not accompanied by a definition, the previous definition of the variable controls.

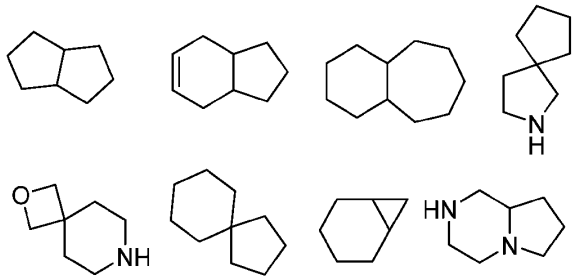
Definitions

[0012] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "-O-alkyl" etc. For purposes of this invention, 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, the entire contents of which are hereby incorporated by reference.

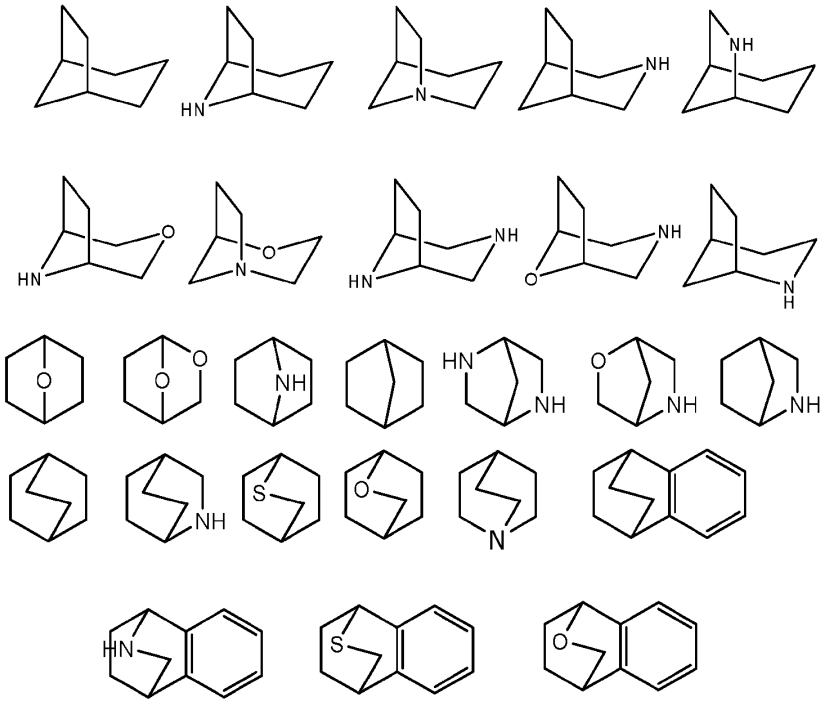
[0013] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "cycloaliphatic"), that has a

single point of attachment to the rest of the molecule. Unless otherwise specified, 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. In some embodiments, "cycloaliphatic" refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0014] As used herein, the term "bicyclic ring" or "bicyclic ring system" refers to any bicyclic ring system, i.e., carbocyclic or heterocyclic, saturated or having one or more units of unsaturation, having one or more atoms in common between the two rings of the ring system. Thus, the term includes any permissible ring fusion, such as *ortho*-fused or spirocyclic. As used herein, the term "heterobicyclic" is a subset of "bicyclic" that requires that one or more heteroatoms are present in one or both rings of the bicycle. Such heteroatoms may be present at ring junctions and are optionally substituted, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphates), boron, etc. In some embodiments, a bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e., carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bicyclic rings include:



[0015] Exemplary bridged bicyclics include:



[0016] The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0017] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

[0018] 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)).

[0019] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0020] As used herein, the term "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0021] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $–(CH_2)_n–$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0022] The term "-(C_0 alkylene)-" refers to a bond. Accordingly, the term "-(C_{0-3} alkylene)-" encompasses a bond (i.e., C_0) and a -(C_{1-3} alkylene)- group.

[0023] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0024] The term "halogen" means F, Cl, Br, or I.

[0025] 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 five 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." In certain embodiments of the present invention, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. 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, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like. The term "haloaryl" refers to an aryl group that is substituted with at least one halogen. Exemplary haloaryl groups include chlorophenyl (e.g., 3-chlorophenyl, 4-chlorophenyl), fluorophenyl, and the like. The term "phenylene" refers to a bivalent phenyl group.

[0026] The terms "heteroaryl" and "heteroar–," used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl,

pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where unless otherwise specified, the radical or point of attachment is on the heteroaromatic ring or on one of the rings to which the heteroaromatic ring is fused. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl. A heteroaryl group may be mono– or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted. The term "haloheteroaryl" refers to a heteroaryl group that is substituted with at least one halogen. Exemplary haloheteroaryl groups include chloropyridine, fluoropyridine, chloropyrazole, fluoropyrazole, and the like. The term "heteroarylene" refers to a bivalent heteroaryl group. Similarly, the terms "pyrazolylene", "imidazolylene", and "pyrrolylene", respectively refer to bivalent pyrazolyl, imidazolyl, and pyrrolyl groups. Similarly, the terms "pyridinylene" and "pyrimidinylene", respectively refer to bivalent pyridinyl and pyrimidinyl groups.

[0027] As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a stable 5– to 7–membered monocyclic or 7–10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to 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. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4–dihydro–2*H*–pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in *N*–substituted pyrrolidinyl).

[0028] 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 optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl,

dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptane, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclyl ring," "heterocyclic group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be mono– or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted. The term "heterocyclylene" refers to a bivalent heterocyclyl group.

[0029] As used herein, the term "heterocycloakyl" refers to a saturated heterocyclyl. The term "heterocycloakyl" refers to a bivalent heterocycloakyl group.

[0030] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. 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.

[0031] As described herein, compounds of the invention may contain "optionally substituted" moieties. 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. 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 disclosed herein.

[0032] Each optional substituent on a substitutable carbon is a monovalent substituent independently selected from halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, 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; -$(CH_2)_{0-4}N(R°)_2$; –$(CH_2)_{0-4}N(R°)C(O)R°$; –$N(R°)C(S)R°$; –$(CH_2)_{0-4}N(R°)C(O)NR°_2$; -$N(R°)C(S)NR°_2$; –$(CH_2)_{0-4}N(R°)C(O)OR°$; –$N(R°)N(R°)C(O)R°$; -$N(R°)N(R°)C(O)NR°_2$; -$N(R°)N(R°)C(O)OR°$; –$(CH_2)_{0-4}C(O)R°$; –$C(S)R°$; –$(CH_2)_{0-4}C(O)OR°$; –$(CH_2)_{0-4}C(O)SR°$; -$(CH_2)_{0-4}C(O)OSiR°_3$; –$(CH_2)_{0-4}OC(O)R°$; –$OC(O)(CH_2)_{0-4}SR$–, $SC(S)SR°$; –$(CH_2)_{0-4}SC(O)R°$; –$(CH_2)_{0-4}C(O)NR°_2$; –$C(S)NR°_2$; –$C(S)SR°$; –$SC(S)SR°$, -$(CH_2)_{0-4}OC(O)NR°_2$; -$C(O)N(OR°)R°$; –$C(O)C(O)R°$; –$C(O)CH_2C(O)R°$; –$C(NOR°)R°$; -$(CH_2)_{0-4}SSR°$; –$(CH_2)_{0-4}S(O)_2R°$; –$(CH_2)_{0-4}S(O)_2OR°$; –$(CH_2)_{0-4}OS(O)_2R°$; –$S(O)_2NR°_2$; –$S(O)(NR°)R°$; –$S(O)_2N=C(NR°_2)_2$; -$(CH_2)_{0-4}S(O)R°$; -$N(R°)S(O)_2NR°_2$; –$N(R°)S(O)_2R°$; –$N(OR°)R°$; –$C(NH)NR°_2$; –$P(O)_2R°$; -$P(O)R°_2$; -$OP(O)R°_2$; –$OP(O)(OR°)_2$; $SiR°_3$; –(C_{1-4} straight or branched alkylene)O–$N(R°)_2$; or –(C_{1-4} straight or branched alkylene)C(O)O–$N(R°)_2$.

[0033] Each R° is independently hydrogen, C_{1-6} aliphatic, –CH_2Ph, –$O(CH_2)_{0-1}Ph$, -CH_2-(5-6 membered heteroaryl ring), or a 5–6–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 3–12–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 by a divalent substituent on a saturated carbon atom of R° selected from =O and =S; or each R° is optionally substituted with a monovalent substituent independently selected from halogen, –$(CH_2)_{0-2}R^•$, –(halo$R^•$), –$(CH_2)_{0-2}OH$, –$(CH_2)_{0-2}OR^•$, –$(CH_2)_{0-2}CH(OR^•)_2$; -O(halo$R^•$), –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 –$SSR^•$.

[0034] Each $R^•$ is independently selected from C_{1-4} aliphatic, –CH_2Ph, –$O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^•$ is unsubstituted or where preceded by halo is substituted only with one or more halogens; or wherein an optional substituent on a saturated carbon is a divalent substituent independently selected from =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, –$O(C(R^*_2))_{2-3}O$–, or –$S(C(R^*_2))_{2-3}S$–, or a divalent substituent bound to vicinal substitutable carbons of an "optionally substituted" group is –$O(CR^*_2)_{2-3}O$–, wherein each independent occurrence of R^* is selected from

hydrogen, C_{1-6} aliphatic or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0035] When R^* is C_{1-6} aliphatic, R^* is optionally substituted with 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 independently selected from C_{1-4} aliphatic, –CH_2Ph, –O$(CH_2)_{0-1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0036] An optional substituent on a substitutable nitrogen is independently –$R^\dagger$, –$NR^\dagger_2$, –C(O)$R^\dagger$, –C(O)O$R^\dagger$, –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, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein when $R^\dagger$ is C_{1-6} aliphatic, $R^\dagger$ is optionally substituted with 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 independently selected from C_{1-4} aliphatic, –CH_2Ph, –O$(CH_2)_{0-1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0037] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. 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.

[0038] Further, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al.*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al.*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al.*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

[0039] 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, loweralkyl sulfonate and aryl sulfonate.

[0040] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. In certain embodiments, the compound is in the form of a single stereoisomer. In certain embodiments, a stereogenic center in a single stereoisomer compound has the R configuration. In certain embodiments, a stereogenic center in

a single stereoisomer compound has the S configuration. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also 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 the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. In certain embodiments, the compound depicted by a chemical structure herein has the natural distribution of isotopes (i.e., it is not isotopically enriched).

[0041] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Alternatively, a particular enantiomer of a compound of the present invention may be prepared by asymmetric synthesis. Still further, where the molecule contains a basic functional group (such as amino) or an acidic functional group (such as carboxylic acid) diastereomeric salts are formed with an appropriate optically active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers.

[0042] Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. Chiral center(s) in a compound of the present invention can have the *S* or *R* configuration as defined by the *IUPAC* 1974 Recommendations. Further, to the extent a compound described herein may exist as an atropisomer (*e.g.*, substituted biaryls), all forms of such atropisomer are considered part of this invention.

[0043] Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name, and an ambiguity exists between the structure and the name, the structure predominates. It should also be noted that any carbon as well as heteroatom

with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

[0044] The terms "a" and "an" as used herein mean "one or more" and include the plural unless the context is inappropriate.

[0045] The term "alkyl" refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C_1-C_{12} alkyl, C_1-C_{10} alkyl, and C_1-C_6 alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[0046] The term "cycloalkyl" refers to a monovalent saturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl) hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein, e.g., as "C_3-C_6 cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include cyclohexyl, cyclopentyl, cyclobutyl, and cyclopropyl. The term "cycloalkylene" refers to a bivalent cycloalkyl group.

[0047] The term "haloalkyl" refers to an alkyl group that is substituted with at least one halogen. Exemplary haloalkyl groups include $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, and the like. The term "chloroalkyl" refers to an alkyl group that is substituted with at least one chloro. The term "bromoalkyl" refers to an alkyl group that is substituted with at least one bromo. The term "haloalkylene" refers to a bivalent haloalkyl group.

[0048] The term "hydroxyalkyl" refers to an alkyl group that is substituted with at least one hydroxyl. Exemplary hydroxyalkyl groups include $-CH_2CH_2OH$, $-C(H)(OH)CH_3$, $-CH_2C(H)(OH)CH_2CH_2OH$, and the like.

[0049] The term "heteroalkyl" refers to an alkyl group in which one or more carbon atoms has been replaced by a heteroatom (e.g., N, O, or S). Exemplary heteroalkyl groups include $-OCH_3$, $-CH_2OCH_3$, $-CH_2CH_2N(CH_3)_2$, and $-CH_2CH_2OH$. The heteroalkyl group may contain, for example, from 2-4, 2-6, or 2-8 atoms selected from the group consisting of carbon and a heteroatom (e.g., N, O, or S). The phrase 3-8 membered heteroalkyl refers to a heteroalkyl

group having from 3 to 8 atoms selected from the group consisting of carbon and a heteroatom. The term "heteroalkylene" refers to a bivalent heteroalkyl group.

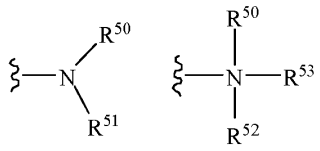
[0050] The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively. The term "haloalkenyl" refers to an alkenyl group that is substituted with at least one halogen. The term "fluoroalkenyl" refers to an alkenyl group that is substituted with at least one fluoro. The term "nitroalkenyl" refers to an alkenyl group that is substituted with at least one nitro.

[0051] The term "carbocyclylene" refers to a bivalent cycloaliphatic group.

[0052] The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, *tert*-butoxy and the like. The term "haloalkoxyl" refers to an alkoxyl group that is substituted with at least one halogen. Exemplary haloalkoxyl groups include $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-OCH_2CF_3$, $-OCF_2CF_3$, and the like.

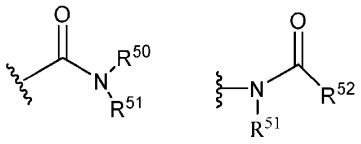
[0053] The term "oxo" is art-recognized and refers to a "=O" substituent. For example, a cyclopentane susbsituted with an oxo group is cyclopentanone.

[0054] The term "amino" is art-recognized and refers to both unsubstituted and substituted amines, *e.g.*, a moiety that may be represented by the general formulas:



wherein R^{50}, R^{51}, R^{52} and R^{53} each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R^{61}$, or R^{50} and R^{51}, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R^{61} represents an aryl, a 3-7 membered cycloalkyl, a 4-7 membered cycloalkenyl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl; and m is zero or an integer in the range of 1 to 8.

[0055] The term "amido" is art-recognized and refers to both unsubstituted and substituted amides, *e.g.*, a moiety that may be represented by the general formulas:



wherein R^{50} and R^{51} each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R^{61}$, or R^{50} and R^{51}, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R^{61} represents an aryl, a 3-7 membered cycloalkyl, a 4-7 membered cycloalkenyl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl; and m is zero or an integer in the range of 1 to 8; and R^{52} is an alkyl, an alkenyl, or $-(CH_2)_m-R^{61}$.

[0056] The symbol "〰" indicates a point of attachment.

[0057] When any substituent or variable occurs more than one time in any constituent or the compound of the invention, its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

[0058] One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

[0059] As used herein, the terms "subject" and "patient" are used interchangeably and refer to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and most preferably includes humans.

[0060] The term "IC_{50}" is art-recognized and refers to the concentration of a compound that is required to achieve 50% inhibition of the target.

[0061] As used herein, the term "effective amount" refers to the amount of a compound sufficient to effect beneficial or desired results (*e.g.*, a therapeutic, ameliorative, inhibitory or

preventative result). An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term "treating" includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0062] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0063] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, s*ee e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0064] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0065] In addition, when a compound of the invention contains both a basic moiety (such as, but not limited to, a pyridine or imidazole) and an acidic moiety (such as, but not limited to, a carboxylic acid) zwitterions ("inner salts") may be formed. Such acidic and basic salts used within the scope of the invention are pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts. Such salts of the compounds of the invention may be formed, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

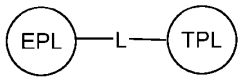
[0066] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited

components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0067] As a general matter, compositions specifying a percentage are by weight unless otherwise specified.

I. Heterobifunctional Compounds

[0068] The invention provides heterobifunctional compounds. The compounds are generally represented by the following formula:

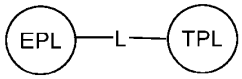


or a pharmaceutically acceptable salt thereof, wherein EPL is a moiety that binds to an effector protein selected from BRD4, CDK1, CDK2, CDK9, or GSPT1; L is a linker; and TPL is a moiety that binds to estrogen receptor.

[0069] The compounds may be used in the pharmaceutical compositions and therapeutic methods described herein. Exemplary compounds are described in the following sections, along with exemplary procedures for making the compounds.

Part A: Compounds of Formula I

[0070] One aspect of the invention provides a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

EPL is a moiety that binds to an effector protein selected from BRD4, CDK1, CDK2, or CDK9;

L is a linker; and

TPL is a moiety that binds to an estrogen receptor.

[0071] The definitions of variables in Formula I above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

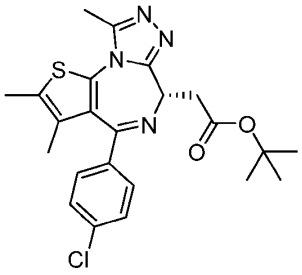
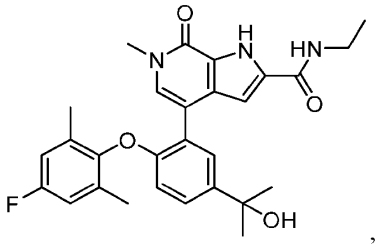
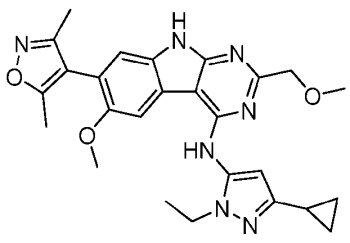
[0072] In certain embodiments, the compound is a compound of Formula I.

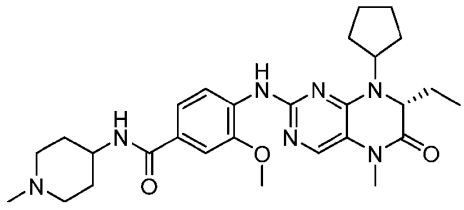
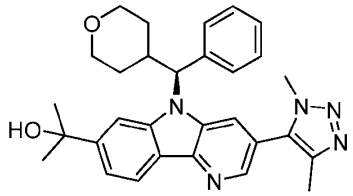
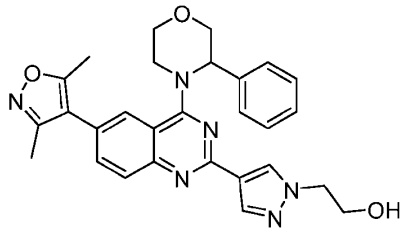
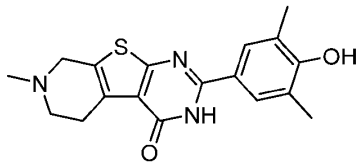
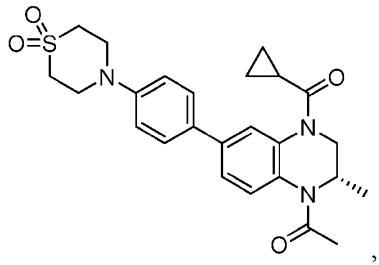
[0073] The compound may be further characterized according to, for example, the identity of L and/or TPL. Exemplary further embodiments for L and TPL are provided in Parts C and D below.

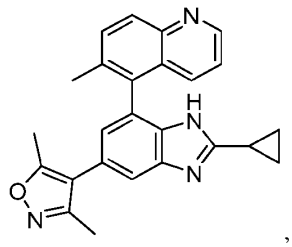
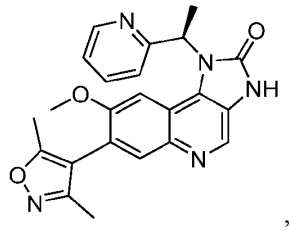
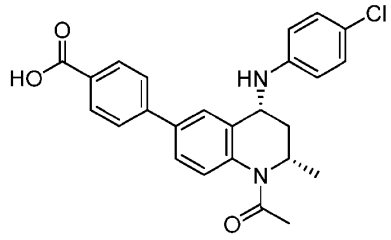
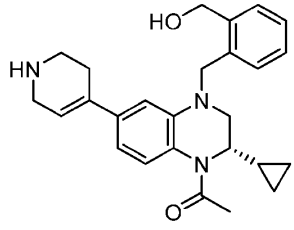
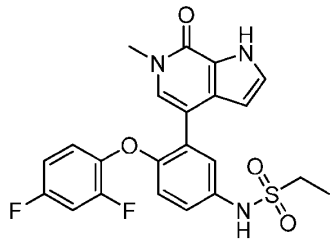
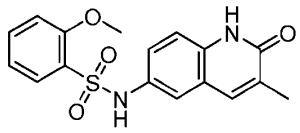
[0074] As generally defined above, EPL is a moiety that binds to an effector protein selected from BRD4, CDK1, CDK2, and CDK9. In certain embodiments, the EPL is a moiety that binds to BRD4. In certain embodiments, the EPL is a moiety that binds to CDK1. In certain embodiments, the EPL is a moiety that binds to CDK2. In certain embodiments, the EPL is a moiety that binds to CDK9.

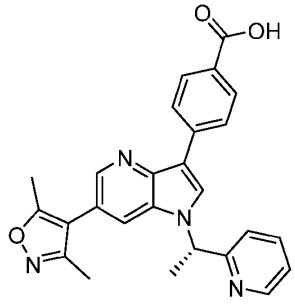
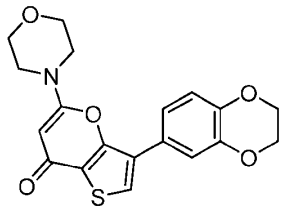
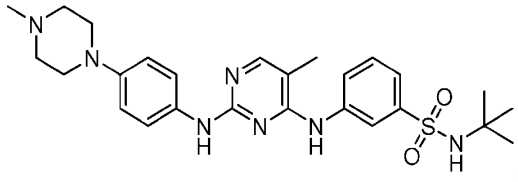
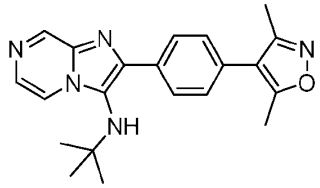
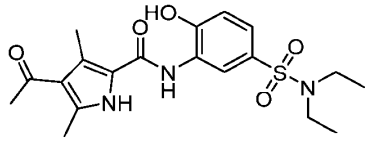
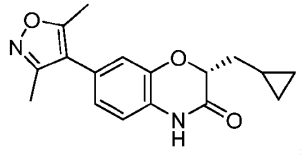
A. Moiety for BRD4

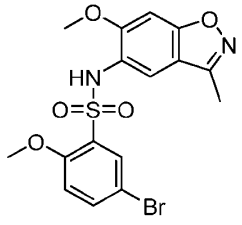
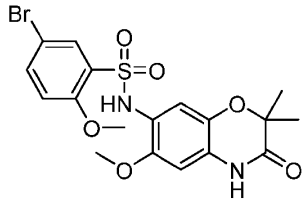
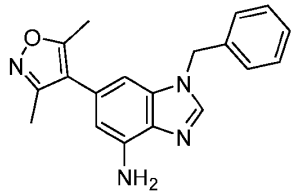
[0075] In certain embodiments, the EPL is a moiety that binds to bromodomain-containing protein 4 (BRD4). Exemplary compounds that bind to BRD4 are reported in the literature, including:

-  , as described by Bradner, J.E., *et al.* in WO 2011/143669;
-  , as described by Fidanze, S.D., *et al.* in WO 2017/177955;
-  , as described by Wang, S., *et al.* in WO 2016/138332;

- , as described by Chen, L., *et al.* in *ACS Med Chem Lett* 2015, vol. 6(7), page 764;
- , as described by Norris, D.J., *et al.* in WO 2015/100282.
- , as described by Yang, S.M., *et al.* in *Bioorg Med Chem Lett* 2018, vol. 28(21), page 3483;
- , as described by Ouyang, L., *et al.* in *J Med Chem* 2017, vol. 60(24), page 9990;
- , as described by Millan, D.S., *et al.* in *ACS Med Chem Lett* 2017, vol. 8(8), page 847;

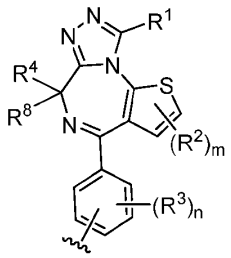
-  , as described by Aktoudianakis, E, *et al.* in WO 2014/182929;
-  , as described by Chekler, E.L.P., *et al.* in WO 2017/037567;
-  , as described by Demont, E.H., *et al.* in WO 2011/054848;
-  , as described in Law, R.P., *et al.*, *et al.* in *J Med Chem* 2018, vol. 61(10), page 4317;
-  , as described by Hu,Y., *et al.*, *et al.* in WO 2018/086605;
-  , as described by Fish, P.V., *et al.* in WO 2013/027168;

-  , as described by Ozer, H.G., *et al.* in *Cancer Discov* 2018, vol. 8(4), page 458;
-  , as described by Andrews, F.H., *et al.* in *Proc Natl Acad Sci USA (PNAS)* 2017, vol. 114(7), page E1072;
-  , as described by Embe, *et al.* in *ACS Chem Biol* 2014, vol. 9(5), page 1160;
-  , as described by Marineau, J.J., *et al.* in WO 2015/013635;
-  , as described by Huegle, M., *et al.* in *J Med Chem* 2016, vol. 59(4), page 1518;
-  , as described by Xue, X.Q., *et al.* in *Eur J Med Chem* 2018, vol. 152, page 542;

-  , as described by Zhang, M., *et al.* in *J Med Chem* 2018, vol. 61(7), page 3037;
-  , as described by Xiang. Q., *et al.* in *ACS Med Chem Lett* 2018, vol. 9(3), page 262;
-  , as described by Kharenko, O.A., *et al.* in *J Med Chem* 2018, vol. 61(18), page 8202.

[0076] In certain embodiments, the EPL is a radical of one of the above compounds, which is attached to L through a modifiable oxygen, nitrogen, or carbon atom.

[0077] In certain embodiments, the EPL has the following formula:



wherein:

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

R^2 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^3 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxyl;

R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur), -(C_{1-6} alkylene)-C(O)N(R^5)(R^6), -(C_{1-6} alkylene)-N(R^5)C(O)R^7, -(C_{1-6} alkylene)-CO_2R^7, -(C_{1-6} alkylene)-OC(O)R^7, -(C_{1-6} alkylene)-cyano, -(C_{1-6} alkylene)-O-(C_{1-6} alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl, or hydrogen; or R^4 and R^8 taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring;

R^5 and R^6 are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom;

R^7 is C_{1-6} alkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

R^8 is hydrogen or C_{1-4} alkyl; and

m and n are independently 0, 1, or 2.

[0078] In certain embodiments, R^3 represents independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl. In certain embodiments, R^3 represents independently for each occurrence hydrogen or halo. In certain embodiments, R^3 represents independently for each occurrence hydrogen, fluoro, or chloro. In certain embodiments, R^3 represents independently for each occurrence hydrogen or fluoro.

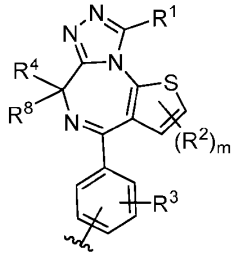
[0079] In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 represents independently for each occurrence halo. In certain embodiments, R^3 represents independently for each occurrence fluoro or chloro. In certain embodiments, R^3 is fluoro. In certain embodiments, R^3 is chloro. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^3 represents independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^3 is methoxy.

[0080] In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

[0081] In certain embodiments, R^1 is C_{1-4} alkyl, R^2 represents independently for each occurrence C_{1-4} alkyl, and m is 2. In certain embodiments, R^1 and R^2 are methyl, and m is 2.

[0082] In certain embodiments, each of variables R^1, R^2, R^4, R^5, R^6, R^7, R^8, and m is as defined in the embodiments below, both singly, and in combination.

[0083] In certain embodiments, the EPL has the following formula:



wherein:

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

R^2 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^3 is hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxyl;

R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur), -(C_{1-6} alkylene)-C(O)N(R^5)(R^6), -(C_{1-6} alkylene)-N(R^5)C(O)R^7, -(C_{1-6} alkylene)-CO_2R^7, -(C_{1-6} alkylene)-OC(O)R^7, -(C_{1-6} alkylene)-cyano, -(C_{1-6} alkylene)-O-(C_{1-6} alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl, or hydrogen; or R^4 and R^8 taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring;

R^5 and R^6 are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom;

R^7 is C_{1-6} alkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

R^8 is hydrogen or C_{1-4} alkyl; and

m is 0, 1, or 2.

[0084] In certain embodiments, R^1 is C_{1-4} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 is C_{3-4} cycloalkyl.

[0085] In certain embodiments, R^2 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 represents independently for each occurrence C_{3-4} cycloalkyl.

[0086] In certain embodiments, R^3 is hydrogen or halo. In certain embodiments, R^3 is hydrogen or fluoro. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is halo. In certain embodiments, R^3 is fluoro. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is C_{1-4} haloalkyl. In certain embodiments, R^3 is C_{1-4} alkoxyl.

[0087] In certain embodiments, R^4 is -CH_2-(oxazolyl), methyl, or -CH_2-(thiazolyl). In certain embodiments, R^4 is -CH_2-(oxazol-2-yl), methyl, or -CH_2-(thiazol-2-yl). In certain embodiments, R^4 is -CH_2-(oxazolyl) or methyl. In certain embodiments, R^4 is -CH_2-(oxazol-2-yl) or methyl.

[0088] In certain embodiments, R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In certain embodiments, R^4 is -CH_2-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In certain embodiments, R^4 is -CH_2-(5-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In certain embodiments, R^4 is -CH_2-(oxazolyl) or -CH_2-(thiazolyl). In certain embodiments, R^4 is -CH_2-(oxazol-2-yl) or -CH_2-(thiazol-2-yl). In certain embodiments, R^4 is -CH_2-(oxazolyl). In certain embodiments, R^4 is -CH_2-(oxazol-2-yl). In certain embodiments, R^4 is -CH_2-(thiazolyl). In certain embodiments, R^4 is -CH_2-(thiazol-2-yl).

[0089] In certain embodiments, R^4 is -(C_{1-6} alkylene)-C(O)N(R^5)(R^6). In certain embodiments, R^4 is -(C_{1-6} alkylene)-N(R^5)C(O)R^7. In certain embodiments, R^4 is -(C_{1-6} alkylene)-CO_2R^7. In certain embodiments, R^4 is -(C_{1-6} alkylene)-OC(O)R^7. In certain embodiments, R^4 is -(C_{1-6} alkylene)-cyano. In certain embodiments, R^4 is -(C_{1-6} alkylene)-O-(C_{1-6} alkyl). In certain embodiments, R^4 is C_{1-6} alkyl. In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is C_{3-6} cycloalkyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 and R^8 taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring. In certain embodiments, R^4 is methyl.

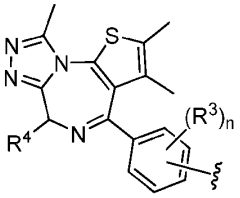
[0090] In certain embodiments, R^5 and R^6 are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is C_{1-6} alkyl. In certain embodiments, R^5 is C_{3-6} cycloalkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 is C_{1-6} alkyl. In certain embodiments, R^6 is C_{3-6} cycloalkyl. In certain embodiments, R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom.

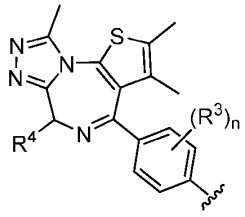
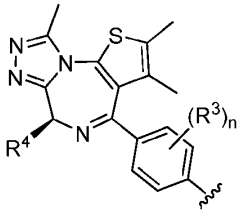
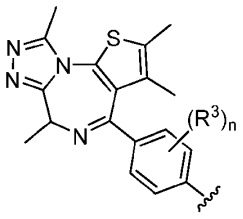
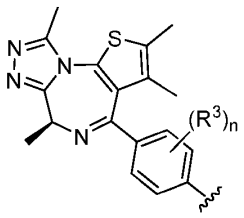
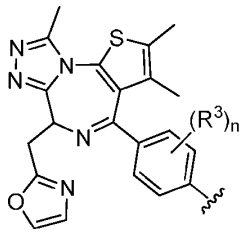
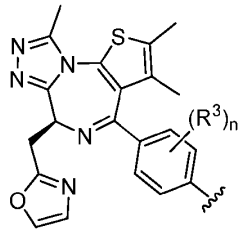
[0091] In certain embodiments, R^7 is C_{1-6} alkyl. In certain embodiments, R^7 is -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl). In certain embodiments, R^7 is C_{3-6} cycloalkyl.

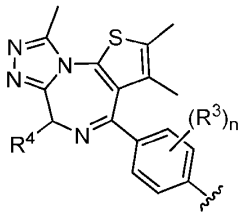
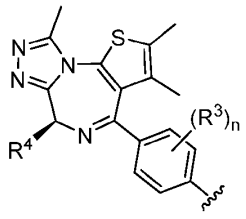
[0092] In certain embodiments, R^8 is hydrogen. In certain embodiments, R^8 is C_{1-4} alkyl.

[0093] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2.

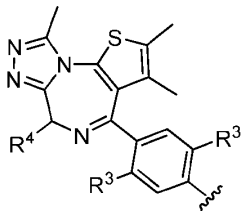
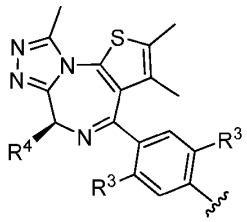
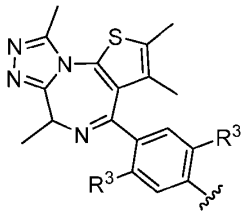
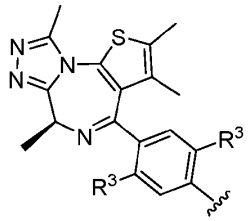
[0094] In certain embodiments, R^1 is C_{1-4} alkyl, R^2 and R^3 are independently C_1-C_6 alkyl, and m is 2. In certain embodiments, R^1 is C_{1-4} alkyl, R^2 represents independently for each occurrence C_{1-4} alkyl, and m is 2. In certain embodiments, R^1 and R^2 are methyl, and m is 2.

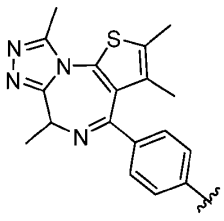
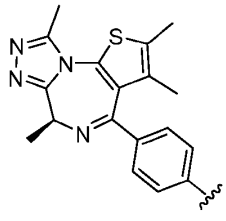
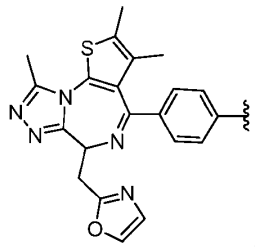


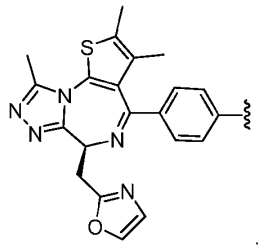
[0095] In certain embodiments, the EPL is . In certain embodiments, the EPL is  . In certain embodiments, the EPL is  . In certain embodiments, the EPL is  . In certain embodiments, the EPL is  . In certain embodiments, the EPL is  . In certain embodiments, the EPL is  . In certain embodiments, the EPL is .

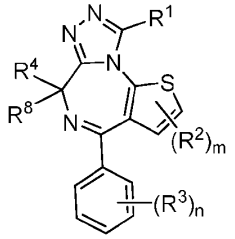
or ; wherein R^3 is independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl; and R^4 is methyl, -CH_2-(oxazolyl), or -CH_2-(thiazolyl).

[0096] In certain embodiments, the EPL is . In certain embodiments, the EPL is . In certain embodiments, the EPL is . In certain embodiments, the EPL is .

[0097] In certain embodiments, the EPL is . In certain embodiments, the EPL is . In certain embodiments, the EPL is . In

certain embodiments, the EPL is .

[0098] In certain embodiments, the EPL has the following formula that is substituted by one occurrence of R^{II-1}:



wherein:

R^{II-1} is a bond to L;

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

R^2 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^3 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxyl;

R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur), -(C_{1-6} alkylene)-C(O)N(R^5)(R^6), -(C_{1-6} alkylene)-N(R^5)C(O)R^7, -(C_{1-6} alkylene)-CO_2R^7, -(C_{1-6} alkylene)-OC(O)R^7, -(C_{1-6} alkylene)-cyano, -(C_{1-6} alkylene)-O-(C_{1-6} alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl, or hydrogen; or R^4 and R^8 taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring;

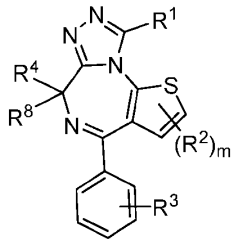
R^5 and R^6 are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom;

R^7 is C_{1-6} alkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

R^8 is hydrogen or C_{1-4} alkyl; and

m and n are independently 0, 1, or 2.

[0099] In certain embodiments, the EPL has the following formula that is substituted by one occurrence of R^{II-1}:



wherein:

R^{II-1} is a bond to L;

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

R^2 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^3 is hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxyl;

R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur), -(C_{1-6} alkylene)-C(O)N(R^5)(R^6), -(C_{1-6} alkylene)-N(R^5)C(O)R^7, -(C_{1-6} alkylene)-CO_2R^7, -(C_{1-6} alkylene)-OC(O)R^7, -(C_{1-6} alkylene)-cyano, -(C_{1-6} alkylene)-O-(C_{1-6} alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl, or hydrogen; or R^4 and R^8 taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring;

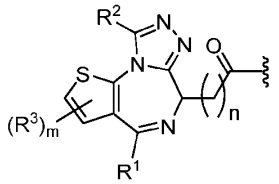
R^5 and R^6 are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom;

R^7 is C_{1-6} alkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

R^8 is hydrogen or C_{1-4} alkyl; and

m is 0, 1, or 2.

[0100] In certain embodiments, the EPL has the following formula:



wherein:

R^1 is phenyl or 6-membered heteroaryl containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the phenyl and heteroaryl are optionally

substituted with 1, 2, or 3 substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxyl, or C_1-C_6 alkoxy;

R^2 and R^3 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

m is 0, 1, or 2; and

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

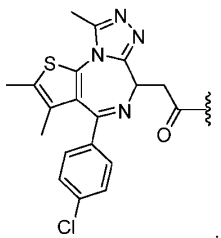
[0101] In certain embodiments, R^1 is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxyl, or C_1-C_6 alkoxy. In certain embodiments, R^1 is 6-membered heteroaryl containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxyl, or C_1-C_6 alkoxy. In certain embodiments, R^1 is phenyl. In certain embodiments, R^1 is 6-membered heteroaryl containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0102] In certain embodiments, R^2 is halo. In certain embodiments, R^2 is C_1-C_6 alkyl. In certain embodiments, R^2 is C_1-C_6 haloalkyl. In certain embodiments, R^2 is C_3-C_6 cycloalkyl. In certain embodiments, R^2 is hydroxyl. In certain embodiments, R^2 is C_1-C_6 alkoxy. In certain embodiments, R^2 is cyano.

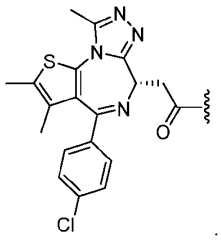
[0103] In certain embodiments, R^3 is halo. In certain embodiments, R^3 is C_1-C_6 alkyl. In certain embodiments, R^3 is C_1-C_6 haloalkyl. In certain embodiments, R^3 is C_3-C_6 cycloalkyl. In certain embodiments, R^3 is hydroxyl. In certain embodiments, R^3 is C_1-C_6 alkoxy. In certain embodiments, R^3 is cyano.

[0104] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3. In certain embodiments, n is 4.

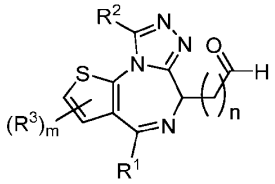
[0105] In certain embodiments, R^2 and R^3 are independently C_1-C_6 alkyl, and m is 2.

[0106] In certain embodiments, the EPL is 

. In certain embodiments, the

EPL is  .

[0107] In certain embodiments, the EPL has the following formula that is substituted by one occurrence of R^{II-1}:



wherein:

R^{II-1} is a bond to L;

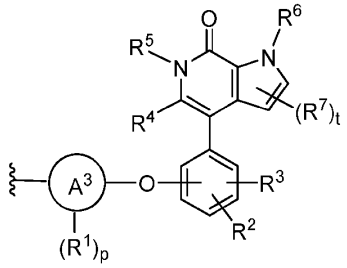
R^1 is phenyl or 6-membered heteroaryl containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the phenyl and heteroaryl are optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxyl, or C_1-C_6 alkoxy;

R^2 and R^3 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

m is 0, 1, or 2; and

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

[0108] In certain embodiments, the EPL has the following formula:



wherein:

R^1 represents independently for each occurrence halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^2 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^3 is $-N(R^8)SO_2R^9$, $-SO_2N(R^8)_2$, $-SO_2R^9$, $-(C_{1-6}$ alkylene$)-SO_2R^9$, C_{1-6} hydroxyalkyl, or a 4-7 membered saturated carbocyclic ring in which one CH_2 is replaced with SO_2;

R^4 is hydrogen, halo, or C_{1-4} alkyl;

R^5 is C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^6 is hydrogen, C_{1-4} alkyl, or C_{3-4} cycloalkyl;

R^7 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^8 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or two occurrences of R^8 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen; or R^8 and R^9 are taken together with their intervening atoms to a form a 5-7 membered ring containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^9 is C_{1-6} alkyl, C_{1-6} haloalkyl, $-(C_{1-6}$ alkylene$)-(C_{3-6}$ cycloalkyl), or C_{3-6} cycloalkyl;

A^3 is phenylene, a 3-10 membered saturated monocyclic, bicyclic or spirocyclic carbocyclylene, or C_{1-6} alkylene; and

p and t are independently 0, 1, or 2.

[0109] In certain embodiments, R^1 represents independently for each occurrence halo. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} haloalkyl.

[0110] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 is halo. In certain embodiments, R^2 is C_{1-4} alkyl. In certain embodiments, R^2 is C_{1-4} haloalkyl.

[0111] In certain embodiments, R^3 is $-N(R^8)SO_2R^9$. In certain embodiments, R^3 is $-SO_2N(R^8)_2$. In certain embodiments, R^3 is $-SO_2R^9$. In certain embodiments, R^3 is $-(C_{1-6}$ alkylene$)-SO_2R^9$. In certain embodiments, R^3 is C_{1-6} hydroxyalkyl. In certain embodiments, R^3 is a 4-7 membered saturated carbocyclic ring in which one CH_2 is replaced with SO_2.

[0112] In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is halo. In certain embodiments, R^4 is C_{1-4} alkyl. In certain embodiments, R^5 is C_{1-4} alkyl. In certain embodiments, R^5 is C_{3-4} cycloalkyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 is C_{1-4} alkyl. In certain embodiments, R^6 is C_{3-4} cycloalkyl. In certain embodiments, R^7 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^7 represents independently for each occurrence C_{3-4} cycloalkyl.

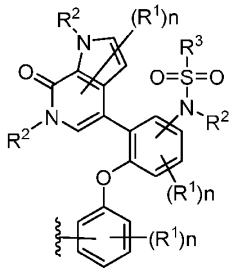
[0113] In certain embodiments, R^8 represents independently for each occurrence hydrogen. In certain embodiments, R^8 represents independently for each occurrence C_{1-4} alkyl. In certain embodiments, two occurrences of R^8 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen; or R^8 and R^9 are taken together with their intervening atoms to a form a 5-7 membered ring containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0114] In certain embodiments, R^9 is C_{1-6} alkyl. In certain embodiments, R^9 is C_{1-6} haloalkyl. In certain embodiments, R^9 is -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl). In certain embodiments, R^9 is C_{3-6} cycloalkyl.

[0115] In certain embodiments, A^3 is phenylene. In certain embodiments, A^3 is a 3-10 membered saturated monocyclic, bicyclic or spirocyclic carbocyclylene. In certain embodiments, A^3 is C_{1-6} alkylene.

[0116] In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, t is 0. In certain embodiments, t is 1. In certain embodiments, t is 2.

[0117] In certain embodiments, the EPL has the following formula:



wherein:

R^1 represents independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, or hydroxyl;

R^2 represents independently for each occurrence hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

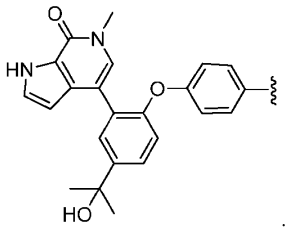
R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

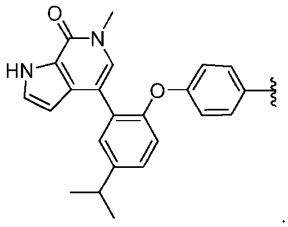
n represents independently for each occurrence 0, 1, 2, or 3.

[0118] In certain embodiments, R^1 represents independently for each occurrence halo. In certain embodiments, R^1 represents independently for each occurrence C_1-C_6 alkyl. In certain embodiments, R^1 represents independently for each occurrence C_1-C_6 haloalkyl. In certain embodiments, R^1 represents independently for each occurrence C_3-C_6 cycloalkyl. In certain embodiments, R^1 represents independently for each occurrence hydroxyl.

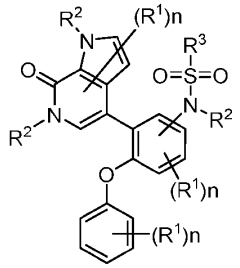
[0119] In certain embodiments, R^2 represents independently for each occurrence hydrogen. In certain embodiments, R^2 represents independently for each occurrence C_1-C_6 alkyl. In certain embodiments, R^2 represents independently for each occurrence C_3-C_6 cycloalkyl.

[0120] In certain embodiments, R^3 is C_1-C_6 alkyl. In certain embodiments, R^3 is C_3-C_6 cycloalkyl. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3.

[0121] In certain embodiments, the EPL is .

[0122] In certain embodiments, the EPL is .

[0123] In certain embodiments, the EPL has the following formula that is substituted by one occurrence of R^{II-1}:



wherein:

R^{II-1} is a bond to L;

R^1 represents independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, or hydroxyl;

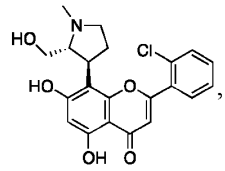
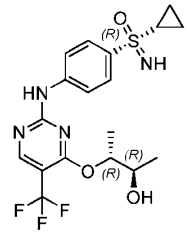
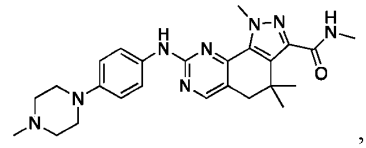
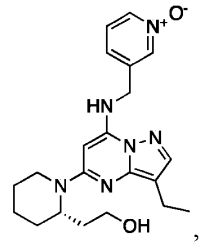
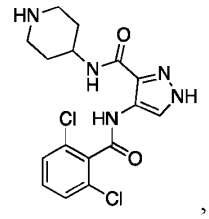
R^2 represents independently for each occurrence hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

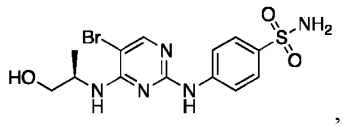
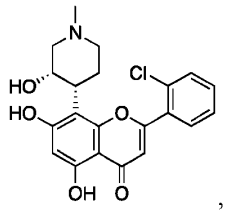
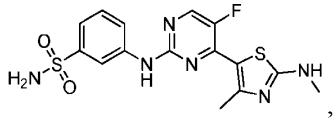
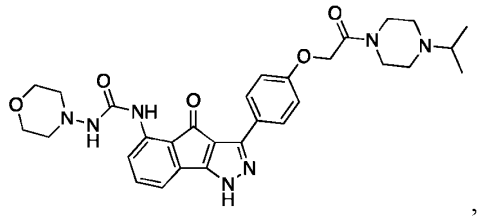
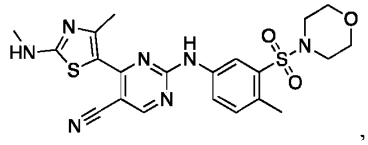
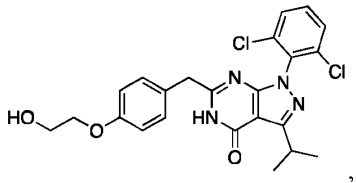
R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

n represents independently for each occurrence 0, 1, 2, or 3.

B. Moiety for CDK1

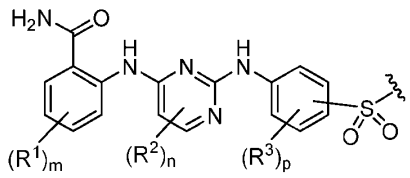
[0124] In certain embodiments, the EPL is a moiety that binds to Cyclin-Dependent Kinase 1 (CDK1). Exemplary compounds that bind to CDK1 are reported in the literature, including:

- , as described by Sivakumar, M., *et al.* in WO2007/148158;
- , as described by Lucking, U., *et al.* in WO2005/037800;
- , as described by D'Alessio, R., *et al.* in WO2004/104007;
- , as described by Guzi, T.J., *et al.* in WO2005/077954 ;
- , as described by Wyatt, P.G., *et al.* in WO2005/012256;

-  , as described by Brumby, T., *et al.* in WO2002/096888;
-  , as described by Dumont, J.A., *et al.* in WO2000/044362;
-  , as described by Wang, S., *et al.* in WO2013/156780;
-  , as described by Wang, Z., *et al.* in WO2004/092139;
-  , as described by Wang, S., *et al.* in WO2009/118567;
-  , as described by Caligiuri, M., *et al.* in Chem Biol (London) 2005, 12(10): 1103.

[0125] In certain embodiments, the EPL is a radical of one of the above compounds, which is attached to L through a modifiable oxygen, nitrogen, or carbon atom.

[0126] In certain embodiments, the EPL has the following formula:



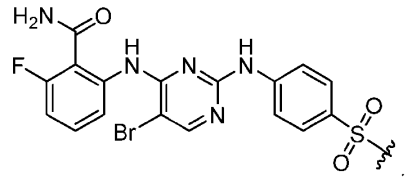
wherein:

R^1, R^2 and R^3 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

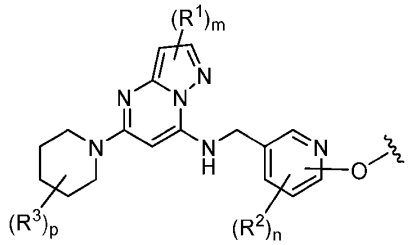
m and p each represent independently 0, 1, or 2; and

n is 0, 1 or 2.

[0127] In certain embodiments the EPL is



[0128] In certain embodiments, the EPL has the following formula:



wherein:

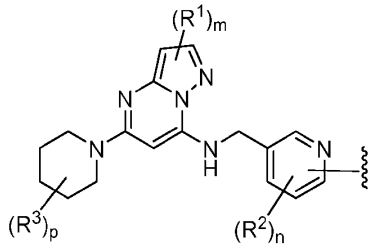
R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

[0129] In certain embodiments, the EPL has the following formula:



wherein:

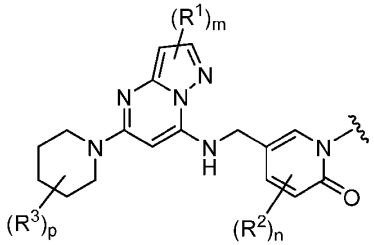
R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

[0130] In certain embodiments, the EPL has the following formula:



wherein:

R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

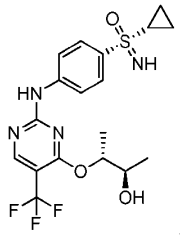
R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

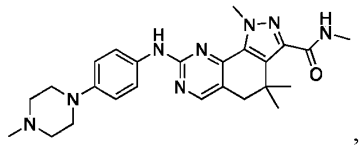
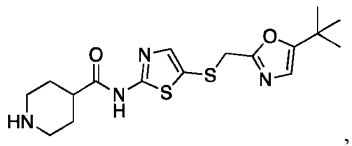
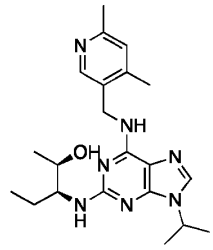
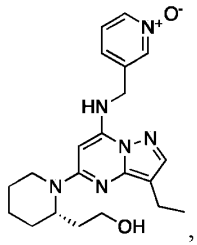
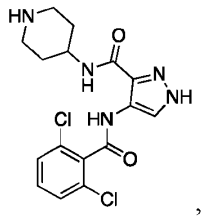
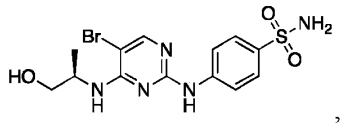
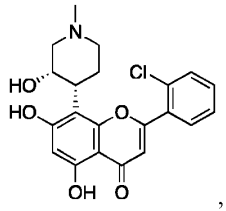
m is 0, 1, or 2; and

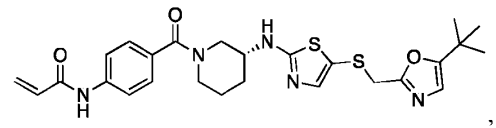
n and p each represent independently 0, 1, 2, or 3.

C. Moiety for CDK2

[0131] In certain embodiments, the EPL is a moiety that binds to Cyclin-Dependent Kinase 2 (CDK2). Exemplary compounds that bind to CDK2 are reported in the literature, including:

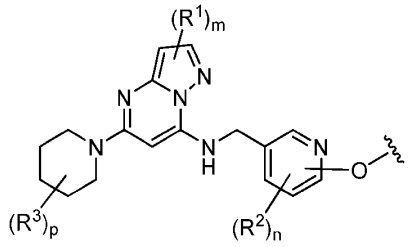
-  , as described by Lucking, U., *et al.* in WO2005/037800;

-  , as described by D'Alessio, R., *et al.* in WO2004/104007;
-  , as described by Misra, R.N., *et al.* in WO2001/044242;
-  , as described bySheldrake, P.W., *et al.* in WO2008/122767 ;
-  , as described by Guzi, T.J., *et al.* in WO2005/077954 ;
-  , as described by Wyatt, P.G., *et al.* in WO2005/012256;
-  , as described by Brumby, T., *et al.* in WO2002/096888;
-  , as described by Dumont, J.A., *et al.* in WO2000/044362;

-  , as described by Hao, M., *et al.* in WO2017/044858.

[0132] In certain embodiments, the EPL is a radical of one of the above compounds, which is attached to L through a modifiable oxygen, nitrogen, or carbon atom.

[0133] In certain embodiments, the EPL has the following formula:



wherein:

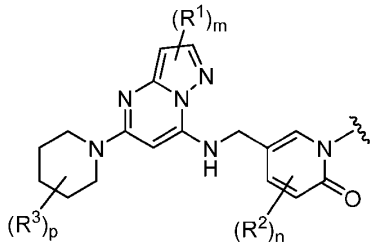
R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

[0134] In certain embodiments, the EPL has the following formula:



wherein:

R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

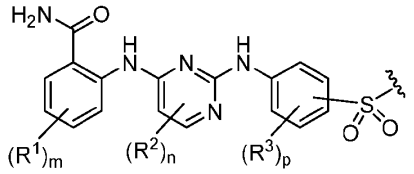
R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6

alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

[0135] In certain embodiments, the EPL has the following formula:



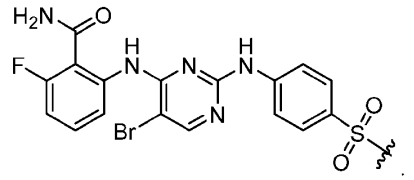
wherein:

R^1, R^2 and R^3 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

m and p each represent independently 0, 1, or 2; and

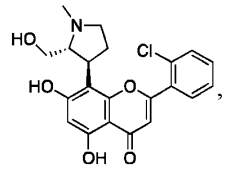
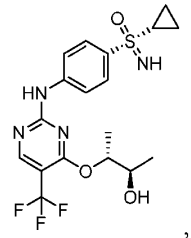
n is 0, 1 or 2.

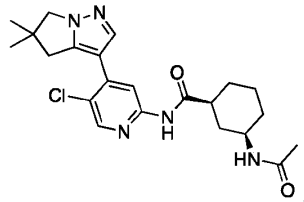
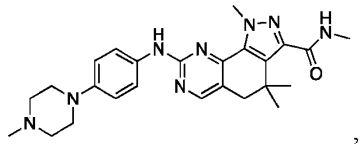
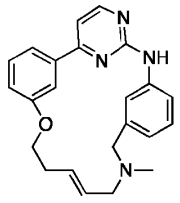
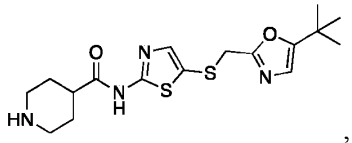
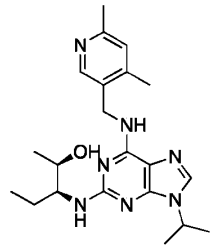
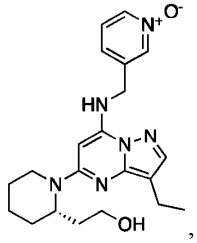
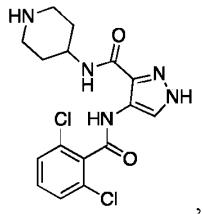
[0136] In certain embodiments the EPL is

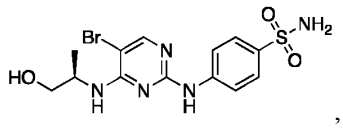
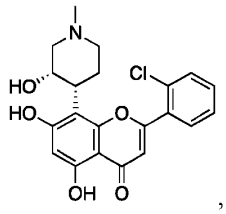
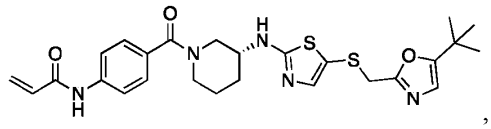
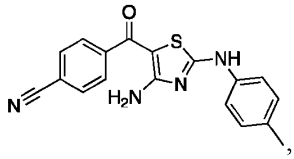
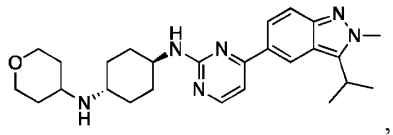


D. Moiety for CDK9

[0137] In certain embodiments, the EPL is a moiety that binds to Cyclin-Dependent Kinase 9 (CDK9). Exemplary compounds that bind to CDK9 are reported in the literature, including:

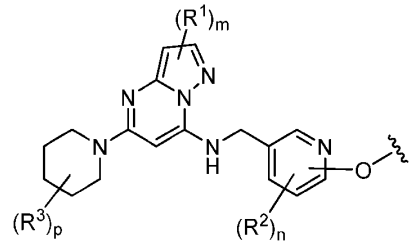
- , as described by Sivakumar, M., *et al.* in WO2007/148158;
- , as described by Lucking, U., *et al.* in WO2005/037800;

-  , as described by Pike, K.G., *et al.* in WO2017001354;
-  , as described by D'Alessio, R., *et al.* in WO2004/104007;
-  , as described by Blanchard, S., *et al.* in WO2007/058628;
-  , as described by Misra, R.N., *et al.* in WO2001/044242;
-  , as described by Sheldrake, P.W. *et al.* in WO2008/122767 ;
-  , as described by Guzi, T.J., *et al.* in WO2005/077954 ;
-  , as described by Wyatt, P.G., *et al.* in WO2005/012256;

-  , as described by Brumby, T., *et al.* in WO2002/096888;
-  , as described by Dumont, J.A., *et al.* in WO2000/044362;
-  , as described by Hao, M., *et al.* in WO2017/044858;
-  , as described by Smith, C.D., *et al.* in WO2018/089902;
-  , as described by Gao, Q., *et al.* in CN105111191.

[0138] In certain embodiments, the EPL is a radical of one of the above compounds, which is attached to L through a modifiable oxygen, nitrogen, or carbon atom.

[0139] In certain embodiments, the EPL has the following formula:



wherein:

R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

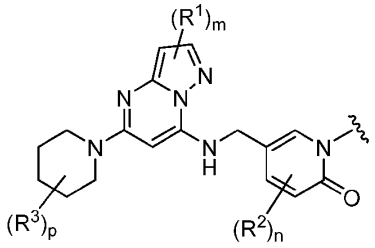
R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6

alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

[0140] In certain embodiments, the EPL has the following formula:



wherein:

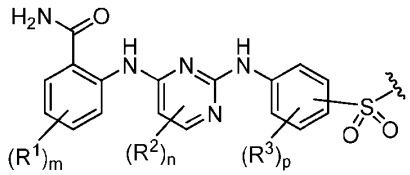
R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

[0141] In certain embodiments, the EPL has the following formula:

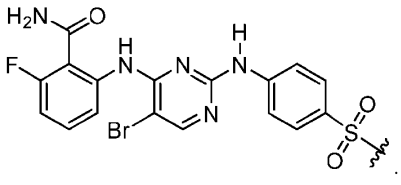


wherein:

R^1, R^2 and R^3 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

m and p each represent independently 0, 1, or 2; and

n is 0, 1 or 2.

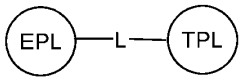
[0142] In certain embodiments, the EPL is .

[0143] In certain embodiments, the EPL is selected from those depicted in the compounds in Tables 1, 3, 4, and 5, below. In certain embodiments, the EPL is selected from those depicted in the compounds in Tables 3 and 4, below. In certain embodiments, the EPL is selected from those depicted in the compounds in Table 1, below. In certain embodiments, the EPL is selected from those depicted in the compounds in Table 3, below. In certain embodiments, the EPL is selected from those depicted in the compounds in Table 4, below. In certain embodiments, the EPL is selected from those depicted in the compounds in Table 5, below.

[0144] The description above regarding the identity of the EPL, and in Parts C and D below regarding the identity of the TPL and linker, describe multiple embodiments relating to compounds of Formula I. The patent application specifically contemplates all combinations of the embodiments.

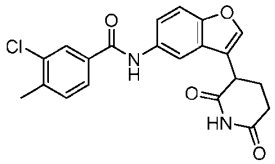
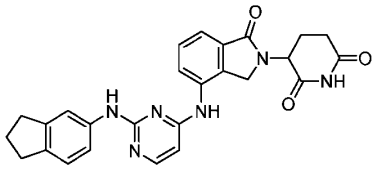
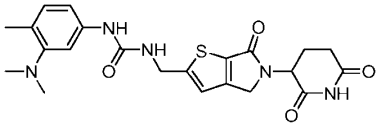
Part B: Compounds of Formula II

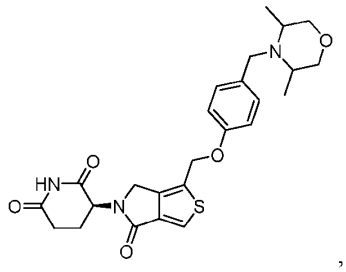
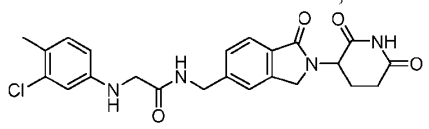
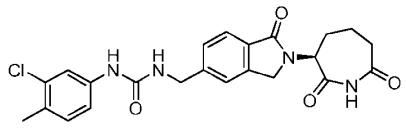
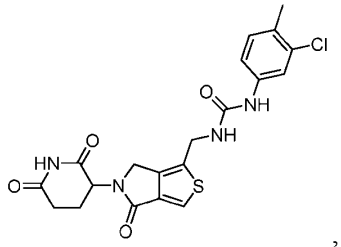
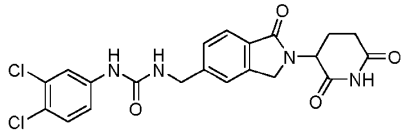
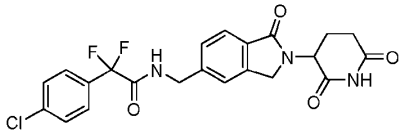
[0145] Another aspect of the invention provides a compound represented by the formula:



or a pharmaceutically acceptable salt thereof, wherein EPL is a moiety that binds to an effector protein selected from Eukaryotic Peptide Chain Release Factor GTP-Binding Subunit ERF3A (GSPT1); L is a linker; and TPL is a moiety that binds to estrogen receptor.

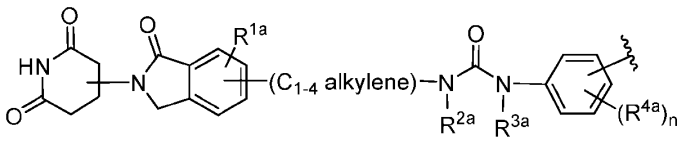
[0146] Exemplary moieties that bind GSPT1 are reported in the literature, including:

-  , as described in Luo, Y. *et al.*, in WO2021047627.
-  , as described in Gray, N. *et al.*, in WO2020006264.
-  , as described in Chan, K. *et al.*, in US2020369679.

-  , as described in Chan, K. *et al.*, in WO2019241271.
-  , as described in Chan, K. *et al.*, in WO2019241274.
-  , as described in Chan, K. *et al.*, in WO2019241274.
-  , as described in Chan, K. *et al.*, in US2018298027.
-  , as described in Muller, G. *et al.*, in US2009142297.
-  , as described in Hansen, J. *et al.*, in WO2016007848.

[0147] In certain embodiments, the EPL is a radical of one of the above compounds, which is attached to L through a modifiable oxygen, nitrogen, or carbon atom.

[0148] In certain embodiments, the EPL has the following formula:



wherein:

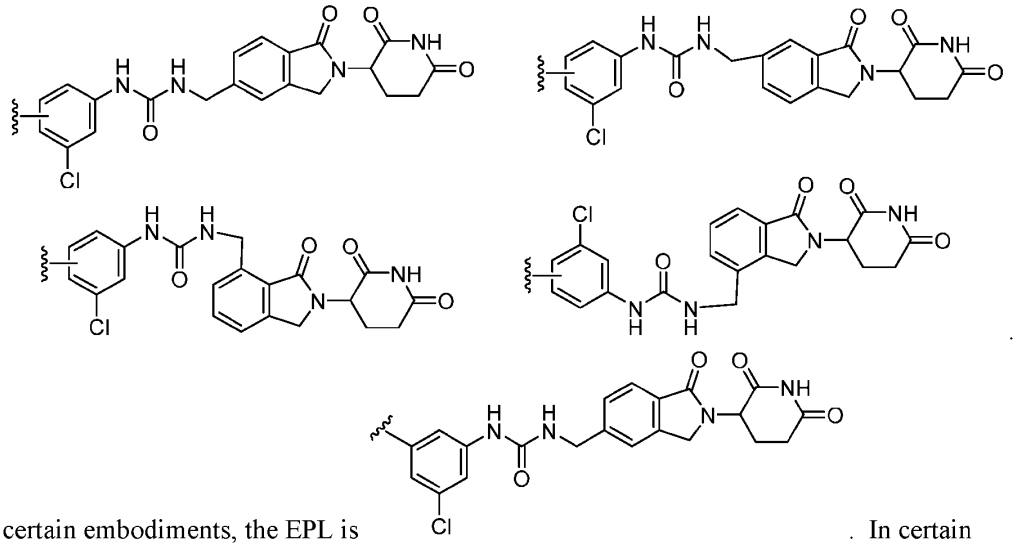
R^{1a} is hydrogen, halo, or C_{1-4} alkyl;

R^{2a} and R^{3a} are independently hydrogen or C_{1-4} alkyl;

R^{4a} represents independently for each occurrence halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, or C_{1-4} alkoxyl; and

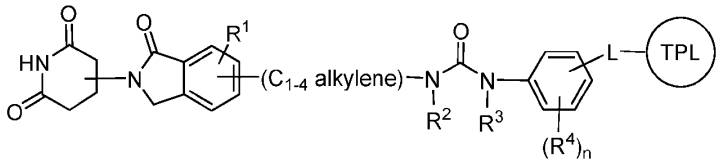
n is 0, 1, 2, or 3.

[0149] In certain embodiments, the EPL is one of the following:



In certain embodiments, the EPL is . In certain embodiments, EPL is selected from those depicted in the compounds in Table 2, below.

[0150] Another aspect of the invention provides a compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is hydrogen, halo, or C_{1-4} alkyl;

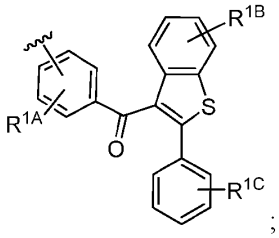
R^2 and R^3 are independently hydrogen or C_{1-4} alkyl;

R^4 represents independently for each occurrence halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, or C_{1-4} alkoxyl;

n is 0, 1, 2, or 3;

L is a linker; and

TPL is represented by:



;

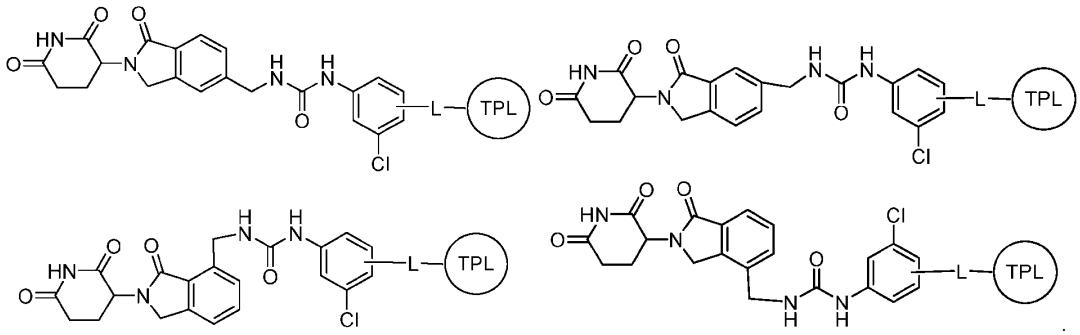
R^{1A} is hydrogen, halo, or C_{1-4} alkyl; and

R^{1B} and R^{1C} are independently hydroxyl, halo, C_{1-4} alkyl, or C_{1-4} alkoxyl.

[0151] As generally defined above for Formula II, R^1 is hydrogen, halo, or C_{1-4} alkyl. In certain embodiments, R^1 is hydrogen. In certain embodiments, R^1 is halo. In certain embodiments, R^1 is C_{1-4} alkyl. In certain embodiments, R^1, R^2, and R^3 are hydrogen.

[0152] As generally defined above for Formula II, R^{1B} and R^{1C} are independently hydroxyl, halo, C_{1-4} alkyl, or C_{1-4} alkoxyl. In certain embodiments, R^{1B} is hydroxyl. In certain embodiments, R^{1B} is halo. In certain embodiments, R^{1B} is C_{1-4} alkyl. In certain embodiments, R^{1B} is C_{1-4} alkoxyl. In certain embodiments, R^{1C} is hydroxyl. In certain embodiments, R^{1C} is halo. In certain embodiments, R^{1C} is C_{1-4} alkyl. In certain embodiments, R^{1C} is C_{1-4} alkoxyl.

[0153] In certain embodiments, the compound is represented by one of the following:



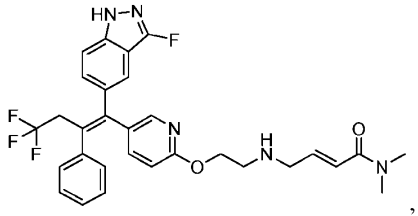
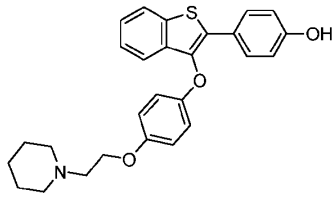
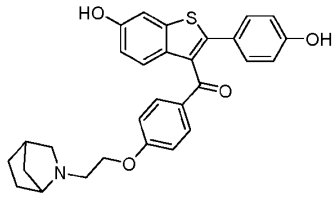
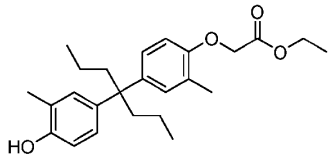
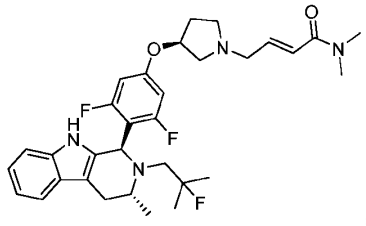
[0154] In certain embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1B} and R^{1C} are hydroxyl. In certain embodiments, R^{1B} is halo, and R^{1C} is hydroxyl.

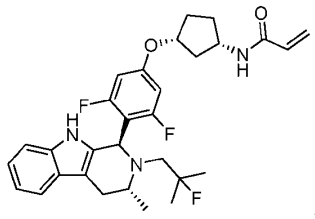
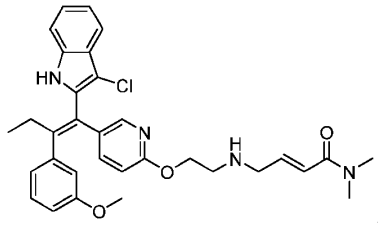
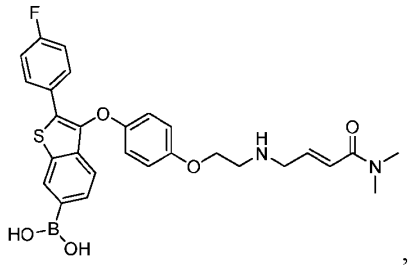
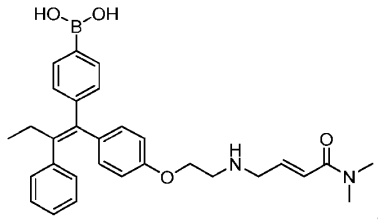
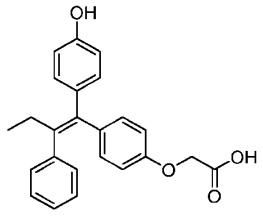
Part C: Exemplary Further Description of the TPL Component of Compounds of Formula I and Formula II

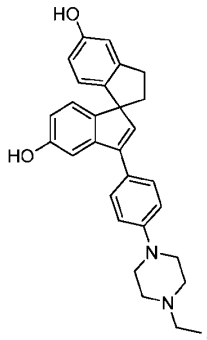
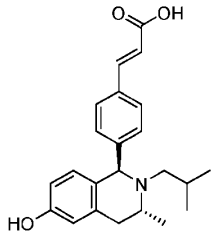
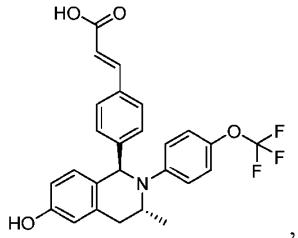
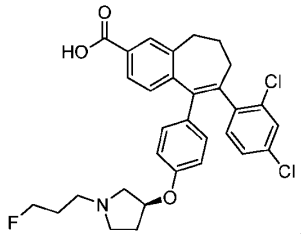
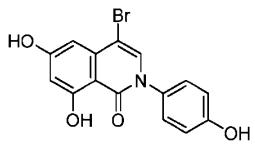
[0155] Compounds of Formula I and II may be further characterized according to, for example, the identity of the TPL component. As generally described above, the TPL is a moiety

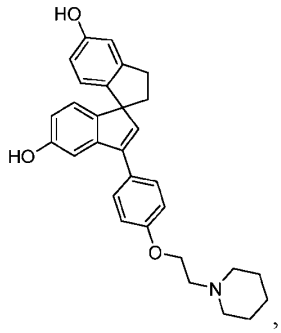
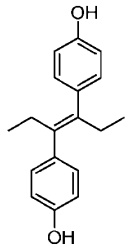
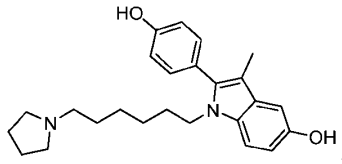
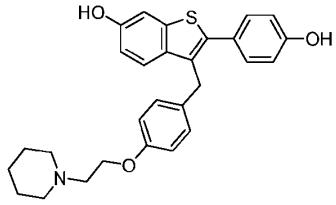
that binds to an estrogen receptor. Exemplary moieties for the TPL component are described in more detail below.

[0156] In certain embodiments, the TPL is a moiety that is an activator, inhibitor, and/or bind to the estrogen receptor (ER). Compounds that activate, inhibit, and/or bind to the ER are reported in the literature, which include:

- , as described in Bock, M. *et al.*, in US20160347717.
- , as described in Palkowitz, A., in US5488058.
- , as described in Cameron, K. *et al.*, in WO1995010513.
- , as described in Nanjyo, S. *et al.*, in Bioorg Med Chem 2019, 27(10): 1952.
- , as described in Yang, F. *et al.*, in WO2019223715.

-  , as described in Yang, F. *et al.*, in WO2019223715.
-  , as described in Duan, S. *et al.*, in WO2020125640.
-  , as described in Wang, G. *et al.*, in WO2020055973.
-  , as described in Wang, G. *et al.*, in WO2020055973.
-  , as described in Ruenitz, P., in 219th Am Chem Soc (ACS) Natl Meet · 2000-03-26 / 2000-03-30 · San Francisco, United States · Abst MEDI 330.

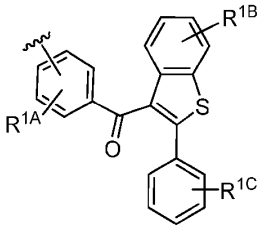
- , as described in Watanabe, N. *et al.*, in Bioorg Med Chem Lett 2003, 13(24): 4317.
- , as described in Scott, J. *et al.*, in ACS Med Chem Lett 2016, 7(1): 94.
- , as described in Scott, J. *et al.*, in ACS Med Chem Lett 2016, 7(1): 94.
- , as described in Bouaboula, M. *et al.*, in US2020392081.
- , as described in Dalton, J. *et al.*, in WO2008091555.

- , as described in Watanabe, N. *et al.*, in J Med Chem 2003, 46(19): 3961.
- , as described in Nanjyo, S. *et al.*, in Bioorg Med Chem 2019, 27(10): 1952.
- , as described in Miller, C. *et al.*, in J Med Chem 2001, 44(11): 1654.
- , as described in Cameron, K. *et al.*, in WO1995010513.

[0157] In certain embodiments, the TPL is a moiety that binds to the estrogen receptor (ER). Exemplary compounds that bind to ER are reported in the literature, such as raloxifene, H3B-6545, and AZD9496. A radical of such compounds reported in the literature that bind ER are amenable for use in the present invention.

[0158] In certain embodiments, the TPL is a radical of one of the above compounds, which is attached to L through a modifiable oxygen, nitrogen, or carbon atom.

[0159] In certain embodiments, the TPL is



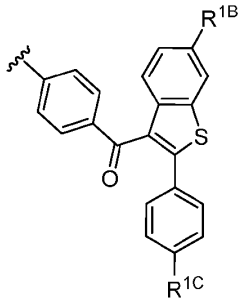
wherein:

R^{1A} is hydrogen, halo, or C_{1-4} alkyl; and

R^{1B} and R^{1C} are independently hydroxyl, halo, C_{1-4} alkyl, or C_{1-4} alkoxyl.

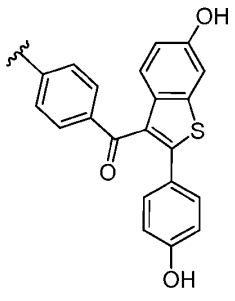
[0160] In certain embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1A} is halo. In certain embodiments, R^{1A} is C_{1-4} alkyl.

[0161] In certain embodiments, the TPL is

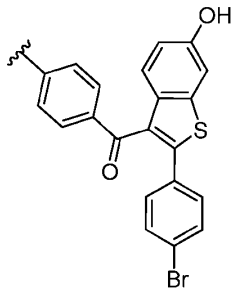
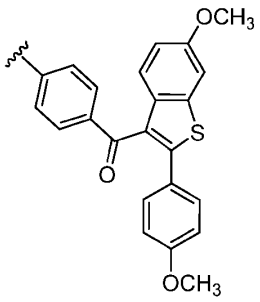


wherein R^{1B} and R^{1C} are independently hydroxyl, halo, C_{1-4} alkyl, or C_{1-4} alkoxyl.

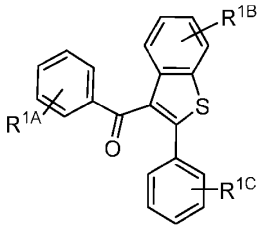
[0162] In certain embodiments, R^{1B} is hydroxyl. In certain embodiments, R^{1B} is halo. In certain embodiments, R^{1B} is C_{1-4} alkyl. In certain embodiments, R^{1B} is C_{1-4} alkoxyl. In certain embodiments, R^{1C} is hydroxyl. In certain embodiments, R^{1C} is halo. In certain embodiments, R^{1C} is C_{1-4} alkyl. In certain embodiments, R^{1C} is C_{1-4} alkoxyl. In certain embodiments, R^{1B} and R^{1C} are hydroxyl. In certain embodiments, R^{1B} is halo, and R^{1C} is hydroxyl. In certain embodiments, R^{1B} and R^{1C} are methoxy.



[0163] In certain embodiments, the TPL is . In certain embodiments, the

TPL is  . In certain embodiments, the TPL is  .

[0164] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



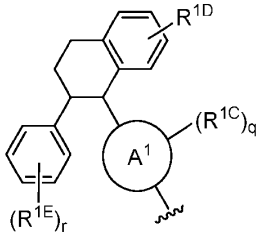
wherein:

$R^{II\text{-}1A}$ is a bond to L;

R^{1A} is hydrogen, halo, or $C_{1\text{-}4}$ alkyl; and

R^{1B} and R^{1C} are independently hydroxyl, halo, $C_{1\text{-}4}$ alkyl, or $C_{1\text{-}4}$ alkoxyl.

[0165] In certain embodiments, the TPL is



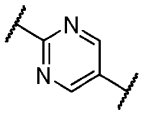
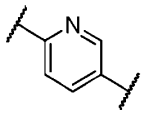
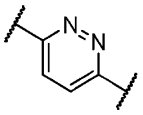
wherein:

A^1 is phenylene or 6-membered heteroarylene containing 1 or 2 heteroatoms that are nitrogen;

R^{1C} and R^{1E} are each independently for each occurrence hydrogen, halo, $C_{1\text{-}4}$ alkoxyl, $C_{1\text{-}4}$ alkyl, or $C_{1\text{-}4}$ haloalkyl;

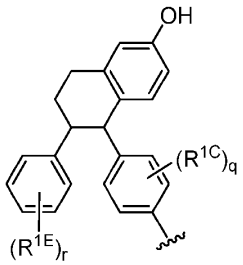
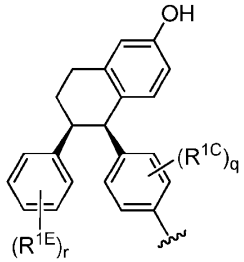
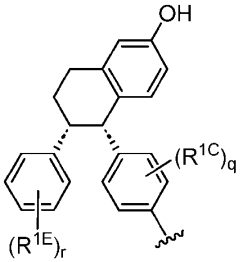
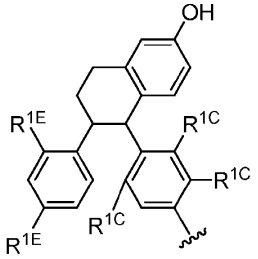
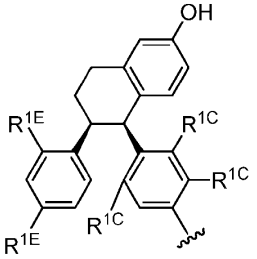
R^{1D} is hydroxyl, $-CO_2H$, or $-B(OH)_2$; and

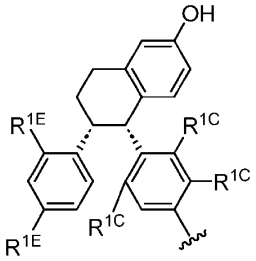
q and r are independently 0, 1, 2, or 3.

[0166] In certain embodiments, A^1 is phenylene. In certain embodiments, A^1 is *para*-phenylene. In certain embodiments, A^1 is a 6-membered heteroarylene containing 1 or 2 heteroatoms that are nitrogen. In certain embodiments, A^1 is pyridinylene, pyrimidinylene, or pyridazinylene. In certain embodiments, A^1 is , , or ; wherein the attachment point adjacent to a nitrogen atom of A^1 is connected to L.

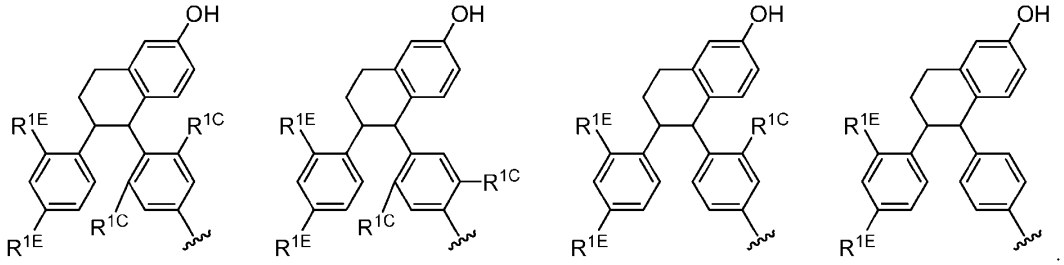
[0167] In certain embodiments, A^1 is *para*-phenylene, and R^{1D} is hydroxyl.

[0168] In certain embodiments, R^{1D} is hydroxyl. In certain embodiments, R^{1D} is $-CO_2H$. In certain embodiments, R^{1D} is $-B(OH)_2$.

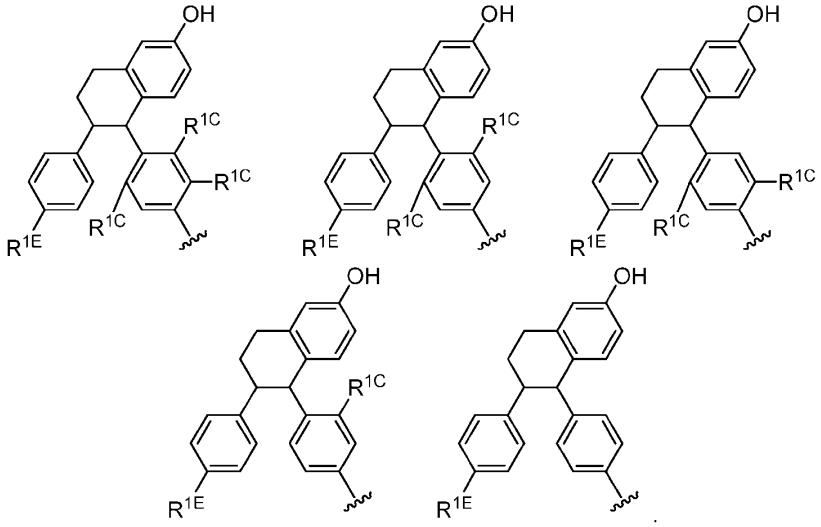
[0169] In certain embodiments, the TPL is . In certain embodiments, the TPL is  or . In certain embodiments, the TPL is . In certain embodiments, the TPL is  or



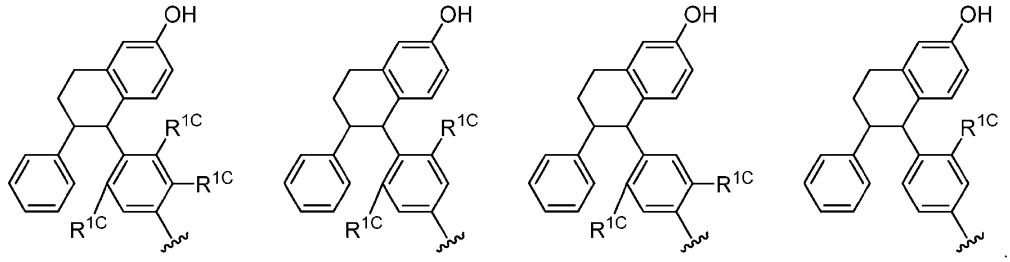
[0170] In certain embodiments, the TPL is one of the following:



[0171] In certain embodiments, the TPL is one of the following:



[0172] In certain embodiments, the TPL is one of the following:



[0173] In certain embodiments, R^{1C} and R^{1E} are each independently for each occurrence hydrogen or halo. In certain embodiments, R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, chloro, methoxy, methyl, or trifluoromethyl. In certain embodiments, R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl.

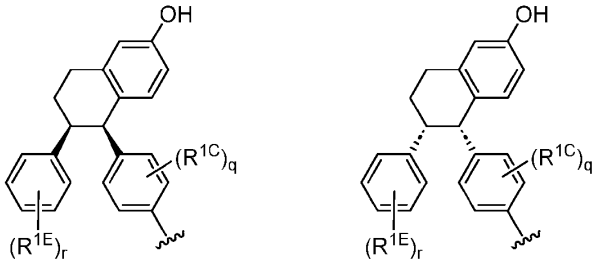
[0174] In certain embodiments, R^{1C} is independently for each occurrence halo, C_{1-4} alkoxyl, or C_{1-4} alkyl. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or halo. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or C_{1-4} alkoxyl. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^{1C} is independently for each occurrence halo or C_{1-4} alkoxyl. In certain embodiments, R^{1C} is independently for each occurrence halo or C_{1-4} alkyl.

[0175] In certain embodiments, R^{1C} is independently for each occurrence halo. In certain embodiments, R^{1C} is independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^{1C} is independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^{1C} is independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^{1C} is $-CF_3$. In certain embodiments, R^{1C} is independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl.

[0176] In certain embodiments, R^{1E} is independently for each occurrence halo, C_{1-4} alkoxyl, or C_{1-4} alkyl. In certain embodiments, R^{1E} is independently for each occurrence hydrogen or halo. In certain embodiments, R^{1E} is independently for each occurrence hydrogen or C_{1-4} alkyl. In certain embodiments, R^{1E} is independently for each occurrence halo or C_{1-4} alkyl.

[0177] In certain embodiments, R^{1E} is independently for each occurrence halo. In certain embodiments, R^{1E} is independently for each occurrence C_{1-4} alkoxyl. In certain embodiments, R^{1E} is independently for each occurrence C_{1-4} alkyl. In certain embodiments, R^{1E} is independently for each occurrence C_{1-4} haloalkyl. In certain embodiments, R^{1E} is $-CF_3$. In certain embodiments, R^{1E} is independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl.

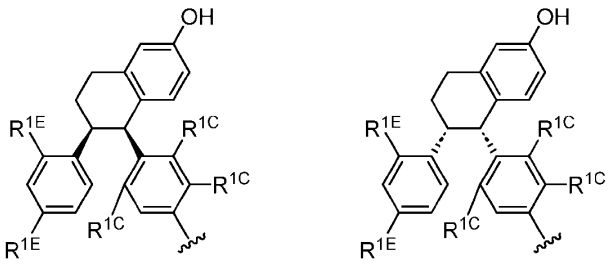
[0178] In certain embodiments, the TPL is one of the following:



wherein R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl; and q and r are independently 0, 1, or 2.

[0179] In certain embodiments, q and r are 0. In certain embodiments, q and r are independently 0 or 1. In certain embodiments, q and r are independently 1 or 2. In certain embodiments, q and r are independently 0, 1, or 2. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2. In certain embodiments, q is 3. In certain embodiments, q is 0 or 1. In certain embodiments, q is 1 or 2. In certain embodiments, q is 0, 1, or 2. In certain embodiments, r is 0. In certain embodiments, r is 1. In certain embodiments, r is 2. In certain embodiments, r is 3. In certain embodiments, r is 0 or 1. In certain embodiments, r is 1 or 2. In certain embodiments, r is 0, 1, or 2.

[0180] In certain embodiments, the TPL is one of the following:



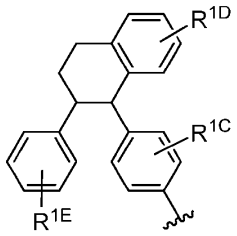
wherein R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl.

[0181] In certain embodiments, R^{1C} and R^{1E} are each independently for each occurrence fluoro, chloro, methoxy, or methyl. In certain embodiments, R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1C} and R^{1E} are each independently for each occurrence hydrogen or fluoro. In certain embodiments, R^{1C} and R^{1E} are hydrogen. In certain embodiments, R^{1C} and R^{1E} are fluoro.

[0182] In certain embodiments, R^{1C} is independently for each occurrence fluoro, chloro, methoxy, or methyl. In certain embodiments, R^{1C} is independently for each occurrence hydrogen, fluoro, chloro, or methoxy. In certain embodiments, R^{1C} is independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or fluoro. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or methoxy. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or methyl. In certain embodiments, R^{1C} is independently for each occurrence fluoro or methoxy. In certain embodiments, R^{1C} is independently for each occurrence fluoro or methyl. In certain embodiments, R^{1C} is methoxy.

[0183] In certain embodiments, R^{1E} is independently for each occurrence fluoro, chloro, methoxy, or methyl. In certain embodiments, R^{1E} is independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1E} is independently for each occurrence hydrogen or fluoro. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or methyl. In certain embodiments, R^{1C} is independently for each occurrence fluoro or methyl. In certain embodiments, R^{1C} is methoxy.

[0184] In certain embodiments, the TPL is



wherein:

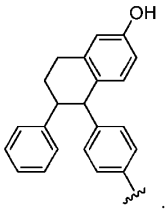
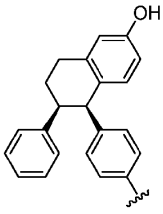
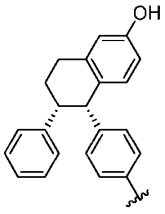
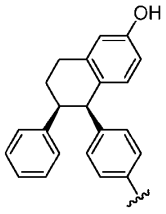
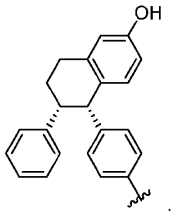
R^{1C} and R^{1E} are independently hydrogen, halo, or C_{1-4} alkyl; and

R^{1D} is hydroxyl.

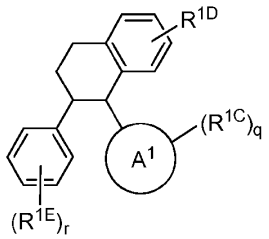
[0185] In certain embodiments, R^{1C} and R^{1E} are independently hydrogen or halo. In certain embodiments, R^{1C} and R^{1E} are independently hydrogen or fluoro. In certain embodiments, R^{1C} and R^{1E} are hydrogen. In certain embodiments, R^{1C} and R^{1E} are fluoro.

[0186] In certain embodiments, R^{1C} is hydrogen or halo. In certain embodiments, R^{1C} is hydrogen or fluoro. In certain embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1C} is halo. In certain embodiments, R^{1C} is fluoro. In certain embodiments, R^{1C} is chloro. In certain embodiments, R^{1C} is C_{1-4} alkyl. In certain embodiments, R^{1C} is methyl.

[0187] In certain embodiments, R^{1E} is hydrogen or halo. In certain embodiments, R^{1E} is hydrogen or fluoro. In certain embodiments, R^{1E} is hydrogen. In certain embodiments, R^{1E} is halo. In certain embodiments, R^{1E} is fluoro. In certain embodiments, R^{1E} is chloro. In certain embodiments, R^{1E} is C_{1-4} alkyl. In certain embodiments, R^{1E} is methyl.

[0188] In certain embodiments, the TPL is . In certain embodiments, the TPL is  or . In certain embodiments, the TPL is . In certain embodiments, the TPL is .

[0189] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



wherein:

$R^{II\text{-}1A}$ is a bond to L;

A^1 is phenyl or 6-membered heteroaryl containing 1 or 2 heteroatoms that are nitrogen;

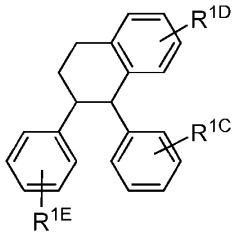
R^{1C} and R^{1E} are each independently for each occurrence hydrogen, halo, C_{1-4} alkoxyl, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^{1D} is hydroxyl, $-CO_2H$, or $-B(OH)_2$; and

q and r are independently 0, 1, 2, or 3.

In certain embodiments, each of the variables is independently as described and defined in embodiments above.

[0190] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



wherein:

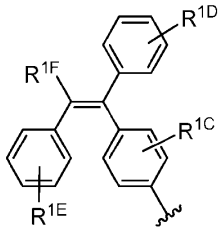
$R^{II\text{-}1A}$ is a bond to L;

R^{1C} and R^{1E} are independently hydrogen, halo, or $C_{1\text{-}4}$ alkyl; and

R^{1D} is hydroxyl.

In certain embodiments, each of the variables is independently as described and defined in embodiments above.

[0191] In certain embodiments, the TPL is



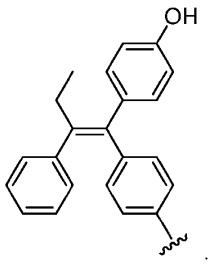
wherein:

R^{1C} and R^{1E} are independently hydrogen, halo, or $C_{1\text{-}4}$ alkyl;

R^{1D} is hydroxyl; and

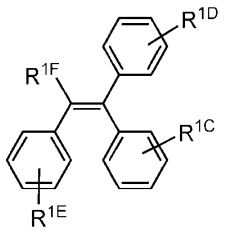
R^{1F} is hydrogen or $C_{1\text{-}4}$ alkyl.

[0192] In certain embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1C} is halo. In certain embodiments, R^{1C} is $C_{1\text{-}4}$ alkyl. In certain embodiments, R^{1E} is hydrogen. In certain embodiments, R^{1E} is halo. In certain embodiments, R^{1E} is $C_{1\text{-}4}$ alkyl. In certain embodiments, R^{1F} is hydrogen. In certain embodiments, R^{1F} is $C_{1\text{-}4}$ alkyl.



[0193] In certain embodiments, the TPL is .

[0194] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



wherein:

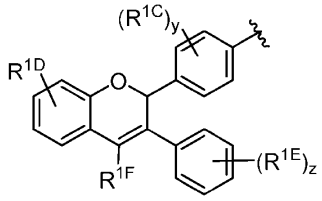
$R^{II\text{-}1A}$ is a bond to L;

R^{1C} and R^{1E} are independently hydrogen, halo, or $C_{1\text{-}4}$ alkyl;

R^{1D} is hydroxyl; and

R^{1F} is hydrogen or $C_{1\text{-}4}$ alkyl.

[0195] In certain embodiments, the TPL is



wherein:

R^{1C} represents independently for each occurrence hydrogen, halo, hydroxyl, or $C_{1\text{-}4}$ alkyl;

R^{1D} is hydroxyl;

R^{1E} represents independently for each occurrence halo, hydroxyl, or $C_{1\text{-}4}$ alkyl;

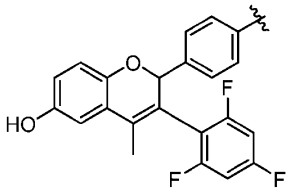
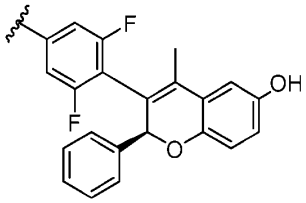
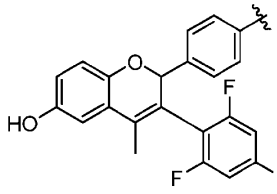
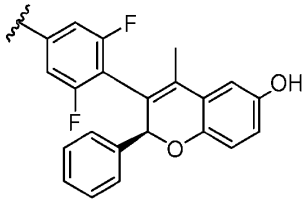
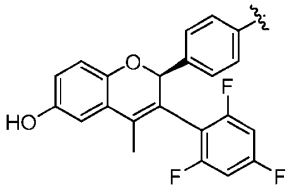
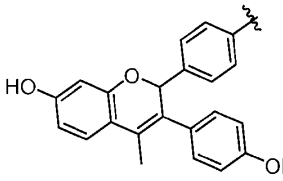
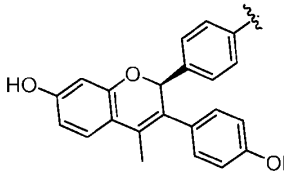
R^{1F} is hydrogen or $C_{1\text{-}4}$ alkyl;

y is 1 or 2; and

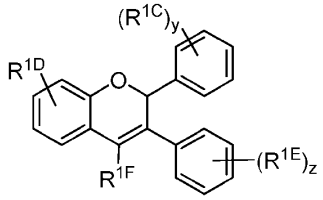
z is 1, 2, or 3.

[0196] In certain embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1C} is halo. In certain embodiments, R^{1C} is hydroxyl. In certain embodiments, R^{1C} is $C_{1\text{-}4}$ alkyl. In certain

embodiments, R^{1E} is halo. In certain embodiments, R^{1E} is fluoro. In certain embodiments, R^{1E} is hydroxyl. In certain embodiments, R^{1E} is C_{1-4} alkyl. In certain embodiments, R^{1F} is hydrogen. In certain embodiments, R^{1F} is C_{1-4} alkyl. In certain embodiments, R^{1F} is $-CH_3$. In certain embodiments, y is 1. In certain embodiments, y is 2. In certain embodiments, z is 1. In certain embodiments, z is 2. In certain embodiments, z is 3.

[0197] In certain embodiments, the TPL is  or . In certain embodiments, the TPL is . In certain embodiments, the TPL is . In certain embodiments, the TPL is . In certain embodiments, the TPL is . In certain embodiments, the TPL is .

[0198] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



wherein:

$R^{II\text{-}1A}$ is a bond to L;

R^{1C} represents independently for each occurrence hydrogen, halo, hydroxyl, or $C_{1\text{-}4}$ alkyl;

R^{1D} is hydroxyl;

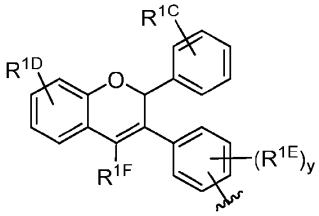
R^{1E} represents independently for each occurrence halo, hydroxyl, or $C_{1\text{-}4}$ alkyl;

R^{1F} is hydrogen or $C_{1\text{-}4}$ alkyl;

y is 1 or 2; and

z is 1, 2, or 3.

[0199] In certain embodiments, the TPL is



wherein:

R^{1C} is hydrogen, hydroxyl, or $C_{1\text{-}4}$ alkyl;

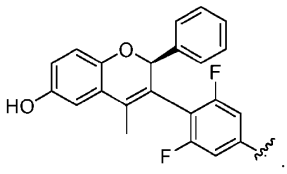
R^{1D} is hydroxyl;

R^{1E} represents independently for each occurrence halo, hydroxyl, or $C_{1\text{-}4}$ alkyl;

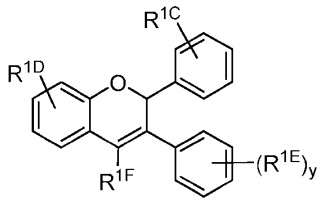
R^{1F} is hydrogen or $C_{1\text{-}4}$ alkyl; and

y is 1, 2, or 3.

[0200] In certain embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1C} is hydroxyl. In certain embodiments, R^{1C} is $C_{1\text{-}4}$ alkyl. In certain embodiments, R^{1E} is halo. In certain embodiments, R^{1E} is fluoro. In certain embodiments, R^{1E} is hydroxyl. In certain embodiments, R^{1E} is $C_{1\text{-}4}$ alkyl. In certain embodiments, R^{1F} is hydrogen. In certain embodiments, R^{1F} is $C_{1\text{-}4}$ alkyl. In certain embodiments, R^{1F} is $-CH_3$. In certain embodiments, y is 1. In certain embodiments, y is 2. In certain embodiments, y is 3.

[0201] In certain embodiments, the TPL is .

[0202] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



wherein:

$R^{II\text{-}1A}$ is a bond to L;

R^{1C} is hydrogen, hydroxyl, or $C_{1\text{-}4}$ alkyl;

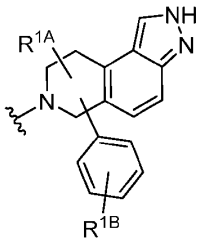
R^{1D} is hydroxyl;

R^{1E} represents independently for each occurrence halo, hydroxyl, or $C_{1\text{-}4}$ alkyl;

R^{1F} is hydrogen or $C_{1\text{-}4}$ alkyl; and

y is 1, 2, or 3.

[0203] In certain embodiments, the TPL is

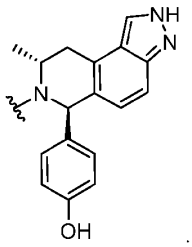


wherein:

R^{1A} is hydrogen or $C_{1\text{-}4}$ alkyl; and

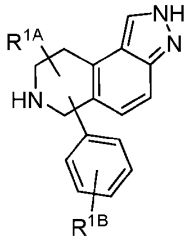
R^{1B} is $-C(O)CH_3$, hydrogen, hydroxyl, or $C_{1\text{-}4}$ alkyl.

[0204] In certain embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1A} is $C_{1\text{-}4}$ alkyl. In certain embodiments, R^{1B} is $-C(O)CH_3$. In certain embodiments, R^{1B} is hydrogen. In certain embodiments, R^{1B} is hydroxyl. In certain embodiments, R^{1B} is $C_{1\text{-}4}$ alkyl.



[0205] In certain embodiments, the TPL is .

[0206] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



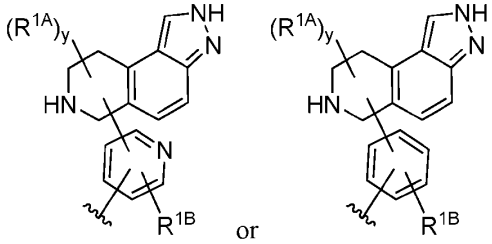
wherein:

$R^{II\text{-}1A}$ is a bond to L;

R^{1A} is hydrogen or $C_{1\text{-}4}$ alkyl; and

R^{1B} is -C(O)CH_3, hydrogen, hydroxyl, or $C_{1\text{-}4}$ alkyl.

[0207] In certain embodiments, the TPL is

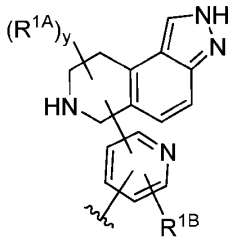


wherein:

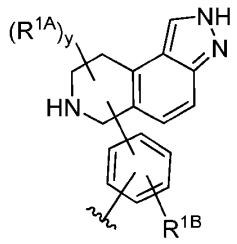
R^{1A} represents independently for each occurrence hydrogen, $C_{1\text{-}4}$ haloalkyl, $C_{1\text{-}4}$ alkyl, or halo;

R^{1B} is hydrogen, halo, or $C_{1\text{-}4}$ alkyl; and

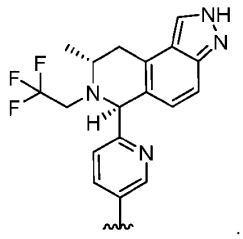
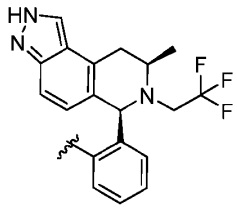
y is 1, 2, or 3.



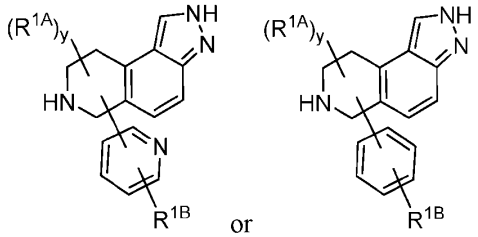
[0208] In certain embodiments, the TPL is . In certain embodiments, the

TPL is .

[0209] In certain embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1A} is C_{1-4} haloalkyl. In certain embodiments, R^{1A} is C_{1-4} alkyl. In certain embodiments, R^{1A} is halo. In certain embodiments, R^{1B} is hydrogen. In certain embodiments, R^{1B} is halo. In certain embodiments, R^{1B} is C_{1-4} alkyl. In certain embodiments, y is 1. In certain embodiments, y is 2. In certain embodiments, y is 3.

[0210] In certain embodiments, the TPL is . In certain embodiments, the TPL is .

[0211] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



wherein:

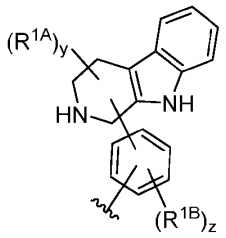
$R^{II\text{-}1A}$ is a bond to L;

R^{1A} represents independently for each occurrence hydrogen, C_{1-4} haloalkyl, C_{1-4} alkyl, or halo;

R^{1B} is hydrogen, halo, or C_{1-4} alkyl; and

y is 1, 2, or 3.

[0212] In certain embodiments, the TPL is



wherein:

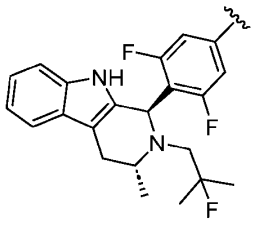
R^{1A} represents independently for each occurrence hydrogen, C_{1-4} haloalkyl, C_{1-4} alkyl, or halo;

R^{1B} represents independently for each occurrence hydrogen, halo, or C_{1-4} alkyl;

y is 1, 2, or 3; and

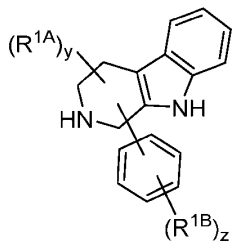
z is 1 or 2.

[0213] In certain embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1A} is C_{1-4} haloalkyl. In certain embodiments, R^{1A} is C_{1-4} alkyl. In certain embodiments, R^{1A} is halo. In certain embodiments, R^{1B} is hydrogen. In certain embodiments, R^{1B} is halo. In certain embodiments, R^{1B} is C_{1-4} alkyl. In certain embodiments, y is 1. In certain embodiments, y is 2. In certain embodiments, y is 3. In certain embodiments, z is 1. In certain embodiments, z is 2.

[0214] In certain embodiments, the TPL is 

.

[0215] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



wherein:

$R^{II\text{-}1A}$ is a bond to L;

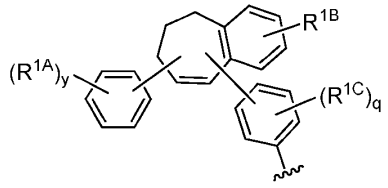
R^{1A} represents independently for each occurrence hydrogen, C_{1-4} haloalkyl, C_{1-4} alkyl, or halo;

R^{1B} represents independently for each occurrence hydrogen, halo, or C_{1-4} alkyl;

y is 1, 2, or 3; and

z is 1 or 2.

[0216] In certain embodiments, the TPL is



wherein:

R^{1A} and R^{1C} each represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

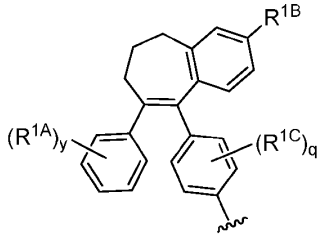
R^{1B} is -C(O)OH, hydrogen, halo, hydroxyl, $-B(OH)_2$, or C_{1-4} alkyl;

q is 1 or 2; and

y is 1, 2, or 3.

[0217] In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, chloro, methyl, or methoxy. In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, halo, or C_{1-4} alkoxy. In certain embodiments, R^{1A} represents independently for each occurrence hydrogen or halo. In certain embodiments, R^{1A} represents independently for each occurrence C_{1-4} alkoxy. In certain embodiments, R^{1B} is -C(O)OH, -OH, or $-B(OH)_2$. In certain embodiments, R^{1C} represents independently for each occurrence hydrogen, fluoro, chloro, methyl, or methoxy. In certain embodiments, R^{1C} represents independently for each occurrence hydrogen, halo, or C_{1-4} alkoxy. In certain embodiments, R^{1C} represents independently for each occurrence hydrogen or halo.

[0218] In certain embodiments, the TPL is



wherein:

R^{1A} and R^{1C} each represents independently for each occurrence hydrogen, fluoro, chloro, methyl, or methoxy;

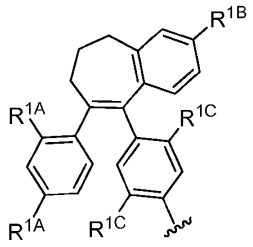
R^{1B} is -C(O)OH, -OH, or $-B(OH)_2$;

q is 1 or 2; and

y is 1, 2, or 3.

[0219] In certain embodiments, q is 1. In certain embodiments, q is 2.

[0220] In certain embodiments, the TPL is



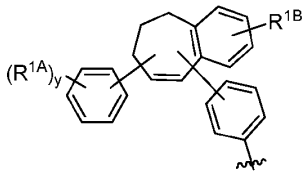
wherein:

R^{1A} and R^{1C} each represents independently for each occurrence hydrogen, fluoro, chloro, methyl, or methoxy; and

R^{1B} is -C(O)OH, -OH, or $-B(OH)_2$.

[0221] In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro, and R^{1C} represents independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro, and R^{1C} is hydrogen or fluoro. In certain embodiments, R^{1A} is methoxy. In certain embodiments, R^{1B} is $-B(OH)_2$. In certain embodiments, R^{1C} represents independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1C} is hydrogen or fluoro. In certain embodiments, R^{1C} is fluoro or chloro. In certain embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1C} is fluoro. In certain embodiments, R^{1C} is chloro. In certain embodiments, R^{1C} is methoxy. In certain embodiments, R^{1C} is methyl.

[0222] In certain embodiments, the TPL is



wherein:

R^{1A} represents independently for each occurrence hydrogen, halo, or C_{1-4} alkyl;

R^{1B} is -C(O)OH, hydrogen, halo, hydroxyl, or C_{1-4} alkyl; and

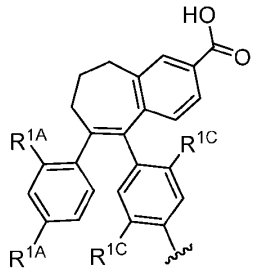
y is 1, 2, or 3.

[0223] In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, chloro, or methyl. In certain embodiments, R^{1A} represents independently for each occurrence hydrogen or halo. In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro. In certain embodiments, R^{1A} is hydrogen, fluoro, or chloro. In certain embodiments, R^{1A} is hydrogen or chloro.

[0224] In certain embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1A} is halo. In certain embodiments, R^{1A} is fluoro. In certain embodiments, R^{1A} is chloro. In certain embodiments, R^{1A} is C_{1-4} alkyl. In certain embodiments, R^{1A} is methyl.

[0225] In certain embodiments, R^{1B} is -C(O)OH or -OH. In certain embodiments, R^{1B} is -C(O)OH. In certain embodiments, R^{1B} is hydrogen. In certain embodiments, R^{1B} is halo. In certain embodiments, R^{1B} is hydroxyl. In certain embodiments, R^{1B} is C_{1-4} alkyl. In certain embodiments, y is 1. In certain embodiments, y is 2. In certain embodiments, y is 3.

[0226] In certain embodiments, the TPL is

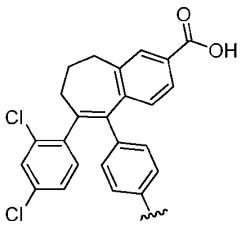
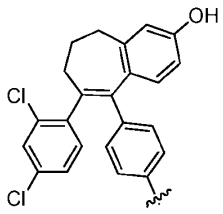


wherein R^{1A} and R^{1C} each represents independently for each occurrence hydrogen, fluoro, chloro, methyl, or methoxy.

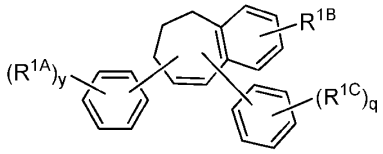
[0227] In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro, and R^{1C} represents independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro, and R^{1C} is hydrogen or fluoro.

[0228] In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro. In certain embodiments, R^{1A} is hydrogen, fluoro, or chloro. In certain embodiments, R^{1A} is hydrogen or chloro. In certain embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1A} is fluoro. In certain embodiments, R^{1A} is chloro.

[0229] In certain embodiments, R^{1C} represents independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1C} is hydrogen or fluoro. In certain embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1C} is fluoro.

[0230] In certain embodiments, the TPL is . In certain embodiments, the TPL is .

[0231] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



wherein:

$R^{II\text{-}1A}$ is a bond to L;

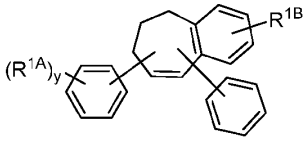
R^{1A} and R^{1C} each represents independently for each occurrence hydrogen, halo, $C_{1\text{-}4}$ alkyl, or $C_{1\text{-}4}$ alkoxy;

R^{1B} is -C(O)OH, hydrogen, halo, hydroxyl, $-B(OH)_2$, or $C_{1\text{-}4}$ alkyl;

q is 1 or 2; and

y is 1, 2, or 3.

[0232] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of $R^{II\text{-}1A}$:



wherein:

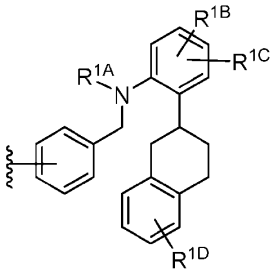
$R^{II\text{-}1A}$ is a bond to L;

R^{1A} represents independently for each occurrence hydrogen, halo, or $C_{1\text{-}4}$ alkyl;

R^{1B} is -C(O)OH, hydrogen, halo, hydroxyl, or $C_{1\text{-}4}$ alkyl; and

y is 1, 2, or 3.

[0233] In certain embodiments, the TPL is



wherein:

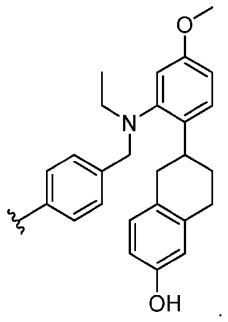
R^{1A} is C_{1-4} alkyl;

R^{1B} is C_{1-4} alkoxyl;

R^{1C} is hydrogen, halo, or C_{1-4} alkyl; and

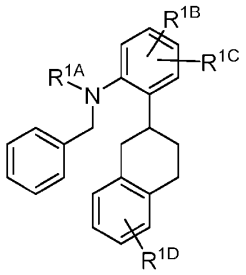
R^{1D} is hydroxyl.

[0234] In certain embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1C} is halo. In certain embodiments, R^{1C} is C_{1-4} alkyl.

[0235] In certain embodiments, the TPL is 

.

[0236] In certain embodiments, the TPL has the following formula that is substituted by one occurrence of R^{II-1A}:



wherein:

R^{II-1A} is a bond to L;

R^{1A} is C_{1-4} alkyl;

R^{1B} is C_{1-4} alkoxyl;

R^{1C} is hydrogen, halo, or C_{1-4} alkyl; and

R^{1D} is hydroxyl.

[0237] In certain embodiments, the TPL is selected from those depicted in the compounds in Tables 1, 2, 3, 4, and 5, below. In certain embodiments, the TPL is selected from those depicted in the compounds in Table 1, below. In certain embodiments, the TPL is selected from those depicted in the compounds in Table 2, below. In certain embodiments, the TPL is selected from those depicted in the compounds in Table 3, below. In certain embodiments, the TPL is selected from those depicted in the compounds in Table 4, below. In certain embodiments, the TPL is selected from those depicted in the compounds in Table 5, below.

Additional Features

[0238] Compounds of Formula I and/or II may be further characterized according to the molecular weight of the TPL. In certain embodiments, the TPL has a molecular weight of less than 1500 Da, 1200 Da, 1000 Da, 800 Da, 600 Da, 400 Da, 300 Da, 200 Da, 150 Da, or 100 Da. Compounds of Formula II may be further characterized according to the molecular weight of the EPL. In certain embodiments, the EPL has a molecular weight of less than 1500 Da, 1200 Da, 1000 Da, 800 Da, 600 Da, 400 Da, 300 Da, 200 Da, 150 Da, or 100 Da.

Part D: Exemplary Further Description of the Linker (L) Component of Compounds of Formula I and II

[0239] Compounds of Formula I and II may be further characterized according to, for example, the identity of the linker (L) component. A variety of linkers are known to one of skill in the art and may be used in the heterobifunctional compounds described herein. For example, in certain embodiments, L comprises one or more optionally substituted groups selected from amino acids, polyether chains, aliphatic groups, and any combinations thereof. In certain embodiments, L consists of one or more optionally substituted groups selected from amino acids, polyether chains, aliphatic groups, and any combinations thereof. In certain embodiments, L consists of one or more groups selected from amino acids, polyether chains, aliphatic groups, and any combinations thereof.

[0240] In some embodiments, L is symmetrical. In some embodiments, L is asymmetric. In certain embodiments, L is a bond.

[0241] In certain embodiments, L is a covalent bond or a bivalent C_{1-30} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein 1-15 methylene units of L are optionally and independently replaced by cyclopropylene, -N(H)-, -N(C_{1-4} alkyl)-, -N(C_{3-5} cycloalkyl)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$N(H)-, -$S(O)_2$N(C_{1-4} alkyl)-, -$S(O)_2$N(C_{3-5} cycloalkyl)-, -N(H)C(O)-, -N(C_{1-4} alkyl)C(O)-, -N(C_{3-5} cycloalkyl)C(O)-, -C(O)N(H)-, -C(O)N(C_{1-4} alkyl)-, -C(O)N(C_{3-5} cycloalkyl)-, phenylene, an 8-10 membered bicyclic arylene, a 4-7 membered saturated or partially unsaturated carbocyclylene, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylene, a 3-7 membered saturated or partially unsaturated heterocyclylene having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylene having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylene having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0242] In certain embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{1-60} hydrocarbon chain, wherein 0-20 methylene units of the hydrocarbon are independently replaced with -O-, -S-, -N(R**)-, -OC(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -N(R**)$S(O)_2$-, -$S(O)_2$N(R**)-, -N(R**)C(O)-, -C(O)N(R**)-, -OC(O)N(R**)-, -N(R**)C(O)O-, optionally substituted 3-10 membered carbocyclyl, or optionally substituted 3-10 membered heterocyclyl containing 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein R** represents independently for each occurrence hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl.

[0243] In certain embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{1-60} hydrocarbon chain, wherein 0-20 methylene units of the hydrocarbon are independently replaced with -O-, -S-, -N(H)-, -N(C_{1-6} alkyl)-, -OC(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -N(H)$S(O)_2$-, -N(C_{1-6} alkyl)$S(O)_2$-, -$S(O)_2$N(H)-, -$S(O)_2$N(C_{1-6} alkyl)-, -N(H)C(O)-, -N(C_{1-6} alkyl)C(O)-, -C(O)N(H)-, -C(O)N(C_{1-6} alkyl)-, -OC(O)N(H)-, -OC(O)N(C_{1-6} alkyl)-, -N(H)C(O)O-, -N(C_{1-6} alkyl)C(O)O-, optionally substituted 3-10 membered carbocyclyl, or optionally substituted 3-10 membered heterocyclyl containing 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0244] In certain embodiments, L is a bivalent, saturated, straight or branched C_{3-30} hydrocarbon chain, wherein 0-15 methylene units of the hydrocarbon are independently replaced

with -O-, -N(H)-, -N(C_{1-6} alkyl)-, -OC(O)-, -C(O)O-, -N(H)C(O)-, -N(C_{1-6} alkyl)C(O)-, -C(O)N(H)-, -C(O)N(C_{1-6} alkyl)-, 3-10 membered carbocyclyl, or 3-10 membered heterocyclyl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0245] In certain embodiments, L is a bivalent, saturated, straight or branched C_{3-30} hydrocarbon chain, wherein 0-15 methylene units of the hydrocarbon are independently replaced with -O-, -N(H)-, -N(C_{1-6} alkyl)-, -OC(O)-, -C(O)O-, -N(H)C(O)-, -N(C_{1-6} alkyl)C(O)-, -C(O)N(H)-, or -C(O)N(C_{1-6} alkyl)-.

[0246] In certain embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{1-60} hydrocarbon chain, wherein 0-20 methylene units of the hydrocarbon are independently replaced with -O-, -S-, -N(H)-, -N(C_{1-6} alkyl)-, -OC(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -N(H)$S(O)_2$-, -N(C_{1-6} alkyl)$S(O)_2$-, -$S(O)_2$N(H)-, -$S(O)_2$N(C_{1-6} alkyl)-, -N(H)C(O)-, -N(C_{1-6} alkyl)C(O)-, -C(O)N(H)-, -C(O)N(C_{1-6} alkyl)-, -OC(O)N(H)-, -OC(O)N(C_{1-6} alkyl)-, -N(H)C(O)O-, -N(C_{1-6} alkyl)C(O)O-, optionally substituted 3-10 membered carbocyclyl, optionally substituted 8-11 membered spirocyclic heterocyclyl containing 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or optionally substituted 3-10 membered heterocyclyl containing 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0247] In certain embodiments, L is a bivalent, saturated, straight or branched C_{3-30} hydrocarbon chain, wherein 0-15 methylene units of the hydrocarbon are independently replaced with -O-, -N(H)-, -N(C_{1-6} alkyl)-, -OC(O)-, -C(O)O-, -N(H)C(O)-, -N(C_{1-6} alkyl)C(O)-, -C(O)N(H)-, -C(O)N(C_{1-6} alkyl)-, 3-10 membered carbocyclyl, optionally substituted 8-11 membered spirocyclic heterocyclyl containing 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 3-10 membered heterocyclyl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0248] In yet other embodiments, L comprises a polyethylene glycol chain ranging in size from about 1 to about 12 ethylene glycol units, from about 1 to about 10 ethylene glycol units, from about 2 to about 6 ethylene glycol units, from about 2 to about 5 ethylene glycol units, or from about 2 to about 4 ethylene glycol units. In yet other embodiments, L is a diradical of a polyethylene glycol chain ranging in size from about 1 to about 12 ethylene glycol units, from about 1 to about 10 ethylene glycol units, from about 2 to about 6 ethylene glycol units, from about 2 to about 5 ethylene glycol units, or from about 2 to about 4 ethylene glycol units.

[0249] In certain embodiments, L is a heteroalkylene having from 4 to 30 atoms selected from carbon, oxygen, nitrogen, and sulfur. In certain embodiments, L is a heteroalkylene having from 4 to 20 atoms selected from carbon, oxygen, nitrogen, and sulfur. In certain embodiments, L is a heteroalkylene having from 4 to 10 atoms selected from carbon, oxygen, nitrogen, and sulfur. In certain embodiments, L is a heteroalkylene having from 4 to 30 atoms selected from carbon, oxygen, and nitrogen. In certain embodiments, L is a heteroalkylene having from 4 to 20 atoms selected from carbon, oxygen, and nitrogen. In certain embodiments, L is a heteroalkylene having from 4 to 10 atoms selected from carbon, oxygen, and nitrogen. In certain embodiments, L is a heteroalkylene having from 4 to 30 atoms selected from carbon and oxygen. In certain embodiments, L is a heteroalkylene having from 4 to 20 atoms selected from carbon and oxygen. In certain embodiments, L is a heteroalkylene having from 4 to 10 atoms selected from carbon and oxygen.

[0250] In additional embodiments, the L is an optionally substituted (poly)ethyleneglycol having between 1 and about 100 ethylene glycol units, between about 1 and about 50 ethylene glycol units, between 1 and about 25 ethylene glycol units, between about 1 and about 10 ethylene glycol units, between 1 and about 8 ethylene glycol units, between 1 and about 6 ethylene glycol units, between 2 and about 4 ethylene glycol units, or optionally substituted alkyl groups interspersed with optionally substituted, O, N, S, P or Si atoms. In certain embodiments, L is substituted with an aryl, phenyl, benzyl, alkyl, alkylene, or heterocycle group.

[0251] In certain embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{1-45} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon are independently replaced with -O-, -S-, -N(R**)-, -OC(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -N(R**)$S(O)_2$-, -$S(O)_2$N(R**)-, -N(R**)C(O)-, -C(O)N(R**)-, -OC(O)N(R**)-, -N(R**)C(O)O-, optionally substituted carbocyclyl, or optionally substituted heterocyclyl, wherein R** represents independently for each occurrence hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl.

[0252] In certain embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{1-45} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon are independently replaced with -O-, -S-, -N(R**)-, -OC(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -N(R**)$S(O)_2$-, -$S(O)_2$N(R**)-, -N(R**)C(O)-, -C(O)N(R**)-, -OC(O)N(R**)-, -N(R**)C(O)O-, optionally substituted 3-10 membered carbocyclyl, or optionally substituted 3-10 membered heterocyclyl containing 1, 2, 3, or 4 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein R** represents independently for each occurrence hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl.

[0253] In certain embodiments, L has the formula -N(R)-(optionally substituted 3-20 membered heteroalkylene)$_p$-CH_2-C(O)-, wherein R is hydrogen or optionally substituted C_1-C_6 alkyl, and p is 0 or 1.

[0254] In certain embodiments, L has the formula -N(R)-(3-20 membered heteroalkylene)$_p$-CH_2-C(O)-; wherein the 3-20 membered heteroalkylene is optionally substituted with 1, 2, 3, or 4 substituents independently selected from halogen, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, and cyano; R is hydrogen or optionally substituted C_1-C_6 alkyl; and p is 0 or 1.

[0255] In certain embodiments, L has the formula -N(R)-(3-20 membered heteroalkylene)$_p$-CH_2-C(O)-; wherein the 3-20 membered heteroalkylene is optionally substituted with 1, 2, or 3 substituents independently selected from halogen and C_1-C_6 haloalkyl; R is hydrogen or C_1-C_6 alkyl; and p is 0 or 1.

[0256] In certain embodiments, L is -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{10-20} alkylene)-O-(C_{1-6} alkylene)-C(O)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{7-15} alkylene)-C(O)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)N(H)-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, or -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL.

[0257] In certain embodiments, L is -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{10-20} alkylene)-O-(C_{1-6} alkylene)-C(O)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{7-15} alkylene)-C(O)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)N(H)-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, or -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL.

[0258] In certain embodiments, L is -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{1-6} alkylene)-N(C_{1-6} alkyl)C(O)-(C_{1-6} alkylene)***, -N(H)-(C_{1-6} alkylene)-N(H)C(O)-(C_{1-6} alkylene)***, -N(H)-(C_{2-6} alkylene)-***, -N(H)-(C_{7-15} alkylene)-***, -N(C_{1-6} alkyl)-(C_{2-6} alkylene)-***, -N(C_{1-6} alkyl)-(C_{7-15} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -N(H)-(C_{1-6} alkylene)-(3-6 membered heterocycloalkylene)-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-(C_{1-6} alkylene)-(3-6 membered heterocycloalkylene)-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-(C_{2-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, or -N(H)-(C_{2-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL.

[0259] In certain embodiments, L is -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{1-6} alkylene)-N(C_{1-6} alkyl)C(O)-(C_{1-6} alkylene)***, -N(H)-(C_{1-6} alkylene)-N(H)C(O)-(C_{1-6} alkylene)***, -N(H)-(C_{2-6} alkylene)-***, -N(H)-(C_{7-15} alkylene)-***, -N(C_{1-6} alkyl)-(C_{2-6} alkylene)-***, -N(C_{1-6} alkyl)-(C_{7-15} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -N(H)-(C_{1-6} alkylene)-(3-6 membered heterocycloalkylene)-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-(C_{1-6} alkylene)-(3-6 membered heterocycloalkylene)-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-(C_{2-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, or -N(H)-(C_{2-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL.

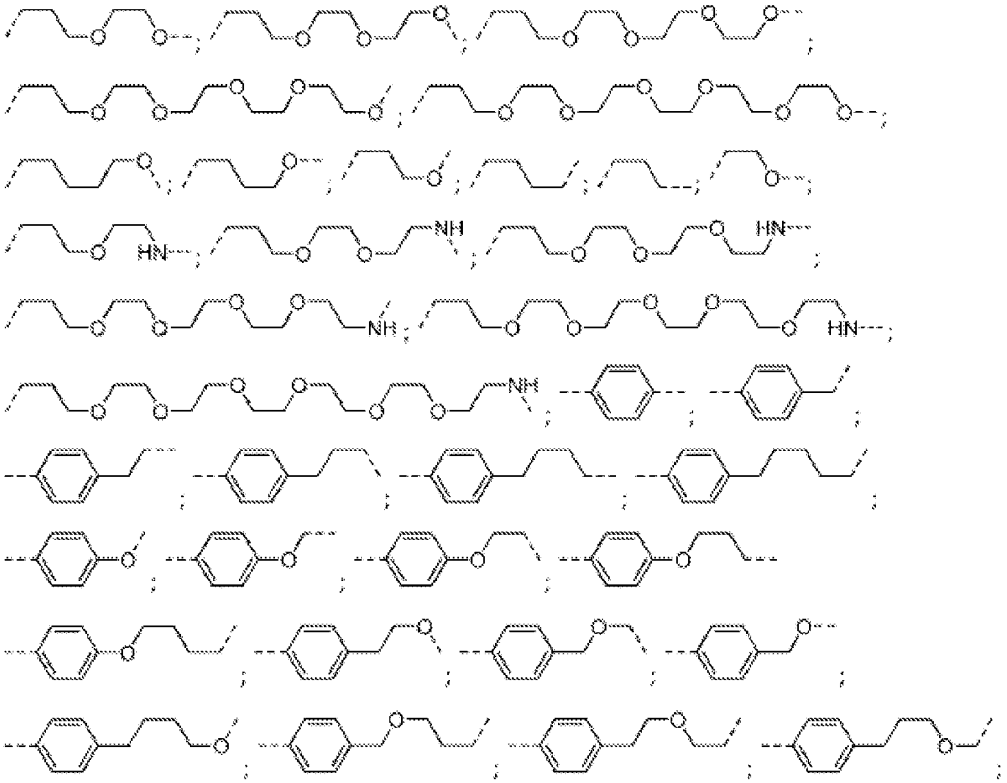
[0260] In certain embodiments, L is -[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)(C_{1-6} alkylene)-***, -[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)(C_{1-6} alkylene)-***, -[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(H)(C_{1-6} alkylene)-***, -[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-N(H)C(O)-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-N(H)C(O)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-N(H)C(O)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-N(H)C(O)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, or -(C_{1-9} alkylene)-N(H)C(O)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL.

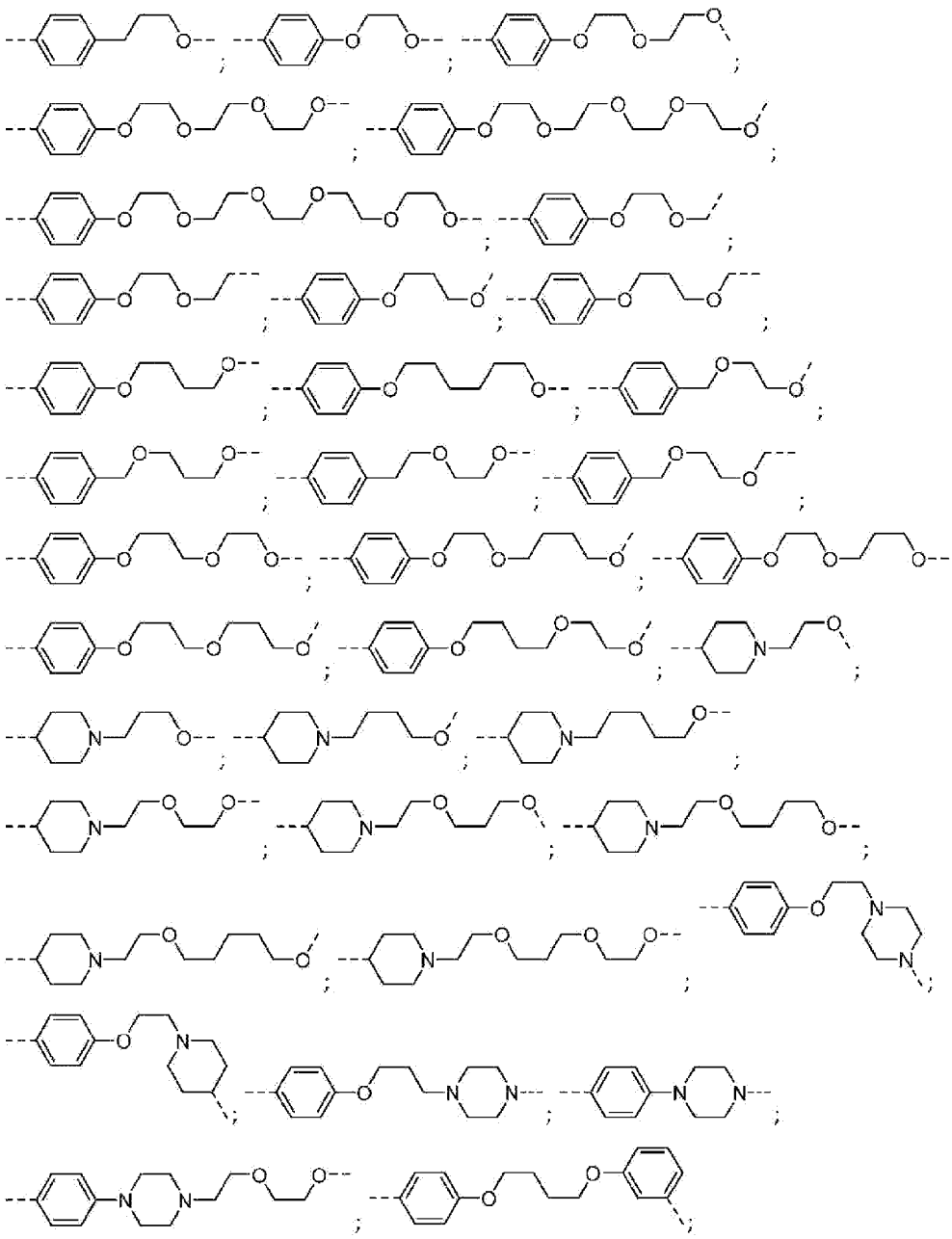
[0261] In certain embodiments, L is -[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)(C_{1-6} alkylene)-***, -[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)(C_{1-6} alkylene)-***, -[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(H)(C_{1-6} alkylene)-***, -[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-N(H)C(O)-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-N(H)C(O)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-N(H)C(O)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-N(H)C(O)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -(C_{1-9} alkylene)-C(O)N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, or -(C_{1-9} alkylene)-N(H)C(O)-[(CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL.

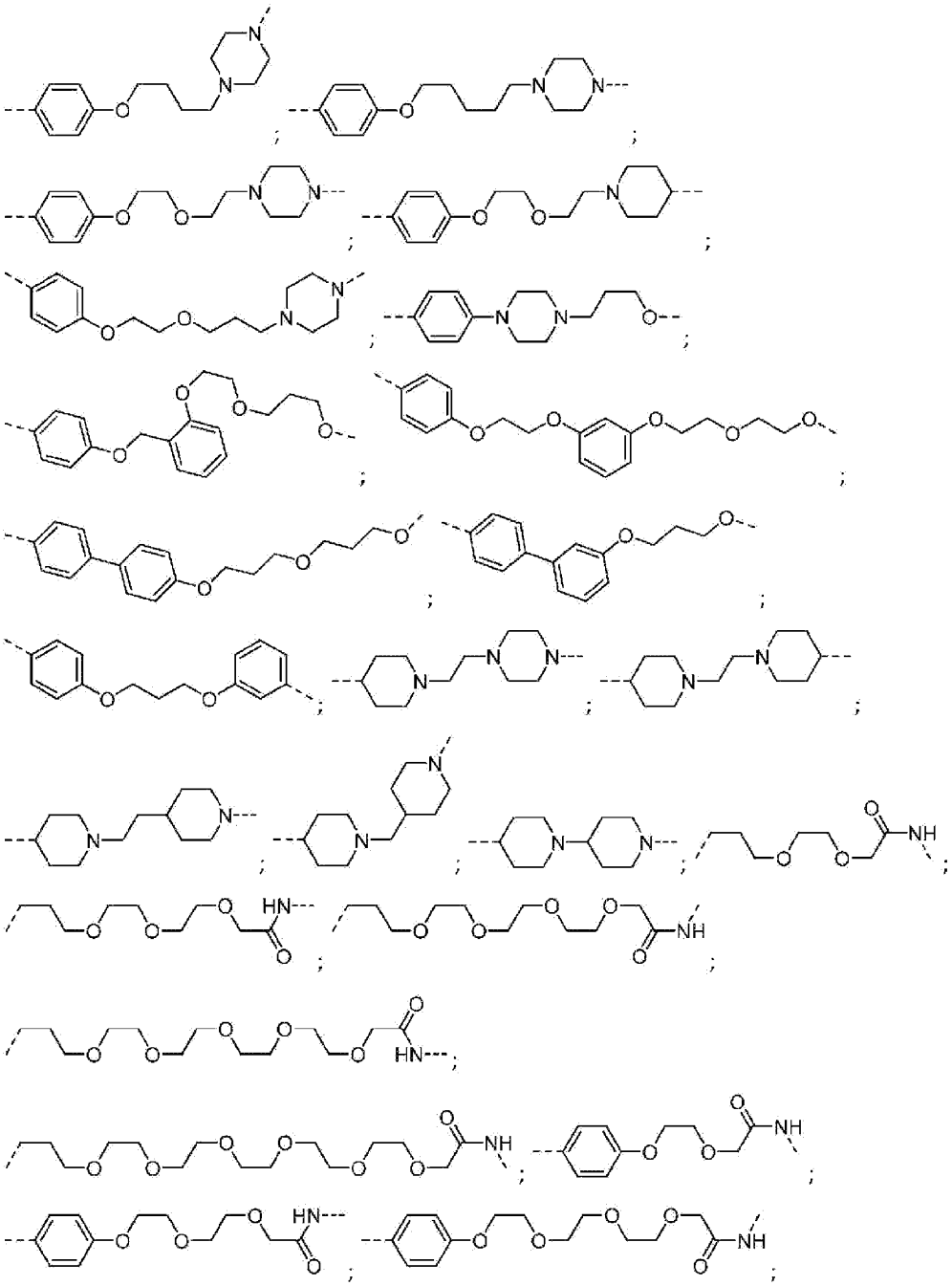
[0262] In certain embodiments, L is -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(H)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)-***, -N(C_{1-6} alkyl)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(H)-***, -N(C_{1-6} alkyl)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)-***, -N(C_{1-6} alkyl)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-***, or -N(C_{1-6} alkyl)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-***, where *** is a point of attachment to TPL.

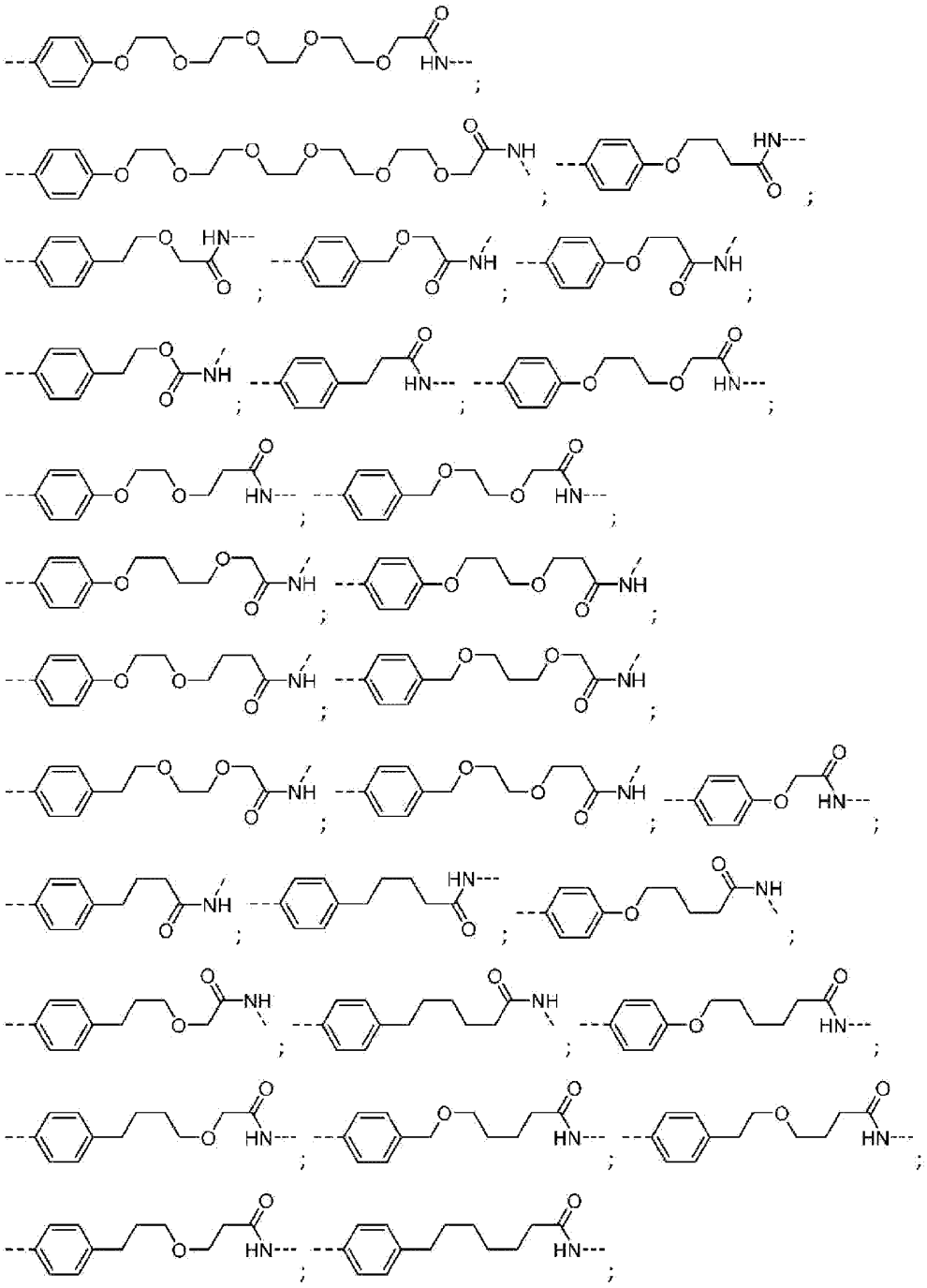
[0263] In certain embodiments, L is -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(H)-***, -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)-***, -N(C_{1-6} alkyl)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(H)-***, -N(C_{1-6} alkyl)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)-***, -N(C_{1-6} alkyl)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-***, or -N(C_{1-6} alkyl)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-***, where *** is a point of attachment to TPL.

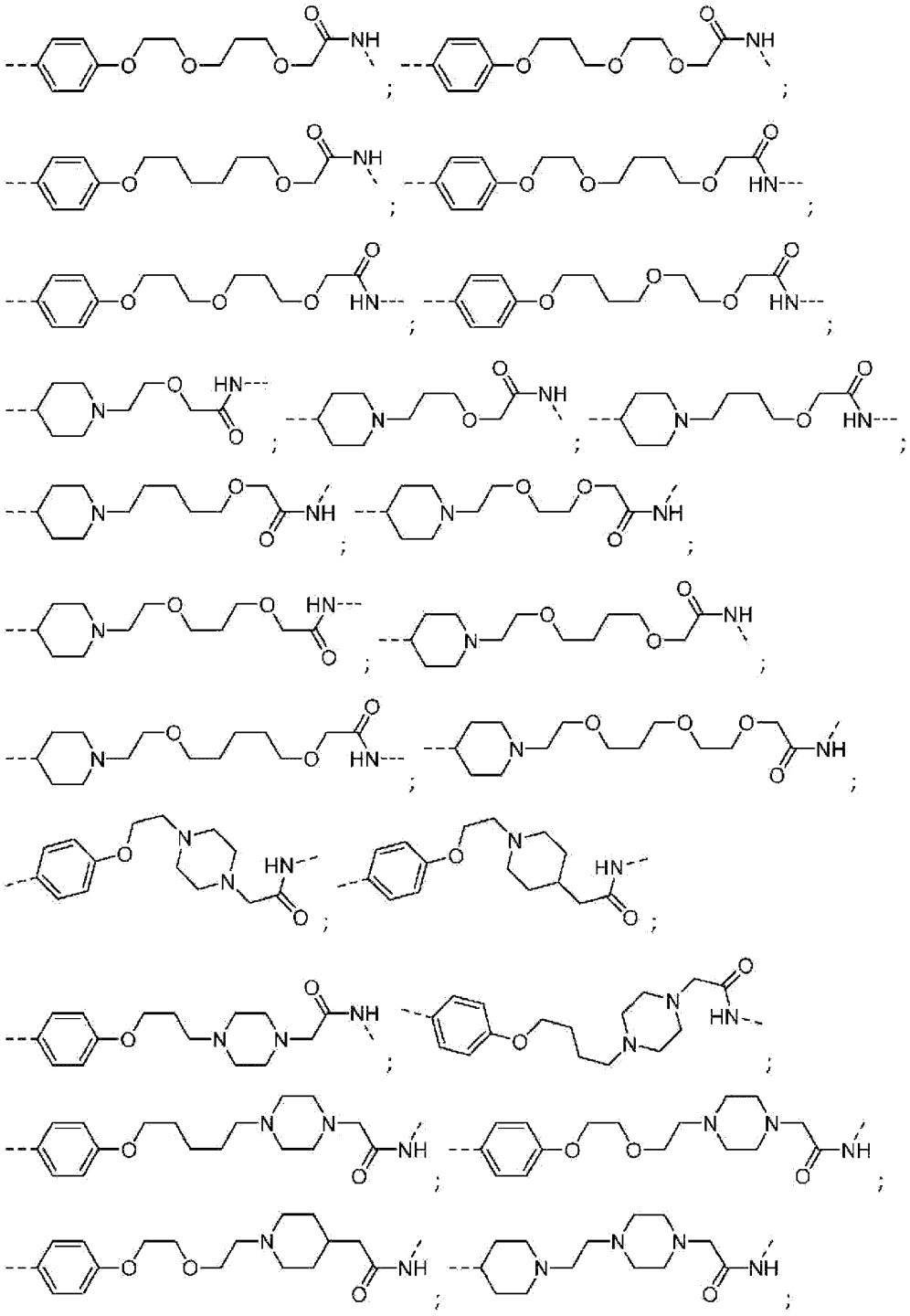
[0264] In some embodiments, L is one of the following:

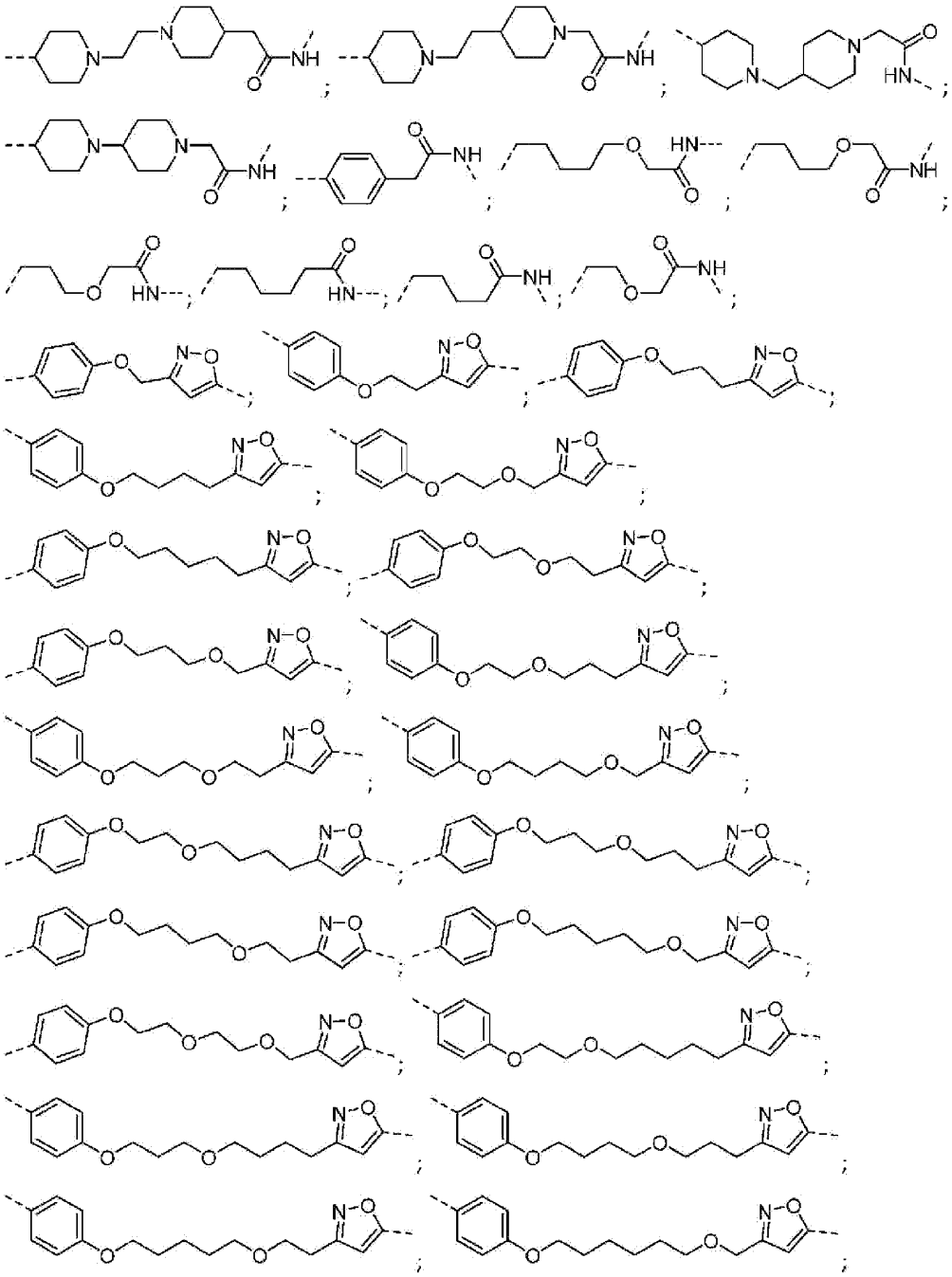


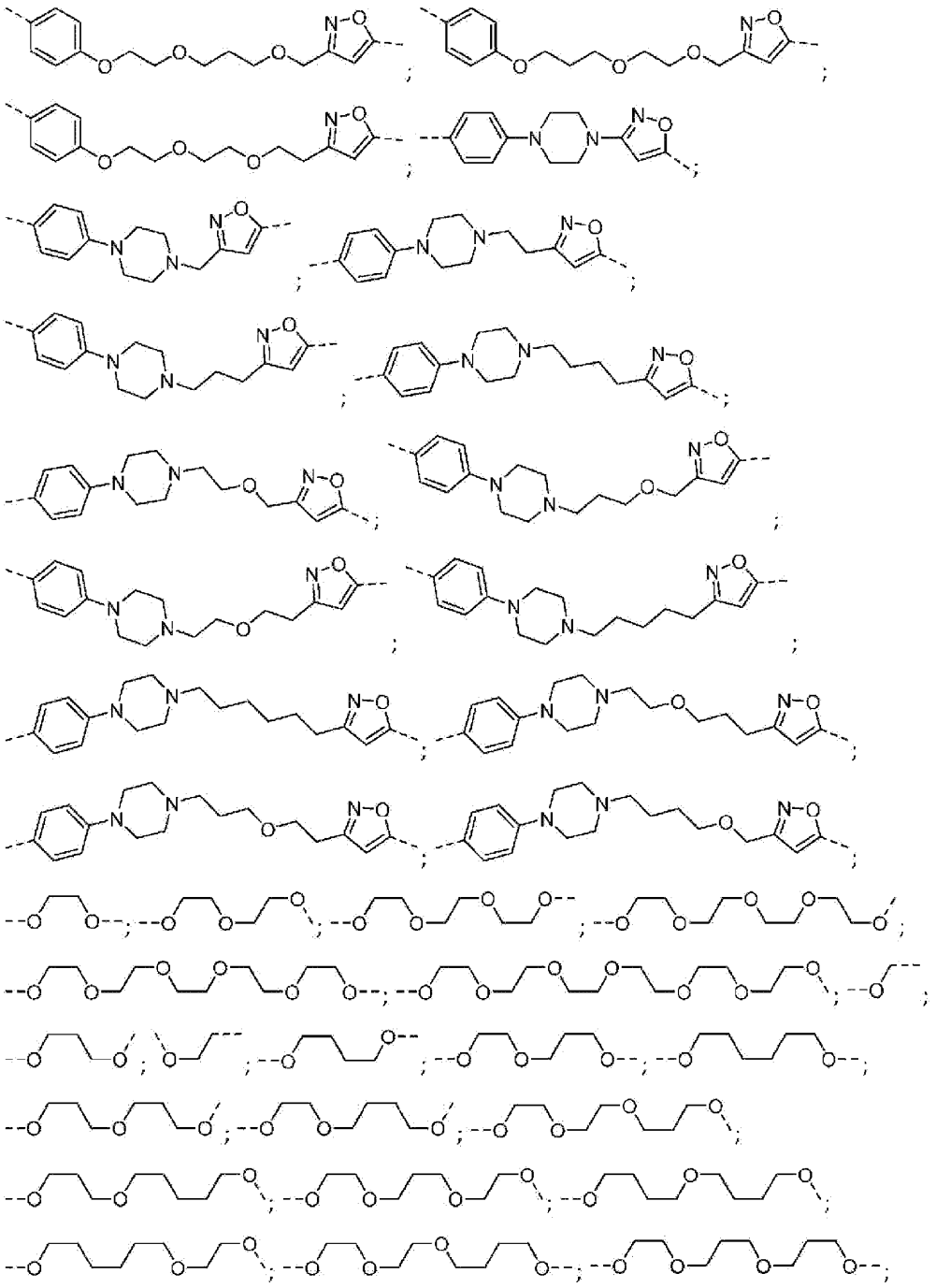


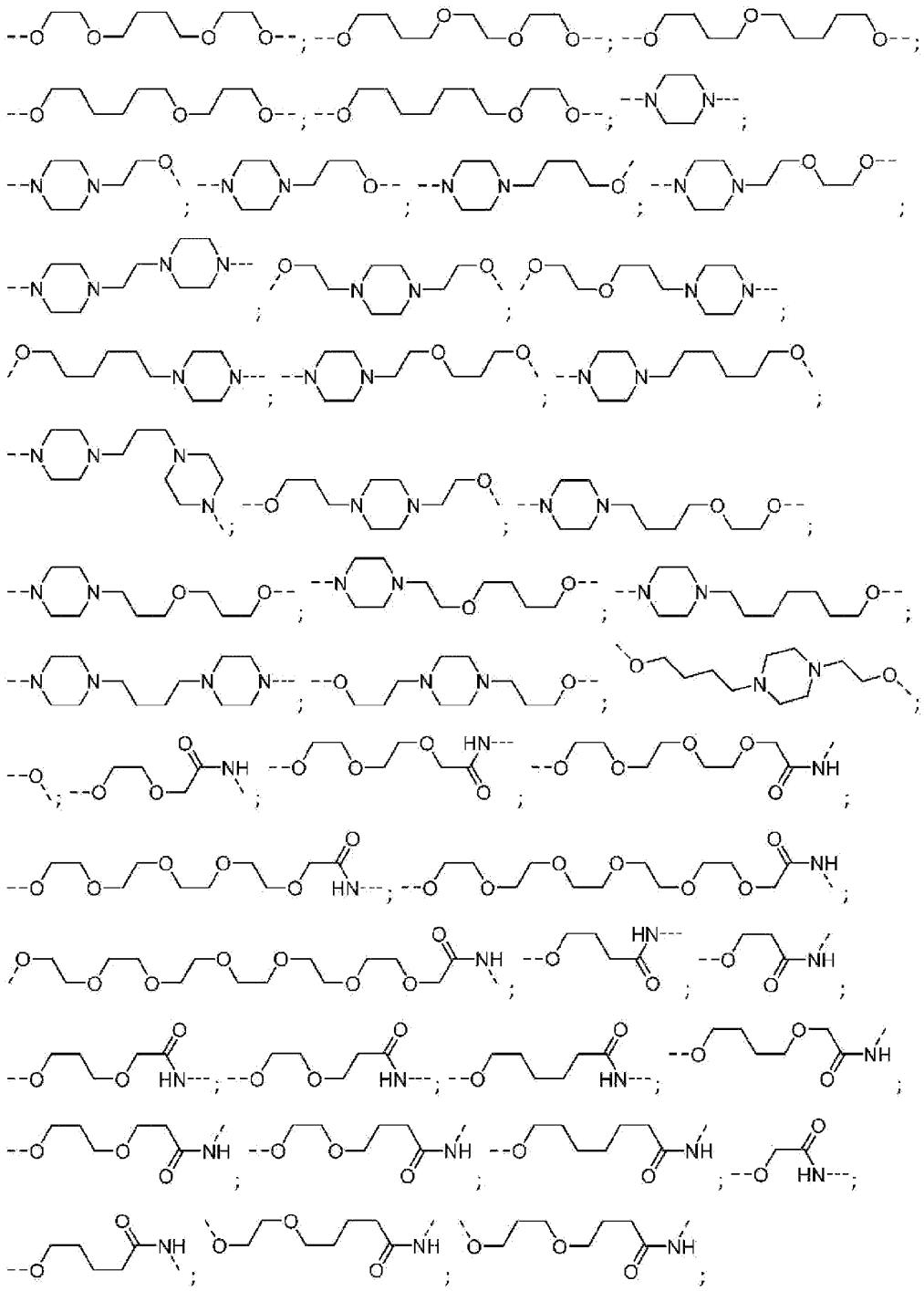


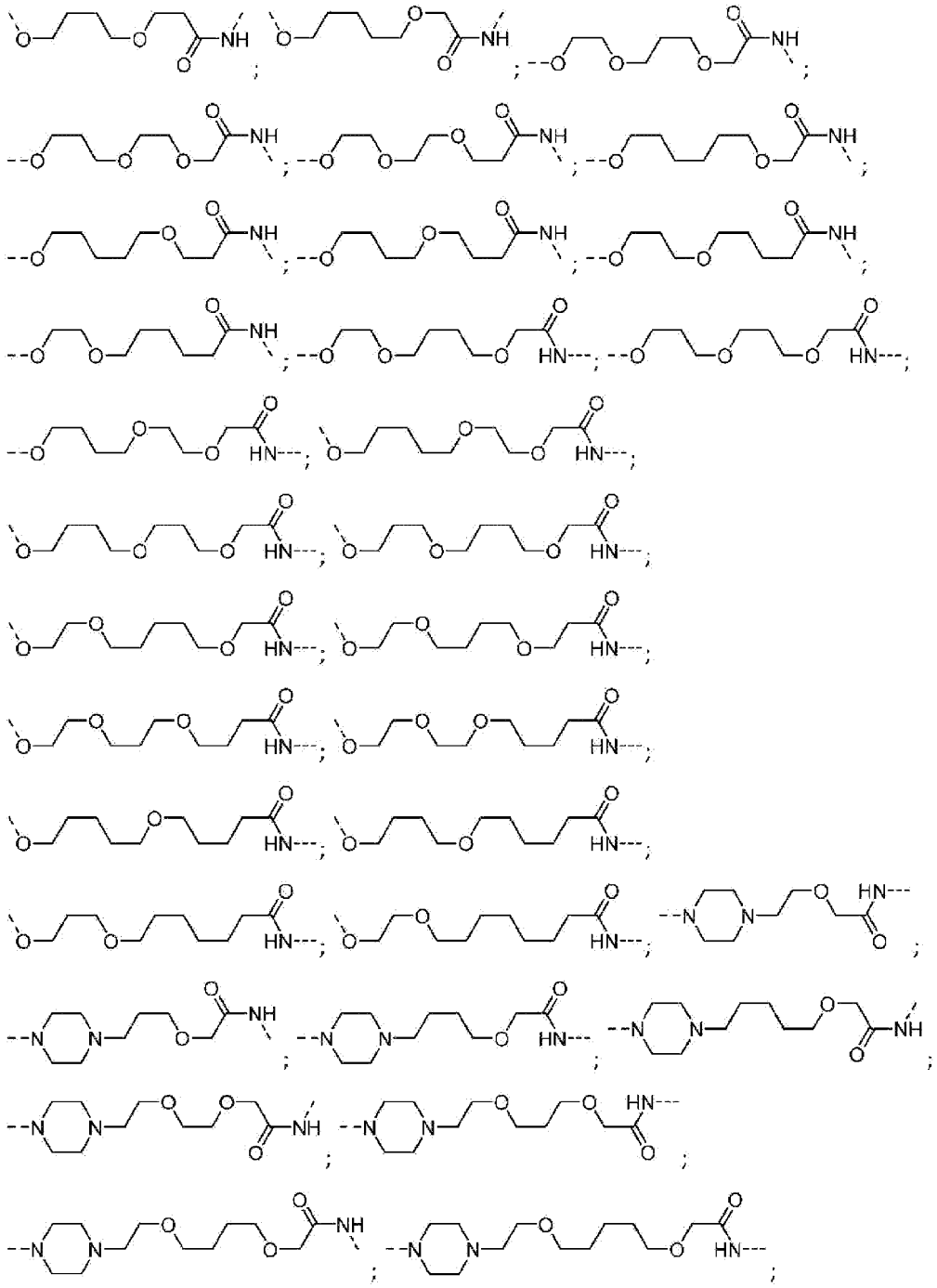


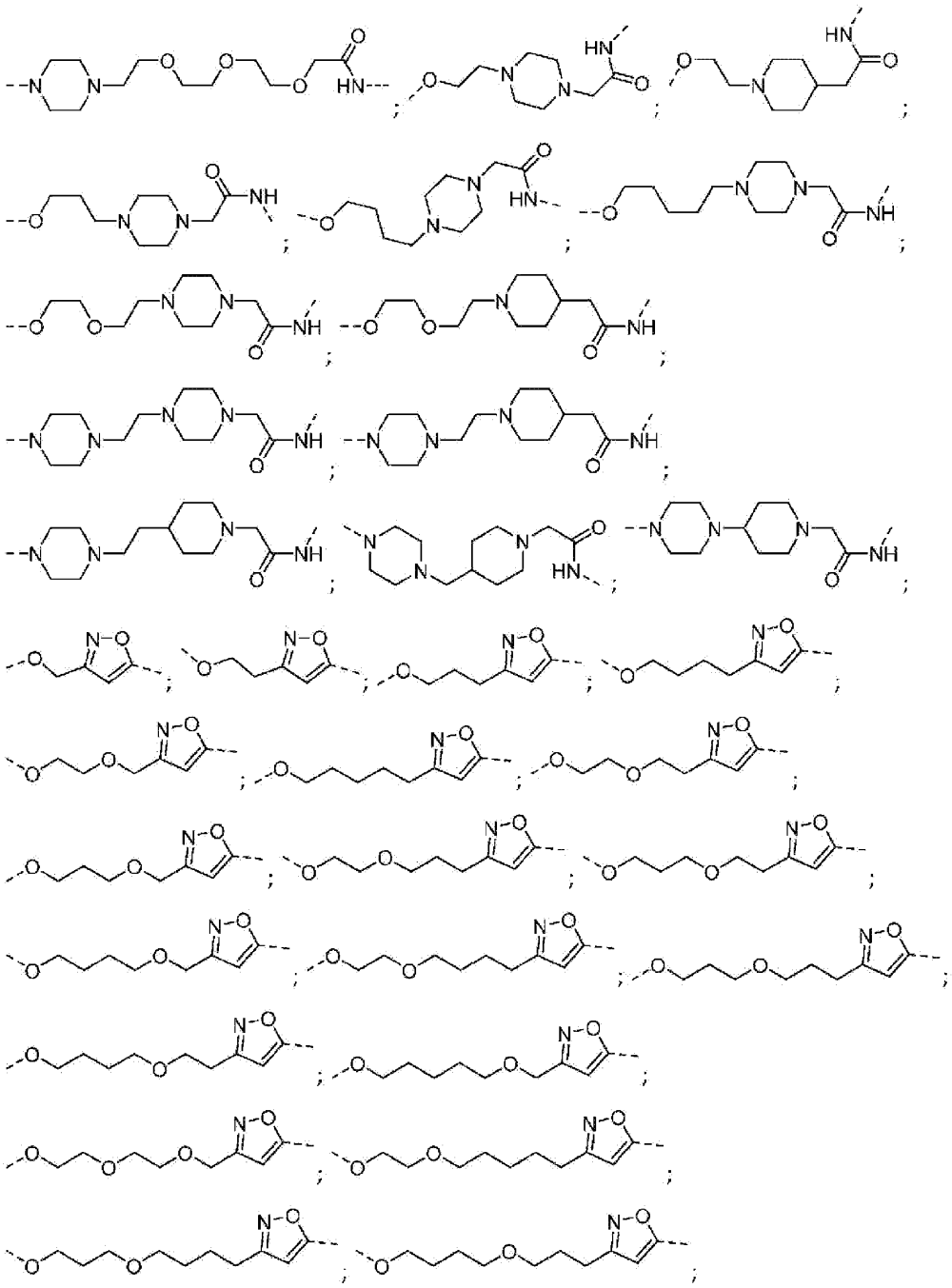


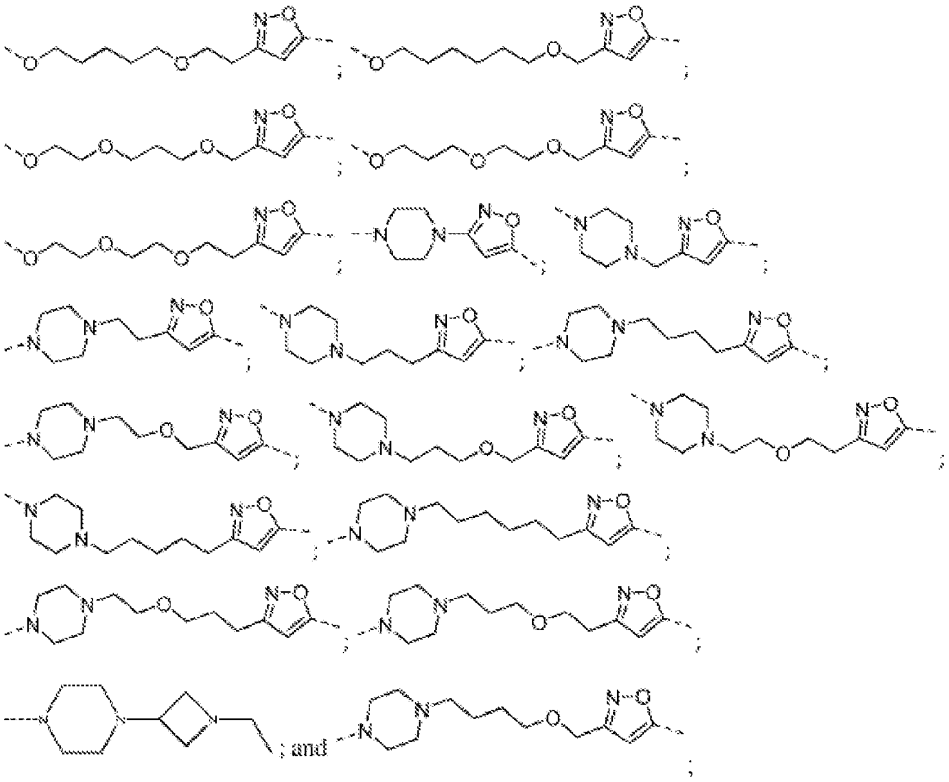












wherein a dashed bond indicates a point of attachment.

[0265] In certain embodiments, L has the formula –(C_{0-12} alkylene)-(optionally substituted 3-40 membered heteroalkylene)-(C_{0-12} alkylene)-. In certain embodiments, L is C_{4-14} alkylene. In certain embodiments, L is -$(CH_2)_{6-10}$-.

[0266] In certain embodiments, L is -$CH_2CH_2(OCH_2CH_2)$-***, -$CH_2CH_2(OCH_2CH_2)_2$-***, -$CH_2CH_2(OCH_2CH_2)_3$-***, -$CH_2CH_2(OCH_2CH_2)_4$-***, -$CH_2CH_2(OCH_2CH_2)_5$-***, -$CH_2CH_2(OCH_2CH_2)_6$-***, -$CH_2CH_2(OCH_2CH_2)_7$-***, -$CH_2CH_2(OCH_2CH_2)_8$-***, -$CH_2CH_2(OCH_2CH_2)_9$-***, -$CH_2CH_2(OCH_2CH_2)_{10}$-***, -$CH_2CH_2(OCH_2CH_2)_{11}$-***, -$CH_2CH_2(OCH_2CH_2)_{12}$-***, -$CH_2CH_2(OCH_2CH_2)_{13}$-***, -$CH_2CH_2(OCH_2CH_2)_{14}$-***, -$CH_2CH_2(OCH_2CH_2)_{15}$-***, or -$CH_2CH_2(OCH_2CH_2)_{16-20}$-***, where *** is a point of attachment to TPL.

[0267] In certain embodiments, L is -(C_{2-20} alkylene)-$(OCH_2CH_2)_{2-4}$-(C_{0-4} alkylene)-***, -(C_{2-20} alkylene)-$(OCH_2CH_2)_{5-7}$-(C_{0-4} alkylene)-***, -(C_{2-20} alkylene)-$(OCH_2CH_2)_{8-10}$-(C_{0-4} alkylene)-***, -(C_{2-20} alkylene)-$(OCH_2CH_2)_{11-13}$-(C_{0-4} alkylene)-***, -(C_{2-20} alkylene)-$(OCH_2CH_2)_{14-16}$-(C_{0-4}

alkylene)-***, -(C_{2-20} alkylene)-(OCH_2CH_2)$_{17-20}$-(C_{0-4} alkylene)-***, -(C_{1-20} alkylene)-(OCH_2CH_2)$_{1-10}$-(C_{0-4} alkylene)-C(O)-***, or -(C_{1-20} alkylene)-(OCH_2CH_2)$_{11-20}$-(C_{0-4} alkylene)-C(O)-***, where *** is a point of attachment to TPL.

[0268] In certain embodiments, L is -O(CH_2CH_2O)$_{2-4}$-(C_{0-4} alkylene)-***, -O(CH_2CH_2O)$_{5-7}$-(C_{0-4} alkylene)-***, -O(CH_2CH_2O)$_{8-10}$-(C_{0-4} alkylene)-***, -O(CH_2CH_2O)$_{11-13}$-(C_{0-4} alkylene)-***, -O(CH_2CH_2O)$_{14-16}$-(C_{0-4} alkylene)-***, -O(CH_2CH_2O)$_{16-20}$-(C_{0-4} alkylene)-***, -O(CH_2CH_2O)$_{2-10}$-(C_{0-4} alkylene)C(O)-***, or -O(CH_2CH_2O)$_{11-20}$-(C_{0-4} alkylene)C(O)-***, where *** is a point of attachment to TPL.

[0269] In certain embodiments, L is -(C_{0-20} alkylene)-(OCH_2CH_2)$_{1-10}$-(N(C_{1-4} alkyl))-***, -(C_{0-20} alkylene)-(OCH_2CH_2)$_{11-20}$-(N(C_{1-4} alkyl))-***, -(C_{0-20} alkylene)-(CH_2CH_2O)$_{1-10}$-(C_{2-10} alkylene)-(N(C_{1-4} alkyl))-(C_{0-10} alkylene)-***, or -(C_{0-20} alkylene)-(CH_2CH_2O)$_{11-20}$-(C_{2-10} alkylene)-(N(C_{1-4} alkyl))-(C_{0-10} alkylene)-***, where *** is a point of attachment to TPL.

[0270] In certain embodiments, L is -(C_{2-10} alkylene)-(OCH_2CH_2)$_{2-4}$-O-(3-6 membered saturated heterocyclylene containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen)-(C_{1-5} alkylene)-***, -(C_{2-10} alkylene)-(3-6 membered saturated heterocyclylene containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen)-(C_{1-5} alkylene)-***, -(C_{2-10} alkylene)-N(H)-(C_{1-5} alkylene)-***, -(C_{2-10} alkylene)-N(C_{1-6} alkyl)-(C_{1-5} alkylene)-***, -N(H)-(C_{1-5} alkylene)-***, -(CH_2CH_2O)$_{1-4}$-(C_{1-4} alkylene)-***, -(CH_2CH_2O)$_{1-4}$-(C_{1-4} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-(C_{2-6} alkylene)-(3-6 membered saturated heterocyclylene containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen)-(C_{1-5} alkylene)-***, -N(H)-(C_{2-6} alkylene)-(OCH_2CH_2)$_{1-4}$-O-(3-6 membered saturated heterocyclylene containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen)-(C_{1-5} alkylene)-***, -N(H)-[-CH_2CH_2O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -(C_{1-6} alkylene)-(3-6 membered saturated heterocyclylene containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen)-(C_{1-6} alkylene)-***, -N(H)-(C_{2-10} alkylene)-***, -(C_{1-6} alkylene)-(3-6 membered saturated heterocyclylene containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen)-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{2-10}$-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)C(O)-(C_{1-6} alkylene)-***, -[CH_2CH_2-O-]$_{1-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-***, -[CH_2CH_2-O-]$_{1-6}$-(C_{1-6} alkylene)-N(H)-***, or -(C_{2-10} alkylene)-(OCH_2CH_2)$_{2-6}$-(C_{3-6} cycloalkylene)-***, where *** is a point of attachment to TPL.

[0271] In certain embodiments, L is -(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of hydroxyl)-(C_{0-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 heteroatoms selected from nitrogen)-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{1-6} alkylene)-O-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of hydroxyl)-(C_{0-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 heteroatoms selected from nitrogen)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(7-11

membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL.

[0272] In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -N(H)-[-(C_{1-6} alkylene)-O-]$_{1-6}$-(C_{1-6} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, -N(H)-(C_{1-10} alkylene)-O-***, -N(H)-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of fluoro)-(C_{0-6} alkylene)-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -N(H)-[-(C_{1-6} alkylene)-O-]$_{1-6}$-(C_{1-6} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is-N(H)-(C_{1-10} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -N(H)-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)- O-***, where *** is

a point of attachment to TPL. In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of fluoro)-(C_{0-6} alkylene)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, where *** is a point of attachment to TPL.

[0273] In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, -(C_{1-10} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, or -(C_{1-15} alkylene)-[-O-(C_{1-6} alkylene)-]$_{1-8}$-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(C_{1-10} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL. In certain embodiments, L is -(C_{1-15} alkylene)-[-O-(C_{1-6} alkylene)-]$_{1-8}$-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL.

[0274] In certain embodiments, L is:

(i) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***,

(ii) -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, or

(iii) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic ring containing 0, 1, or 2 nitrogen atoms, wherein the ring is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***;

wherein *** is the point of attachment to TPL.

[0275] In certain embodiments, L is:

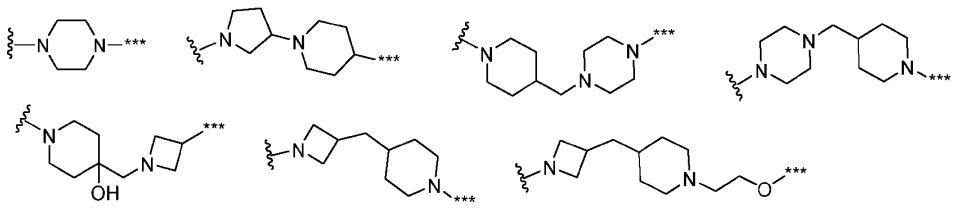
(i) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, or

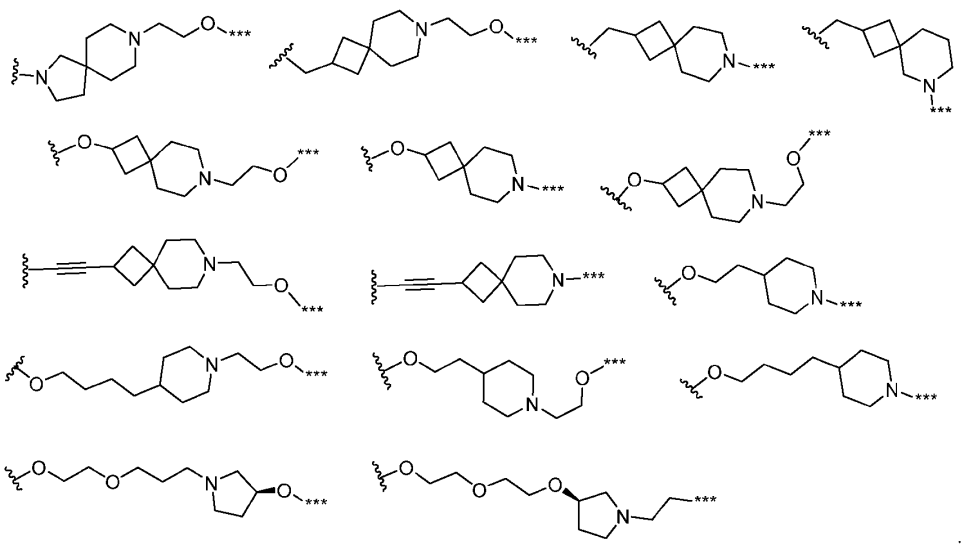
(ii) -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***;

wherein *** is the point of attachment to TPL.

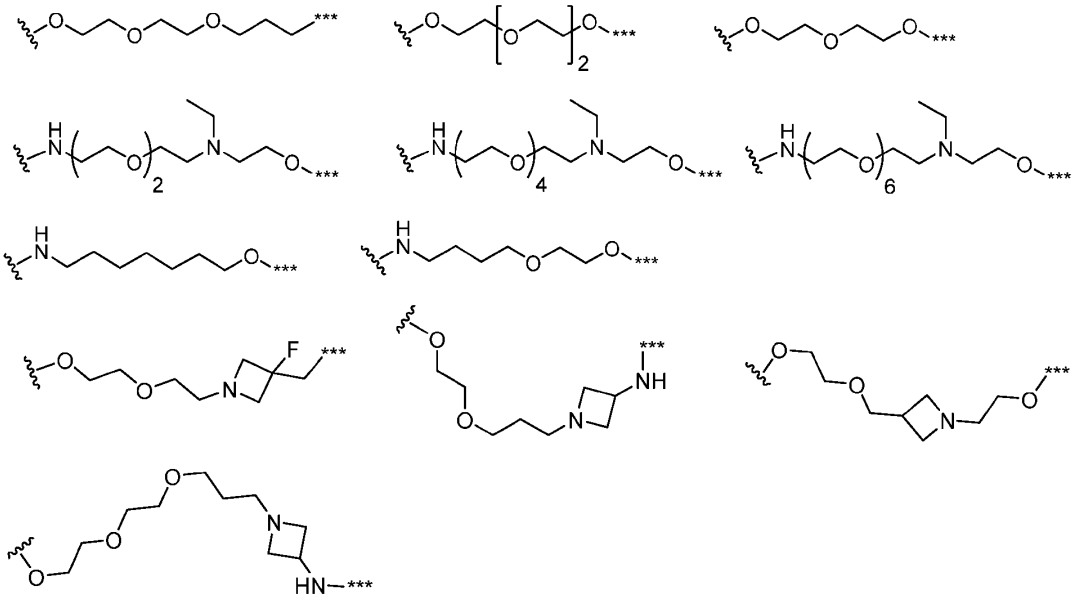
[0276] In certain embodiments, L is -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; wherein *** is the point of attachment to TPL. In certain embodiments, L is -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; wherein *** is the point of attachment to TPL. In certain embodiments, L is -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic ring containing 0, 1, or 2 nitrogen atoms, wherein the ring is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; wherein *** is the point of attachment to TPL. In certain embodiments, L is -(azetidinylene)-CH_2-(piperazinylene or piperidinylene)-CH_2-(azetidinylene)-.

[0277] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:

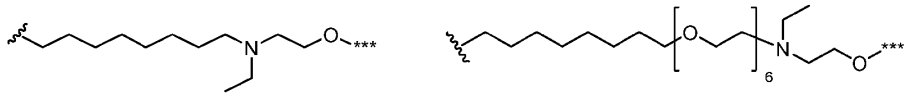


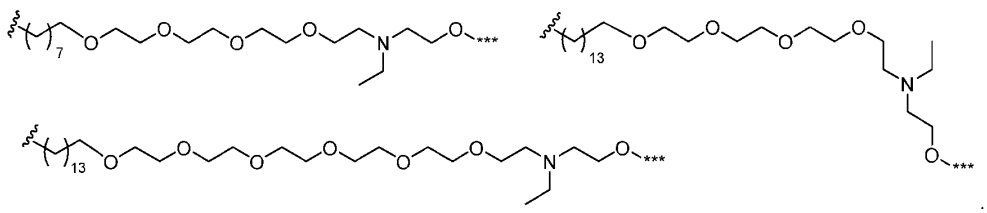


[0278] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:

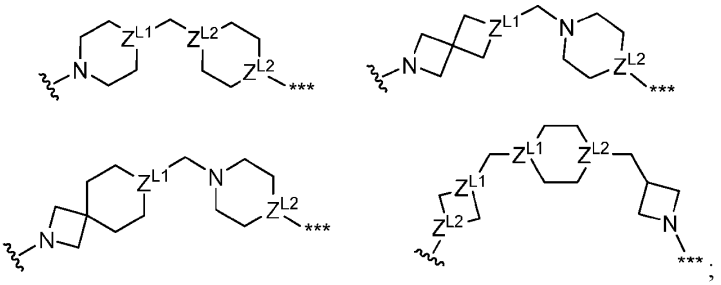


[0279] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:





[0280] In certain embodiments, L is one of the following:

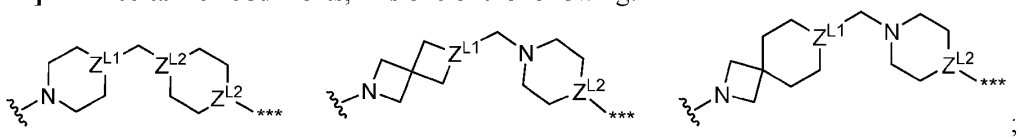


wherein: Z^{L1} is C(OH), C(H), C(F), or N;

Z^{L2} is independently for each occurrence N or C(H); and

*** is the point of attachment to TPL.

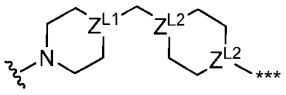
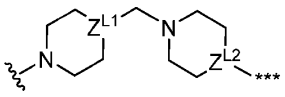
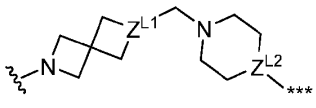
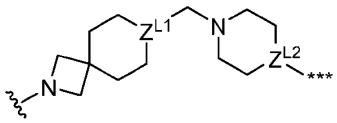
[0281] In certain embodiments, L is one of the following:

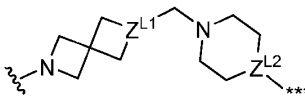
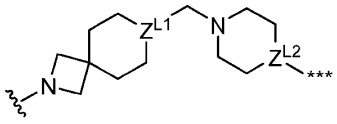
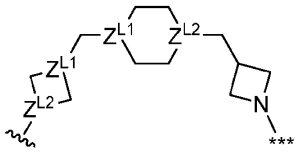


wherein: Z^{L1} is C(OH), C(H), C(F), or N;

Z^{L2} is independently for each occurrence N or C(H); and

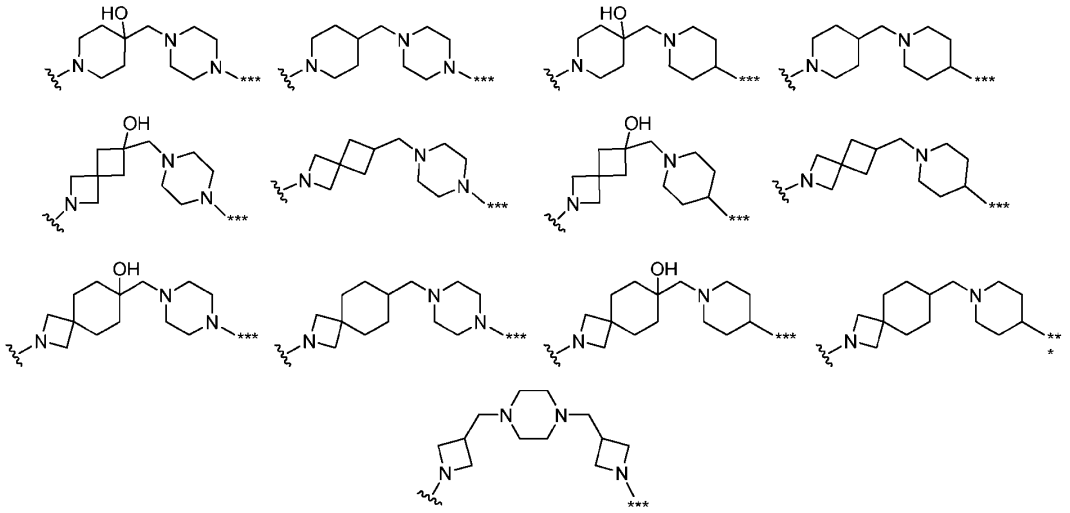
*** is the point of attachment to TPL.

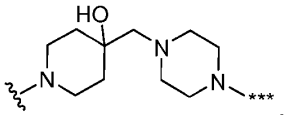
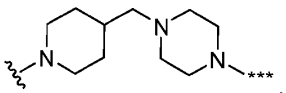
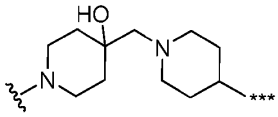
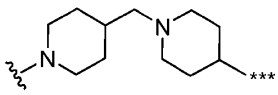
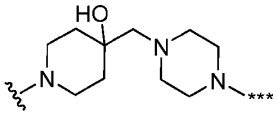
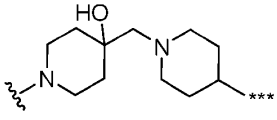
[0282] In certain embodiments, L is , wherein *** is the point of attachment to TPL. In certain embodiments, L is , wherein *** is the point of attachment to TPL. In certain embodiments, L is  or , wherein *** is the point of attachment to TPL. In certain

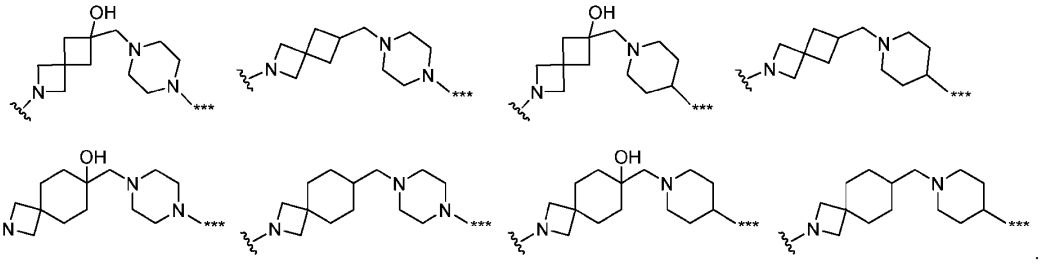
embodiments, L is , wherein *** is the point of attachment to TPL. In certain embodiments, L is , wherein *** is the point of attachment to TPL. In certain embodiments, L is , wherein *** is the point of attachment to TPL.

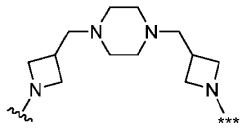
[0283] In certain embodiments, Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H). In certain embodiments, Z^{L1} is C(OH), and Z^{L2} is N. In certain embodiments, Z^{L1} is C(OH), C(H), or C(F). In certain embodiments, Z^{L1} is C(OH) or C(H). In certain embodiments, Z^{L1} is C(OH). In certain embodiments, Z^{L1} is C(H). In certain embodiments, Z^{L1} is C(F). In certain embodiments, Z^{L1} is N. In certain embodiments, Z^{L2} is independently for each occurrence N or C(H). In certain embodiments, Z^{L2} is N or C(H). In certain embodiments, Z^{L2} is N. In certain embodiments, Z^{L2} is C(H).

[0284] In certain embodiments, L is one of the following, wherein *** is the point of attachment to TPL:



[0285] In certain embodiments, L is , , , or , wherein *** is the point of attachment to TPL. In certain embodiments, L is  or , wherein *** is the point of attachment to TPL. In certain embodiments, L is one of the following, wherein *** is the point of attachment to TPL:



In certain embodiments, L is , wherein *** is the point of attachment to TPL.

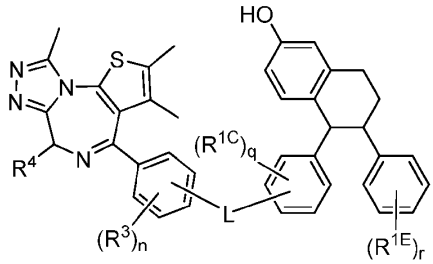
[0286] In certain embodiments, L is selected from those depicted in the compounds in Table 1, 3, 4, and 5, below. In certain embodiments, L is selected from those depicted in the compounds in Table 1, below. In certain embodiments, L is selected from those depicted in the compounds in Table 2, below. In certain embodiments, L is selected from those depicted in the compounds in Table 3, below. In certain embodiments, L is selected from those depicted in the compounds in Table 4, below. In certain embodiments, L is selected from those depicted in the compounds in Table 5, below.

Part E: Exemplary More Specific Embodiments

[0287] Embodiments described above may be combined to provide more specific embodiments defining compounds. All combinations and permutations are contemplated.

[0288] For example, in certain embodiments, the compound of Formula I is a compound of Formula I-A or I-B, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I-A or I-B. In certain embodiments, the compound of each of Formula I-A and I-B is as defined and described in the following embodiments.

[0289] In certain embodiments, the compound of Formula I is represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^3, R^{1C}, and R^{1E} are each independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl;

R^4 is methyl, -CH_2-(oxazolyl), or -CH_2-(thiazolyl);

L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:

(i) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, or

(ii) -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; and

n, q, and r are independently 0, 1, or 2.

[0290] In certain embodiments, the compound is a compound of Formula I-A.

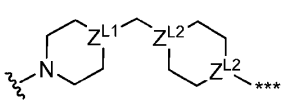
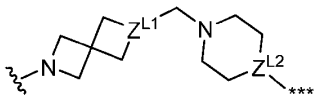
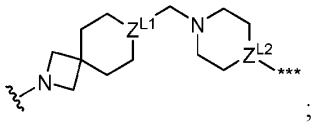
[0291] In certain embodiments, R^3 represents independently for each occurrence hydrogen, fluoro, or chloro. In certain embodiments, R^3 represents independently for each occurrence hydrogen or fluoro. In certain embodiments, R^3 represents independently for each occurrence fluoro or chloro. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is fluoro.

In certain embodiments, R^3 is chloro. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is methoxy.

[0292] In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is -CH_2-(oxazolyl) or -CH_2-(thiazolyl). In certain embodiments, R^4 is -CH_2-(oxazol-2-yl) or -CH_2-(thiazol-2-yl). In certain embodiments, R^4 is -CH_2-(oxazolyl). In certain embodiments, R^4 is -CH_2-(oxazol-2-yl). In certain embodiments, R^4 is -CH_2-(thiazolyl). In certain embodiments, R^4 is -CH_2-(thiazol-2-yl).

[0293] In certain embodiments, L is -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; wherein *** is the point of attachment to the phenyl ring bearing R^{1C}.

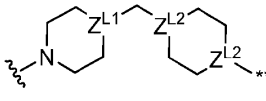
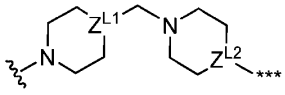
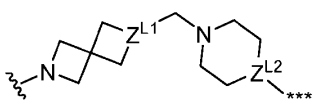
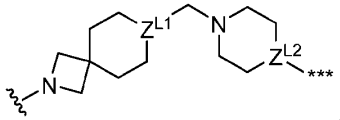
[0294] In certain embodiments, L is one of the following:

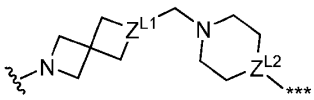
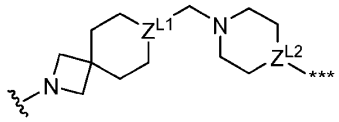



;

wherein: Z^{L1} is C(OH), C(H), C(F), or N;

Z^{L2} is independently for each occurrence N or C(H); and

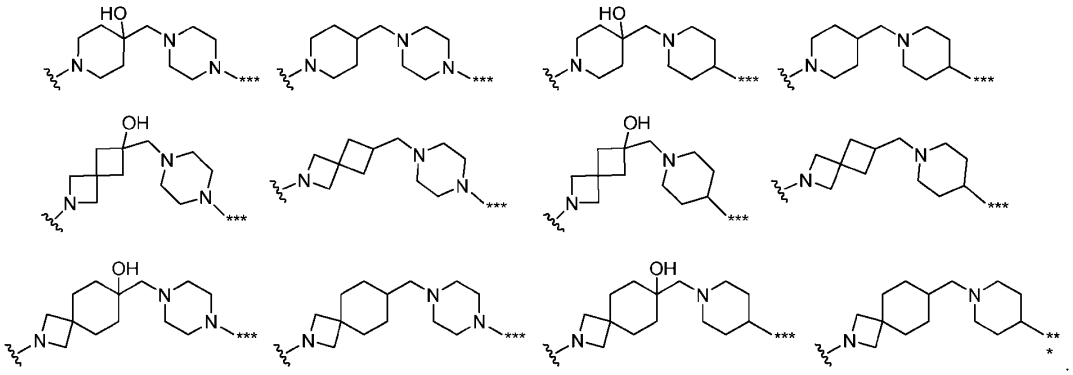
*** is the point of attachment to the phenyl ring bearing R^{1C}.

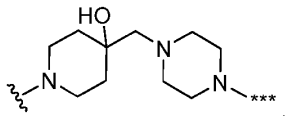
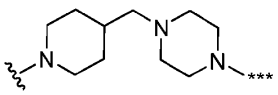
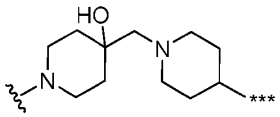
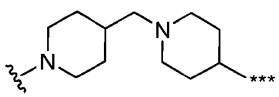
[0295] In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is  or , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L

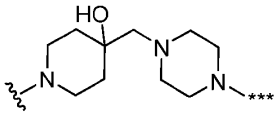
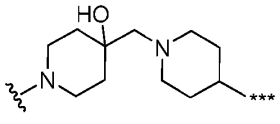
is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}.

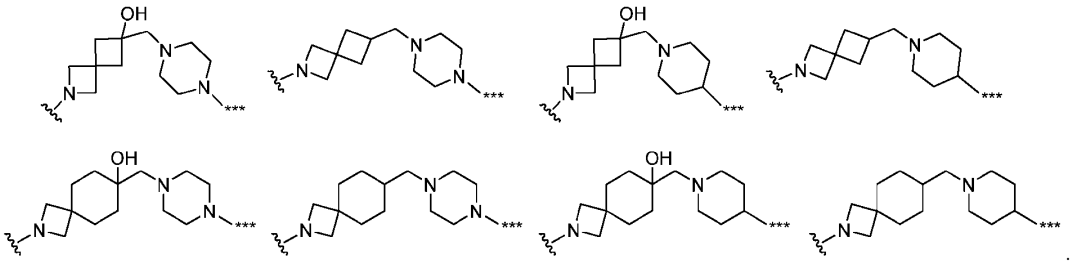
[0296] In certain embodiments, Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H). In certain embodiments, Z^{L1} is C(OH), and Z^{L2} is N. In certain embodiments, Z^{L1} is C(OH), C(H), or C(F). In certain embodiments, Z^{L1} is C(OH) or C(H). In certain embodiments, Z^{L1} is C(OH). In certain embodiments, Z^{L1} is C(H). In certain embodiments, Z^{L1} is C(F). In certain embodiments, Z^{L1} is N. In certain embodiments, Z^{L2} is independently for each occurrence N or C(H). In certain embodiments, Z^{L2} is N or C(H). In certain embodiments, Z^{L2} is N. In certain embodiments, Z^{L2} is C(H).

[0297] In certain embodiments, L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:



[0298] In certain embodiments, L is , , , or , wherein *** is the point of attachment to

the phenyl ring bearing R^{1C}. In certain embodiments, L is  or , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:



[0299] In certain embodiments, R^{1C} and R^{1E} are each independently for each occurrence fluoro, chloro, methoxy, or methyl. In certain embodiments, R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1C} and R^{1E} are each independently for each occurrence hydrogen or fluoro. In certain embodiments, R^{1C} and R^{1E} are hydrogen. In certain embodiments, R^{1C} and R^{1E} are fluoro.

[0300] In certain embodiments, R^{1C} is independently for each occurrence fluoro, chloro, methoxy, or methyl. In certain embodiments, R^{1C} is independently for each occurrence hydrogen, fluoro, chloro, or methoxy. In certain embodiments, R^{1C} is independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or fluoro. In certain embodiments, R^{1C} is hydrogen or fluoro. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or methoxy. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or methyl. In certain embodiments, R^{1C} is independently for each occurrence fluoro or methoxy. In certain embodiments, R^{1C} is independently for each occurrence fluoro or methyl. In certain embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1C} is fluoro. In certain embodiments, R^{1C} is chloro. In certain embodiments, R^{1C} is methyl. In certain embodiments, R^{1C} is methoxy.

[0301] In certain embodiments, R^{1E} is independently for each occurrence fluoro, chloro, methoxy, or methyl. In certain embodiments, R^{1E} is independently for each occurrence hydrogen,

fluoro, or methoxy. In certain embodiments, R^{1E} is independently for each occurrence hydrogen or fluoro. In certain embodiments, R^{1E} is hydrogen or fluoro. In certain embodiments, R^{1C} is independently for each occurrence hydrogen or methyl. In certain embodiments, R^{1C} is independently for each occurrence fluoro or methyl. In certain embodiments, R^{1E} is hydrogen. In certain embodiments, R^{1E} is fluoro. In certain embodiments, R^{1E} is chloro. In certain embodiments, R^{1E} is methyl. In certain embodiments, R^{1C} is methoxy.

[0302] In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

[0303] In certain embodiments, q and r are 0. In certain embodiments, q and r are independently 0 or 1. In certain embodiments, q and r are independently 1 or 2. In certain embodiments, q and r are independently 0, 1, or 2. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2. In certain embodiments, q is 3. In certain embodiments, q is 0 or 1. In certain embodiments, q is 1 or 2. In certain embodiments, q is 0, 1, or 2. In certain embodiments, r is 0. In certain embodiments, r is 1. In certain embodiments, r is 2. In certain embodiments, r is 3. In certain embodiments, r is 0 or 1. In certain embodiments, r is 1 or 2. In certain embodiments, r is 0, 1, or 2.

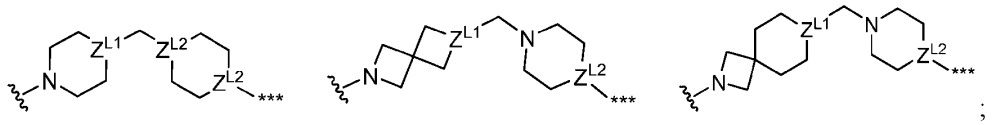
[0304] In certain embodiments:

R^3 represents independently for each occurrence hydrogen, fluoro, or chloro;

R^4 is methyl or -CH_2-(oxazolyl);

R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, or methoxy; and

L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:



;

wherein: Z^{L1} is C(OH), C(H), C(F), or N;

Z^{L2} is independently for each occurrence N or C(H); and

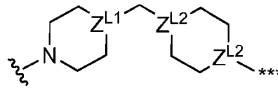
*** is the point of attachment to the phenyl ring bearing R^{1C}.

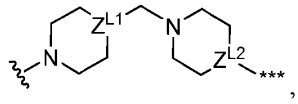
[0305] In certain embodiments:

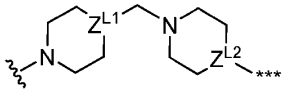
R^3 represents independently for each occurrence hydrogen or fluoro;

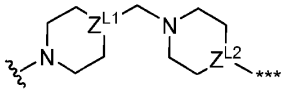
R^4 is methyl;

R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, or methoxy; and

L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}, Z^{L1} is C(OH), C(H), C(F), or N, and Z^{L2} is independently for each occurrence N or C(H).

[0306] In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}, Z^{L1} is C(OH), C(H), C(F), or N, and Z^{L2} is N or C(H).

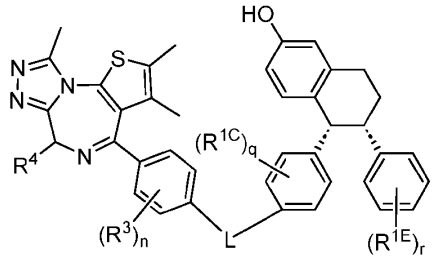
In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}, Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H).

[0307] In certain embodiments, R^4 is methyl, and L is .

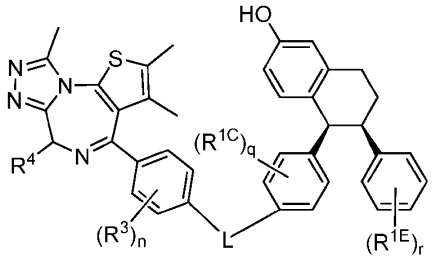
[0308] In certain embodiments, R^3 represents independently for each occurrence hydrogen, fluoro, or chloro, and R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^3 represents independently for each occurrence hydrogen and fluoro, and R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, or methoxy.

[0309] The description above describes multiple embodiments relating to compounds of Formula I-A. The patent application specifically contemplates all combinations of the embodiments.

[0310] In certain embodiments, the compound of Formula I or I-A is represented by Formula I-A-1 or I-A-2, or a pharmaceutically acceptable salt thereof:



(I-A-1)

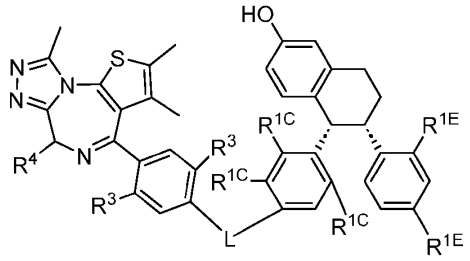


(I-A-2).

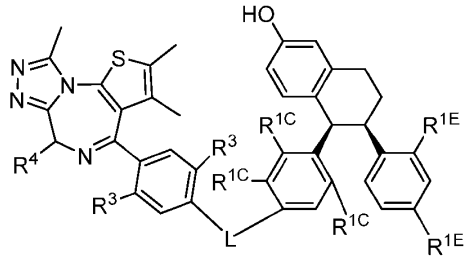
[0311] In certain embodiments, the compound is a compound of Formula I-A-1, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I-A-2, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I-A-1 or I-A-2. In certain embodiments, the compound is a compound of Formula I-A-1. In certain embodiments, the compound is a compound of Formula I-A-2.

[0312] In certain embodiments, each of variables R^3, R^4, L, R^{1C}, R^{1E} , n, q, and r in Formula I-A-1 and I-A-2 is as defined and described in embodiments above for compounds of Formula I-A, both singly and in combination. The description above describes multiple embodiments relating to compounds of Formula I-A-1 and I-A-2. The patent application specifically contemplates all combinations of the embodiments.

[0313] In certain embodiments, the compound of Formula I or I-A is represented by Formula I-A-3* or I-A-4*, or a pharmaceutically acceptable salt thereof:



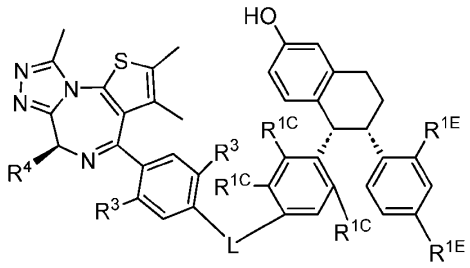
(I-A-3*)



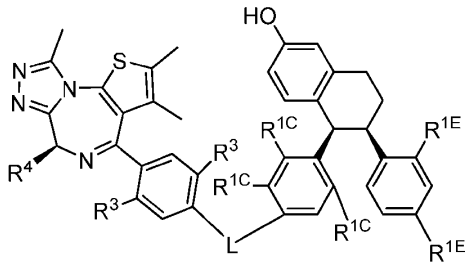
(I-A-4*).

[0314] In certain embodiments, the compound is a compound of Formula I-A-3*, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I-A-4*, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I-A-3* or I-A-4*. In certain embodiments, the compound is a compound of Formula I-A-3*. In certain embodiments, the compound is a compound of Formula I-A-4*.

[0315] In certain embodiments, the compound of Formula I or I-A is represented by Formula I-A-3 or I-A-4, or a pharmaceutically acceptable salt thereof:

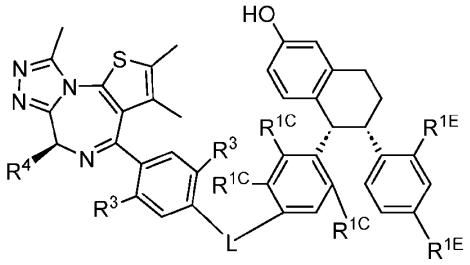


(I-A-3)



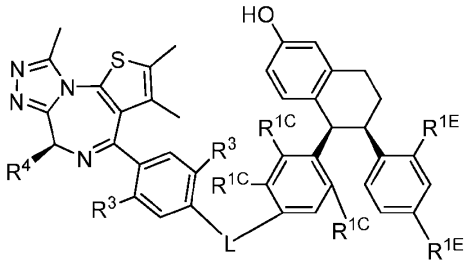
(I-A-4).

[0316] In certain embodiments, the compound is a compound of Formula I-A-3, or a pharmaceutically acceptable salt thereof:



(I-A-3).

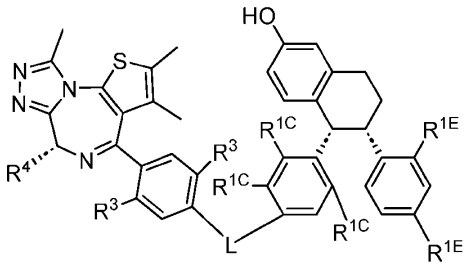
[0317] In certain embodiments, the compound is a compound of Formula I-A-4, or a pharmaceutically acceptable salt thereof:



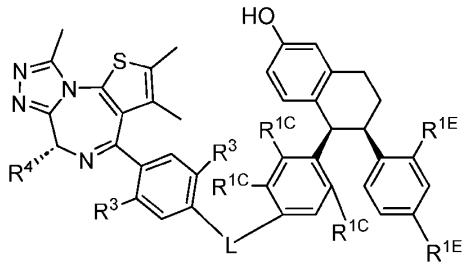
(I-A-4).

[0318] In certain embodiments, the compound is a compound of Formula I-A-3 or I-A-4. In certain embodiments, the compound is a compound of Formula I-A-3. In certain embodiments, the compound is a compound of Formula I-A-4.

[0319] In certain embodiments, the compound of Formula I or I-A is represented by Formula I-A-3** or I-A-4**, or a pharmaceutically acceptable salt thereof:

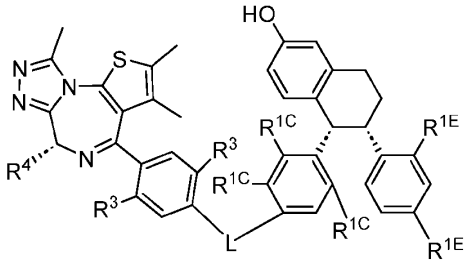


(I-A-3**)



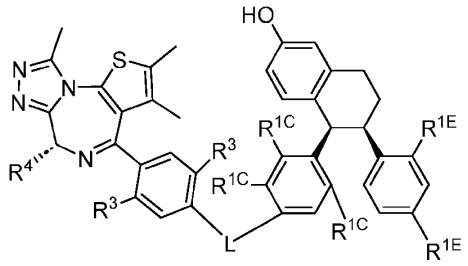
(I-A-4**).

[0320] In certain embodiments, the compound is a compound of Formula I-A-3**, or a pharmaceutically acceptable salt thereof:



(I-A-3**).

[0321] In certain embodiments, the compound is a compound of Formula I-A-4**, or a pharmaceutically acceptable salt thereof:



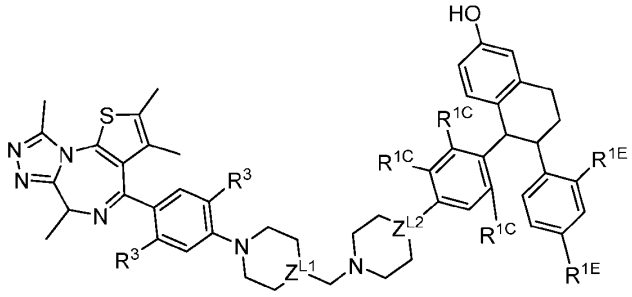
(I-A-4**).

[0322] In certain embodiments, the compound is a compound of Formula I-A-3** or I-A-4**. In certain embodiments, the compound is a compound of Formula I-A-3**. In certain embodiments, the compound is a compound of Formula I-A-4**.

[0323] In certain embodiments, each of variables R^3, R^4, L, R^{1C}, and R^{1E} in Formula I-A-3*, I-A-4*, I-A-3, I-A-4, I-A-3** and I-A-4** is as defined and described in embodiments above for compounds of Formula I-A, both singly and in combination. The description above describes

multiple embodiments relating to compounds of Formula I-A-3*, I-A-4*, I-A-3, I-A-4, I-A-3** and I-A-4**. The patent application specifically contemplates all combinations of the embodiments.

[0324] In certain embodiments, the compound of Formula I or I-A is represented by Formula I-A-5, or a pharmaceutically acceptable salt thereof:



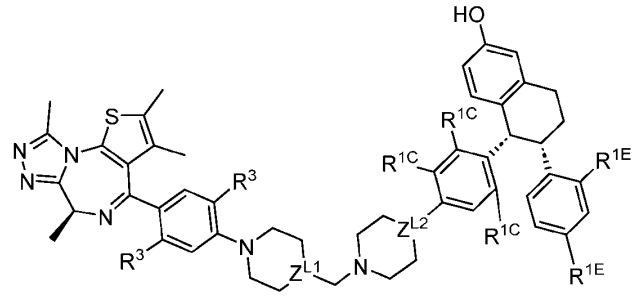
(I-A-5)

wherein Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H).

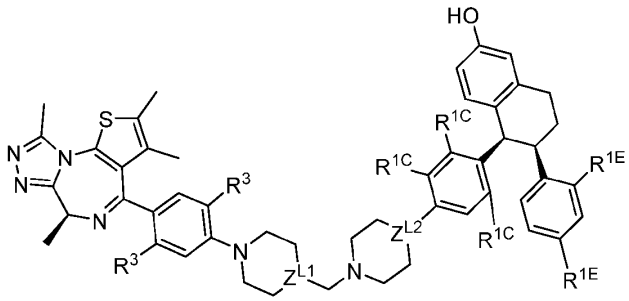
[0325] In certain embodiments, the compound is a compound of Formula I-A-5. In certain embodiments, Z^{L1} is C(OH). In certain embodiments, Z^{L1} is C(H). In certain embodiments, Z^{L2} is N. In certain embodiments, Z^{L2} is C(H). In certain embodiments, Z^{L1} is C(OH), and Z^{L2} is N.

[0326] In certain embodiments, each of variables R^3, R^{1C}, and R^{1E} in Formula I-A-5 is as defined and described in embodiments above for compounds of Formula I-A, both singly and in combination. The description above describes multiple embodiments relating to compounds of Formula I-A-5. The patent application specifically contemplates all combinations of the embodiments.

[0327] In certain embodiments, the compound of Formula I or I-A is represented by Formula I-A-6 or I-A-7, or a pharmaceutically acceptable salt thereof:



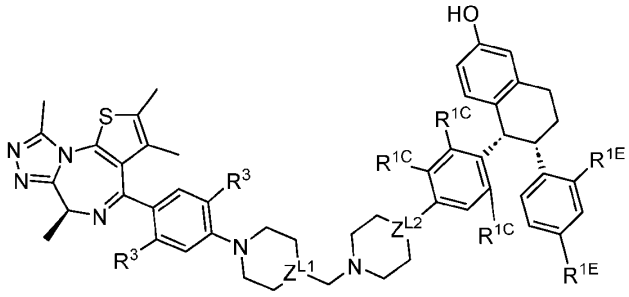
(I-A-6)



(I-A-7)

wherein Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H).

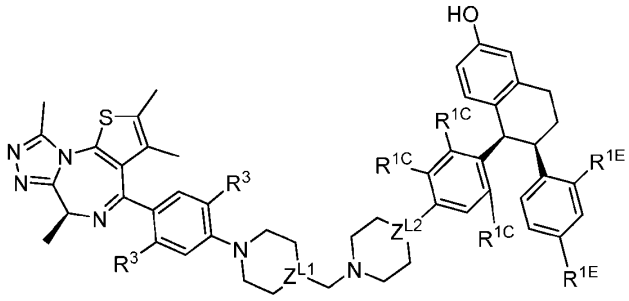
[0328] In certain embodiments, the compound is a compound of Formula I-A-6, or a pharmaceutically acceptable salt thereof:



(I-A-6)

wherein Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H).

[0329] In certain embodiments, the compound is a compound of Formula I-A-7, or a pharmaceutically acceptable salt thereof:



(I-A-7)

wherein Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H).

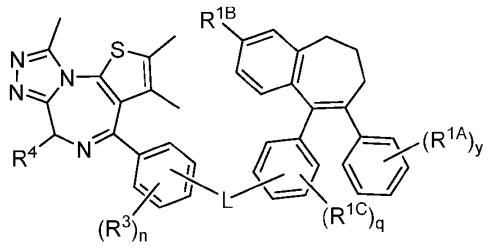
[0330] In certain embodiments, the compound is a compound of Formula I-A-6 or I-A-7. In certain embodiments, the compound is a compound of Formula I-A-6. In certain embodiments, the compound is a compound of Formula I-A-7.

[0331] In certain embodiments, Z^{L1} is C(OH). In certain embodiments, Z^{L1} is C(H). In certain embodiments, Z^{L2} is N. In certain embodiments, Z^{L2} is C(H). In certain embodiments, Z^{L1} is C(OH), and Z^{L2} is N.

[0332] In certain embodiments, R^3 represents independently for each occurrence hydrogen, fluoro, or chloro, and R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^3 represents independently for each occurrence hydrogen and fluoro, and R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, or methoxy.

[0333] In certain embodiments, each of variables R^3, R^{1C}, and R^{1E} in Formula I-A-6 and I-A-7 is as defined and described in embodiments above for compounds of Formula I-A, both singly and in combination. The description above describes multiple embodiments relating to compounds of Formula I-A-6 and I-A-7. The patent application specifically contemplates all combinations of the embodiments.

[0334] In certain embodiments, the compound of Formula I is represented by Formula I-B:



(I-B)

or a pharmaceutically acceptable salt thereof; wherein:

R^3 represents independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl;

R^4 is methyl, -CH_2-(oxazolyl), or -CH_2-(thiazolyl);

n is 0, 1, or 2;

L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:

(i) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or

fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***,

(ii) -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, or

(iii) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic ring containing 0, 1, or 2 nitrogen atoms, wherein the ring is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***;

R^{1A} and R^{1C} each represents independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl;

R^{1B} is -C(O)OH, -OH, or $-B(OH)_2$;

q is 1 or 2; and

y is 1, 2, or 3.

[0335] In certain embodiments, the compound is a compound of Formula I-B.

[0336] In certain embodiments, R^3 represents independently for each occurrence hydrogen, fluoro, or chloro. In certain embodiments, R^3 represents independently for each occurrence hydrogen or fluoro. In certain embodiments, R^3 represents independently for each occurrence fluoro or chloro. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is fluoro. In certain embodiments, R^3 is chloro. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is methoxy.

[0337] In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is $-CH_2$-(oxazolyl) or $-CH_2$-(thiazolyl). In certain embodiments, R^4 is $-CH_2$-(oxazol-2-yl) or $-CH_2$-(thiazol-2-yl). In certain embodiments, R^4 is $-CH_2$-(oxazolyl). In certain embodiments, R^4 is $-CH_2$-(oxazol-2-yl). In certain embodiments, R^4 is $-CH_2$-(thiazolyl). In certain embodiments, R^4 is $-CH_2$-(thiazol-2-yl).

[0338] In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

[0339] In certain embodiments, L is:

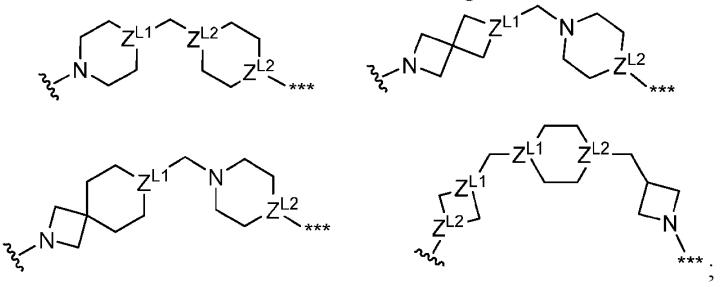
(i) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, or

(ii) -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***;

wherein *** is the point of attachment to the phenyl ring bearing R^{1C}.

[0340] In certain embodiments, L is -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic ring containing 0, 1, or 2 nitrogen atoms, wherein the ring is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is -(azetidinylene)-CH_2-(piperazinylene or piperidinylene)-CH_2-(azetidinylene)-.

[0341] In certain embodiments, L is one of the following:

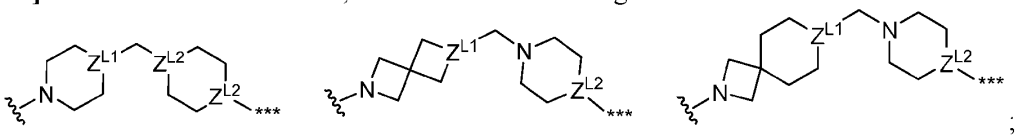


wherein: Z^{L1} is C(OH), C(H), C(F), or N;

Z^{L2} is independently for each occurrence N or C(H); and

*** is the point of attachment to the phenyl ring bearing R^{1C}.

[0342] In certain embodiments, L is one of the following:

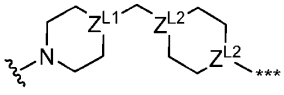
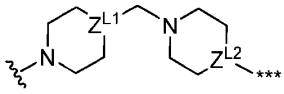
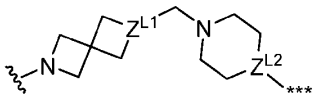
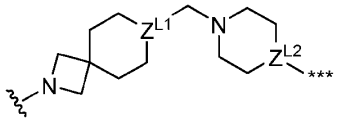
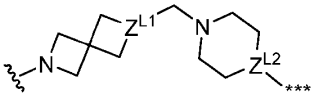
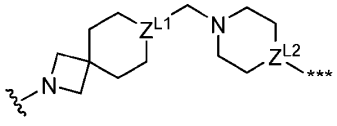
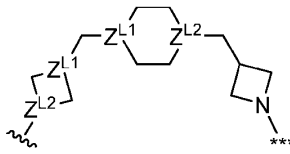


;

wherein: Z^{L1} is C(OH), C(H), C(F), or N;

Z^{L2} is independently for each occurrence N or C(H); and

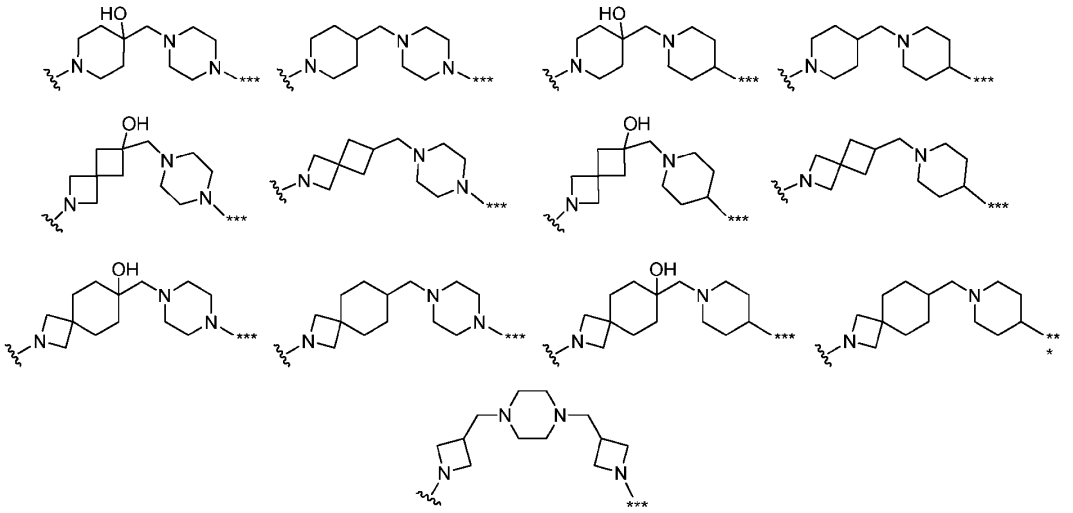
*** is the point of attachment to the phenyl ring bearing R^{1C}.

[0343] In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is  or , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is , wherein *** is the point of attachment to the phenyl ring bearing R^{1C}.

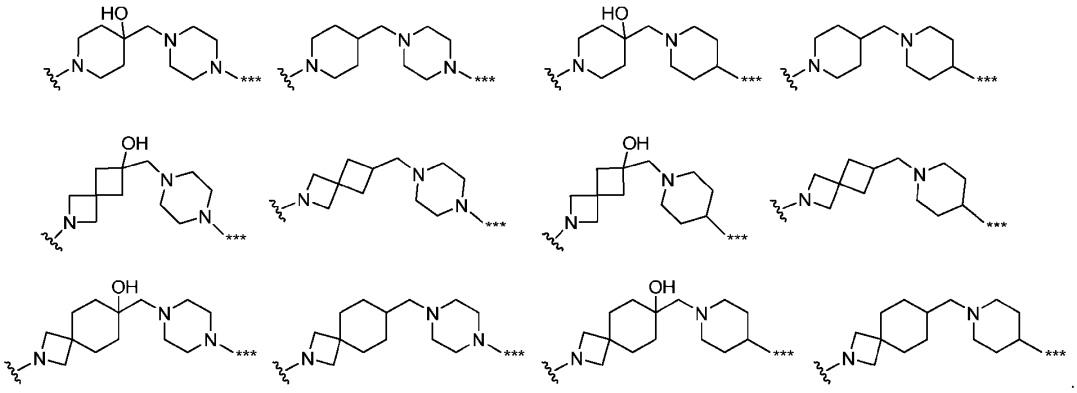
[0344] In certain embodiments, Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H). In certain embodiments, Z^{L1} is C(OH), and Z^{L2} is N. In certain embodiments, Z^{L1} is C(OH), C(H), or C(F).

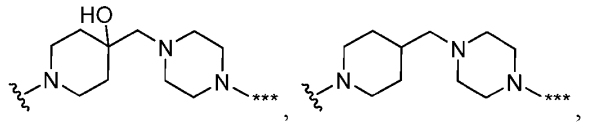
In certain embodiments, Z^{L1} is C(OH) or C(H). In certain embodiments, Z^{L1} is C(OH). In certain embodiments, Z^{L1} is C(H). In certain embodiments, Z^{L1} is C(F). In certain embodiments, Z^{L1} is N. In certain embodiments, Z^{L2} is independently for each occurrence N or C(H). In certain embodiments, Z^{L2} is N or C(H). In certain embodiments, Z^{L2} is N. In certain embodiments, Z^{L2} is C(H).

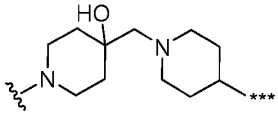
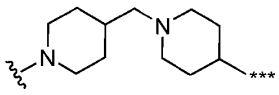
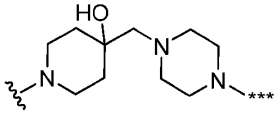
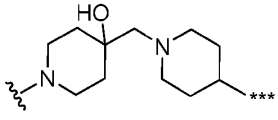
[0345] In certain embodiments, L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:

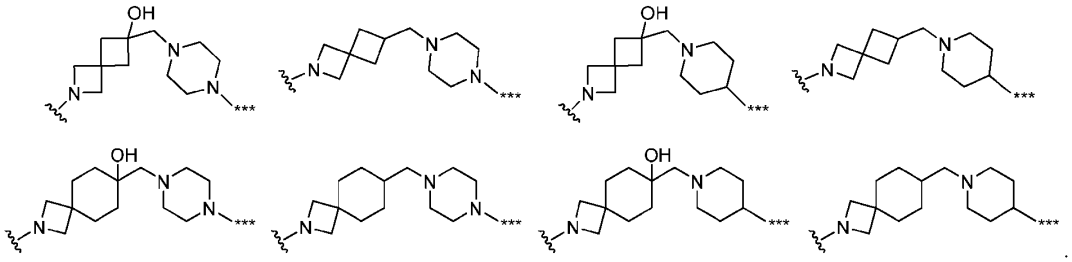
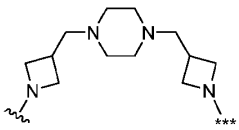


[0346] In certain embodiments, L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:



[0347] In certain embodiments, L is ,


, or 
, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is 
or 
, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}. In certain embodiments, L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:


In certain embodiments, L is 
, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}.

[0348] In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro, and R^{1C} represents independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro. In certain embodiments, R^{1A} is hydrogen, fluoro, or chloro. In certain embodiments, R^{1A} is hydrogen or chloro. In certain embodiments, R^{1A} is hydrogen. In certain embodiments, R^{1A} is fluoro. In certain embodiments, R^{1A} is chloro. In certain embodiments, R^{1A} is methyl. In certain embodiments, R^{1A} is methoxy.

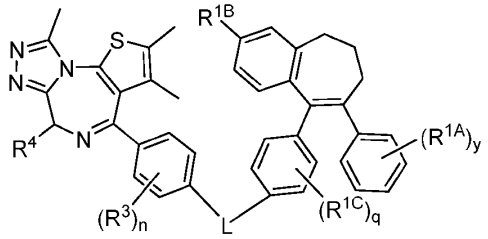
[0349] In certain embodiments, R^{1B} is -C(O)OH or -OH. In certain embodiments, R^{1B} is -C(O)OH. In certain embodiments, R^{1B} is hydroxyl. In certain embodiments, R^{1B} is $-B(OH)_2$. In certain embodiments, R^{1C} represents independently for each occurrence hydrogen, fluoro, or methoxy. In certain embodiments, R^{1C} is hydrogen or fluoro. In certain embodiments, R^{1C} is

fluoro or chloro. In certain embodiments, R^{1C} is hydrogen. In certain embodiments, R^{1C} is fluoro. In certain embodiments, R^{1C} is chloro. In certain embodiments, R^{1C} is methoxy. In certain embodiments, R^{1C} is methyl.

[0350] In certain embodiments, q is 1. In certain embodiments, q is 2. In certain embodiments, y is 1. In certain embodiments, y is 2. In certain embodiments, y is 3.

[0351] The description above describes multiple embodiments relating to compounds of Formula I-B. The patent application specifically contemplates all combinations of the embodiments.

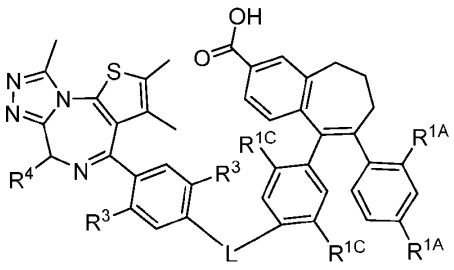
[0352] In certain embodiments, the compound of Formula I or Formula I-B is represented by Formula I-B-1, or a pharmaceutically acceptable salt thereof:



(I-B-1).

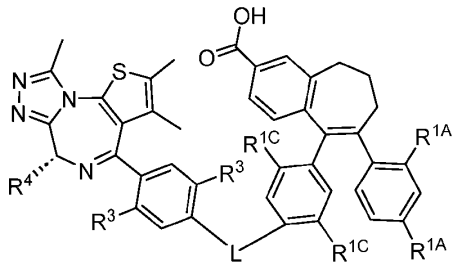
[0353] In certain embodiments, the compound is a compound of Formula I-B-1. In certain embodiments, each of variables R^3, R^4, L, R^{1A}, R^{1B}, R^{1C}, n, q, and y in Formula I-B-1 is as defined and described in embodiments above for compounds of Formula I-B, both singly and in combination. The description above describes multiple embodiments relating to compounds of Formula I-B-1. The patent application specifically contemplates all combinations of the embodiments.

[0354] In certain embodiments, the compound of Formula I or Formula I-B is represented by Formula I-B-2, or a pharmaceutically acceptable salt thereof:



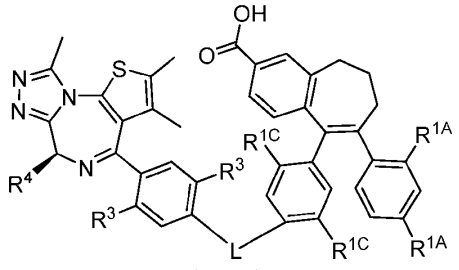
(I-B-2).

[0355] In certain embodiments, the compound of Formula I or Formula I-B is represented by Formula I-B-3, or a pharmaceutically acceptable salt thereof:



(I-B-3).

[0356] In certain embodiments, the compound of Formula I or Formula I-B is represented by Formula I-B-4, or a pharmaceutically acceptable salt thereof:

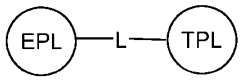


(I-B-4).

[0357] In certain embodiments, the compound is a compound of Formula I-B-2. In certain embodiments, the compound is a compound of Formula I-B-3. In certain embodiments, the compound is a compound of Formula I-B-4.

[0358] In certain embodiments, each of variables R^3, R^4, L, R^{1A}, and R^{1C} in Formula I-B-2, I-B-3, and I-B-4 is as defined and described in embodiments above for compounds of Formula I-B, both singly and in combination. The description above describes multiple embodiments relating to compounds of Formula I-B-2, I-B-3, and I-B-4. The patent application specifically contemplates all combinations of the embodiments.

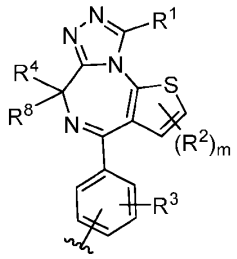
[0359] Another aspect of the invention provides a compound of Formula I-1:



(I-1)

or a pharmaceutically acceptable salt thereof; wherein:

EPL has the following formula:



wherein:

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

R^2 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^3 is hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxyl;

R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur), -(C_{1-6} alkylene)-C(O)N(R^5)(R^6), -(C_{1-6} alkylene)-N(R^5)C(O)R^7, -(C_{1-6} alkylene)-CO_2R^7, -(C_{1-6} alkylene)-OC(O)R^7, -(C_{1-6} alkylene)-cyano, -(C_{1-6} alkylene)-O-(C_{1-6} alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl, or hydrogen; or R^4 and R^8 taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring;

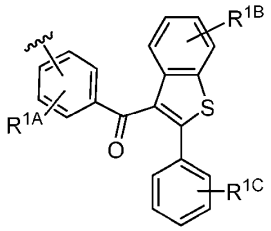
R^5 and R^6 are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom;

R^7 is C_{1-6} alkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

R^8 is hydrogen or C_{1-4} alkyl; and

m is 0, 1, or 2;

TPL is



wherein:

R^{1A} is hydrogen, halo, or C_{1-4} alkyl; and

R^{1B} and R^{1C} are independently hydroxyl, halo, C_{1-4} alkyl, or C_{1-4} alkoxyl; and

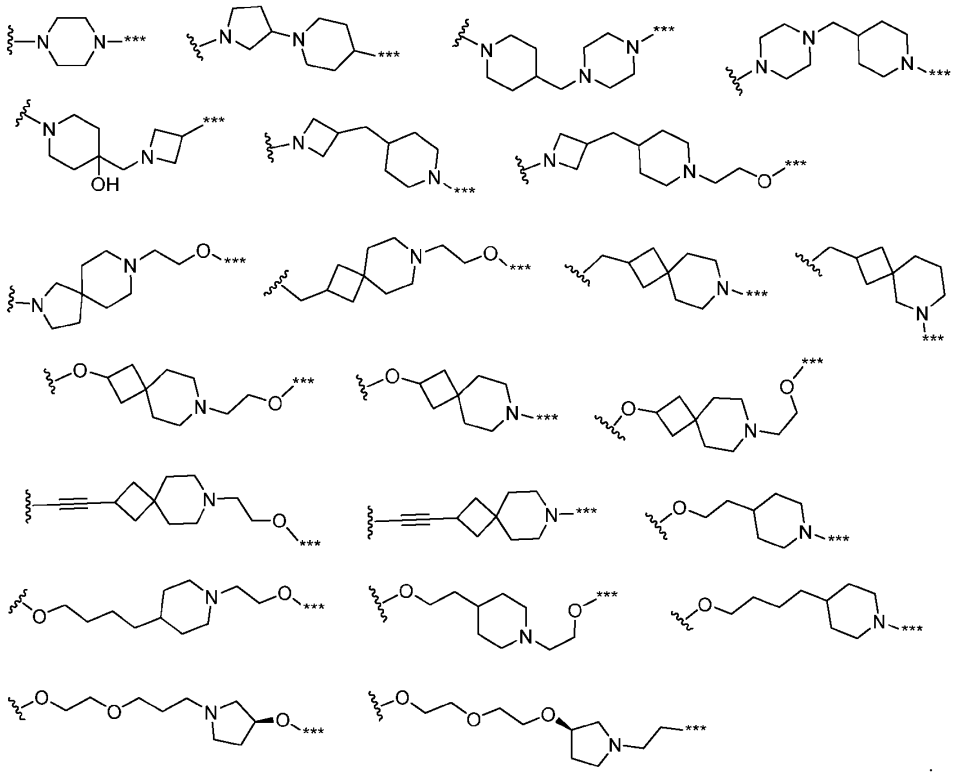
L is one of the following:

(i) -(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of hydroxyl)-(C_{0-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 heteroatoms selected from nitrogen)-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{1-6} alkylene)-O-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL;

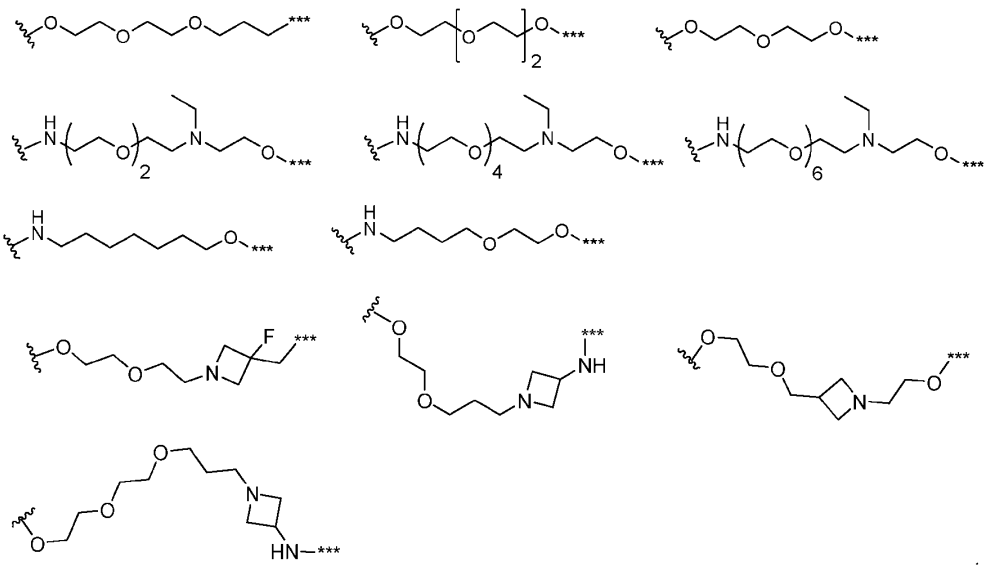
(ii) -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -N(H)-[-(C_{1-6} alkylene)-O-]$_{1-6}$-(C_{1-6} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, -N(H)-(C_{1-10} alkylene)-O-***, -N(H)-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of fluoro)-(C_{0-6} alkylene)-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, where *** is a point of attachment to TPL; or

(iii) -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, -(C_{1-10} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, or -(C_{1-15} alkylene)-[-O-(C_{1-6} alkylene)-]$_{1-8}$-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL.

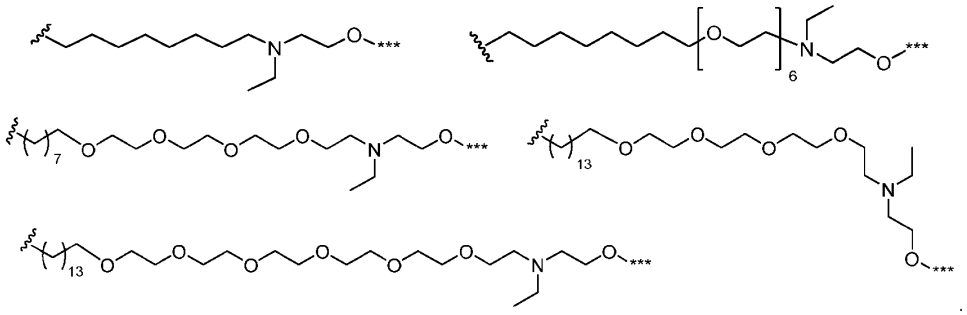
[0360] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



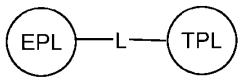
[0361] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



[0362] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



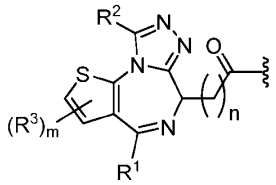
[0363] Another aspect of the invention provides a compound of Formula I-2:



(I-2)

or a pharmaceutically acceptable salt thereof; wherein:

EPL has the following formula:



wherein:

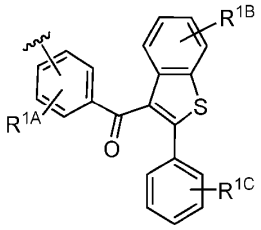
R^1 is phenyl or 6-membered heteroaryl containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the phenyl and heteroaryl are optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxyl, or C_1-C_6 alkoxy;

R^2 and R^3 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

m is 0, 1, or 2; and

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

TPL is



wherein:

R^{1A} is hydrogen, halo, or C_{1-4} alkyl; and

R^{1B} and R^{1C} are independently hydroxyl, halo, C_{1-4} alkyl, or C_{1-4} alkoxyl; and

L is one of the following:

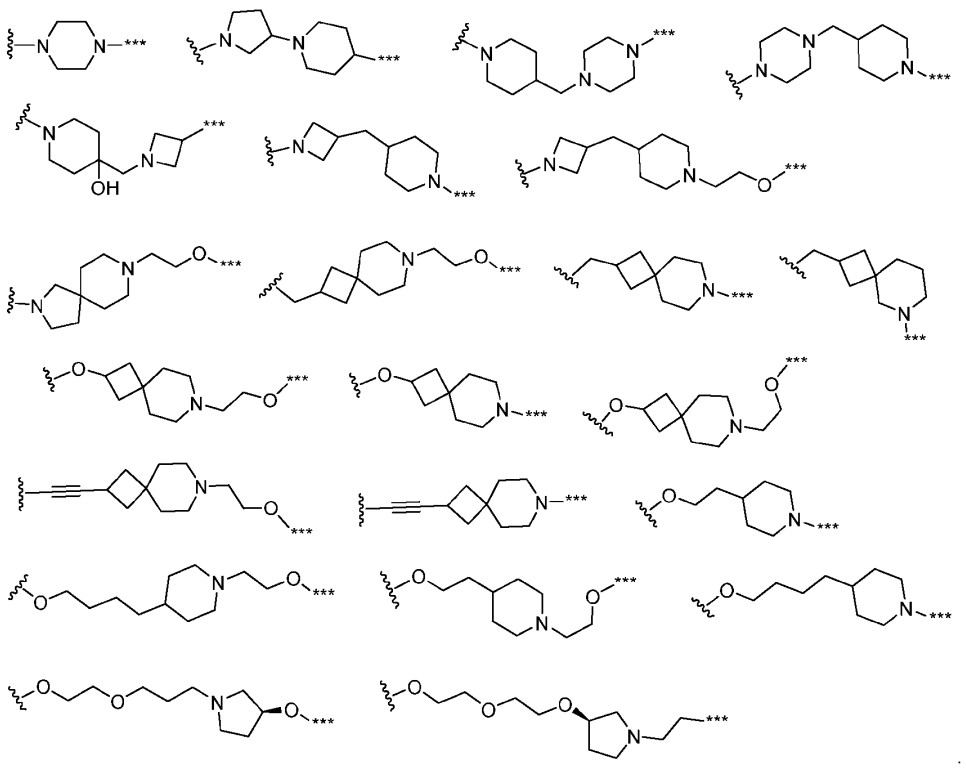
(i) -(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of hydroxyl)-(C_{0-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 heteroatoms selected from nitrogen)-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{1-6} alkylene)-O-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL;

(ii) -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -N(H)-[-(C_{1-6} alkylene)-O-]$_{1-6}$-(C_{1-6} alkylene)-N(C_{1-4}

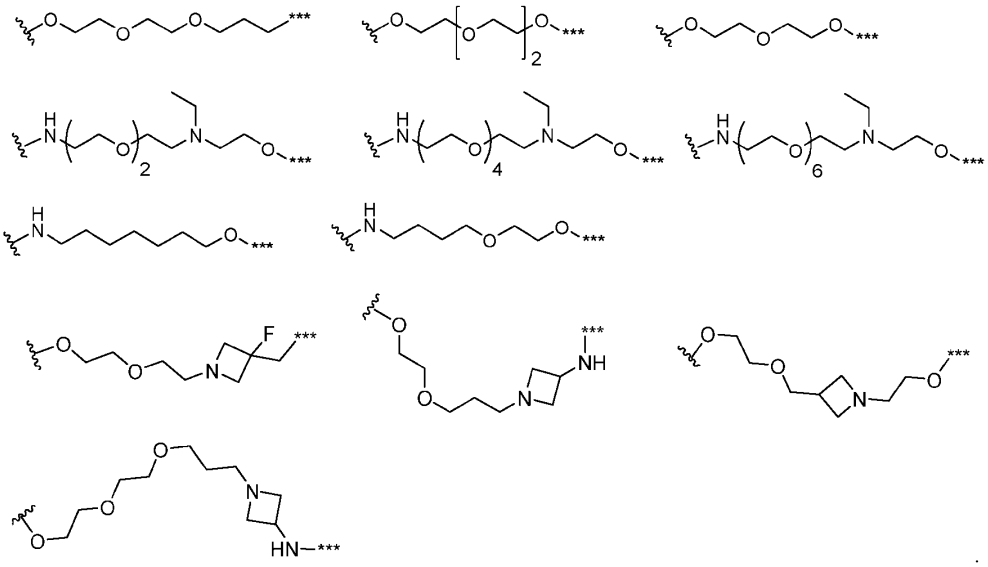
alkyl)-(C_{1-6} alkylene)-O-***, -N(H)-(C_{1-10} alkylene)-O-***, -N(H)-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of fluoro)-(C_{0-6} alkylene)-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, where *** is a point of attachment to TPL; or

(iii) -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, -(C_{1-10} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, or -(C_{1-15} alkylene)-[-O-(C_{1-6} alkylene)-]$_{1-8}$-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL.

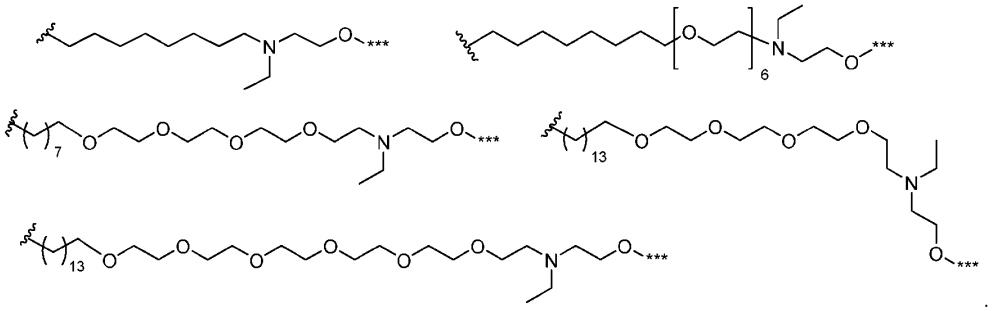
[0364] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



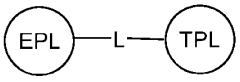
[0365] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



[0366] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



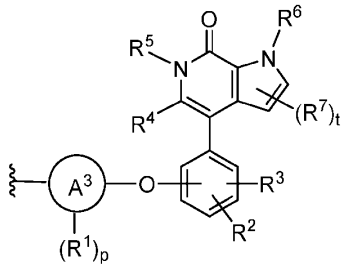
[0367] Another aspect of the invention provides a compound of Formula I-3:



(I-3)

or a pharmaceutically acceptable salt thereof; wherein:

EPL has the following formula:



wherein:

R^1 represents independently for each occurrence halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^2 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^3 is $-N(R^8)SO_2R^9$, $-SO_2N(R^8)_2$, $-SO_2R^9$, $-(C_{1-6}$ alkylene$)-SO_2R^9$, C_{1-6} hydroxyalkyl, or a 4-7 membered saturated carbocyclic ring in which one CH_2 is replaced with SO_2;

R^4 is hydrogen, halo, or C_{1-4} alkyl;

R^5 is C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^6 is hydrogen, C_{1-4} alkyl, or C_{3-4} cycloalkyl;

R^7 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

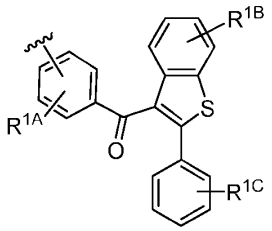
R^8 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or two occurrences of R^8 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen; or R^8 and R^9 are taken together with their intervening atoms to a form a 5-7 membered ring containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^9 is C_{1-6} alkyl, C_{1-6} haloalkyl, $-(C_{1-6}$ alkylene$)-(C_{3-6}$ cycloalkyl), or C_{3-6} cycloalkyl;

A^3 is phenylene, a 3-10 membered saturated monocyclic, bicyclic or spirocyclic carbocyclylene, or C_{1-6} alkylene; and

p and t are independently 0, 1, or 2;

TPL is



wherein:

R^{1A} is hydrogen, halo, or C_{1-4} alkyl; and

R^{1B} and R^{1C} are independently hydroxyl, halo, C_{1-4} alkyl, or C_{1-4} alkoxyl; and

L is one of the following:

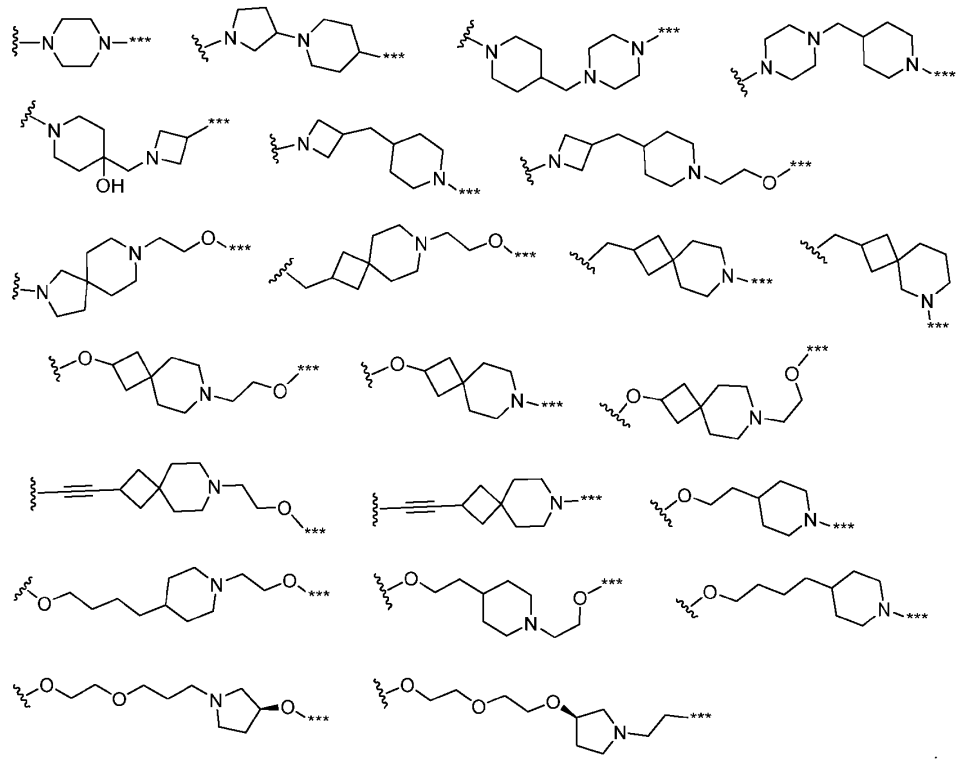
(i) -(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of hydroxyl)-(C_{0-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 heteroatoms selected from nitrogen)-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{1-6} alkylene)-O-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL;

(ii) -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -N(H)-[-(C_{1-6} alkylene)-O-]$_{1-6}$-(C_{1-6} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, -N(H)-(C_{1-10} alkylene)-O-***, -N(H)-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of fluoro)-(C_{0-6} alkylene)-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, where *** is a point of attachment to TPL; or

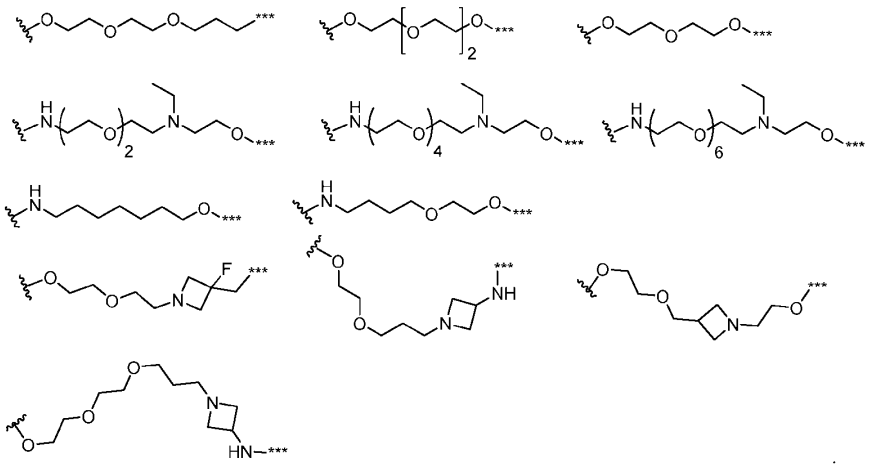
(iii) -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, -(C_{1-10} alkylene)-N(C_{1-4} alkyl)-(C_{1-6}

alkylene)-O-***, or -(C_{1-15} alkylene)-[-O-(C_{1-6} alkylene)-]$_{1-8}$-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL.

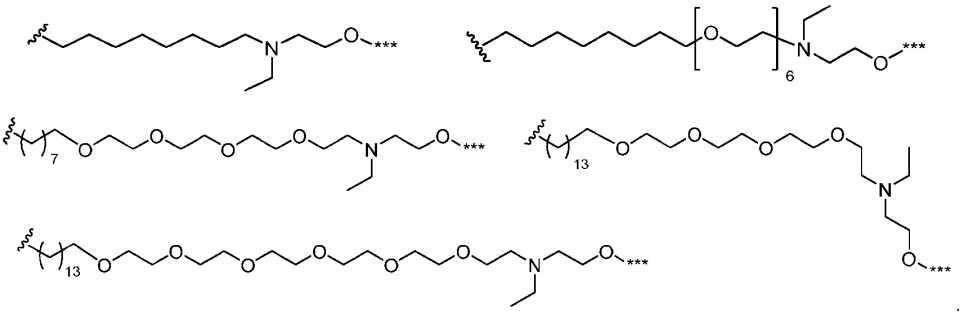
[0368] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



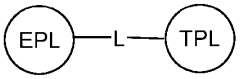
[0369] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



[0370] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



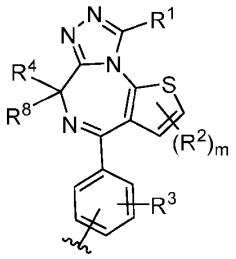
[0371] Another aspect of the invention provides a compound of Formula I-4:



(I-4)

or a pharmaceutically acceptable salt thereof; wherein:

EPL has the following formula:



wherein:

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

R^2 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^3 is hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxyl;

R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur), -(C_{1-6} alkylene)-C(O)N(R^5)(R^6), -(C_{1-6} alkylene)-N(R^5)C(O)R^7, -(C_{1-6} alkylene)-CO_2R^7, -(C_{1-6} alkylene)-OC(O)R^7, -(C_{1-6} alkylene)-cyano, -(C_{1-6} alkylene)-O-(C_{1-6} alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl, or hydrogen; or R^4 and R^8 taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring;

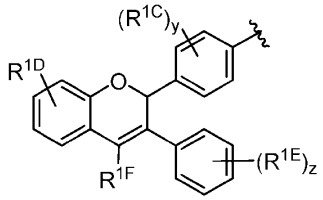
R^5 and R^6 are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom;

R^7 is C_{1-6} alkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

R^8 is hydrogen or C_{1-4} alkyl; and

m is 0, 1, or 2;

TPL is



wherein:

R^{1C} represents independently for each occurrence hydrogen, halo, hydroxyl, or C_{1-4} alkyl;

R^{1D} is hydroxyl;

R^{1E} represents independently for each occurrence halo, hydroxyl, or C_{1-4} alkyl;

R^{1F} is hydrogen or C_{1-4} alkyl;

y is 1 or 2; and

z is 1, 2, or 3; and

L is one of the following:

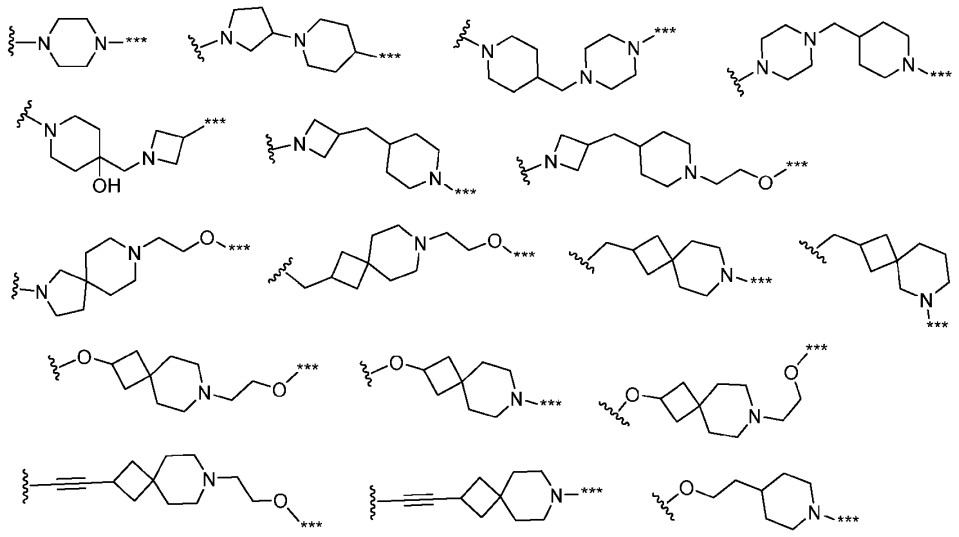
(i) -(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of hydroxyl)-(C_{0-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 heteroatoms selected from nitrogen)-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{1-6} alkylene)-O-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4-6 membered

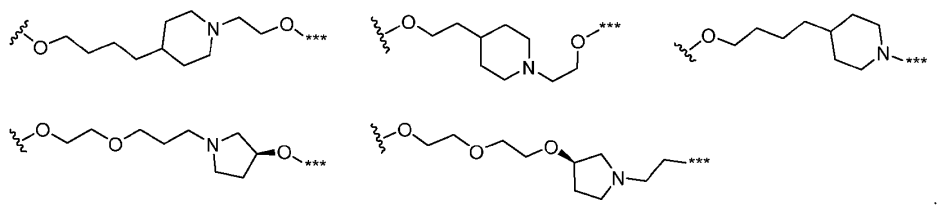
monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL;

(ii) -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -N(H)-[-(C_{1-6} alkylene)-O-]$_{1-6}$-(C_{1-6} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, -N(H)-(C_{1-10} alkylene)-O-***, -N(H)-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of fluoro)-(C_{0-6} alkylene)-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, where *** is a point of attachment to TPL; or

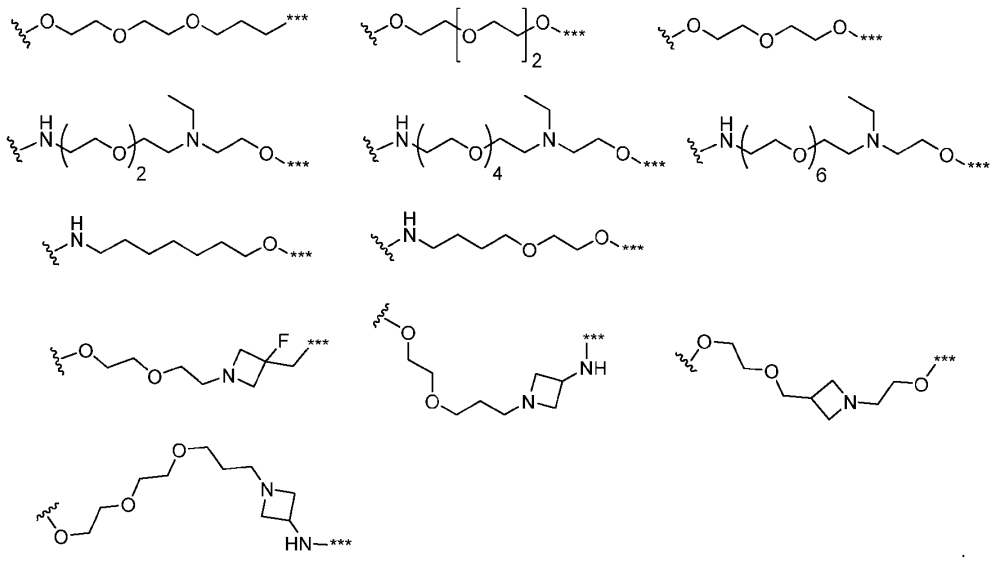
(iii) -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, -(C_{1-10} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, or -(C_{1-15} alkylene)-[-O-(C_{1-6} alkylene)-]$_{1-8}$-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL.

[0372] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:

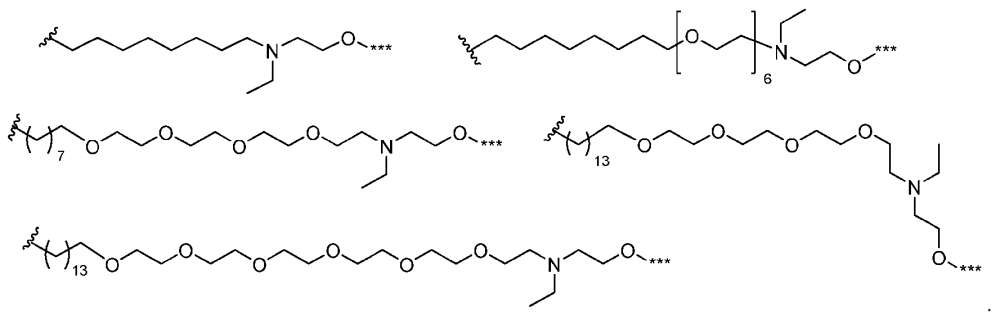




[0373] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



[0374] In certain embodiments, L is one of the following, where *** is a point of attachment to TPL:



Part F: Exemplary Specific Compounds

[0375] Another aspect of the invention provides specific compounds of Formula I or II. In certain embodiments, the compound is a compound described in one of the embodiments below, a stereoisomer thereof, or a pharmaceutically acceptable salt of either of the foregoing. In certain

embodiments, the compound is a compound described in one of the embodiments below, or a stereoisomer thereof.

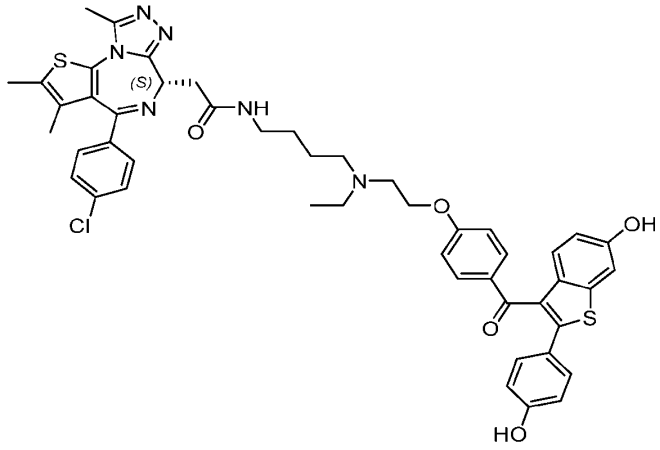
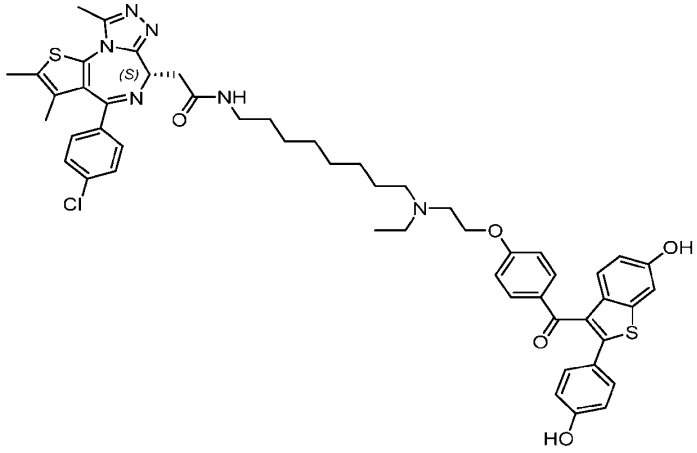
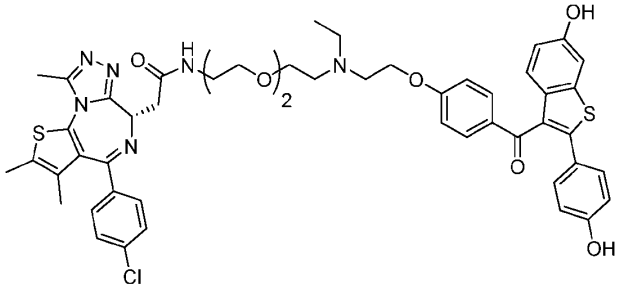
[0376] In certain embodiments, the compound is a compound in Table 1, 2, 3, 4, or 5, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1, 2, 3, 4, or 5. In certain embodiments, the compound is a compound in Table 1, 3, 4, or 5, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1, 3, 4, or 5. In certain embodiments, the compound is a compound in Table 3, 4, or 5, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 3, 4, or 5.

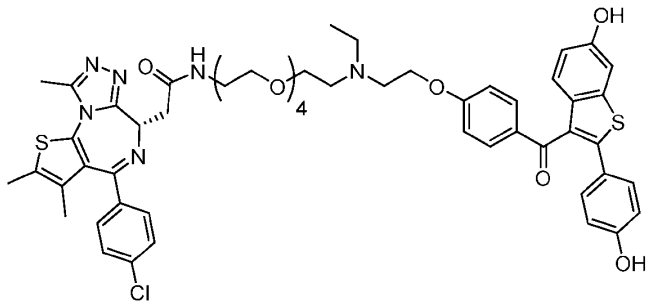
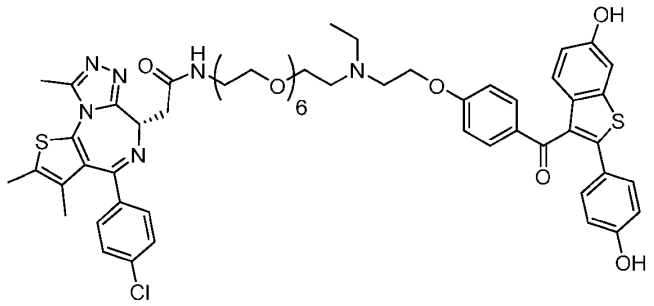
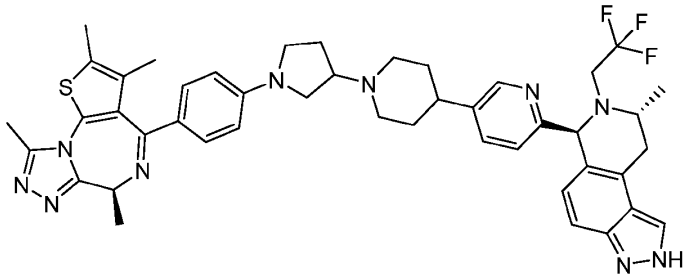
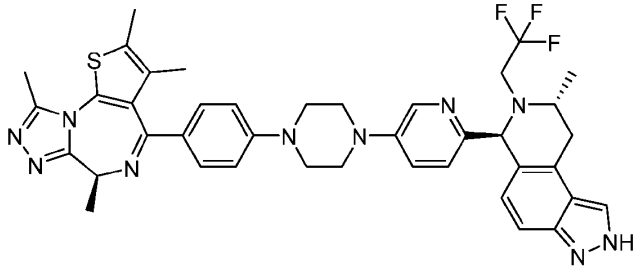
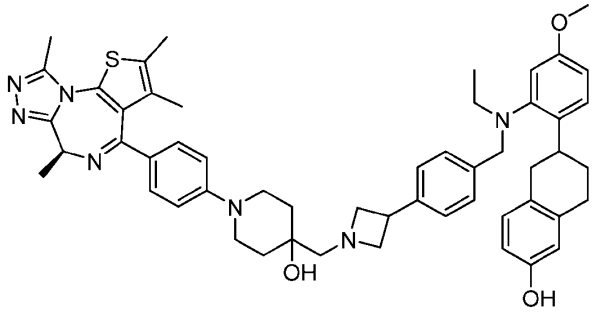
[0377] In certain embodiments, the compound is a compound in Table 1 or 3, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula I-A, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1 or 3, wherein the compound is a compound of Formula I-A. In certain embodiments, the compound is a compound in Table 1 or 3, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula I-A-1, I-A-2, I-A-3, I-A-4, I-A-3*, I-A-4*, I-A-3**, I-A-4**, I-A-5, I-A-6, or I-A-7, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1 or 3, wherein the compound is a compound of Formula I-A-1, I-A-2, I-A-3, I-A-4, I-A-3*, I-A-4*, I-A-3**, I-A-4**, I-A-5, I-A-6, or I-A-7. In certain embodiments, the compound is a compound in Table 1 or 4, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula I-B or I-B-1, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1 or 4, wherein the compound is a compound of Formula I-B or I-B-1.

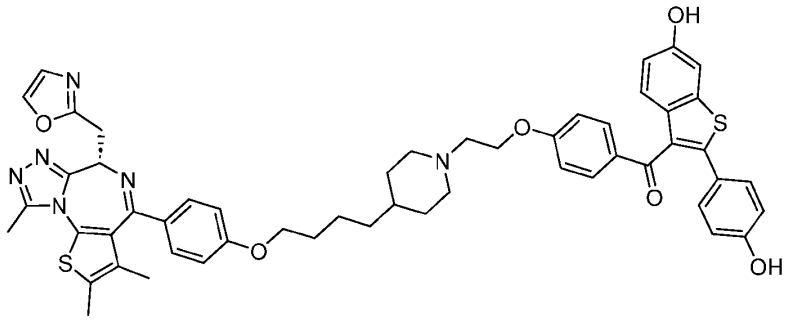
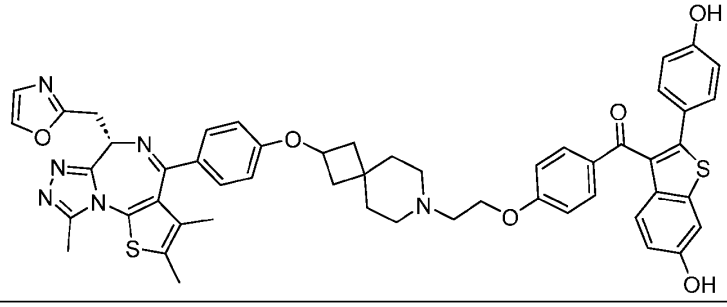
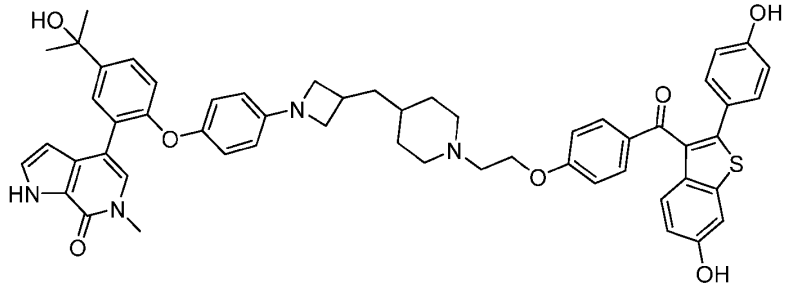
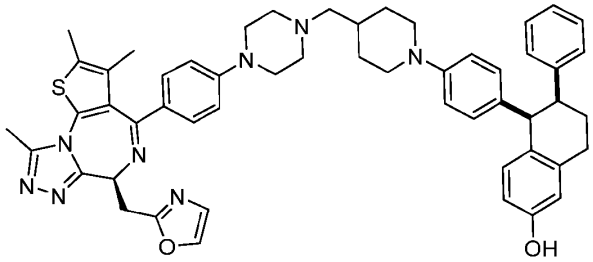
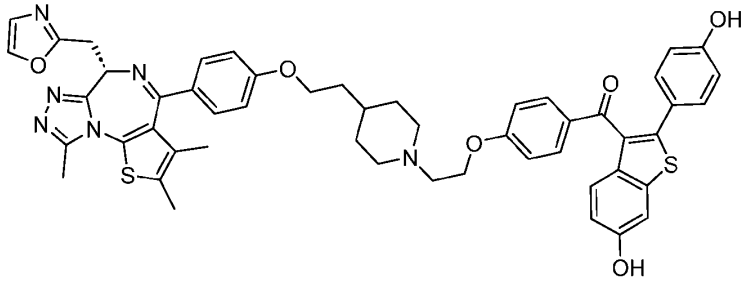
[0378] In certain embodiments, the compound is one of compounds III-244, III-245, III-250, III-251, III-275, III-276, III-307, III-308, III-311, III-312, III-321, III-322, III-327, III-328, or III-333 through III-346, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is one of compounds III-244, III-245, III-250, III-251, III-275, III-276, III-307, III-308, III-311, III-312, III-321, III-322, III-327, III-328, or III-333 through III-346. In certain embodiments, the compound is one of compounds III-245, III-251, III-276, III-307, III-311, III-321, III-328, III-334, III-336, III-338, III-339, III-341, III-344, or III-346, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is one of compounds III-245, III-251, III-276, III-307, III-311, III-321, III-328, III-334, III-336, III-338, III-339, III-341, III-344, or III-346.

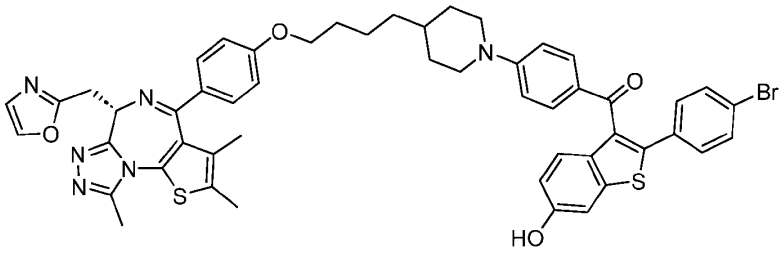
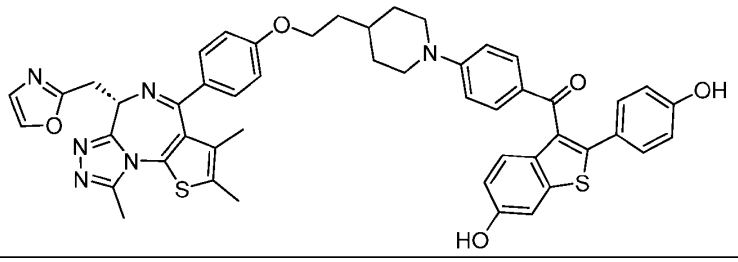
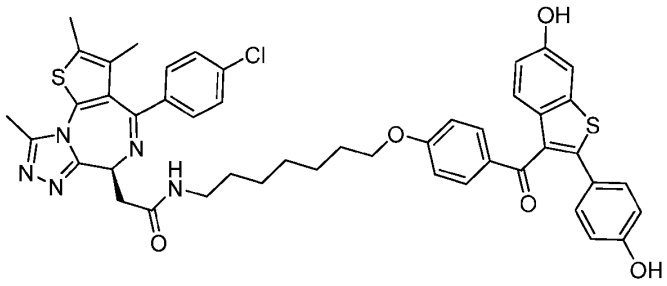
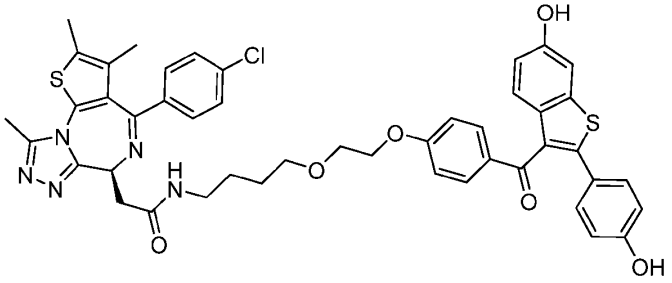
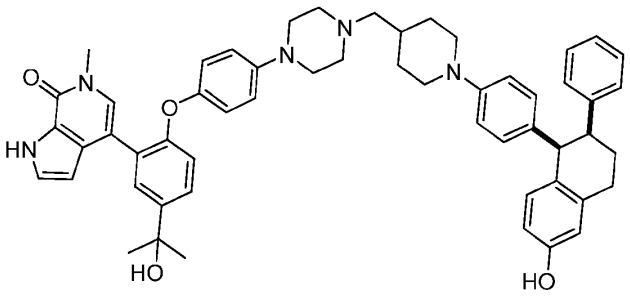
[0379] In certain embodiments, the compound is a compound in Table 1, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1.

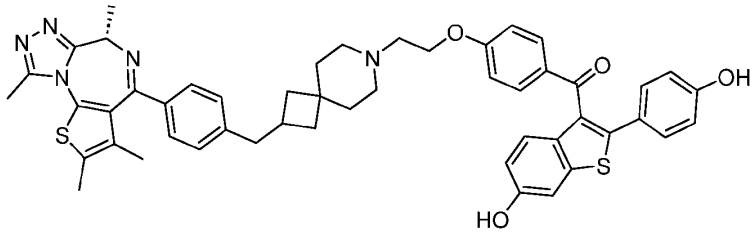
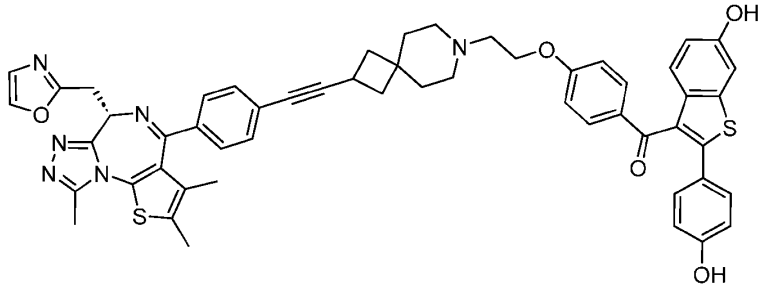
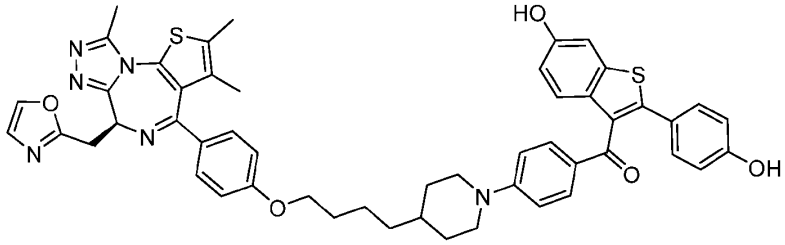
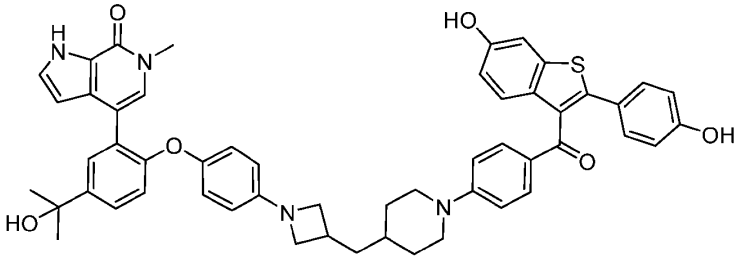
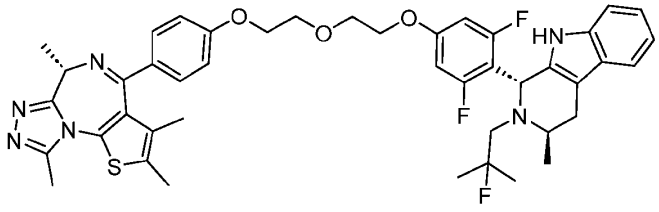
TABLE 1.

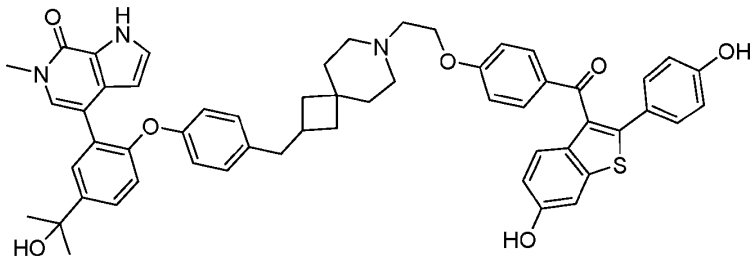
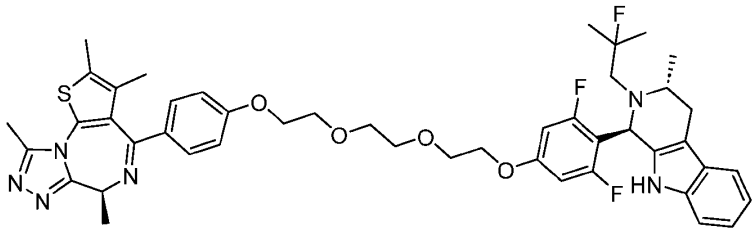
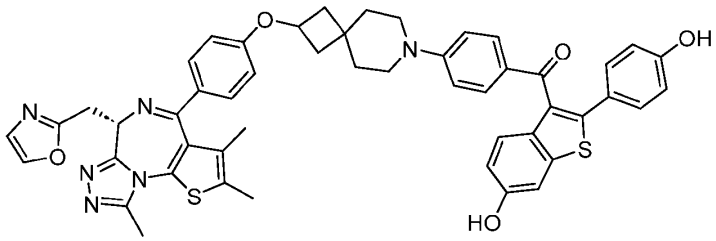
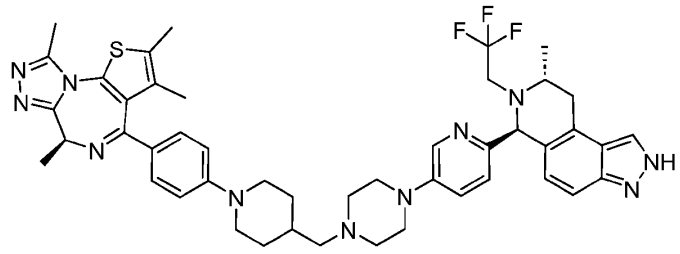
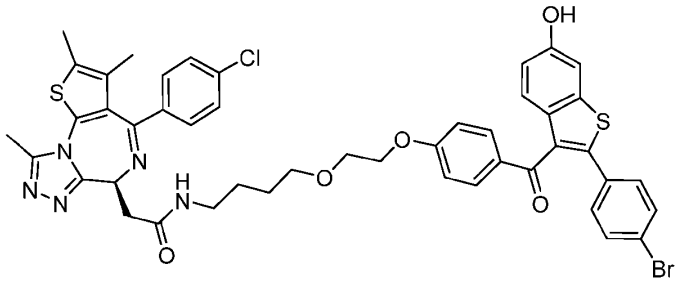
Compound No.	Structure
I-1	
I-2	
I-3	

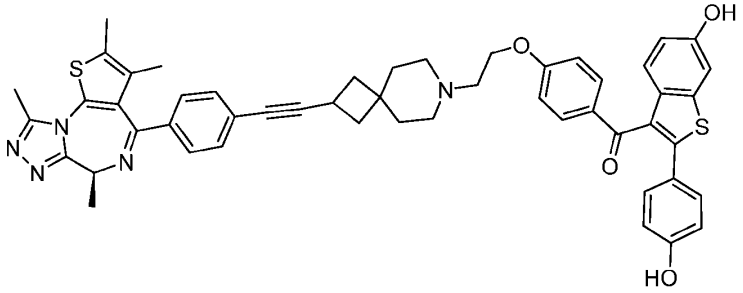
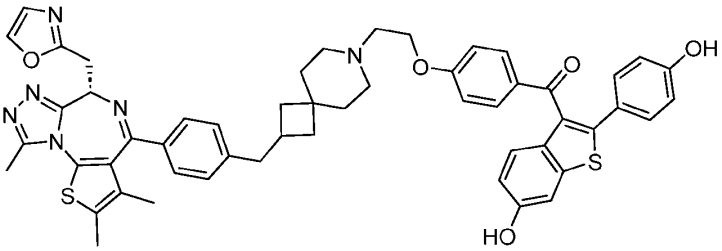
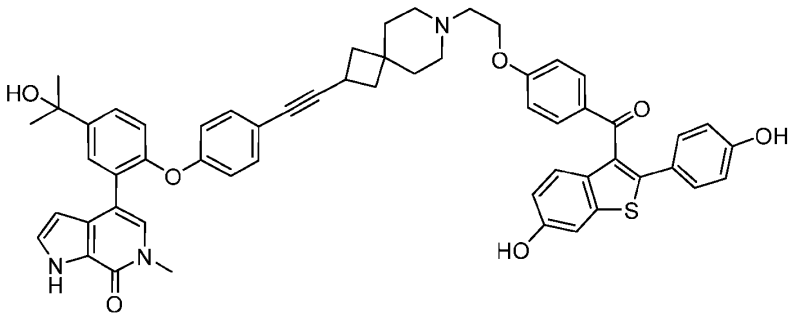
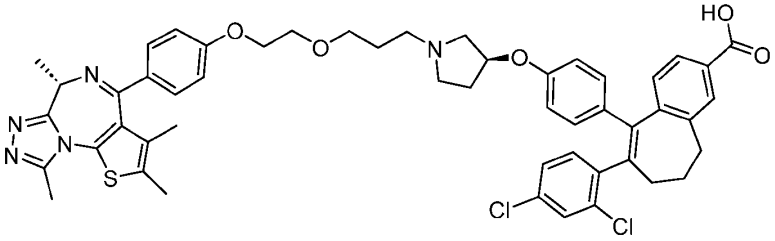
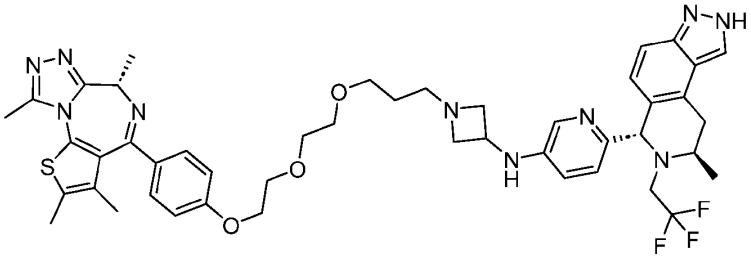
I-4	
I-5	
I-6	
I-7	
I-8	

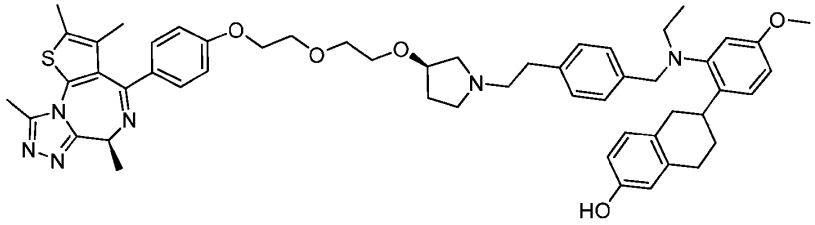
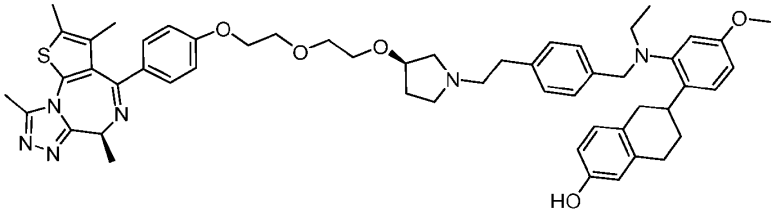
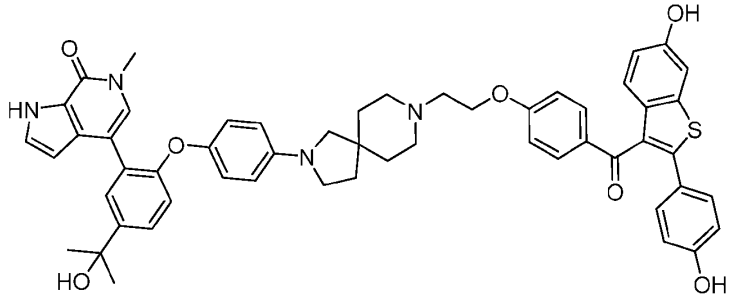
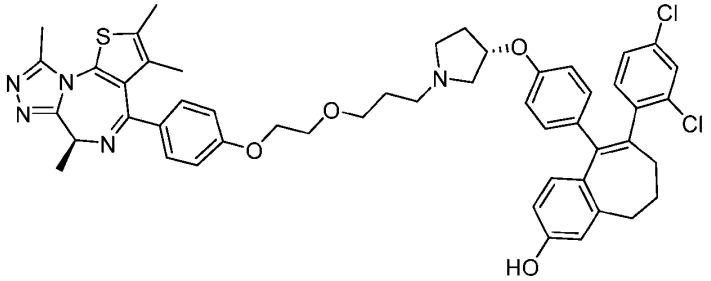
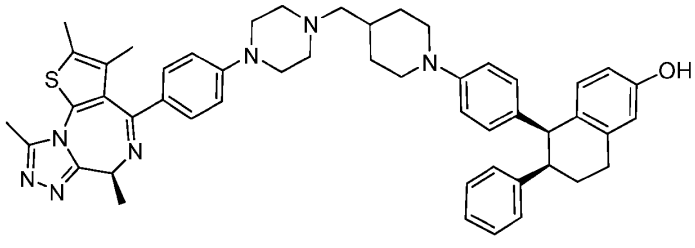
I-9	
I-10	
I-11	
I-12	
I-13	

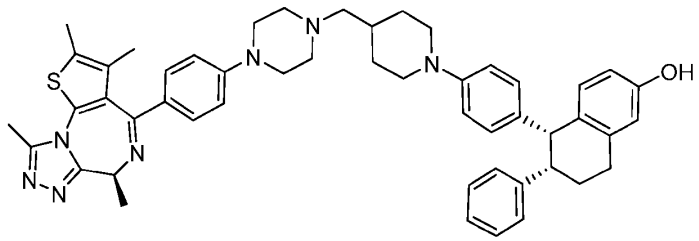
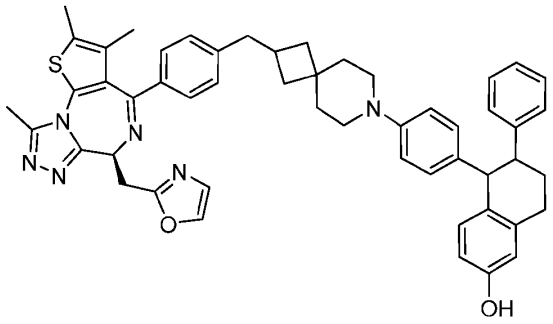
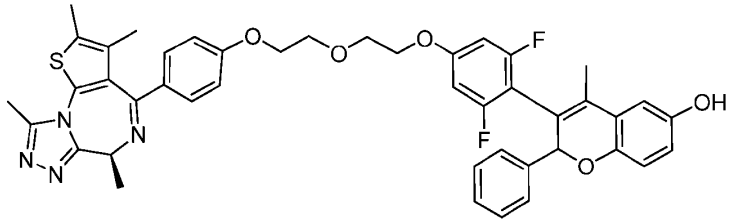
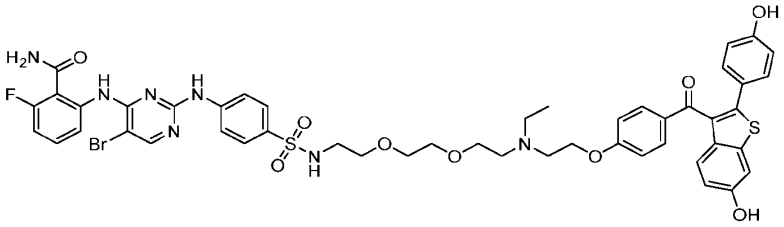
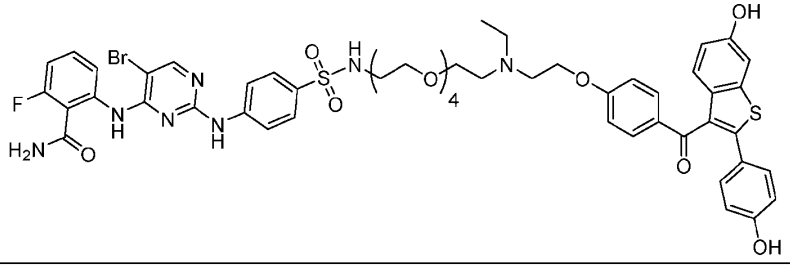
I-14	
I-15	
I-16	
I-17	
I-18	

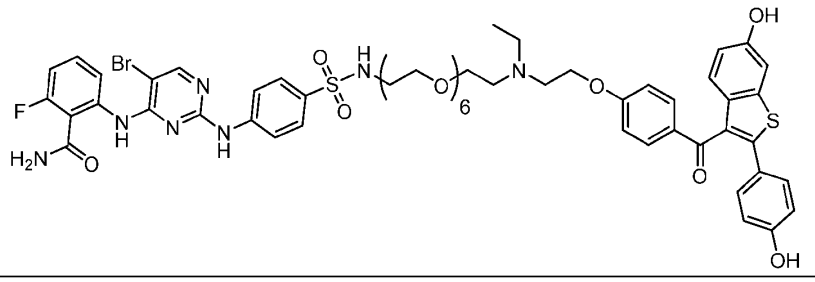
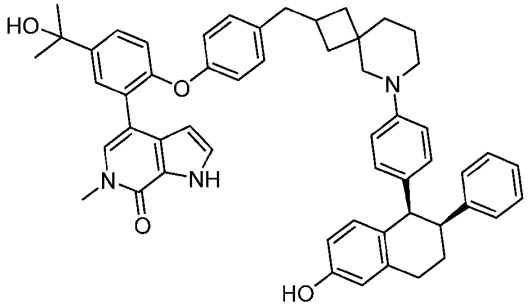
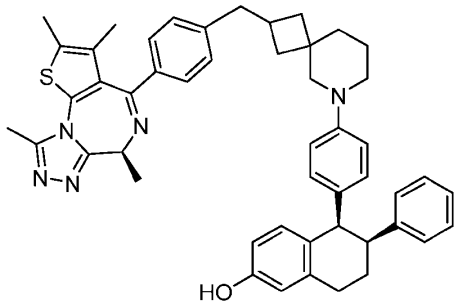
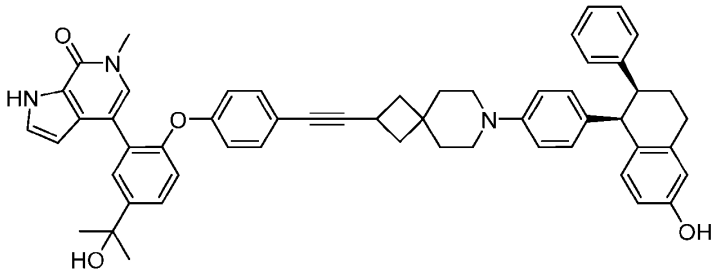
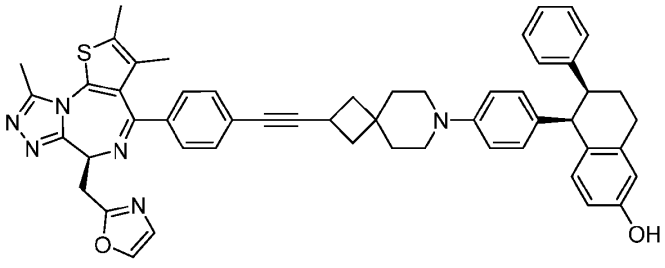
I-19	
I-20	
I-21	
I-22	
I-23	

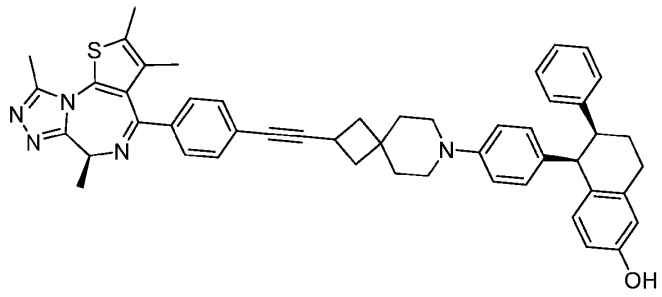
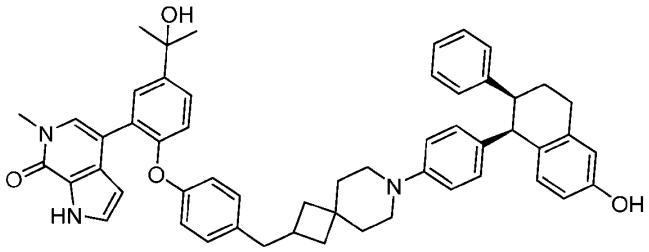
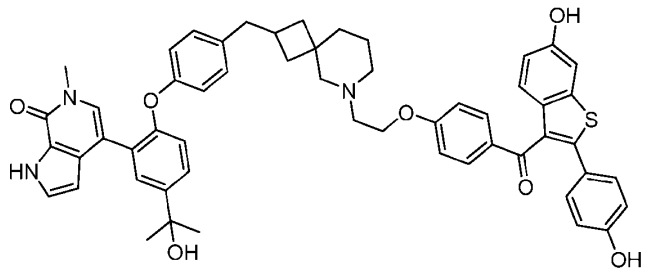
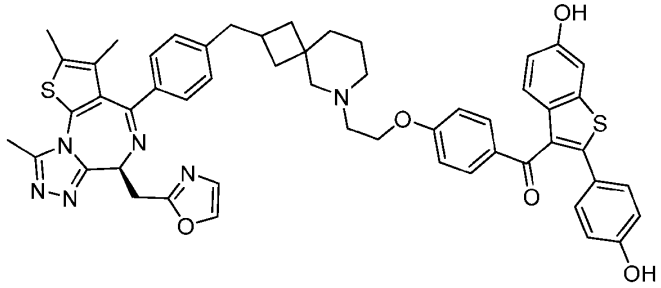
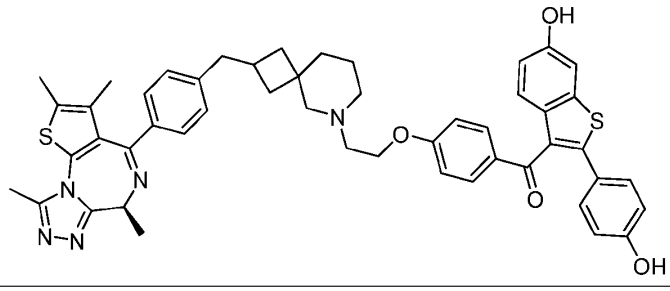
I-24	
I-25	
I-26	
I-27	
I-28	

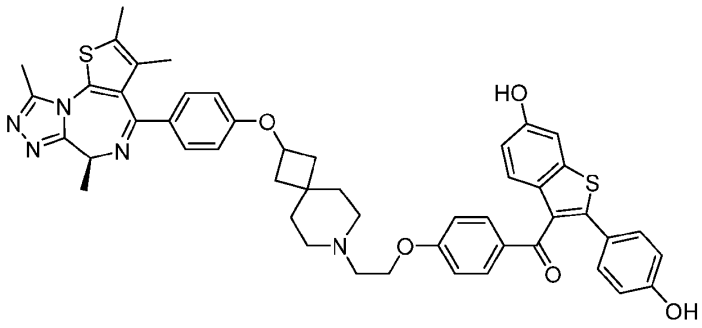
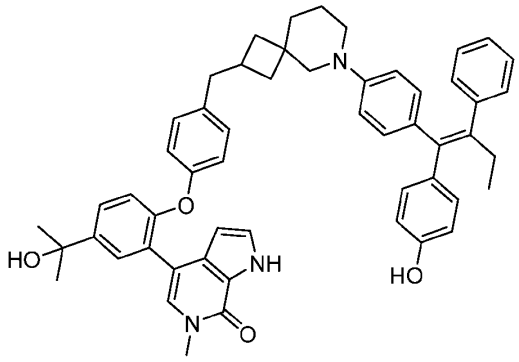
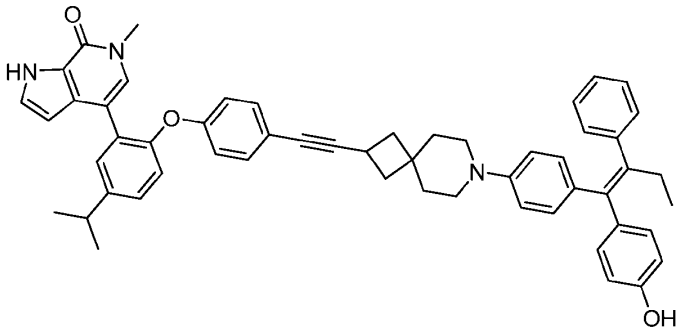
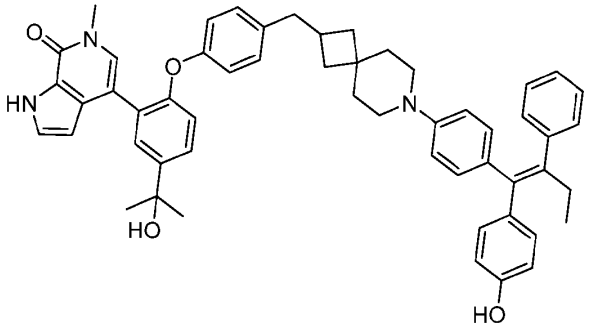
I-29	
I-30	
I-31	
I-32	
I-33	

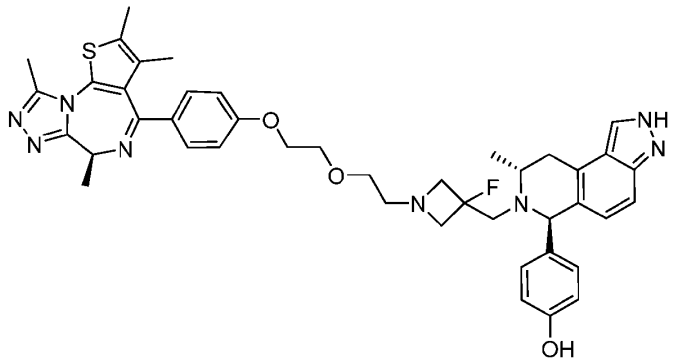
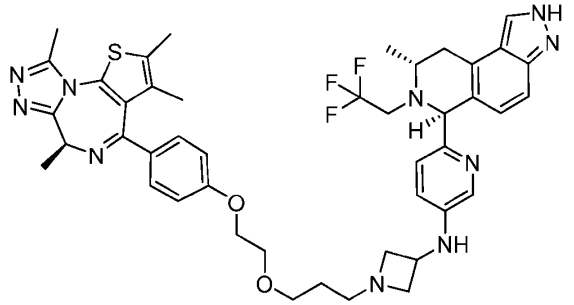
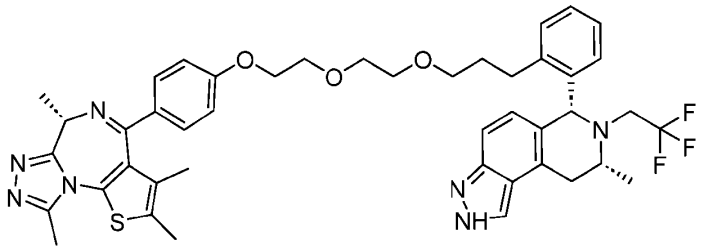
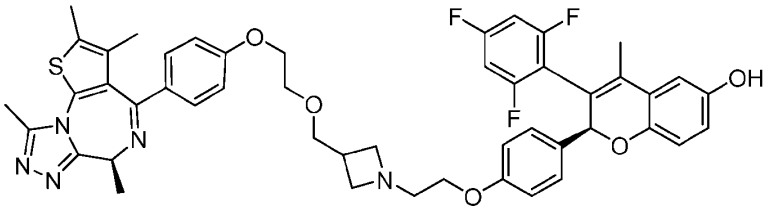
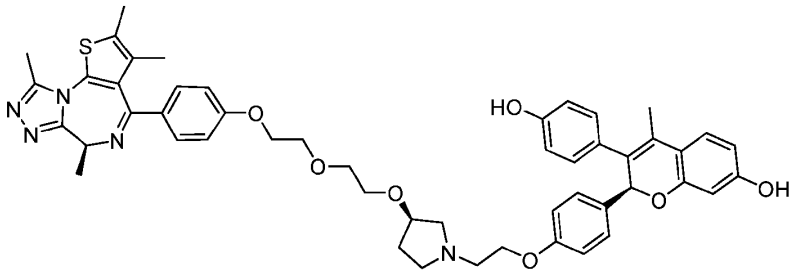
I-34a	 Stereoisomer I
I-34b	 Stereoisomer II
I-35	
I-36	
I-37a	

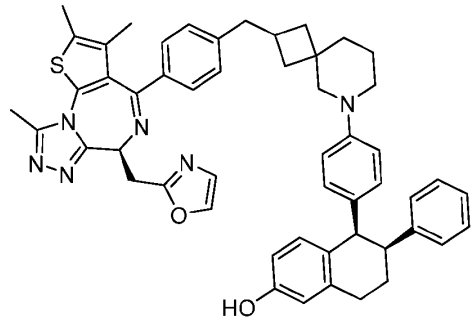
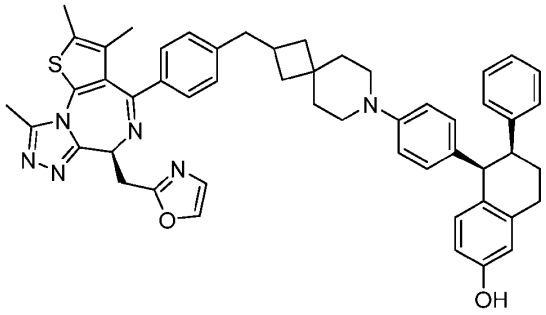
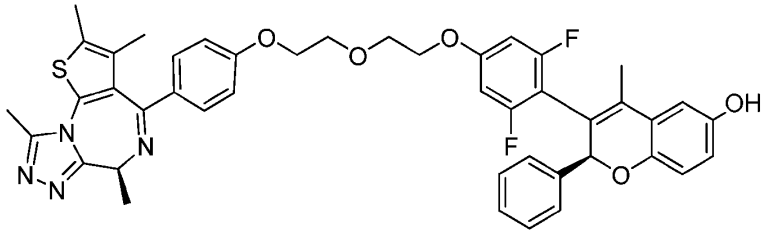
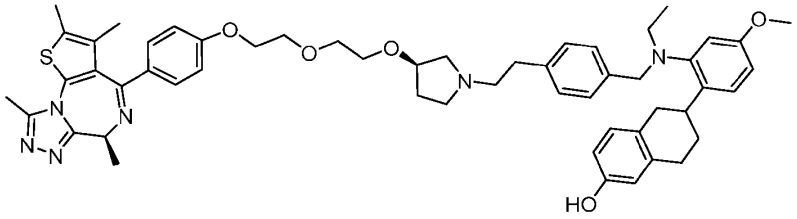
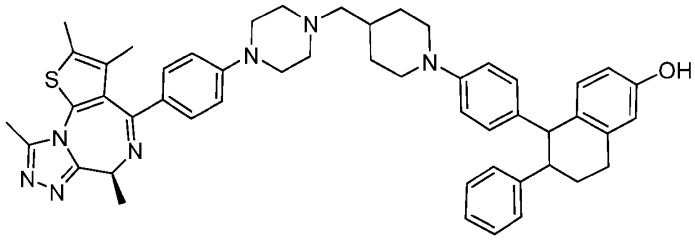
I-37b	
I-38	
I-39	 Mixture of Stereoisomer I and Stereoisomer II
I-40	
I-41	

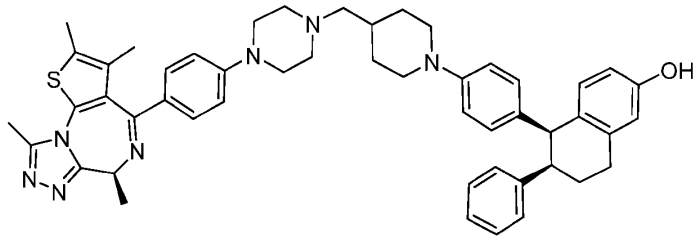
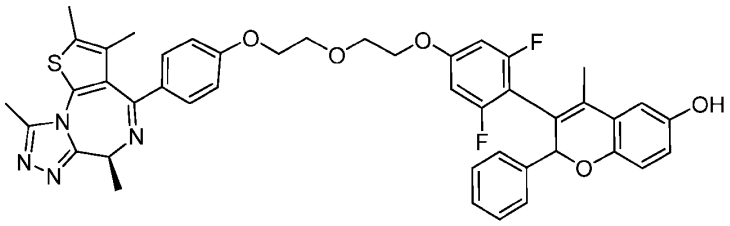
I-42	
I-43	
I-44	
I-45	
I-46	

I-47	
I-48	
I-49	
I-50	
I-51	

I-52	
I-53	
I-54	
I-55	

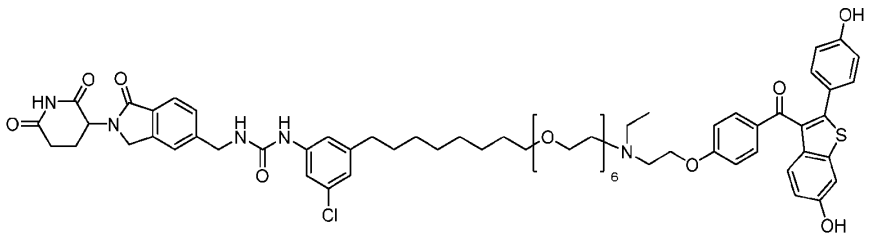
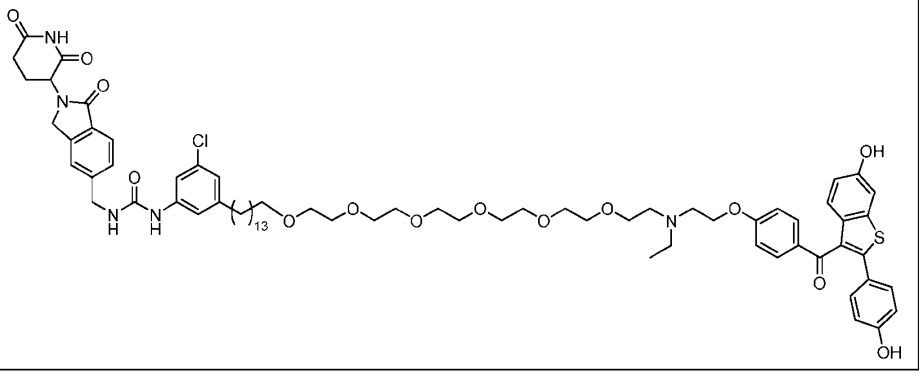
I-56	
I-57	
I-58	
I-59	
I-60	

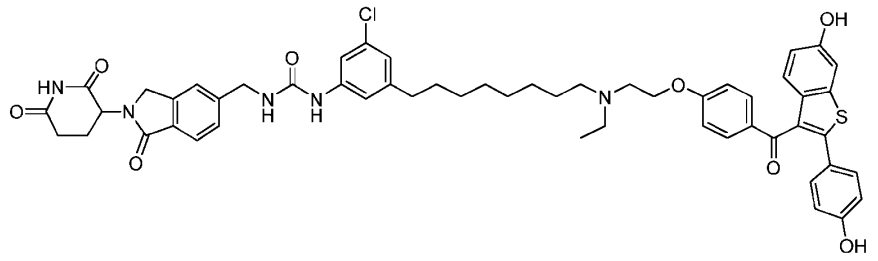
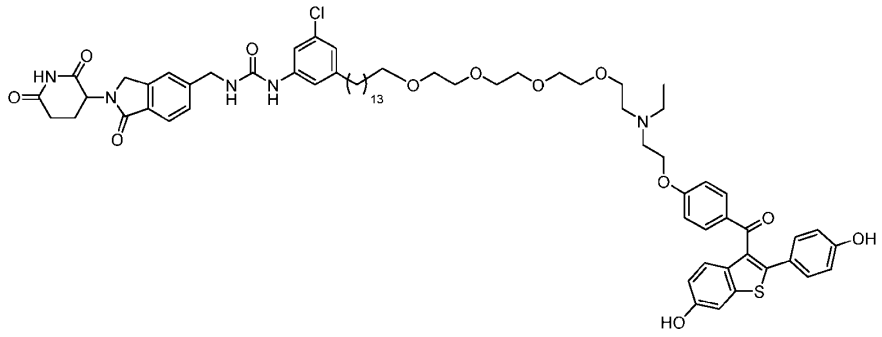
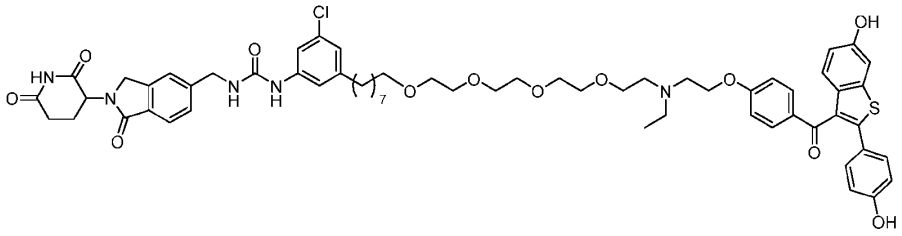
I-61	
I-62	
I-63	
I-64	
I-65	

I-66	
I-67	

[0380] In certain embodiments, the compound is a compound in Table 2, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 2.

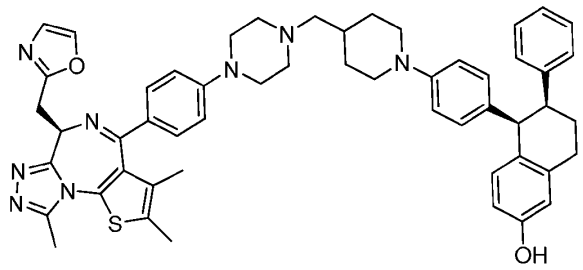
TABLE 2.

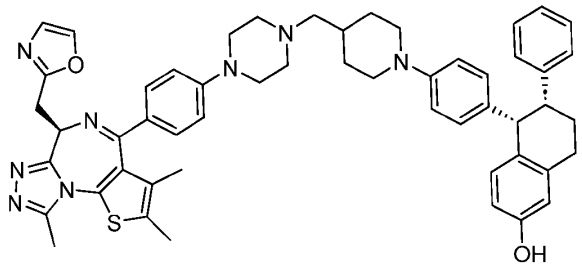
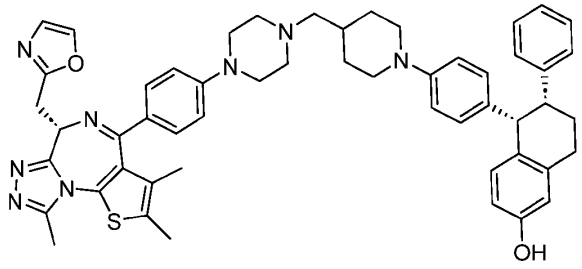
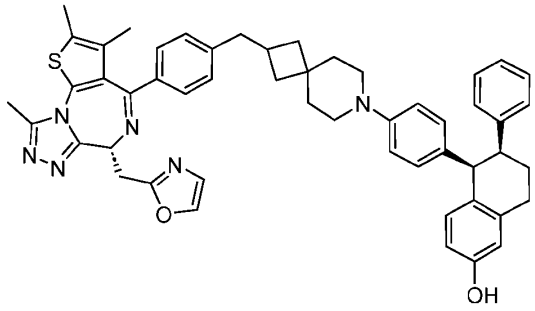
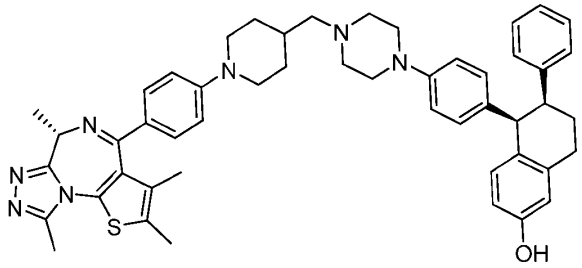
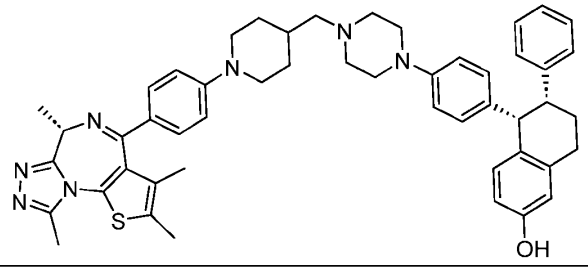
Compound No.	Structure
II-1	
II-2	

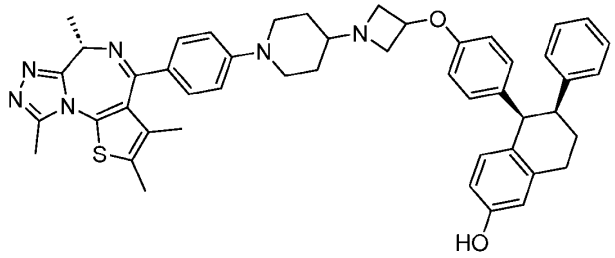
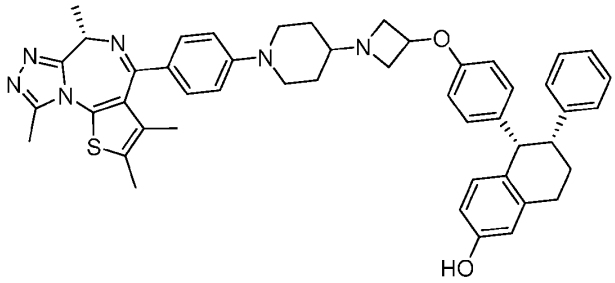
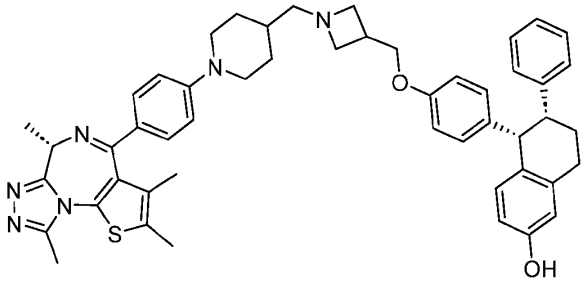
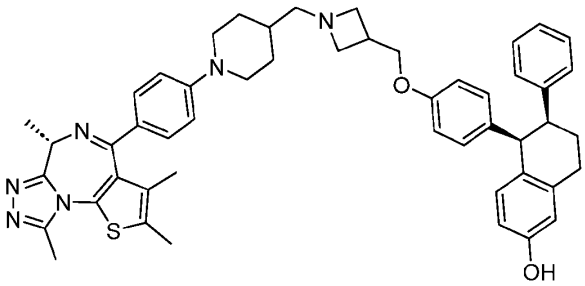
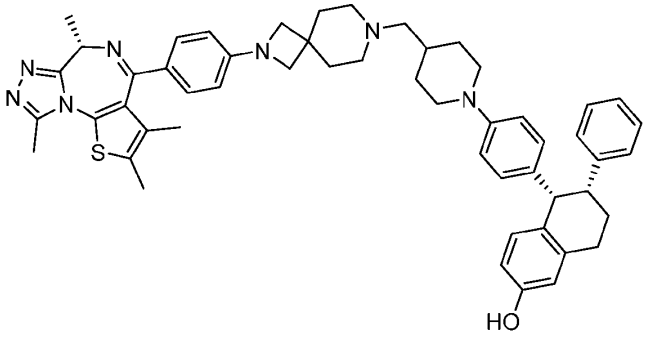
II-3	
II-4	
II-5	

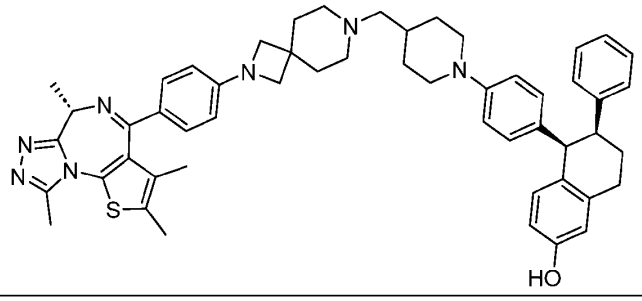
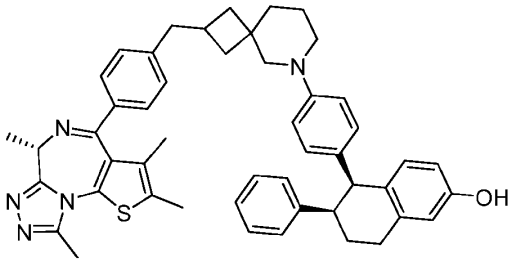
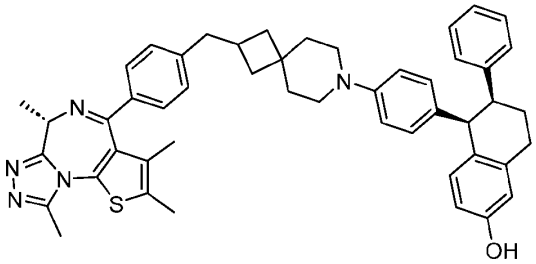
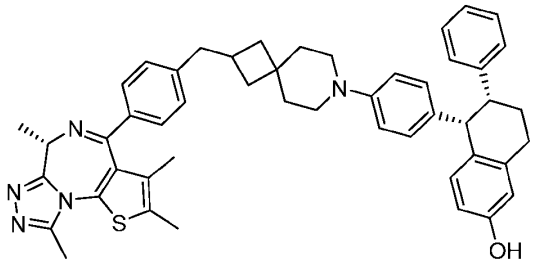
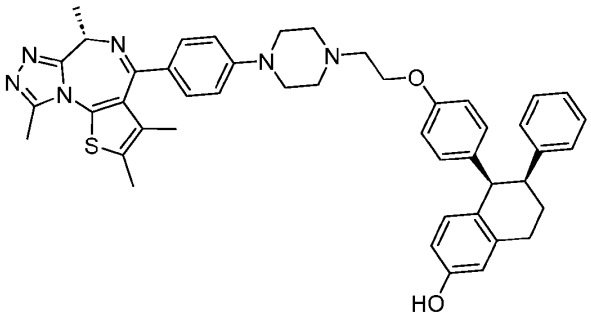
[0381] In certain embodiments, the compound is a compound in Table 3, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 3.

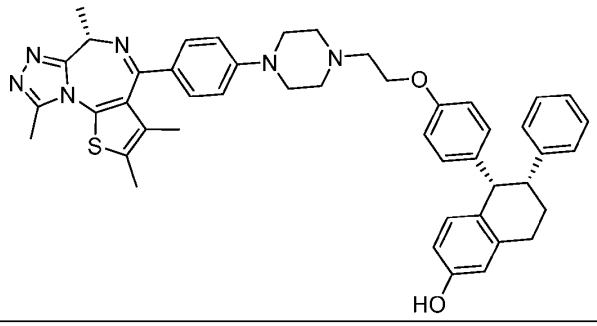
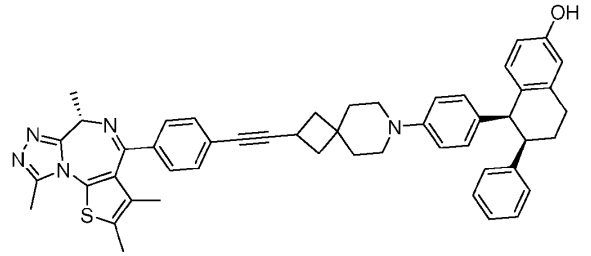
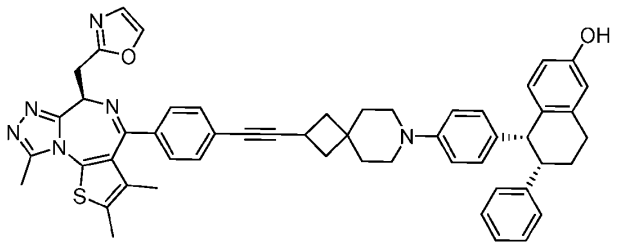
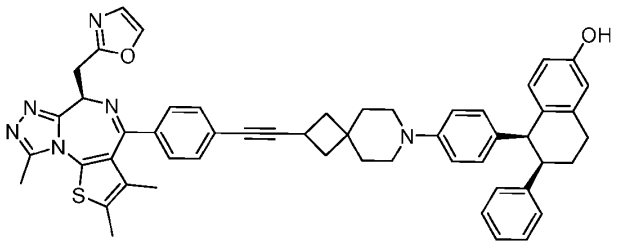
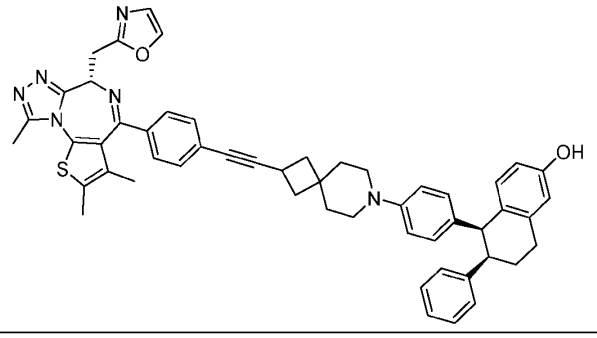
TABLE 3.

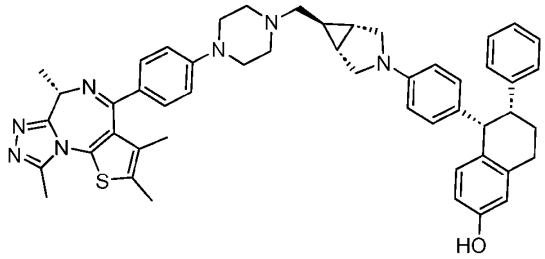
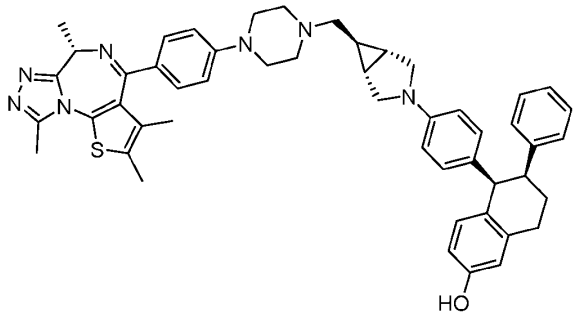
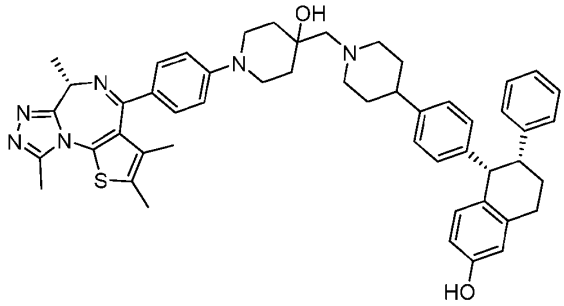
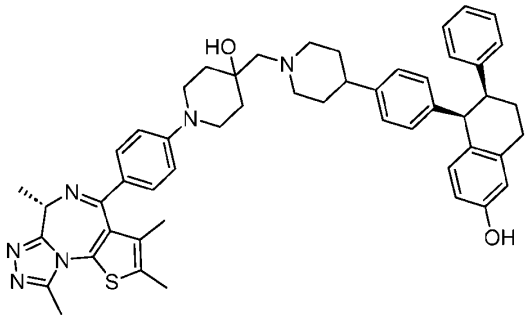
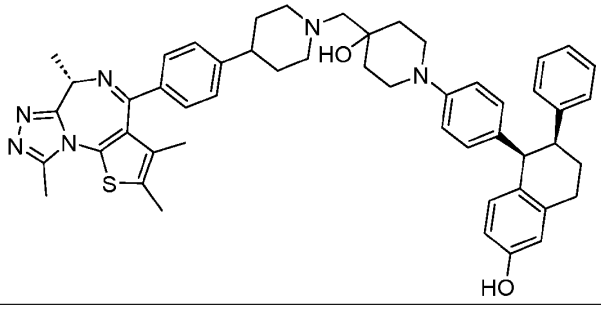
Compound No.	Compound Structure
III-1	

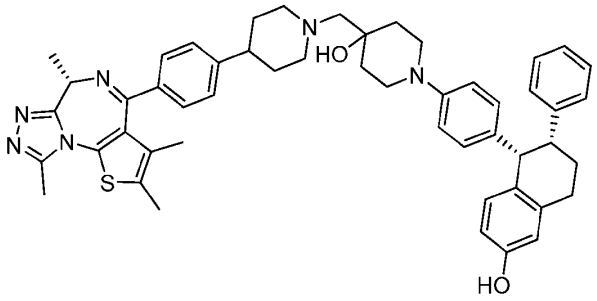
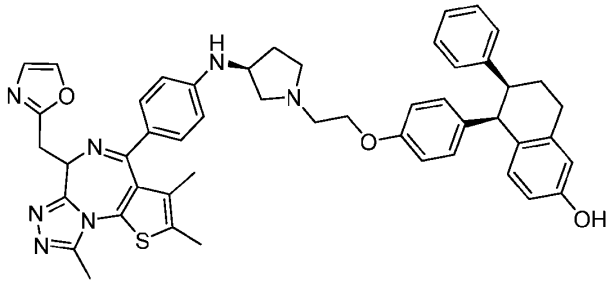
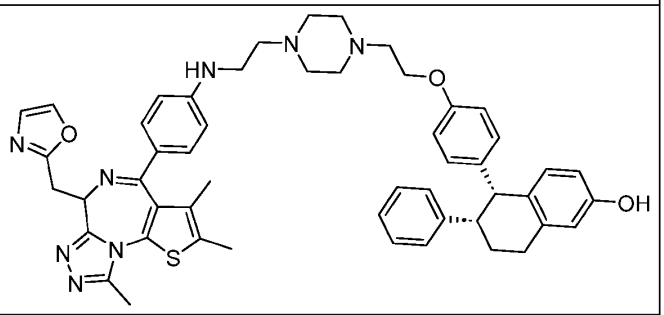
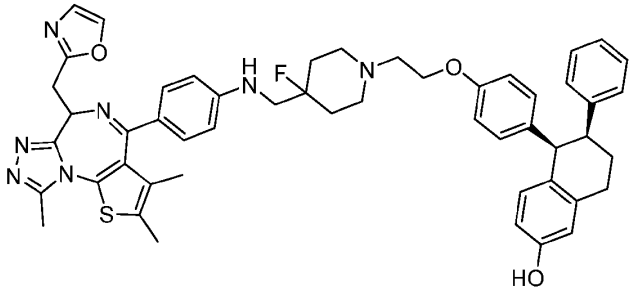
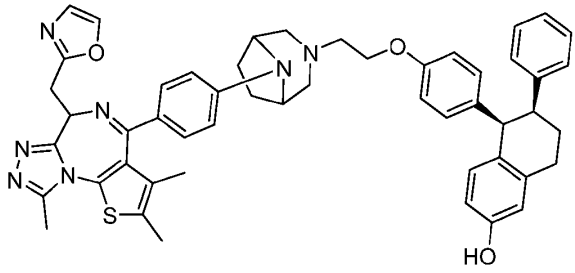
III-2	
III-3	
III-4	
III-5	
III-6	

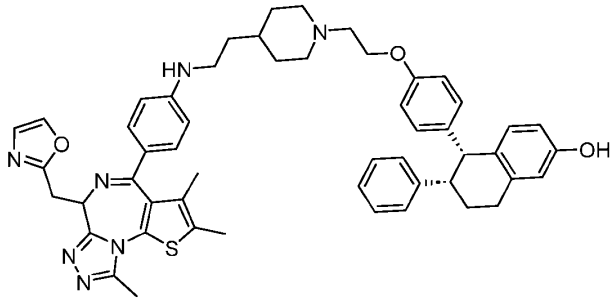
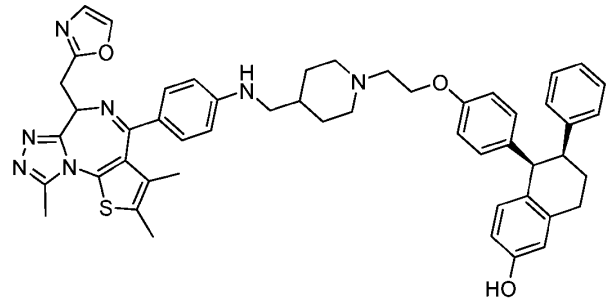
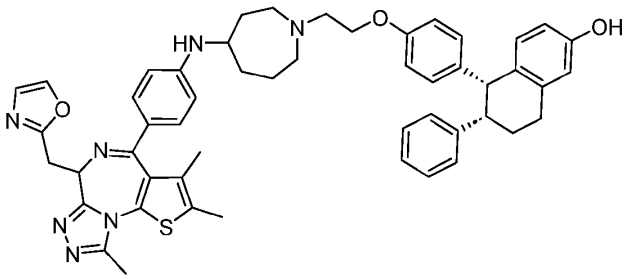
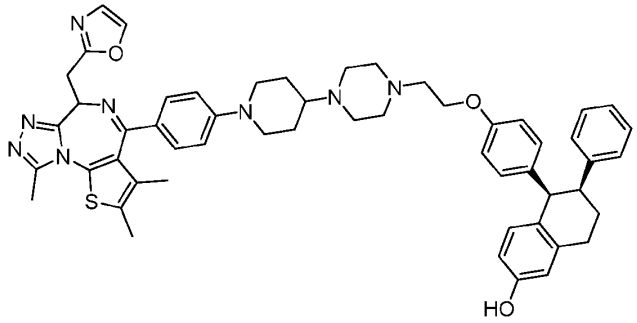
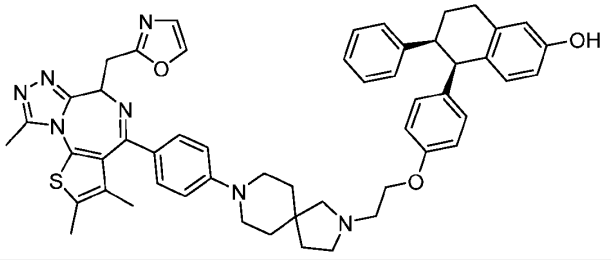
III-7	
III-8	
III-9	
III-10	
III-11	

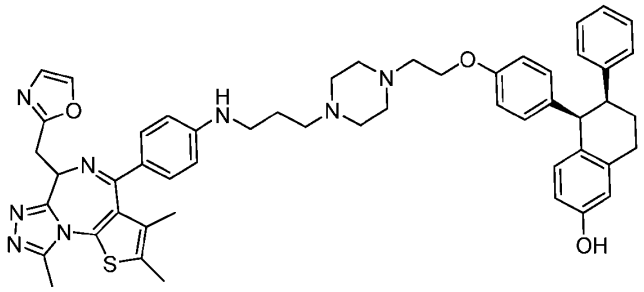
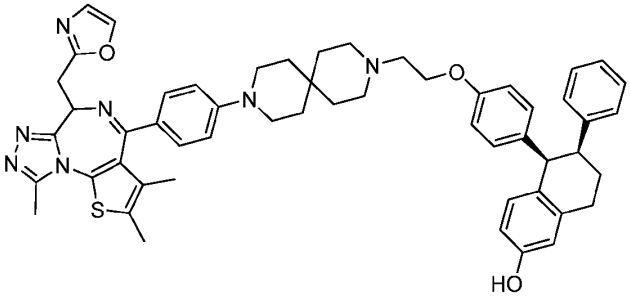
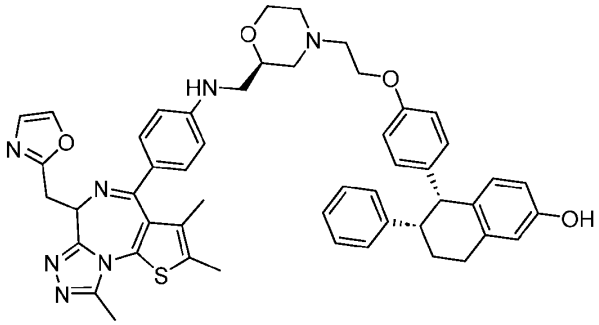
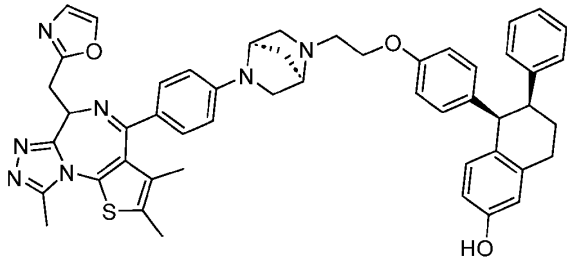
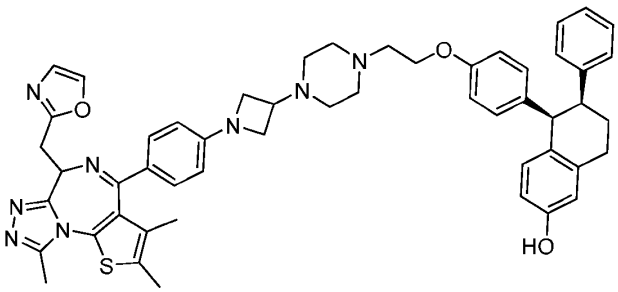
III-12	
III-13	
III-14	
III-15	
III-16	

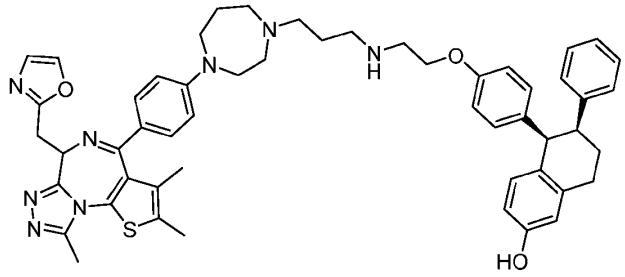
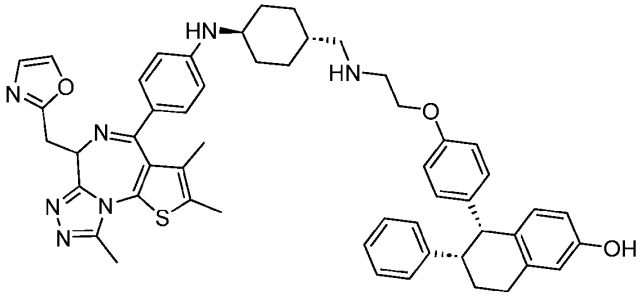
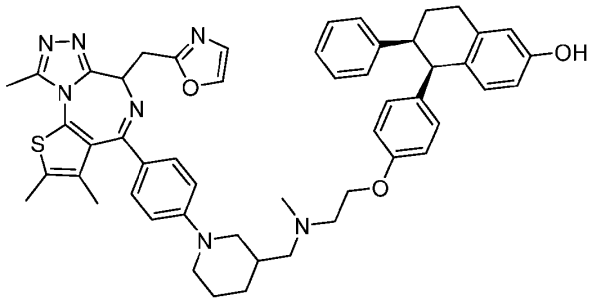
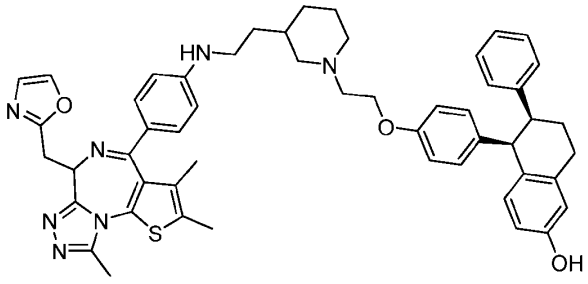
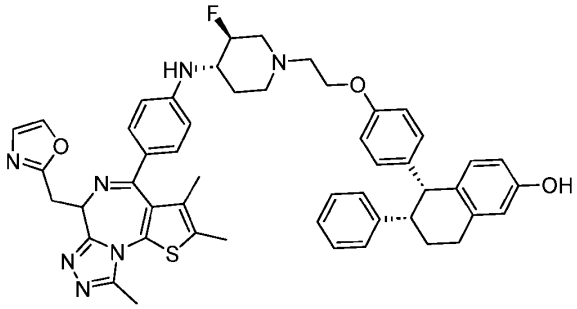
III-17	
III-18	
III-19	
III-20	
III-21	

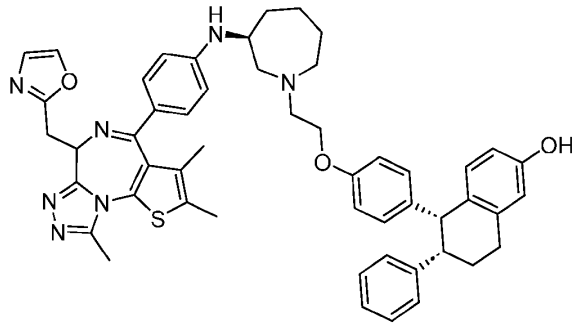
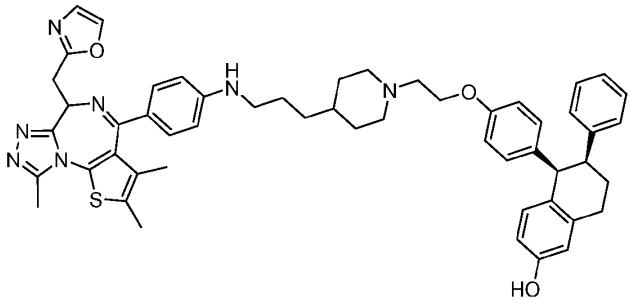
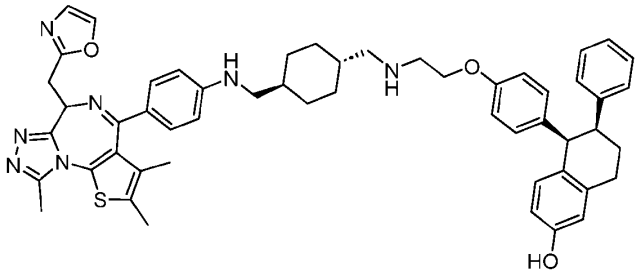
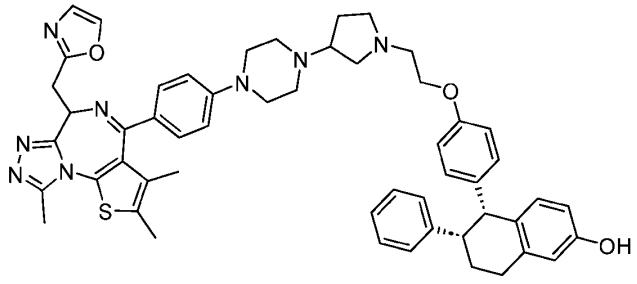
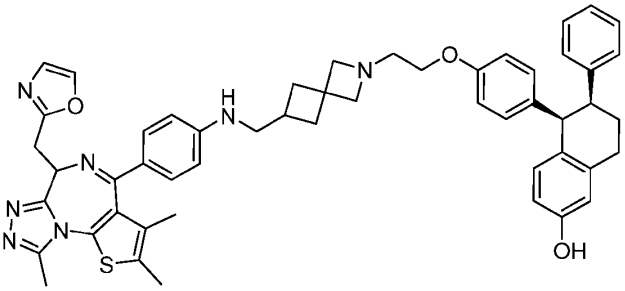
III-22	
III-23	
III-24	
III-25	
III-26	

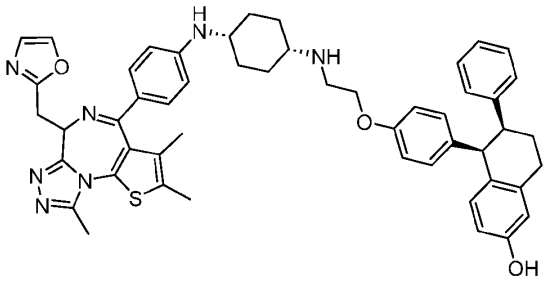
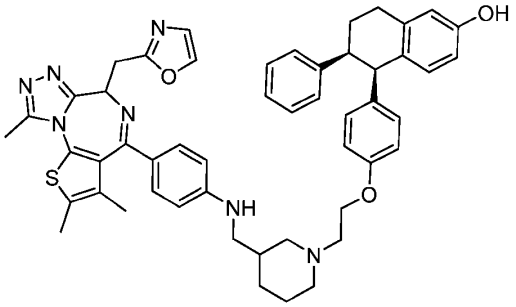
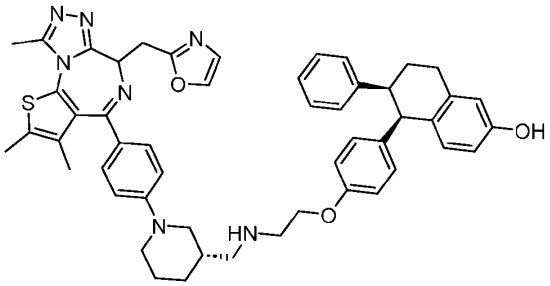
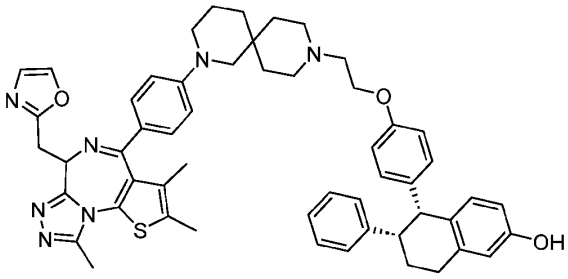
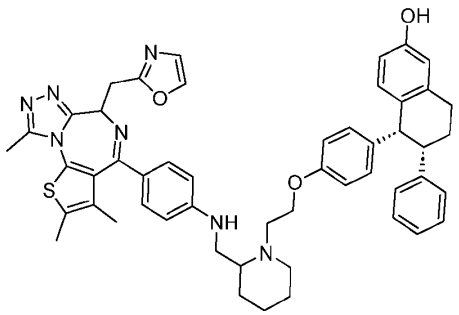
III-27	
III-28	
III-29	
III-30	
III-31	

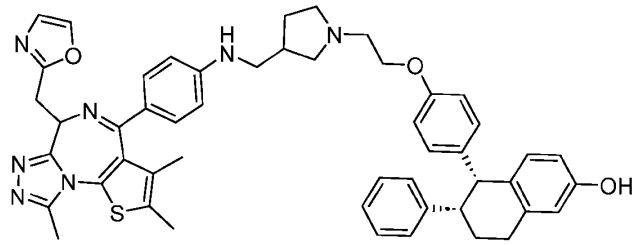
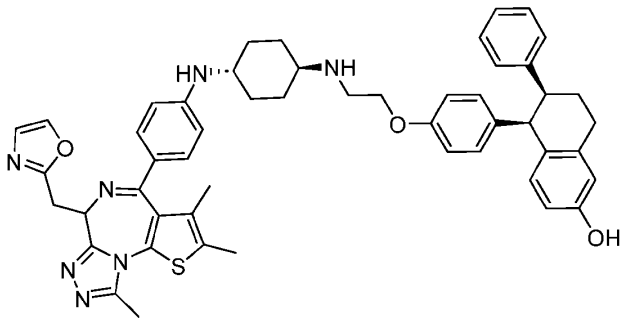
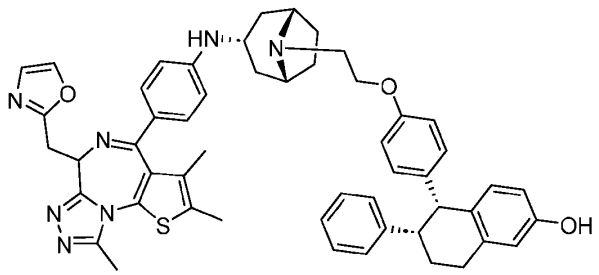
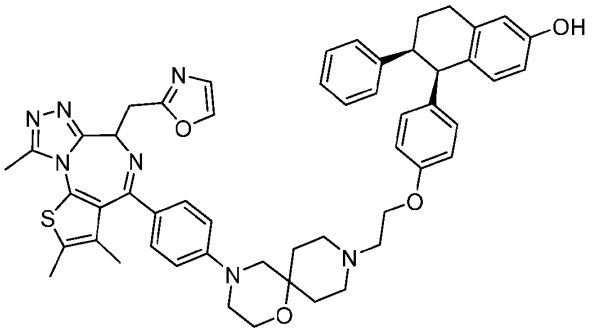
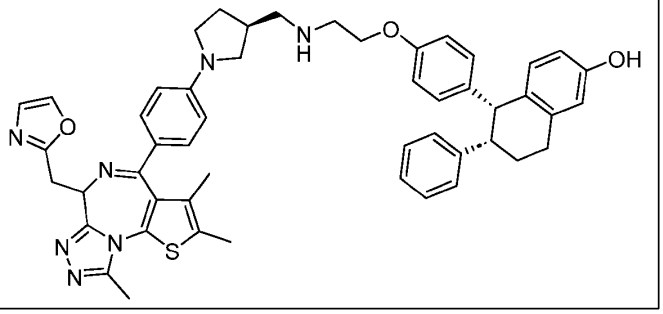
III-32	
III-33	
III-34	
III-35	
III-36	

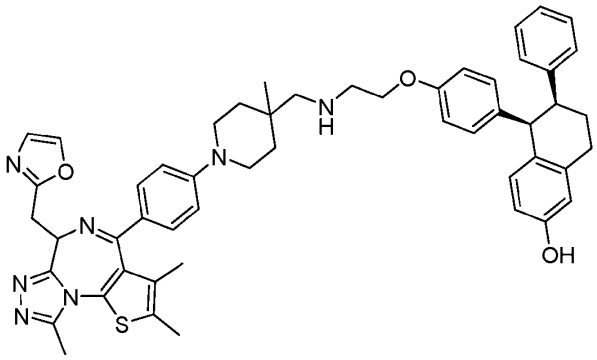
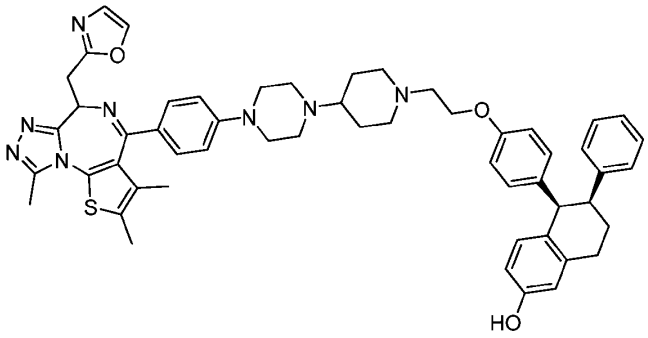
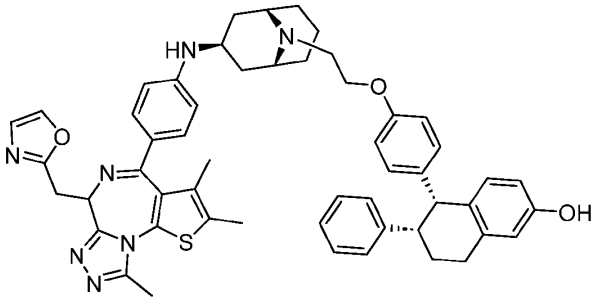
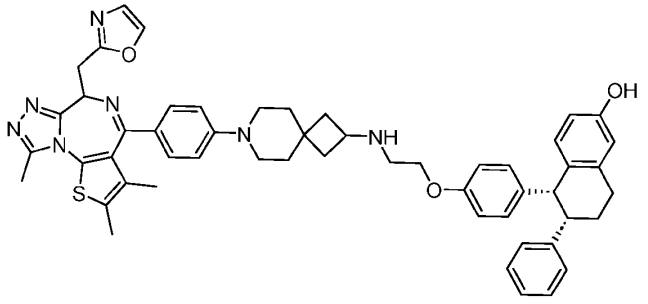
III-37	
III-38	
III-39	
III-40	
III-41	

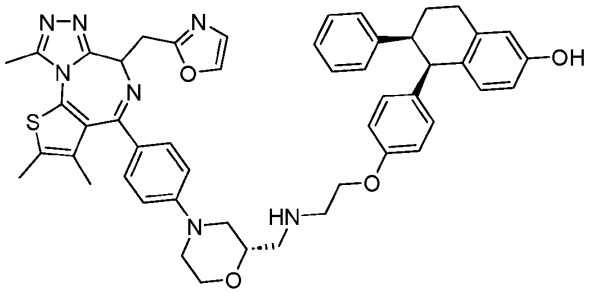
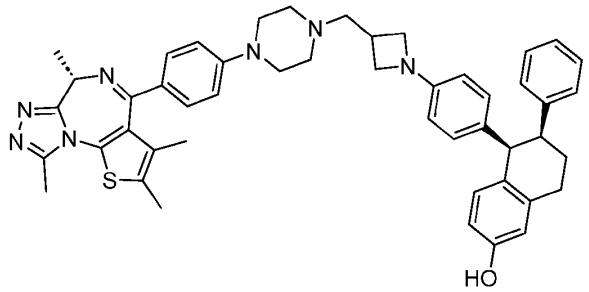
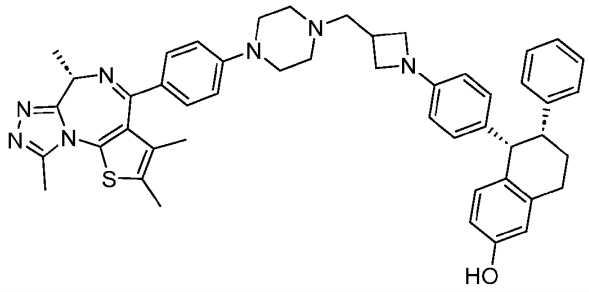
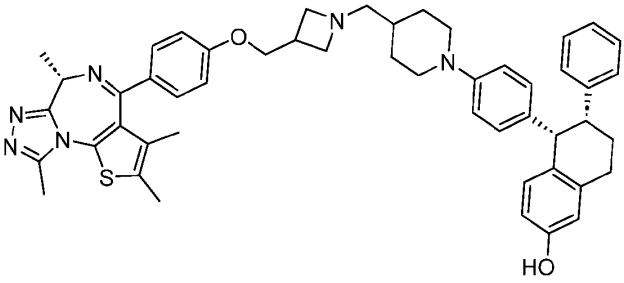
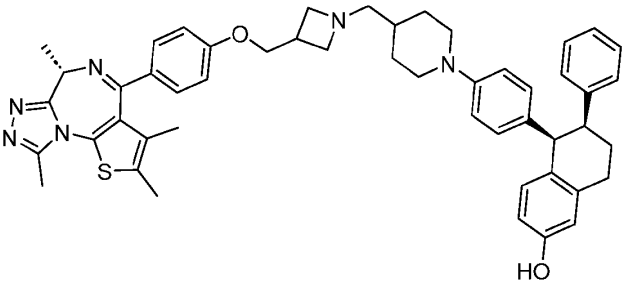
III-42	
III-43	
III-44	
III-45	
III-46	

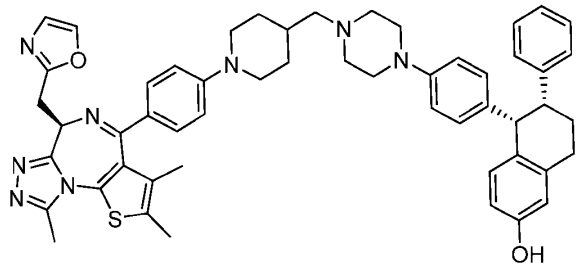
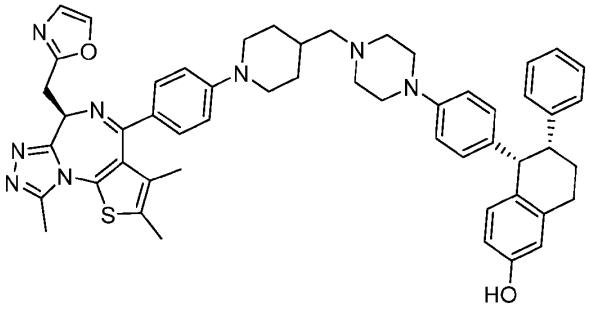
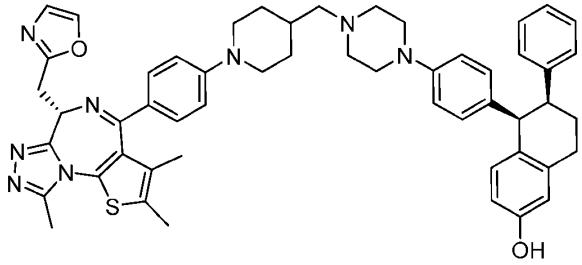
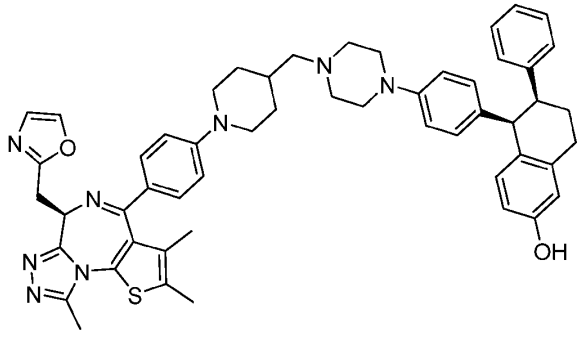
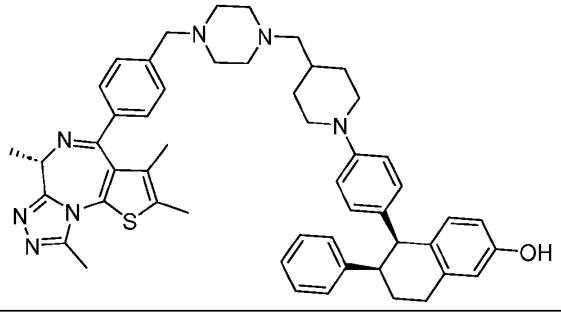
III-47	
III-48	
III-49	
III-50	
III-51	

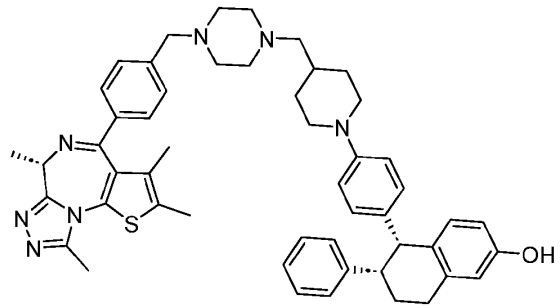
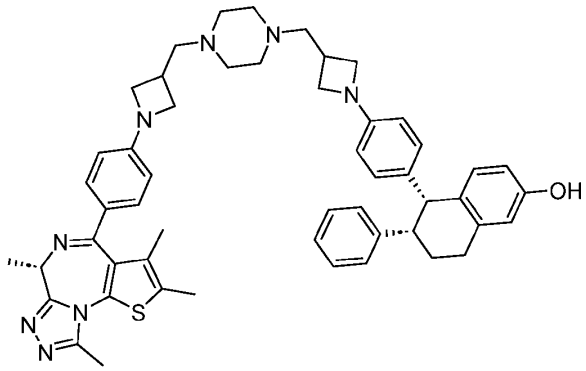
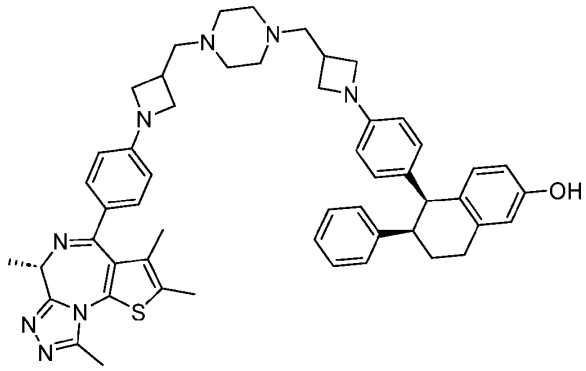
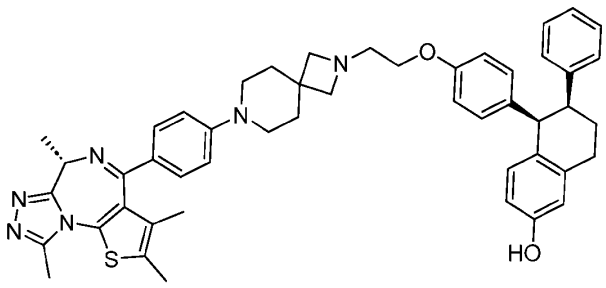
III-52	
III-53	
III-54	
III-55	
III-56	

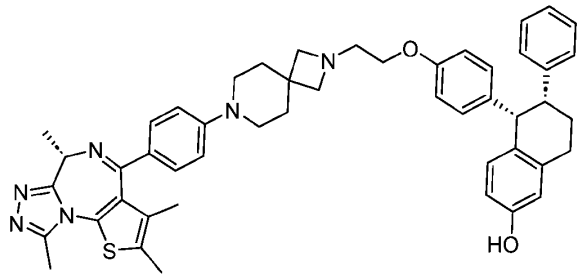
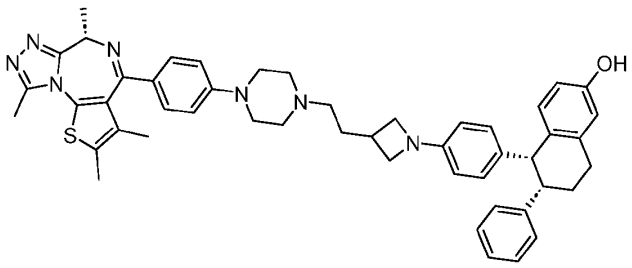
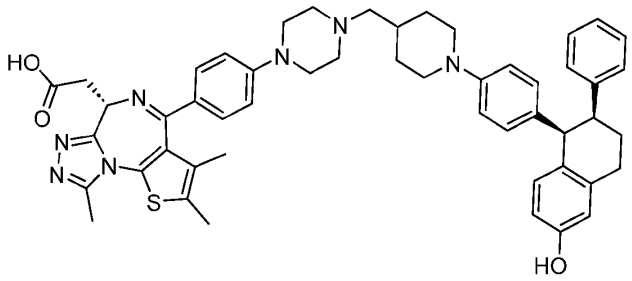
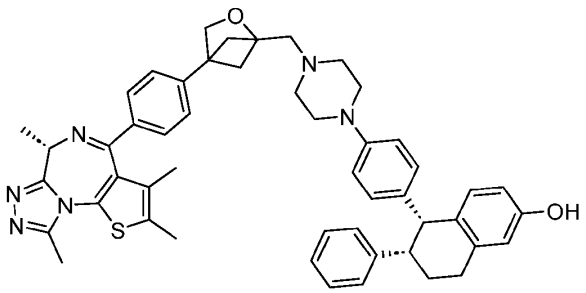
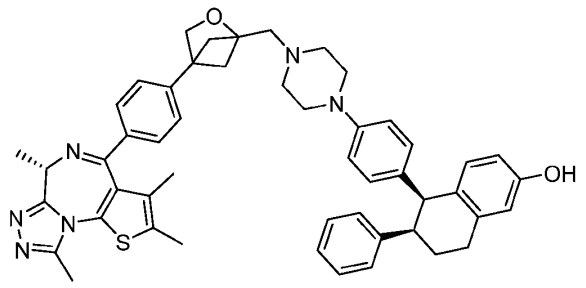
III-57	
III-58	
III-59	
III-60	
III-61	

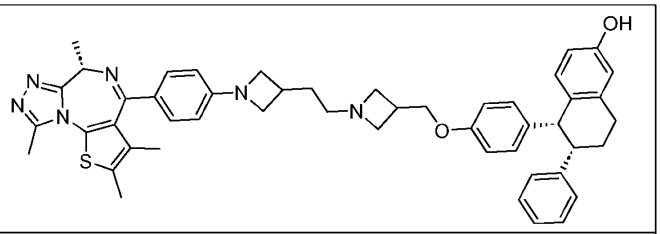
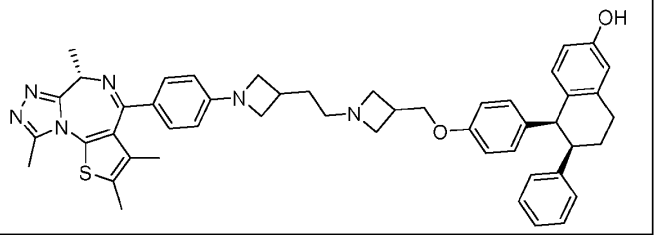
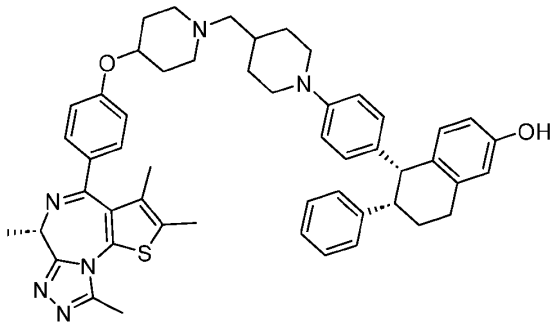
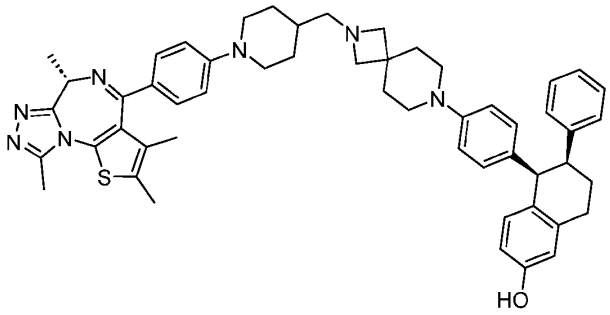
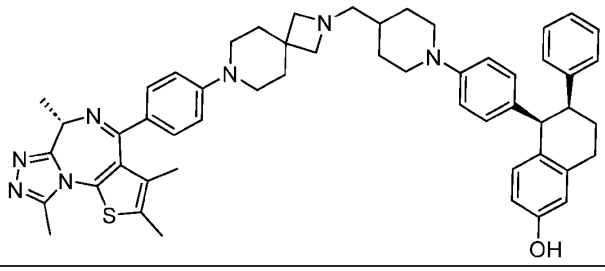
III-62	
III-63	
III-64	
III-65	

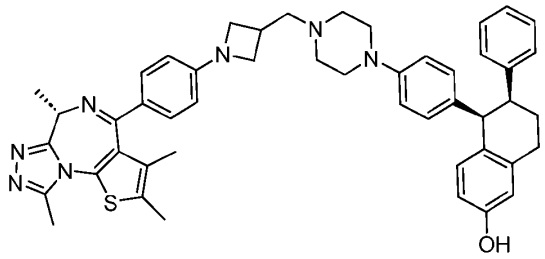
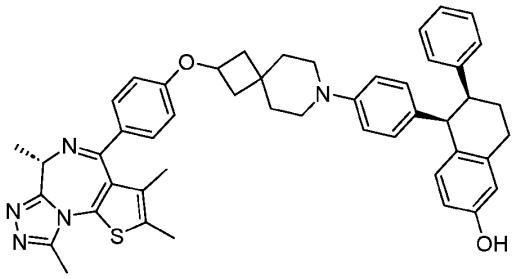
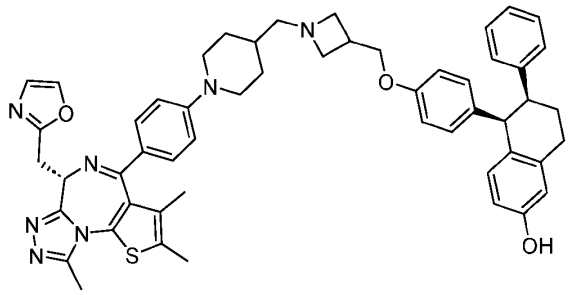
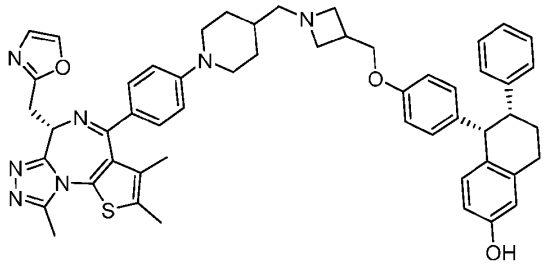
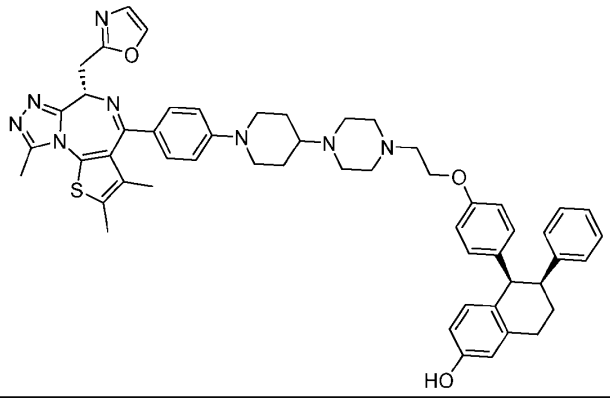
III-66	
III-67	
III-68	
III-69	
III-70	

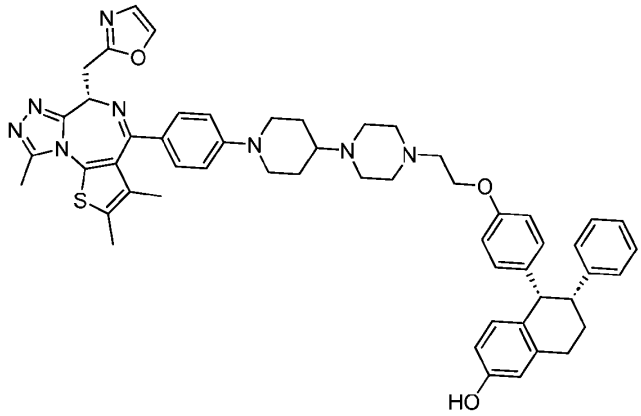
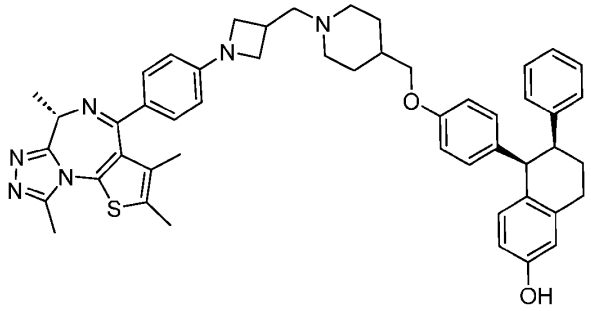
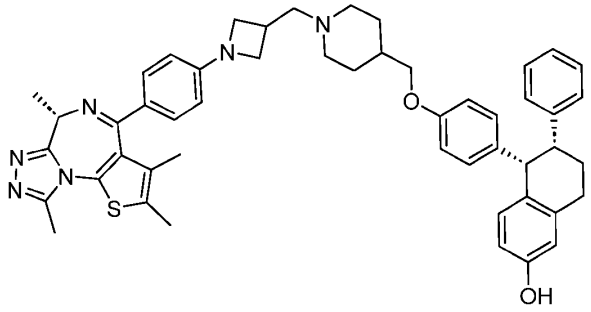
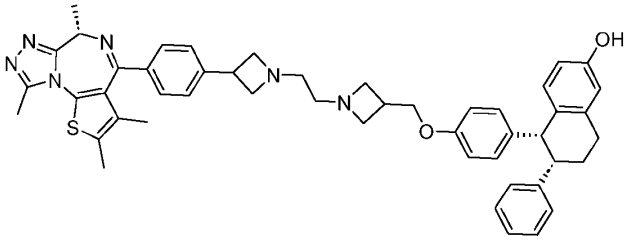
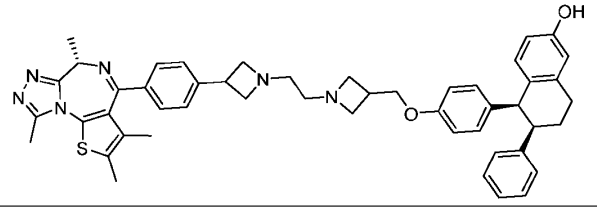
III-71	
III-72	
III-73	
III-74	
III-75	

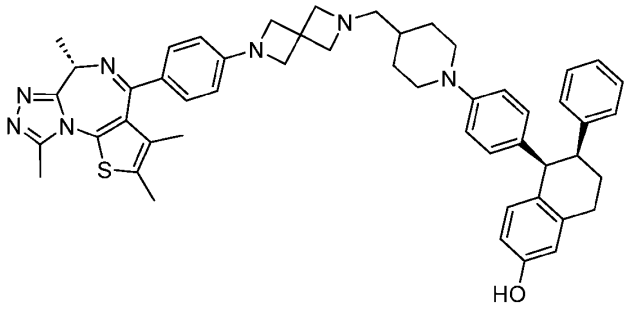
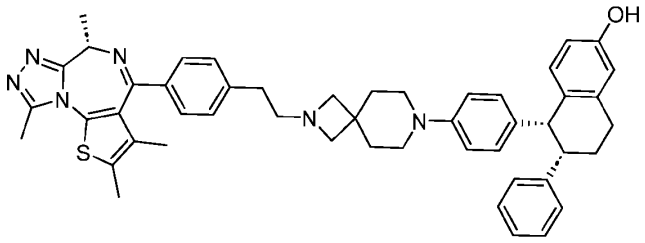
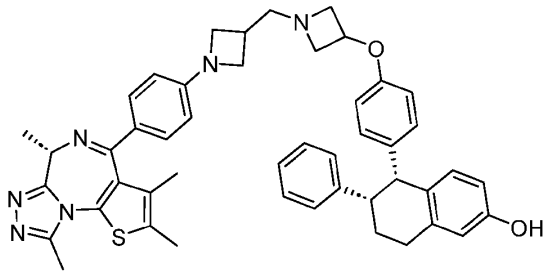
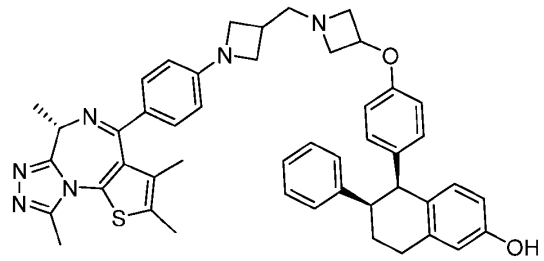
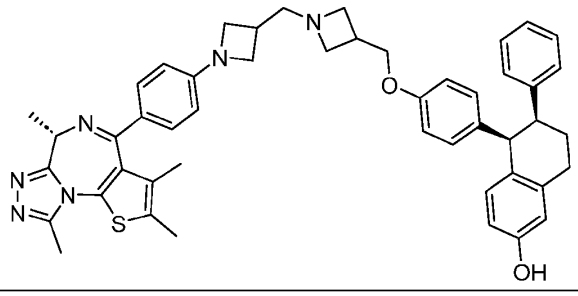
III-76	
III-77a	
III-77b	
III-78	

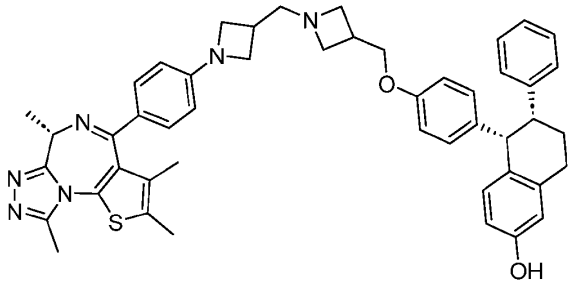
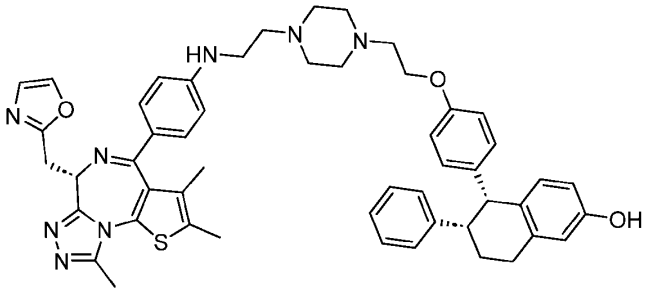
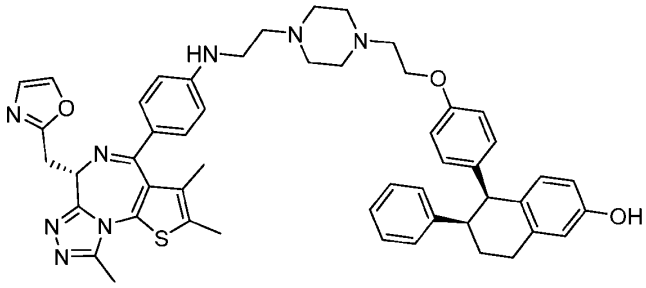
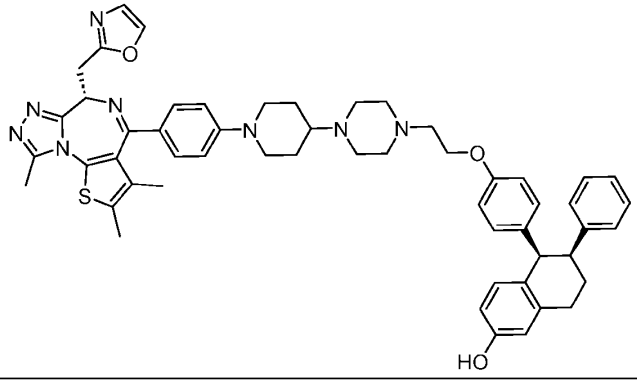
III-79	
III-80	
III-81	
III-82	
III-83	

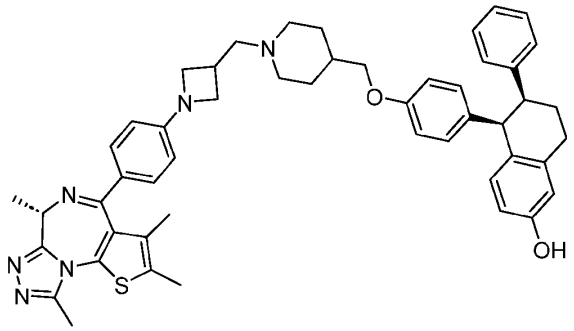
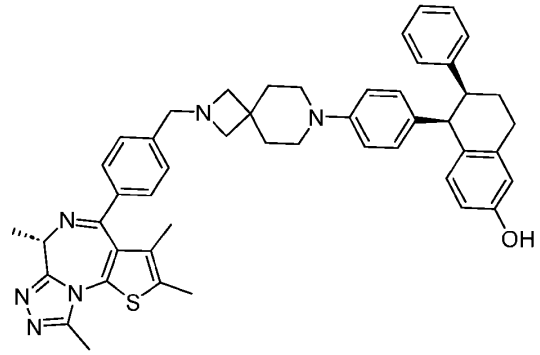
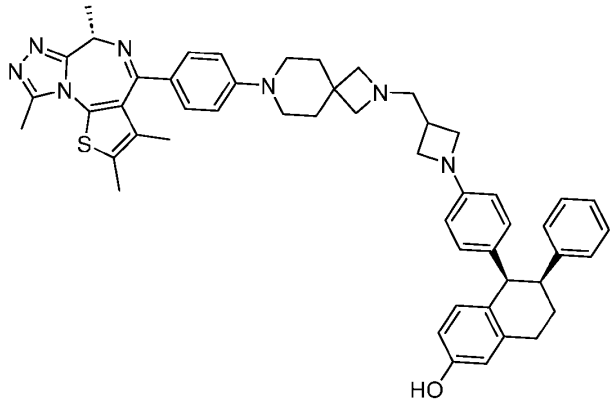
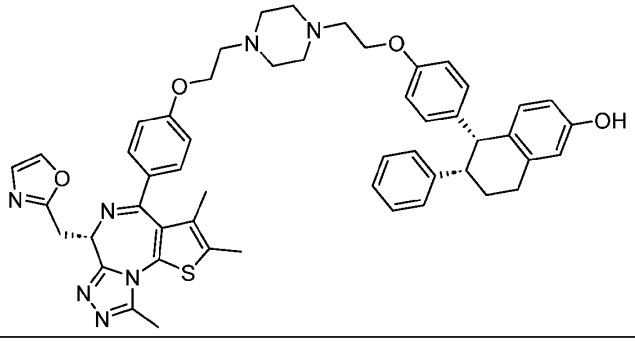
III-84	
III-85	
III-86	
III-87	
III-88	

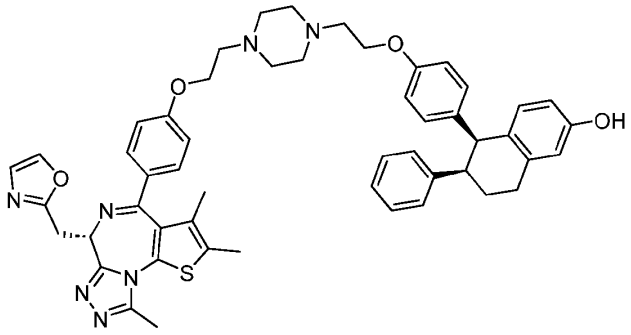
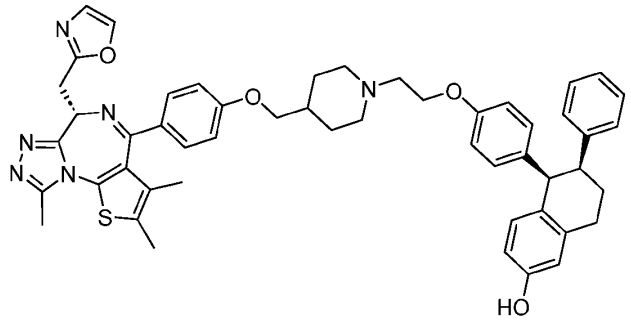
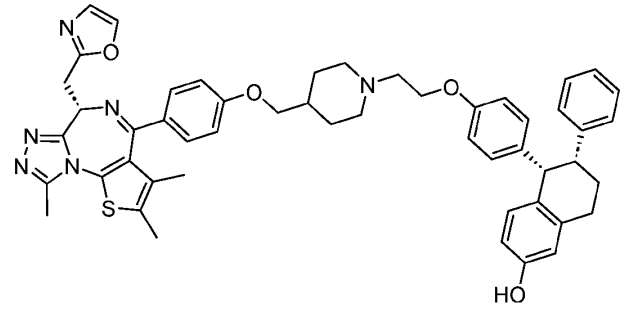
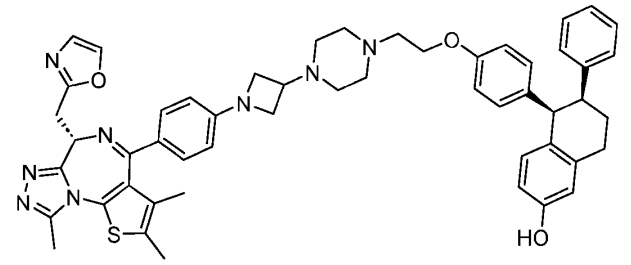
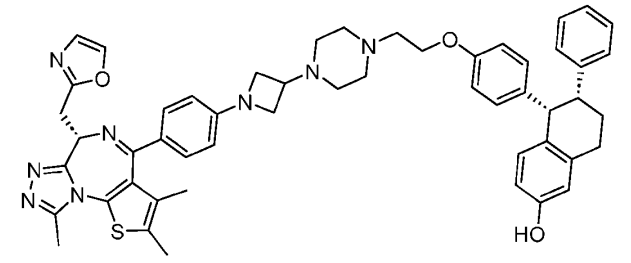
III-89	
III-90	
III-91	
III-92	
III-93a	

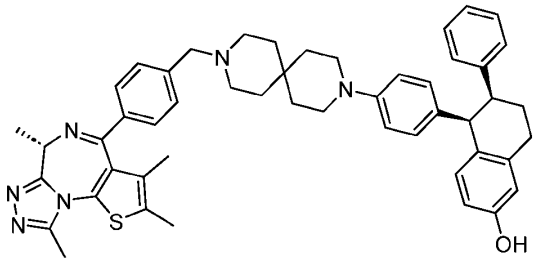
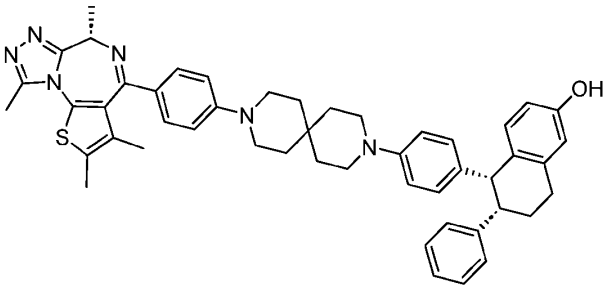
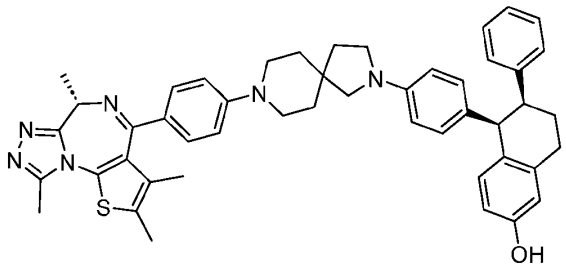
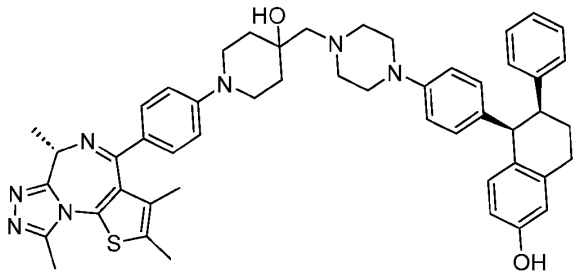
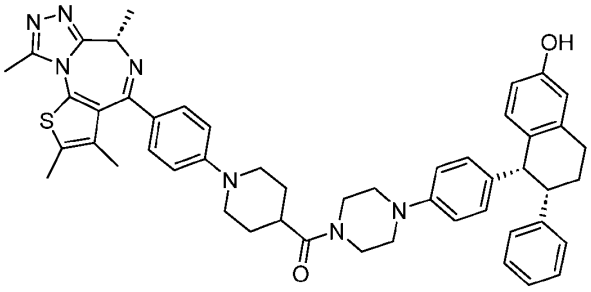
III-93b	
III-94a	
III-94b	
III-95	
III-96	

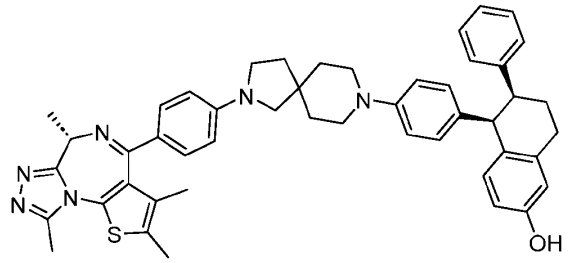
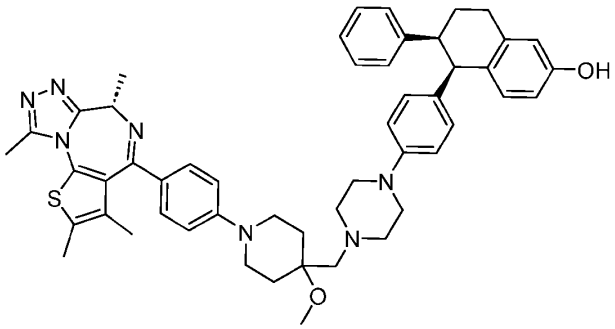
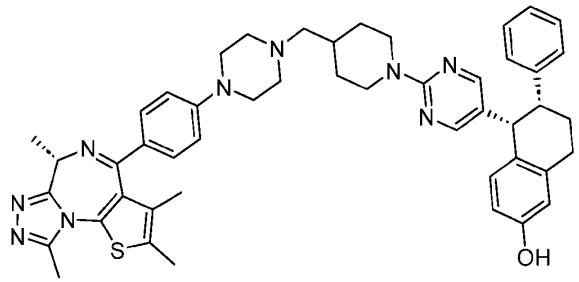
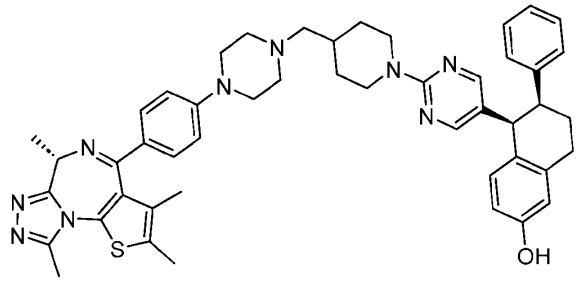
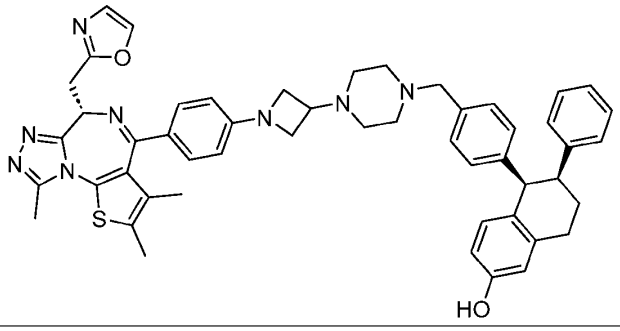
III-97	
III-98	
III-99	
III-100	
III-101	

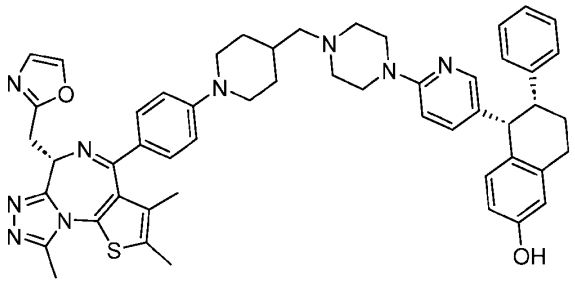
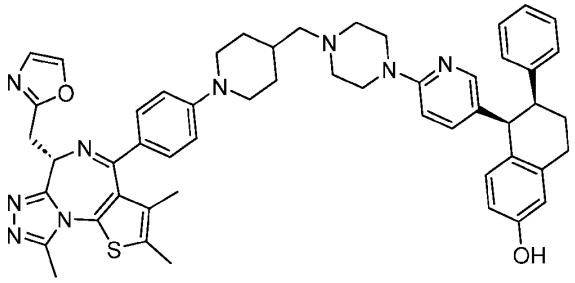
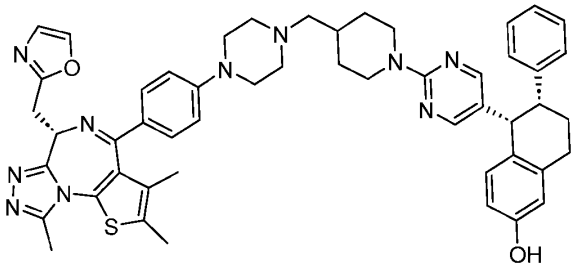
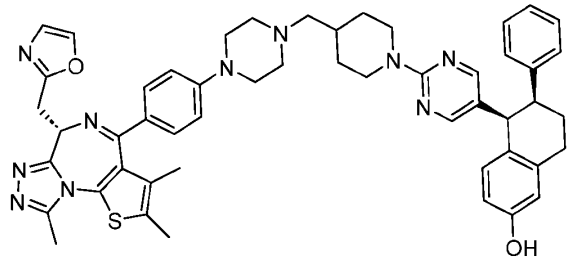
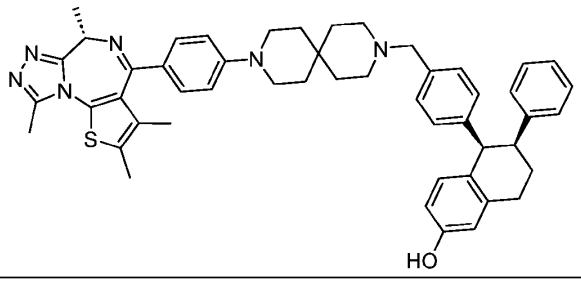
III-102	
III-103	
III-104	
III-105	

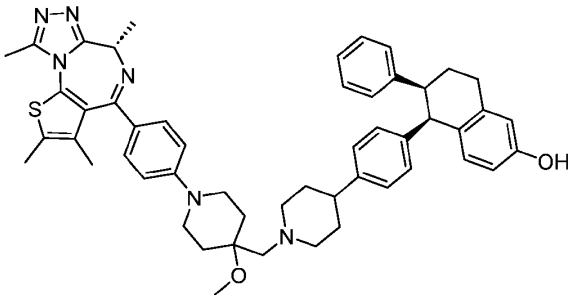
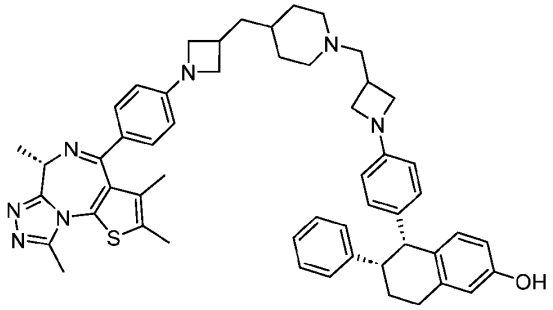
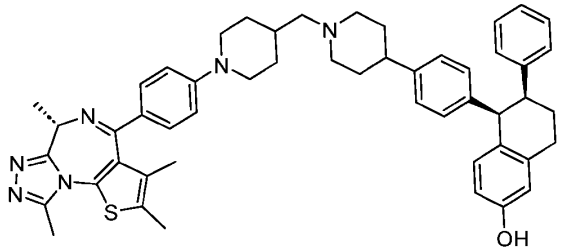
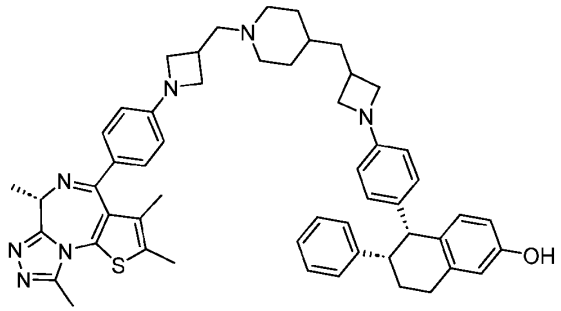
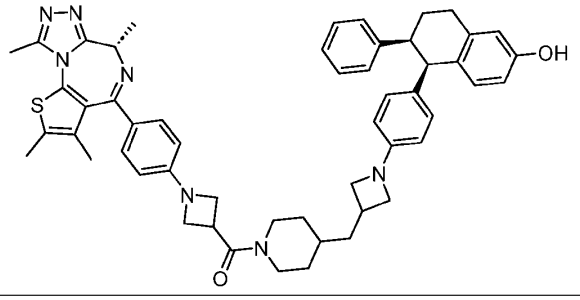
III-106	
III-107	
III-108	
III-109	

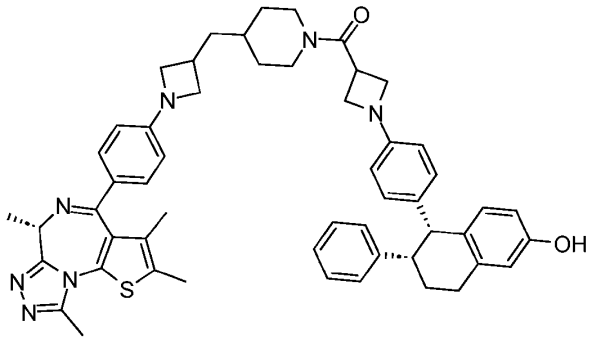
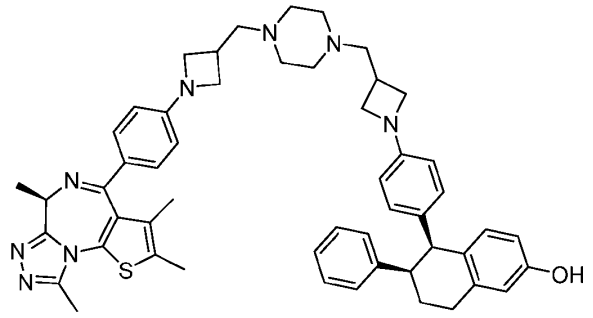
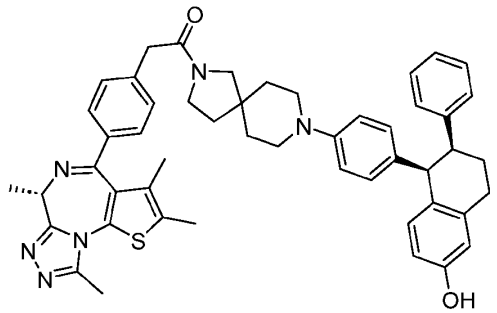
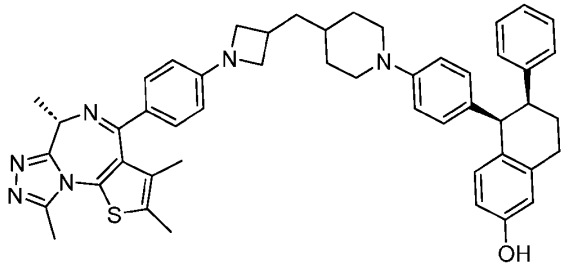
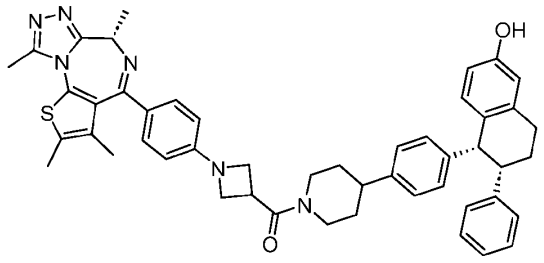
III-110	
III-111	
III-112	
III-113	
III-114	

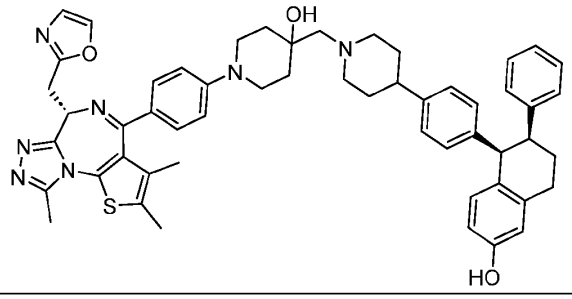
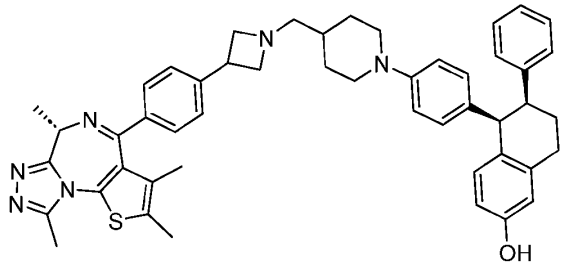
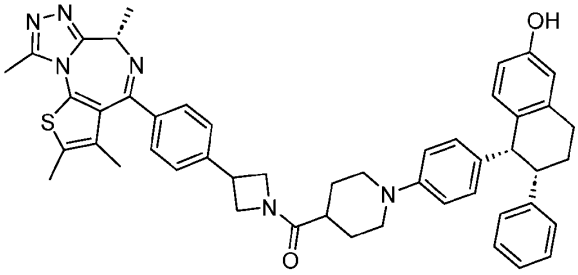
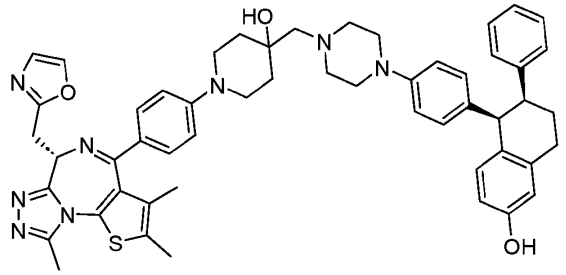
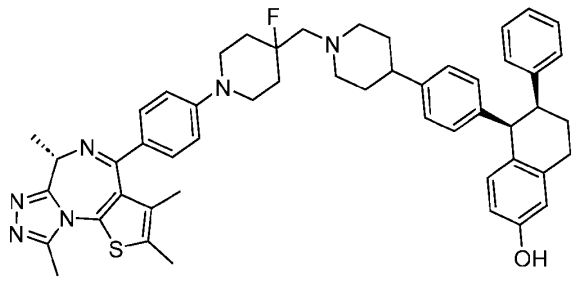
III-115	
III-116	
III-117	
III-118	
III-119	

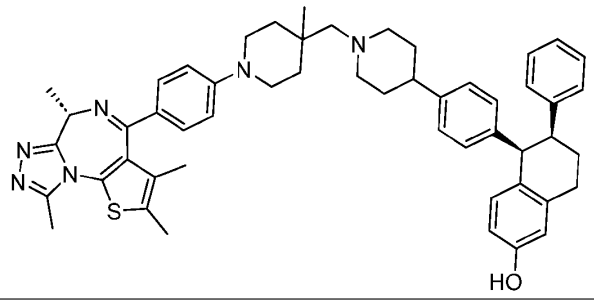
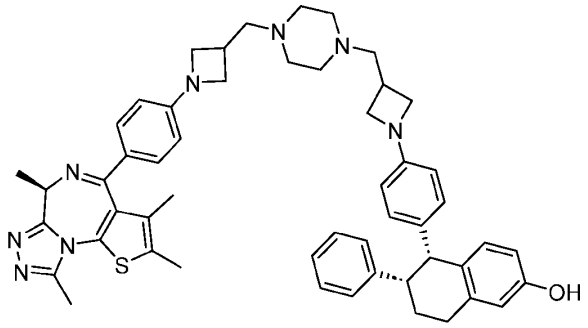
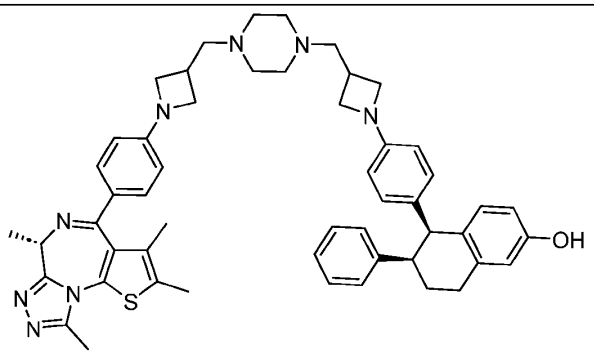
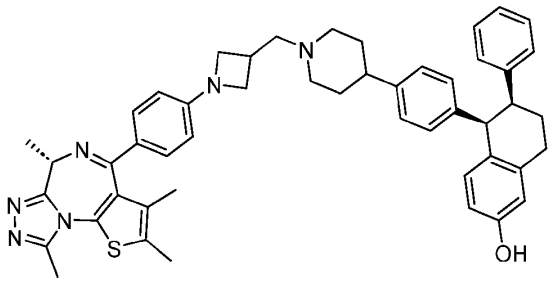
III-120	
III-121	
III-122	
III-123	
III-124	

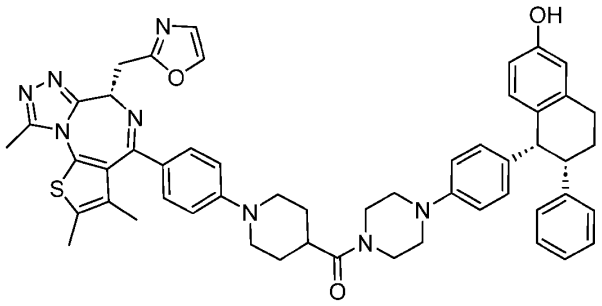
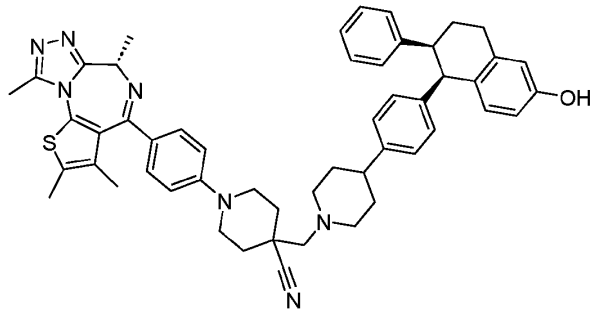
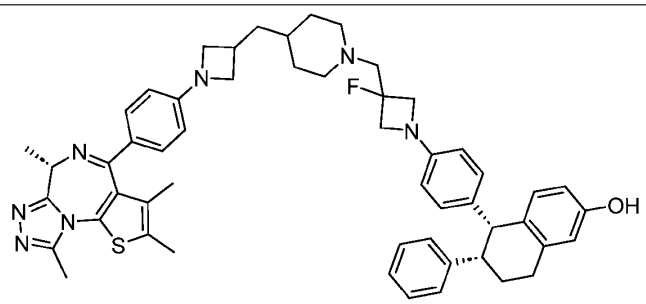
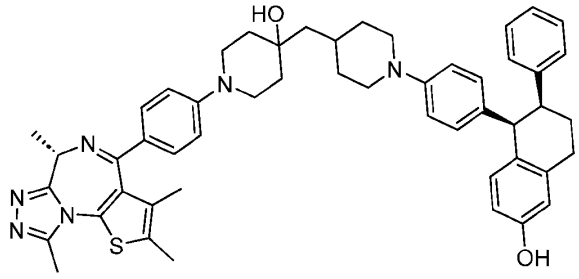
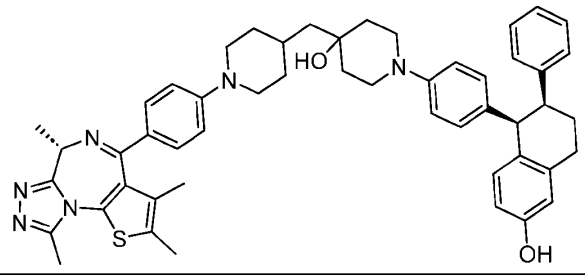
III-125	
III-126	
III-127	
III-128	
III-129	

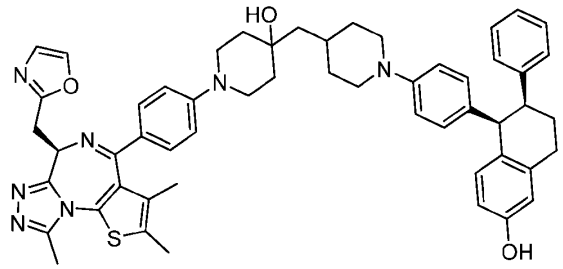
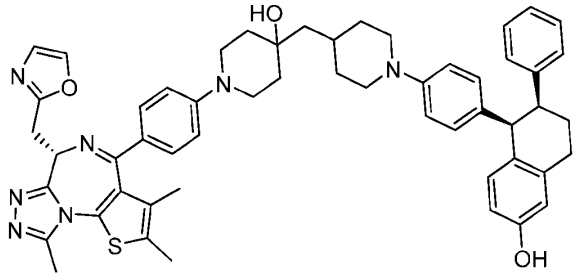
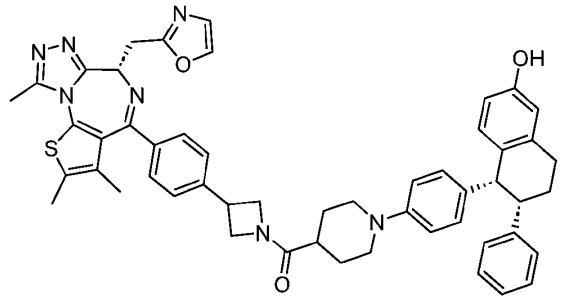
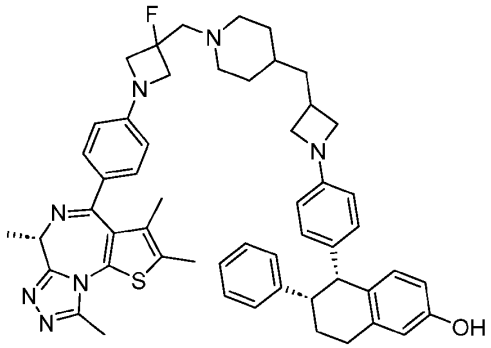
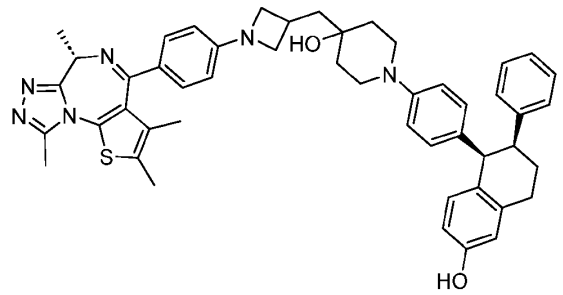
III-130	
III-131	
III-132	
III-133	
III-134	

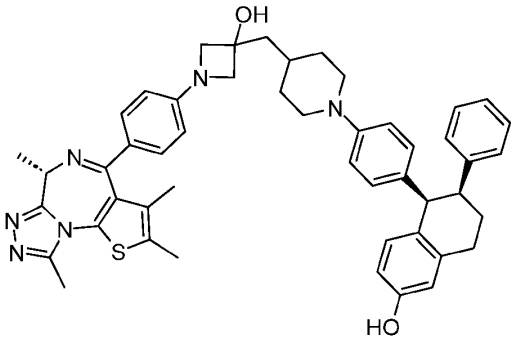
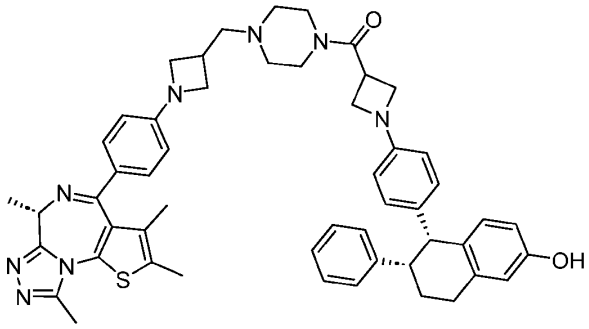
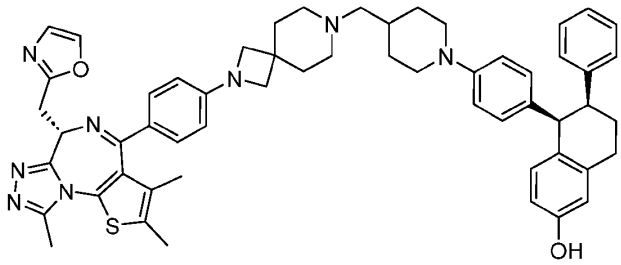
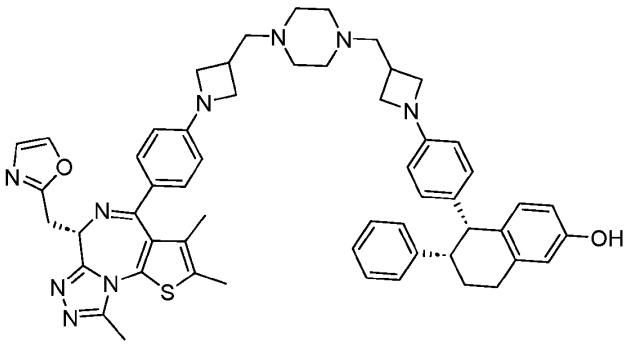
III-135	
III-136	
III-137	
III-138	
III-139	

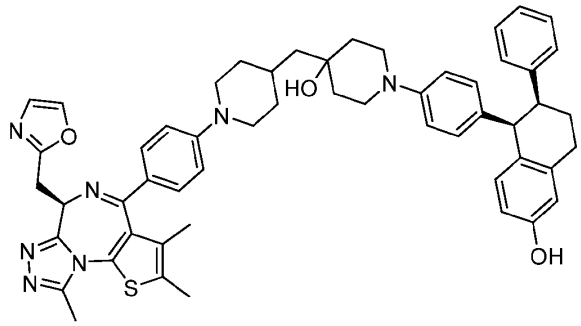
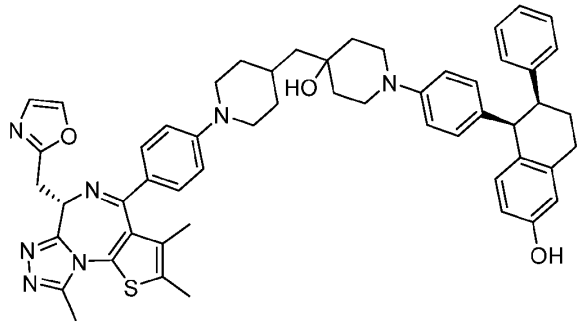
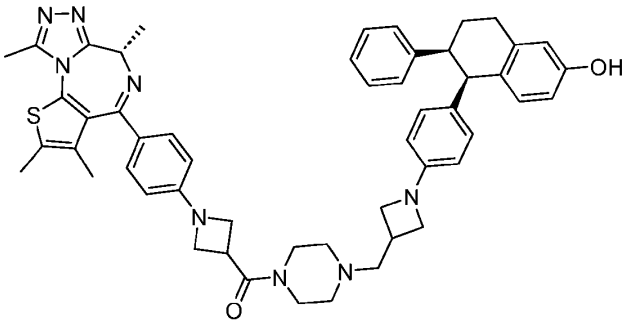
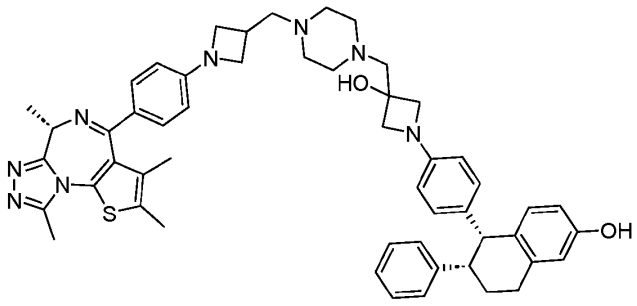
III-140	
III-141	
III-142	
III-143	
III-144	

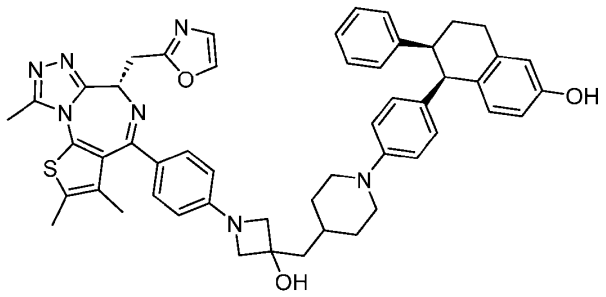
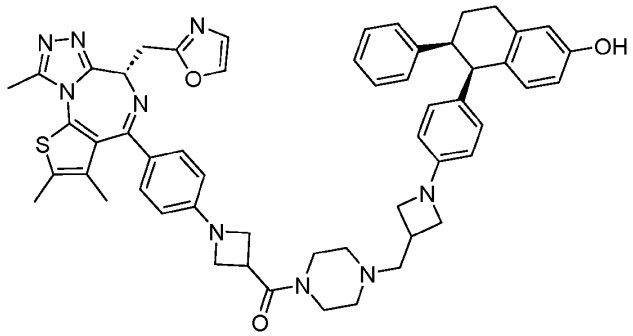
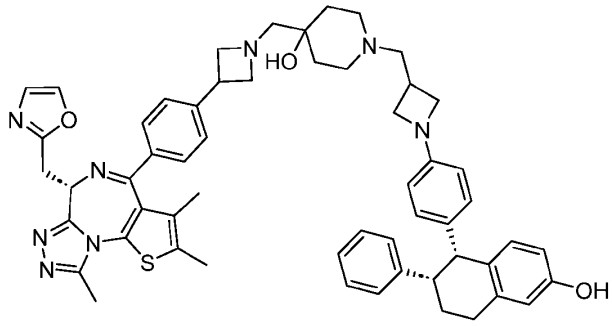
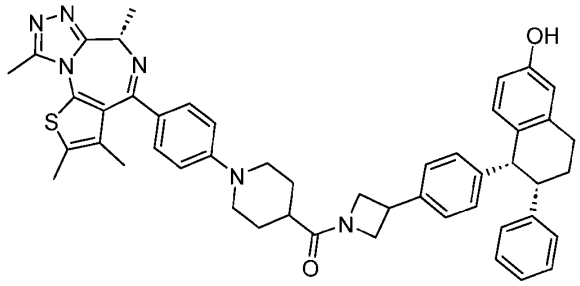
III-145	
III-146	
III-147	
III-148	

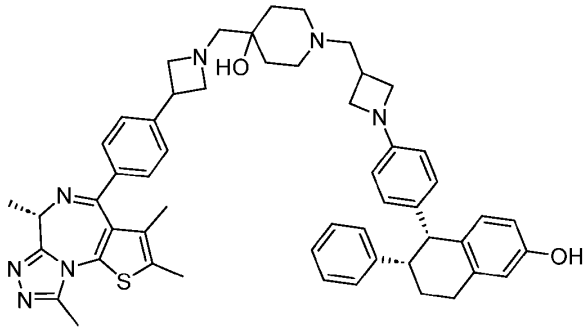
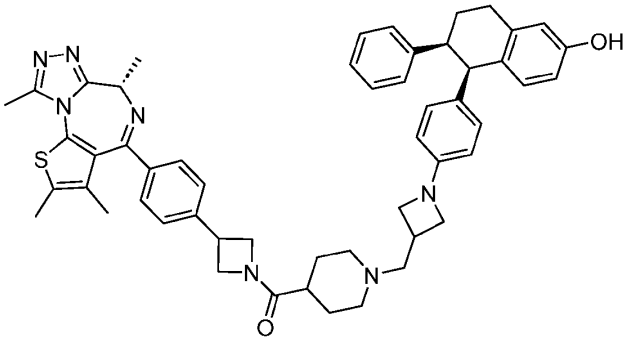
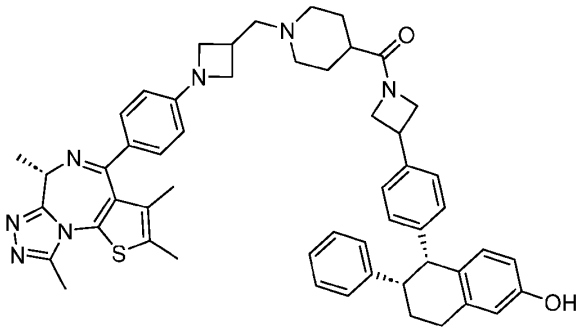
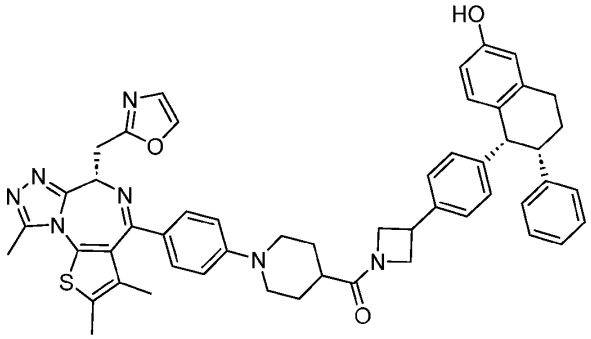
III-149	
III-150	
III-151	
III-152	
III-153	

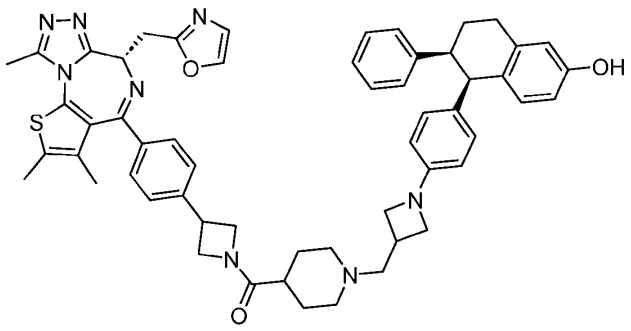
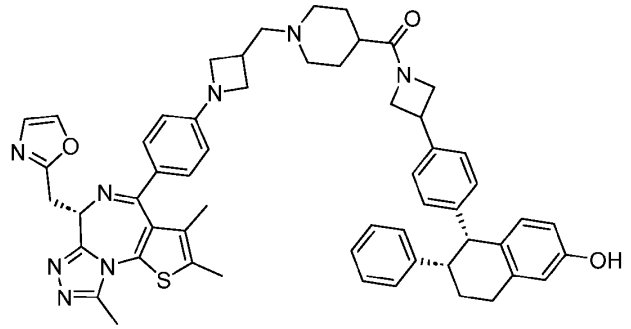
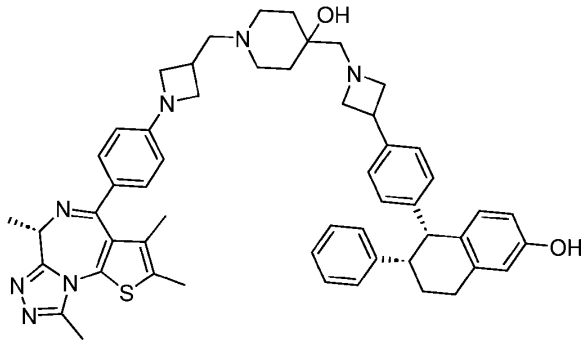
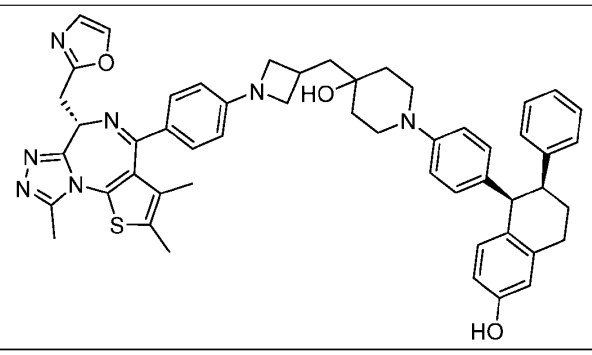
III-154	
III-155	
III-156	
III-157	
III-158	

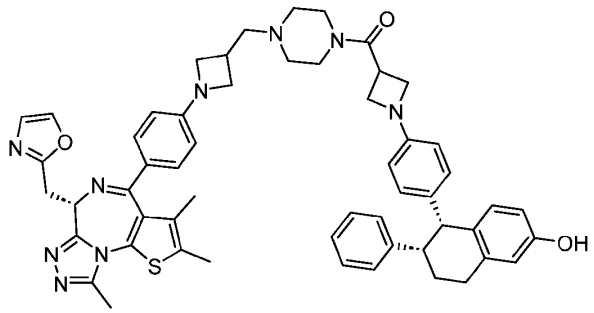
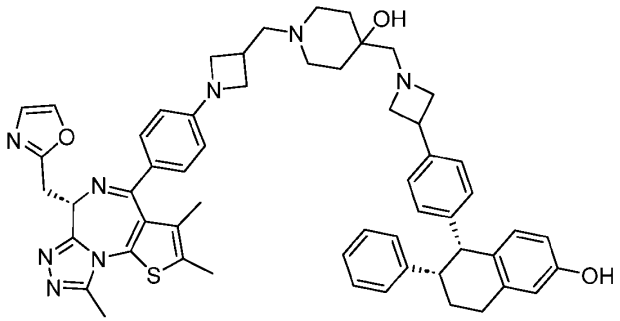
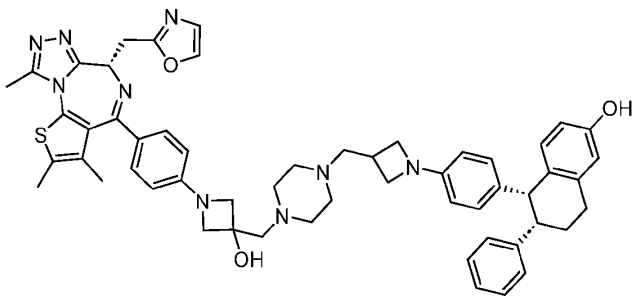
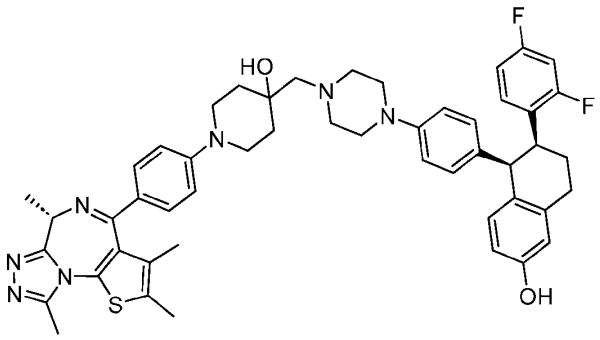
III-159	
III-160	
III-161	
III-162	

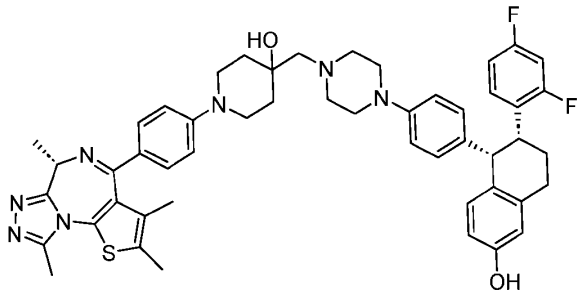
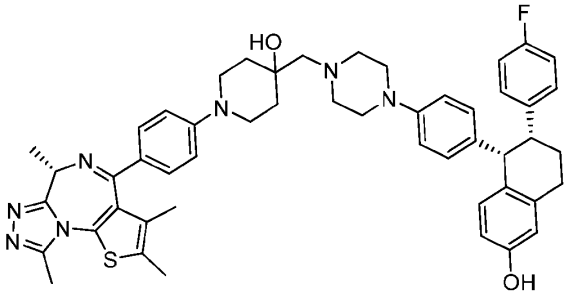
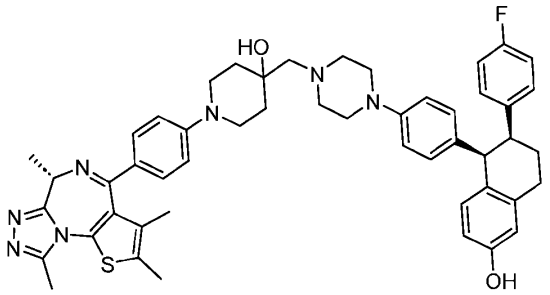
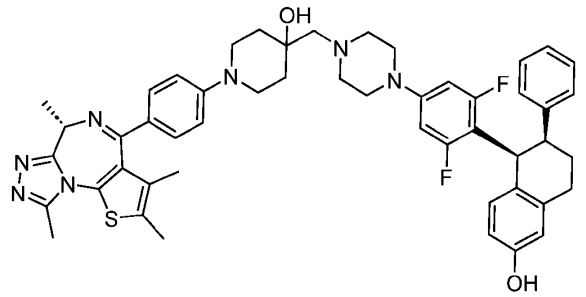
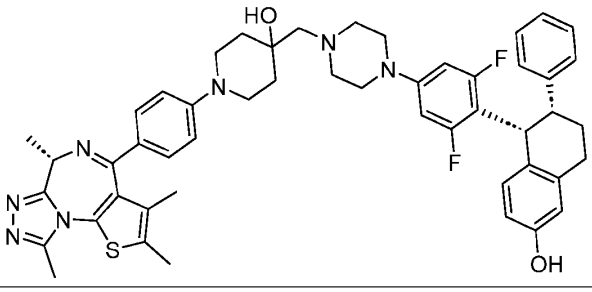
III-163	
III-164	
III-165	
III-166	

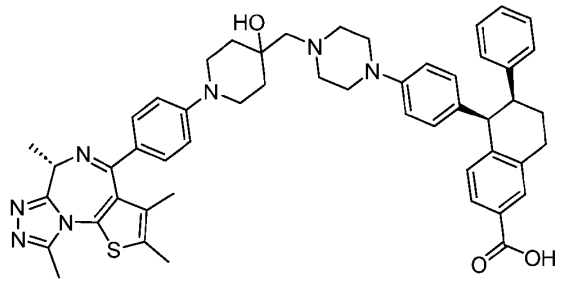
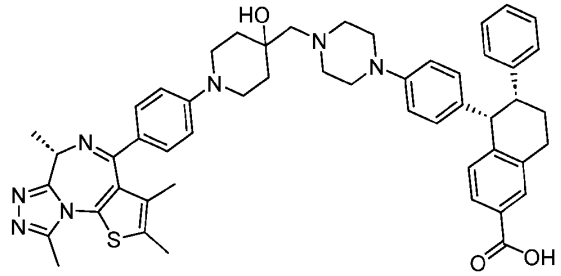
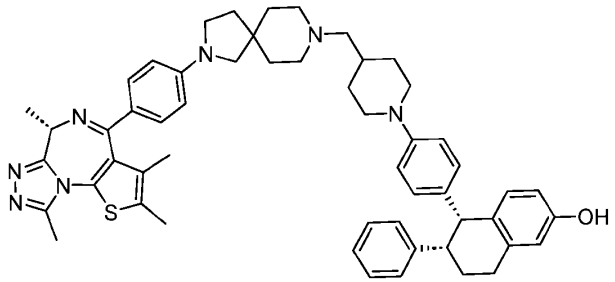
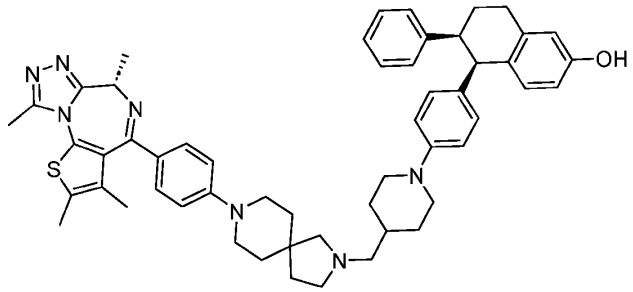
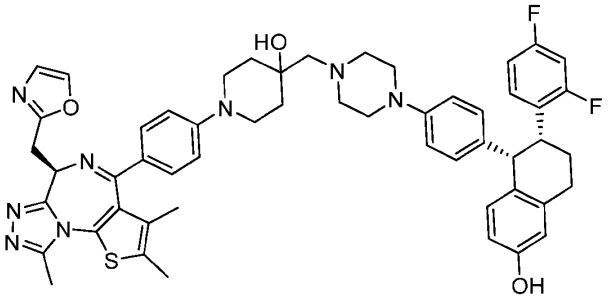
III-167	
III-168	
III-169	
III-170	

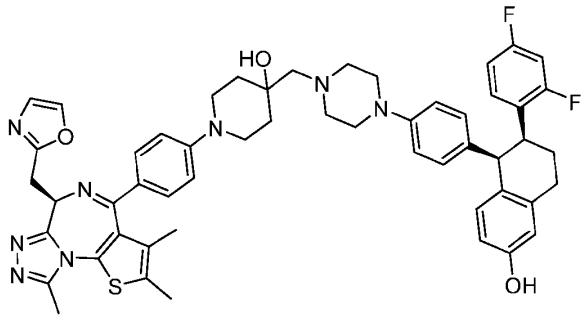
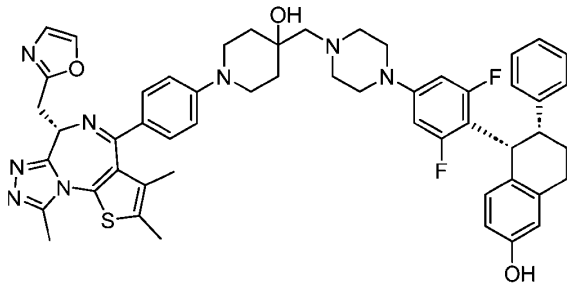
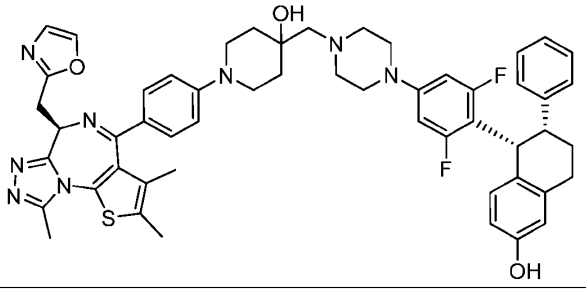
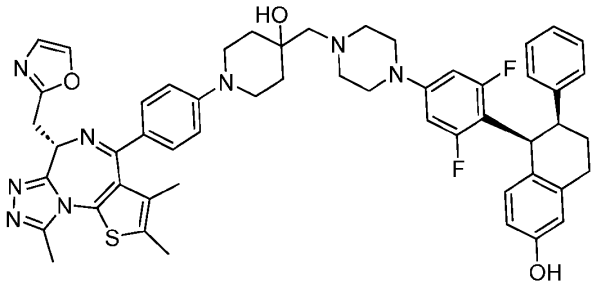
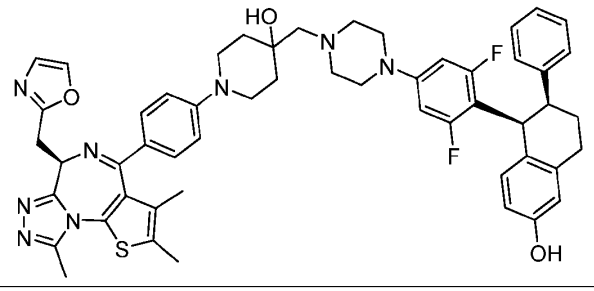
III-171	
III-172	
III-173	
III-174	

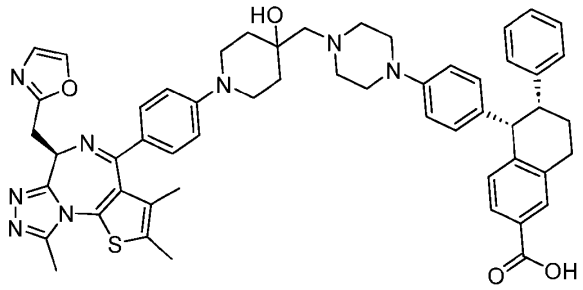
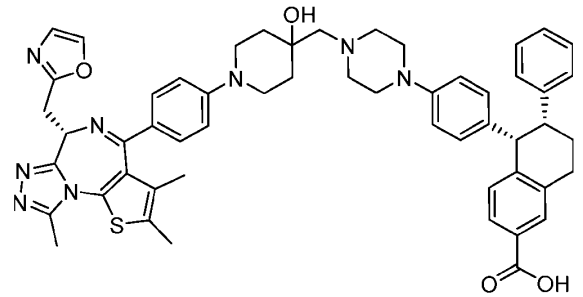
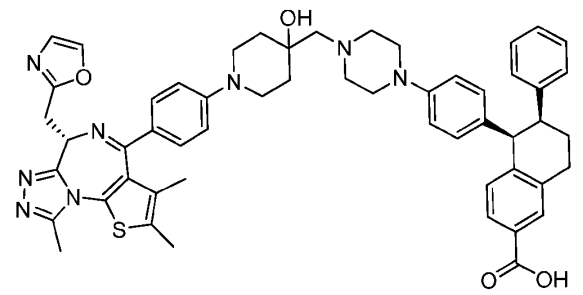
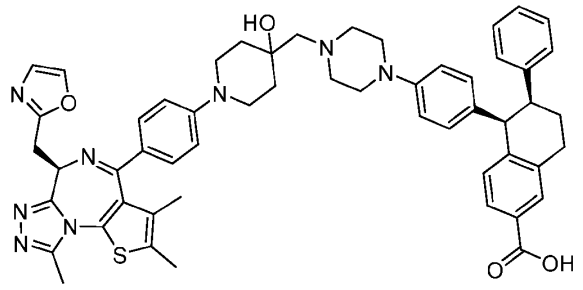
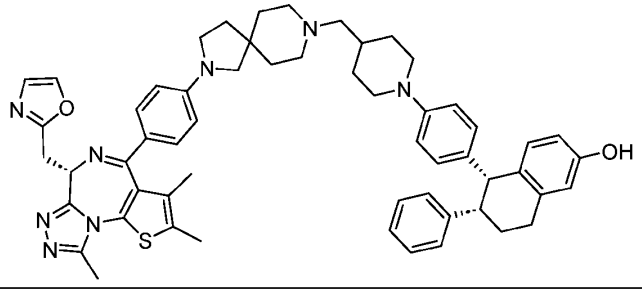
III-175	
III-176	
III-177	
III-178	

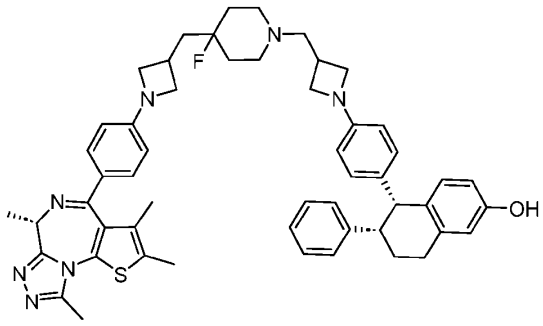
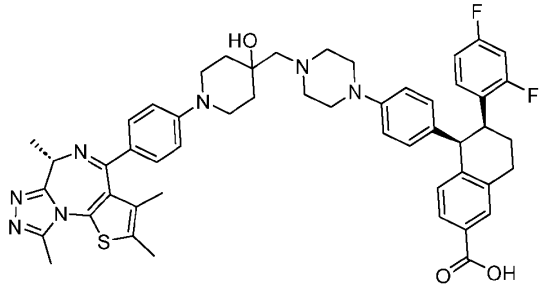
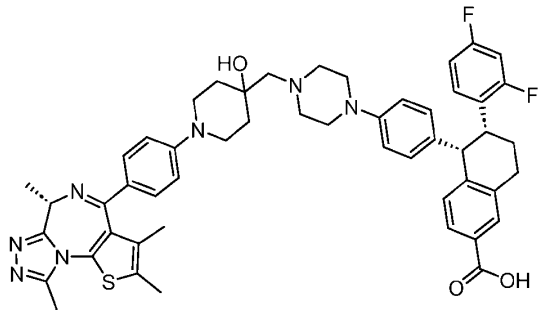
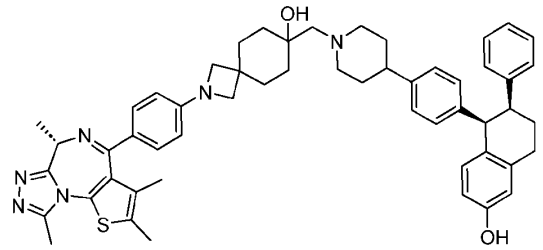
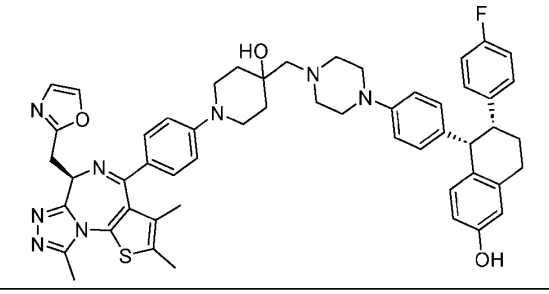
III-179	
III-180	
III-181	
III-182	

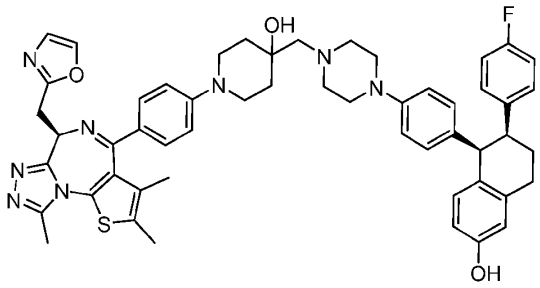
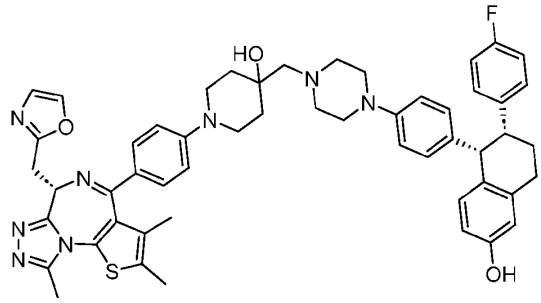
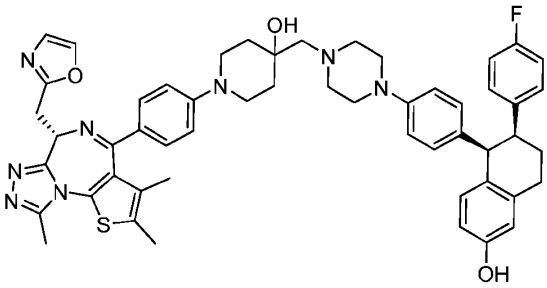
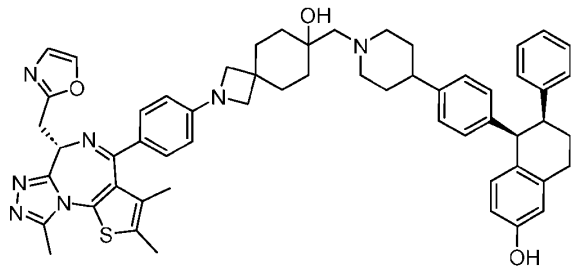
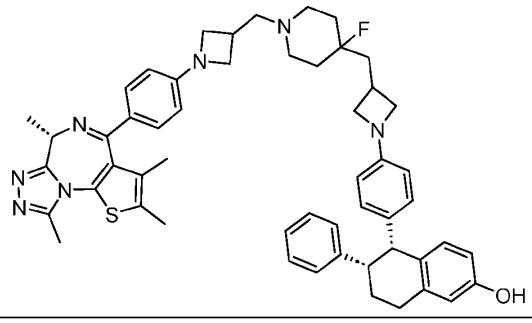
III-183	
III-184	
III-185	
III-186	
III-187	

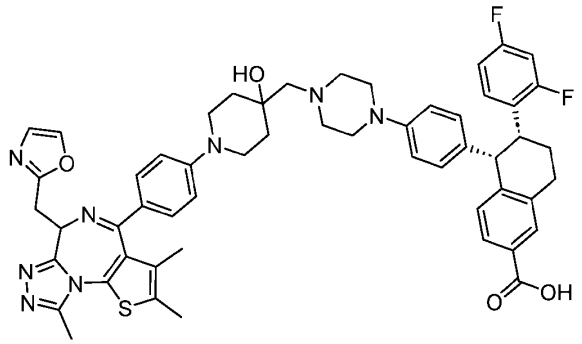
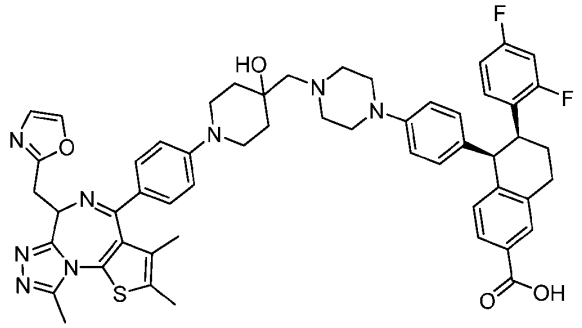
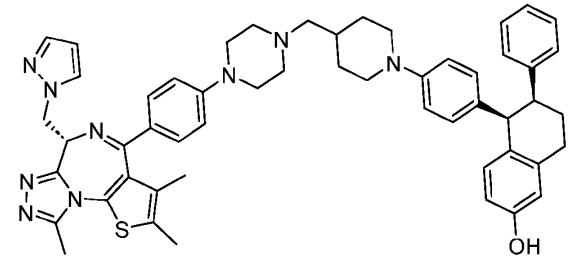
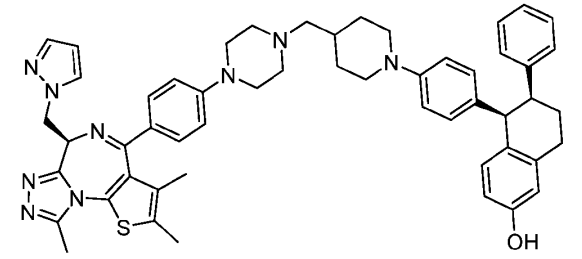
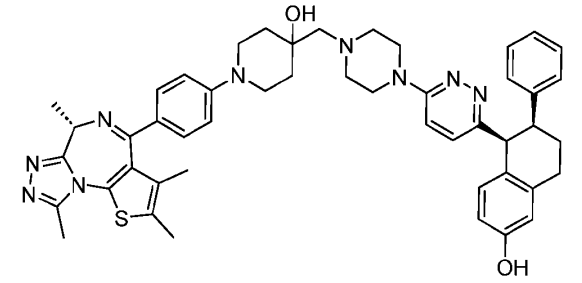
III-188	
III-189	
III-190	
III-191	
III-192	

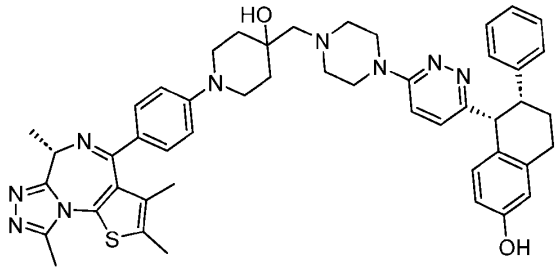
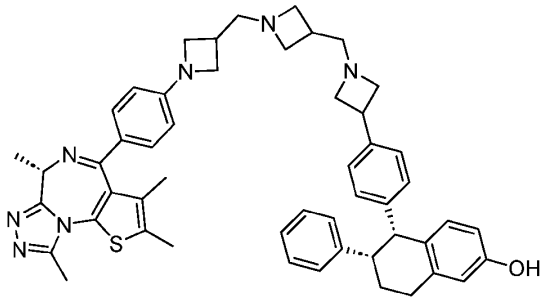
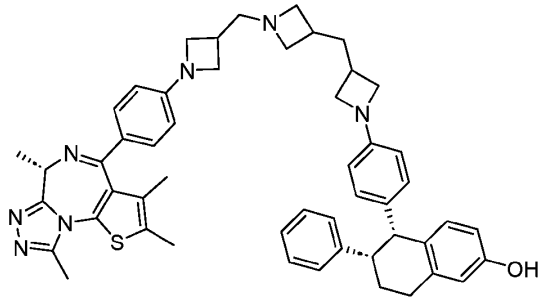
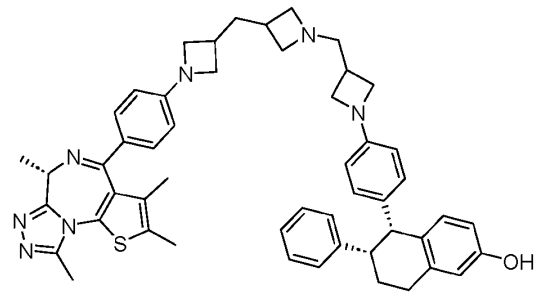
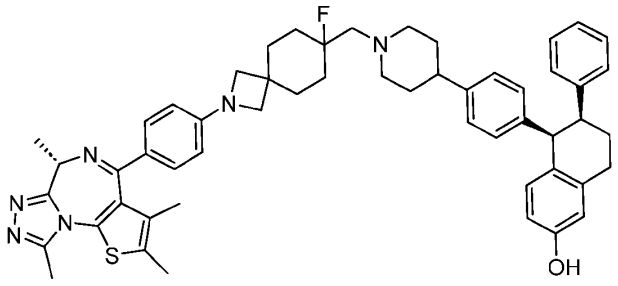
III-193	
III-194	
III-195	
III-196	
III-197	

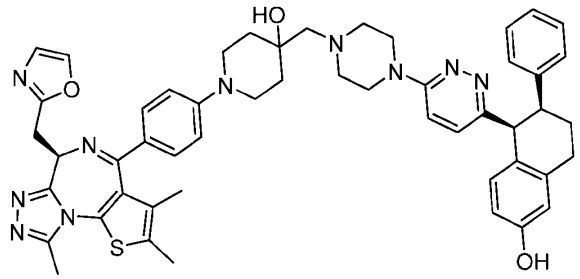
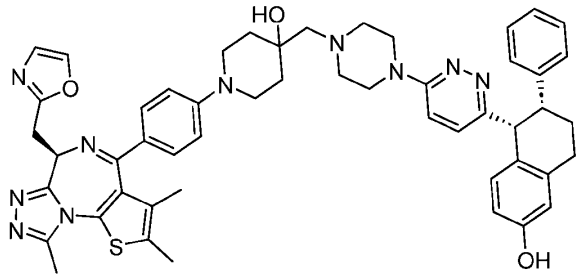
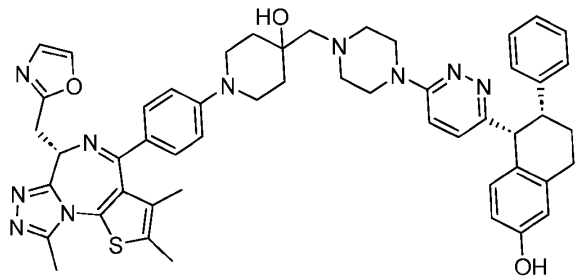
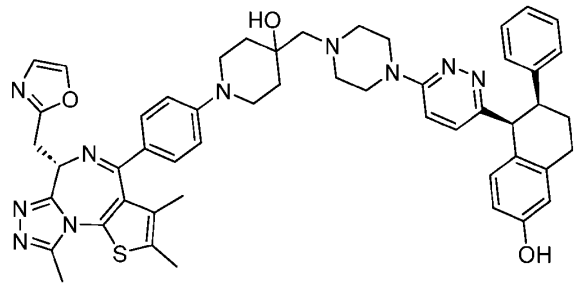
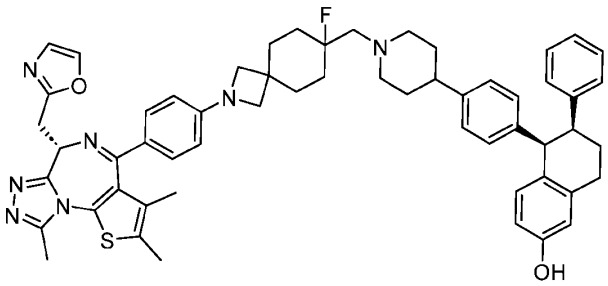
III-198	
III-199	
III-200	
III-201	
III-202	

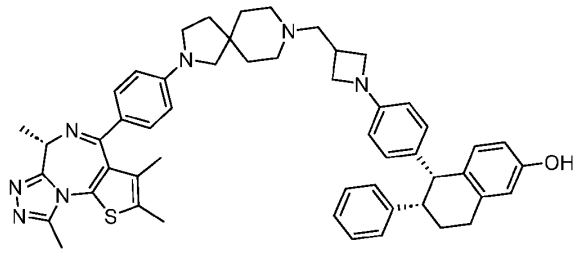
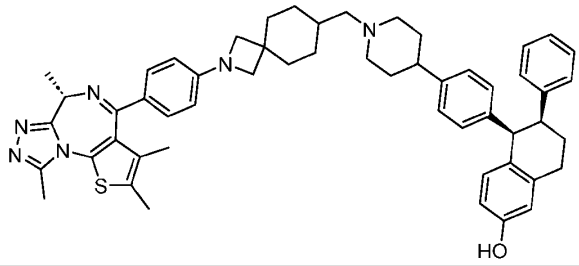
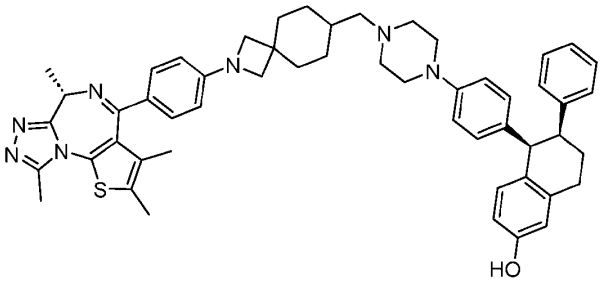
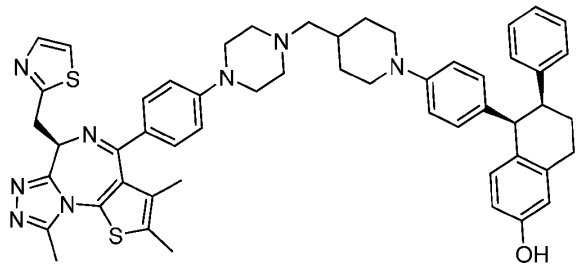
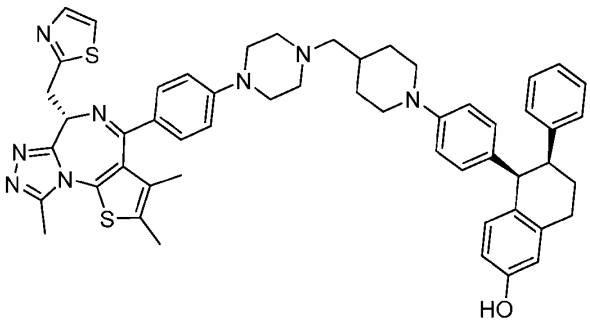
III-203	
III-204	
III-205	
III-206	
III-207	

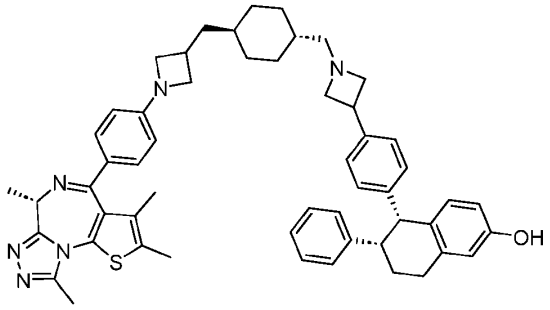
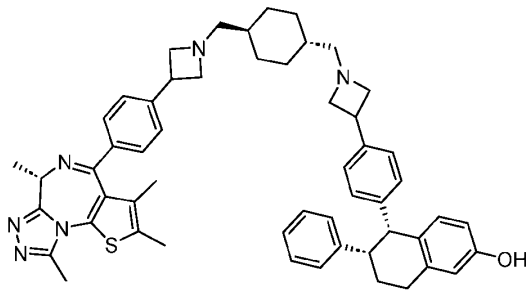
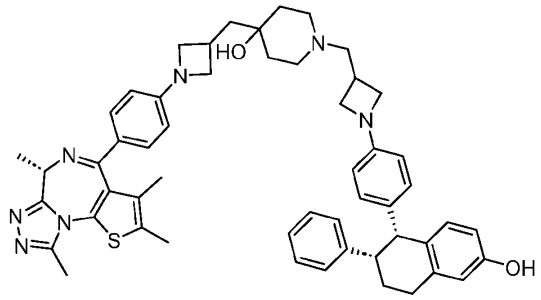
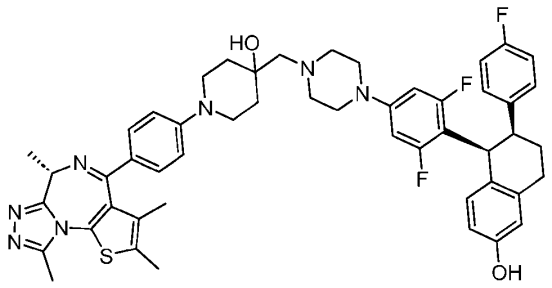
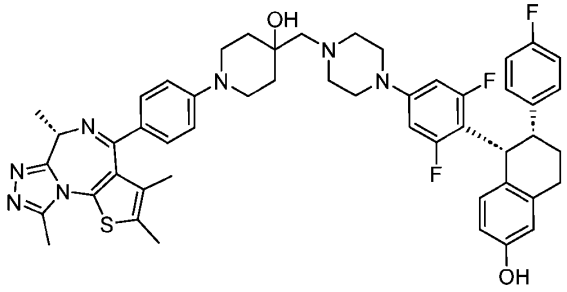
III-208	
III-209	
III-210	
III-211	
III-212	

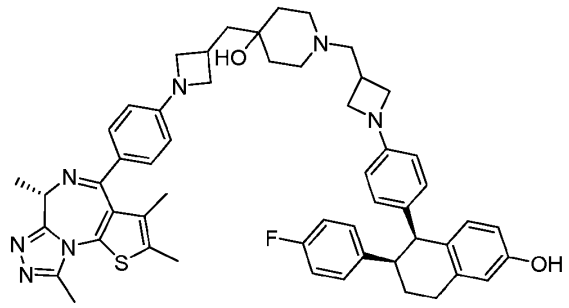
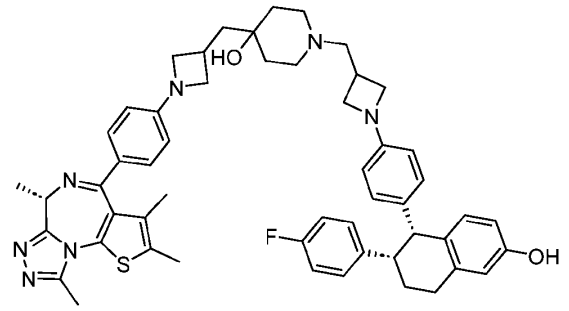
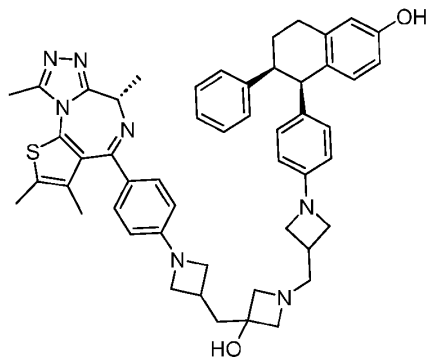
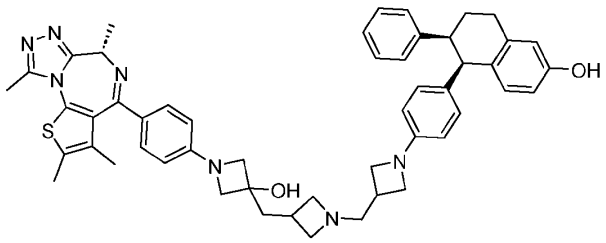
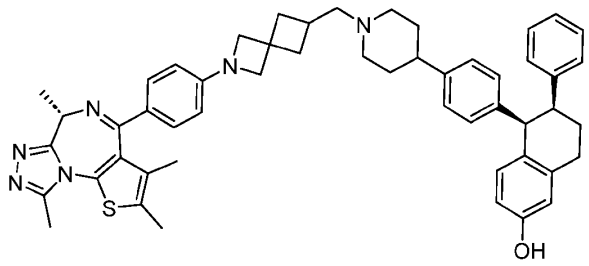
III-213	
III-214	
III-215	
III-216	
III-217	

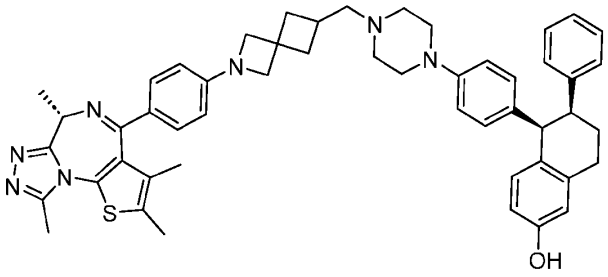
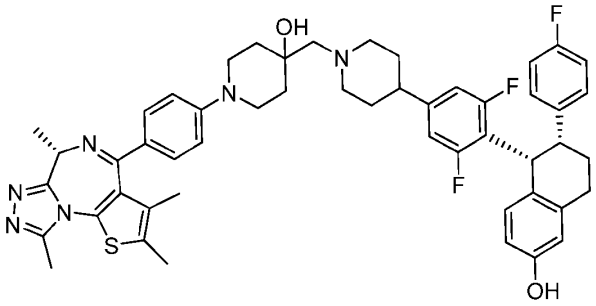
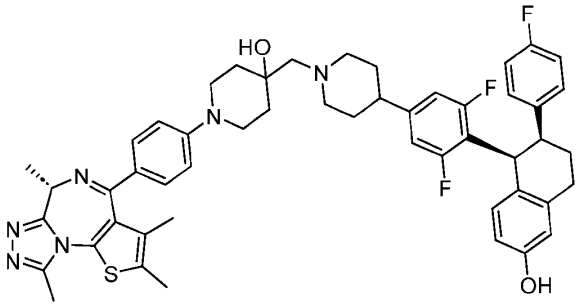
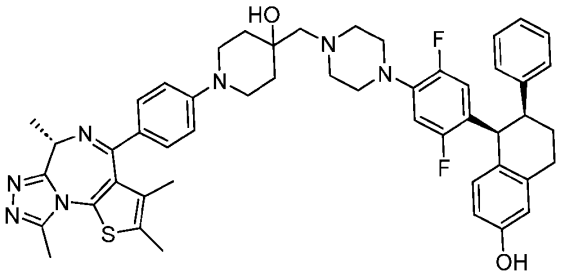
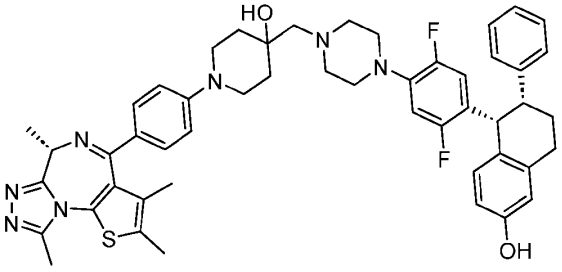
III-218	
III-219	
III-220	
III-221	
III-222	

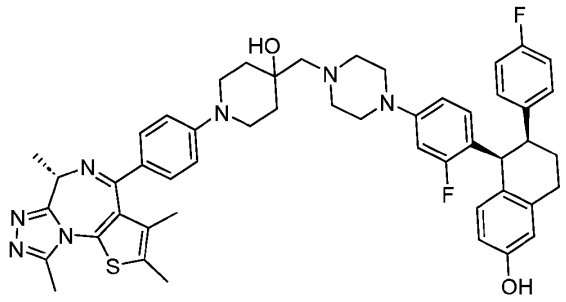
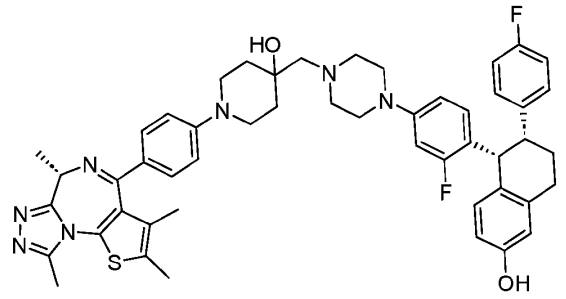
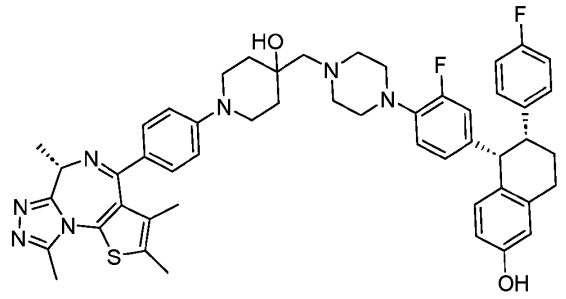
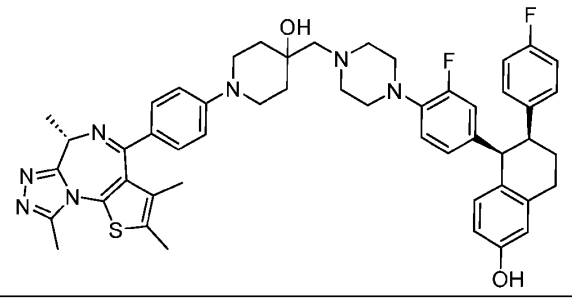
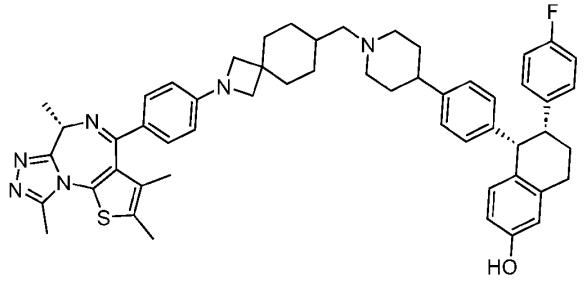
III-223	
III-224	
III-225	
III-226	
III-227	

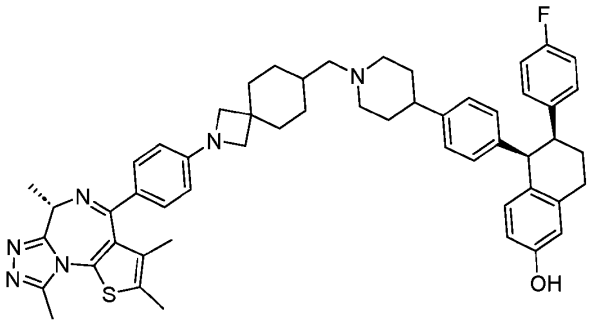
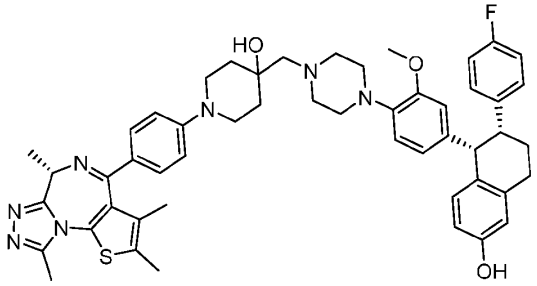
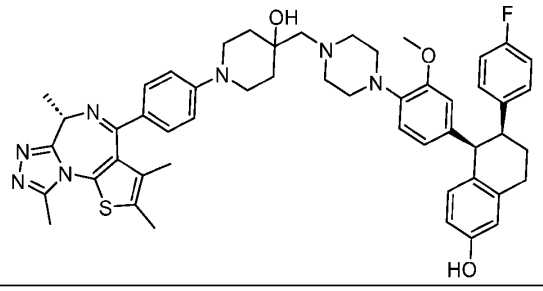
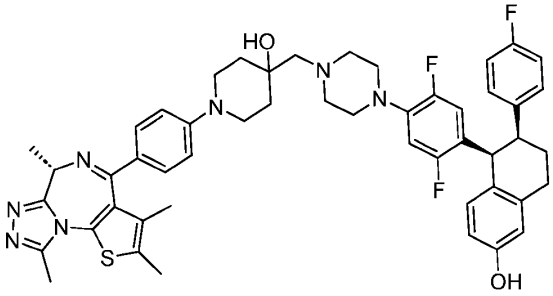
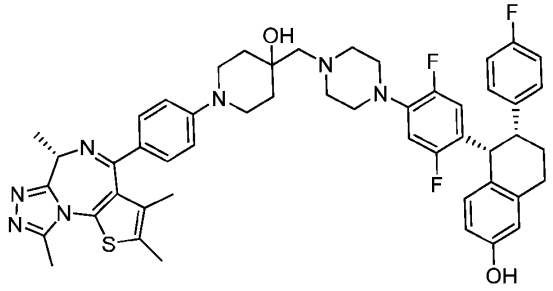
III-228	
III-229	
III-230	
III-231	
III-232	

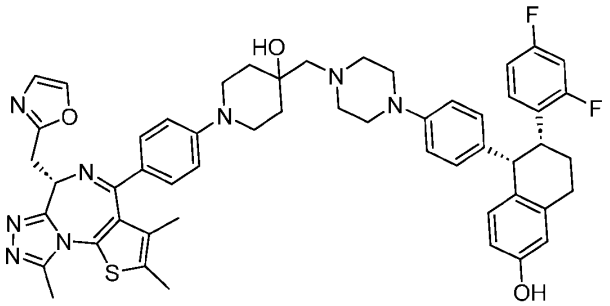
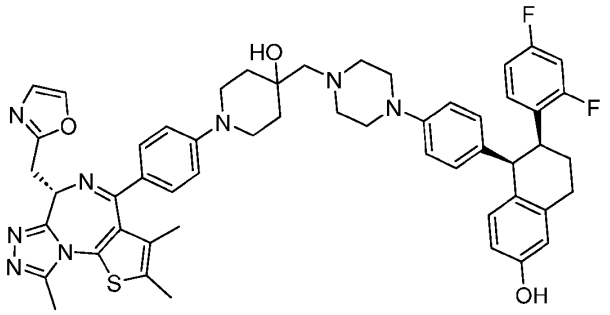
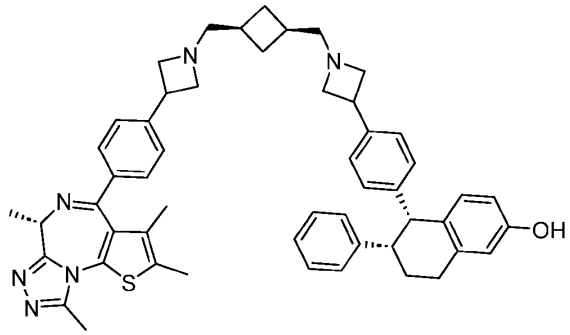
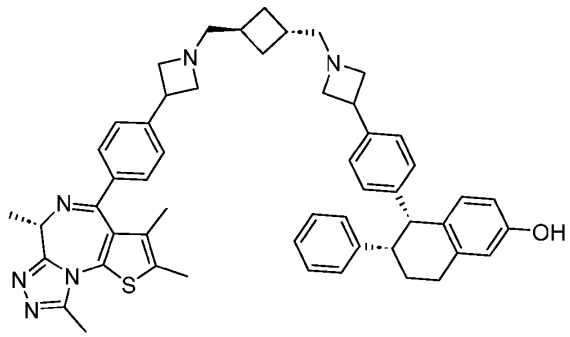
III-233	
III-234	
III-235	
III-236	
III-237	

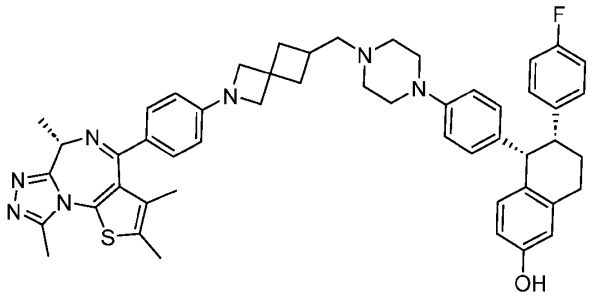
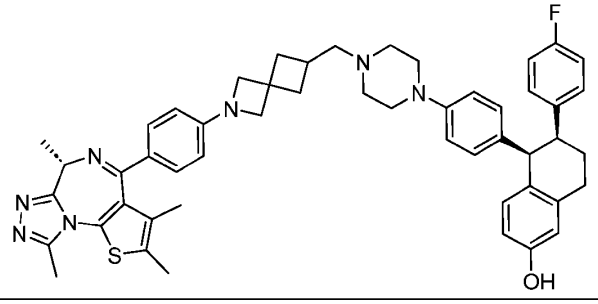
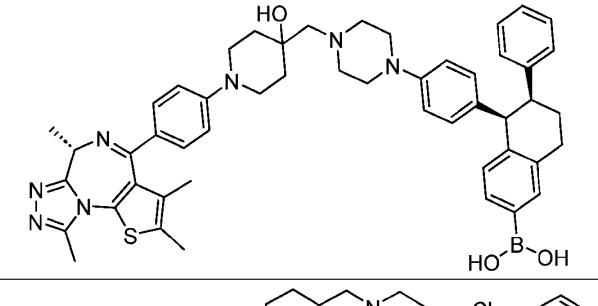
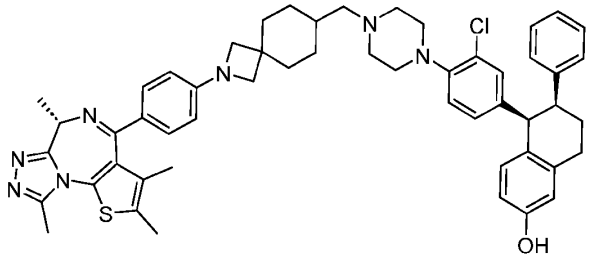
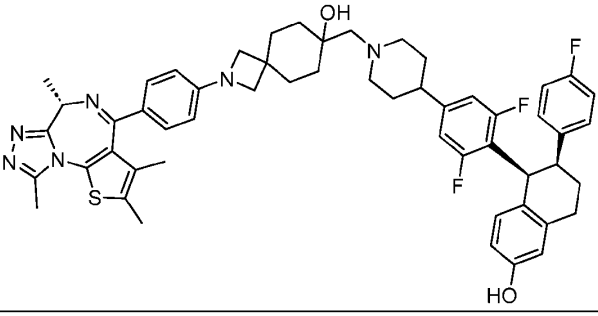
III-238	
III-239	
III-240	
III-241	
III-242	

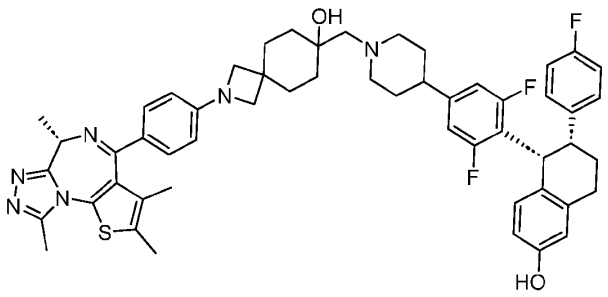
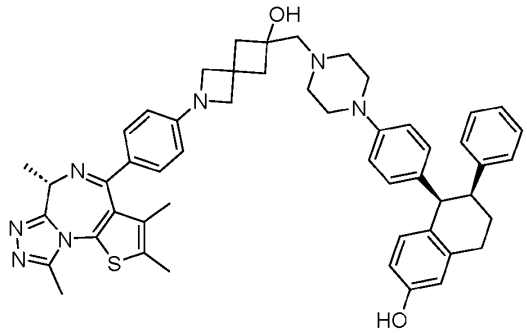
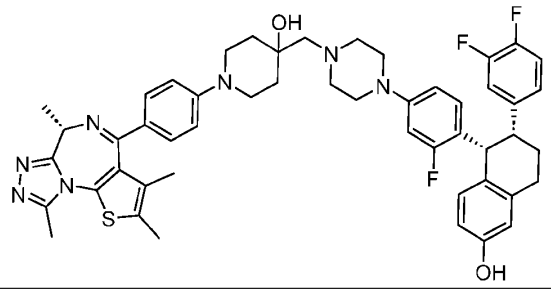
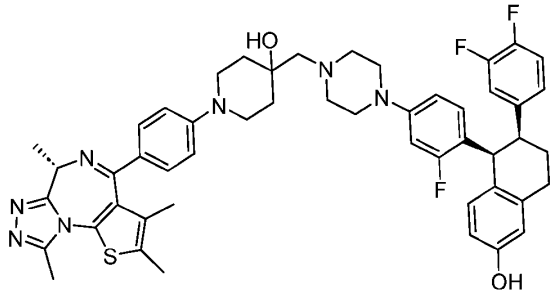
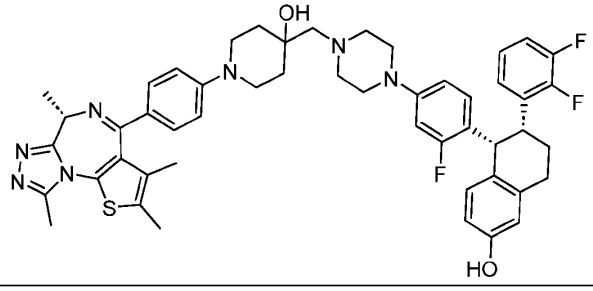
III-243	
III-244	
III-245	
III-246	
III-247	

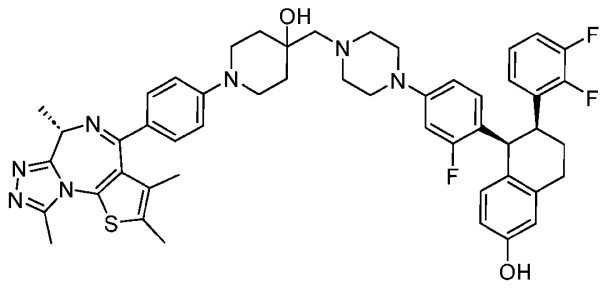
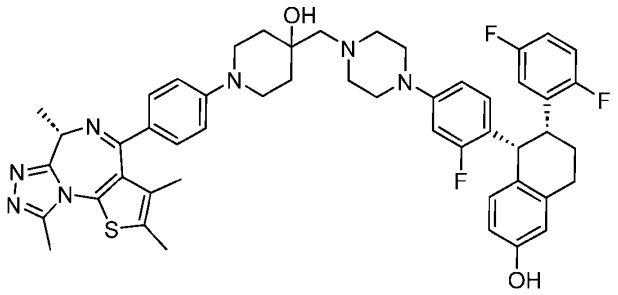
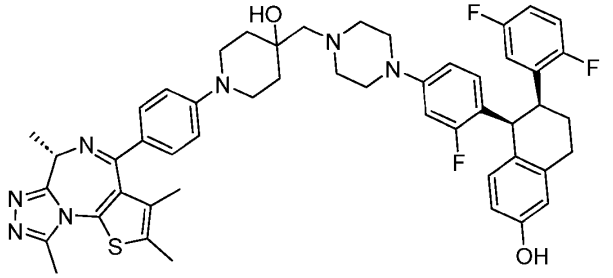
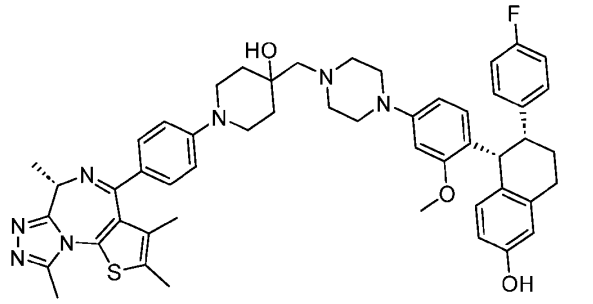
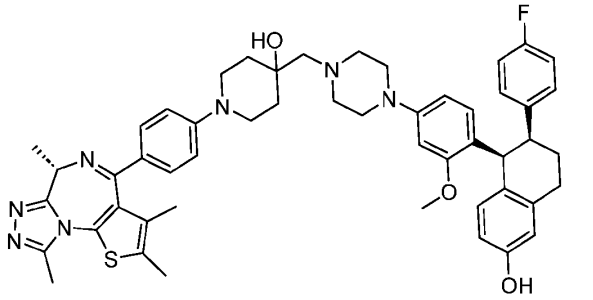
III-248	
III-249	
III-250	
III-251	
III-252	

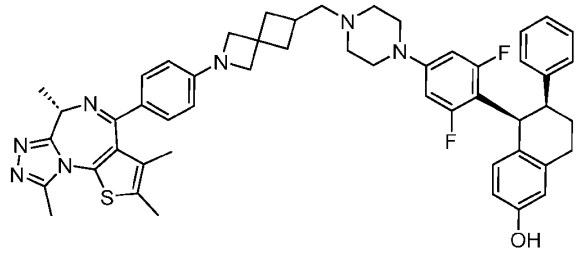
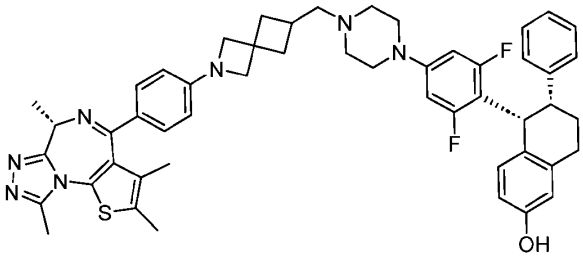
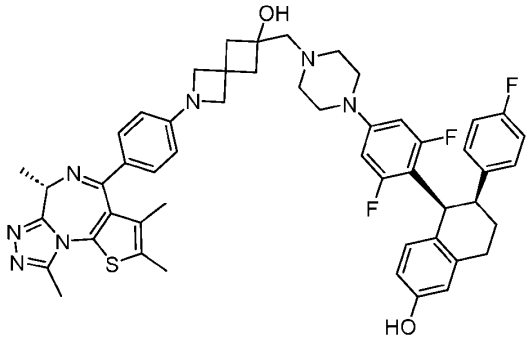
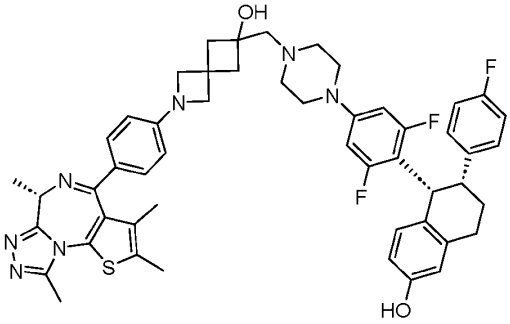
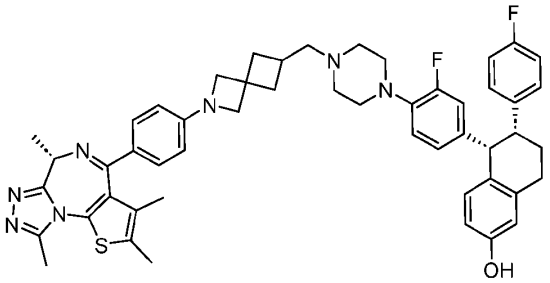
III-253	
III-254	
III-255	
III-256	
III-257	

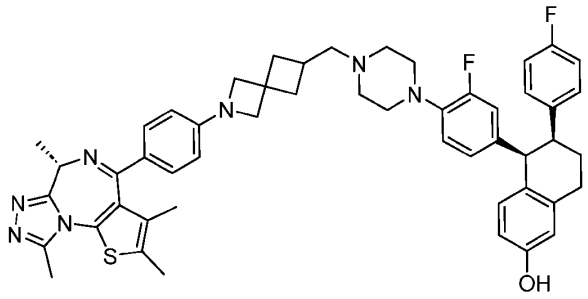
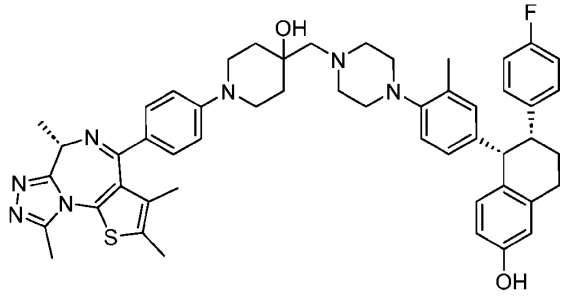
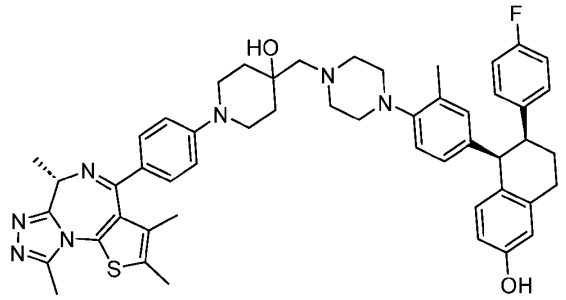
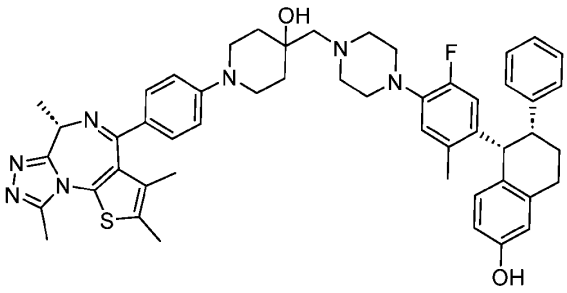
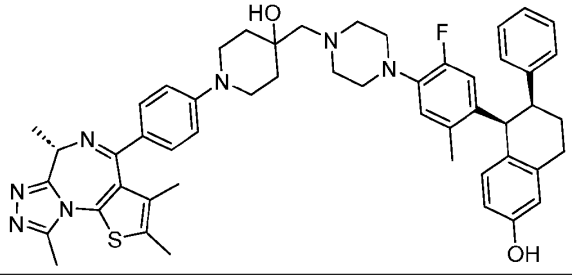
III-258	
III-259	
III-260	
III-261	

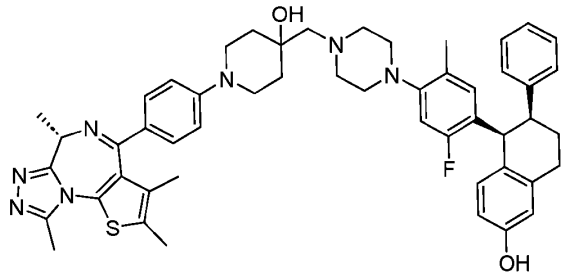
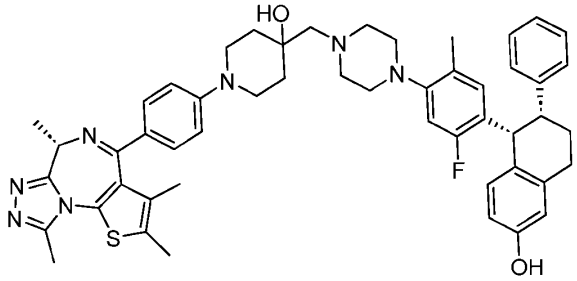
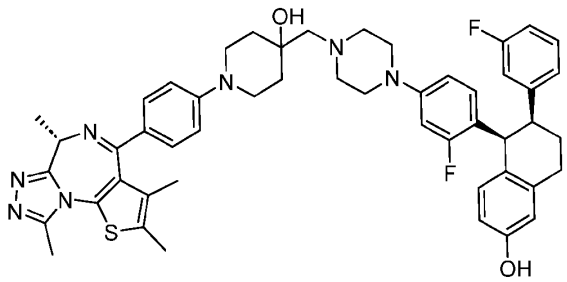
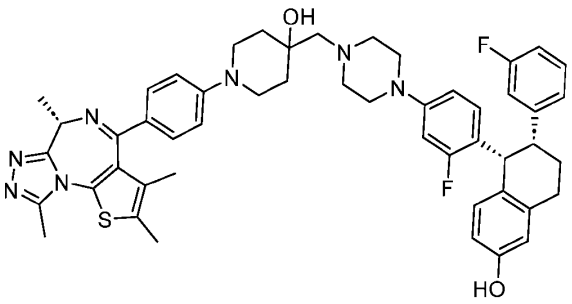
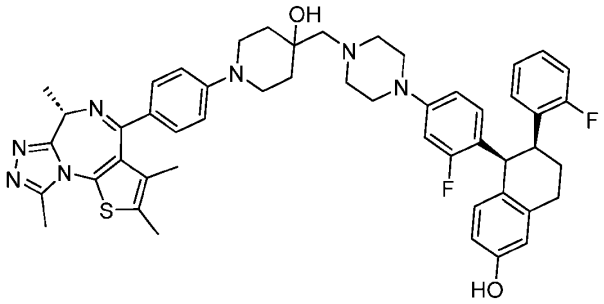
III-262	
III-263	
III-264	
III-265	
III-266	

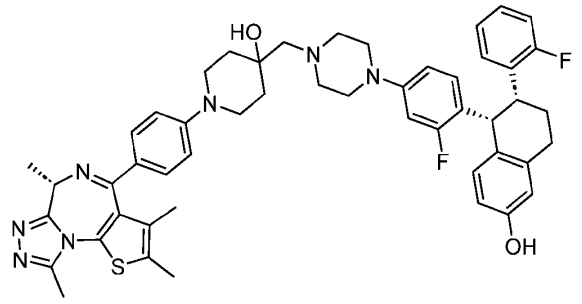
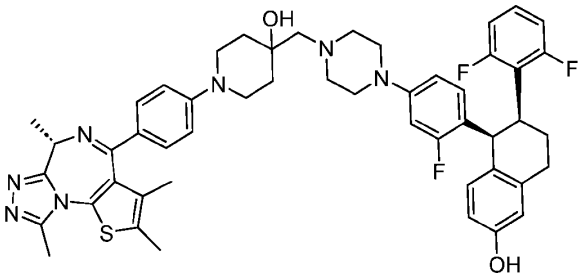
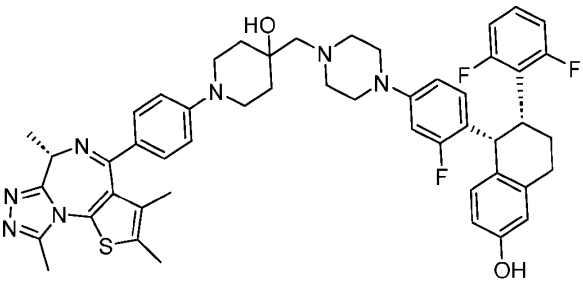
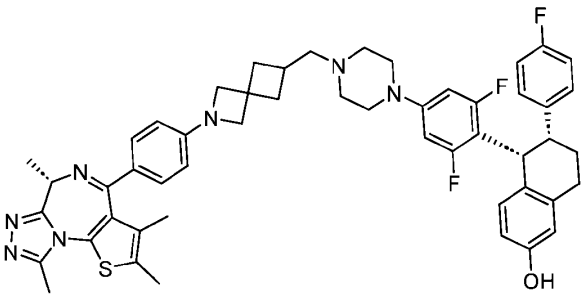
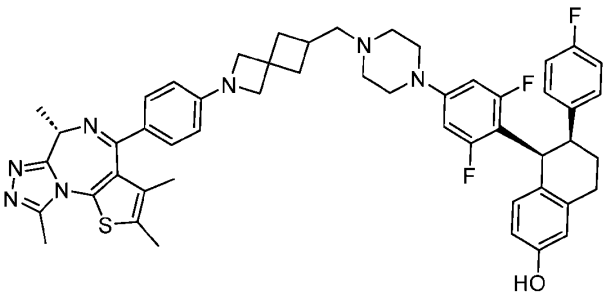
III-267	
III-268	
III-269	
III-270	
III-271	

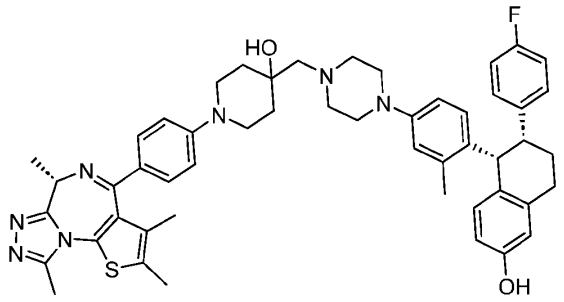
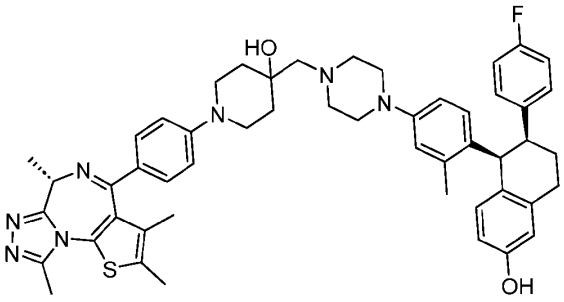
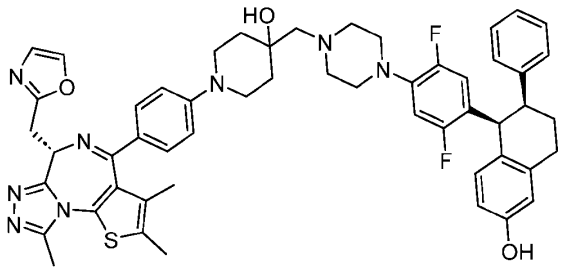
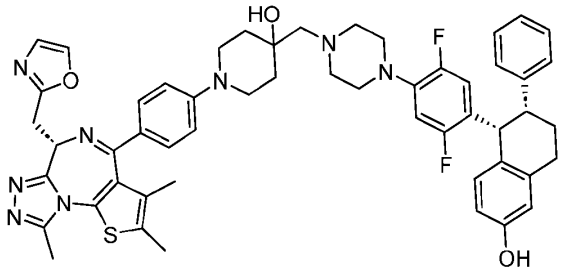
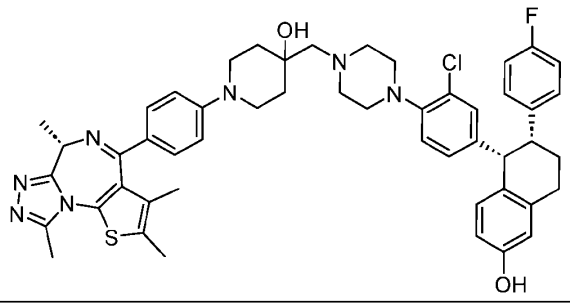
III-272	
III-273	
III-274	
III-275	
III-276	

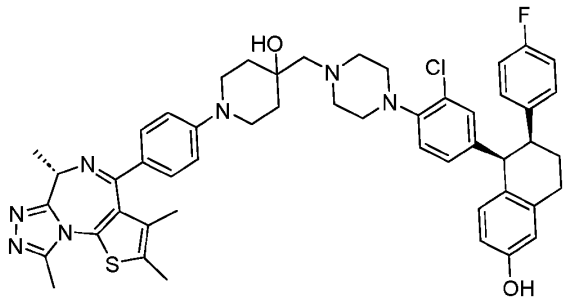
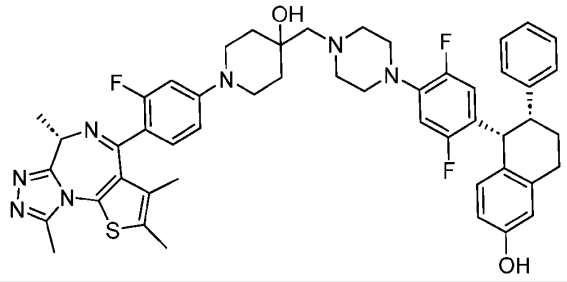
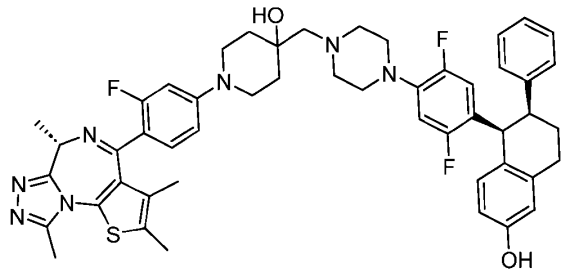
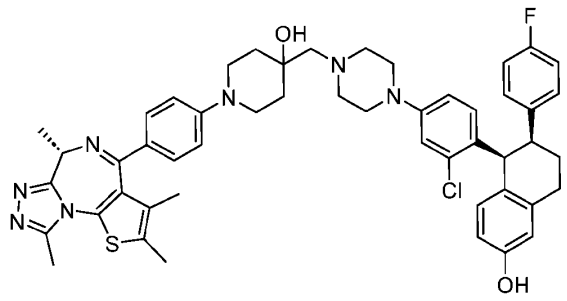
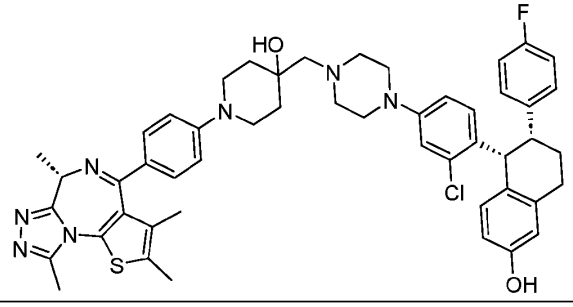
III-277	
III-278	
III-279	
III-280	
III-281	

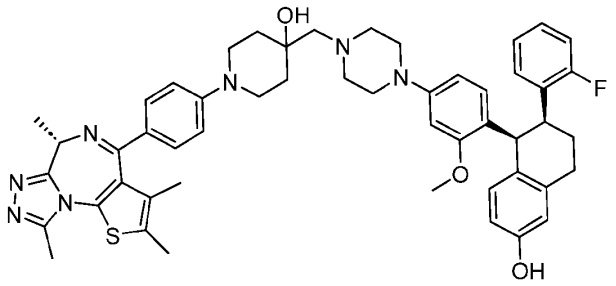
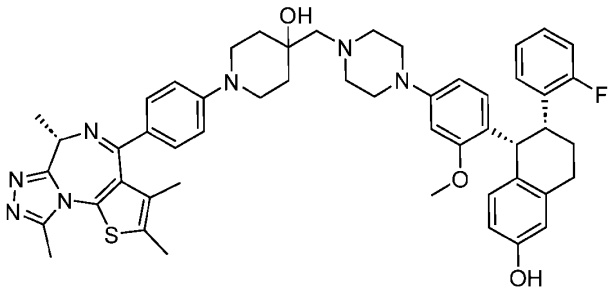
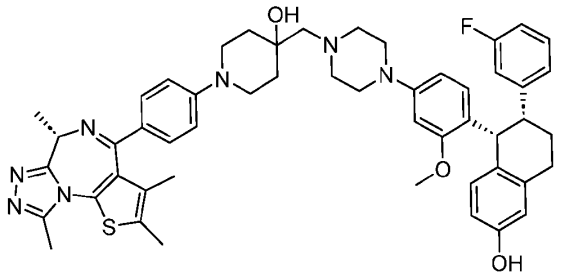
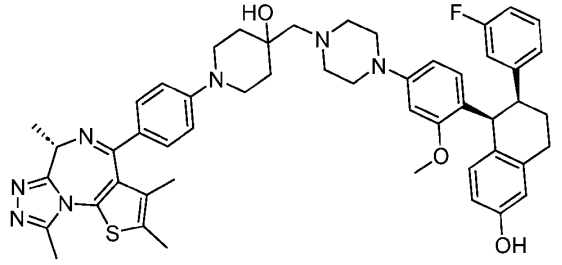
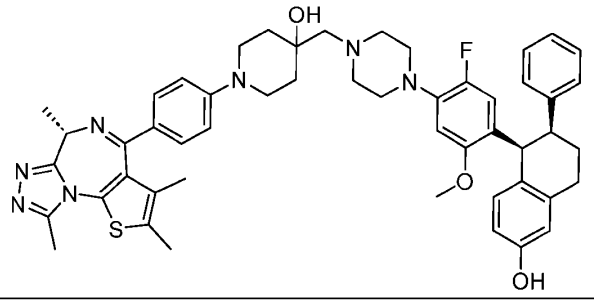
III-282	
III-283	
III-284	
III-285	
III-286	

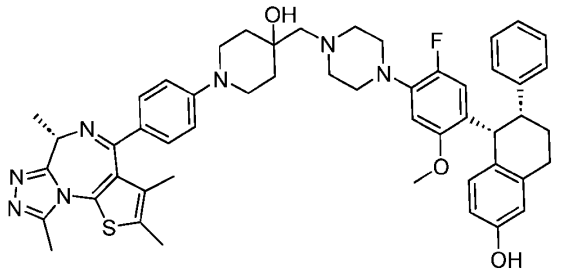
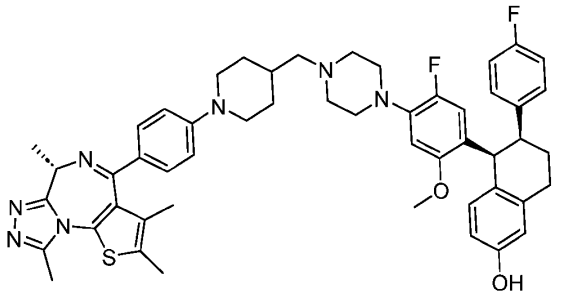
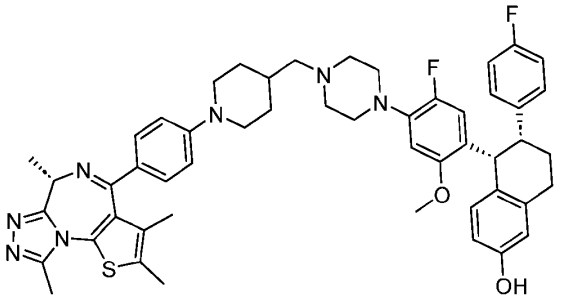
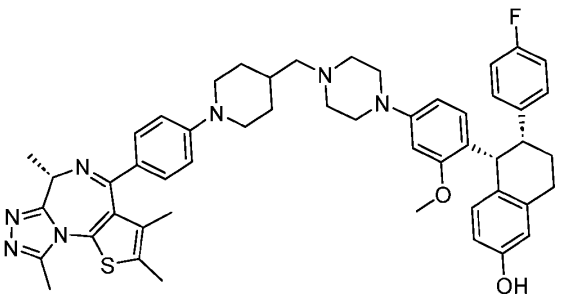
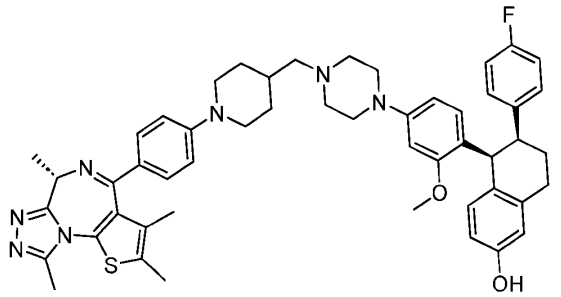
III-287	
III-288	
III-289	
III-290	
III-291	

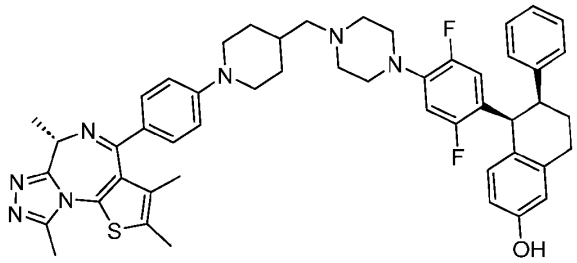
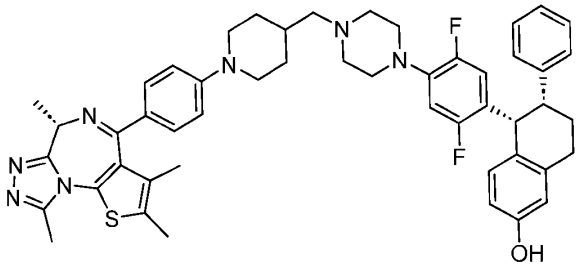
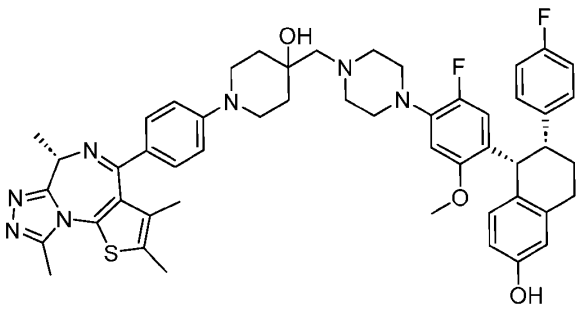
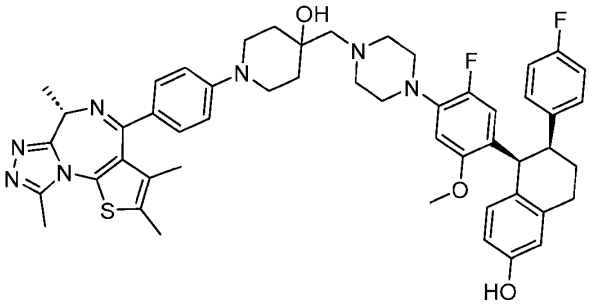
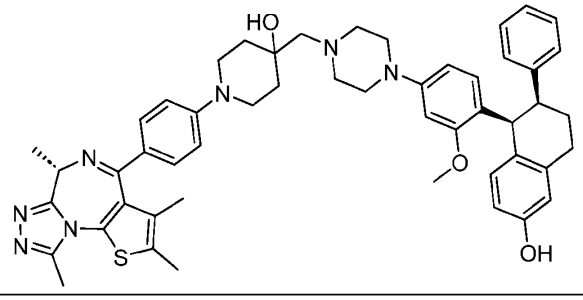
III-292	
III-293	
III-294	
III-295	
III-296	

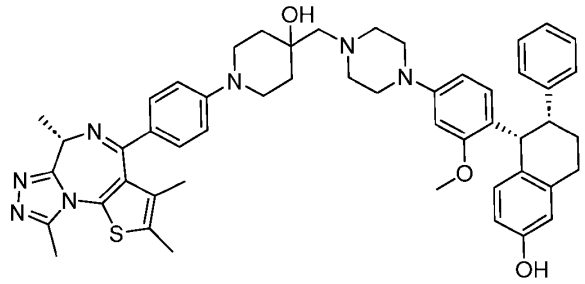
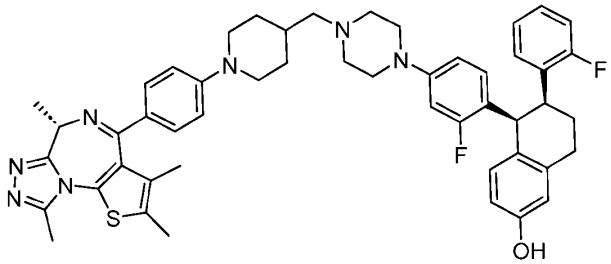
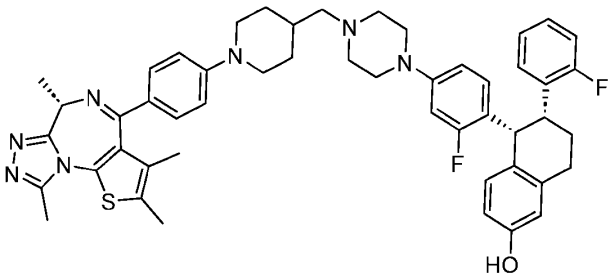
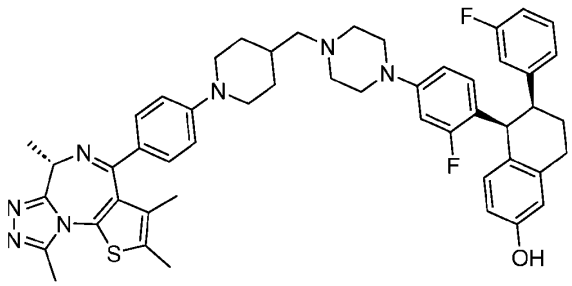
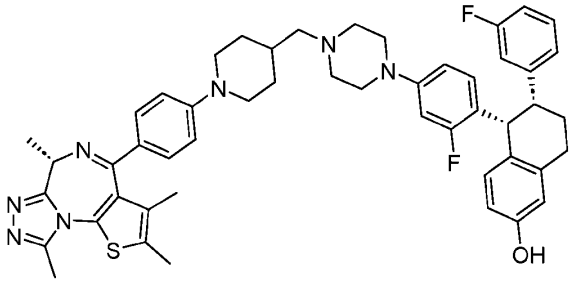
III-297	
III-298	
III-299	
III-300	
III-301	

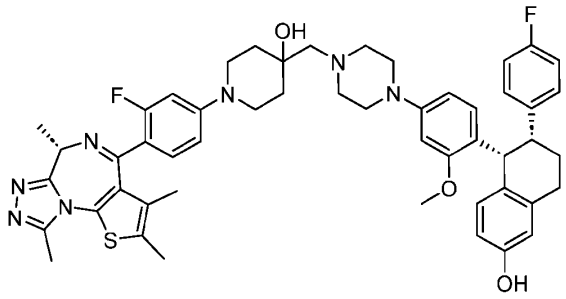
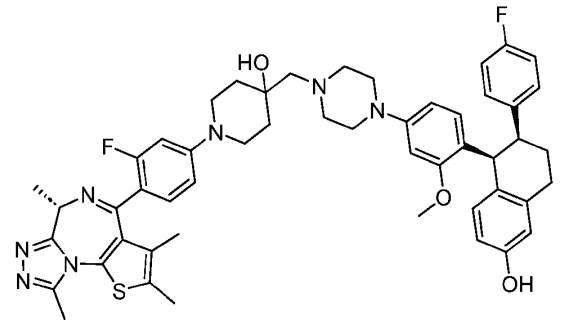
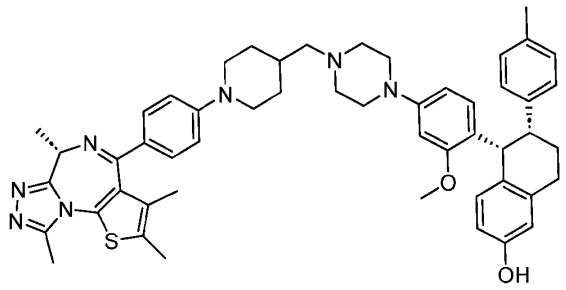
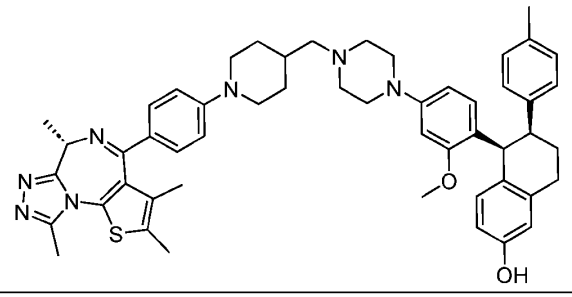
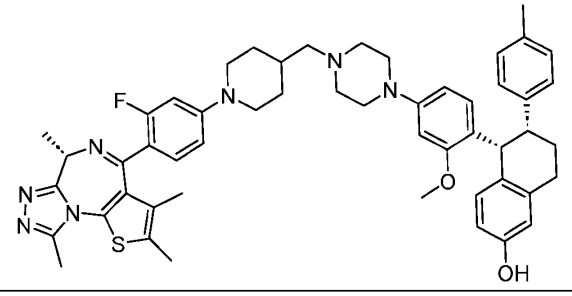
III-302	
III-303	
III-304	
III-305	
III-306	

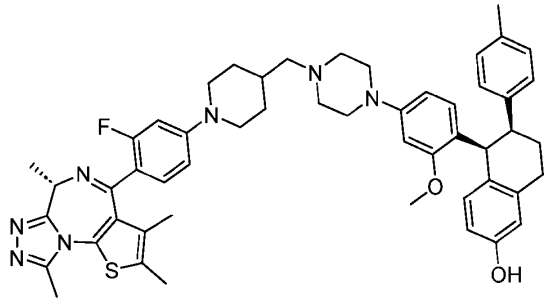
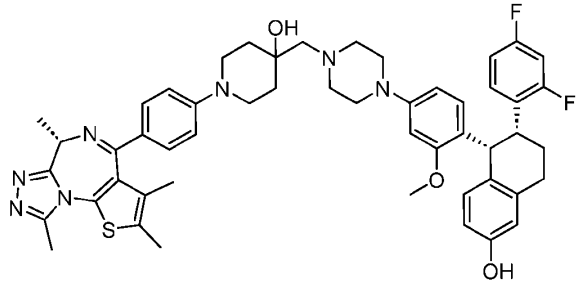
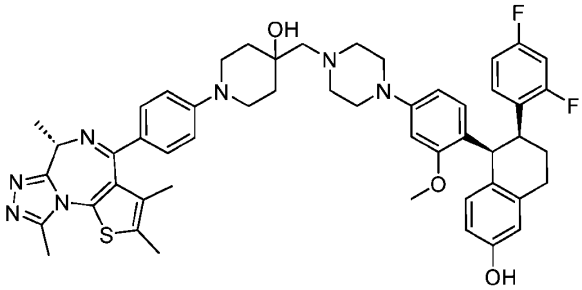
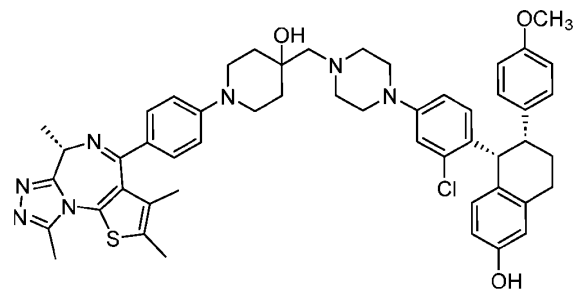
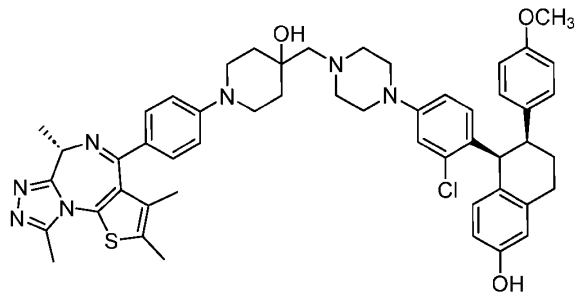
III-307	
III-308	
III-309	
III-310	
III-311	

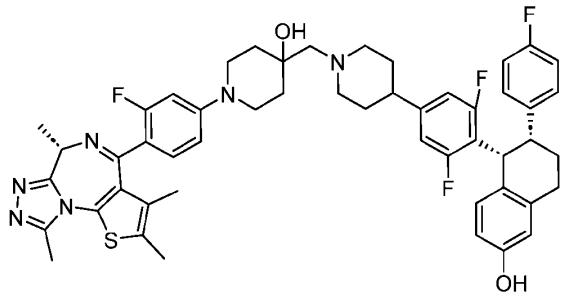
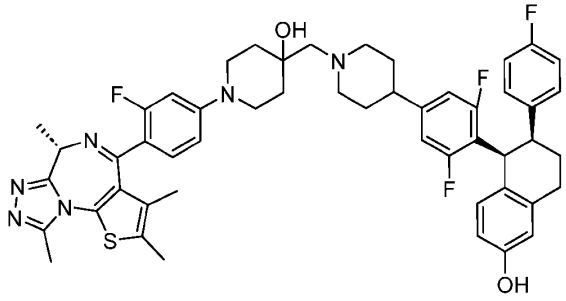
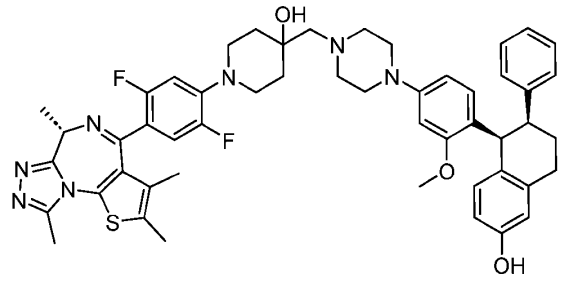
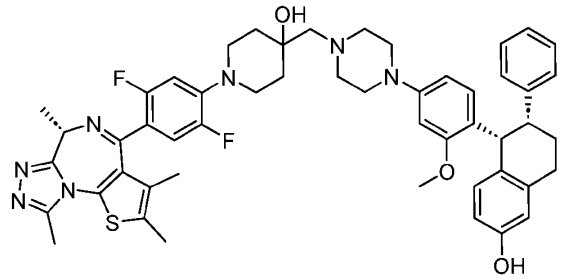
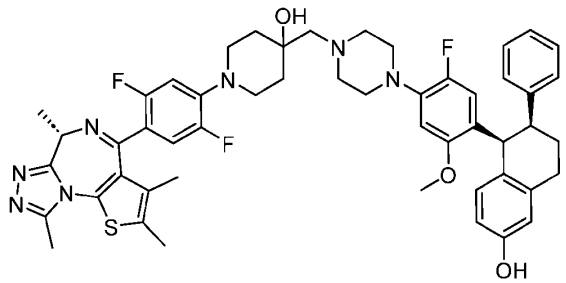
III-312	
III-313	
III-314	
III-315	
III-316	

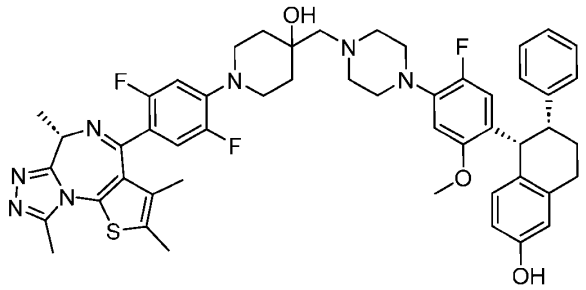
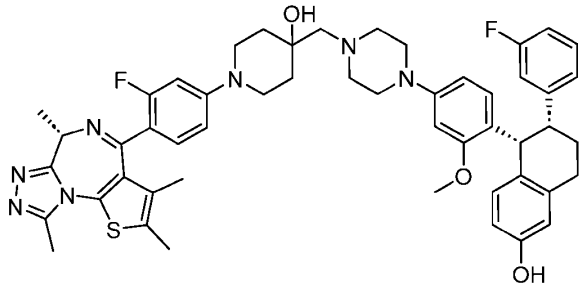
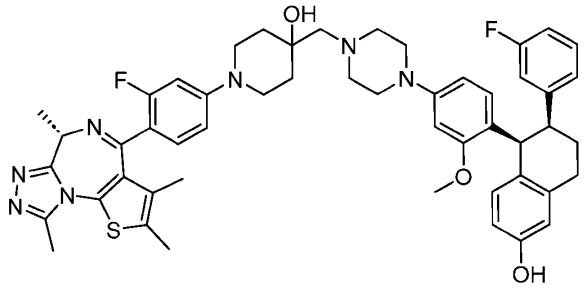
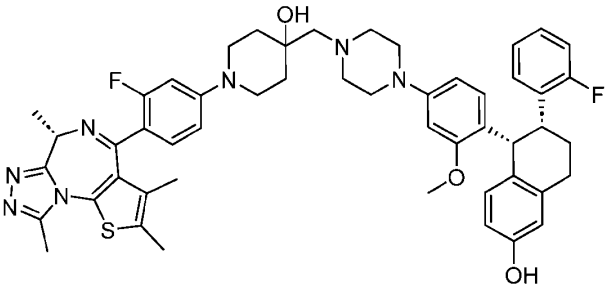
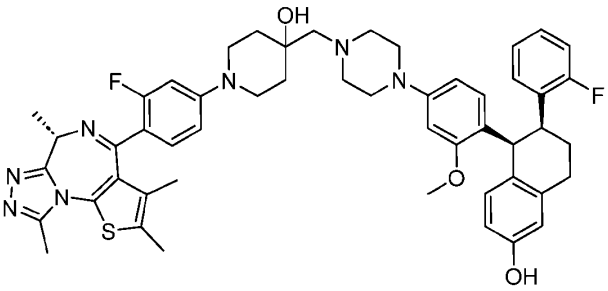
III-317	
III-318	
III-319	
III-320	
III-321	

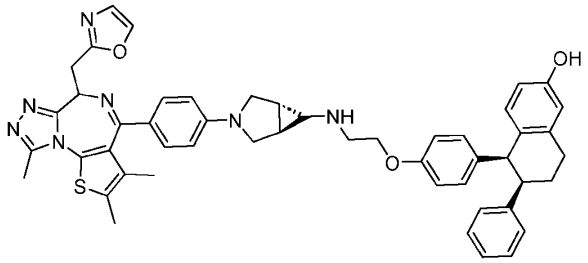
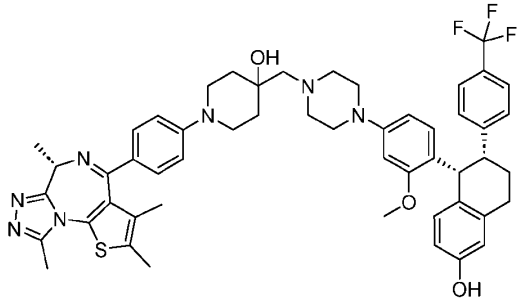
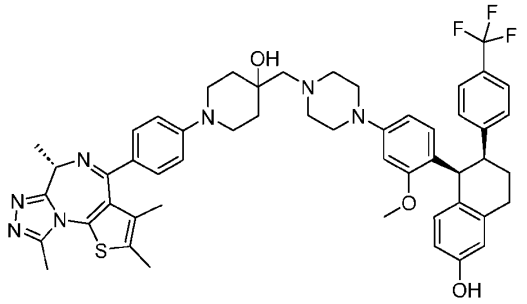
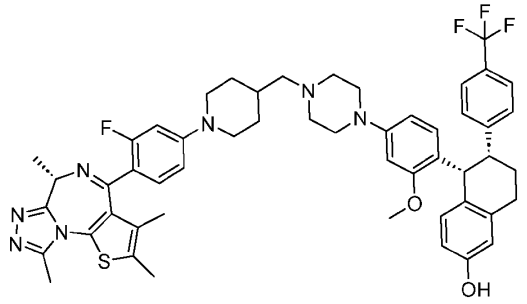
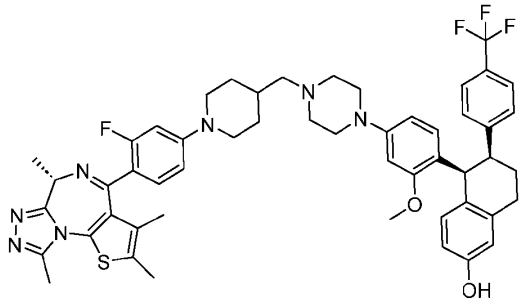
III-322	
III-323	
III-324	
III-325	
III-326	

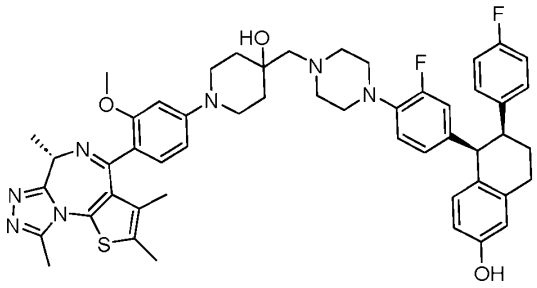
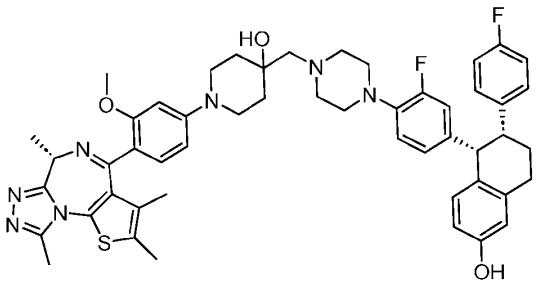
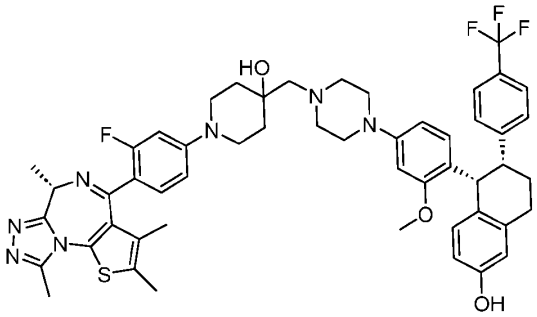
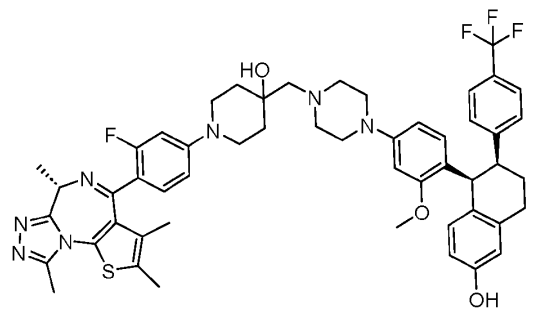
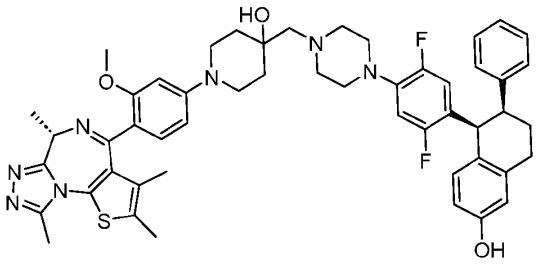
III-327	
III-328	
III-329	
III-330	
III-331	

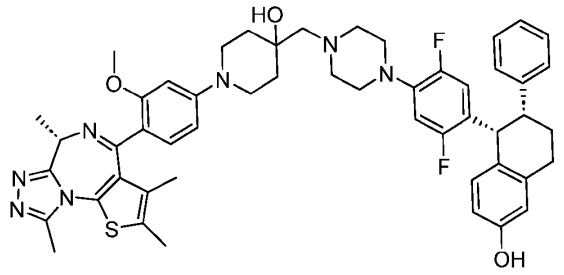
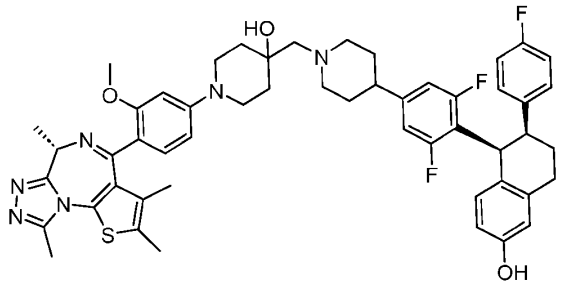
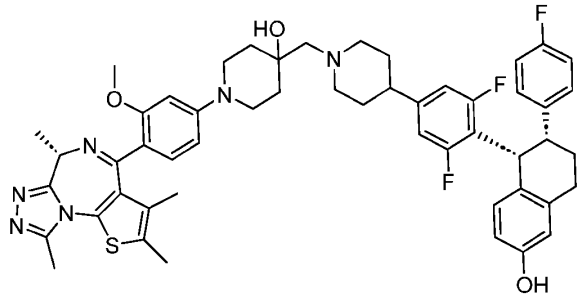
III-332	
III-333	
III-334	
III-335	
III-336	

III-337	
III-338	
III-339	
III-340	
III-341	

III-342	
III-343	
III-344	
III-345	
III-346	

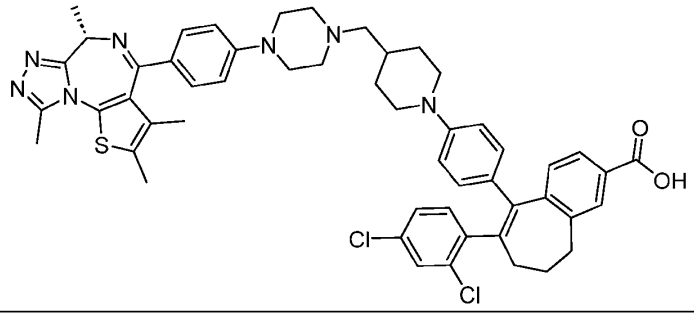
III-347	
III-348	
III-349	
III-350	
III-351	

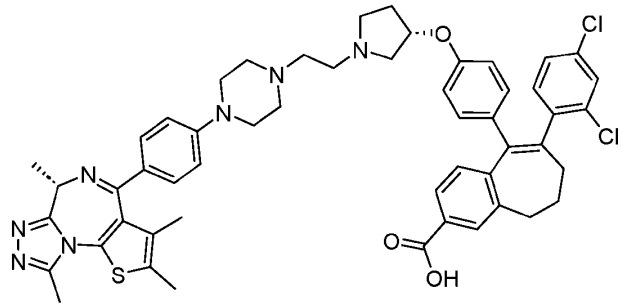
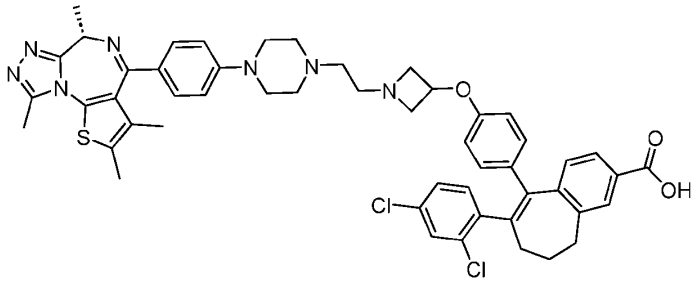
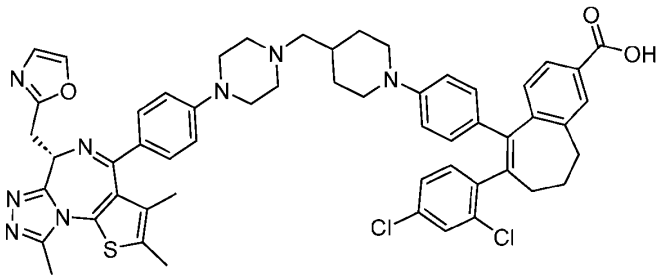
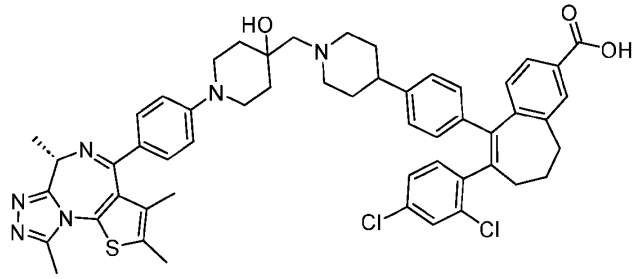
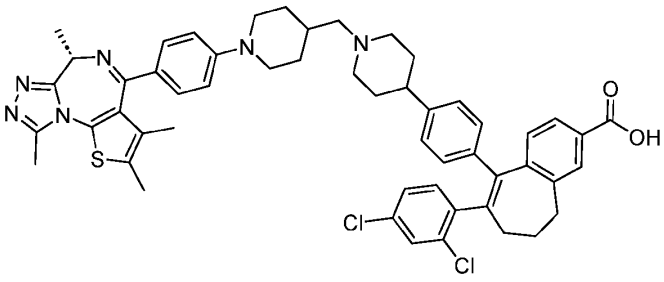
III-352	
III-353	
III-354	
III-355	
III-356	

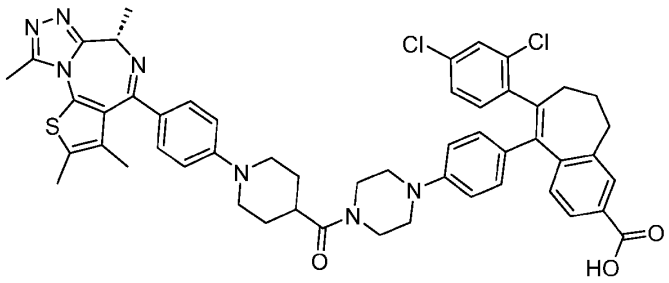
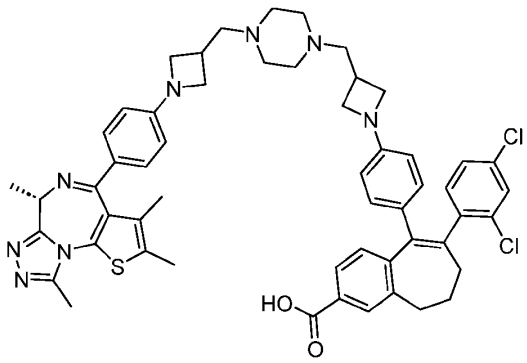
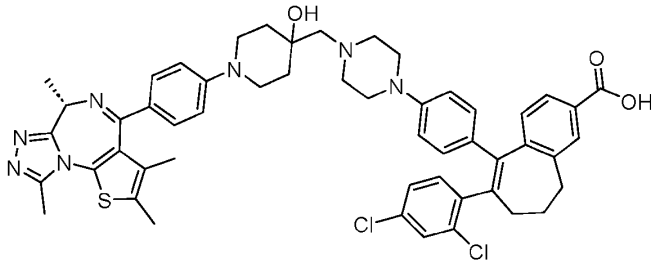
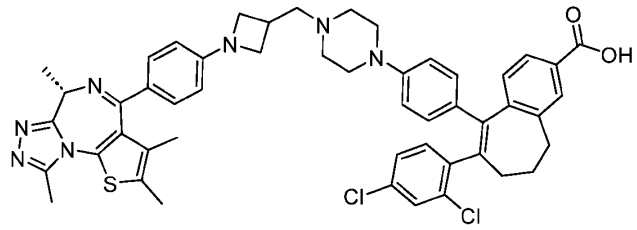
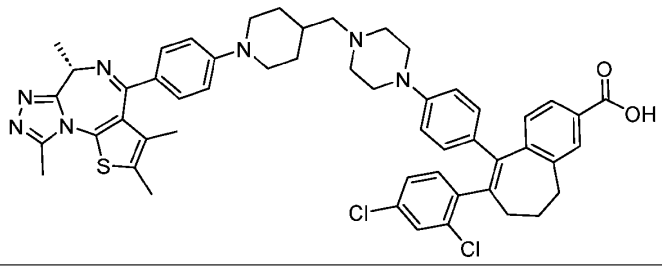
III-357	
III-358	
III-359	

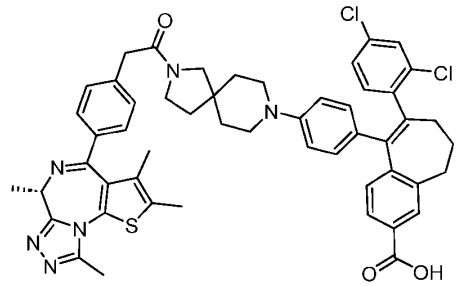
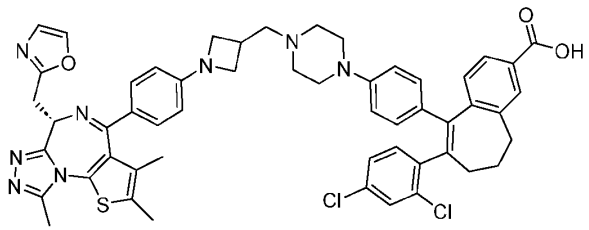
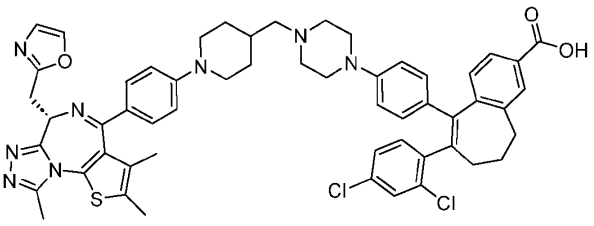
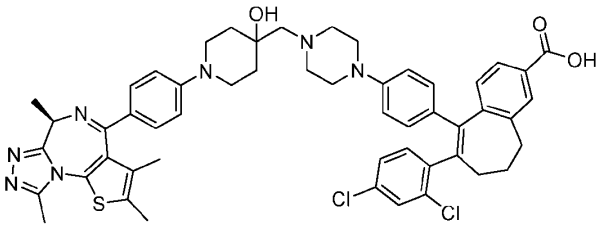
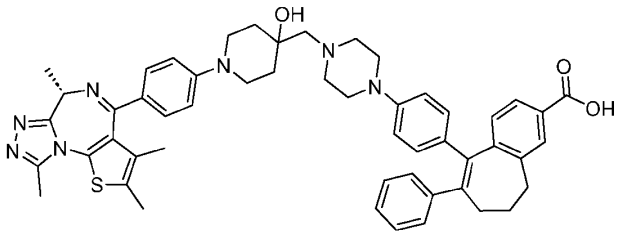
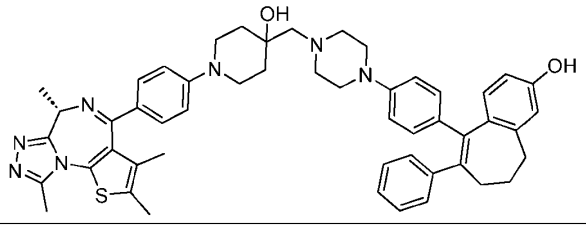
[0382] In certain embodiments, the compound is a compound in Table 4, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 4.

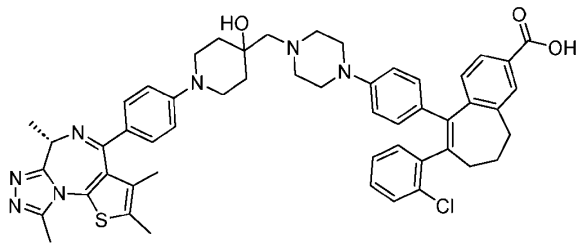
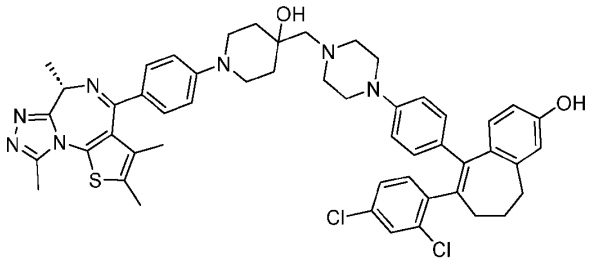
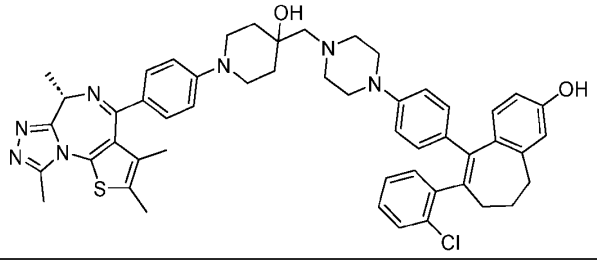
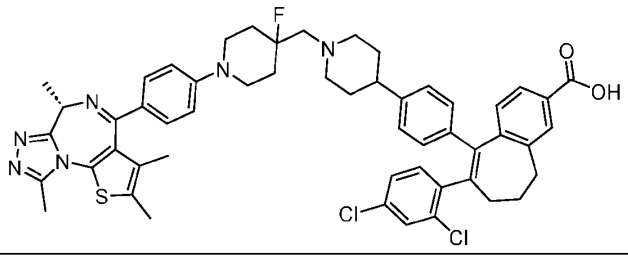
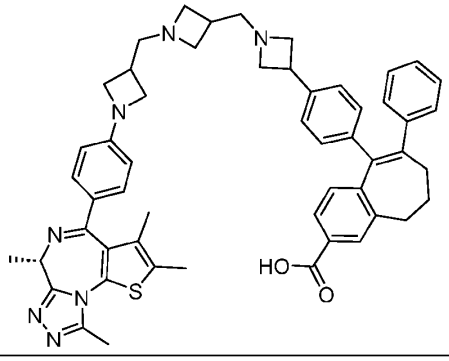
TABLE 4.

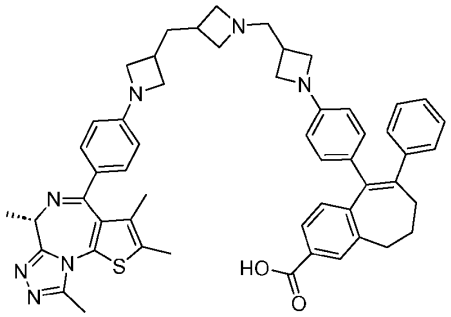
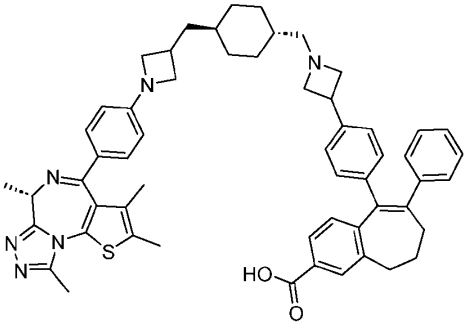
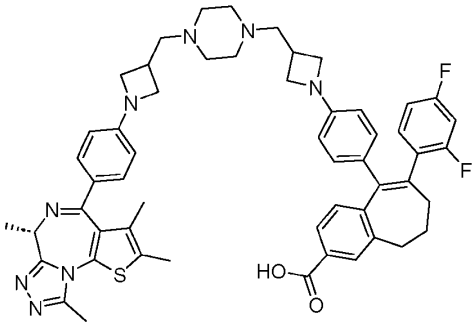
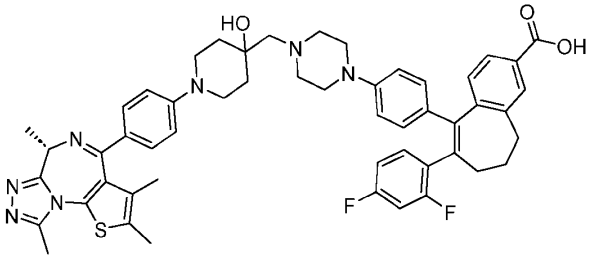
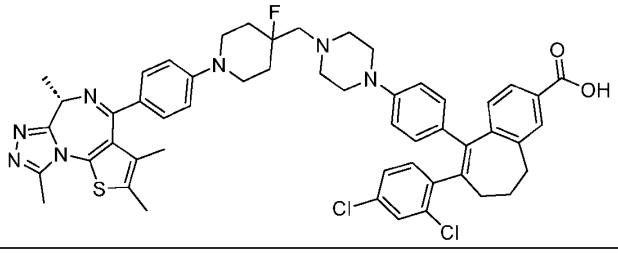
Compound No.	Compound Structure
IV-1	

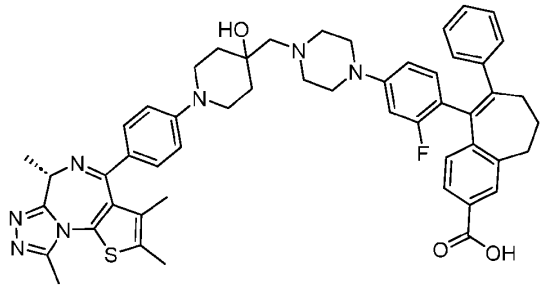
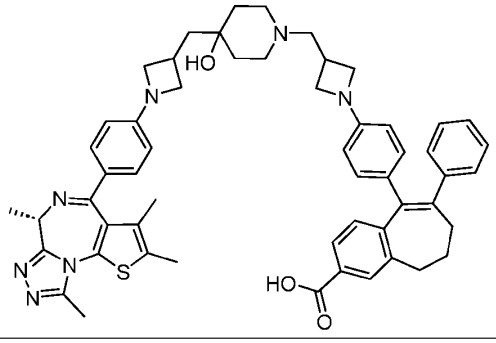
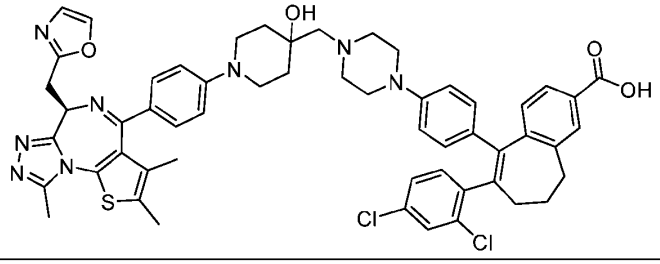
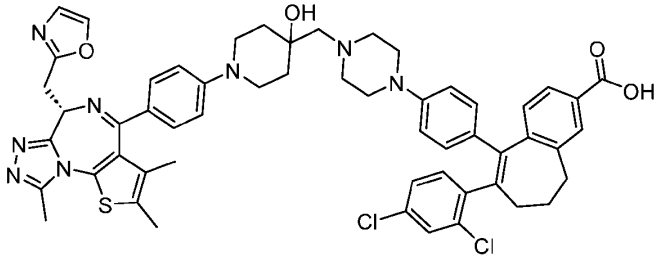
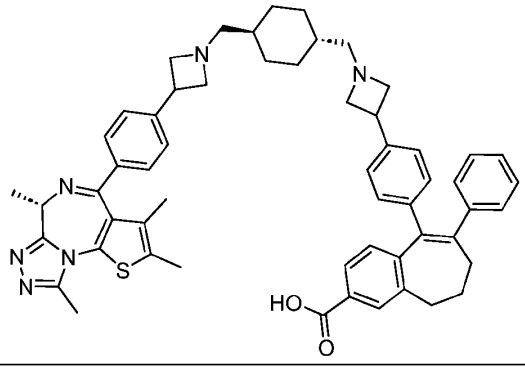
IV-2	
IV-3	
IV-4	
IV-5	
IV-6	

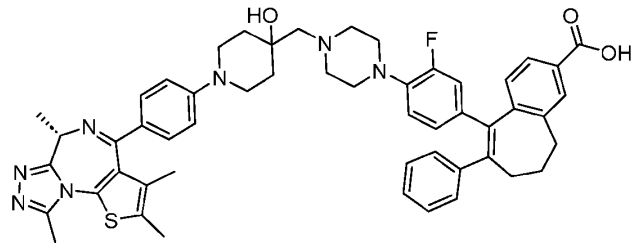
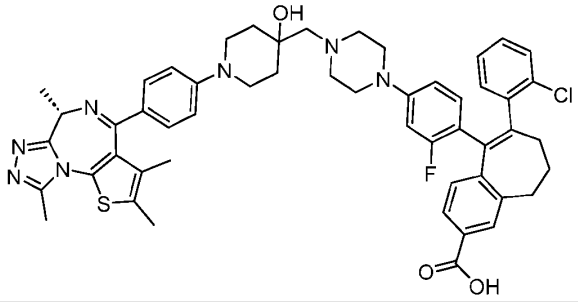
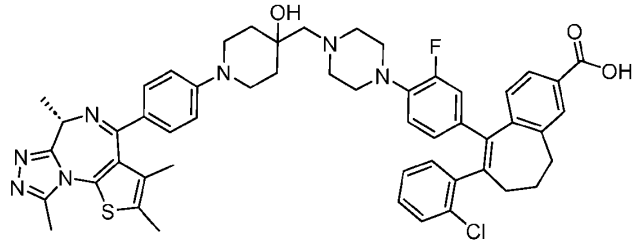
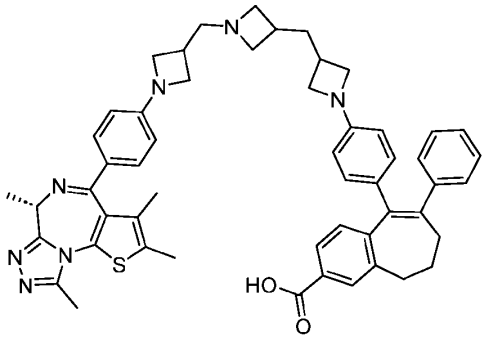
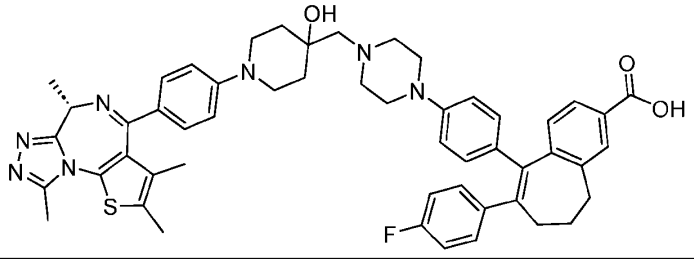
IV-7	
IV-8	
IV-9	
IV-10	
IV-11	

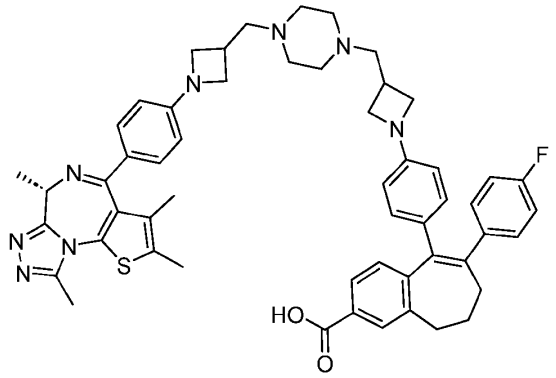
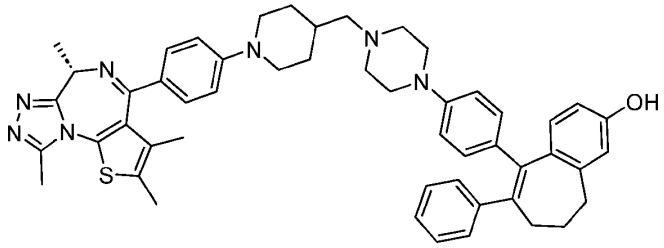
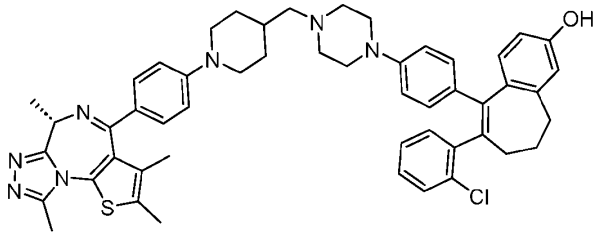
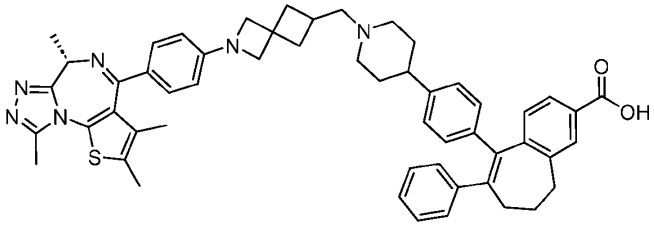
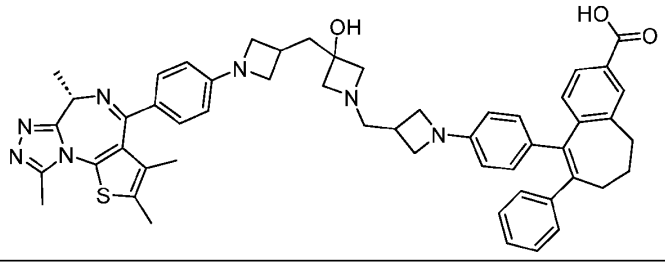
IV-12	
IV-13	
IV-14	
IV-15	
IV-16	
IV-17	

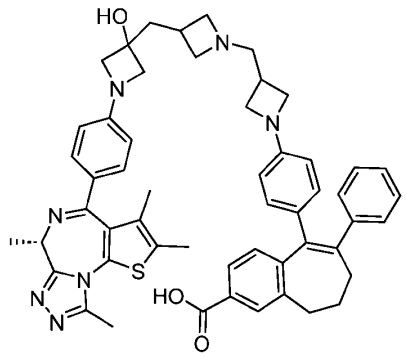
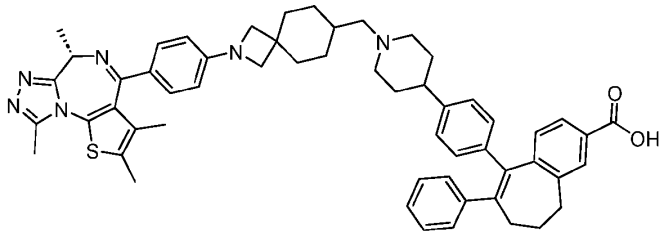
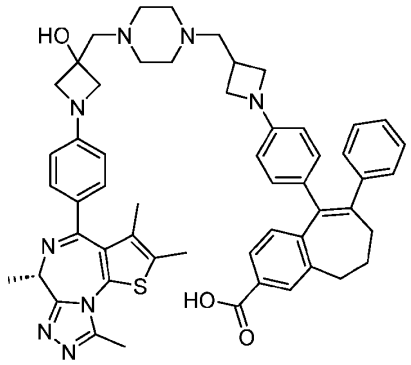
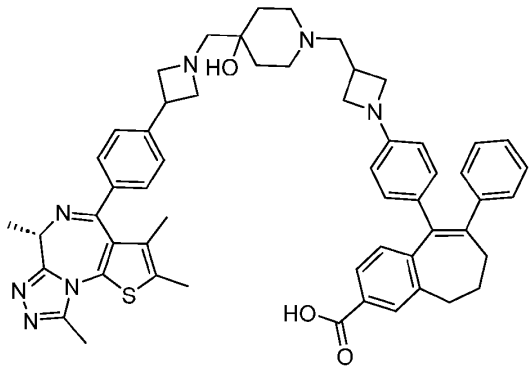
IV-18	
IV-19	
IV-20	
IV-21	
IV-22	

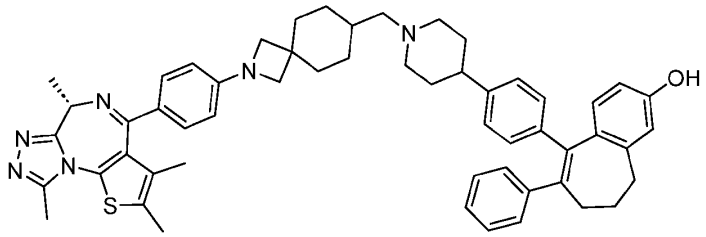
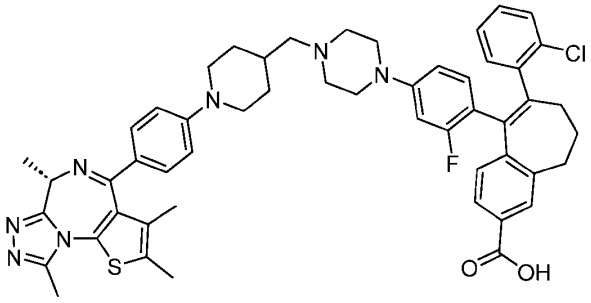
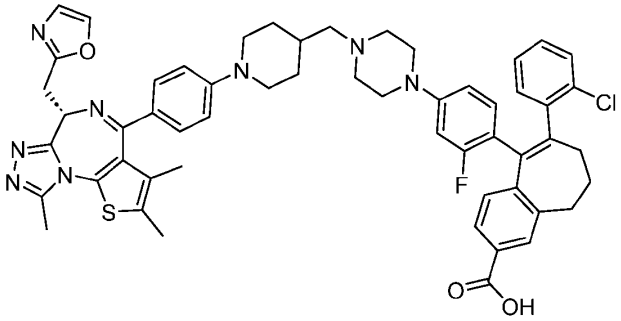
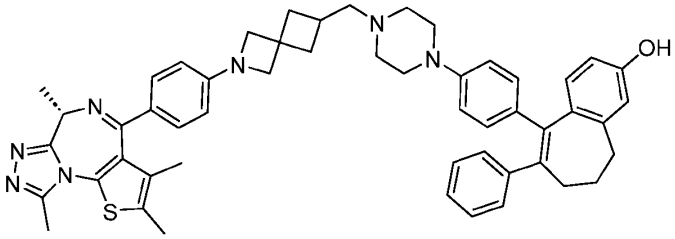
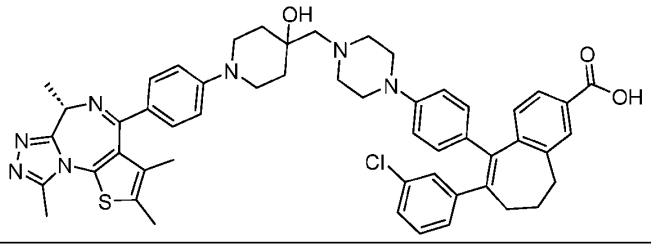
IV-23	
IV-24	
IV-25	
IV-26	
IV-27	

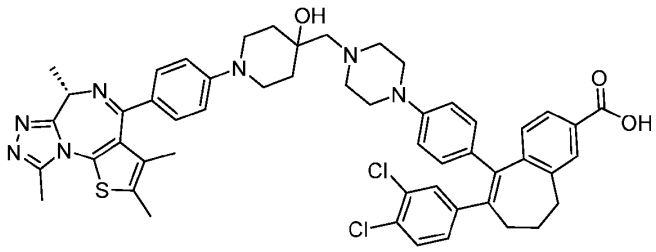
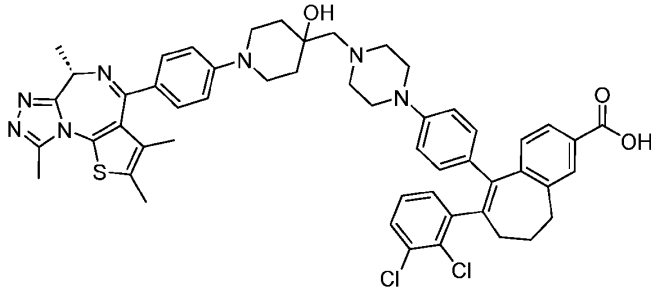
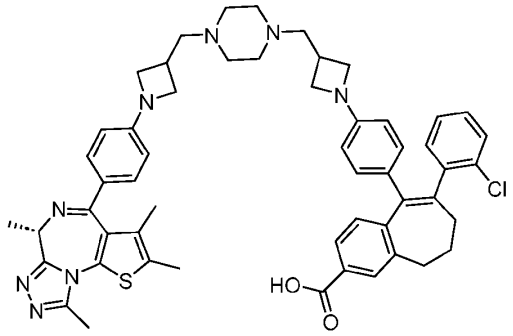
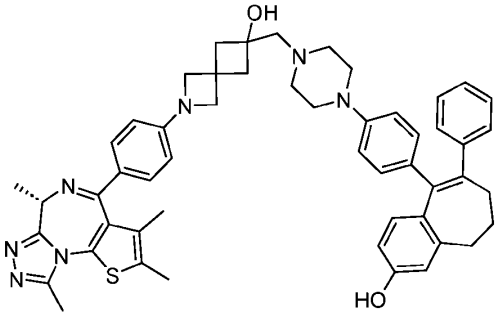
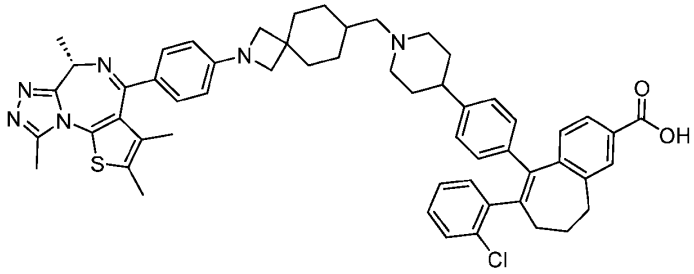
IV-28	
IV-29	
IV-30	
IV-31	
IV-32	

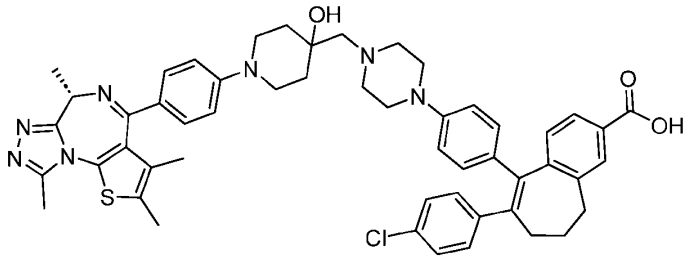
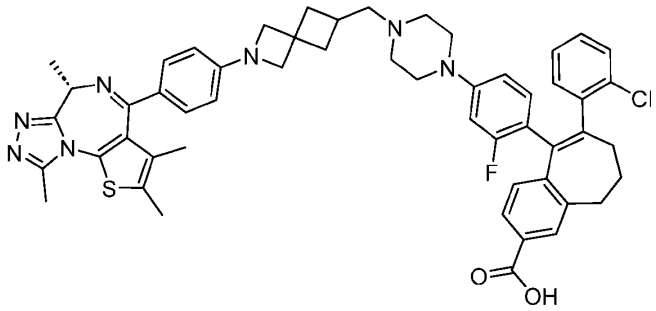
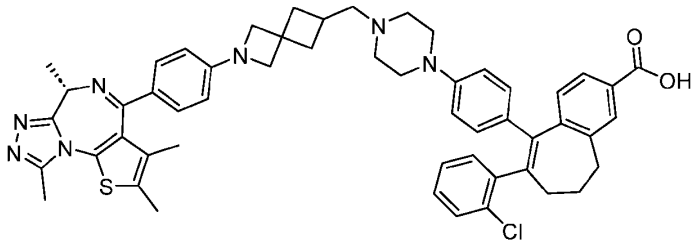
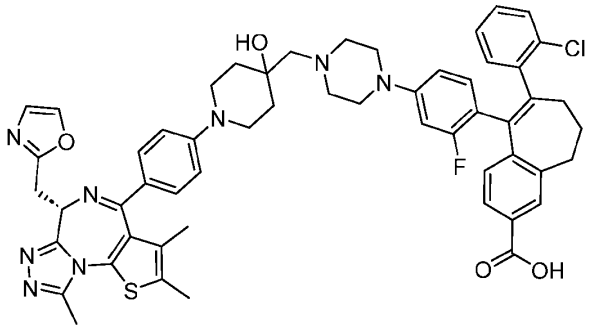
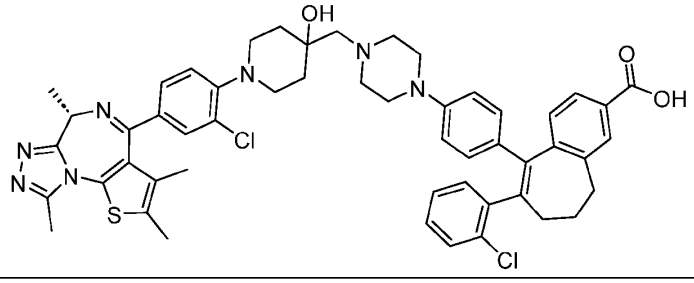
IV-33	
IV-34	
IV-35	
IV-36	
IV-37	

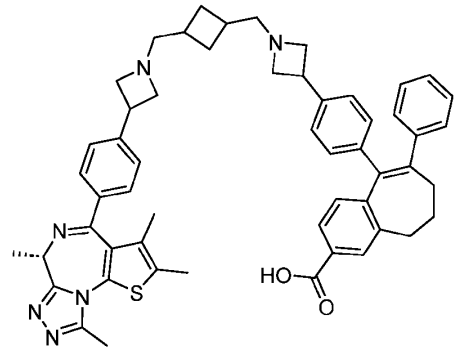
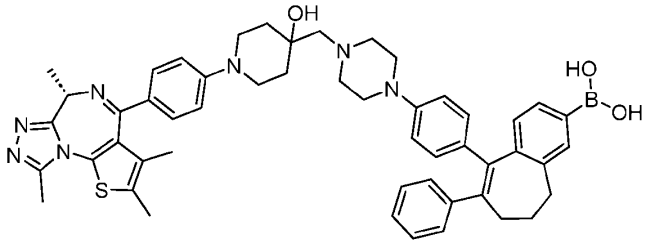
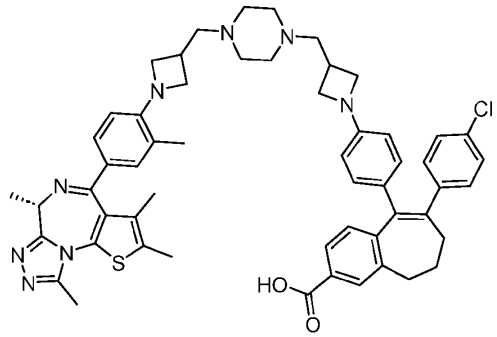
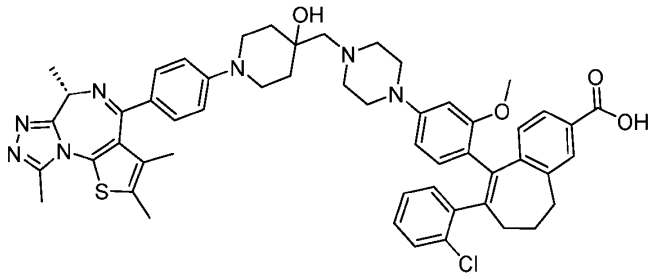
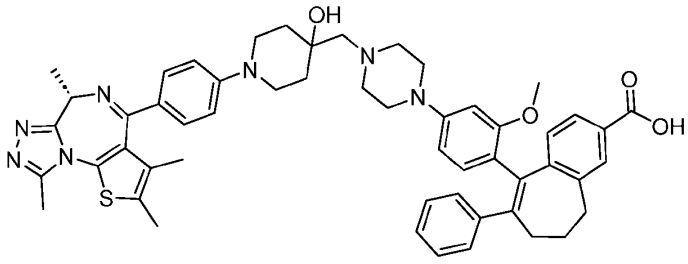
IV-38	
IV-39	
IV-40	
IV-41	
IV-42	

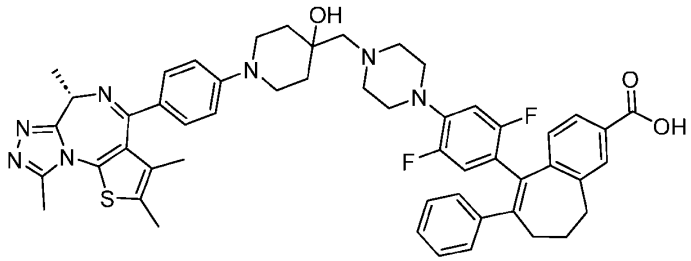
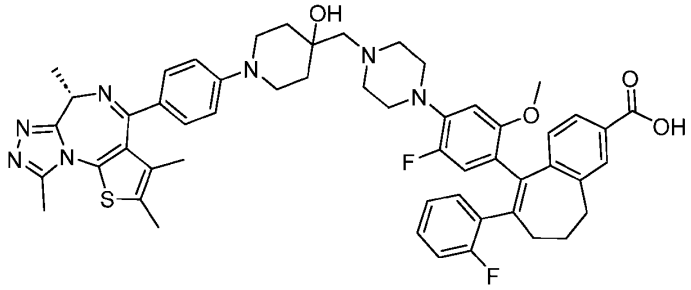
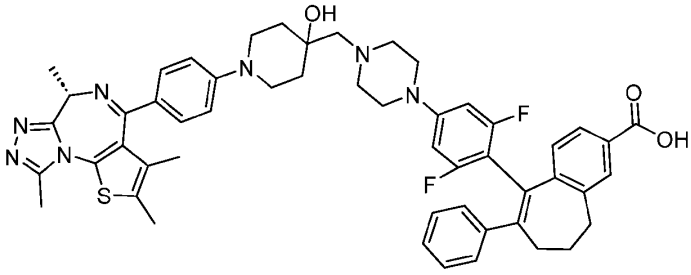
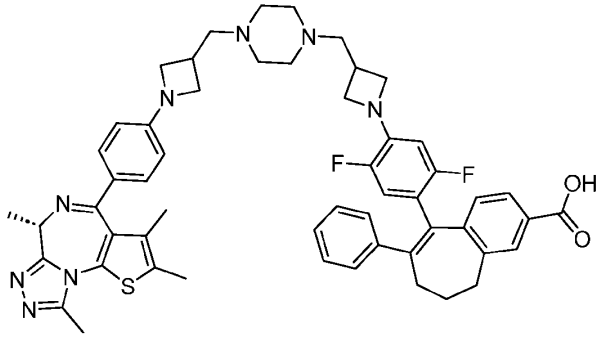
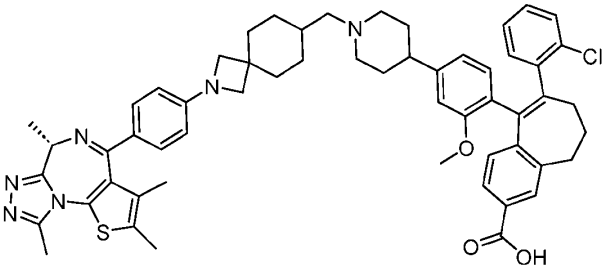
IV-43	
IV-44	
IV-45	
IV-46	

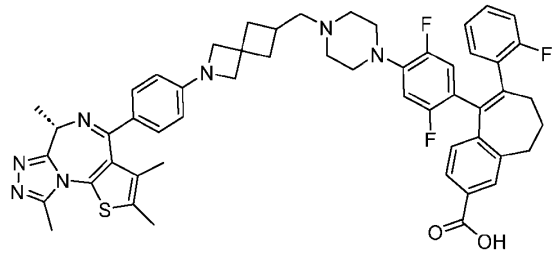
IV-47	
IV-48	
IV-49	
IV-50	
IV-51	

IV-52	
IV-53	
IV-54	
IV-55	
IV-56	

IV-57	
IV-58	
IV-59	
IV-60	
IV-61	

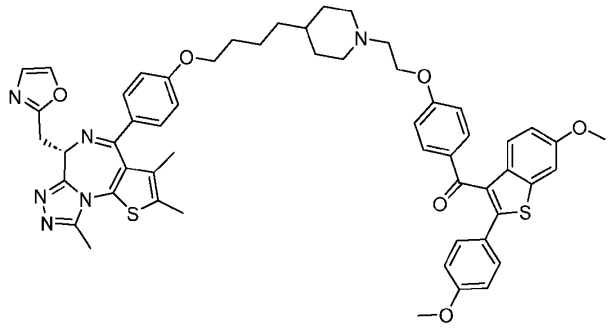
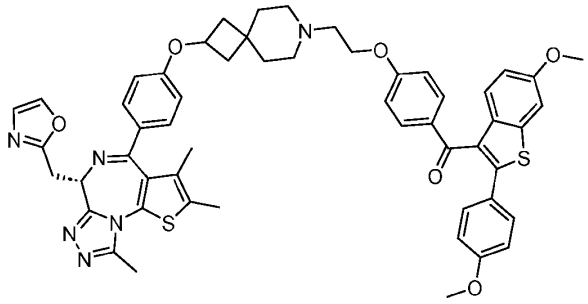
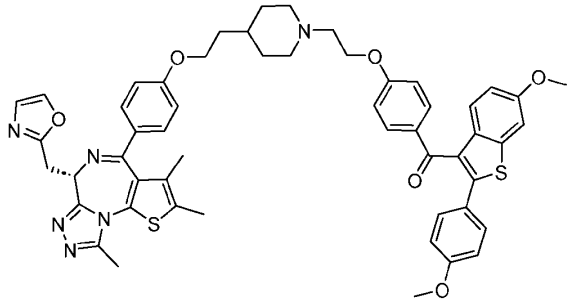
IV-62	
IV-63	
IV-64	
IV-65	
IV-66	

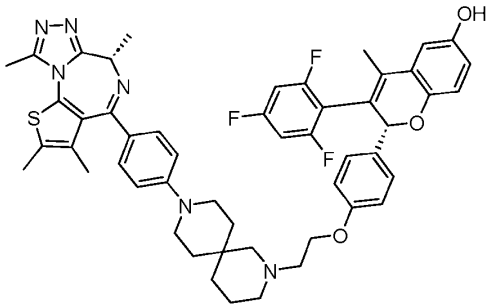
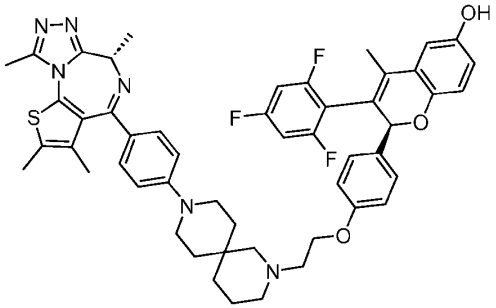
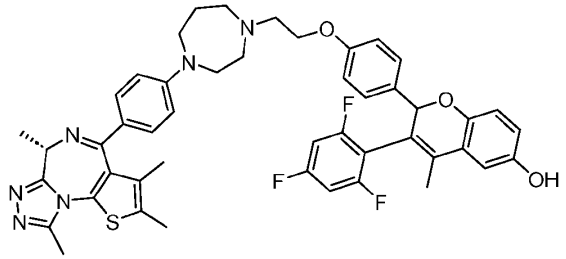
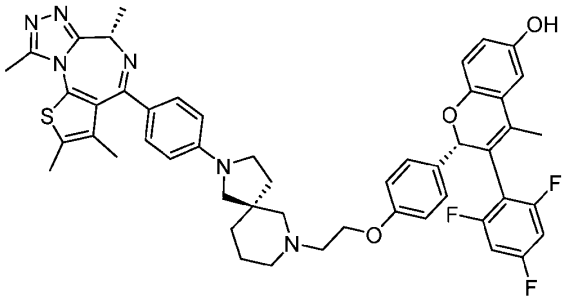
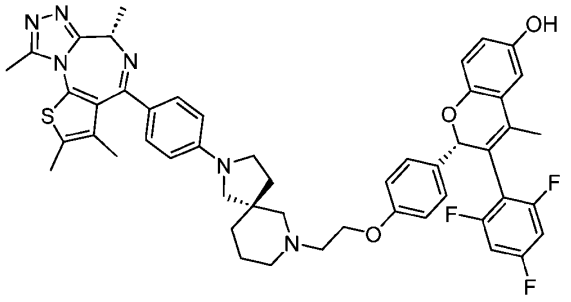
IV-67	
IV-68	
IV-69	
IV-70	
IV-71	

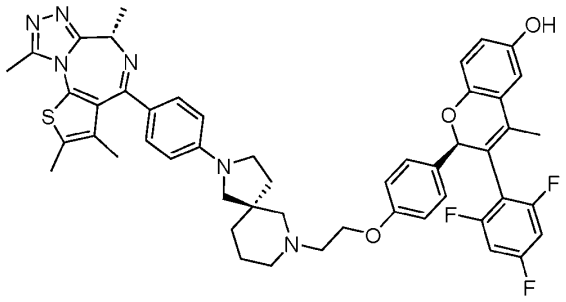
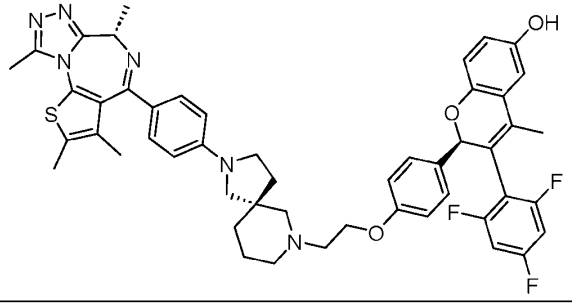
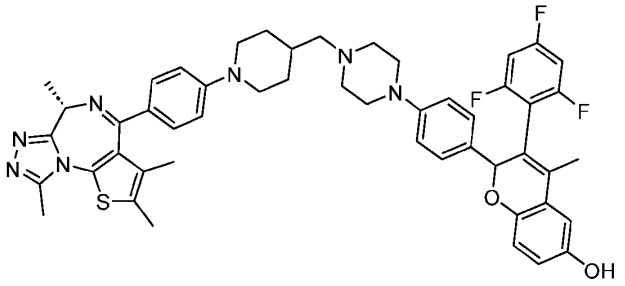
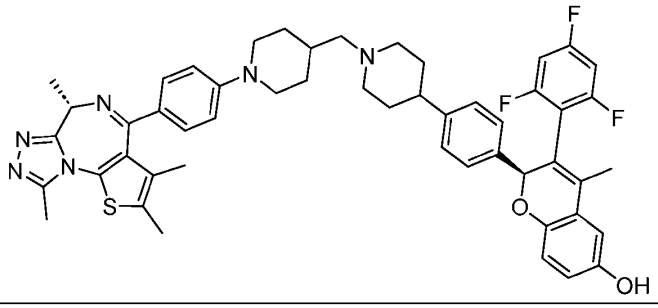
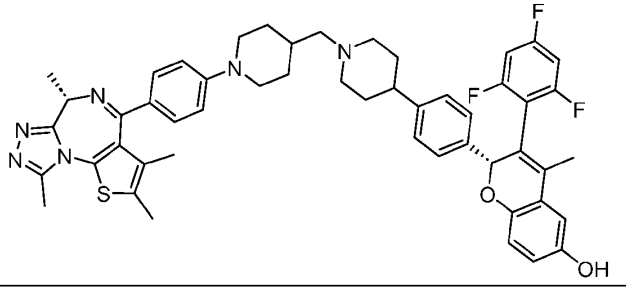
IV-72	

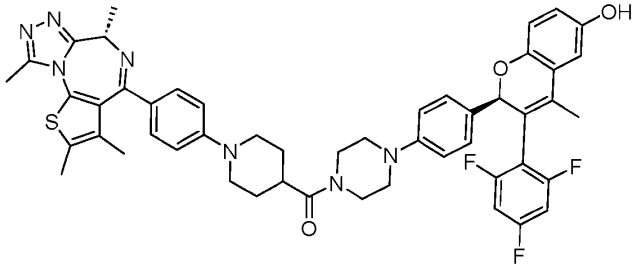
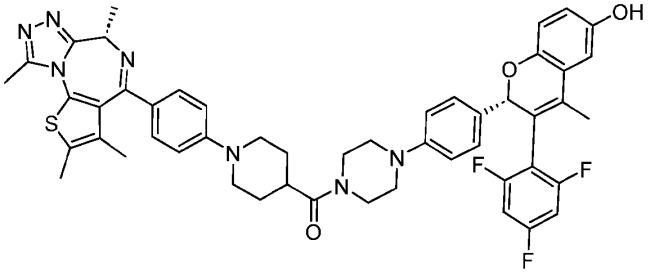
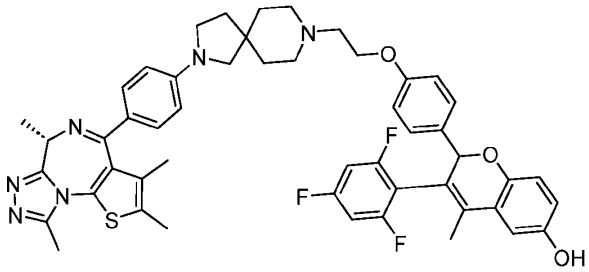
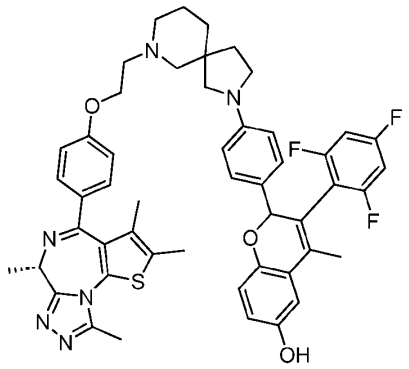
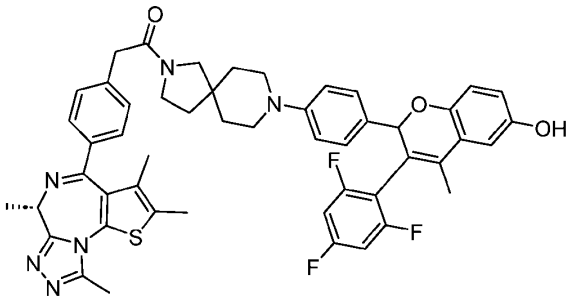
[0383] In certain embodiments, the compound is a compound in Table 5, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 5.

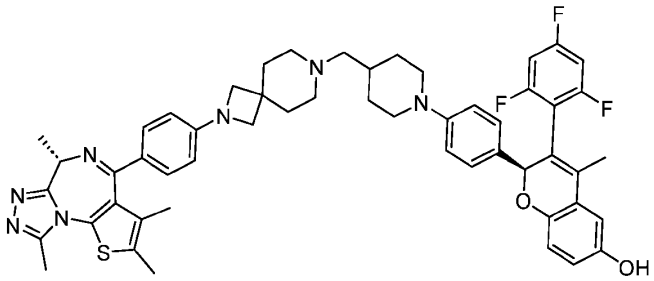
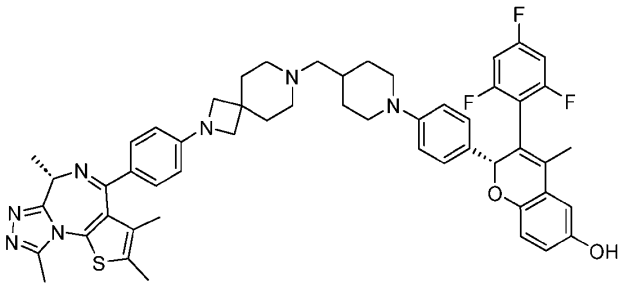
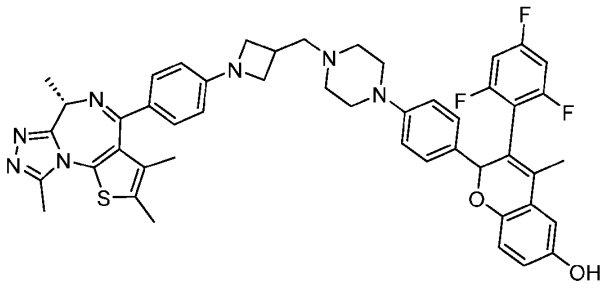
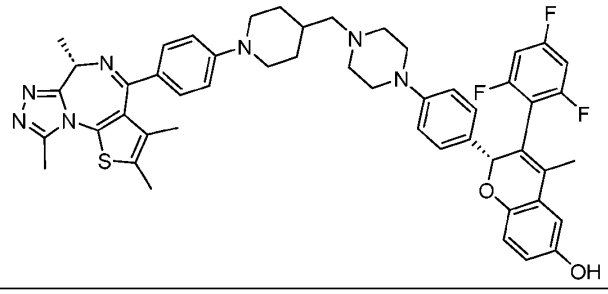
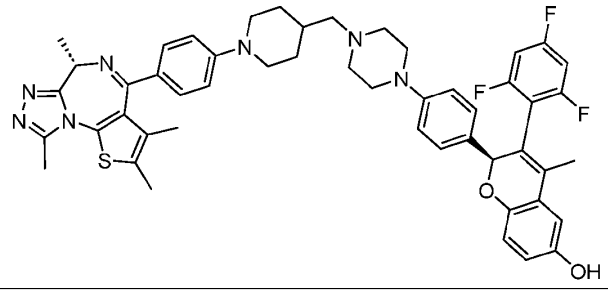
TABLE 5.

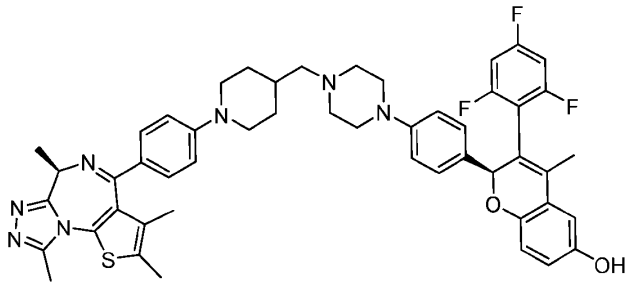
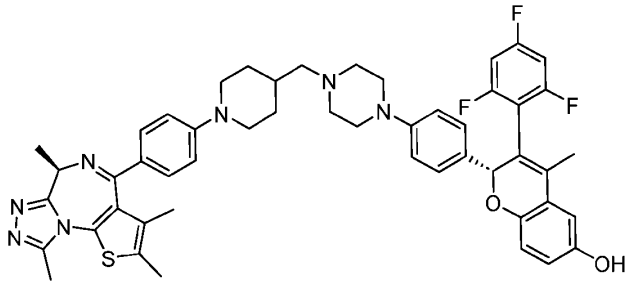
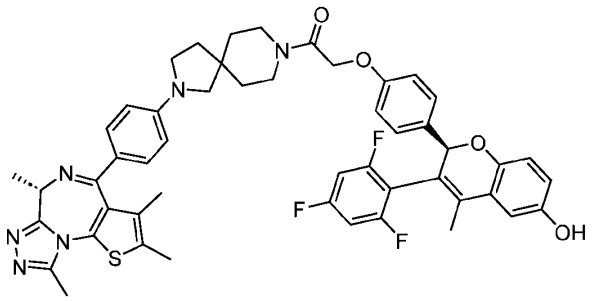
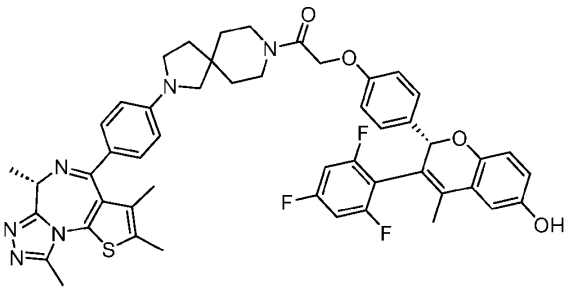
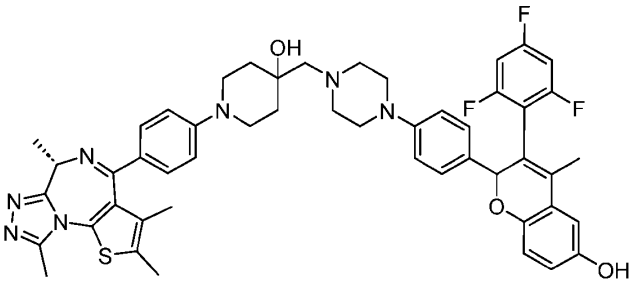
Compound No.	Compound Structure
V-1	
V-2	
V-3	

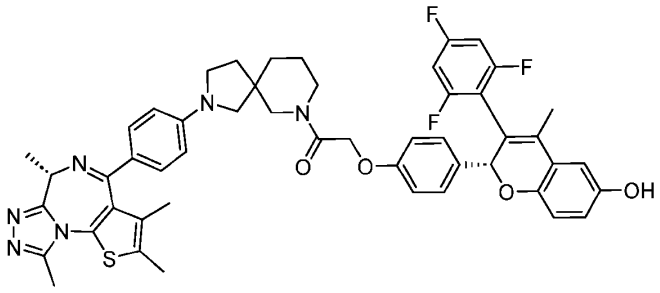
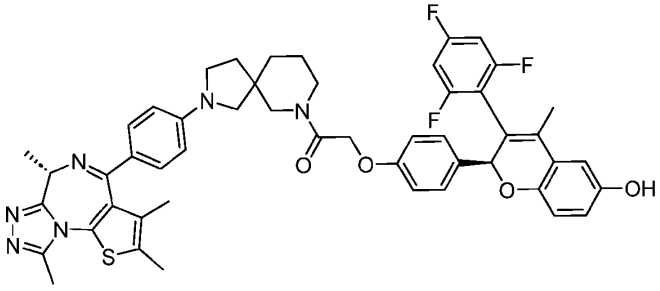
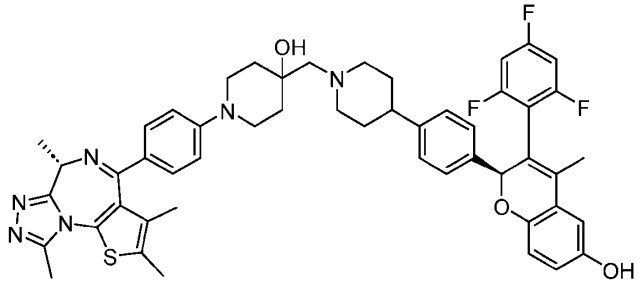
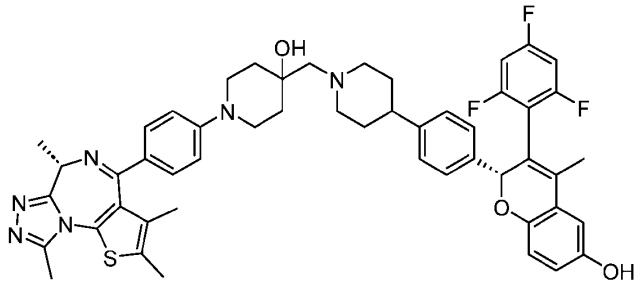
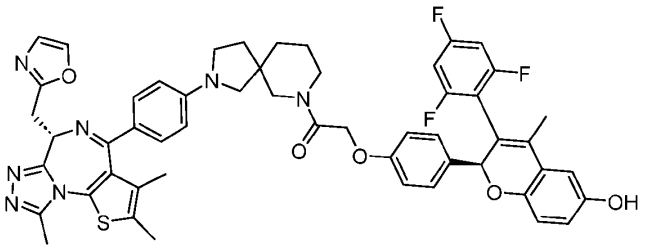
V-4	
V-5	
V-6	
V-7	
V-8	

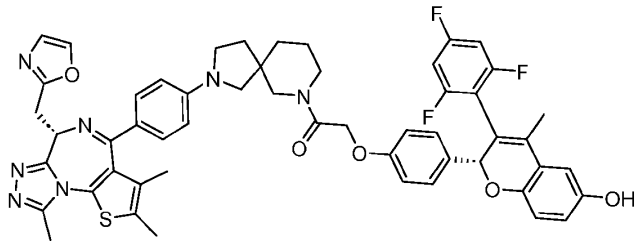
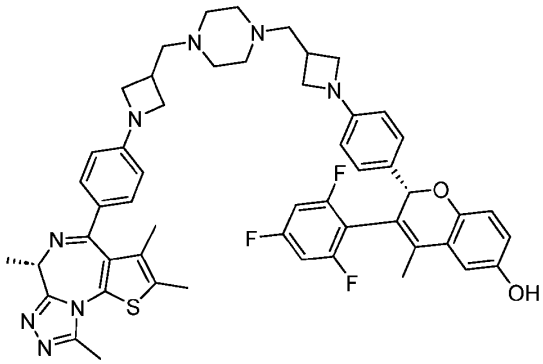
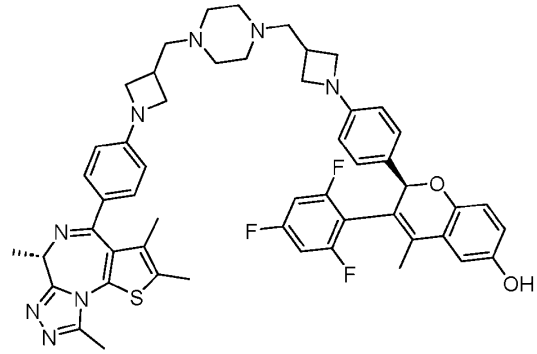
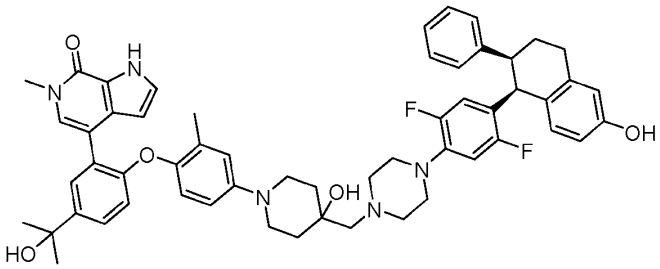
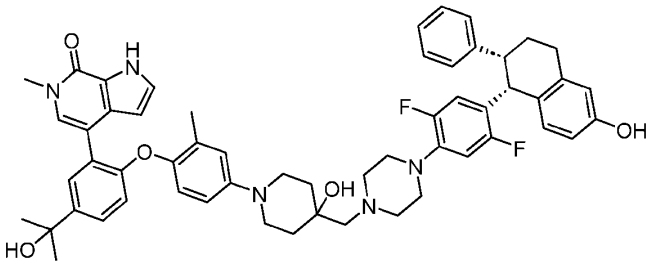
V-9	
V-10	
V-11	
V-12	
V-13	

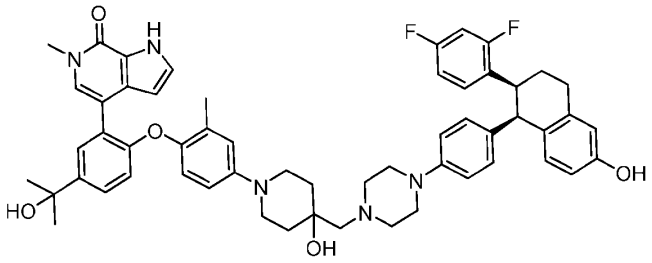
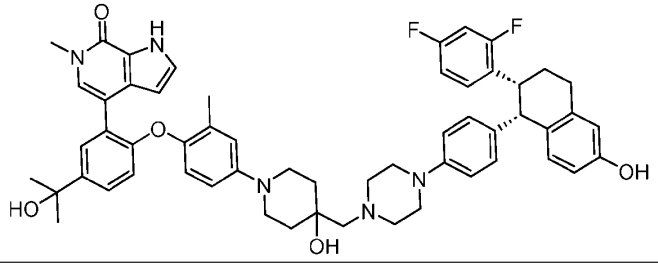
V-14	
V-15	
V-16	
V-17	
V-18	

V-19	
V-20	
V-21	
V-22	
V-23	

V-24	
V-25	
V-26	
V-27	
V-28	

V-29	
V-30	
V-31	
V-32	
V-33	

V-34	
V-35	
V-36	
V-37	
V-38	

V-39	
V-40	

Synthetic Methods

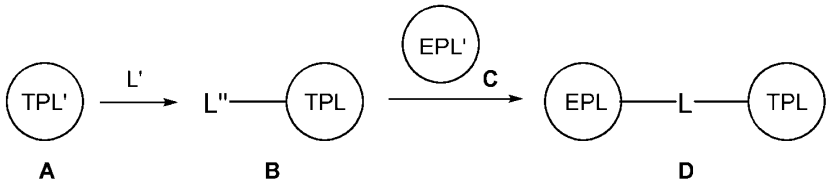
[0384] Methods for preparing compounds described herein are illustrated in the following synthetic Schemes. The Schemes are given for the purpose of illustrating the invention, and are not intended to limit the scope or spirit of the invention. Starting materials shown in the Schemes can be obtained from commercial sources or can be prepared based on procedures described in the literature.

[0385] In the Schemes, it is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated (for example, use of protecting groups or alternative reactions). Protecting group chemistry and strategy is well known in the art, for example, as described in detail in "Protecting Groups in Organic Synthesis", T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entire contents of which are hereby incorporated by reference.

[0386] The synthetic route illustrated in Scheme 1 is a general method for preparing heterobifunctional compounds **D**. Coupling compound **A** (a precursor of TPL, for example, a discrete compound that is a target protein ligand) with L' (a precursor to linker L, containing functionality for coupling to the precursors of both TPL and EPL) affords intermediate **B** (wherein L" is a precursor to linker L that contains functionality for coupling to the EPL

precursor). Coupling intermediate **B** with compound **C** (a precursor of EPL) affords heterobifunctional compound **D**. Alternatively, the order of coupling compounds **A** and **C** to L' may be reversed, such that L' is first coupled with compound **C**, before being coupled to compound **A**.

SCHEME 1.



[0387] The coupling of compound **A** with L', and the coupling of intermediate **B** with compound **C**, can be accomplished with a wide variety of strategies. For example, amide coupling conditions can be employed when compound **A** (or compound **C**) is to be attached at a modifiable nitrogen atom and L' (or L") contains a carboxylic acid group, or vice versa (i.e. compound **A** contains a carboxylic acid group and L' contains a nucleophilic amine nitrogen atom). Alternatively, reductive amination conditions can be employed when compound **A** (or compound **C**) is to be attached at a modifiable nitrogen atom and L' (or L") contains an aldehyde group, or vice versa. Alternatively, nucleophilic substitution conditions can be employed when compound **A** (or compound **C**) is to be attached at a modifiable oxygen, nitrogen, or sulfur atom and L' (or L") contains a leaving group (such as an alkyl triflate, α-bromoketone, or aryl chloride), or vice versa. As yet another option, transition-metal-mediated coupling conditions can be employed when compound **A** (or compound **C**) is to be attached at a modifiable carbon, oxygen, or nitrogen atom (where the carbon atom may be activated, for example, with a bromide or sulfonate) and L' (or L") contains a suitable coupling partner (for example, an olefin for a Heck coupling, a trialkylstannane for a Stille coupling, or a boronic acid or boronate ester for a Suzuki coupling, Buchwald-Hartwig amination, or Chan-Lam coupling), or vice versa.

[0388] It is understood by one skilled in the art of organic synthesis that protecting group strategies may be employed as necessary, for example, if L' contains two of the same functional group that are to be selectively coupled to compound **A** and compound **C**. For example, L' may contain, for example, both an unprotected carboxylic acid for coupling to compound **A**, and a carboxylic acid group that is protected (for example, as a methyl or benzyl ester) during the

coupling with compound **A** and subsequently deprotected (for example, via basic hydrolysis of a methyl ester or hydrogenolysis of a benzyl ester) prior to coupling with compound **C**.

II. Therapeutic Applications

[0389] The heterobifunctional compounds described herein, such as a compound of Formula I or II, or other compounds in Section I, provide therapeutic benefits to patients suffering from cancer. Accordingly, one aspect of the invention provides a method of treating cancer. The method comprises administering to a patient in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I or II, or other compounds in Section I, to treat the cancer. In certain embodiments, the particular compound of Formula I or II is a compound defined by one of the embodiments described above. In certain embodiments, the compound is a compound of Formula I, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I. In certain embodiments, the compound is a compound of Formula I-A or I-B, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I-A or I-B. In certain embodiments, the particular compound of Formula I, I-A, or I-B is a compound defined by one of the embodiments described above (including, for example, a compound of Formula I-A-1, I-A-2, I-A-3, I-A-4, etc.).

Cancer

[0390] In certain embodiments, the cancer is ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct and gallbladder cancers, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney cancer, eye cancer, thyroid cancer, lymphoma, or leukemia. In certain embodiments, the cancer is ovarian cancer. In certain embodiments, the cancer is endometrial cancer. In certain embodiments, the cancer is cervical cancer.

[0391] In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is advanced breast cancer. In certain embodiments, the cancer is metastatic breast cancer. In certain embodiments, the cancer is ER+ breast cancer or ER+/HER2- breast cancer. In certain embodiments, the cancer is ER+ advanced breast cancer, ER+ metastatic breast cancer ER+/HER2- advanced breast cancer, or ER+/HER2- metastatic breast cancer. In certain

embodiments, the cancer is ER+ breast cancer. In certain embodiments, the cancer is ER+ advanced breast cancer or ER+ metastatic breast cancer. In certain embodiments, the cancer is ER+/HER2- breast cancer. In certain embodiments, the cancer is ER+/HER2- advanced breast cancer or ER+/HER2- metastatic breast cancer. In certain embodiments, the cancer is sporadic breast cancer. In certain embodiments, the cancer is Cowden disease.

[0392] In certain embodiments, the cancer has a mutant estrogen receptor alpha protein. In certain embodiments, the cancer has an estrogen receptor alpha protein containing one or more of the following mutations: D538G, Y537S, and L536R.

[0393] In certain embodiments, the cancer is squamous cell cancer, lung cancer including small cell lung cancer, non-small cell lung cancer, vulval cancer, thyroid cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, and head and neck cancer. In certain embodiments, the cancer is at least one selected from the group consisting of ALL, T-lineage Acute lymphoblastic Leukemia (T-ALL), T-lineage lymphoblastic Lymphoma (T-LL), Peripheral T-cell lymphoma, Adult T-cell Leukemia, Pre-B ALL, Pre-B Lymphomas, Large B-cell Lymphoma, Burkitts Lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, lymphoma, leukemia, multiple myeloma myeloproliferative diseases, large B cell lymphoma, or B cell Lymphoma.

[0394] In certain embodiments, the cancer is a solid tumor or leukemia. In certain other embodiments, the cancer is colon cancer, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, lung cancer, leukemia, bladder cancer, stomach cancer, cervical cancer, testicular cancer, skin cancer, rectal cancer, thyroid cancer, kidney cancer, uterus cancer, espophagus cancer, liver cancer, an acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma, or retinoblastoma. In certain other embodiments, the cancer is small cell lung cancer, non-small cell lung cancer, melanoma, cancer of the central nervous system tissue, brain cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, or diffuse large B-Cell lymphoma. In certain other embodiments, the cancer is

breast cancer, colon cancer, small-cell lung cancer, non-small cell lung cancer, prostate cancer, renal cancer, ovarian cancer, leukemia, melanoma, or cancer of the central nervous system tissue. In certain other embodiments, the cancer is colon cancer, small-cell lung cancer, non-small cell lung cancer, renal cancer, ovarian cancer, renal cancer, or melanoma.

[0395] In certain embodiments, the cancer is a fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, or hemangioblastoma.

[0396] In certain embodiments, the cancer is a neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adeno carcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, metastatic melanoma, localized melanoma, malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scelroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unrescectable hepatocellular carcinoma, Waidenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, or leiomyoma.

[0397] In certain embodiments, the cancer is bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal, and

duodenal), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, testicular cancer, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, non-Hodgkins's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma, or a combination of one or more of the foregoing cancers.

[0398] In certain embodiments, the cancer is hepatocellular carcinoma, ovarian cancer, ovarian epithelial cancer, or fallopian tube cancer; papillary serous cystadenocarcinoma or uterine papillary serous carcinoma (UPSC); prostate cancer; testicular cancer; gallbladder cancer; hepatocholangiocarcinoma; soft tissue and bone synovial sarcoma; rhabdomyosarcoma; osteosarcoma; chondrosarcoma; Ewing sarcoma; anaplastic thyroid cancer; adrenocortical adenoma; pancreatic cancer; pancreatic ductal carcinoma or pancreatic adenocarcinoma; gastrointestinal/stomach (GIST) cancer; lymphoma; squamous cell carcinoma of the head and neck (SCCHN); salivary gland cancer; glioma, or brain cancer; neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST); Waldenstrom's macroglobulinemia; or medulloblastoma.

[0399] In certain embodiments, the cancer is hepatocellular carcinoma (HCC), hepatoblastoma, colon cancer, rectal cancer, ovarian cancer, ovarian epithelial cancer, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, anaplastic thyroid cancer, adrenocortical adenoma, pancreatic cancer, pancreatic ductal carcinoma, pancreatic adenocarcinoma, glioma, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0400] In certain embodiments, the cancer is a solid tumor, such as a sarcoma, carcinoma, or lymphoma. In certain embodiments, the cancer is kidney cancer; hepatocellular carcinoma (HCC) or hepatoblastoma, or liver cancer; melanoma; breast cancer; colorectal carcinoma, or colorectal cancer; colon cancer; rectal cancer; anal cancer; lung cancer, such as non-small cell lung cancer

(NSCLC) or small cell lung cancer (SCLC); ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, or fallopian tube cancer; papillary serous cystadenocarcinoma or uterine papillary serous carcinoma (UPSC); prostate cancer; testicular cancer; gallbladder cancer; hepatocholangiocarcinoma; soft tissue and bone synovial sarcoma; rhabdomyosarcoma; osteosarcoma; chondrosarcoma; Ewing sarcoma; anaplastic thyroid cancer; adrenocortical carcinoma; pancreatic cancer; pancreatic ductal carcinoma or pancreatic adenocarcinoma; gastrointestinal/stomach (GIST) cancer; lymphoma; squamous cell carcinoma of the head and neck (SCCHN); salivary gland cancer; glioma, or brain cancer; neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST); Waldenstrom's macroglobulinemia; or medulloblastoma.

[0401] In certain embodiments, the cancer is renal cell carcinoma, hepatocellular carcinoma (HCC), hepatoblastoma, colorectal carcinoma, colorectal cancer, colon cancer, rectal cancer, anal cancer, ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, anaplastic thyroid cancer, adrenocortical carcinoma, pancreatic cancer, pancreatic ductal carcinoma, pancreatic adenocarcinoma, glioma, brain cancer, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0402] In certain embodiments, the cancer is hepatocellular carcinoma (HCC), hepatoblastoma, colon cancer, rectal cancer, ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, anaplastic thyroid cancer, adrenocortical carcinoma, pancreatic cancer, pancreatic ductal carcinoma, pancreatic adenocarcinoma, glioma, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0403] In certain embodiments, the cancer is hepatocellular carcinoma (HCC). In some embodiments, the cancer is hepatoblastoma. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is rectal cancer. In some embodiments, the cancer is ovarian cancer, or ovarian carcinoma. In some embodiments, the cancer is ovarian epithelial cancer. In some embodiments, the cancer is fallopian tube cancer. In some embodiments, the cancer is

papillary serous cystadenocarcinoma. In some embodiments, the cancer is uterine papillary serous carcinoma (UPSC). In some embodiments, the cancer is hepatocholangiocarcinoma. In some embodiments, the cancer is soft tissue and bone synovial sarcoma. In some embodiments, the cancer is rhabdomyosarcoma. In some embodiments, the cancer is osteosarcoma. In some embodiments, the cancer is anaplastic thyroid cancer. In some embodiments, the cancer is adrenocortical carcinoma. In some embodiments, the cancer is pancreatic cancer, or pancreatic ductal carcinoma. In some embodiments, the cancer is pancreatic adenocarcinoma. In some embodiments, the cancer is glioma. In some embodiments, the cancer is malignant peripheral nerve sheath tumors (MPNST). In some embodiments, the cancer is neurofibromatosis-1 associated MPNST. In some embodiments, the cancer is Waldenstrom's macroglobulinemia. In some embodiments, the cancer is medulloblastoma.

Causing Death of Cancer Cell

[0404] Another aspect of the invention provides a method of causing death of a cancer cell. The method comprises contacting a cancer cell with an effective amount of a compound described herein, such as a compound of Formula I or II, or other compounds in Section I, to cause death of the cancer cell. In certain embodiments, the compound is a compound of Formula I, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I. In certain embodiments, the compound is a compound of Formula I-A or I-B, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I-A or I-B. In certain embodiments, the particular compound of Formula I, I-A, or I-B is a compound defined by one of the embodiments described above (including, for example, a compound of Formula I-A-1, I-A-2, I-A-3, I-A-4, etc.).

[0405] In certain embodiments, the cancer cell is selected from ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct and gallbladder cancers, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney cancer, eye cancer, thyroid cancer, lymphoma, or leukemia cell. In certain embodiments, the cancer cell is a breast cancer cell. In certain embodiments, the cancer cell is a uterine cancer cell. In certain embodiments, the cancer cell is one or more of the cancers recited in the section above entitled “Cancer.”

Diseases Mediated by the Estrogen Receptor

[0406] Another aspect of the invention provides a method of treating a disease or condition mediated by the estrogen receptor. The method comprises administering to a patient in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I or II, or other compounds in Section I, to treat the disease or condition. In certain embodiments, the particular compound of Formula I or II is a compound defined by one of the embodiments described above, including, for example, a compound of Formula I, I-A, I-A-1, I-A-2, I-A-3, I-A-4, etc.). In certain embodiments, the disease or condition is mediated by the estrogen receptor alpha protein. In certain embodiments, the patient has a mutant estrogen receptor alpha protein. In certain embodiments, the patient has an estrogen receptor alpha protein containing one or more of the following mutations: D538G, Y537S, and L536R. In certain embodiments, the disease or condition is endometriosis.

Combination Therapies

[0407] The compounds useful within the methods of the invention may be used in combination with one or more additional therapeutic agents useful for treating any disease contemplated herein. These additional therapeutic agents may comprise compounds that are commercially available or synthetically accessible to those skilled in the art. These additional therapeutic agents are known to treat, prevent, or reduce the symptoms, of a disease or disorder contemplated herein.

[0408] Accordingly, in certain embodiments, the method further comprises administering to the subject an additional therapeutic agent that treats the disease contemplated herein.

[0409] In certain embodiments, administering the compound of the invention to the subject allows for administering a lower dose of the additional therapeutic agent as compared to the dose of the additional therapeutic agent alone that is required to achieve similar results in treating the disease contemplated herein. For example, in certain embodiments, the compound of the invention enhances the therapeutic activity of the additional therapeutic compound, thereby allowing for a lower dose of the additional therapeutic compound to provide the same effect.

[0410] A synergistic effect may be calculated, for example, using suitable methods such as, for example, the Sigmoid-E_{max} equation (Holford & Scheiner, 1981, Clin. Pharmacokinet. 6:429-453), the equation of Loewe additivity (Loewe & Muischnek, 1926, Arch. Exp. Pathol Pharmacol. 114:313-326) and the median-effect equation (Chou & Talalay, 1984, Adv. Enzyme Regul. 22:27-55). Each equation referred to above may be applied to experimental data to generate a

corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

[0411] In certain embodiments, the compound of the invention and the therapeutic agent are co-administered to the subject. In other embodiments, the compound of the invention and the therapeutic agent are coformulated and co-administered to the subject.

[0412] In certain embodiments, the compound is administered in combination with a second therapeutic agent having activity against cancer.

[0413] Accordingly, one aspect of the invention provides a method for treating cancer. The method comprises administering to a patient in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I or II, or other compounds in Section I, in combination with a second therapeutic agent having activity against cancer, in order to treat the cancer. In certain embodiments, the compound is a compound of Formula I, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I. In certain embodiments, the compound is a compound of Formula I-A or I-B, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula I-A or I-B. In certain embodiments, the particular compound of Formula I, I-A, or I-B is a compound defined by one of the embodiments described above (including, for example, a compound of Formula I-A-1, I-A-2, I-A-3, I-A-4, etc.).

[0414] In certain embodiments, the method further comprises administering a third therapeutic agent having activity against cancer. In certain embodiments, the method further comprises administering a fourth therapeutic agent having activity against cancer.

[0415] In certain embodiments, the second therapeutic agent is mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha,

interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, and leutinizing hormone releasing factor.

[0416] In certain embodiments, the second therapeutic agent is an mTOR inhibitor, which inhibits cell proliferation, angiogenesis and glucose uptake. Approved mTOR inhibitors useful in the present invention include everolimus (Afinitor®, Novartis); temsirolimus (Torisel®, Pfizer); and sirolimus (Rapamune®, Pfizer).

[0417] In certain embodiments, the second therapeutic agent is a Poly ADP ribose polymerase (PARP) inhibitor. Approved PARP inhibitors useful in the present invention include olaparib (Lynparza®, AstraZeneca); rucaparib (Rubraca®, Clovis Oncology); and niraparib (Zejula®, Tesaro). Other PARP inhibitors being studied which may be used in the present invention include talazoparib (MDV3800/BMN 673/LT00673, Medivation/Pfizer/Biomarin); veliparib (ABT-888, AbbVie); and BGB-290 (BeiGene, Inc.).

[0418] In certain embodiments, the second therapeutic agent is a phosphatidylinositol 3 kinase (PI3K) inhibitor. Approved PI3K inhibitors useful in the present invention include idelalisib (Zydelig®, Gilead). Other PI3K inhibitors being studied which may be used in the present invention include alpelisib (BYL719, Novartis); taselisib (GDC-0032, Genentech/Roche); pictilisib (GDC-0941, Genentech/Roche); copanlisib (BAY806946, Bayer); duvelisib (formerly IPI-145, Infinity Pharmaceuticals); PQR309 (Piqur Therapeutics, Switzerland); and TGR1202 (formerly RP5230, TG Therapeutics).

[0419] In certain embodiments, the second therapeutic agent is a proteasome inhibitor. Approved proteasome inhibitors useful in the present invention include bortezomib (Velcade®, Takeda); carfilzomib (Kyprolis®, Amgen); and ixazomib (Ninlaro®, Takeda).

[0420] In certain embodiments, the second therapeutic agent is a histone deacetylase (HDAC) inhibitor. Approved HDAC inhibitors useful in the present invention include vorinostat (Zolinza®, Merck); romidepsin (Istodax®, Celgene); panobinostat (Farydak®, Novartis); and belinostat (Beleodaq®, Spectrum Pharmaceuticals). Other HDAC inhibitors being studied which may be used in the present invention include entinostat (SNDX-275, Syndax Pharmaceuticals) (NCT00866333); and chidamide (Epidaza®, HBI-8000, Chipscreen Biosciences, China).

[0421] In certain embodiments, the second therapeutic agent is a CDK inhibitor, such as a CDK 4/6 inhibitor. Approved CDK 4/6 inhibitors useful in the present invention include palbociclib (Ibrance®, Pfizer); and ribociclib (Kisqali®, Novartis). Other CDK 4/6 inhibitors

being studied which may be used in the present invention include abemaciclib (Ly2835219, Eli Lilly); and trilaciclib (G1T28, G1 Therapeutics).

[0422] In certain embodiments, the second therapeutic agent is an indoleamine (2,3)-dioxygenase (IDO) inhibitor. IDO inhibitors being studied which may be used in the present invention include epacadostat (INCB024360, Incyte); indoximod (NLG-8189, NewLink Genetics Corporation); capmanitib (INC280, Novartis); GDC-0919 (Genentech/Roche); PF-06840003 (Pfizer); BMS:F001287 (Bristol-Myers Squibb); Phy906/KD108 (Phytoceutica); and an enzyme that breaks down kynurenine (Kynase, Kyn Therapeutics).

[0423] In certain embodiments, the second therapeutic agent is a growth factor antagonist, such as an antagonist of platelet-derived growth factor (PDGF), or epidermal growth factor (EGF) or its receptor (EGFR). Approved PDGF antagonists which may be used in the present invention include olaratumab (Lartruvo®; Eli Lilly). Approved EGFR antagonists which may be used in the present invention include cetuximab (Erbitux®, Eli Lilly); necitumumab (Portrazza®, Eli Lilly), panitumumab (Vectibix®, Amgen); and osimertinib (targeting activated EGFR, Tagrisso®, AstraZeneca).

[0424] In certain embodiments, the second therapeutic agent is an aromatase inhibitor. Approved aromatase inhibitors which may be used in the present invention include exemestane (Aromasin®, Pfizer); anastazole (Arimidex®, AstraZeneca) and letrozole (Femara®, Novartis).

[0425] In certain embodiments, the second therapeutic agent is an antagonist of the hedgehog pathway. Approved hedgehog pathway inhibitors which may be used in the present invention include sonidegib (Odomzo®, Sun Pharmaceuticals); and vismodegib (Erivedge®, Genentech), both for treatment of basal cell carcinoma.

[0426] In certain embodiments, the second therapeutic agent is a folic acid inhibitor. Approved folic acid inhibitors useful in the present invention include pemetrexed (Alimta®, Eli Lilly).

[0427] In certain embodiments, the second therapeutic agent is a CC chemokine receptor 4 (CCR4) inhibitor. CCR4 inhibitors being studied that may be useful in the present invention include mogamulizumab (Poteligeo®, Kyowa Hakko Kirin, Japan).

[0428] In certain embodiments, the second therapeutic agent is an isocitrate dehydrogenase (IDH) inhibitor. IDH inhibitors being studied which may be used in the present invention include AG120 (Celgene; NCT02677922); AG221 (Celgene, NCT02677922; NCT02577406); BAY1436032 (Bayer, NCT02746081); IDH305 (Novartis, NCT02987010).

[0429] In certain embodiments, the second therapeutic agent is an arginase inhibitor. Arginase inhibitors being studied which may be used in the present invention include AEB1102 (pegylated recombinant arginase, Aeglea Biotherapeutics), which is being studied in Phase 1 clinical trials for acute myeloid leukemia and myelodysplastic syndrome (NCT02732184) and solid tumors (NCT02561234); and CB-1158 (Calithera Biosciences).

[0430] In certain embodiments, the second therapeutic agent is a glutaminase inhibitor. Glutaminase inhibitors being studied which may be used in the present invention include CB-839 (Calithera Biosciences).

[0431] In certain embodiments, the second therapeutic agent is an antibody that binds to tumor antigens, that is, proteins expressed on the cell surface of tumor cells. Approved antibodies that bind to tumor antigens which may be used in the present invention include rituximab (Rituxan®, Genentech/BiogenIdec); ofatumumab (anti-CD20, Arzerra®, GlaxoSmithKline); obinutuzumab (anti-CD20, Gazyva®, Genentech), ibritumomab (anti-CD20 and Yttrium-90, Zevalin®, Spectrum Pharmaceuticals); daratumumab (anti-CD38, Darzalex®, Janssen Biotech), dinutuximab (anti-glycolipid GD2, Unituxin®, United Therapeutics); trastuzumab (anti-HER2, Herceptin®, Genentech); ado-trastuzumab emtansine (anti-HER2, fused to emtansine, Kadcyla®, Genentech); and pertuzumab (anti-HER2, Perjeta®, Genentech); and brentuximab vedotin (anti-CD30-drug conjugate, Adcetris®, Seattle Genetics).

[0432] In certain embodiments, the second therapeutic agent is a topoisomerase inhibitor. Approved topoisomerase inhibitors useful in the present invention include irinotecan (Onivyde®, Merrimack Pharmaceuticals); topotecan (Hycamtin®, GlaxoSmithKline). Topoisomerase inhibitors being studied which may be used in the present invention include pixantrone (Pixuvri®, CTI Biopharma).

[0433] In certain embodiments, the second therapeutic agent is a nucleoside inhibitor, or other therapeutic that interfere with normal DNA synthesis, protein synthesis, cell replication, or will otherwise inhibit rapidly proliferating cells. Such nucleoside inhibitors or other therapeutics include trabectedin (guanidine alkylating agent, Yondelis®, Janssen Oncology), mechlorethamine (alkylating agent, Valchlor®, Aktelion Pharmaceuticals); vincristine (Oncovin®, Eli Lilly; Vincasar®, Teva Pharmaceuticals; Marqibo®, Talon Therapeutics); temozolomide (prodrug to alkylating agent 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC) Temodar®, Merck); cytarabine injection (ara-C, antimetabolic cytidine analog, Pfizer); lomustine (alkylating agent,

CeeNU®, Bristol-Myers Squibb; Gleostine®, NextSource Biotechnology); azacitidine (pyrimidine nucleoside analog of cytidine, Vidaza®, Celgene); omacetaxine mepesuccinate (cephalotaxine ester) (protein synthesis inhibitor, Synribo®; Teva Pharmaceuticals); asparaginase Erwinia chrysanthemi (enzyme for depletion of asparagine, Elspar®, Lundbeck; Erwinaze®, EUSA Pharma); eribulin mesylate (microtubule inhibitor, tubulin-based antimitotic, Halaven®, Eisai); cabazitaxel (microtubule inhibitor, tubulin-based antimitotic, Jevtana®, Sanofi-Aventis); capacetrine (thymidylate synthase inhibitor, Xeloda®, Genentech); bendamustine (bifunctional mechlorethamine derivative, believed to form interstrand DNA cross-links, Treanda®, Cephalon/Teva); ixabepilone (semi-synthetic analog of epothilone B, microtubule inhibitor, tubulin-based antimitotic, Ixempra®, Bristol-Myers Squibb); nelarabine (prodrug of deoxyguanosine analog, nucleoside metabolic inhibitor, Arranon®, Novartis); clorafabine (prodrug of ribonucleotide reductase inhibitor, competitive inhibitor of deoxycytidine, Clolar®, Sanofi-Aventis); and trifluridine and tipiracil (thymidine-based nucleoside analog and thymidine phosphorylase inhibitor, Lonsurf®, Taiho Oncology).

[0434] In certain embodiments, the second therapeutic agent is a platinum-based therapeutic, also referred to as platins. Platins cause cross-linking of DNA, such that they inhibit DNA repair and/or DNA synthesis, mostly in rapidly reproducing cells, such as cancer cells. Approved platinum-based therapeutics which may be used in the present invention include cisplatin (Platinol®, Bristol-Myers Squibb); carboplatin (Paraplatin®, Bristol-Myers Squibb; also, Teva; Pfizer); oxaliplatin (Eloxitin® Sanofi-Aventis); and nedaplatin (Aqupla®, Shionogi). Other platinum-based therapeutics which have undergone clinical testing and may be used in the present invention include picoplatin (Poniard Pharmaceuticals); and satraplatin (JM-216, Agennix).

[0435] In certain embodiments, the second therapeutic agent is a taxane compound, which causes disruption of microtubules, which are essential for cell division. Approved taxane compounds which may be used in the present invention include paclitaxel (Taxol®, Bristol-Myers Squibb), docetaxel (Taxotere®, Sanofi-Aventis; Docefrez®, Sun Pharmaceutical), albumin-bound paclitaxel (Abraxane®; Abraxis/Celgene), and cabazitaxel (Jevtana®, Sanofi-Aventis). Other taxane compounds which have undergone clinical testing and may be used in the present invention include SID530 (SK Chemicals, Co.) (NCT00931008).

[0436] In certain embodiments, the second therapeutic agent is an inhibitor of anti-apoptotic proteins, such as BCL-2. Approved anti-apoptotics which may be used in the present invention include venetoclax (Venclexta®, AbbVie/Genentech); and blinatumomab (Blincyto®, Amgen).

Other therapeutic agents targeting apoptotic proteins which have undergone clinical testing and may be used in the present invention include navitoclax (ABT-263, Abbott), a BCL-2 inhibitor (NCT02079740).

[0437] In certain embodiments, the second therapeutic agent is a selective estrogen receptor modulator (SERM), which interferes with the synthesis or activity of estrogens. Approved SERMs useful in the present invention include raloxifene (Evista®, Eli Lilly).

[0438] In certain embodiments, the second therapeutic agent is an inhibitor of interaction between the two primary p53 suppressor proteins, MDMX and MDM2. Inhibitors of p53 suppression proteins being studied which may be used in the present invention include ALRN-6924 (Aileron), a stapled peptide that equipotently binds to and disrupts the interaction of MDMX and MDM2 with p53. ALRN-6924 is currently being evaluated in clinical trials for the treatment of AML, advanced myelodysplastic syndrome (MDS) and peripheral T-cell lymphoma (PTCL) (NCT02909972; NCT02264613).

[0439] In certain embodiments, the second therapeutic agent is an inhibitor of transforming growth factor-beta (TGF-beta or TGFβ). Inhibitors of TGF-beta proteins being studied which may be used in the present invention include NIS793 (Novartis), an anti-TGF-beta antibody being tested in the clinic for treatment of various cancers, including breast, lung, hepatocellular, colorectal, pancreatic, prostate and renal cancer (NCT 02947165). In some embodiments, the inhibitor of TGF-beta proteins is fresolimumab (GC1008; Sanofi-Genzyme), which is being studied for melanoma (NCT00923169); renal cell carcinoma (NCT00356460); and non-small cell lung cancer (NCT02581787). Additionally, in some embodiments, the additional therapeutic agent is a TGF-beta trap, such as described in Connolly et al. (2012) Int'l J. Biological Sciences 8:964-978. One therapeutic compound currently in clinical trials for treatment of solid tumors is M7824 (Merck KgaA—formerly MSB0011459X), which is a bispecific, anti-PD-L1/TGFβ trap compound (NCT02699515); and (NCT02517398). M7824 is comprised of a fully human IgG1 antibody against PD-L1 fused to the extracellular domain of human TGF-beta receptor II, which functions as a TGFβ "trap."

[0440] In certain embodiments, the second therapeutic agent is a cancer vaccine. In some embodiments, the cancer vaccine is selected from sipuleucel-T (Provenge®, Dendreon/Valeant Pharmaceuticals), which has been approved for treatment of asymptomatic, or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer; and talimogene

laherparepvec (Imlygic®, BioVex/Amgen, previously known as T-VEC), a genetically modified oncolytic viral therapy approved for treatment of unresectable cutaneous, subcutaneous and nodal lesions in melanoma. In some embodiments, the additional therapeutic agent is selected from an oncolytic viral therapy such as pexastimogene devacirepvec (PexaVec/JX-594, SillaJen/formerly Jennerex Biotherapeutics), a thymidine kinase- (TK-) deficient vaccinia virus engineered to express GM-CSF, for hepatocellular carcinoma (NCT02562755) and melanoma (NCT00429312); pelareorep (Reolysin®, Oncolytics Biotech), a variant of respiratory enteric orphan virus (reovirus) which does not replicate in cells that are not RAS-activated, in numerous cancers, including colorectal cancer (NCT01622543); prostate cancer (NCT01619813); head and neck squamous cell cancer (NCT01166542); pancreatic adenocarcinoma (NCT00998322); and non-small cell lung cancer (NSCLC) (NCT 00861627); enadenotucirev (NG-348, PsiOxus, formerly known as ColoAd1), an adenovirus engineered to express a full length CD80 and an antibody fragment specific for the T-cell receptor CD3 protein, in ovarian cancer (NCT02028117); metastatic or advanced epithelial tumors such as in colorectal cancer, bladder cancer, head and neck squamous cell carcinoma and salivary gland cancer (NCT02636036); ONCOS-102 (Targovax/formerly Oncos), an adenovirus engineered to express GM-CSF, in melanoma (NCT03003676); and peritoneal disease, colorectal cancer or ovarian cancer (NCT02963831); GL-ONC1 (GLV-1h68/GLV-1h153, Genelux GmbH), vaccinia viruses engineered to express beta-galactosidase (beta-gal)/beta-glucoronidase or beta-gal/human sodium iodide symporter (hNIS), respectively, were studied in peritoneal carcinomatosis (NCT01443260); fallopian tube cancer, ovarian cancer (NCT 02759588); or CG0070 (Cold Genesys), an adenovirus engineered to express GM-CSF, in bladder cancer (NCT02365818).

[0441] In certain embodiments, the second therapeutic agent is an immune checkpoint inhibitor selected from a PD-1 antagonist, a PD-L1 antagonist, or a CTLA-4 antagonist. In some embodiments, a compound disclosed herein or a pharmaceutically acceptable salt thereof is administered in combination with nivolumab (anti-PD-1 antibody, Opdivo®, Bristol-Myers Squibb); pembrolizumab (anti-PD-1 antibody, Keytruda®, Merck); ipilimumab (anti-CTLA-4 antibody, Yervoy®, Bristol-Myers Squibb); durvalumab (anti-PD-L1 antibody, Imfinzi®, AstraZeneca); or atezolizumab (anti-PD-L1 antibody, Tecentriq®, Genentech). Other immune checkpoint inhibitors suitable for use in the present invention include REGN2810 (Regeneron), an anti-PD-1 antibody tested in patients with basal cell carcinoma (NCT03132636); NSCLC (NCT03088540); cutaneous squamous cell carcinoma (NCT02760498); lymphoma

(NCT02651662); and melanoma (NCT03002376); pidilizumab (CureTech), also known as CT-011, an antibody that binds to PD-1, in clinical trials for diffuse large B-cell lymphoma and multiple myeloma; avelumab (Bavencio®, Pfizer/Merck KGaA), also known as MSB0010718C), a fully human IgG1 anti-PD-L1 antibody, in clinical trials for non-small cell lung cancer, Merkel cell carcinoma, mesothelioma, solid tumors, renal cancer, ovarian cancer, bladder cancer, head and neck cancer, and gastric cancer; and PDR001 (Novartis), an inhibitory antibody that binds to PD-1, in clinical trials for non-small cell lung cancer, melanoma, triple negative breast cancer and advanced or metastatic solid tumors. Tremelimumab (CP-675,206; Astrazeneca) is a fully human monoclonal antibody against CTLA-4 that has been in studied in clinical trials for a number of indications, including: mesothelioma, colorectal cancer, kidney cancer, breast cancer, lung cancer and non-small cell lung cancer, pancreatic ductal adenocarcinoma, pancreatic cancer, germ cell cancer, squamous cell cancer of the head and neck, hepatocellular carcinoma, prostate cancer, endometrial cancer, metastatic cancer in the liver, liver cancer, large B-cell lymphoma, ovarian cancer, cervical cancer, metastatic anaplastic thyroid cancer, urothelial cancer, fallopian tube cancer, multiple myeloma, bladder cancer, soft tissue sarcoma, and melanoma. AGEN-1884 (Agenus) is an anti-CTLA4 antibody that is being studied in Phase 1 clinical trials for advanced solid tumors (NCT02694822).

[0442] In certain embodiments, the third therapeutic agent is one of the second therapeutic agents described above. In certain embodiments, the fourth therapeutic agent is one of the second therapeutic agents described above.

[0443] Another aspect of the invention provides a compound described herein (such as a compound of Formula I, Formula II, or other compounds in Section I) for use in treating a medical disease, such a disease described herein (*e.g.*, cancer).

[0444] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I, Formula II, or other compounds in Section I) in the manufacture of a medicament. In certain embodiments, the medicament is for treating a disease described herein, such as cancer.

[0445] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I, Formula II, or other compounds in Section I) for treating a medical disease, such a disease described herein (*e.g.*, cancer).

III. Pharmaceutical Compositions and Dosing Considerations

[0446] As indicated above, the invention provides pharmaceutical compositions, which comprise a therapeutically effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. The pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally. In certain embodiments, the invention provides a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula I) and a pharmaceutically acceptable carrier.

[0447] The phrase "therapeutically effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

[0448] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0449] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0450] Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium

metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0451] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[0452] In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, *e.g.*, bile acids, and polymeric carriers, *e.g.*, polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

[0453] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0454] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as

an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[0455] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, trouches and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0456] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0457] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes

and/or microspheres. They may be formulated for rapid release, *e.g.*, freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0458] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0459] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0460] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0461] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[0462] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate. Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[0463] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0464] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0465] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0466] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0467] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0468] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0469] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0470] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0471] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[0472] When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0473] The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

[0474] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0475] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0476] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0477] Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

[0478] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0479] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the

particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0480] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0481] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Preferably, the compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. When the compounds described herein are co-administered with another agent (*e.g.*, as sensitizing agents), the effective amount may be less than when the agent is used alone.

[0482] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day.

[0483] The invention further provides a unit dosage form (such as a tablet or capsule) comprising a heterobifunctional compound described herein in a therapeutically effective amount for the treatment of a medical disorder described herein.

IV. MEDICAL KITS

[0484] Another aspect of this invention is a kit comprising (i) a compound described herein, such as a compound of Formula I, and (ii) instructions for use, such as treating cancer.

EXAMPLES

[0485] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and is not intended to limit the invention.

General Methods

[0486] All reactions were carried out under an atmosphere of dry nitrogen or argon. Glassware was oven-dried prior to use. Unless otherwise indicated, common reagents or materials were obtained from commercial sources and used without further purification. *N*,*N*-Diisopropylethylamine (DIPEA) was obtained anhydrous by distillation over potassium hydroxide. Tetrahydrofuran (THF), Dichloromethane (CH_2Cl_2), and dimethylformamide (DMF) was dried by a PureSolv™ solvent drying system. PTLC refers to preparatory thin layer chromatographic separation. Abbreviations: HFIP (hexafluoroisopropanol), HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV or $KMnO_4$.

[0487] ^1H and ^{13}C NMR spectra were recorded on an Agilent DD_2 500 (500 MHz ^1H; 125 MHz ^{13}C) or Agilent DD_2 600 (600 MHz ^1H; 150 MHz ^{13}C) or Agilent DD_2 400 (400 MHz ^1H; 100 MHz ^{13}C) spectrometer at room temperature. Chemical shifts were reported in ppm relative to the residual $CDCl_3$ (δ 7.26 ppm ^1H; δ 77.0 ppm ^{13}C), CD_3OD (δ 3.31 ppm ^1H; δ 49.00 ppm ^{13}C), or d_6-DMSO (δ 2.50 ppm ^1H; δ 39.52 ppm ^{13}C). NMR chemical shifts were expressed in ppm relative to internal solvent peaks, and coupling constants were measured in Hz. (bs = broad signal). In most cases, only peaks of the major rotamer are reported.

[0488] Mass spectra were obtained using Agilent 1100 series LC/MSD spectrometers. Analytical HPLC analyses were carried out on 250 x 4.6 mm C-18 column using gradient conditions (10-100% B, flow rate = 1.0 mL/min, 20 min), or as described in the LC-MS Method tables.

[0489] Unless indicated otherwise, preparative HPLC was carried out on 250 x 21.2 mm C-18 column using gradient conditions (10-100% B, flow rate = 10.0 mL/min, 20 min). The eluents used were: solvent A (H_2O with 0.1% TFA) and solvent B (CH_3CN with 0.1% TFA). Final products were typically purified via reversed-phase HPLC, PTLC, or flash column chromatography. The abbreviation "TFA" refers to trifluoroacetic acid.

LC-MS Method 01		
Instrument		Agilent 1100 LC & Agilent G1956A
Software		Agilent Chemstation Rev. B. 04.03[54]
HPLC	Column	Agilent ZORBAX 5μm SB-Aq, 2.1*50mm
	Mobile Phase	A: 0.0375% TFA in water (v/v)
		B: 0.01875% TFA in Acetonitrile (v/v)

	Gradient	Time(min)	B(%)	Flow(mL/min)
		0.00	1	0.8
		0.40	1	0.8
		3.40	90	0.8
		3.90	100	0.8
		3.91	1	0.8
		4.00	1	1.0
		4.50	1	1.0
	Post time(min)	0		
	Column Temp	50°C		
	Detector	DAD		
MS	Ionization source	ESI		
	Drying Gas	N_2		
	Drying Gas Flow	10(L/min)		
	Nebulizer Pressure	40(psi)		
	Drying Gas Temperature	350 °C		
	Capillary Voltage	2500(V)		
	MS Polarity	Positive		
	MS Mode	Scan		
	Mass Range	100-1500		

LC-MS Method 5-95				
Instrument		SHIMADZU LCMS-2020		
Software		LabSolution Version 5.93		
HPLC	Column	Kinetex EVO C18 2.1X30mm,5um		
	Mobile Phase	A: 0.0375% TFA in water (v/v)		
		B: 0.01875% TFA in Acetonitrile (v/v)		
	Gradient	Time(min)	B(%)	Flow(mL/min)
		0.0	5	1.5
		0.80	95	1.5
		1.20	95	1.5
		1.21	5	1.5
		1.55	5	1.5
	Column Temp	50°C		
	Detector	PDA（220nm&254nm）		
MS	Ionization source	ESI		
	Drying Gas Flow	15(L/min)		
	DL Voltage	120(v)		
	Qarray DC Voltage	20(V)		
	MS Polarity	Positive		
	MS Mode	Scan		
	Mass range	100-1000		

LC-MS Method 10				
Instrument	Agilent 1100 LC & Agilent G1956A			
Software		Agilent Chemstation Rev. B. 04.03[54]		
HPLC	Column	Agilent ZORBAX 5μm SB-Aq, 2.1*50mm		
	Mobile Phase	A: 0.0375% TFA in water (v/v)		
		B: 0.01875% TFA in Acetonitrile (v/v)		
	Gradient	Time(min)	B(%)	Flow(mL/min)
		0.00	10	0.8
		0.40	10	0.8
		3.40	100	0.8
		3.90	100	0.8
		3.91	10	0.8
		4.00	10	1.0
		4.50	10	1.0
	Post time(min)	0		
	Column Temp	50℃		
	Detector	DAD		
MS	Ionization source	ESI		
	Drying Gas	N_2		
	Drying Gas Flow	10(L/min)		
	Nebulizer Pressure	40(psi)		
	Drying Gas Temperature	350 ℃		
	Capillary Voltage	2500(V)		
	MS Polarity	Positive		
	MS Mode	Scan		
	Mass Range	100-1500		

LC-MS Method 25				
Instrument		Agilent 1100 LC & Agilent G1956A		
Software		Agilent Chemstation Rev. B. 04.03[54]		
HPLC	Column	Agilent ZORBAX 5μm SB-Aq, 2.1*50mm		
	Mobile Phase	A: 0.0375% TFA in water (v/v)		
		B: 0.01875% TFA in Acetonitrile (v/v)		
	Gradient	Time(min)	B(%)	Flow(mL/min)
		0.00	25	0.8
		0.40	25	0.8
		3.40	100	0.8
		3.90	100	0.8
		3.91	25	0.8
		4.00	25	1.0
		4.50	25	1.0
	Post time(min)	0		
	Column Temp	50℃		
	Detector	DAD		
MS	Ionization source	ESI		

	Drying Gas	N_2
	Drying Gas Flow	10(L/min)
	Nebulizer Pressure	40(psi)
	Drying Gas Temperature	350 °C
	Capillary Voltage	2500(V) Positive
	MS Polarity	Positive
	MS Mode	Scan
	Mass Range	100-1500

LC-MS METHOD 40				
Instrument		Agilent 1100 LC & Agilent G1956A		
Software		Agilent Chemstation Rev. B. 04.03[16]		
HPLC	Column	Agilent ZORBAX 5µm SB-Aq, 2.1*50mm		
	Mobile Phase	A: 0.0375% TFA in water (v/v)		
		B: 0.01875% TFA in Acetonitrile (v/v)		
	Gradient	Time(min)	B(%)	Flow(mL/min)
		0.00	40	0.8
		0.40	40	0.8
		3.40	100	0.8
		3.90	100	0.8
		3.91	40	0.8
		4.00	40	1.0
		4.50	40	1.0
	Post time(min)	0		
	Column Temp	50°C		
	Detector	DAD(Agilent 1100)/ELSD(Agilent 1260 Infinity)		
MS	Ionization source	ESI		
	Drying Gas	N_2		
	Drying Gas Flow	10(L/min)		
	Nebulizer Pressure	2070(Torr)		
	Drying Gas Temperature	350 °C		
	Capillary Voltage	2500(V) Positive		

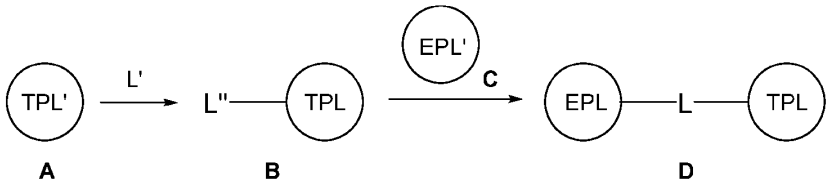
LC-MS METHOD 100				
Instrument		Agilent 1100 LC & Agilent G1956A		
Software		Agilent Chemstation Rev. B. 04.03[16]		
HPLC	Column	Agilent ZORBAX 5µm SB-Aq, 2.1*50mm		
	Mobile Phase	A: 0.0375% TFA in water (v/v)		
		B: 0.01875% TFA in Acetonitrile (v/v)		
	Gradient	Time(min)	B(%)	Flow(mL/min)
		0.00	0	0.6
		0.40	0	0.6
		3.40	80	0.6
		3.90	100	0.6
		3.91	0	0.6

		4.00	0	1.0
		4.50	0	1.0
	Post time(min)	1.20		
	Column Temp	50°C		
	Detector	DAD		
MS	Ionization source	ESI		
	Drying Gas	N2		
	Drying Gas Flow	10(L/min)		
	Nebulizer Pressure	2070(Torr)		
	Drying Gas Temperature	350 °C		
	Capillary Voltage	2500(V) Positive		
	MS Polarity	Positive		
	MS Mode	Scan		
	Mass Range	50-1500		

[0490] The following abbreviations are used herein: ACN: acetonitrile; Bn: benzyl; Boc: tert-butoxycarbonyl; DCM: dichloromethane; DIEA: diisopropylethylamine; DMF: dimethylformamide; DMSO: dimethylsulfoxide; EtOH: ethanol; EA or EtOAc: ethyl acetate; equiv. or eq.: molar equivalents; FA: formic acid; h: hour or hours; HATU: 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate; HPLC: high-pressure liquid chromatography; LCMS or LC-MS: liquid chromatography-mass spectrometry; MeCN: acetonitrile; MeOH: methanol; MS: mass spectrometry; NMP: N-methylpyrrolidone; NMR: nuclear magnetic resonance; PE: petroleum ether; rt: room temperature; TEA: triethylamine; TFA: trifluoroacetic acid; THF: tetrahydrofuran; TLC: thin-layer chromatography; psi: pounds-per-square inch; and Tos or Ts: *p*-toluenesulfonyl.

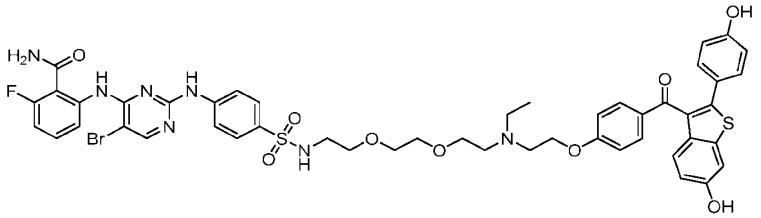
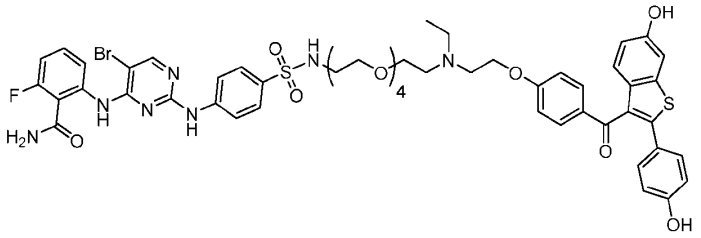
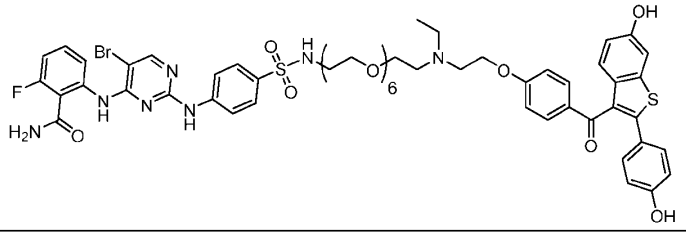
EXAMPLE 1 – Synthesis of Exemplary Compounds

[0491] The compounds set forth in the table below were prepared, according to the following general approach, a related synthetic strategy, or based on procedures described herein below.



[0492] Coupling compound **A** (a precursor of TPL, for example, a discrete compound that is a target protein ligand) with L' (a precursor to linker L, containing functionality for coupling to the precursors of both TPL and EPL) affords intermediate **B** (wherein L" is a precursor to linker L

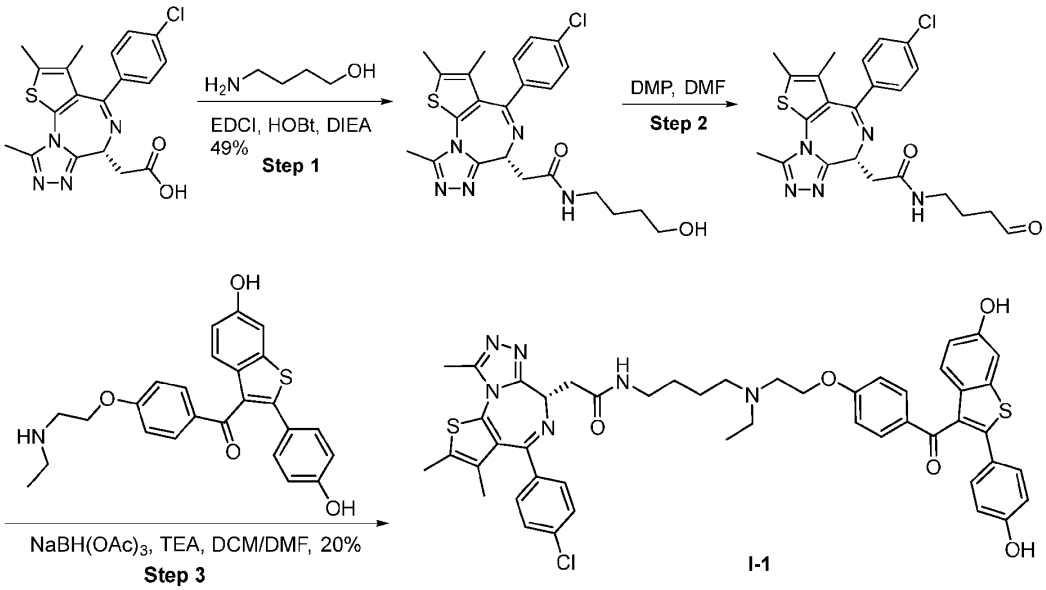
that contains functionality for coupling to the EPL precursor). The coupling of compound **A** with L' can be accomplished using, for example, amide coupling conditions. Coupling intermediate **B** with compound **C** (a precursor of EPL) affords heterobifunctional compound **D**. The coupling of intermediate **B** with compound **C** can be accomplished using, for example, amide coupling conditions.

Compound No.	Structure
I-40	
I-41	
I-42	

[0493] Physical characterization data for compounds I-40, I-41, and I-42 is provided below.

Compound No.	Observed Mass	Retention Time (min)	LCMS Method
I-40	515.7, 1030.3	220-1.970	25
I-41	559.7, 1118.3	220-2.013	25
I-42	603.8, 1206.4	220-1.064	40

EXAMPLE 2 – Synthesis of (*S*)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(4-(ethyl(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[*b*]thiophene-3-carbonyl)phenoxy)ethyl)amino)butyl)acetamide (I-1)



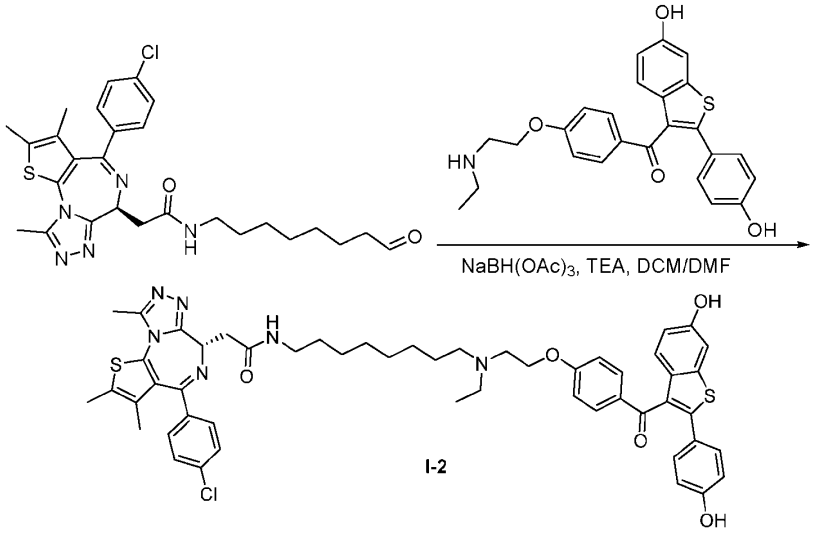
[0494] Step 1: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-hydroxybutyl)acetamide. To a solution of 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}] trideca-2(6),4,7,10,12-pentaen-9-yl]acetic acid (219 mg, 546 μmol, 1.0 *equiv*), 4-aminobutan-1-ol (48.7 mg, 546 μmol, 50.7 μL, 1.0 *equiv*), EDCI (209 mg, 1.09 mmol, 2.0 *equiv*) and HOBt (148 mg, 1.09 mmol, 2.0 *equiv*) in DMF (3 mL) was added DIEA (282 mg, 2.19 mmol, 381 μL, 4.0 *equiv*) and the mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Unisil 3-100 C18 Ultra 150x50mmx3 um; mobile phase: [water (0.225% FA)-ACN]; B%: 30%-60%, 10min) to give (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-hydroxybutyl)acetamide (130 mg, 49% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.683 min, m/z = 472.0 [M +H^+].

[0495] Step 2: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-oxobutyl)acetamide. To a solution of 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-

2(6),4,7,10,12-pentaen-9-yl]-N-(4-hydroxybutyl)acetamide (50.0 mg, 106 μmol, 1.0 *equiv*) in DMF (1 mL) was added DMP (67.4 mg, 159 μmol, 49.2 μL, 1.5 *equiv*) and the mixture was stirred at 25 °C for 1 h. The mixture was filtered to give (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-oxobutyl)acetamide (50 mg) as a light yellow oil. LC-MS: MS (ES^+): RT = 0.621 min, m/z = 470.1 [$M+H^+$].

[0496] Step 3: Preparation of (*S*)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(4-(ethyl(2-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophene-3-carbonyl)phenoxy)ethyl)amino)butyl)acetamide. To a solution of [4-[2-(ethylamino)ethoxy]phenyl]-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]methanone(58.3 mg, 106 μmol, 1.0 *equiv*, TFA salt) and $NaBH(OAc)_3$ (225 mg, 1.06 mmol, 10 *equiv*) in DCM (1 mL) was added TEA (53.8 mg, 532 μmol, 74.0 μL, 5.0 *equiv*), then to the mixture solution was added a solution of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-oxobutyl) acetamide (50.0 mg, 106 μmol, 1.0 *equiv*) in DMF (1 mL) and the mixture solution was stirred at 25 °C for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with DCM (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge 150x25mmx5um;mobile phase: [water (10Mm NH_4HCO_3)-ACN]; B%: 36%-66%, 9min) to give compound (*S*)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*] [1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(4-(ethyl(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[*b*]thiophene-3-carbonyl)phenoxy)ethyl)amino)butyl) acetamide (**I-1**,18.5 mg, 20% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 1.326 min, m/z = 887.3 [$M + H^+$], m/z = 443.3 [$M + 2H^+$]/2; LCMS method: 40. ^1H NMR (400 MHz, DMSO-d^6) δ 9.76 (s, 2 H), 8.17 (s, 1 H), 7.63 - 7.61 (m, 2 H), 7.45-7.42 (m, 4 H), 7.33 (s, 1 H), 7.32 (s, 1 H), 7.17-7.15 (m, 2 H), 6.89 - 6.87 (m, 3 H), 6.68-6.65 (m, 2 H), 4.51-4.50 (m, 1 H), 4.03-4.00 (m, 2 H), 3.32 -3.30 (m, 2 H), 3.21-3.18 (m, 4 H), 2.73-2.67 (m, 2 H), 2.58 (s, 3 H), 2.50-2.44(m, 2 H), 2.37 (s, 3 H), 1.42-1.41 (m, 4 H), 1.09 (t, *J*=6.8 Hz, 3 H).

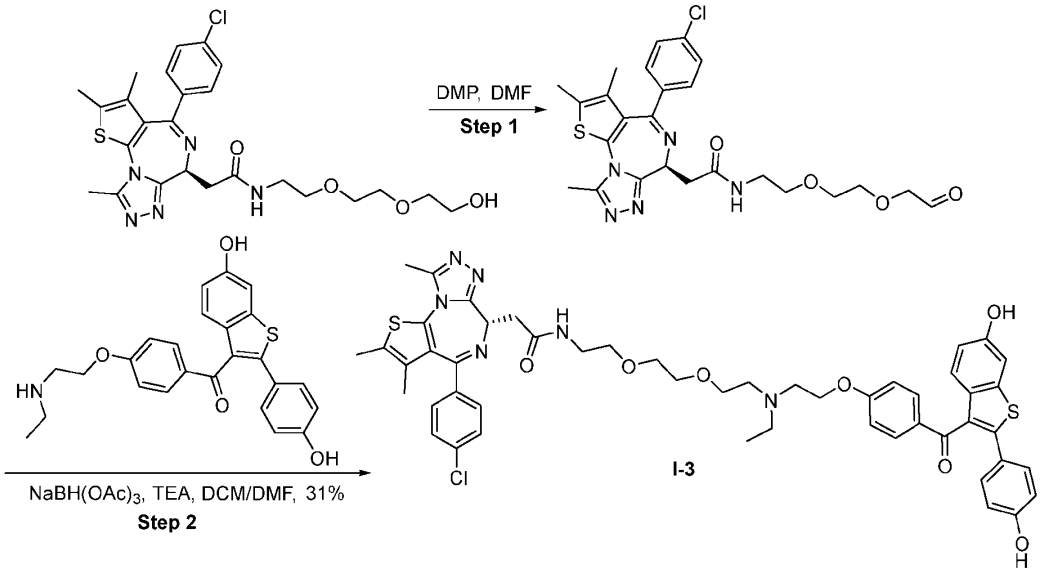
EXAMPLE 3 – Synthesis of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f] [1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(8-(ethyl(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)amino)octyl)acetamide (I-2)



[0497] To a solution of [4-[2-(ethylamino)ethoxy]phenyl]-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]methanone(52.0 mg, 95.0 μmol, 1.0 *equiv*, TFA salt) and $NaBH(OAc)_3$ (201 mg, 950 μmol, 10 *equiv*) in DCM (1 mL) was added TEA (48.1 mg, 475 μmol, 66.1 μL, 5.0 *equiv*), then to the mixture solution was added a solution of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(8-oxooctyl) acetamide (50.0 mg, 95.0 μmol, 1.0 *equiv*) in DMF (1 mL), the mixture solution was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (30 mL), extracted with DCM (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Unisil 3-100 C18 Ultra 150x50mmx3 um; mobile phase:[water (0.225%FA)-ACN]; B%: 28%-58%, 10min) to give a crude product, then the crude product was purified by *prep*-HPLC (column: Unisil 3-100 C18 Ultra 150x50mmx3 um; mobile phase: [water(0.225%FA)-ACN];B%: 25%-55%, 10min) to give 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$] trideca-2(6),4,7,10,12-pentaen-9-yl]-N-[8-[ethyl-[2-[4-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophene-3-carbonyl]phenoxy]ethyl] amino]octyl] acetamide (**I-2**, 27.8 mg, 31% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 1.695 min, m/z = 943.3 [$M + H^+$]; m/z = 472.3 [$M + 2H^-$]/2; LCMS method: 40. ^1H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.16 – 8.15 (m, 1 H), 7.66-7.64 (m, 2 H), 7.45-4.42 (m, 4 H), 7.34-7.33 (m, 1H), 7.23 (s, 1 H), 7.17-7.15 (m, 2 H), 7.00-

6.88 (m, 3 H), 6.68-6.66 (m, 2 H), 4.52-4.48 (m, 1 H), 4.03-4.00 (m, 2 H), 3.24-3.16 (m, 2 H), 3.14 - 3.12 (m, 4 H), 2.73-2.71 (m, 2 H), 2.58 (s, 3 H), 2.50-2.39 (m, 5 H), 1.61 (s, 3 H), 1.41-1.33 (m, 4 H), 1.23-1.21(m, 8 H), 1.93-0.90 (t, *J*=6.8 Hz, 3 H).

EXAMPLE 4 – Synthesis of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-(2-(2-(ethyl(2-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)amino)ethoxy)ethoxy)ethyl) acetamide (I-3)

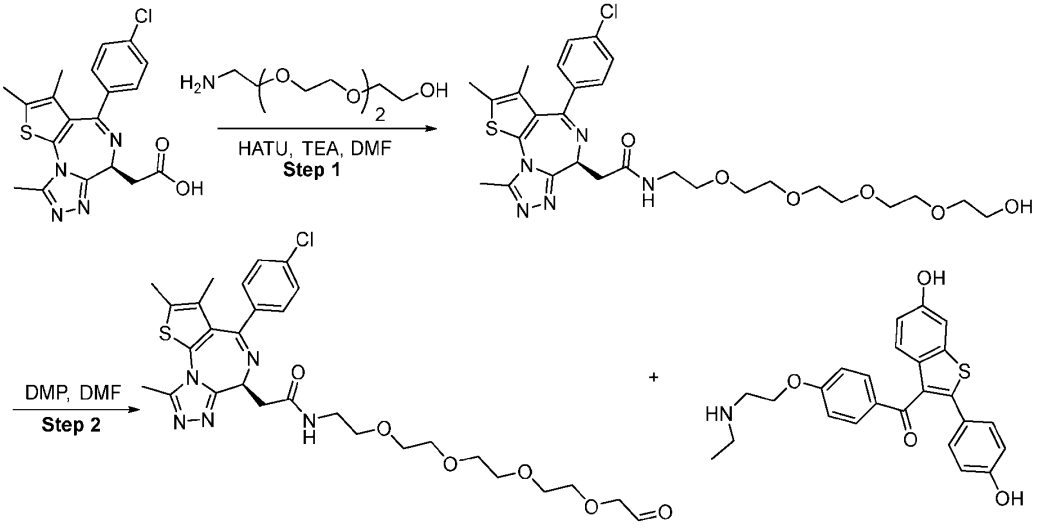


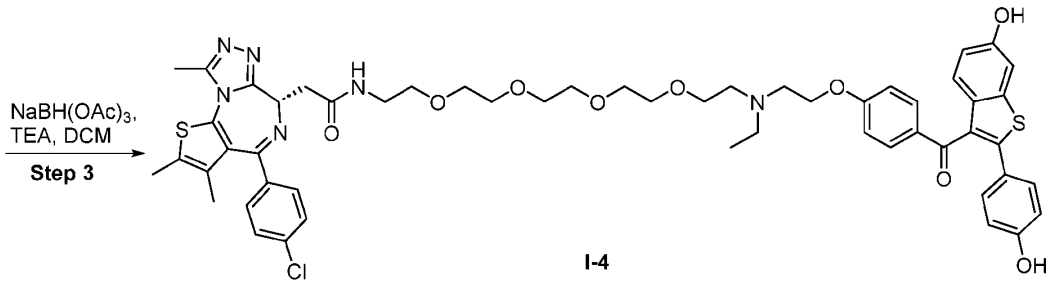
[0498] Step 1: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-(2-(2-oxoethoxy)ethoxy)ethyl)acetamide. To a solution of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-(2-(2-oxoethoxy)ethoxy)ethyl)acetamide (55.0 mg, 103 μmol, 1.0 *equiv*) in DMF(1.5 mL) was added DMP (110 mg, 258 μmol, 80.0 μL, 2.5 *equiv*). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated to give (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-(2-(2-oxoethoxy)ethoxy)ethyl)acetamide (54 mg) as a yellow oil. LC-MS: MS (ES^+): RT = 0.851 min, m/z = 530.3 [$M+H^+$].

[0499] Step 2: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-(2-(2-(ethyl(2-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)amino)ethoxy)ethoxy)ethyl)

acetamide. To a solution of [4-[2-(ethylamino)ethoxy]phenyl]-[6-hydroxy-2-(4-hydroxy-phenyl)benzothiophen-3-yl]methanone (50.0 mg, 91.3 μmol, 1.0 *equiv*, TFA salt) in DCM (3 mL) was added TEA (92.4 mg, 913 μmol, 127 μL, 10 *equiv*) and $NaBH(OAc)_3$ (194 mg, 913 μmol, 10 *equiv*), then (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-(2-(2-oxoethoxy)ethoxy)ethyl)acetamide (48.4 mg, 91.3 μmol, 1.0 *equiv*) was added and the mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by *prep*-HPLC (column: Waters Xbridge 150x25mmx5um;mobile phase: [water (10mM NH_4HCO_3)-ACN] ;B%: 44%-74%, 9min)) to give compound (S)-2-(4-(4-chloro phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f] [1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-(2-(2-(ethyl(2-(4-(6-hydroxy-2-(4-hydroxy phenyl)benzo[b]thiophene-3-carbonyl)phenoxy)ethyl) amino)ethoxy)ethoxy)ethyl) acetamide (**I-3**, 20 mg, 23% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 2.064 min, m/z = 947.2 [M + H^+]; m/z = 474.3 [M + $2H^+$]/2 LCMS Method: 25. ^1H NMR (400 MHz, CD_3OD) δ 7.64 (d, *J*=8.8 Hz, 2 H), 7.33 - 7.43 (m, 5 H), 7.27 (d, *J*=2.1 Hz, 1 H), 7.18 (d, *J*=8.6 Hz, 2 H), 6.87 (dd, *J*=8.8, 2.2 Hz, 1 H), 6.76 (d, *J*=8.9 Hz, 2 H), 6.63 (d, *J*=8.5 Hz, 2 H), 4.62 (dd, *J*=9.1, 5.1 Hz, 1 H), 4.07 (t, *J*=5.7 Hz, 2 H), 3.58 - 3.64 (m, 7 H), 3.38 - 3.49 (m, 5 H), 2.94 (t, *J*=5.5 Hz, 2 H), 2.79(t, *J*=5.6 Hz, 2 H), 2.64 - 2.73 (m, 5 H), 2.44 (s, 3 H), 1.68 (s, 3 H), 1.06 (t, *J*=7.1 Hz, 3 H).

<u>EXAMPLE 5</u> – Synthesis of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-ethyl-1-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)-6,9,12,15-tetraoxa-3-azaheptadecan-17-yl) acetamide (I-4)





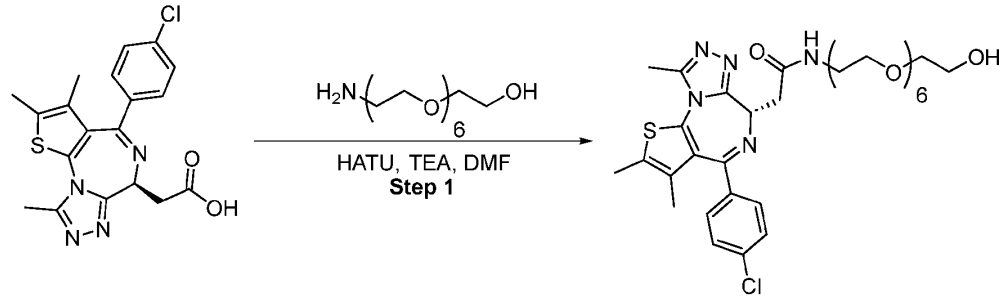
[0500] Step 1: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(14-hydroxy-3,6,9,12-tetraoxa-tetradecyl) acetamide. To a solution of 2-[2-[2-[2-(2-aminoethoxy)ethoxy] ethoxy]ethoxy]ethanol (200 mg, 569 μmol, 1.0 *equiv*, TFA salt) and 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]acetic acid (293 mg, 569 μmol, 1.0 *equiv*, TFA salt) in DMF (2 mL) was added DIEA (368 mg, 2.85 mmol, 496 μL, 5.0 *equiv*) and HATU (238 mg, 626 μmol, 1.1 *equiv*). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 150x25mmx10um; mobile phase: [water (0.225%FA)-ACN]; B%: 33%-63%, 10min) to give compound (S)-2-(4-(4-chloro phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f] [1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(14-hydroxy-3,6,9,12-tetraoxatetradecyl)acetamide (47.0 mg, 13% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 0.857 min, m/z = 620.2 [$M+H^+$].

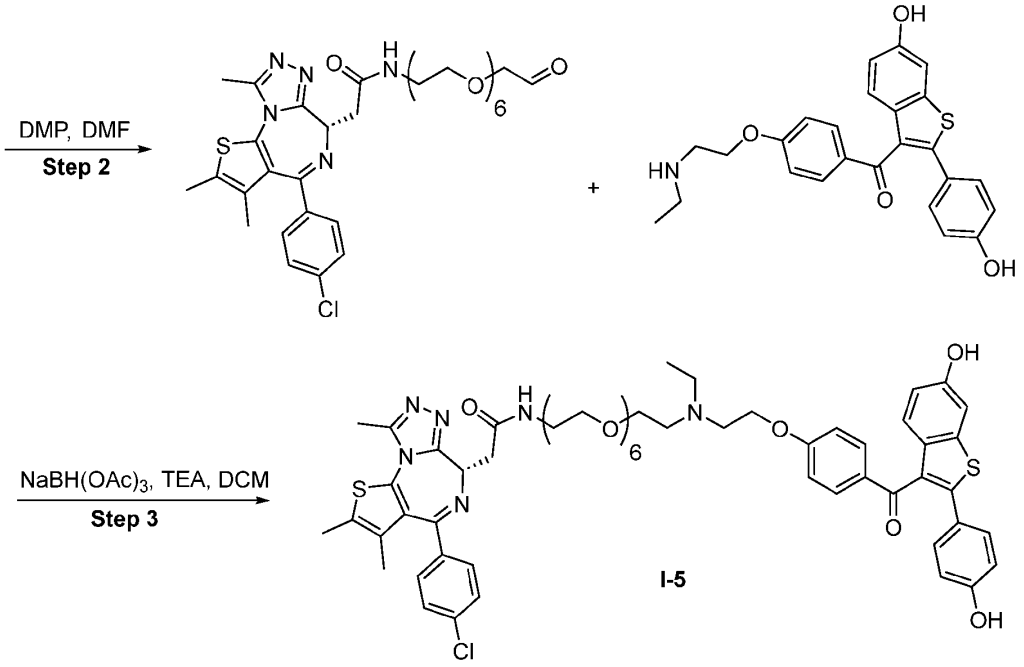
[0501] Step 2: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(14-oxo-3,6,9,12-tetraoxatetradecyl) acetamide. To a solution of 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo [8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]-N-[2-[2-[2-[2-(2-hydroxy-ethoxy)ethoxy] ethoxy]ethoxy]ethyl]acetamide (47.0 mg, 75.8 μmol, 1.0 *equiv*) in DMF (1.5 mL) was added DMP (80.4 mg, 189 μmol, 58.7 μL, 2.5 *equiv*). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated to give (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(14-oxo-3,6,9,12-tetraoxatetradecyl) acetamide (46.5 mg) as a yellow oil. LC-MS: MS (ES^+): RT = 0.824 min, m/z = 620 [$M+H^+$]

[0502] Step 3: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-ethyl-1-(4-(6-hydroxy-2-(4-hydroxy phenyl)benzo[b]thiophene-3-carbonyl)phenoxy)-6,9,12,15-tetraoxa-3-azaheptadecan-17-

yl)acetamide. To a solution of 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]-N-[2-[2-[2-[2-(2-oxoethoxy) ethoxy] ethoxy]ethoxy]ethyl]acetamide (46.0 mg, 74.4 μmol,1.0 *equiv*) and [4-[2-(ethylamino) ethoxy]phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (40.8 mg, 74.4 μmol, 1.0 *equiv*, TFA salt) in DCM (2 mL) was added $NaBH(OAc)_3$ (158 mg, 744 μmol, 10 *equiv*) and TEA (75.3 mg, 744 μmol, 104 μL, 10 *equiv*). The mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150x25mmx10um; mobile phase:[water(0.225%FA)-ACN];B%: 25%-55%,10min)) to give (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-ethyl-1-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene-3-carbonyl)phenoxy)-6,9,12,15-tetraoxa-3-azaheptadecan-17-yl)acetamide (**I-4**, 15.4 mg, 20% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 1.077 min, m/z = 1035.3 [M + H^+]; m/z = 518.3 [M + $2H^+$]/2 LCMS Method: 40. ^1H NMR (400 MHz, CD_3OD) δ 7.69 - 7.41 (m, 2 H), 7.29-7.35 (m, 5 H), 7.26-7.25 (m, 1 H), 7.16-6.82 (m, 3 H), 6.62-6.61 (m, 2 H), 4.86-4.60 (m, 1 H), 4.16 (s, 2 H), 3.64-3.58 m, 2 H), 3.58 - 3.55 (m, 14 H), 3.43 - 3.32 (m, 3 H), 3.31-3.30 (m, 1 H), 3.15 (s, 2 H), 2.65 - 2.42 (m, 4 H), 2.65 (s, 3 H), 2.42 (s, 3 H), 1.67 (s, 3 H), 1.15-1.12 (t, *J*=7 Hz, 3 H).

<u>EXAMPLE 6</u> – Synthesis of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-ethyl-1-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)-6,9,12,15,18,21-hexaoxa-3-azatricosan-23-yl) acetamide (I-5)





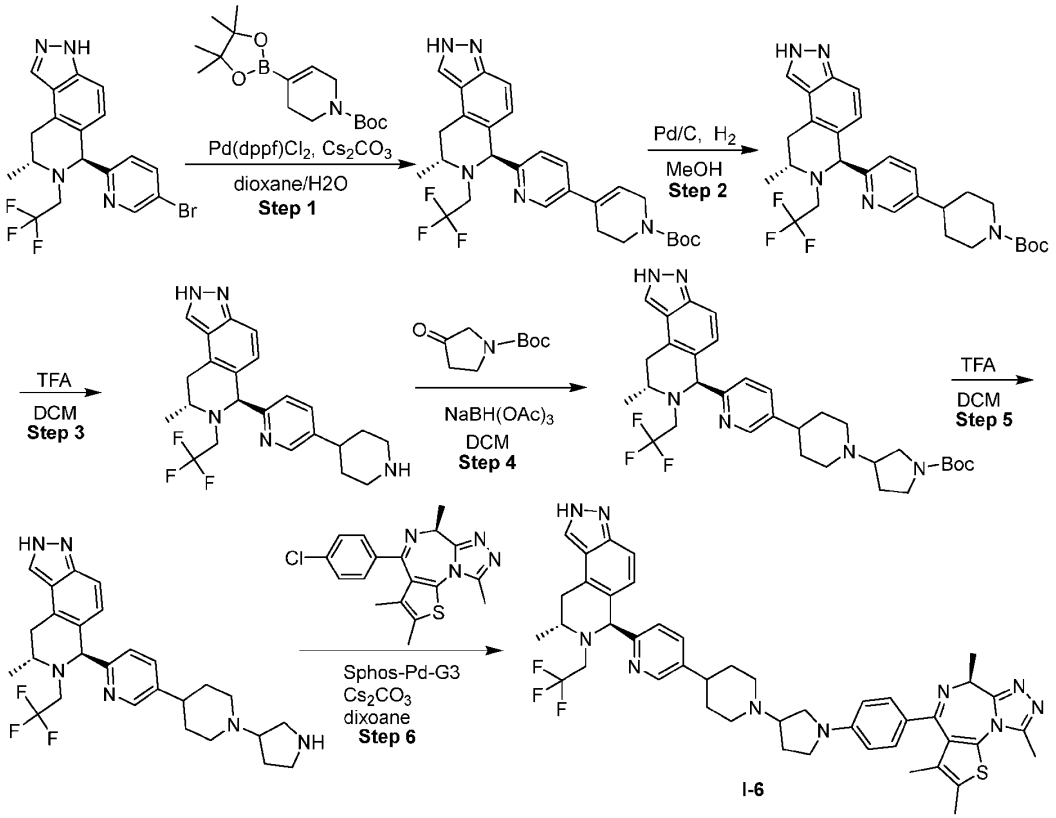
[0503] Step 1: Preparation of 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-9-yl]-N-[2-[2-[2-[2-[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethyl]acetamide. To a solution of 2-[2-[2-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethanol (200 mg, 455 μmol, 1.0 *equiv*, TFA salt) and 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-9-yl]acetic acid (234 mg, 455 μmol, 1.0 *equiv*, TFA salt) in DMF (4 mL) was added DIEA (176 mg, 1.37 mmol, 238 μL, 3.0 *equiv*) and HATU (190 mg, 501 μmol, 1.1 *equiv*). The mixture was stirred at 20 °C for 0.1 h. The reaction mixture was concentrated. It was purified by *prep*-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um; mobile phase:[water(0.225%FA)-ACN]; B%: 20%-50%,7min) to give 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-9-yl]-N-[2-[2-[2-[2-[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]ethoxy] ethoxy]ethoxy]ethyl]acetamide (50.0 mg, 70.6 μmol, 16% yield) as a yellow gum. LC-MS: MS (ES$^+$): RT = 0.625 min, m/z = 708.1 [M +H$^+$].

[0504] Step 2: Preparation of 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-9-yl]-N-[2-[2-[2-[2-[2-[2-(2-oxoethoxy)ethoxy] ethoxy]ethoxy]ethoxy]ethoxy]ethyl]acetamide. To a solution of 2-[(9*S*)-7-

(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]-N-[2-[2-[2-[2-[2-[2-(2-hydroxyethoxy) ethoxy] ethoxy]ethoxy] ethoxy]ethoxy]ethyl]acetamide (50.0 mg, 70.6 μmol, 1.0 *equiv*) in DMF (1 mL) was added DMP (74.9 mg, 176 μmol, 54.6 μL, 2.5 *equiv*). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated to give 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]-N-[2-[2-[2-[2-[2-[2-(2-oxoethoxy)ethoxy] ethoxy]ethoxy]ethoxy]ethoxy]ethyl]acetamide (49.0 mg, 69.4 μmol, 98% yield) as a yellow oil.

[0505] Step 3: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-ethyl-1-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)-6,9,12,15,18,21-hexaoxa-3-azatricosan-23-yl) acetamide. To a solution of [4-[2-(ethylamino)ethoxy]phenyl]-[6-hydroxy-2-(4-hydroxy phenyl)benzothiophen-3-yl]methanone (40.0 mg, 73.1 μmol, 1.0 *equiv*, TFA salt) in DCM (3 mL) was added TEA (73.9 mg, 731 μmol, 102 μL, 10 *equiv*) and $NaBH(OAc)_3$ (155 mg, 731 μmol, 10 *equiv*), then 2-[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetra zatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]-N-[2-[2-[2-[2-[2-[2-(2-oxo ethoxy) ethoxy]ethoxy] ethoxy]ethoxy]ethoxy]ethyl]acetamide (49.0 mg, 69.4 μmol, 1.0 *equiv*) was added and the mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by *prep*-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (0.225%FA)-ACN]; B%: 25%-55%, 10min and column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 35%-65%,8 min and column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase:[water(10mM NH_4HCO_3)-ACN];B%: 35%-65%,8min) to give compound (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-ethyl-1-(4-(6-hydroxy-2-(4-hydroxy-phenyl)benzo[b]thiophene-3-carbonyl)phenoxy)-6,9,12,15,18,21-hexaoxa-3-azatricosan-23-yl)acetamide (**I-5**, 15.3 mg, 18% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 1.327 min, m/z = 1123.4 [$M + H^+$]; m/z = 562.3 [$M + 2H^+$]/2; LCMS Method: 40. ^1H NMR (400 MHz, CD_3OD) δ7.71 (d, *J*=9.0 Hz, 2 H), 7.37 - 7.49 (m, 5 H), 7.27 (d, *J*=2.3 Hz, 1 H), 7.20 (d, *J*=8.8 Hz, 2 H), 6.80 - 6.91 (m, 3 H), 6.64 (d, *J*=8.8 Hz, 2 H), 4.65 (d, *J*=5.3 Hz, 1 H), 4.13 (s, 2 H), 3.43 -3.65 (m, 28 H), 3.00 (s, 2 H), 2.69 (s, 6 H), 2.44 (s, 3 H), 1.70 (s, 3 H), 1.09 (t, *J*=7.6 Hz, 3 H).

EXAMPLE 7 – Synthesis of (6S)-2,3,6,9-tetramethyl-4-(4-(3-(4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperidin-1-yl)pyrrolidin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4] diazepine (I-6)



[0506] Step 1: Preparation of *tert*-butyl 6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate. To a solution of (6S,8R)-6-(5-bromopyridin-2-yl)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinoline (700 mg, 1.65 mmol, 1.00 *equiv*), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (610 mg, 1.98 mmol, 1.20 *equiv*), and cesium carbonate (1.61 g, 4.94 mmol, 3.00 *equiv*) in dioxane (12 mL) and water (3 mL) was added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (240 mg, 0.32 mmol, 0.20 *equiv*) and the mixture was stirred at 90 °C for 2 h under a nitrogen atmosphere. The reaction mixture was quenched with water (60 mL), and then extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced

pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=1/0 to 1/1) to afford *tert*-butyl 6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (550 mg, 63% yield) as a yellow oil. LCMS: MS (ES^+): RT = 0.530 min, m/z = 528.3 $[M+H]^+$.

[0507] Step 2: Preparation of *tert*-butyl 4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoro-ethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperidine-1-carboxylate. To a solution of *tert*-butyl 6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (550 mg, 1.04 mmol, 1.00 *equiv*) in methanol (15 mL) was added palladium on activated carbon (100 mg, 10% purity) and then the mixture was degassed and purged with hydrogen three times, and then the mixture was stirred at 25 °C for 5 h under a hydrogen (15 psi) atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to afford *tert*-butyl 4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperidine-1-carboxylate (426 mg, 77% yield) as a yellow oil, which was used in the next step without further purification. LCMS: MS (ES^+): RT = 0.544 min, m/z = 530.3 $[M+H]^+$.

[0508] Step 3: Preparation of (6S,8R)-8-methyl-6-(5-(piperidin-4-yl)pyridin-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinoline. To a solution of *tert*-butyl 4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperidine-1-carboxylate (426 mg, 0.80 mmol, 1.00 *equiv*) in dichloromethane (4.5 mL) was added trifluoroacetic acid (2.30 g, 20.19 mmol, 25.10 *equiv*) dropwise and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford (6S,8R)-8-methyl-6-(5-(piperidin-4-yl)pyridin-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinoline (345 mg, 99% yield) as a white solid, which was used in the next step without further purification. LCMS: MS (ES^+): RT = 0.432 min, m/z = 430.3 $[M+H]^-$.

[0509] Step 4: Preparation of *tert*-butyl 3-(4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperidin-1-yl)pyrrolidine-1-carboxylate. To a solution of (6S,8R)-8-methyl-6-(5-(piperidin-4-yl)pyridin-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinoline (345 mg, 0.80 mmol, 1.00 *equiv*), *tert*-butyl 3-oxopyrrolidine-1-carboxylate (446 mg, 2.41 mmol, 3.00 *equiv*) in dichloromethane (8 mL) was added sodium triacetoxy borohydride (510 mg, 2.41 mmol, 3.00

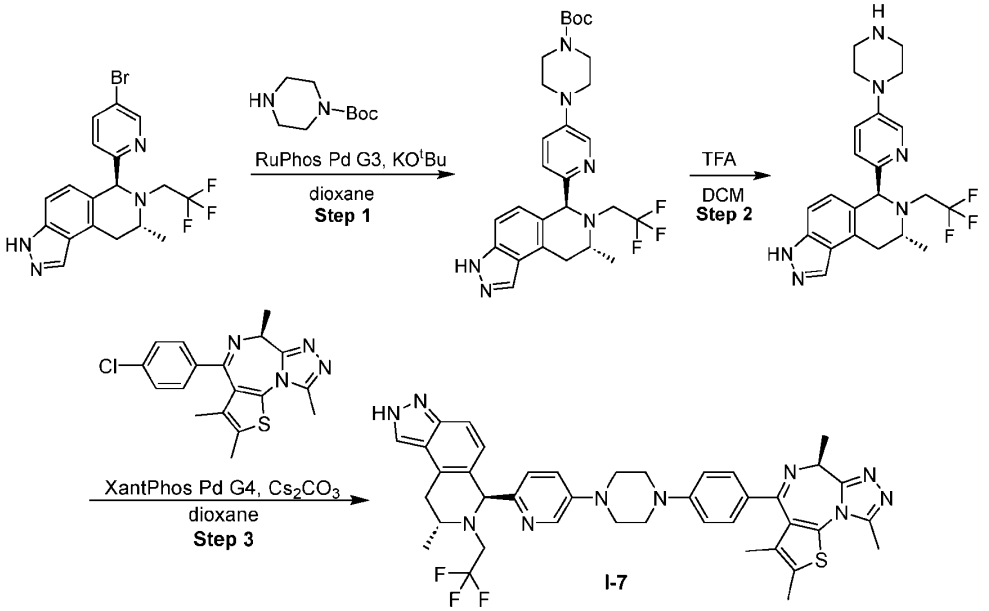
equiv) and the mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (dichloromethane: methanol = 10:1) to afford *tert*-butyl 3-(4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin -6-yl)pyridin-3-yl)piperidin-1-yl)pyrrolidine-1-carboxylate (450 mg, 93% yield) as a white solid. LCMS: MS (ES^+): RT = 0.440 min, m/z = 599.3 $[M+H]^+$.

[0510] Step 5: Preparation of (6S,8R)-8-methyl-6-(5-(1-(pyrrolidin-3-yl)piperidin-4-yl)pyridin-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinoline. To a solution of *tert*-butyl 3-(4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperidin-1-yl)pyrrolidine-1-carboxylate (450 mg, 0.75 mmol, 1.00 *equiv*) in dichloromethane (4.5 mL) was added trifluoroacetic acid (2.30 g, 20.19 mmol, 26.87 *equiv*) dropwise and then the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 20%-50% B over 20 min] to afford (6S,8R)-8-methyl-6-(5-(1-(pyrrolidin-3-yl)piperidin-4-yl)pyridin-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinoline (230 mg, 61% yield) as a white solid. LCMS: MS (ES^+): RT = 0.381 min, m/z = 499.4 $[M+H]^+$.

[0511] Step 6: Preparation of (6S)-2,3,6,9-tetramethyl-4-(4-(3-(4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperidin-1-yl)pyrrolidin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4] diazepine. To a solution of (6S,8R)-8-methyl-6-(5-(1-(pyrrolidin-3-yl)piperidin-4-yl)pyridin-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinoline (150 mg, 0.30 mmol, 1.00 *equiv*), (S)-4-(4-chlorophenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo [4,3-a][1,4]diazepine (161 mg, 0.45 mmol, 1.50 *equiv*), cesium carbonate (294 mg, 0.90 mmol, 3.00 *equiv*) in dioxane (3 mL) was added (2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl) [2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (46 mg, 0.060 mmol, 0.20 *equiv*) and the mixture was stirred at 90 °C for 4 h under nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient:8%-38% B over 1 min] to give the crude product. The product was purified by SFC [column: DAICEL CHIRALCEL OX (250mm*30mm, 10um); mobile phase: [CO_2-

ACN/MeOH (0.1% NH_3H_2O)];B%:70%, isocratic elution mode] to give the crude product (peak 1). The crude product was further purified by prep-HPLC [column: Phenomenex luna C18 150mm x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 8%-38% B over 1 min] to afford (6S)-2,3,6,9-tetramethyl-4-(4-(3-(4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoro ethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperidin-1-yl) pyrrolidin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (**I-6**, 10.37 mg, 4.17% yield) as a yellow solid. LCMS: MS (ES^+): RT = 0.981 min, m/z = 819.6 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.06 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.42 - 7.35 (m, 3H), 7.23 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 2H), 5.13 (s, 1H), 4.16 - 4.08 (m, 1H), 3.63 - 3.54 (m, 2H), 3.52 - 3.45 (m, 1H), 3.40 - 3.25 (m, 4H), 3.23 - 3.15 (m, 1H), 3.12 - 2.95 (m, 3H), 2.93 - 2.86 (m, 1H), 2.67 (s, 3H), 2.61 - 2.53 (m, 1H), 2.41 (s, 3H), 2.34 - 2.14 (m, 4H), 2.07 (d, *J* = 6.4 Hz, 3H), 1.92 - 1.85 (m, 4H), 1.78 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H).

EXAMPLE 8 – Synthesis of (S)-2,3,6,9-tetramethyl-4-(4-(4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl) piperazin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (I-7)



[0512] Step 1: Preparation of *tert*-butyl 4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperazine-1-carboxylate. To a solution of (6S,8R)-6-(5-bromopyridin-2-yl)-8-methyl-7-(2,2,2-trifluoro ethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinoline (1.00 g, 2.35 mmol, 1.00 *equiv*), tert-butyl piperazine-

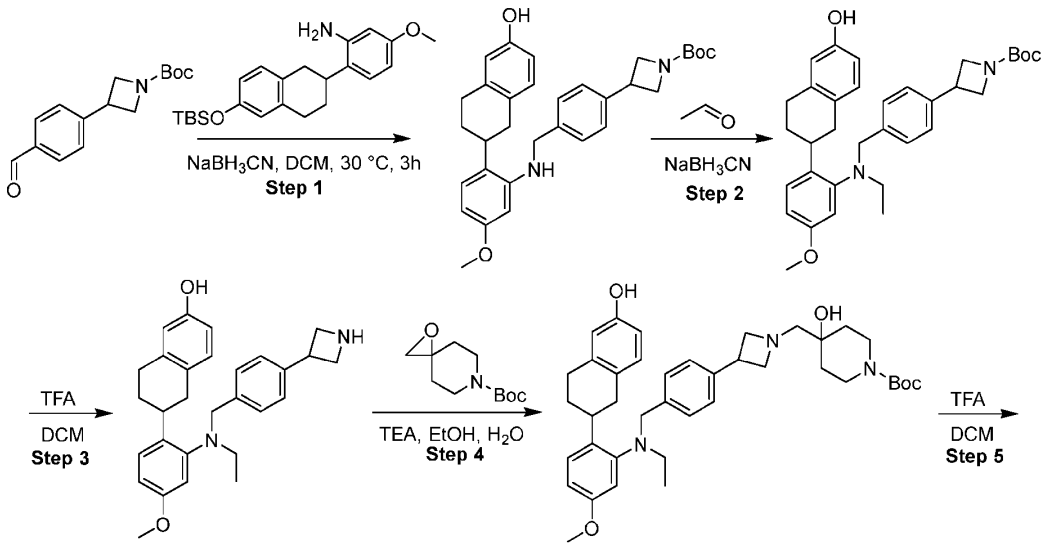
1-carboxylate (1.75 g, 9.41 mmol, 4.00 *equiv*), and potassium tert-butoxide (1.06 g, 9.41 mmol, 4.00 *equiv*) in dioxane (20 mL) was added methanesulfonato(2-dicyclo hexylphosphino-2,6-di-i-propoxy-1,1-biphenyl)(2-amino-1,1-biphenyl-2-yl)palladium(ii) (393 mg, 0.47 mmol, 0.20 *equiv*) and the mixture was stirred at 100 °C for 10 h under a nitrogen atmosphere. The reaction mixture was quenched with water (100 mL), and then extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1/0 to 1/1) to afford *tert*-butyl 4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperazine-1-carboxylate (400 mg, 32% yield) as a yellow solid. LCMS: MS (ES^+): RT = 0.493 min, m/z = 531.4 $[M+H]^+$.

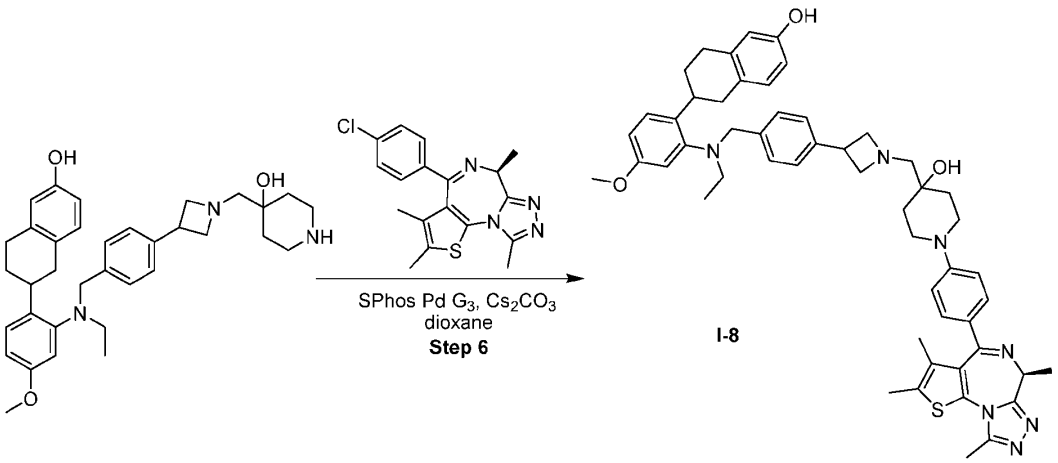
[0513] Step 2: Preparation of (6S,8R)-8-methyl-6-(5-(piperazin-1-yl)pyridin-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinoline. To a solution of *tert*-butyl 4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperazine-1-carboxylate (400 mg, 0.75 mmol, 1.00 *equiv*) in dichloromethane (4.5 mL) was added dropwise trifluoroacetic acid (2.30 g, 20.19 mmol, 26.79 *equiv*) and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Waters Xbridge 150 x 25mm x 5um; mobile phase: [water (ammonia hydroxide v/v)-ACN]; gradient:20%-50% B over 10 min] to afford (6S,8R)-8-methyl-6-(5-(piperazin-1-yl)pyridin-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinoline (130 mg, 40% yield) as a white solid. LCMS: MS (ES^+): RT = 0.585 min, m/z = 431.2 $[M+H]^+$.

[0514] Step 3: Preparation of (S)-2,3,6,9-tetramethyl-4-(4-(4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperazin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine. To a solution of (6S,8R)-8-methyl-6-(5-(piperazin-1-yl)pyridin-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinoline (35 mg, 0.08 mmol, 1.00 *equiv*), (S)-4-(4-chlorophenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (43 mg, 0.12 mmol, 1.50 *equiv*), and cesium carbonate (79 mg, 0.24 mmol, 3.00 *equiv*) in dioxane (1 mL) was added dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane; methanesulfonate; [2-[2-(methylamino)phenyl]phenyl]palladium(1+) (13 mg, 0.01 mol, 0.20 *equiv*) and the mixture was stirred at 90 °C for 2 h under nitrogen atmosphere. The reaction mixture was filtered and

concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient:15%-45% B over 1 min] to give the crude product. The crude product was purified by SFC [column: DAICEL CHIRALCEL OD (250mm * 30 mm, 10um); mobile phase: [CO_2-ACN/EtOH (0.1% NH3H2O)]; B%: 60%, isocratic elution mode] to give a product that was further purified by prep-HPLC [column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; gradient:15%-45% B over 1 min] to afford (S)-2,3,6,9-tetramethyl-4-(4-(4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperazin-1-yl)phenyl)-6H-thieno [3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (**I-7,** 8.61 mg, 13.53% yield) as a yellow solid. LCMS: MS (ES^+): RT = 1.483 min, m/z = 751.6 $[M+H]^+$; LCMS Method: 10. ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 2.8 Hz, 1H), 8.07 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 9.2 Hz, 1H), 7.24 - 7.18 (m, 2H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.08 (s, 1H), 4.15 (q, *J* = 6.8 Hz, 1H), 3.66 - 3.56 (m, 1H), 3.46 - 3.38 (m, 4H), 3.38 - 3.30 (m, 5H), 3.29 - 3.18 (m, 1H), 3.08 - 2.99 (m, 1H), 2.93 - 2.85 (m, 1H), 2.68 (s, 3H), 2.42 (s, 3H), 2.08 (d, *J* = 6.8 Hz, 3H), 1.76 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H).

EXAMPLE 9 – Synthesis of 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidin-1-yl)methyl)-1-(4-((S)-2,3,6,9-tetra methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (I-8)





[0515] Step 1: Preparation of *tert*-butyl3-(4-(((2-(6-hydroxy-1,2,3,4-tetrahydro naphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidine-1-carboxylate. To a solution of *tert*-butyl 3-(4-formylphenyl)azetidine-1-carboxylate (900 mg, 2 mmol, 1 *equiv*) and 2-(6-((tert-butyldimethylsilyl)oxy)-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyaniline (603 mg, 2 mmol, 1 *equiv*) in DCM (5 mL) was added AcOH (201.65 mg, 3.36 mmol, 1.5 *equiv*). The mixture was stirred at 30 °C for 2 h, then $NaBH_3CN$ (281.36 mg, 4.48 mmol, 2 *equiv*) was added, and the mixture was stirred at 30 °C for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15um; mobile phase: [water(FA)-ACN]; gradient:55%-85% B over 15 min) to afford *tert*-butyl3-(4-(((2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidine-1-carboxylate (610 mg, 52 % yield) as a white solid. LC-MS: MS (ES^+): RT = 0.608 min, m/z = 515.3 [$M+H^+$].

[0516] Step 2: Preparation of *tert*-butyl 3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydro naphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidine-1-carboxylate. To a solution of *tert*-butyl3-(4-(((2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxy phenyl)amino)methyl)phenyl)azetidine-1-carboxylate (380 mg, 0.74 mmol, 1 *equiv*) and acetaldehyde (5 M, 2.22 mL, 15 *equiv*) in MeOH (3 mL) was added $NaBH_3CN$ (92.80 mg, 1.48 mmol, 2 *equiv*). The mixture was stirred at 20 °C for 2 hr. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to

give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/ethyl acetate=3/1) to afford *tert*-butyl 3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidine-1-carboxylate (362 mg, 84% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.21 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 3H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.71 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.66 - 6.59 (m, 2H), 4.31 (t, *J* = 8.8 Hz, 2H), 4.01 (s, 2H), 3.94 (dd, *J* = 6.4, 8.0 Hz, 2H), 3.81 (s, 3H), 3.74 - 3.56 (m, 2H), 3.03 - 2.90 (m, 2H), 2.85 - 2.75 (m, 2H), 2.75 - 2.64 (m, 2H), 1.84 - 1.69 (m, 2H), 1.62 (d, *J* = 6.8 Hz, 2H), 1.48 (s, 9H), 0.96 (t, *J* = 7.2 Hz, 3H). LC-MS: MS (ES+): RT = 0.530 min, m/z = 543.4 [M + H^+].

[0517] Step 3: Preparation of 6-(2-((4-(azetidin-3-yl)benzyl)(ethyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol. To a solution of *tert*-butyl 3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)amino)methyl) phenyl)azetidine-1-carboxylate (380 mg, 0.7 mmol, 1 *equiv*) in DCM (3 mL) was added TFA (1.77 g, 15.48 mmol, 22 *equiv*). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent to afford 6-(2-((4-(azetidin-3-yl)benzyl)(ethyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (310 mg, crude) as a yellow solid. LC-MS: MS (ES^+): RT = 0.414 min, m/z = 443.2 [M +H^+].

[0518] Step 4: Preparation of *tert*-butyl 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidin-1-yl)methyl)-4-hydroxypiperidine-1-carboxylate. *tert*-Butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (223 mg, 1 mmol, 1.5 *equiv*), 6-(2-((4-(azetidin-3-yl)benzyl)(ethyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (309 mg, 0.7 mmol, 1 *equiv*) and TEA (211 mg, 2.09 mmol, 3 *equiv*) were taken up into a microwave tube in ethyl alcohol (5 mL) and water (1 mL). The sealed tube was heated at 100 °C for 3 h under microwave irradiation. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/ethyl acetate = 0/1) to afford *tert*-butyl 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidin-1-yl)methyl)-4-hydroxypiperidine-1-carboxylate (210 mg, 44% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.456 min, m/z = 656.5 [M +H^+].

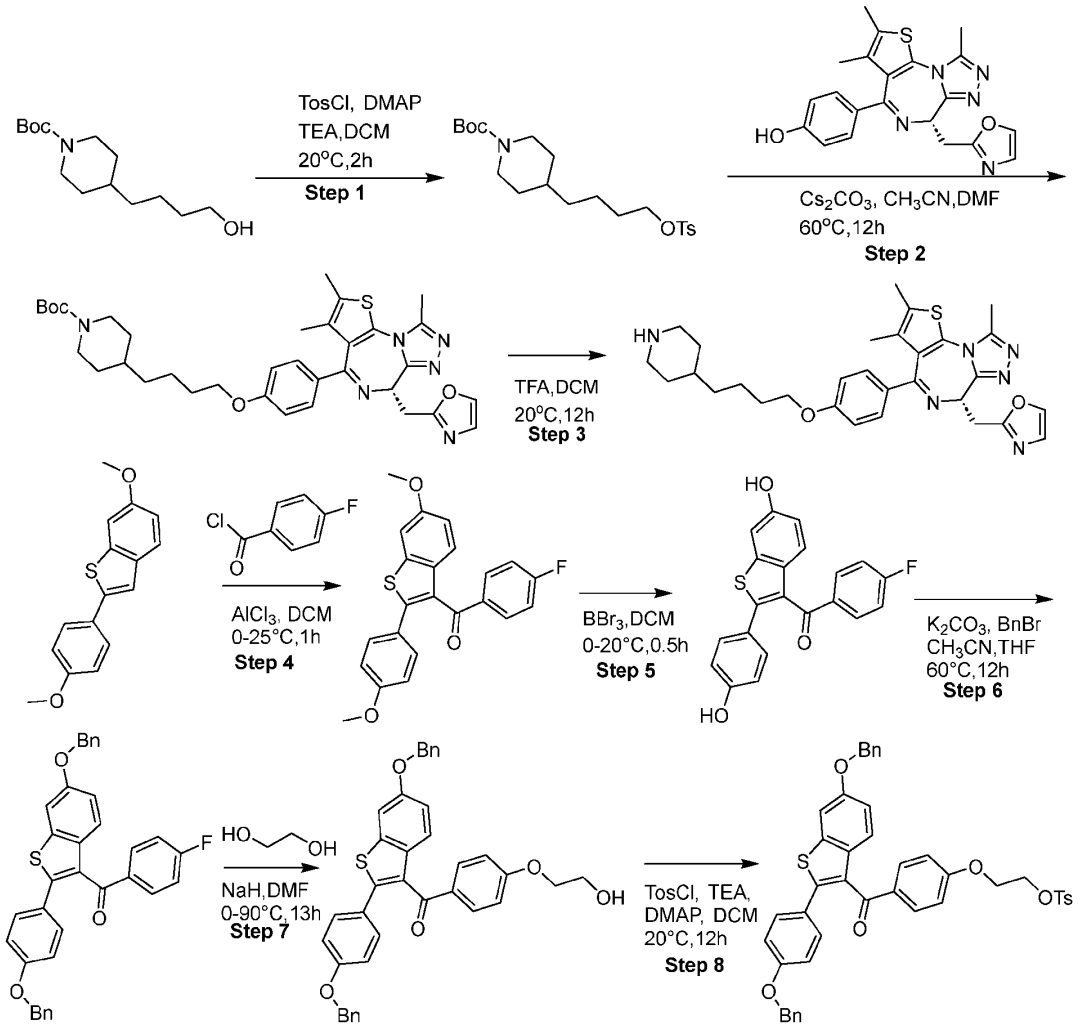
[0519] Step 5: Preparation of 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidin-1-yl)methyl)piperidin-4-

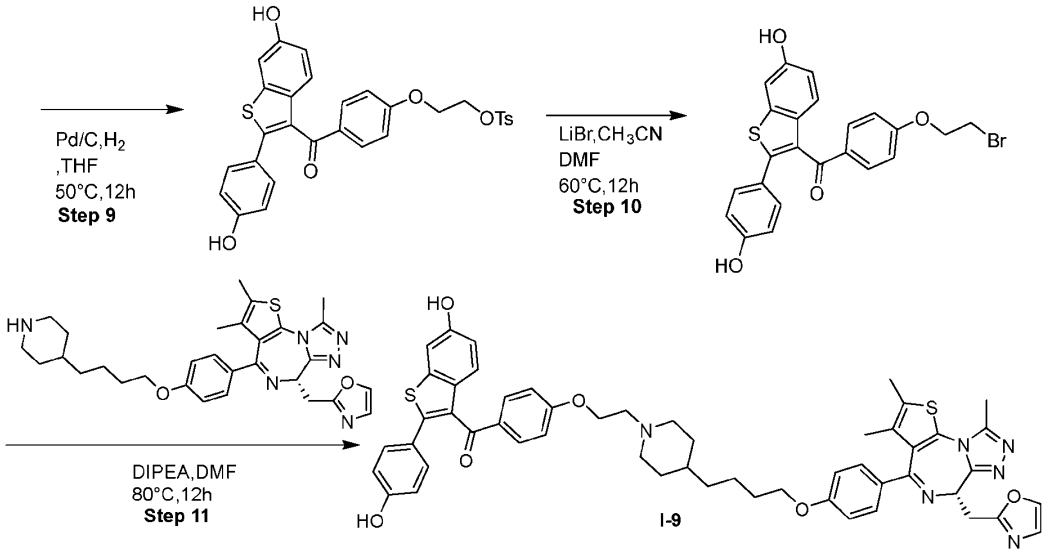
ol. To a solution of *tert*-butyl 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidin-1-yl)methyl)-4-hydroxypiperidine-1-carboxylate (110 mg, 0.16 mmol, 1 *equiv*) in DCM (2 mL) was added TFA (57.37 mg, 0.5 mmol, 3 *equiv*). The mixture was stirred at 20 °C for 0.5 hr. The reaction mixture was quenched by the addition of a saturated solution of aqueous sodium bicarbonate (10 mL) and then diluted with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydro naphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidin-1-yl)methyl)piperidin-4-ol (166 mg, crude) as a yellow solid. LC-MS: MS (ES^+): RT = 0.398 min, m/z = 556.4 [$M+H^+$].

[0520] Step 6: Preparation of 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidin-1-yl)methyl)-1-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin -4-yl)phenyl) piperidin-4-ol. A mixture of 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydro naphthalen-2-yl)-5-methoxyphenyl)amino)methyl)phenyl)azetidin-1-yl)methyl)piperidin-4-ol (160 mg, 0.28 mmol, 1 *equiv*), (S)-4-(4-chlorophenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepine (123.29 mg, 0.34 mmol, 1.2 *equiv*), Cs_2CO_3 (281.41 mg, 0.86 mmol, 3 *equiv*), and dicyclohexyl-[2-(2,6-dimethoxyphenyl)phenyl]phosphane; methanesulfonate;(2-phenylanilino)palladium(1^+) (22.46 mg, 0.03 mmol, 0.1 *equiv*) in dioxane (3 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 90 °C for 3 hr under an N_2 atmosphere. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM/MeOH=10/1) to afford 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)amino)methyl) phenyl)azetidin-1-yl)methyl)-1-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol as a white solid. The solid was purified by SFC (column: DAICEL CHIRALCEL OX (250mm x 30mm,10um); mobile phase: [CO_2-ACN/EtOH (0.1% NH_3H_2O)]; B%:70%, isocratic elution mode) to afford 4-((3-(4-((ethyl(2-(6-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-5-methoxyphenyl)amino)methyl) phenyl)azetidin-1-yl)methyl)-1-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenyl) piperidin-4-ol (**I-8**, 40 mg, 46% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 7.27

(d, J = 8.4 Hz, 2H), 7.21 - 7.12 (m, 5H), 6.90 (d, J = 9.0 Hz, 2H), 6.83 - 6.77 (m, 2H), 6.66 (dd, J = 2.8, 8.8 Hz, 1H), 6.55 - 6.45 (m, 2H), 4.17 - 4.07 (m, 2H), 3.98 (d, J = 2.8 Hz, 2H), 3.71 (s, 3H), 3.65 (t, J = 7.2 Hz, 2H), 3.56 - 3.46 (m, 5H), 3.14 - 3.07 (m, 4H), 2.87 (d, J = 7.2 Hz, 2H), 2.73 (d, J = 3.6 Hz, 2H), 2.57 (s, 3H), 2.40 (s, 5H), 1.84 (d, J = 6.4 Hz, 3H), 1.70 (s, 3H), 1.62 - 1.41 (m, 6H), 1.27 - 1.19 (m, 1H), 0.87 (t, J = 7.2 Hz, 3H). LC-MS: MS (ES^+): RT = 1.513 min, m/z = 876.5 [M +H^+]. LCMS Method: 5-95.

EXAMPLE 10 – Synthesis of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)ethoxy)phenyl)methanone (I-9)





[0521] Step 1: Preparation of tert-butyl-4-[4-(p-tolylsulfonyloxy)butyl]piperidine-1-carboxylate. To a solution of tert-butyl 4-(4-hydroxybutyl)piperidine-1-carboxylate (1 g, 3.89 mmol, 1 eq) in DCM (10 mL) were added TosCl (1.1 g, 5.77 mmol, 1.48 eq) and TEA (1.16 g, 11.50 mmol, 1.60 mL, 2.96 eq), DMAP (48.00 mg, 392.90 μmol, 1.01e-1 eq). The mixture was stirred at 20 °C for 2 hours. The mixture was concentrated in vacuum. The residue was purified by column chromatography (0~30% ethyl acetate/petroleum ether) to give tert-butyl-4-[4-(p-tolylsulfonyloxy)butyl]piperidine-1-carboxylate (1.5 g, 94% yield) as a colorless oil.

[0522] Step 2: Preparation of tert-butyl (S)-4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)butyl) piperidine-1-carboxylate. To a solution of tert-butyl-4-[4-(*p*-tolylsulfonyloxy) butyl] piperidine-1-carboxylate (500 mg, 1.21 mmol, 1.64 eq) in MeCN (4 mL) and DMF (4 mL) were added Cs_2CO_3 (500 mg, 1.53 mmol, 2.07 eq) and 4-[(9*S*)-4,5,13-trimethyl-9- (oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.02,6]trideca-2(6),4,7,10,12-pentaen-7-yl]phenol (300 mg, 739.88 μmol, 1 eq). The mixture was stirred at 60 °C for 12 hours. The reaction mixture was poured into water (10 mL). The aqueous phase was extracted with EA (30 mLx2). The combined organic phase was washed with brine (20 mLx3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (0~100% ethyl acetate/petroleum ether). tert-butyl-4-[4-[4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12- tetrazatricyclo[8.3.0.02,6]trideca-2(6),4, 7,10,12-pentaen-7-yl]phenoxy]butyl]piperidine-1-carboxylate (400 mg, 84% yield) was obtained as a yellow oil.

[0523] Step 3: Preparation of 2-[[(9*S*)-4,5,13-trimethyl-7-[4-[4-(4-piperidyl)butoxy] phenyl]-3-thia-1,8,11,12- tetrazatricyclo[8.3.0.02,6]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole. To a solution of tert-butyl-4-[4-[4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12- tetrazatricyclo[8.3.0.02,6]trideca-2(6),4,7,10,12-pentaen-7-yl] phenoxy]butyl]piperidine-1-carboxylate (400 mg, 620.32 μmol, 1 eq) in DCM (15 mL) was added TFA (7.68 g, 67.31 mmol, 5 mL, 108.51 eq). The mixture was stirred at 20 °C for 12 hours. The mixture was concentrated under vacuum. To the mixture was added $NaHCO_3$ to adjust the pH to 8-10. The mixture was poured into water (20 mL). The aqueous phase was extracted with DCM (20 mL x 2). The combined organic phase was washed with brine (20 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25 mm x 10 um; mobile phase: water (FA)-ACN; B%: 16%-46%, 10min; Flow rate: 25 ml/min). 2-[[(9*S*)-4,5,13-trimethyl-7-[4-[4-(4-piperidyl)butoxy]phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.02,6] trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (200 mg, 59% yield) was obtained as a yellow solid.

[0524] Step 4: Preparation of (4-fluorophenyl)-[6-methoxy-2-(4-methoxyphenyl) benzothiophen-3-yl]methanone. To a solution of 6-methoxy-2-(4-methoxyphenyl)benzo thiophene (13 g, 48.09 mmol, 1 eq) and 4-fluorobenzoylchloride (10 g, 63.07 mmol, 7.56 mL, 1.31 eq) in DCM (150 mL) was added portion-wise $AlCl_3$ (7.80 g, 58.50 mmol, 3.20 mL, 1.22 eq) at 0 °C. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was quenched by the addition of H_2O (150.0 mL) at 0 °C, and then extracted with DCM (50.0 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, PE/EtOAc = 1/0 to 8/1). Compound (4-fluorophenyl)-[6-methoxy-2-(4-methoxyphenyl) benzo thiophen-3-yl]methanone (12 g, 64% yield) was obtained as a yellow oil.

[0525] Step 5: Preparation of (4-fluorophenyl)-[6-hydroxy-2-(4-hydroxyphenyl)benzo thiophen-3-yl]methanone. To a solution of (4-fluorophenyl)-[6-methoxy-2-(4-methoxy phenyl)benzothiophen-3-yl]methanone (6 g, 15.29 mmol, 1 eq) in DCM (50 mL) was added dropwise BBr_3 (15.60 g, 62.27 mmol, 6 mL, 4.07 eq) at 0 °C and the mixture was stirred at 20 °C for 0.5 hour. The reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ (60.0 mL) at 0 °C, and then diluted with H_2O (10.0 mL) and extracted with DCM (40.0 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (0~30%

ethyl acetate/petroleum ether). (4-fluorophenyl)-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]methanone (5 g, 90% yield) was obtained as a yellow solid.

[0526] Step 6: Preparation of [6-benzyloxy-2-(4-benzyloxyphenyl)benzothiophen-3-yl]-(4-fluorophenyl)methanone. To a solution of (4-fluorophenyl)-[6-hydroxy-2-(4-hydroxy phenyl)benzothiophen-3-yl]methanone (5 g, 13.72 mmol, 1 eq) in CH_3CN (10 mL), THF (50 mL) were added K_2CO_3 (6 g, 43.41 mmol, 3.16 eq) and BnBr (10.08 g, 58.94 mmol, 7 mL, 4.30 eq). The mixture was stirred at 60 °C for 12 hours. The mixture was filtered and the filtrate was concentrated. The crude product was triturated with EA and PE to afford [6-benzyl oxy-2-(4-benzyloxyphenyl)benzothiophen-3-yl]-(4-fluorophenyl)methanone (5.9 g, 80% yield) as a yellow solid.

[0527] Step 7: Preparation of [6-benzyloxy-2-(4-benzyloxyphenyl)benzothiophen-3-yl]-[4-(2-hydroxyethoxy)phenyl]methanone. To a solution of ethylene glycol (700 mg, 11.28 mmol, 0.6 mL, 2.05 eq) in DMF (30 mL) was added NaH (550 mg, 13.75 mmol, 60% purity, 2.5 eq) at 0 °C. After the addition, the mixture was stirred at 20 °C for 0.5 hours. Then [6- benzyloxy-2-(4-benzyloxyphenyl)benzothiophen-3-yl]-(4-fluorophenyl)methanone (3 g, 5.51 mmol, 1 eq) was added to the mixture and the resulting mixture was stirred at 20 °C for 0.5 hour. The mixture was then stirred at 90 °C for 12 hours. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl (60.0 mL), and then diluted with H_2O (20.0 mL) and extracted with EtOAc (50.0 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (0~80% ethyl acetate/petroleum ether). [6-benzyloxy-2-(4-benzyloxy phenyl)benzothiophen-3-yl]-[4-(2-hydroxyethoxy)phenyl] methanone (1.4 g, 43% yield) was obtained as a yellow solid.

[0528] Step 8: Preparation of 2-[4-[6-benzyloxy-2-(4-benzyloxyphenyl) benzothiophene-3-carbonyl]phenoxy]ethyl-4-methylbenzenesulfonate. To a solution of [6-benzyloxy-2-(4-benzyloxyphenyl)benzothiophen-3-yl]-[4-(2-hydroxyethoxy)phenyl] methanone (1.4 g, 2.39 mmol, 1 eq) in DCM (15 mL) was added tosylchloride (700.00 mg, 3.67 mmol, 1.54 eq) and TEA (1.45 g, 14.37 mmol, 2 mL, 6.02 eq), DMAP (70.00 mg, 572.98 µmol, 0.24 eq). The mixture was stirred at 20 °C for 12 hours. The mixture was concentrated in vacuum. The residue was purified by flash silica gel chromatography (0~50% Ethyl acetate/Petroleum ether). The residue was purified by a second time by column chromatography (gradient of 80 – 100% water (1% formic acid)/ACN). 2-(4-(6-(benzyloxy)-2-(4-(benzyloxy)phenyl)benzo[b] thiophene-3-

carbonyl)phenoxy)ethyl 4-methylbenzenesulfonate (800 mg, 45% yield) was obtained as a yellow solid.

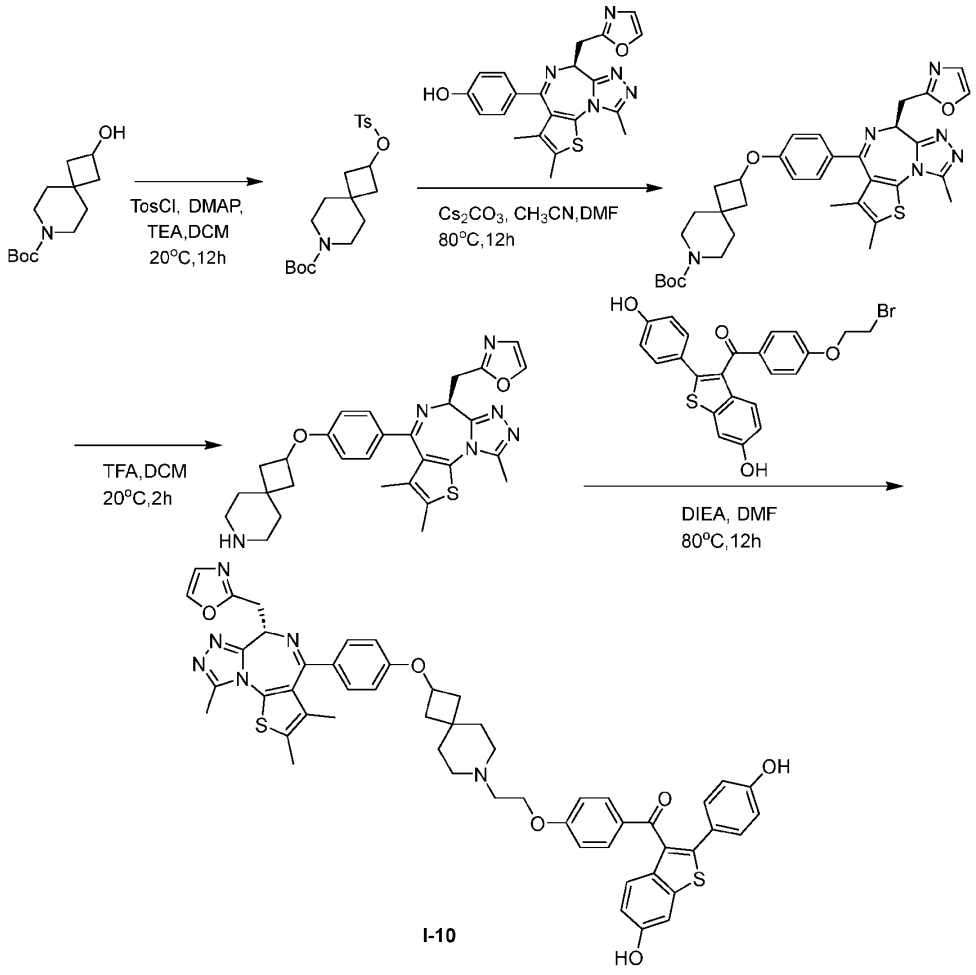
[0529] Step 9: Preparation of 2-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b] thiophene-3-carbonyl)phenoxy)ethyl 4-methylbenzenesulfonate. To a solution of 2-(4-(6-(benzyloxy)-2-(4-(benzyloxy)phenyl)benzo[b]thiophene-3-carbonyl)phenoxy)ethyl 4-methylbenzene sulfonate (500 mg, 674.87 μmol, 1 eq) in THF (5 mL) was added Pd/C (100 mg, 10% w/w) under an N_2 atmosphere. The suspension was degassed and purged with H_2 3 times. The mixture was stirred under H_2 (50 psi) at 50 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)ethyl 4-methylbenzenesulfonate (400 mg, crude) was obtained as a yellow oil.

[0530] Step 10: Preparation of [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone. To a solution of 2-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene-3-carbonyl)phenoxy)ethyl 4-methylbenzenesulfonate (400 mg, 713.47 μmol, 1 eq) in CH_3CN (3 mL), and DMF (2 mL) was added LiBr (188.00 mg, 2.16 mmol, 54.34 μL, 3.03 eq). The mixture was stirred at 60 °C for 12 hours. The mixture was concentrated in vacuum. The residue was purified by column chromatography (0~30% ethyl acetate/petroleum ether). [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzo thiophen-3-yl]methanone (300 mg, 90% yield) was obtained as a yellow oil.

[0531] Step 11: Preparation of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)ethoxy)phenyl) methanone. To a solution of [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (40 mg, 85.22 μmol, 1 eq) in DMF (1 mL) were added DIEA (40 mg, 309.49 μmol, 53.91 μL, 3.63 eq) and 2-[[(9S)-4,5,13-trimethyl-7-[4-[4-(4-piperidyl)butoxy]phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12- pentaen-9-yl]methyl]oxazole (20 mg, 36.7 μmol, 0.4 eq). The mixture was stirred at 80 °C for 12 hours. The mixture was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25 mm x 10 um; mobile phase: water (FA)-ACN; B%: 27%-57%, 10min; Flow rate: 25 ml/min). (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4] diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)ethoxy)phenyl)methanone (**I-9**, 20.41 mg, 24% yield) was obtained as a yellow solid. ^{1}H NMR

(400 MHz, DMSO-d_6) δ (ppm) 8.20 (s, 1H), 8.03 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.12 (s, 1H), 6.91 (dd, J = 8.8, 2.4 Hz, 4H), 6.84 (dd, J = 8.8, 2.4 Hz, 1H), 6.67 (d, J = 8.4 Hz, 2H), 4.61 (t, J = 7.2 Hz, 1H), 4.07 (br t, J = 5.6 Hz, 2H) 3.97 (br t, J = 6.4 Hz, 2H), 3.92-3.85 (m, 1H), 3.83-3.77 (m, 1H), 2.86 (br d, J = 11.2 Hz, 2H), 2.67-2.62 (m, 1H), 2.59 (s, 3H), 2.45 (br d, J = 2.0 Hz, 1H), 2.41 (s, 3H), 2.36-2.30 (m, 1H), 1.95 (br t, J = 10.4 Hz, 2H), 1.68 (br d, J = 7.2 Hz, 1H), 1.64 (s, 3H), 1.59 (br d, J = 12.0 Hz, 2H), 1.38 (br d, J = 6.0 Hz, 2H), 1.24-1.05 (m, 5H). LC-MS: MS (ES^+): RT = 1.798 min, m/z = 933.2[M + H^+]. LCMS Method: 25.

<u>EXAMPLE 11</u> – Synthesis of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl)methanone (I-10)



I-10

[0532] Step 1: Preparation of tert-butyl 2-(p-tolylsulfonyloxy)-7-azaspiro[3.5]nonane-7-carboxylate. To a solution of tert-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (1 g, 4.14 mmol, 1 eq) in DCM (10 mL) were added TosCl (1.2 g, 6.29 mmol, 1.52 eq), TEA (1.31 g, 12.93 mmol, 1.80 mL, 3.12 eq), DMAP (52.00 mg, 425.64 μmol, 0.1 eq). The mixture was stirred at 20 °C for 12 hours. The mixture was concentrated in vacuum. The residue was purified by column chromatography (0~25% ethyl acetate/petroleum ether). Compound tert-butyl 2-(p-tolylsulfonyloxy)-7-azaspiro[3.5]nonane-7-carboxylate (1.3 g, 79% yield) was obtained as a black solid.

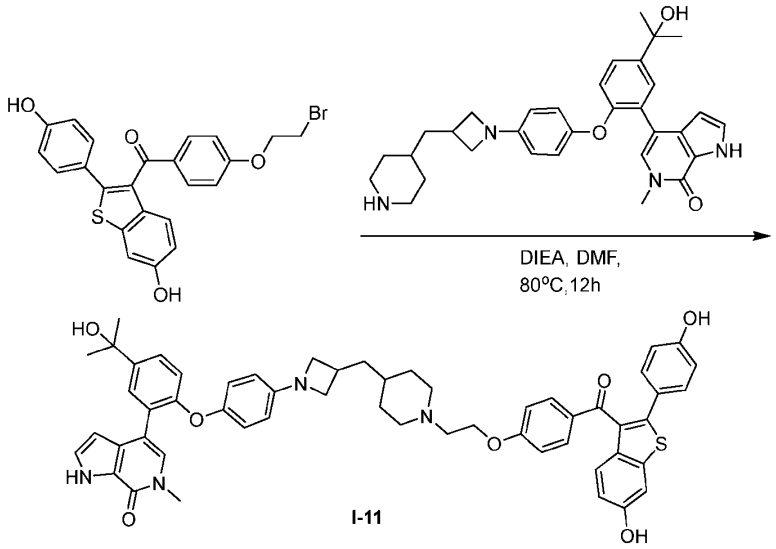
[0533] Step 2: Preparation of tert-butyl 2-[4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12- tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]-7-azaspiro[3.5]nonane-7-carboxylate. To a solution of tert-butyl 2-(*p*-tolylsulfonyloxy)-7-azaspiro[3.5]nonane-7-carboxylate (600 mg, 1.52 mmol, 1.54 eq) in MeCN (2 mL), DMF (4 mL) were added Cs_2CO_3 (650 mg, 1.99 mmol, 2.02 eq) and 4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10, 12-pentaen-7-yl]phenol (400 mg, 986.50 μmol, 1 eq). The mixture was stirred at 80 °C for 12 hours. The residue was poured into water (10 mL). The aqueous phase was extracted with EA (30 mL x 2). The combined organic phase was washed with brine (20 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (0~20% DCM/MeOH). Compound tert-butyl-2-[4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12- tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]-7-azaspiro[3.5]nonane-7-carboxylate (450 mg, 73% yield) was obtained as a yellow solid.

[0534] Step 3: Preparation of 2-[[(9*S*)-7-[4-(7-azaspiro[3.5]nonan-2-yloxy)phenyl]-4,5,13-trimethyl-3-thia-1,8,11,12- tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole. To a solution of tert-butyl 2-[4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12- tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]-7-azaspiro[3.5]nonane-7-carboxylate (450 mg, 715.67 μmol, 1 eq) in DCM (5 mL) was added TFA (10.75 g, 94.24 mmol, 7 mL, 131.67 eq). The mixture was stirred at 20 °C for 2 hours. The mixture was concentrated in vacuum. The mixture was added $NaHCO_3$ adjust to pH 8-10. The residue was poured into water (20 mL). The aqueous phase was extracted with DCM (20 mL x 2). The combined organic phase was washed with brine (20 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25 mm x 10 um; mobile phase: water (FA)-ACN; B%: 19%-35%,

8min; Flow rate: 25 ml/min). Compound 2-[[(9*S*)-7-[4-(7-azaspiro[3.5] nonan-2-yloxy)phenyl]-4,5,13-trimethyl-3-thia-1,8,11,12- tetrazatricyclo [8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (200 mg, 49% yield) was obtained as a white solid.

[0535] Step 4: Preparation of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl)methanone. To a solution of 2-[[(9*S*)-7-[4-(7-azaspiro[3.5]nonan-2-yloxy)phenyl]-4,5,13-trimethyl-3-thia-1,8,11,12- tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (70 mg, 132.41 μmol, 1 eq), [4-(2- bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzo thiophen-3-yl]methanone (77.00 mg, 164.06 μmol, 1.24 eq) in DMF (1 mL) was added DIEA (74.20 mg, 574.13 μmol, 0.1 mL, 4.34 eq). The mixture was stirred at 80 °C for 12 hours. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC (FA condition: Instrument: ACS-WH-GX-E; column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: water (FA)-ACN; B%: 25%-55%, 10min; Flow rate: 25 ml/min; Column temperature: R.T.; Wavelength: 220nm). (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b] thiophen-3-yl)(4-(2-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4] diazepin-4-yl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl) methanone (**I-10**, 35.68 mg, 29% yield) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.27 (s, 1H), 8.03 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 2.0 Hz, 1H), 7.25 (dd, J = 11.2, 8.8 Hz, 3H), 7.17 (d, J = 8.8 Hz, 2H), 7.12 (s, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.86-6.80 (m, 3H), 6.67 (d, J = 8.8 Hz, 2H), 4.73 (br t, J = 6.8 Hz, 1H), 4.61 (t, J = 7.2 Hz, 1H), 4.07 (br t, J = 5.6 Hz, 2H), 3.93-3.73 (m, 3H), 2.62-2.61 (m, 1H), 2.59 (s, 3H), 2.41 (s, 3H), 2.40-2.23 (m, 6H), 1.73 (br dd, J = 12.4, 6.0 Hz, 2H), 1.64 (s, 3H), 1.59-1.51 (m, 4H). LC-MS: MS (ES+): RT = 1.687 min, m/z = 917.4 [M + H^+]. LCMS Method: 25.

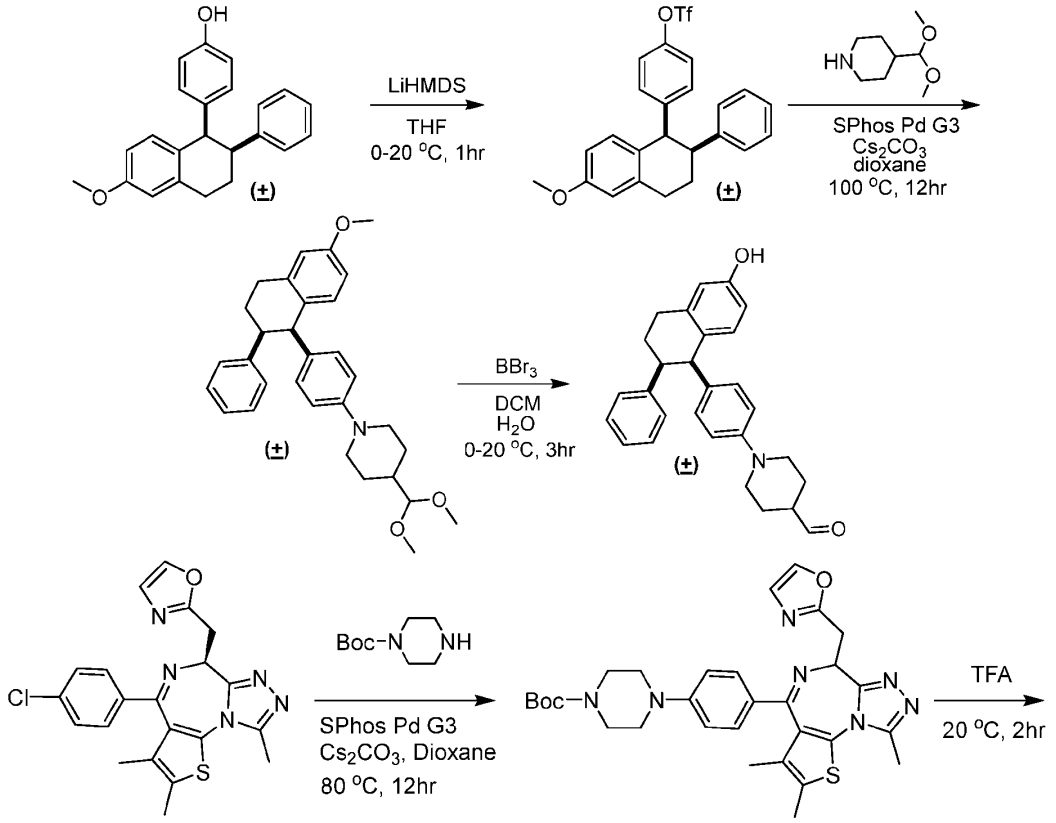
EXAMPLE 12 – Synthesis of 4-(2-(4-(3-((1-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)piperidin-4-yl)methyl)azetidin-1-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (I-11)

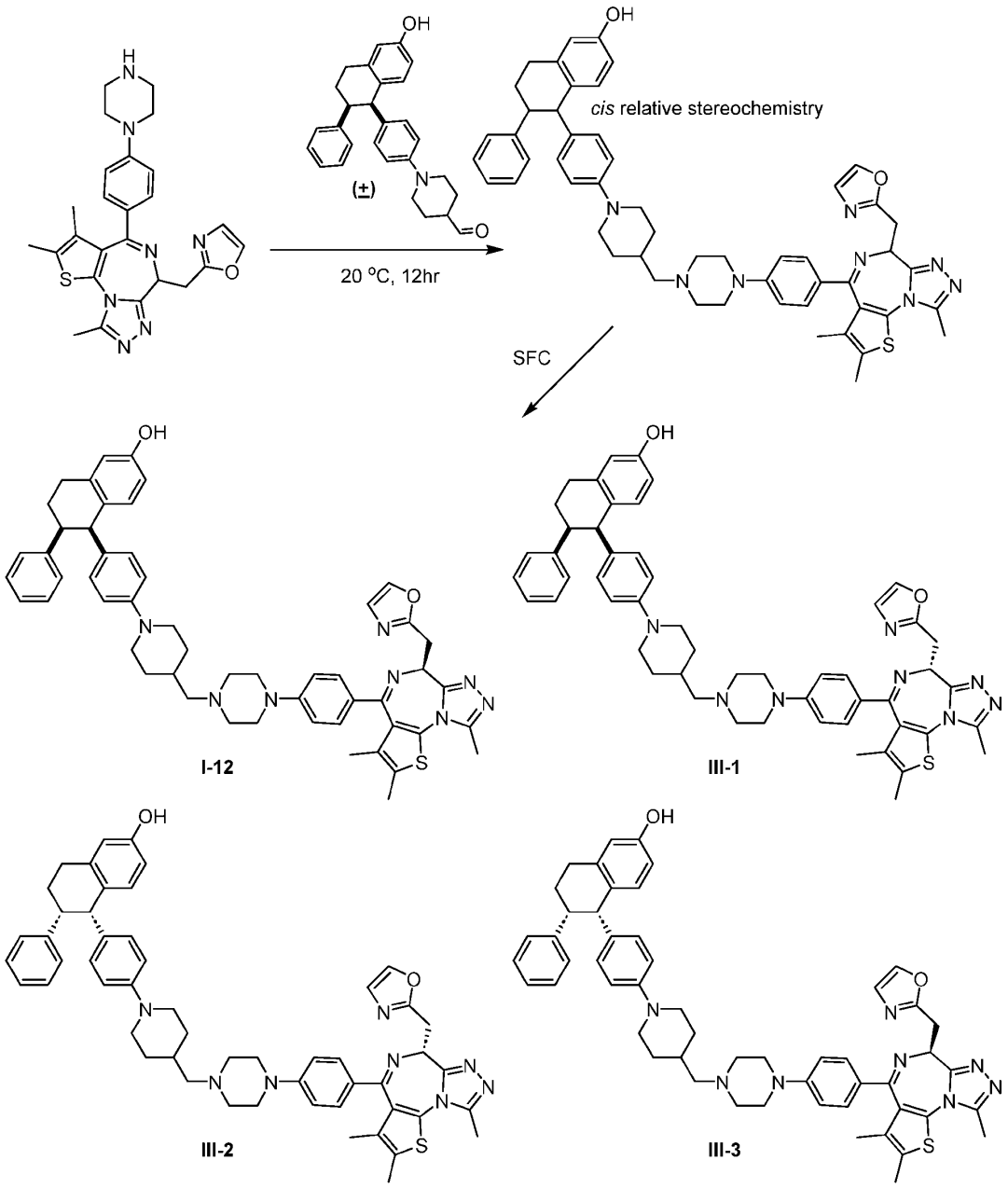


[0536] To a solution of 4-[5-(1-hydroxy-1-methyl-ethyl)-2-[4-[3-(4-piperidylmethyl) azetidin-1-yl]phenoxy]phenyl]-6- methyl-1*H*-pyrrolo[2,3-*c*]pyridin-7-one (50 mg, 94.94 μmol, 1 eq), [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4- hydroxyphenyl)benzothiophen-3-yl] methanone (55.00 mg, 117.18 μmol, 1.23 eq) in DMF (1 mL) was added DIEA (74.20 mg, 574.13 μmol, 0.1 mL, 6.05 eq). The mixture was stirred at 80 °C for 12 hours. The mixture was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25 mm x 10 um; mobile phase: water (FA)-ACN; B%: 23%-53%, 10min; Flow rate: 25 ml/min). 4-(2-(4-(3-((1-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)piperidin-4-yl)methyl)azetidin-1-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (**I-11**, 17.07 mg, 19% yield) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.97 (br s, 1H), 9.88-9.69 (m, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 2.4 Hz, 1H), 7.36-7.32 (m, 2H), 7.27-7.22 (m, 3H), 7.19-7.14 (m, 2H), 6.91 (d, J = 9.2 Hz, 2H), 6.85 (dd, J = 8.8, 2.4 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.72-6.66 (m, 3H), 6.34 (d, J = 8.8 Hz, 2H), 6.23 (t, J = 2.4 Hz, 1H), 5.04-4.89 (m, 1H), 4.08 (br t, J = 5.6 Hz, 2H), 3.88 (br t, J = 7.2 Hz, 2H), 3.54 (s, 3H), 2.86 (br d, J = 11.2 Hz, 2H), 2.77-2.67 (m, 2H), 2.62 (br d, J = 6.0 Hz, 2H), 1.96 (br t, J = 10.8 Hz, 2H), 1.58-1.49 (m, 4H),

1.44 (s, 6H), 1.27-0.98 (m, 4H). LC-MS: MS (ES+): RT = 1.528 min, m/z = 915.4 [M + H^+]. LCMS Method: 25.

EXAMPLE 13 – Synthesis of (5R,6S)-6-phenyl-5-(4-(4-((4-(4-((S)-2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl) piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (I-12), (5R,6S)-6-phenyl-5-(4-(4-((4-(4-((R)-2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl) piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (III-1), (5S,6R)-6-phenyl-5-(4-(4-((4-(4-((R)-2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl) piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (III-2), and (5S,6R)-6-phenyl-5-(4-(4-((4-(4-((S)-2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl) piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (III-3)





[0537] Step 1: Preparation of (±)-*cis*-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl]trifluoro-methanesulfonate. To a solution of (±)-*cis*-4-(6-methoxy-2-phenyl-tetralin-1-yl)phenol (500 mg, 1.51 mmol, 1 eq) in THF (20 mL) was added LiHMDS (1 M, 2.50 mL, 1.65 eq) and 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (800.00 mg, 2.24 mmol, 1.48 eq) under N_2 at 0°C. The mixture was stirred at 20°C for 1 hour. The reaction

mixture was quenched by addition H_2O 5 mL at 0 °C, and then extracted with EA 8 mL (4 mL x 2). The combined organic layers were washed with brine 5 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (0-15% Ethyl acetate/Petroleum ether). Compound (±)-*cis*-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl]trifluoromethanesulfonate (650 mg, 93% yield) was obtained as a white solid.

[0538] Step 2: Preparation of (±)-*cis*-4-(dimethoxymethyl)-1-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl]piperidine. A mixture of (±)-*cis*-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl] trifluoromethanesulfonate (630.00 mg, 1.36 mmol, 1 eq), 4-(dimethoxymethyl) piperidine (315.00 mg, 1.98 mmol, 1.45 eq), SPhos Pd G3 (100.00 mg, 128.16 μmol, 9.41e-2 eq), Cs_2CO_3 (1.10 g, 3.38 mmol, 2.48 eq) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The reaction mixture was diluted with brine 5 mL and extracted with EA 15 mL (5 mL x 3). The combined organic layers were washed with brine 10 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (5:1 Petroleum ether: Ethyl acetate). Compound (±)-*cis*-4-(dimethoxymethyl)-1-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl]piperidine (420 mg, 65% yield) was obtained as a brown gum.

[0539] Step 3: Preparation of (±)-*cis*-1-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)phenyl] piperidine-4-carbaldehyde. To a solution of (±)-*cis*-4-(dimethoxymethyl)-1-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl]piperidine (400 mg, 848.12 μmol, 1 eq) in DCM (4 mL) was added BBr_3 (2.60 g, 10.38 mmol, 1 mL, 12.24 eq) at 0°C. The mixture was stirred at 20 °C for 1 hours. And then H_2O (4 mL) was added dropwise at 0°C. The resulting mixture was stirred at 20 °C for 2 hours. The reaction mixture was adjusted to pH 7~8 with aqueous Na_2CO_3 and extracted with EA 15 mL (5 mL x 3). The combined organic layers were washed with brine 10 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether: Ethyl acetate = 1:1). Compound (±)-*cis*-1-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)phenyl]piperidine-4-carbaldehyde (300 mg, 86% yield) was obtained as a brown solid.

[0540] Step 4: Preparation of tert-butyl-4-[4-[4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl] piperazine-1-carboxylate. A mixture of 2-[[(9*S*)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (200 mg,

471.79 μmol, 1 eq), tert-butyl piperazine-1-carboxylate (150.00 mg, 805.37 μmol, 1.71 eq), SPhos Pd G3 (70.00 mg, 89.71 μmol, 0.19 eq), Cs_2CO_3 (461.15 mg, 1.42 mmol, 3 eq) in dioxane (0.5 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at 80 °C for 12 hours under N_2 atmosphere. The reaction mixture was diluted with H_2O 5 mL and extracted with EA 15 mL (5 mL x 3). The combined organic layers were washed with brine 10 mL (5 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (10:1 DCM: MeOH). Compound tert-butyl 4-[4-[4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$] trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperazine-1-carboxylate (210 mg, 78% yield) was obtained as a yellow solid.

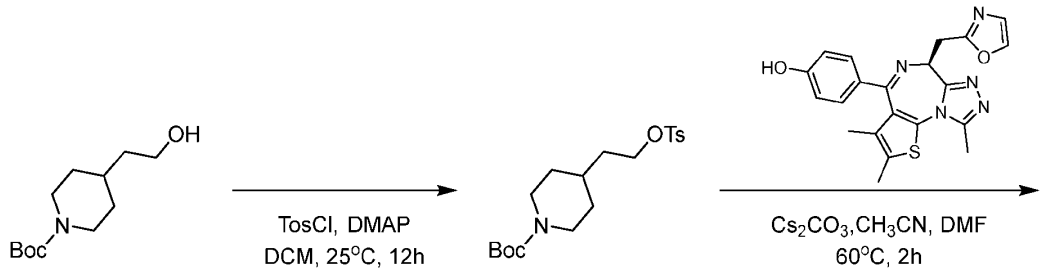
[0541] Step 5: Preparation of 2-[[4,5,13-trimethyl-7-(4-piperazin-1-ylphenyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole. To a solution of tert-butyl 4-[4-[4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperazine-1-carboxylate (200 mg, 348.61 μmol, 1 eq) in DCM (2 mL) was added TFA (1.23 g, 10.77 mmol, 800 μL, 30.89 eq). The mixture was stirred at 20 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition: column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; gradient: 8%-38% B over 9 min). Compound 2-[[(9*S*)-4,5,13-trimethyl-7-(4-piperazin-1-ylphenyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (200 mg, 98% yield, TFA) was obtained as a yellow solid.

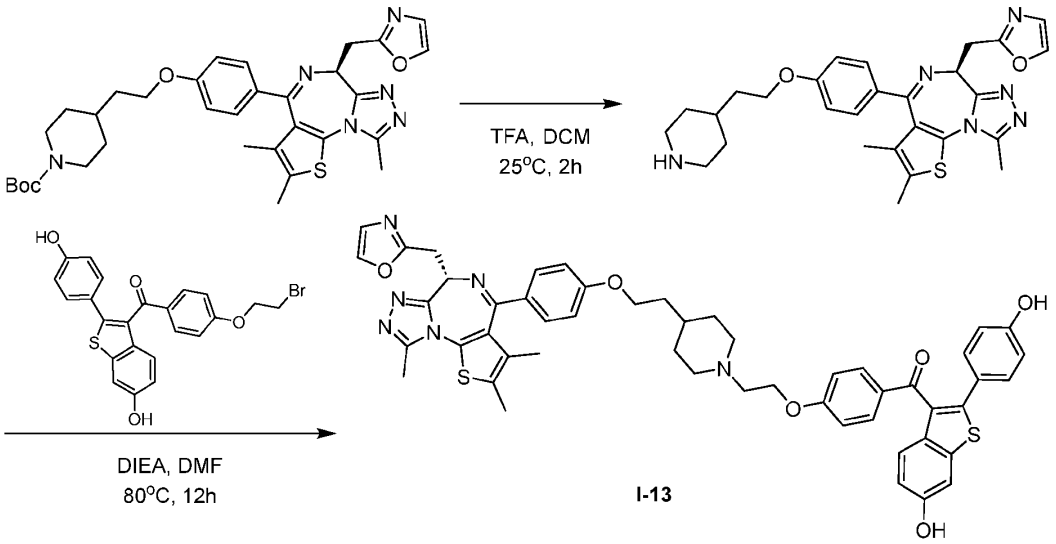
[0542] Step 6: Preparation of Four *cis*-Tetraline Diastereomers of 6-phenyl-5-(4-(4-((4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl) piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol. To a solution of 2-[[4,5,13-trimethyl-7-(4-piperazin-1-ylphenyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (190 mg, 323.34 μmol, 1 eq, TFA) and (±)-*cis*-1-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)phenyl]piperidine-4-carbaldehyde (150 mg, 364.49 μmol, 1.13 eq) in MeOH (2 mL) was added AcOH (1.94 mg, 32.33 μmol, 1.85 μL, 0.1 eq). After addition, the mixture was stirred at 20 °C for 0.5 hour, and then $NaBH(OAc)_3$ (137.06 mg, 646.68 μmol, 2 eq), 1-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)phenyl] piperidine-4-carbaldehyde (150 mg, 364.49 μmol, 1.13 eq) was added. The resulting mixture was stirred at 20 °C for 12 hours. The reaction mixture was diluted with H_2O 5 mL and extracted with

EA15 mL (5 mL x 3). The combined organic layers were washed with brine 10 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25 mm x 10 um; mobile phase: [water(FA)-ACN]; gradient: 21%-51% B over 10 min). A mixture of the four *cis*-tetraline diastereomers of 2-phenyl-1-[4-[4-[[4-[4-[4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]tetralin-6-ol (100 mg, 115.06 μmol, 35.58% yield) was obtained as a yellow solid.

[0543] Step 7: Preparation of Compounds I-12, III-1, III-2, and III-3. The yellow solid from the preceding step was separated by SFC (condition: column: (s,s) WHELK-O1 (250mm*30mm,10um);mobile phase: [CO_2-ACN/MeOH(0.1% NH_3H_2O)]; B%:60%, isocratic elution mode). The second fraction was further separated by SFC (condition:column: DAICEL CHIRALCEL OD (250mm*30mm,10um);mobile phase: [CO_2-ACN/MeOH(0.1% NH3H2O)]; B%:55%, isocratic elution mode). The diastereomer that was found to be the most potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below) was obtained as a yellow solid (13.58 mg, 16% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.62 (s, 1H), 7.31 (br d, J = 8.4 Hz, 2H), 7.19-7.09 (m, 3H), 7.04 (s, 1H), 6.85-6.75 (m, 5H), 6.70 (s, 1H), 6.61-6.50 (m, 3H), 6.29 (br d, J = 8.4 Hz, 2H), 4.70 (t, J = 7.2 Hz, 1H), 4.19 (br d, J = 4.8 Hz, 1H), 4.15-3.99 (m, 2H), 3.54 (br d, J = 8.8 Hz, 2H), 3.38-3.23 (m, 5H), 3.08-2.95 (m, 2H), 2.68-2.54 (m, 9H), 2.41 (s, 3H), 2.31 (br d, J = 6.4 Hz, 2H), 2.19-2.14 (m, 1H), 1.84 (br d, J = 13.6 Hz, 3H), 1.73 (s, 3H), 1.66 (br d, J = 4.2 Hz, 1H), 1.40-1.27 (m, 2H). LC-MS: MS (ES^+): RT = 1.438 min, m/z = 869.4 [M + H]; LCMS Method: 25.

<u>EXAMPLE 14</u> – Synthesis of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenoxy)ethyl)piperidin-1-yl)ethoxy)phenyl)methanone (I-13)





I-13

[0544] Step 1: Preparation of tert-butyl 4-[2-(p-tolylsulfonyloxy)ethyl]piperidine-1-carboxylate. To a solution of tert-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (1 g, 4.36 mmol, 1 eq) in DCM (20 mL) were added DMAP (106.55 mg, 872.16 μmol, 0.2 eq), TosCl (1.66 g, 8.72 mmol, 2 eq) and TEA (1.32 g, 13.08 mmol, 1.82 mL, 3 eq). The mixture was stirred at 25 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (0~21% Ethyl acetate/Petroleum ether). Compound tert-butyl 4-[2-(p-tolylsulfonyloxy)ethyl] piperidine-1-carboxylate (1.5 g, 90% yield) was obtained as yellow oil.

[0545] Step 2: Preparation of tert-butyl 4-[2-[4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy] ethyl]piperidine-1-carboxylate. To a solution of tert-butyl 4-[2-(*p*-tolylsulfonyl oxy)ethyl] piperidine-1-carboxylate (605.32 mg, 1.58 mmol, 1.6 eq) in CH_3CN (4 mL) and DMF (4 mL) was added Cs_2CO_3 (964.27 mg, 2.96 mmol, 3 eq) and 4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenol (400 mg, 986.50 μmol, 1 eq). The mixture was stirred at 60 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O 15 mL and extracted with EA 45 mL (15mL x 3). The combined organic layers were washed with brine 20 mL (10 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (0~100% Ethyl acetate/Petroleum ether). tert-butyl 4-[2-[4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-

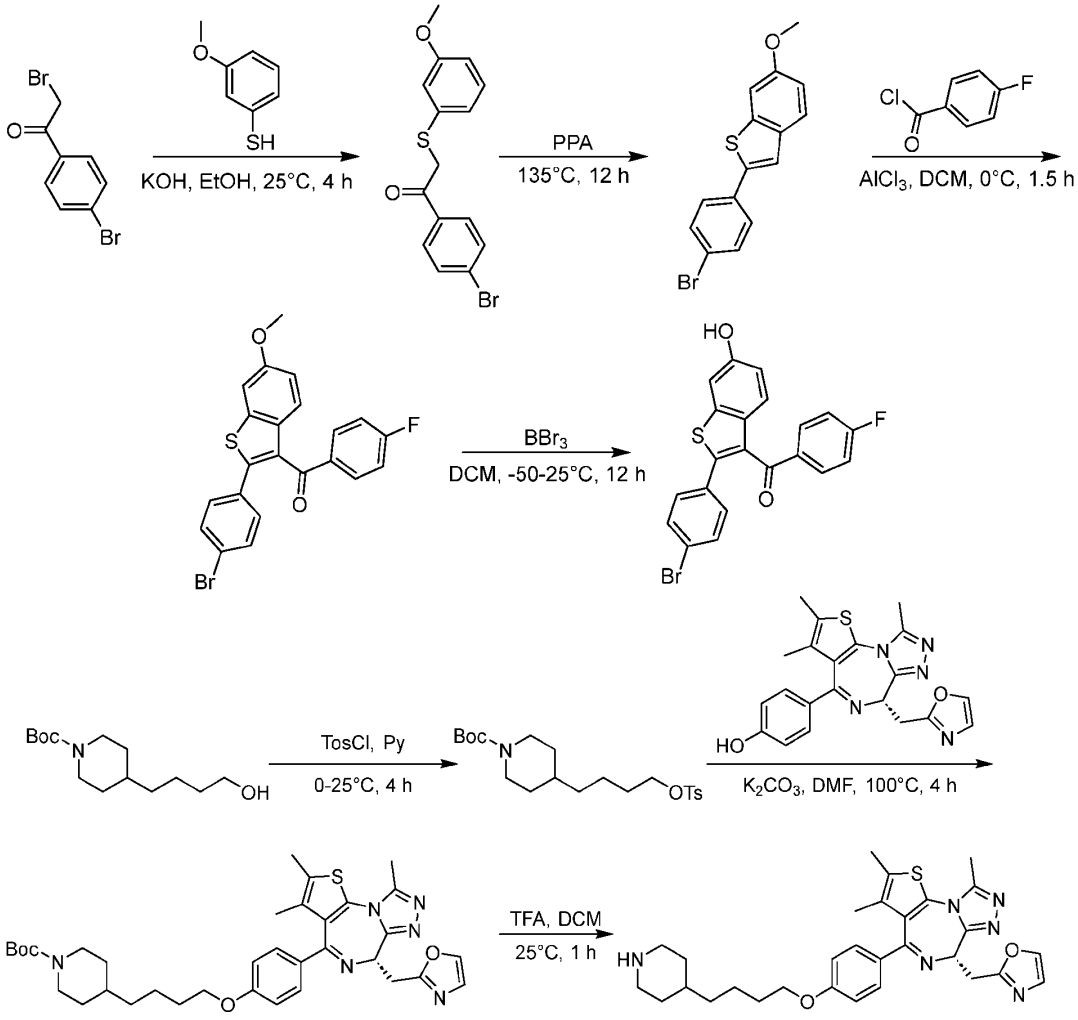
1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$] trideca-2(6),4,7, 10,12-pentaen-7-yl]phenoxy]ethyl]piperidine-1-carboxylate (468 mg, 77% yield) was obtained as yellow oil.

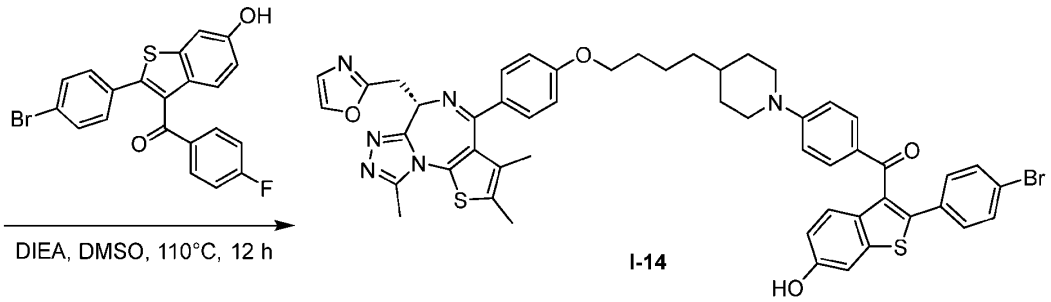
[0546] Step 3: Preparation of 2-[[(9*S*)-4,5,13-trimethyl-7-[4-[2-(4-piperidyl)ethoxy] phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole. To a solution of tert-butyl 4-[2-[4-[(9*S*)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]ethyl]piperidine-1-carboxylate (440 mg, 713.39 μmol, 1 eq) in DCM (5 mL) was added TFA (1.54 g, 13.46 mmol, 1.00 mL, 18.87 eq). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with $NaHCO_3$ 15 mL and extracted with DCM 45 mL (15 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25 mm x 10 um; mobile phase: [water(FA)-ACN]; gradient: 12%-42% B over 10 min). Compound 2-[[(9*S*)-4,5,13-trimethyl-7-[4-[2-(4-piperidyl)ethoxy]phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (368 mg, 99% yield) was obtained as a yellow solid.

[0547] Step 4: Preparation of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenoxy)ethyl)piperidin-1-yl)ethoxy)phenyl)methanone. To a solution of 2-[[(9S)-4,5,13-trimethyl-7-[4-[2-(4-piperidyl)ethoxy]phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (75 mg, 145.16 μmol, 1 eq) in DMF (1 mL) was added DIEA (56.28 mg, 435.49 μmol, 75.85 μL, 3 eq) and [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (81.76 mg, 174.20 μmol, 1.2 eq). The mixture was stirred at 80 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 25%-55% B over 10 min). (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethyl)piperidin-1-yl)ethoxy)phenyl)methanone (**I-13**, 27.6 mg, 21% yield) was obtained as a yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.95-9.54 (m, 1H), 8.04 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 2.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.8 Hz, 1H), 7.20-7.16 (m, 2H), 7.13 (s,

1H), 6.93 (dd, J = 8.8, 5.6 Hz, 4H), 6.85 (dd, J = 8.8, 2.2 Hz, 1H), 6.68 (d, J = 8.8 Hz, 2H), 4.62 (t, J = 7.2 Hz, 1H), 4.12-3.99 (m, 4H), 3.92-3.85 (m, 1H), 3.84-3.77 (m, 1H), 2.87 (br d, J = 10.8 Hz, 2H), 2.63 (br t, J = 5.8 Hz, 2H), 2.60 (s, 3H), 2.42 (s, 3H), 1.97 (br t, J = 10.8 Hz, 2H), 1.68-1.59 (m, 7H), 1.46-1.37 (m, 1H), 1.24-1.13 (m, 2H). LC-MS: MS (ES^-): RT = 1.663 min, m/z = 905.4 [M + H^+]. LCMS Method: 25.

EXAMPLE 15 – Synthesis of (S)-(2-(4-bromophenyl)-6-hydroxybenzo[b]thiophen-3-yl)(4-(4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)phenyl)methanone (I-14)





I-14

[0548] Step 1: Preparation of 1-(4-bromophenyl)-2-(3-methoxyphenyl)sulfanyl-ethanone. To a solution of KOH (88.82 g, 1.58 mol, 10 equiv) in EtOH (300 mL) was added 3-methoxybenzenethiol (24.41 g, 174.14 mmol, 21.40 mL, 1.1 equiv) at 25 °C. The miture was stirred at 25 °C for 30 min. Then the mixture was cooled to 0 °C and 2-bromo-1-(4-bromophenyl)ethanone (44 g, 158.31 mmol, 1 equiv) in EtOAc (300 mL) were added subsequently at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction mixture was warmed to 25 °C and stirred for 4 h. The solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (500 mL x 2), washed with brine (300 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate, 1/0 to 10/1) to afford 1-(4-bromophenyl)-2-(3-methoxyphenyl)sulfanyl-ethanone (43 g, 80% yield) was obtained as a white solid.

[0549] Step 2: Preparation of 2-(4-bromophenyl)-6-methoxy-benzothiophene. To a stirring solution of PPA (30 mL) at 80°C was added 1-(4-bromophenyl)-2-(3-methoxy phenyl)sulfanyl-ethanone (3 g, 8.90 mmol, 1 equiv) in portions within 30 min. Then the reaction was heated to 90 °C and stirred for 1.5 h. The solution was stirred at 135 °C, for another 10 h. The reaction mixture was poured into ice water. The crude product was collected by filtration and the solid was washed with water to afford 2-(4-bromophenyl)-6-methoxy-benzothiophene (2.3 g, 80% yield) as a white solid.

[0550] Step 3: Preparation of [2-(4-bromophenyl)-6-methoxy-benzothiophen-3-yl]-(4-fluorophenyl)methanone. To a solution of 2-(4-bromophenyl)-6-methoxy-benzothiophene (2.2 g, 6.89 mmol, 1 equiv) in DCM (20 mL) was added $AlCl_3$ (1.38 g, 10.34 mmol, 564.94 µL, 1.5 equiv) and 4-fluorobenzoyl chloride (1.64 g, 10.34 mmol, 1.24 mL, 1.5 equiv) at 0 °C. The mixture was stirred at 0 °C for 2h. To a solution of $NaHCO_3$ (aq) (100 mL) was added the reaction mixture at 25°C, and then diluted with water 100 mL and extracted with EtOAc (100 mL

x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 (250mm x 70mm,10 um); mobile phase: [water (FA)-ACN]; gradient 30%-95% B over 45 min) to give [2-(4-bromophenyl)-6-methoxy-benzothiophen-3-yl]-(4-fluorophenyl)methanone (140 mg, 4% yield) as a white solid.

[0551] Step 4: Preparation of [2-(4-bromophenyl)-6-hydroxy-benzothiophen-3-yl]-(4-fluorophenyl)methanone. To a solution of [2-(4-bromophenyl)-6-methoxy-benzothiophen-3-yl]-(4-fluorophenyl)methanone (140 mg, 317.24 μmol, 1 equiv) in DCM (6 mL) was added BBr_3 (1 M, 317.24 μL, 1 equiv)at -50°C under N_2. Then the mixture was stirred at 25°C for 2 h. The reaction was poured into water (70 mL). The aqueous phase was extracted with ethyl acetate (15 mL x 3). The reaction mixture was quenched by dropwise addition of $NaHCO_3$ (aq) 5 mL to pH 5 at 25 °C under N_2, and then diluted with H_2O 20 mL and extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO2, PE:EtOAc = 3:1) to afford [2-(4-bromophenyl)-6-hydroxy-benzothiophen-3-yl]-(4-fluorophenyl)methanone (120 mg, 88% yield) as a yellow solid.

[0552] Step 5: Preparation of tert-butyl 4-[4-(p-tolylsulfonyloxy)butyl]piperidine-1-carboxylate. To a solution of tert-butyl 4-(4-hydroxybutyl)piperidine-1-carboxylate (2.5 g, 9.71 mmol, 1 equiv) in pyridine (20 mL) was added TosCl (5.56 g, 29.14 mmol, 3.0 equiv)at 0°C. Then the mixture was stirred at 25°C for 4 h. The reaction mixture was partitioned between H_2O (100 mL) and EtOAc (100 mL x 3). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate, 1/0 to 10/1) to afford tert-butyl 4-[4-(p-tolylsulfonyloxy)butyl]piperidine-1-carboxylate (1.4 g, 35% yield) as a white oil.

[0553] Step 6: Preparation of tert-butyl 4-[4-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]butyl]piperidine-1-carboxylate. To a solution of tert-butyl 4-[4-(p-tolylsulfonyloxy)butyl]piperidine-1-carboxylate (203.00 mg, 493.25 μmol, 2.0 equiv) and 4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}] trideca-2(6),4,7,10,12-pentaen-7-yl]phenol (100 mg, 246.63 μmol, 1 equiv) in DMF (3 mL) was added K_2CO_3 (68.17 mg, 493.25 μmol, 2.0 equiv). The mixture was stirred at 100 °C for 3h. The reaction mixture was partitioned between H_2O 50 mL and EtOAc (50 mL x 3). The organic phase

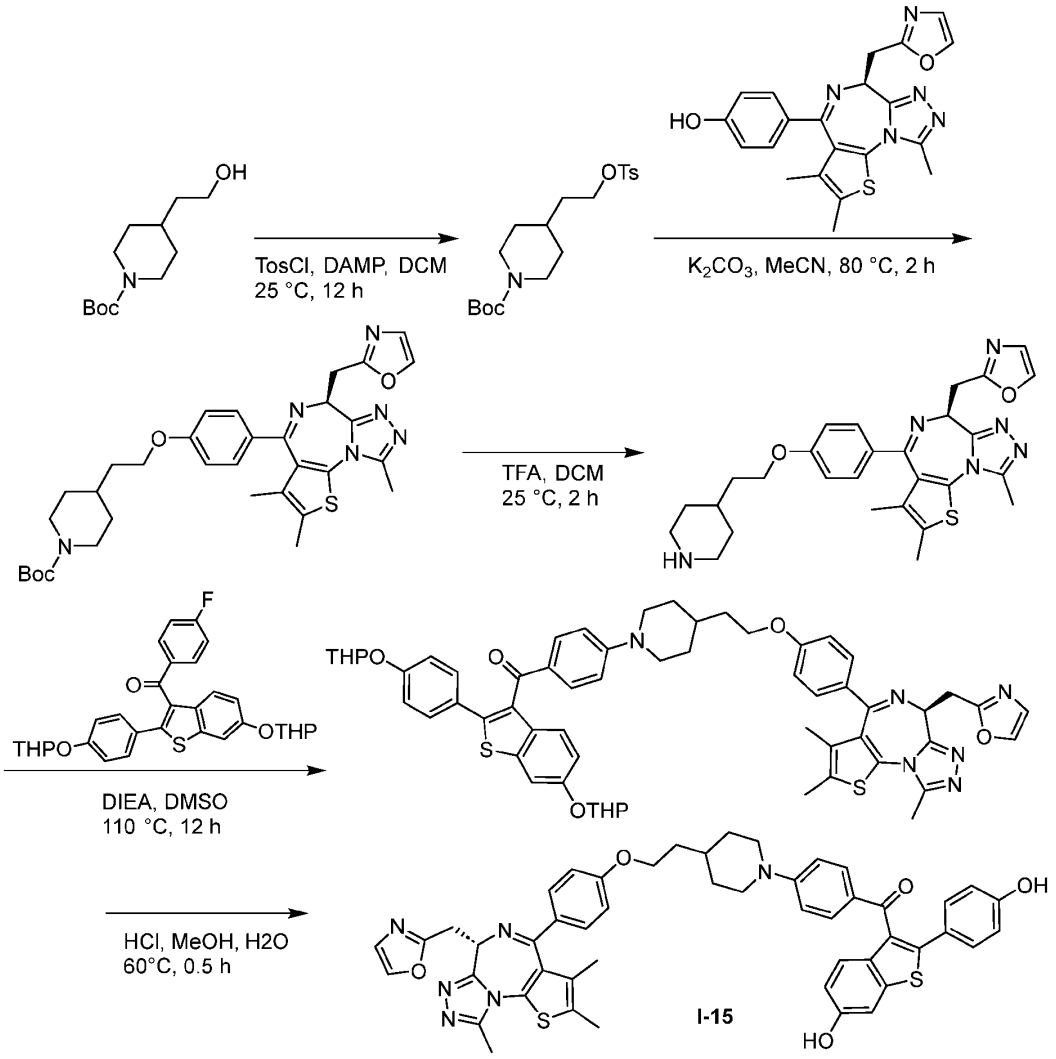
was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to afford tert-butyl 4-[4-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]butyl] piperidine-1-carboxylate (150 mg, 94% yield) as a yellow oil.

[0554] Step 7: Preparation of 2-[[(9S)-4,5,13-trimethyl-7-[4-[4-(4-piperidyl)butoxy] phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole. To a solution of tert-butyl 4-[4-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]butyl]piperidine-1-carboxylate (130 mg, 201.61 μmol, 1 equiv) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1.00 mL, 66.78 equiv). The mixture was stirred at 25 °C for 1h. The reaction mixture was quenched by addition $NaHCO_3$ (aq) 30 mL at 25 °C, and then diluted with H_2O (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue to afford 2-[[(9S)-4,5,13-trimethyl-7-[4-[4-(4-piperidyl)butoxy]phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (100 mg, 91% yield) as a yellow oil.

[0555] Step 8: Preparation of (S)-(2-(4-bromophenyl)-6-hydroxybenzo[b]thiophen-3-yl)(4-(4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)phenyl)methanone. To a solution of 2-[[(9S)-4,5,13-trimethyl-7-[4-[4-(4-piperidyl)butoxy]phenyl]-3-thia-1,8,11,12-tetraza tricyclo [8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (60 mg, 110.15 μmol, 1 equiv) and [2-(4-bromophenyl)-6-hydroxy-benzothiophen-3-yl]-(4-fluorophenyl)methanone (51.77 mg, 121.17 μmol, 1.1 equiv) in DMSO (2 mL) was added DIEA (42.71 mg, 330.45 μmol, 57.56 μL, 3.0 equiv). The mixture was stirred at 110 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150mm x 30mm x 7um; mobile phase: [water (FA)-ACN]; gradient 80%-100% B over 10 min) to afford (S)-(2-(4-bromophenyl)-6-hydroxybenzo [b]thiophen-3-yl)(4-(4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)phenyl)methanone (**I-14**, 24.97 mg, 23% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.03 (s, 1H), 7.57 - 7.48 (m, 4H), 7.37 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 1H), 7.12 (s,

1H), 6.92 (d, J = 8.8 Hz, 2H), 6.88 - 6.80 (m, 3H), 4.66 - 4.58 (m, 1H), 4.01 - 3.95 (m, 2H), 3.94 - 3.85 (m, 3H), 3.84 - 3.76 (m, 1H), 2.81 (t, J = 12.0 Hz, 2H), 2.59 (s, 3H), 2.41 (s, 3H), 1.74 - 1.66 (m, 4H), 1.63 (s, 3H), 1.53 - 1.36 (m, 3H), 1.27 - 1.22 (m, 2H), 1.15 - 1.02 (m, 2H). LC-MS: MS (ES^+): RT = 3.536 min, m/z = 953.3 [M +H^+], LC-MS Method: 25.

EXAMPLE 16 – Synthesis of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethyl)piperidin-1-yl)phenyl)methanone (I-15).



[0556] Step 1: Preparation of tert-butyl 4-[2-(p-tolylsulfonyloxy)ethyl]piperidine-1-carboxylate. To a solution of tert-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (24 g, 104.66 mmol, 1 equiv) in DCM (240 mL) was added 4-methylbenzenesulfonyl chloride (29.93 g,

156.99 mmol, 1.5 equiv) and DMAP (12.79 g, 104.66 mmol, 1 equiv). The mixture was stirred at 25 °C for 12h. The reaction mixture was partitioned between H_2O 300 mL and DCM 300 mL. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 10/1) to afford tert-butyl 4-[2-(p-tolylsulfonyloxy)ethyl]piperidine-1-carboxylate (17g, 42% yield) as a colorless oil.

[0557] Step 2: Preparation of afford tert-butyl 4-[2-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]ethyl]piperidine-1-carboxylate. To a solution of tert-butyl 4-[2-(p-tolylsulfonyl oxy) ethyl]piperidine-1-carboxylate (141.87 mg, 369.94 μmol, 1.5 equiv) in MeCN (10 mL) was added K_2CO_3 (68.17 mg, 493.25 μmol, 2 equiv) and 4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenol (100 mg, 246.63 μmol, 1 equiv). The mixture was stirred at 80 °C for 2h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to afford tert-butyl 4-[2-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}] trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]ethyl]piperidine-1-carboxylate (130 mg, 85% yield) as a yellow oil.

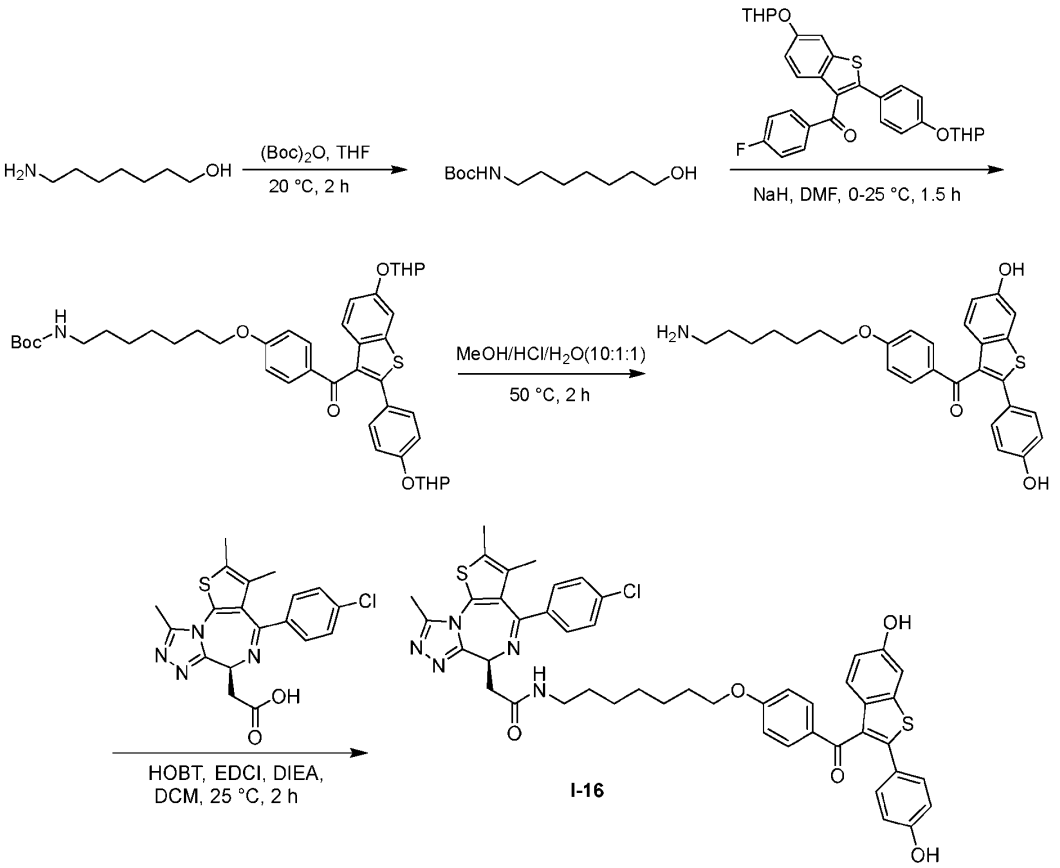
[0558] Step 3: Preparation of 2-[[(9S)-4,5,13-trimethyl-7-[4-[2-(4-piperidyl)ethoxy] phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl] oxazole. To a solution of tert-butyl 4-[2-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.02,6]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]ethyl] piperidine-1-carboxylate (170 mg, 275.63 μmol, 1 equiv) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 49 equiv). The mixture was stirred at 25 °C for 2h. The reaction mixture was quenched by addition $NaHCO_3$ (aq) 10 mL at 25 °C, adjust PH to 8, and then diluted with H_2O 20 mL and extracted with EA 40 mL (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-[[(9S)-4,5,13-trimethyl-7-[4-[2-(4-piperidyl)ethoxy]phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7, 10,12-pentaen-9-yl]methyl]oxazole (140 mg, 98% yield) as a white solid.

[0559] Step 4: Preparation of [6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl) benzothiophen-3-yl]-[4-[4-[2-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy] ethyl]-1-piperidyl]phenyl]methanone. To a solution of 2-[[(9S)-4,5,13-trimethyl-7-[4-[2-(4-

piperidyl)ethoxy]phenyl]-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$] trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (60 mg, 116.13 μmol, 1 equiv) in DMSO (2 mL) was added DIEA (45.03 mg, 348.39 μmol, 60.68 μL, 3 equiv) and (4-fluorophenyl)-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophen-3-yl]methanone (61.85 mg, 116.13 μmol, 1 equiv). The mixture was stirred at 110 °C for 12h. The reaction mixture was partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic phase was separated, washed with NaCl 20 mL (10 mL x 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to afford [6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl) benzothiophen-3-yl]-[4-[4-[2-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo [8.3.0.$0^{2,6}$] trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]ethyl]-1-piperidyl]phenyl]methanone (40 mg, 33% yield) as a white solid.

[0560] Step 5: Preparation of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethyl)piperidin-1-yl)phenyl)methanone. To a solution of [6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophen-3-yl]-[4-[4-[2-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo [8.3.0.$0^{2,6}$] trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]ethyl]-1-piperidyl]phenyl]methanone (38 mg, 36.92 μmol, 1 equiv) in MeOH (3 mL) and H_2O (0.3 mL) was added HCl (306.00 mg, 8.39 mmol, 0.3 mL, 227 equiv). The mixture was stirred at 60 °C for 0.5h. The reaction mixture was added HCl (4M) and adjust PH to 7, then partitioned between EA (10 mL) and H_2O (10 mL). The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: C18 150×30mm; mobile phase: [water(FA)-ACN]; gradient of 60%-90% over 7 min) to afford (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethyl)piperidin-1-yl)phenyl) methanone (**I-15**, 16 mg, 49% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.72 (br dd, *J* = 6.4, 2.4 Hz, 2 H) 8.03 (s, 1 H) 7.48 - 7.54 (m, 2 H) 7.26 - 7.32 (m, 3 H) 7.20 (d, *J* = 8.4 Hz, 2 H) 7.11 - 7.18 (m, 2 H) 6.90 - 6.96 (m, 2 H) 6.82 (dd, *J* = 8.8, 2.8 Hz, 3 H) 6.69 (d, *J* = 8.8 Hz, 2 H) 4.58 - 4.65 (m, 1 H) 4.01 - 4.06 (m, 2 H) 3.78 - 3.93 (m, 4 H) 2.78 - 2.86 (m, 2 H) 2.59 (s, 3 H) 2.41 (s, 3 H) 1.72 - 1.77 (m, 2 H) 1.64 (s, 3 H) 1.23 (br s, 5 H). LC-MS: MS (ES^+): RT = 2.979 min, m/z = 861.4 [M +H^+]. LCMS Method: 01.

EXAMPLE 17 – Synthesis of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(7-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)heptyl)acetamide (I-16)



[0561] Step 1: Preparation of tert-butyl N-(7-hydroxyheptyl)carbamate. To a solution of 7-aminoheptan-1-ol (4 g, 30.48 mmol, 1 equiv) in THF (40 mL) was added $(Boc)_2O$ (7.98 g, 36.58 mmol, 8.40 mL, 1.2 equiv). The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica, Eluent of 0~30% Ethyl acetate/Petroleum ether) to afford tert-butyl N-(7-hydroxyheptyl)carbamate (6.3 g, 89% yield) as a colorless oil.

[0562] Step 2: Preparation of tert-butyl N-[7-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl]phenoxy]heptyl]carbamate. To a solution of tert-butyl N-(7-hydroxyheptyl)carbamate (260.60 mg, 1.13 mmol, 2 equiv)in THF (4 mL) was added portion wise NaH (56.33 mg, 1.41 mmol, 60% purity, 2.5 equiv) at 0 °C under N_2,

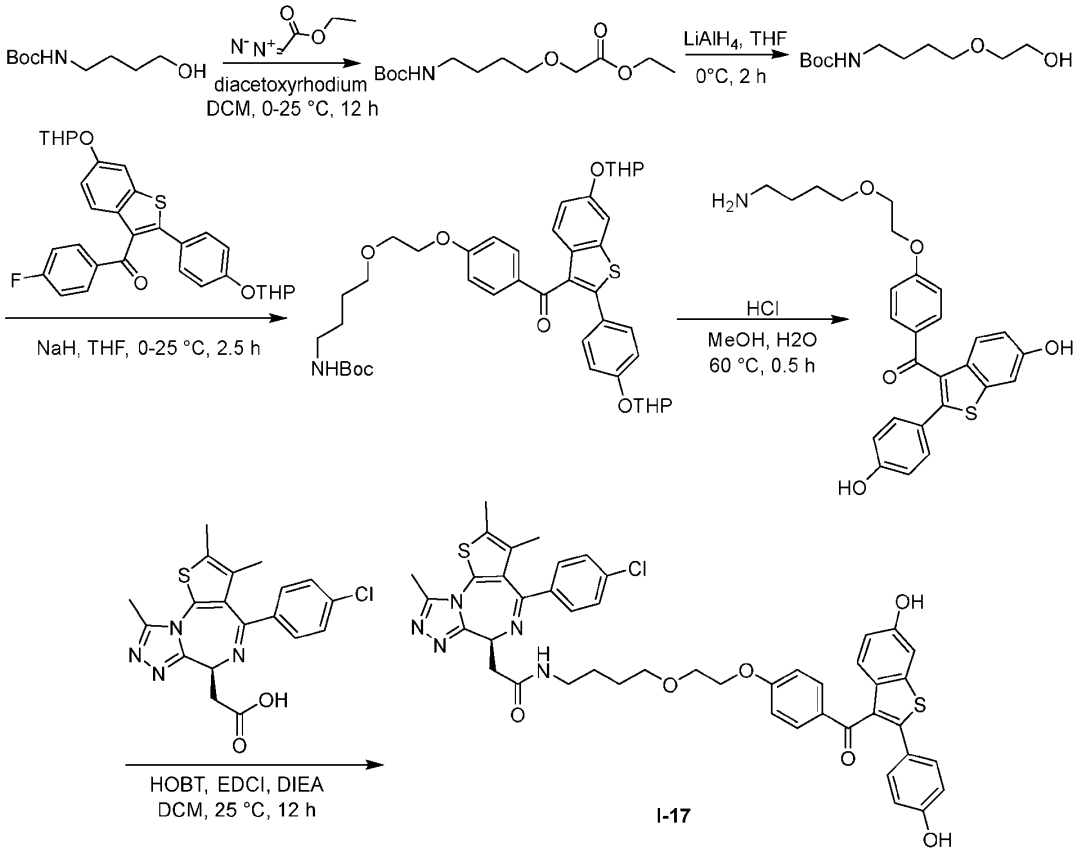
the mixture was stirred at 0 °C for 0.5 h under N_2, then (4-fluorophenyl)-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophen-3-yl]methanone (300 mg, 563.25 μmol, 1 equiv) was added. The mixture was stirred at 25 °C for 1 h under N_2. The reaction mixture was quenched by addition NH_4Cl (10 mL) at 25 °C, and then extracted with EA 27 mL (9 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica, Eluent of 0~30% Ethyl acetate/Petroleum ether) to afford tert-butyl N-[7-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl) benzothiophene-3-carbonyl]phenoxy]heptyl]carbamate (300 mg, 71% yield) as a yellow solid.

[0563] Step 3: Preparation of [4-(7-aminoheptoxy)phenyl]-[6-hydroxy-2-(4-hydroxy phenyl) benzothiophen-3-yl]methanone. Tert-butyl N-[7-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl]phenoxy] heptyl] carbamate (300 mg, 403.26 μmol, 1 *equiv*) was added H_2O (0.25 mL), MeOH (2.5 mL)and HCl (0.25 mL). The mixture was stirred at 50 °C for 2 h. The reaction mixture was quenched by addition $NaHCO_3$ (9 mL) at 25 °C, and then extracted with EtOAc (12 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue to afford [4-(7-aminoheptoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]methanone (230 mg, crude) as a yellow solid.

[0564] Step 4: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(7-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)heptyl)acetamide. To a solution of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (110 mg, 274.40 μmol, 1 equiv) in DCM (2 mL) was added HOBT (55.61 mg, 411 μmol, 1.5 equiv) and EDCI (78.90 mg, 411 μmol, 1.5 equiv). Then the mixture was added the solution of [4-(7-aminoheptoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (195.75 mg, 411 μmol, 1.5 equiv) in DCM (1 mL) and DIEA (106.39 mg, 823.19 μmol, 143 μL, 3 equiv). The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH=9:1). Then the residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 mm x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 55%-85% B over 10 min) to afford (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(7-(4-(6-hydroxy-2-(4-hydroxy-phenyl) benzo[b] thiophene-3-

carbonyl)phenoxy)heptyl)acetamide (**I-16**, 81.64 mg, 34% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (d, J = 17.2 Hz, 2H), 8.15 (t, J = 5.6 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.49 – 7.44 (m, 2H), 7.43 – 7.38 (m, 2H), 7.33 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.20 – 7.12 (m, 2H), 6.92 – 6.82 (m, 3H), 6.71 – 6.64 (m, 2H), 4.49 (dd, J = 6.0, 8.0 Hz, 1H), 3.96 (t, J = 6.4 Hz, 2H), 3.27 – 3.02 (m, 4H), 2.58 (s, 3H), 2.39 (s, 3H), 1.73 – 1.62 (m, 2H), 1.60 (s, 3H), 1.48 – 1.39 (m, 2H), 1.31 (d, J = 3.6 Hz, 6H). LC-MS: MS (ES$^+$): RT = 2.766 min, m/z = 858.4 [M +H$^+$], LCMS Method: 25.

<u>EXAMPLE 18</u> – Synthesis of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)ethoxy)butyl)acetamide (I-17)



[0565] Step 1: Preparation of Ethyl 2-[4-(tert-butoxycarbonylamino)butoxy]acetate. To a solution of tert-butyl N-(4-hydroxybutyl) carbamate (8 g, 42.27 mmol, 1.0 equiv) in DCM (100 mL) was added diacetoxyrhodium (467.08 mg, 2.11 mmol, 0.05 equiv) and ethyl 2-diazoacetate

(48.23 g, 422.72 mmol, 44.45 mL, 10.0 equiv) at 0 °C. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (silica, 0~50% Ethyl acetate/Petroleum ether) to afford ethyl 2-[4-(tert-butoxycarbonylamino)butoxy]acetate (12.3 g, crude) as a yellow oil.

[0566] Step 2: Preparation of Tert-butyl N-[4-(2-hydroxyethoxy)butyl]carbamate. To a solution of ethyl 2-[4-(tert-butoxycarbonylamino)butoxy]acetate (12.3 g, 44.67 mmol, 1 equiv) in THF (100 mL) was added portion-wise $LiAlH_4$ (2.5 M, 44.67 mL, 2.5 equiv) at 0 °C under N_2. The mixture was stirred at 0 °C for 2 hr under N_2. The reaction mixture was quenched with water (4.5 mL), 15% NaOH (4.5 mL) and water (13.5 mL) in turn at 0 °C under N_2. The reaction mixture was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica, 0-50% Ethyl acetate/Petroleum ether) to afford tert-butyl N-[4-(2-hydroxyethoxy) butyl]carbamate (2.9 g, 27% yield) as a light yellow oil.

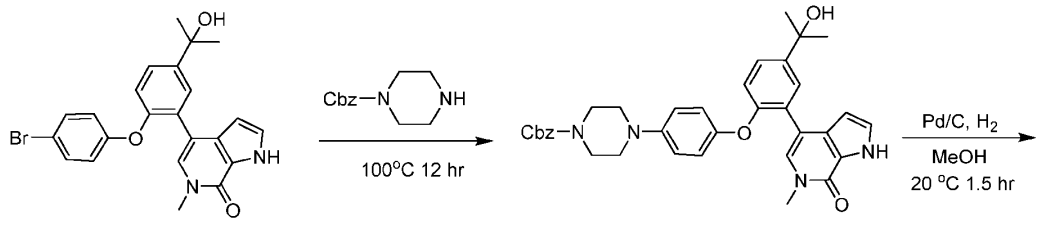
[0567] Step 3: Preparation of tert-butyl N-[4-[2-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl]phenoxy]ethoxy]butyl] carbamate. To a solution of tert-butyl N-[4-(2-hydroxyethoxy)butyl]carbamate (262.82 mg, 1.13 mmol, 2 equiv) in THF (5 mL) was added portion-wise NaH (67.58 mg, 1.69 mmol, 60% purity, 3 equiv) at 0 °C under N_2, the mixture was stirred at 0 °C for 0.5 h under N_2, then (4-fluorophenyl)-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl) benzothiophen-3-yl]methanone (300 mg, 563.25 μmol, 1 equiv) was added. The mixture was stirred at 25 °C for 2 h under N_2. The reaction mixture was quenched by addition saturated NH_4Cl (50 ml) under N_2 at 25 °C and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica, 0-50% Ethyl acetate / Petroleum ether) to afford tert-butyl N-[4-[2-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl) benzothiophene-3-carbonyl]phenoxy]ethoxy]butyl]carbamate (400 mg, 95% yield) as a yellow oil.

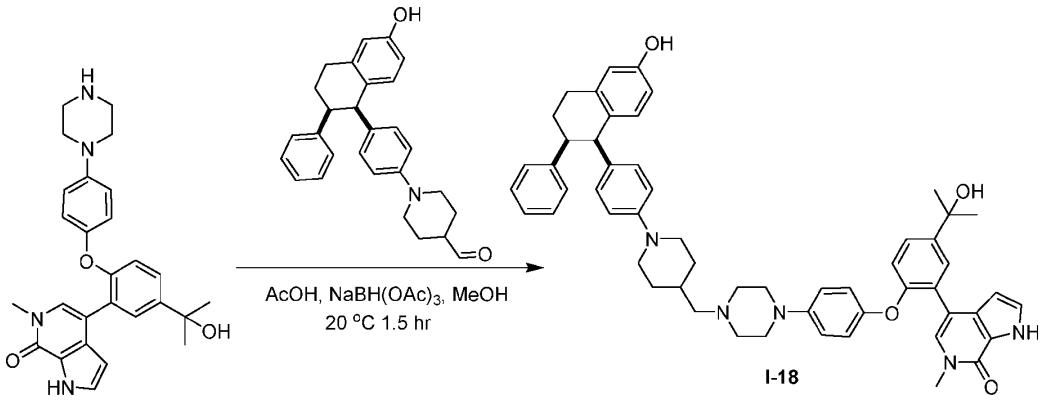
[0568] Step 4: Preparation of [4-[2-(4-aminobutoxy)ethoxy]phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone. To a solution of tert-butyl N-[4-[2-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl] phenoxy] ethoxy]butyl]carbamate (250 mg, 335.16 μmol, 1 equiv) in MeOH (3 mL), H_2O (0.3 mL) and HCl (0.3 mL). The mixture was stirred at 60 °C for 0.5h. The reaction mixture was

concentrated under reduced pressure to afford [4-[2-(4-aminobutoxy)ethoxy] phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (200 mg, crude, HCl) as a yellow oil.

[0569] Step 5: Preparation of (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)ethoxy)butyl)acetamide. To a solution of [4-[2-(4-aminobutoxy)ethoxy]phenyl]-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl] methanone (115.40 mg, 224 μmol, 1.2 equiv, HCl) and 2-[(9S)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]acetic acid (75 mg, 187 μmol, 1 equiv) in DCM (2 mL) was added HOBT (37.92 mg, 280 μmol, 1.5 eq), EDCI (53.80 mg, 280 μmol, 1.5 eq) and DIEA (120.90 mg, 935 μmol, 162.94 μL, 5 eq). The mixture was stirred at 25 °C for 12h. The reaction mixture was diluted with H_2O (100 mL) and extracted with DCM (100 mL). The combined organic layers were washed with brine (15 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25 mm x 5 um; mobile phase: [water(FA)-ACN]; gradient: 53%-73% over 10 min) to afford (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene-3-carbonyl)phenoxy) ethoxy)butyl)acetamide (**I-17**, 36 mg, 22% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.79 (br d, *J* = 16.0 Hz, 2H), 8.18 (br t, *J* = 5.6 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.49 - 7.44 (m, 2H), 7.43 - 7.38 (m, 2H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.19 - 7.14 (m, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.84 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.70 - 6.64 (m, 2H), 4.49 (dd, *J* = 6.0, 8.0 Hz, 1H), 4.14 - 4.05 (m, 2H), 3.70 - 3.63 (m, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 3.28 - 3.16 (m, 2H), 3.16 - 3.04 (m, 2H), 2.58 (s, 3H), 2.39 (s, 3H), 1.59 (s, 3H), 1.56 - 1.43 (m, 4H). LC-MS: MS (ES$^+$): RT = 2.471 min, m/z = 860.3 [M +H$^+$]; LC-MS Method: 25.

<u>EXAMPLE 19</u> – Synthesis of 4-(2-(4-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (I-18)





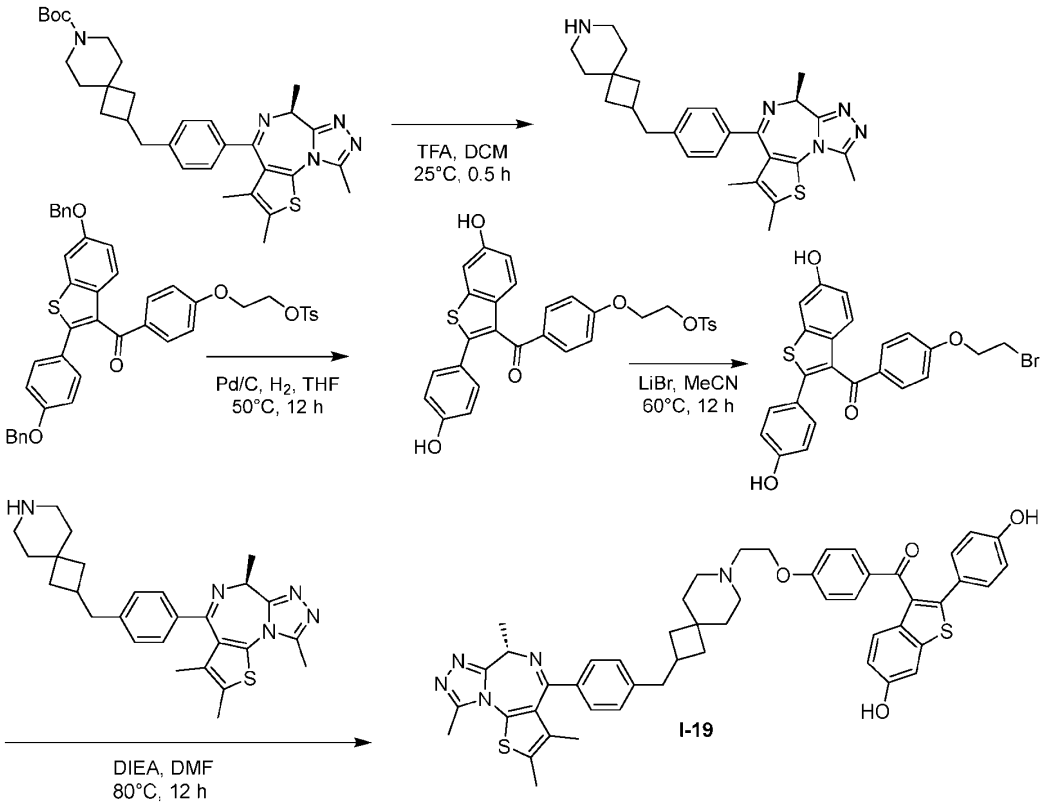
I-18

[0570] Step 1: Preparation of Benzyl 4-[4-[4-(1-hydroxy-1-methyl-ethyl)-2-(6-methyl-7-oxo-1*H*-pyrrolo[2,3-*c*]pyridin-4-yl)phenoxy]phenyl]piperazine-1-carboxylate. A mixture of 4-[2-(4-bromophenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-7-one (400 mg, 882 μmol, 1 equiv), benzyl piperazine-1-carboxylate (600 mg, 2.72 mmol, 525.39 μL, 3.09 equiv), K_3PO_4 (561.90 mg, 2.65 mmol, 3 equiv), CuI (168.05 mg, 882 μmol, 1 equiv) and 2-(2,6-dimethylanilino)-2-oxo-acetic acid (170.47 mg, 882 μmol, 1 equiv) in DMSO (5 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at 100 °C for 12 hours under a N_2 atmosphere. The reaction mixture was diluted with H_2O (5 mL) and extracted with EA (5 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Waters Xbridge C18 150 x 50mm x 10um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 35-65% over 10 min) to afford benzyl 4-[4-[4-(1-hydroxy-1-methyl-ethyl)-2-(6-methyl-7-oxo-1*H*-pyrrolo[2,3-*c*]pyridin-4-yl)phenoxy]phenyl]piperazine-1-carboxylate (240 mg, 46% yield) as a white solid.

[0571] Step 2: Preparation of 4-[5-(1-hydroxy-1-methyl-ethyl)-2-(4-piperazin-1-ylphenoxy) phenyl]-6-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-7-one. To a solution of benzyl 4-[4-[4-(1-hydroxy-1-methyl-ethyl)-2-(6-methyl-7-oxo-1*H*-pyrrolo[2,3-*c*]pyridin-4-yl)phenoxy] phenyl]piperazine-1-carboxylate (240 mg, 404 μmol, 1 equiv) in MeOH (5 mL) was added Pd/C (50 mg, 47 μmol, 10% purity) under N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (50 Psi) at 50 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give 4-[5-(1-hydroxy-1-methyl-ethyl)-2-(4-piperazin-1-ylphenoxy)phenyl]-6-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-7-one (180 mg, 97% yield) as a white solid.

[0572] Step 3: Preparation of 4-(2-(4-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one. To a solution of 4-[5-(1-hydroxy-1-methyl-ethyl)-2-(4-piperazin-1-ylphenoxy)phenyl]-6-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-7-one (180.00 mg, 392 μmol, 1.24 equiv) and 1-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)phenyl]piperidine-4-carbaldehyde (130 mg, 315 μmol, 1 equiv) in MeOH (1 mL) was added AcOH (18.97 mg, 315 μmol, 18.08 μL, 1 equiv). After addition, the mixture was stirred at 20 °C for 0.5 hour, and then $NaBH(OAc)_3$ (66.95 mg, 315 μmol, 1 equiv), 1-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)phenyl]piperidine-4-carbaldehyde (130 mg, 315 μmol, 1 equiv) was added. The resulting mixture was stirred at 20°C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 21%-51% over 10 min). 4-(2-(4-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (**I-18**, 100 mg, 37% yield) was obtained as a white solid. The white solid was further separated by SFC (column: DAICEL CHIRALPAK AS (250mm x 30mm x 10um); mobile phase: [CO_2-ACN/*i*-PrOH (0.1% NH_3)]; 55% B, isocratic). 4-(2-(4-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (**I-18**, 22.3 mg, 27% yield) was isolated as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 10.05 (br s, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.43-7.38 (m, 1H), 7.23 (t, *J* = 2.8 Hz, 1H), 7.19-7.13 (m, 3H), 7.09 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.87-6.79 (m, 7H), 6.72 (d, *J* = 2.8 Hz, 1H), 6.63-6.54 (m, 3H), 6.40 (t, *J* = 2.4 Hz, 1H), 6.29 (d, *J* = 8.8 Hz, 2H), 4.20 (d, *J* = 4.8 Hz, 1H), 3.65 (s, 3H), 3.60-3.48 (m, 2H), 3.39-3.29 (m, 1H), 3.16 (br s, 4H), 3.08-2.97 (m, 2H), 2.66 (br d, *J* = 18.8 Hz, 4H), 2.60-2.53 (m, 2H), 2.36 (br d, *J* = 6.4 Hz, 2H), 2.18 (br d, *J* = 4.8 Hz, 1H), 1.90-1.75 (m, 4H), 1.64 (s, 6H), 1.40-1.29 (m, 2H). LC-MS: MS (ES^+): RT = 1.510 min, m/z = 854.4 [M + H]; LCMS Method: 25.

EXAMPLE 20 – Synthesis of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzyl)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl)methanone (I-19)



[0573] Step 1: Preparation of (9S)-7-[4-(7-azaspiro[3.5]nonan-2-ylmethyl)phenyl]-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaene. To a solution of tert-butyl 2-[[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo [8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]methyl]-7-azaspiro [3.5]nonane-7-carboxylate (200 mg, 357 μmol, 1 equiv) in DCM (3 mL) was added TFA (3.07 g, 27 mmol, 2.00 mL, 75 equiv). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was adjusted to pH 8-9 by $NaHCO_3$ (aq) and then diluted with H_2O (20 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (9S)-7-[4-(7-azaspiro[3.5]nonan-2-ylmethyl)phenyl]-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaene (160 mg, 97% yield) as a yellow solid.

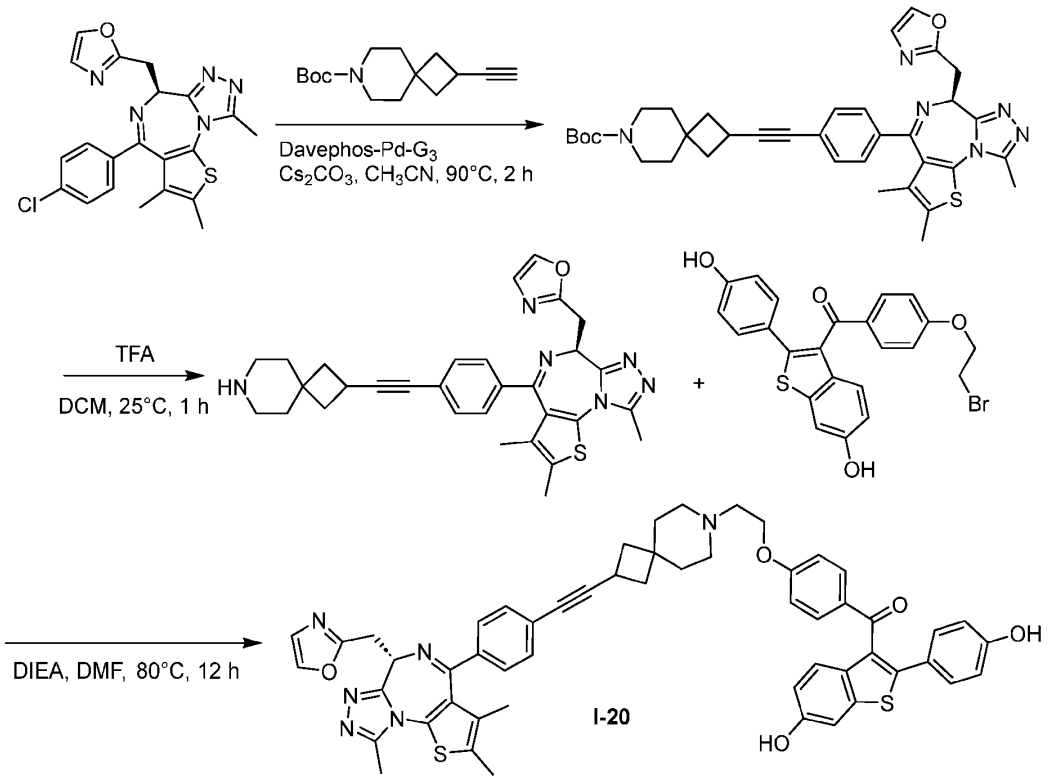
[0574] Step 2: Preparation of 2-[4-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophene-3-carbonyl]phenoxy]ethyl 4-methylbenzenesulfonate. The hydrogenation flask was filled with N_2, and H_2 was slowly added in the N_2 atmosphere, then 2-[4-[6-benzyloxy-2-(4-benzyloxyphenyl)benzothiophene-3-carbonyl]phenoxy]ethyl 4-methylbenzenesulfonate (430 mg, 580 μmol, 1.0 equiv) and Pd/C (200 mg, 187 μmol, 10% purity, 0.32 equiv) in THF (5 mL) was added under N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (50 Psi) at 50 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, PE: EA = 1:1) to afford 2-[4-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophene-3-carbonyl]phenoxy]ethyl 4-methylbenzenesulfonate (300 mg, 92% yield) as a white solid.

[0575] Step 3: Preparation of [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]methanone. To a solution of 2-[4-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophene-3-carbonyl]phenoxy]ethyl 4-methylbenzenesulfonate (300 mg, 535 μmol, 1 equiv) in MeCN (5 mL) was added LiBr (140.81 mg, 1.62 mmol, 3.03 equiv). The mixture was stirred at 60 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/1) to afford [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (120 mg, 47% yield) as a white solid.

[0576] Step 4: Preparation of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzyl)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl)methanone. To a solution of [4-(2-bromoethoxy) phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (40 mg, 85 μmol, 1 equiv) in DMF (1 mL) was added DIEA (38.55 mg, 298 μmol, 52 μL, 3.5 equiv) and (9S)-7-[4-(7-azaspiro[3.5]nonan-2-ylmethyl)phenyl]-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo [8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaene (58.76 mg, 127 μmol, 1.5 equiv). The mixture was stirred at 80 °C for 12h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: [water (FA)-I]; gradient: 28-58% over 9 min) to afford (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b] thiophen-3-yl)(4-(2-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzyl)-7-azaspiro[3.5] nonan-7-yl)ethoxy)phenyl)methanone (**I-19**, 29 mg, 38% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.80 (s, 1 H) 9.75 (s, 1 H) 7.70 (d, *J* = 8.0 Hz, 2 H) 7.31 - 7.36

(m, 3 H) 7.25 (d, J = 8.8 Hz, 1 H) 7.18 (dd, J = 8.0, 5.2 Hz, 4 H) 6.96 (d, J = 8.8 Hz, 2 H) 6.85 (dd, J = 8.8, 2.4 Hz, 1 H) 6.64 - 6.70 (m, 2 H) 4.34 (d, J = 5.2 Hz, 2 H) 4.20 (q, J = 6.4 Hz, 1 H) 3.43 - 3.46 (m, 2 H) 3.37 (s, 4 H) 2.66 - 2.74 (m, 3 H) 2.59 (s, 3 H) 2.39 (s, 3 H) 1.86 (d, J = 6.4 Hz, 3 H) 1.74 - 1.80 (m, 1 H) 1.68 (d, J = 8.0 Hz, 3 H) 1.61 (s, 3 H) 1.44 - 1.56 (m, 2 H) 1.22 - 1.29 (m, 2 H). LC-MS: MS (ES^+): RT = 1.868 min, m/z = 848.5 [M +H^+], LCMS Method: 25.

EXAMPLE 21 – Synthesis of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-((4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)ethynyl)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl) methanone (I-20)



[0577] Step 1: Preparation of tert-butyl 2-[2-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]ethynyl]-7-azaspiro[3.5]nonane-7-carboxylate. To a solution of 2-[[(9S)-7-(4-chlorophenyl)-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10, 12-pentaen-9-yl]methyl]oxazole (500 mg, 1.18 mmol, 1 equiv) and tert-butyl 2-ethynyl-7-azaspiro[3.5]nonane-7-carboxylate (735.25 mg, 2.95 mmol, 2.5 equiv) in MeCN (15 mL) was

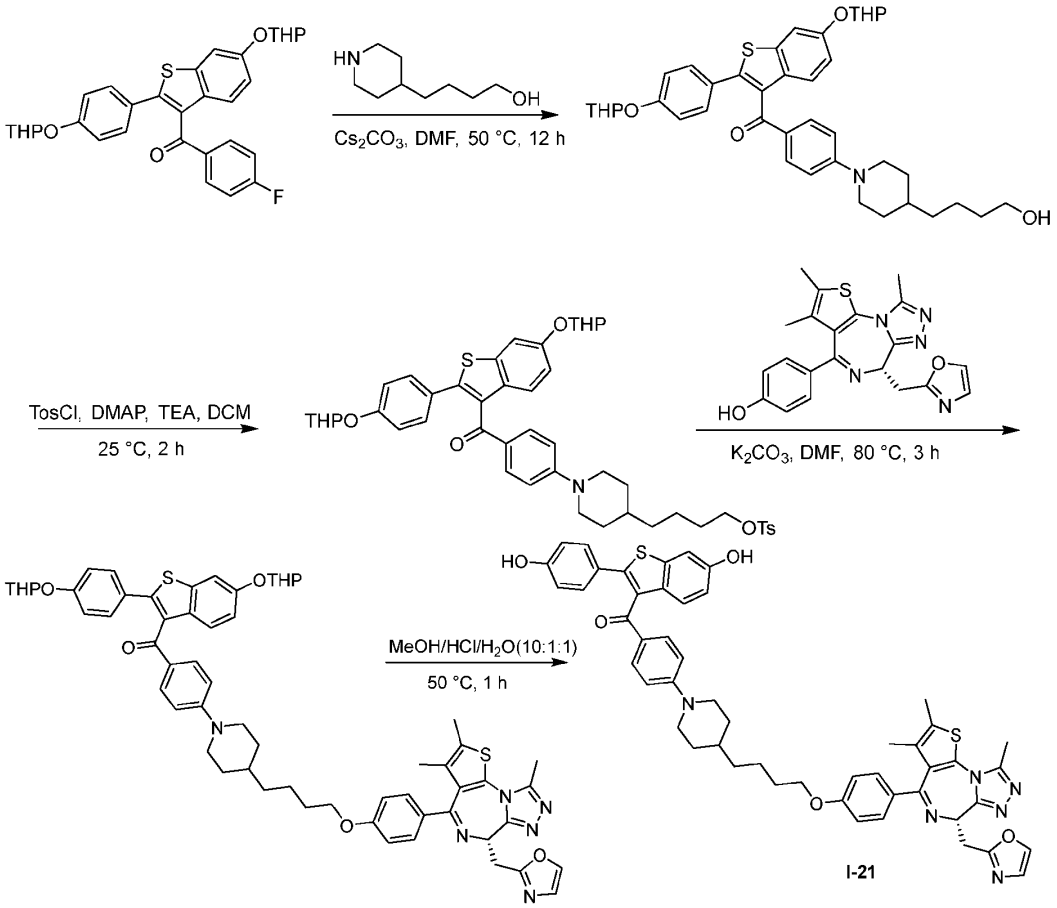
added Cs_2CO_3 (768.59 mg, 2.36 mmol, 2.0 equiv) and DavePhos Pd G_3 (90.03 mg, 117.95 μmol, 0.1 equiv) under N_2. The mixture was stirred at 90 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate 1/0 to 1/1) to afford tert-butyl 2-[2-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo [8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]ethynyl]-7-azaspiro[3.5]nonane-7-carboxylate (700 mg, 93% yield) as a white solid.

[0578] Step 2: Preparation of 2-[[(9S)-7-[4-[2-(7-azaspiro[3.5]nonan-2-yl)ethynyl] phenyl]-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole. To a solution of tert-butyl 2-[2-[4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10, 12-pentaen-7-yl]phenyl]ethynyl]-7-azaspiro[3.5]nonane-7-carboxylate (350 mg, 549 μmol, 1 equiv) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 24 equiv). The mixture was stirred at 25 °C for 1h. The reaction mixture was quenched by addition $NaHCO_3$ 25 mL at 25 °C, and then diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-[[(9S)-7-[4-[2-(7-azaspiro[3.5]nonan-2-yl)ethynyl]phenyl]-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (200 mg, 67% yield) as a brown solid.

[0579] Step 3: Preparation of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-((4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)ethynyl)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl) methanone. To a solution of [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]methanone (40 mg, 85 μmol, 1 equiv) and 2-[[(9S)-7-[4-[2-(7-azaspiro [3.5]nonan-2-yl) ethynyl] phenyl]-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo [8.3.0.$0^{2,6}$]trideca-2(6),4,7, 10, 12-pentaen-9-yl]methyl]oxazole (45.74 mg, 85 μmol, 1 equiv) in DMF (1 mL) was added DIEA (40.00 mg, 309 μmol, 53.91 μL, 3.63 equiv). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: [water (FA)-ACN]; gradient: 30-60% over 9 min) to afford (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-((4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)ethynyl)-7-azaspiro[3.5]nonan-7-

yl)ethoxy)phenyl)methanone (**I-20**, 10.41 mg, 12% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.76 (s, 1H), 8.04 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.42 - 7.37 (m, 2H), 7.36 - 7.34 (m, 2H), 7.32 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.13 (s, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.86 (J = 2.4, 8.8 Hz, 1H), 6.71 - 6.65 (m, 2H), 4.68 (t, J = 7.2 Hz, 1H), 4.39 (s, 2H), 3.98 - 3.77 (m, 2H), 3.54 - 3.39 (m, 3H), 3.06 - 2.89 (m, 2H), 2.60 (s, 3H), 2.41 (s, 3H), 2.38 - 2.32 (m, 1H), 2.18 (t, J = 9.2 Hz, 1H), 2.00 - 1.92 (m, 3H), 1.88 - 1.72 (m, 3H), 1.60 (s, 3H), 1.32 - 1.17 (m, 2H). LC-MS: MS (ES$^+$): RT = 1.260 min, m/z = 925.3 [M +H$^+$]. LCMS Method: 5-95.

EXAMPLE 22 – Synthesis of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)phenyl)methanone (I-21)



[0580] Step 1: Preparation of [4-[4-(4-hydroxybutyl)-1-piperidyl]phenyl]-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophen-3-

yl]methanone. To a solution of (4-fluorophenyl)-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl) benzothiophen-3-yl]methanone (300 mg, 563 μmol, 1 equiv) in DMF (3 mL) was added Cs_2CO_3 (550.56 mg, 1.69 mmol, 3 equiv) and 4-(4-piperidyl)butan-1-ol (177.15 mg, 1.13 mmol, 2 equiv). The mixture was stirred at 50 °C for 12 h. LCMS showed that the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 9:1) to afford [4-[4-(4-hydroxybutyl)-1-piperidyl] phenyl]-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophen-3-yl] methanone (220 mg, 58% yield) as a brown solid.

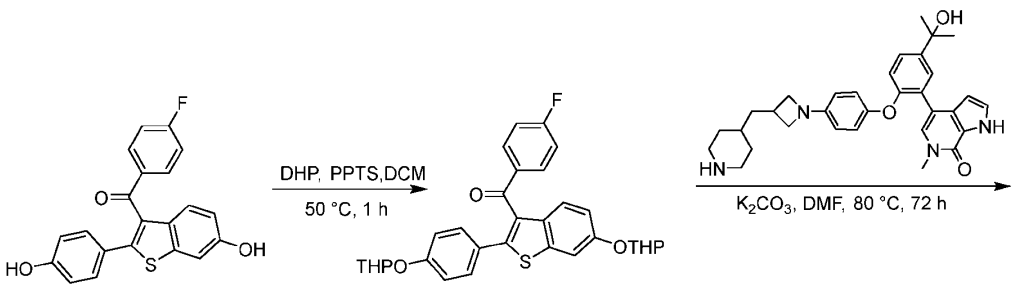
[0581] Step 2: Preparation of 4-[1-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl]phenyl]-4-piperidyl]butyl 4-methylbenzenesulfonate. To a solution of [4-[4-(4-hydroxybutyl)-1-piperidyl]phenyl]-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophen-3-yl]methanone (200 mg, 298 μmol, 1 equiv) in DCM (2 mL) was added DMAP (3.65 mg, 30 μmol, 0.1 equiv) and TEA (75.53 mg, 746 μmol, 103.89 μL, 2.5 equiv). Then the mixture was added TosCl (85.38 mg, 448 μmol, 1.5 *equiv*). The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica, 0-50% Ethyl acetate/Petroleum ether) to afford 4-[1-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl] phenyl]-4-piperidyl]butyl 4-methylbenzenesulfonate (230 mg, 93% yield) as a yellow solid.

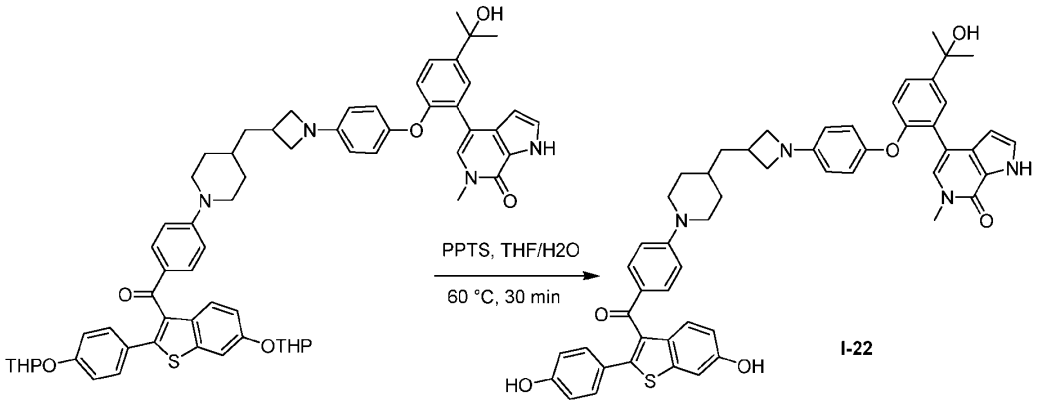
[0582] Step 3: Preparation of (6-((tetrahydro-2H-pyran-2-yl)oxy)-2-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)benzo[b]thiophen-3-yl)(4-(4-(4-(4-((S)-2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy) butyl) piperidin-1-yl)phenyl)methanone. To a solution of 4-[1-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl]phenyl]-4-piperidyl]butyl 4-methylbenzenesulfonate (101.62 mg, 123 μmol, 1 equiv) in DMF (1.5 mL) was added K_2CO_3 (34.09 mg, 246 μmol, 2 equiv) and 4-[(9S)-4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenol (50 mg, 123 μmol, 1 equiv). The mixture was stirred at 80 °C for 3 h. The reaction mixture was quenched by addition H_2O (3 mL) at 25 °C, and then extracted with EA (5 mL x 3). The combined organic layers were washed with aqueous NaCl 15 mL (5 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC

(SiO_2, DCM: MeOH = 10:1) to afford (6-((tetrahydro-2H-pyran-2-yl)oxy)-2-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)benzo[b] thiophen-3-yl)(4-(4-(4-(4-((S)-2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)phenyl)methanone (100 mg, 77% yield) as a brown solid.

[0583] Step 4: Preparation of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)phenyl)methanone. To a solution of (6-((tetrahydro-2H-pyran-2-yl)oxy)-2-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)benzo[b] thiophen-3-yl)(4-(4-(4-(4-((S)-2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)butyl)piperidin-1-yl)phenyl)methanone (100 mg, 94 μmol, 1 *equiv*) in MeOH (1 mL) was added HCl (0.1 mL) and H_2O (0.1 mL). The mixture was stirred at 50 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water(FA)-ACN]; gradient:65%-85% B over 10 min) to afford (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(4-(4-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)butyl) piperidin-1-yl)phenyl)methanone (**I-21**, 32.74 mg, 39% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 - 9.56 (m, 2H), 8.04 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.33 - 7.26 (m, 3H), 7.22 - 7.16 (m, 3H), 7.13 (s, 1H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.82 (dd, *J* = 2.0, 8.8 Hz, 3H), 6.72 - 6.66 (m, 2H), 4.63 (t, *J* = 7.2 Hz, 1H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.93 - 3.84 (m, 3H), 3.84 - 3.77 (m, 1H), 2.79 (t, *J* = 11.6 Hz, 2H), 2.60 (s, 3H), 2.41 (s, 3H), 1.70 (d, *J* = 8.4 Hz, 4H), 1.64 (s, 3H), 1.49 - 1.37 (m, 3H), 1.28 - 1.22 (m, 2H), 1.15 - 1.03 (m, 2H). LC-MS: MS (ES^+): RT = 2.815 min, m/z = 889.4 [M +H^+]; LCMS Method: 25.

<u>EXAMPLE 23</u> – Synthesis of 4-(2-(4-(3-((1-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b] thiophene-3-carbonyl)phenyl)piperidin-4-yl)methyl)azetidin-1-yl)phenoxy)-5-(2-hydroxy-propan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (I-22)



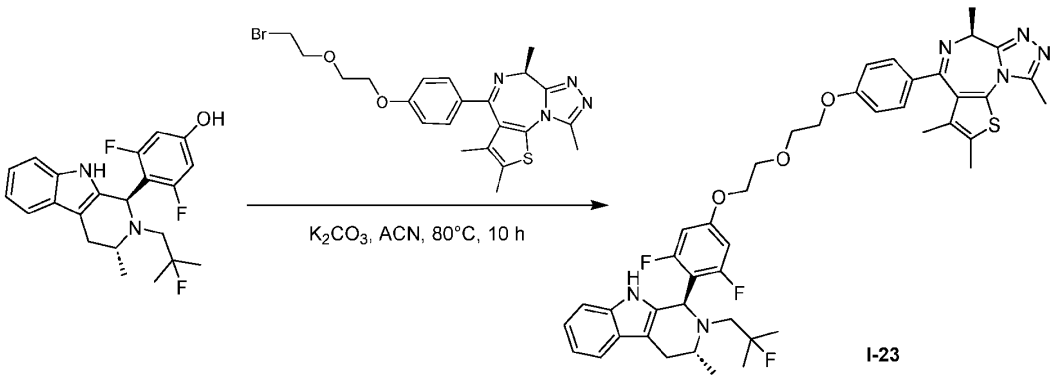


[0584] Step 1: Preparation of (4-fluorophenyl)-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophen-3-yl]methanone. To a solution of (4-fluorophenyl)-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (1 g, 2.74 mmol, 1 *equiv*) in DCM (10 mL) was added 4-methylbenzenesulfonic acid-pyridine (206.90 mg, 823 μmol, 0.3 *equiv*) and DHP (2.31 g, 27 mmol, 2.51 mL, 10 *equiv*). The mixture was stirred at 50 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (Silica, 0-20 % Ethyl acetate/Petroleum ether) to afford (4-fluorophenyl)-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl) benzothiophen-3-yl]methanone (1.4 g, 91% yield) as a green oil.

[0585] Step 2: Preparation of 4-[5-(1-hydroxy-1-methyl-ethyl)-2-[4-[3-[[1-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl]phenyl]-4-piperidyl]methyl]pyridine-1-yl]phenoxy]phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridine-7-one. To a solution of 4-[5-(1-hydroxy-1-methyl-ethyl)-2-[4-[3-(4-piperidylmethyl)pyridine-1-yl]phenoxy]phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridine-7-one (51.91 mg, 99 μmol, 1.5 *equiv*) in DMF (1 mL) was added K_2CO_3 (27.25 mg, 197 μmol, 3 *equiv*) and (4-fluorophenyl)-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl) benzothiophen-3-yl]methanone (35 mg, 65 μmol, 1 *equiv*). The mixture was stirred at 80 °C for 72 h. The reaction mixture was added to H_2O (10 mL), and extracted with EtOAc (10 mL x 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 (SiO_2, DCM: MeOH = 10:1) to afford 4-[5-(1-hydroxy-1-methyl-ethyl)-2-[4-[3-[[1-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl]phenyl]-4-piperidyl] methyl]pyridine-1-yl]phenoxy]phenyl]-6-methyl-1H-pyrrolo [2,3-c]pyridine-7-one (50 mg, 58% yield) as a green solid.

[0586] Step 3: Preparation of 4-(2-(4-(3-((1-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenyl)piperidin-4-yl)methyl)azetidin-1-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one. To a solution of 4-[5-(1-hydroxy-1-methyl-ethyl)-2-[4-[3-[[1-[4-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophene-3-carbonyl]phenyl]-4-piperidyl]methyl] pyridine-1-yl]phenoxy]phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridine-7-one (35 mg, 34 μmol, 1 *equiv*) in THF (0.5 mL) was added H_2O (0.1 mL) and PPTS (11.00 mg, 44 μmol, 1.3 *equiv*). The mixture was stirred at 60 °C for 0.5 h. The reaction mixture was added H_2O (10 mL), pH was adjusted to 9-10 by adding saturated $NaHCO_3$ (aq) and extracted with DCM (10 mL x 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-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um;mobile phase: [water(FA)-ACN]; gradient: 50%-70% B over 10 min) to afford 4-(2-(4-(3-((1-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b] thiophene-3-carbonyl)phenyl)piperidin-4-yl)methyl)azetidin-1-yl)phenoxy)-5-(2-hydroxy propan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (**I-22**, 15 mg, 50% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 9.73 (d, 2H, J = 9.2 Hz), 7.52 (dd, 3H, J = 2.8, 5.2 H), 7.38 - 7.30 (m, 2H), 7.28 - 7.15 (m, 5H), 6.86 - 6.76 (m, 5H), 6.74 - 6.65 (m, 3H), 6.34 (d, 2H, J = 9.2 H), 6.23 (t, 1H, J = 2.4 Hz), 4.99 (s, 1H), 3.89 (t, 4H, J = 7.2 Hz), 3.54 (s, 3H), 3.30 (s, 2H), 2.85 - 2.70 (m, 3H), 1.66 (d, 2H, J = 11.6 Hz), 1.57 - 1.47 (m, 3H), 1.44 (s, 6H), 1.19 - 1.03 (m, 2H). LC-MS: MS (ES^+): RT = 2.111 min, m/z = 871.5 [M +H^+], LCMS Method: 10.

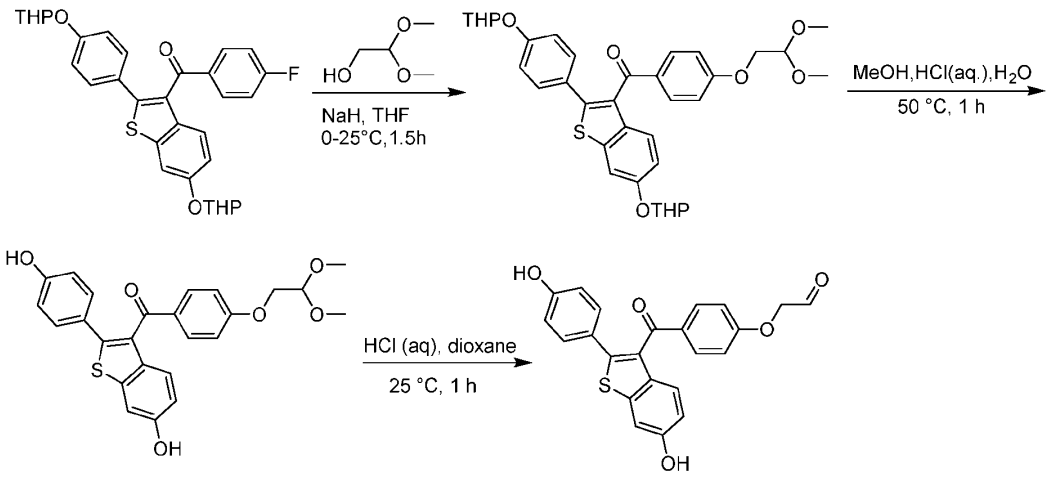
<u>EXAMPLE 24</u> – Synthesis of (S)-4-(4-(2-(2-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methyl propyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenoxy)ethoxy) ethoxy) phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (I-23)

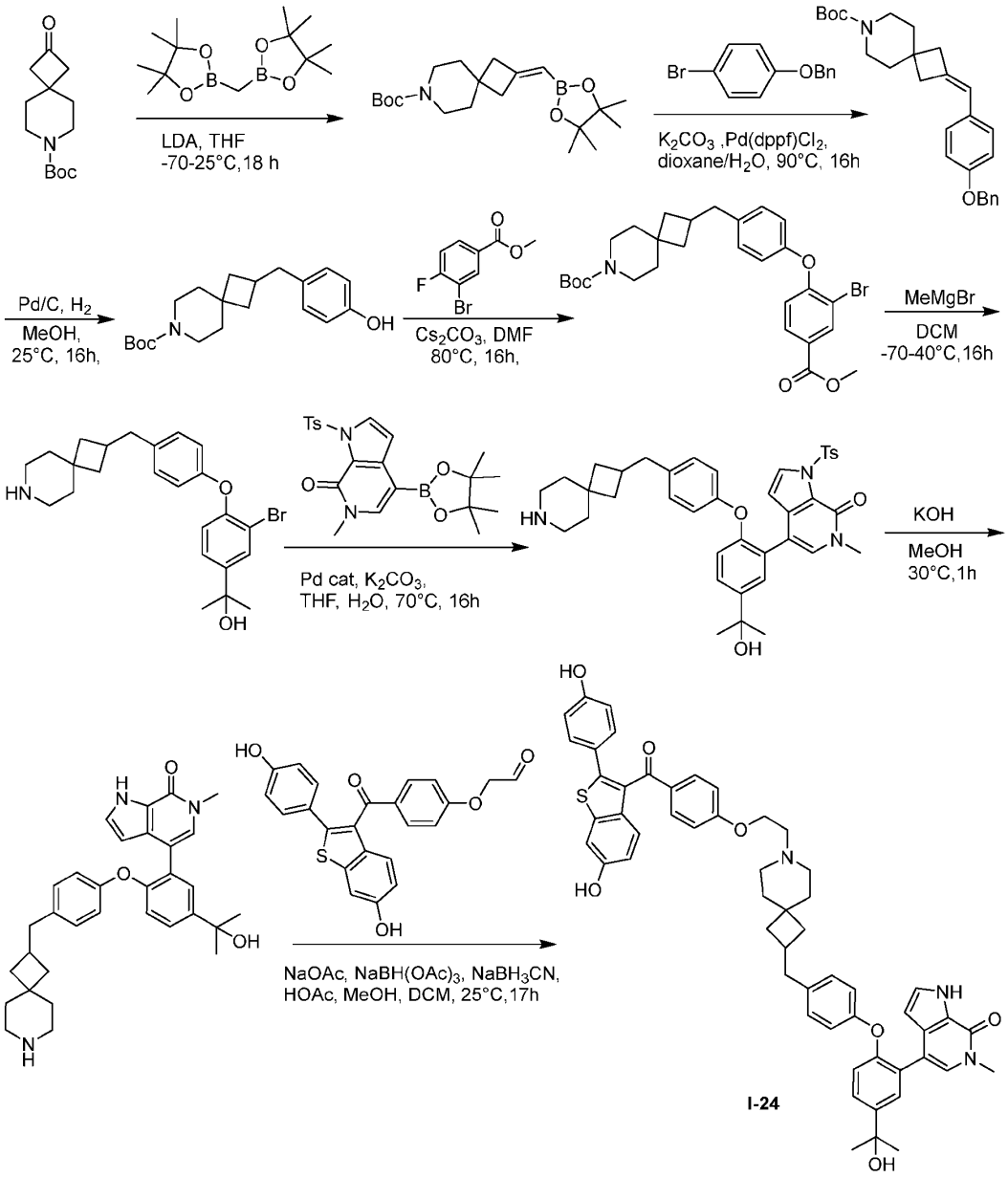


I-23

[0587] To a solution of 3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido [3,4-b]indol-1-yl]phenol (70 mg, 0.18 mmol, 1 *equiv*) and (S)-4-(4-(2-(2-bromoethoxy)ethoxy) phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (105.84 mg, 0.21 mmol, 1.2 *equiv*) in ACN (5 mL) was added K_2CO_3 (74.72 mg, 0.54 mmol, 3 *equiv*). The mixture was stirred at 80 °C for 10 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150 x 30mm x 7um; mobile phase: [water(FA)-ACN]; gradient: 55%-85% B over 10 min) to afford (S)-4-(4-(2-(2-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenoxy) ethoxy)ethoxy)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (**I-23**, 70.65 mg, 46% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 7.42 - 7.31 (m, 3H), 7.17 (d, J = 7.6 Hz, 1H), 7.04 - 6.87 (m, 4H), 6.67 (d, J = 11.2 Hz, 2H), 5.11 (s, 1H), 4.20 - 4.07 (m, 5H), 3.83 - 3.75 (m, 4H), 3.55 - 3.47 (m, 2H), 2.91 - 2.77 (m, 3H), 2.58 (s, 3H), 2.39 (s, 3H), 1.85 (d, J = 6.4 Hz, 3H), 1.64 (s, 3H), 1.22 - 1.01 (m, 9H). LC-MS: MS (ES$^+$): RT = 2.125 min, m/z = 680.4 [M -116], m/z = 796.6; LC-MS Method: 25.

EXAMPLE 25 – Synthesis of 4-(2-(4-((7-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)-7-azaspiro[3.5]nonan-2-yl)methyl) phenoxy) -5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (I-24)





[0588] Step 1: Preparation of [4-(2, 2-dimethoxyethoxy)phenyl]-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2- yloxyphenyl)benzothiophen-3-yl]methanone. To a solution of 2,2-dimethoxyethanol (398.48 mg, 3.76 mmol, 2 *equiv*) in THF (11 ml) was added portion wise NaH (187.75 mg, 4.69 mmol, 60% purity, 2.5 *equiv*) at 0 °C under N_2, the mixture was stirred at 0 °C for 0.5 h under N_2, then (4-fluorophenyl)-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophen-3-yl]methanone (1 g, 1.88 mmol, 1 *equiv*) was added. The mixture

was stirred at 25 °C for 1 h under N_2. The reaction mixture was quenched by addition saturated NH_4Cl (10 ml) under N_2 at 25 °C, and then extracted with EA (12 ml x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (0-30% Ethyl acetate/Petroleum ether) to afford [4-(2, 2-dimethoxyethoxy) phenyl]-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2- yloxyphenyl)benzothiophen-3-yl]methanone (1 g, 86% yield) as a yellow oil.

[0589] Step 2: Preparation of [4-(2, 2-dimethoxyethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]methanone. To a solution of [4-(2,2-dimethoxy ethoxy)phenyl]-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothio phen-3-yl]methanone (980 mg, 1.58 mmol, 1 *equiv*) in MeOH (10 ml) was added HCl (1 ml) and H_2O (1 ml). The mixture was stirred at 50 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford [4-(2, 2-dimethoxyethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]methanone (710 mg, crude) as a yellow solid.

[0590] Step 3: Preparation of 2-[4-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophene-3-carbonyl]phenoxy]acetaldehyde. To a solution of [4-(2,2-dimethoxyethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (710 mg, 1.58 mmol, 1 *equiv*) in dioxane (7.5 ml) was added HCl (12 M, 2.5 ml, 19 *equiv*). The mixture was stirred at 25 °C for 1 hr. The residue was purified by flash silica gel chromatography (0-50% Ethyl acetate/ Petroleum ether) to afford 2-[4-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophene-3-carbonyl] phenoxy] acetaldehyde (340 mg, 53 % yield) as a yellow solid.

[0591] Step 4: Preparation of tert-butyl 2-[(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) methylene]-7-azaspiro [3.5] nonane-7-carboxylate. To a solution of 4,4,5,5-tetramethyl -2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-1,3,2-dioxaborolane (13.44 g, 50.14 mmol, 1.2 *equiv*) in THF (180ml) was added LDA (2 M, 31.34 ml, 1.5 *equiv*) at -75 °C under N_2 atmosphere and the reaction mixture was stirred for 2 h. A solution of tert-butyl 2-oxo-7-azaspiro [3.5] nonane-7-carboxylate (10 g, 41.79 mmol, 1 *equiv*) in THF (20 ml) was added below -70 °C. After 1 h, the mixture was stirred under N_2 at 25 °C for 15 h. The reaction mixture was quenched by addition H_2O (80 ml), and then extracted with EA (100 ml x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate 1/0 to 20/1) to afford tert-butyl 2-[(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) methylene]-7-azaspiro [3.5] nonane-7-carboxylate (7.9 g, 52% yield) as a colorless oil.

[0592] Step 5: Preparation of tert-butyl 2-[(4-benzyloxyphenyl) methylene]-7-azaspiro [3.5] nonane-7-carboxylate. To a solution of tert-butyl 2-[(4,4,5,5-tetramethyl-1,3,2-dioxa borolan-2-yl)methylene]-7-azaspiro[3.5]nonane-7-carboxylate (2 g, 5.51 mmol, 1 *equiv*) and 1-benzyloxy-4-bromo-benzene (2.17 g, 8.26 mmol, 1.5 *equiv*) in dioxane (40 ml) and H_2O (10 ml) was added K_2CO_3 (1.52 g, 11.01 mmol, 2 *equiv*) and $Pd(dppf)Cl_2$ (402.82 mg, 550 µmol, 0.1 *equiv*) was degassed and purged with N_2 three times, and then the mixture was stirred at 90 °C for 16 h under N_2 atmosphere. The reaction mixture was quenched by addition H_2O (20 ml), and then extracted with EA (30 ml x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate, 1/0 to 20/1) to afford tert-butyl 2-[(4-benzyloxyphenyl) methylene]-7-azaspiro [3.5] nonane-7-carboxylate (1.51 g, 65% yield) as a yellow oil.

[0593] Step 6: Preparation of tert-butyl 2-[(4-hydroxyphenyl) methyl]-7-azaspiro [3.5] nonane-7-carboxylate. To a solution of tert-butyl 2-[(4-benzyloxyphenyl) methylene]-7-azaspiro [3.5] nonane-7-carboxylate (1.51 g, 3.60 mmol, 1 *equiv*) in MeOH (20 ml) was added Pd/C (10%, 0.5 g) under N_2 atmosphere. The suspension was degassed and purged with H_2 three times. The mixture was stirred under H_2 (50 Psi) at 25 °C for 16 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue that was diluted with H_2O (30 ml) and extracted with EA (30 ml x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate, 1/0 to 10/1) to afford tert-butyl 2-[(4-hydroxyphenyl)methyl]-7-azaspiro [3.5] nonane-7-carboxylate (0.88 g, 73% yield) as a colorless oil.

[0594] Step 7: Preparation of tert-butyl 2-[[4-(2-bromo-4-methoxycarbonyl-phenoxy) phenyl] methyl]-7-azaspiro [3.5] nonane-7-carboxylate. To a solution of tert-butyl 2-[(4-hydroxyphenyl)methyl]-7-azaspiro [3.5] nonane-7-carboxylate (0.88 g, 2.66 mmol, 1 *equiv*) in DMF (50 ml) was added Cs_2CO_3 (2.60 g, 7.97 mmol, 3 *equiv*) and methyl 3-bromo-4-fluoro-benzoate (804.32 mg, 3.45 mmol, 1.3 *equiv*). The mixture was stirred at 80 °C for 16 hr. The reaction mixture was quenched by addition H_2O (50 ml), and then extracted with EA (50 ml x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate, 1/0 to 10/1) to afford tert-butyl 2-[[4-(2-

bromo-4-methoxycarbonyl-phenoxy) phenyl] methyl]-7-azaspiro [3.5] nonane-7-carboxylate (0.97 g, 67% yield) as a colorless oil.

[0595] Step 8: Preparation of 2-[4-[4-(7-azaspiro [3.5] nonan-2-ylmethyl)phenoxy]-3-bromo-phenyl]propan-2-ol. A mixture of tert-butyl 2-[[4-(2-bromo-4-methoxycarbonyl-phenoxy)phenyl]methyl]-7-azaspiro[3.5]nonane-7-carboxylate (0.97 g, 1.78 mmol , 1 *equiv*) in DCM (50 ml) was degassed and purged with N_2 three times, and then to the mixture was added drop-wise MeMgBr (3 M, 8.91 ml, 15 *equiv*) at -70 °C under an N_2 atmosphere. The resulting mixture was stirred at 40 °C for 16 hours. The reaction mixture was quenched by adding to NH_4Cl.aq (100 ml) at 0-5 °C under N_2, and then mixture was extracted with DCM : MeOH (10:1, 150 ml x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-[4-[4-(7-azaspiro [3.5] nonan-2-ylmethyl)phenoxy]-3-bromo-phenyl]propan-2-ol (700 mg, 88% yield) as a yellow gum.

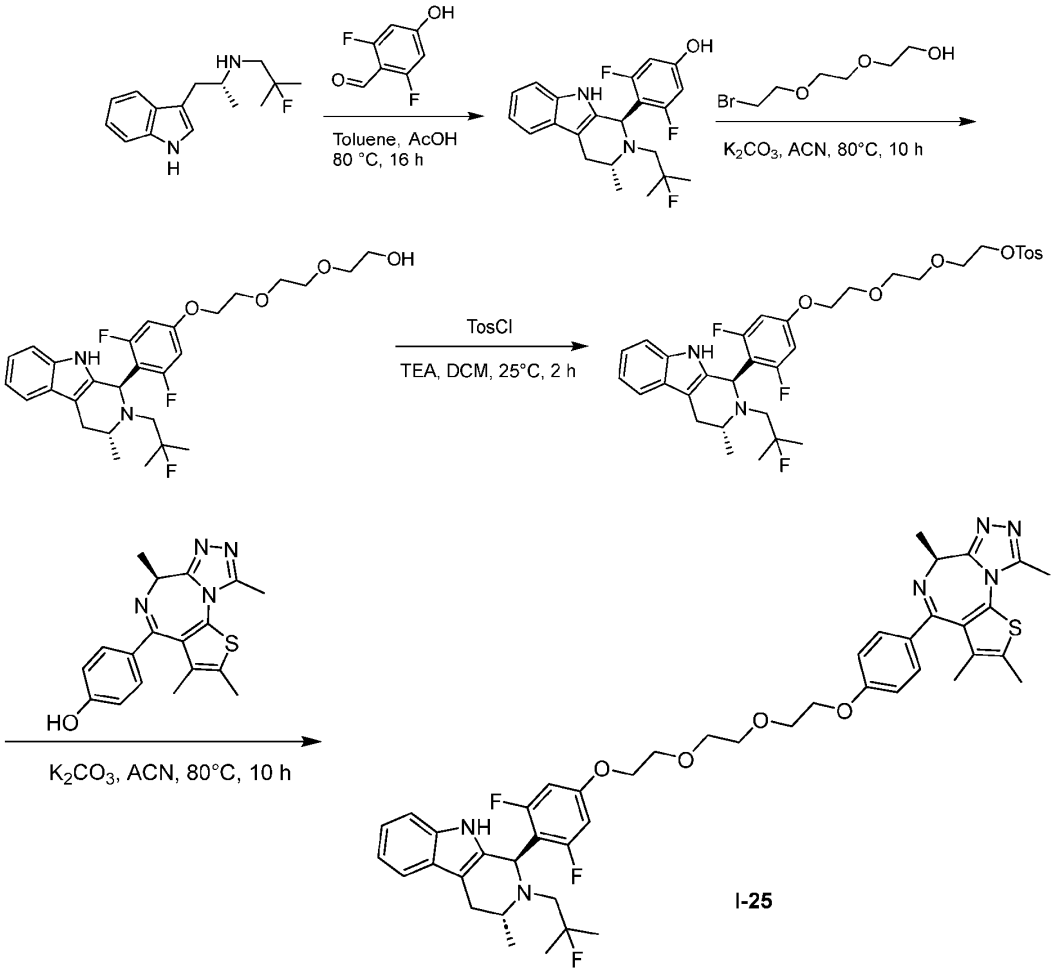
[0596] Step 9: Preparation of 4-[2-[4-(7-azaspiro[3.5]nonan-2-ylmethyl)phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridin-7-one. A mixture of 2-[4-[4-(7-azaspiro[3.5]nonan-2-ylmethyl)phenoxy]-3-bromo-phenyl]propan-2-ol (700 mg, 1.58 mmol, 1 *equiv*), 6-methyl-1-(p-tolylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-c]pyridin-7-one (674.65 mg, 1.58 mmol, 1 *equiv*), K_2CO_3 (478.93 mg, 3.47 mmol, 2.2 *equiv*) , [2-(2-aminophenyl)phenyl]palladium(1+); bis(1-adamantyl)-butyl-phosphane;methanesulfonate (114.71 mg, 157.51 μmol, 0.1 *equiv*) in THF (20 ml) and H_2O (2 ml) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 70 °C for 16 hr under N_2 atmosphere. The mixture was concentrated to afford 4-[2-[4-(7-azaspiro[3.5]nonan-2-ylmethyl)phenoxy]-5-(1-hydroxy-1-methyl-ethyl) phenyl]-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridin-7-one (900 mg, 1.35 mmol, 85% yield) as a yellow oil.

[0597] Step 10: Preparation of 4-[2-[4-(7-azaspiro[3.5]nonan-2-ylmethyl)phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridin-7-one. To a solution of 4-[2-[4-(7-azaspiro[3.5]nonan-2-ylmethyl)phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridin-7-one (900 mg, 1.35 mmol, 1 *equiv*) in MeOH (40 ml) was added KOH (1.67 g, 29.7 mmol, 22 *equiv*). The mixture was stirred at 30 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 (250 x 70mm x 10 um); mobile phase: [water(FA)-ACN]; gradient: 15%-45% B over 20 min) to afford 4-[2-[4-(7-azaspiro[3.5]nonan-2-

ylmethyl)phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridin-7-one (290 mg, 41% yield) as a white solid.

[0598] Step 11: Preparation of 4-[2-[4-[[7-[2-[4-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophene-3-carbonyl]phenoxy]ethyl]-7-azaspiro[3.5]nonan-2-yl]methyl]phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridin-7-one. To a solution of 4-[2-[4-(7-azaspiro [3.5]nonan-2-ylmethyl)phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1H-pyrrolo [2,3-c]pyridin-7-one (40 mg, 78.2 μmol, 1 *equiv*) in MeOH (1 ml) and DCM (1 ml) was added NaOAc (12.83 mg, 156 μmol, 2 *equiv*). The mixture was stirred at 25 °C for 1h , then the mixture was added 2-[4-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophene-3-carbonyl]phenoxy]acetaldehyde (79.04 mg, 195 μmol, 2.5 *equiv*), the mixture was stirred at 25 °C for 1 h, then the mixture was added $NaBH(OAc)_3$ (49.71 mg, 234 μmol, 3*equiv*) and the mixture was stirred at 25 °C for 1 h, after the mixture was added $NaBH_3CN$ (9.83 mg, 156 μmol, 2 *equiv*) and HOAc (104.90 mg, 1.75 mmol, 0.1 ml, 22.34 *equiv*), then the mixture was stirred at 25 °C for 14 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water(FA)-ACN]; gradient: 30%-50% B over 10 min) to afford 4-(2-(4-((7-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)-7-azaspiro[3.5]nonan-2-yl)methyl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (**I-24**, 14.6 mg, 19% yield) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ = 7.73 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 2.4, 8.6 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.20 - 7.15 (m, 2H), 7.14 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.90 - 6.85 (m, 3H), 6.67 - 6.59 (m, 4H), 6.35 (d, *J* = 2.8 Hz, 1H), 4.63 - 4.52 (m, 1H), 4.33 - 4.21 (m, 2H), 3.61 - 3.56 (m, 3H), 3.28 - 3.25 (m, 1H), 3.16 - 2.79 (m, 4H), 2.62 - 2.54 (m, 2H), 2.49 - 2.33 (m, 1H), 1.96 - 1.77 (m, 4H), 1.68 (br t, *J* = 5.2 Hz, 2H), 1.59 (s, 6H), 1.49 (br dd, *J* = 8.8, 11.6 Hz, 2H) LC-MS: MS (ES^+): RT = 2.095 min, m/z = 900.3 [$M+H^+$], LC-MS Method: 25.

EXAMPLE 26 – Synthesis of (S)-4-(4-(2-(2-(2-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenoxy) ethoxy)ethoxy)ethoxy)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (I-25)



[0599] Step 1: Preparation of 3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydro pyrido[3,4-b]indol-1-yl]phenol. To a solution of 2-fluoro-N-[(1R)-2-(1H-indol-3-yl)-1-methyl-ethyl]-2-methyl-propan-1-amine (113 mg, 0.45 mmol, 1 *equiv*) and 2,6-difluoro-4-hydroxy-benzaldehyde (71.94 mg, 0.45 mmol, 1 *equiv*) in toluene (2 mL) was added AcOH (54.65 mg, 0.90 mmol, 2 *equiv*). The mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched by addition aqueous saturated sodium bicarbonate (10 mL) and then diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic

layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate, 3/1) to afford 3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydro pyrido[3,4-b]indol-1-yl]phenol (136 mg, 71 % yield) as a yellow solid.

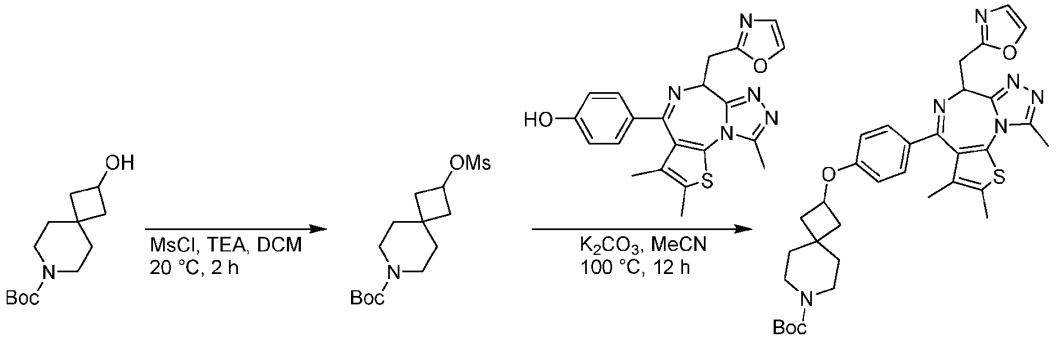
[0600] Step 2: Preparation of 2-[2-[2-[3,5-difluoro-4- [(1R,3R)-2-(2- fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenoxy]ethoxy]ethoxy] ethanol. To a solution of 3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido [3,4-b]indol-1-yl]phenol (136 mg, 0.35 mmol, 1 *equiv*) and 2-[2-(2-bromoethoxy)ethoxy]ethanol (82.06 mg, 0.38 mmol, 1.1 *equiv*) in ACN (3 mL) was added K_2CO_3 (48.39 mg, 0.35 mmol, 1 *equiv*). The mixture was stirred at 80 °C for 10 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate, 1/1) to afford 2-[2-[2-[3,5-difluoro-4- [(1R,3R)-2-(2- fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenoxy]ethoxy]ethoxy]ethanol (135 mg, 60% yield) as a yellow solid.

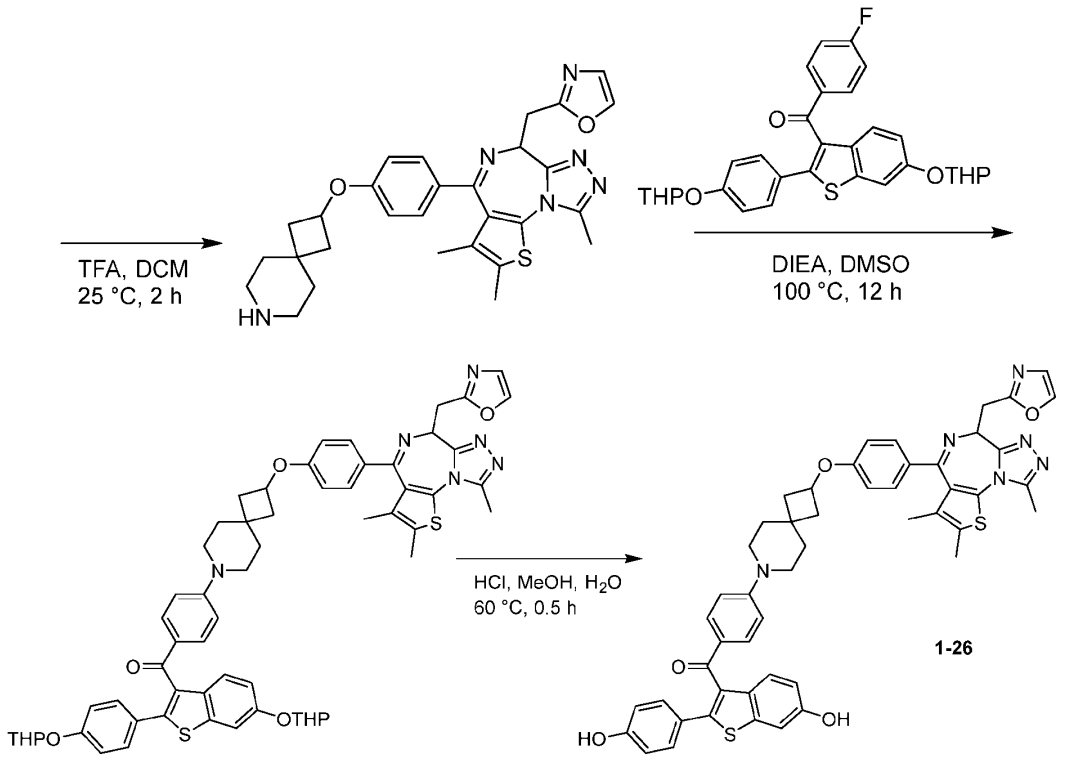
[0601] Step 3: Preparation of 2-[2-[2-[3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate. To a solution of 2-[2-[2-[3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9- tetrahydropyrido[3,4-b]indol-1-yl]phenoxy]ethoxy] ethoxy]ethanol (132 mg, 0.25 mmol, 1 *equiv*) in CH_2Cl_2 (3 mL) was added TosCl (62.84 mg, 0.30 mmol, 1.3 *equiv*), TEA (51.32 mg, 0.50 mmol, 2 *equiv*) and DMAP (3.10 mg, 25.36 µmol, 0.1 *eq*). The mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, dichloromethane / methanol, 3/1) to afford 2-[2-[2-[3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]phenoxy]ethoxy] ethoxy]ethyl 4-methylbenzenesulfonate (98 mg, 51% yield) as a yellow oil.

[0602] Step 4: Preparation of (S)-4-(4-(2-(2-(2-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenoxy)ethoxy)

ethoxy)ethoxy)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepine. To a solution of 2-[2-[2-[3,5-difluoro-4-[(1R,3R)-2-(2-fluoro-2-methyl-propyl)-3-methyl-1,3,4,9- tetrahydropyrido[3,4-b]indol-1-yl]phenoxy]ethoxy] ethoxy]ethyl 4-methylbenzenesulfonate (95 mg, 0.14 mmol, 1 *equiv*) and (S)-4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenol (47.65 mg, 0.14 mmol, 1 *equiv*) in ACN (5 mL) was added K_2CO_3 (58.37 mg, 0.4 mmol, 3 *equiv*). The mixture was stirred at 80 °C for 10 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150 x 30 mm x 7 um; mobile phase: [water (FA)-ACN]; gradient: 50%-80% B over 10 min) to afford (S)-4-(4-(2-(2-(2-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenoxy)ethoxy)ethoxy)ethoxy)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (**I-25**, 13.52 mg, 11% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) 10.51 (s, 1H), 7.41 - 7.33 (m, 3H), 7.16 (d, J = 7.6 Hz, 1H), 7.01 - 6.88 (m, 4H), 6.66 (d, J = 10.8 Hz, 2H), 5.11 (d, J = 0.8 Hz, 1H), 4.10 (d, J = 3.2 Hz, 4H), 3.76 - 3.70 (m, 4H), 3.59 (s, 4H), 2.89 - 2.82 (m, 3H), 2.68 - 2.66 (m, 3H), 2.34 - 2.31 (m, 3H), 1.85 (d, J = 6.4 Hz, 3H), 1.64 (s, 3H), 1.25 - 1.00 (m, 12H). LC-MS: MS (ES$^+$): RT = 1.821 min, m/z = 841.7 [M +H$^+$], LC-MS Method: 25.

<u>EXAMPLE 27</u> – Synthesis of (6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl)(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)phenyl)methanone (I-26)





[0603] Step 1: Preparation of tert-butyl 2-methylsulfonyloxy-7-azaspiro[3.5]nonane-7-carboxylate. To a solution of tert-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (2 g, 8.29 mmol, 1 *equiv*) in DCM (30 mL) was added TEA (2.10 g, 20.72 mmol, 2.88 mL, 2.5 *equiv*) and MsCl (1.34 g, 11.70 mmol, 905 µL, 1.41 *equiv*) was added at 0 °C. The mixture was stirred at 20 °C for 2h. The reaction mixture was poured into ice water (50 mL) and then diluted with DCM (50 mL) and extracted with DCM (50 mL x 2). The combined organic layers were washed with citric acid (100 mL) and brine (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford tert-butyl 2-methylsulfonyloxy-7-azaspiro[3.5]nonane-7-carboxylate (2.6 g, 98% yield) as a white solid.

[0604] Step 2: Preparation of tert-butyl 2-[4-[4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenoxy]-7-azaspiro[3.5]nonane-7-carboxylate. To a solution of 4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenol (200 mg, 493 µmol, 1 *equiv*) in DMF (7 mL) was added K_2CO_3 (136.34 mg, 986 µmol, 2 *equiv*) and tert-butyl 2-methylsulfonyloxy-7-azaspiro[3.5]nonane-7-carboxylate (787.76 mg, 2.47 mmol, 5 *equiv*). The mixture was stirred at 100 °C for 12h. The reaction mixture was filtered and concentrated under

reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH, 10:1) to afford tert-butyl 2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)-7-azaspiro[3.5]nonane-7-carboxylate (240 mg, 77% yield) as a white solid.

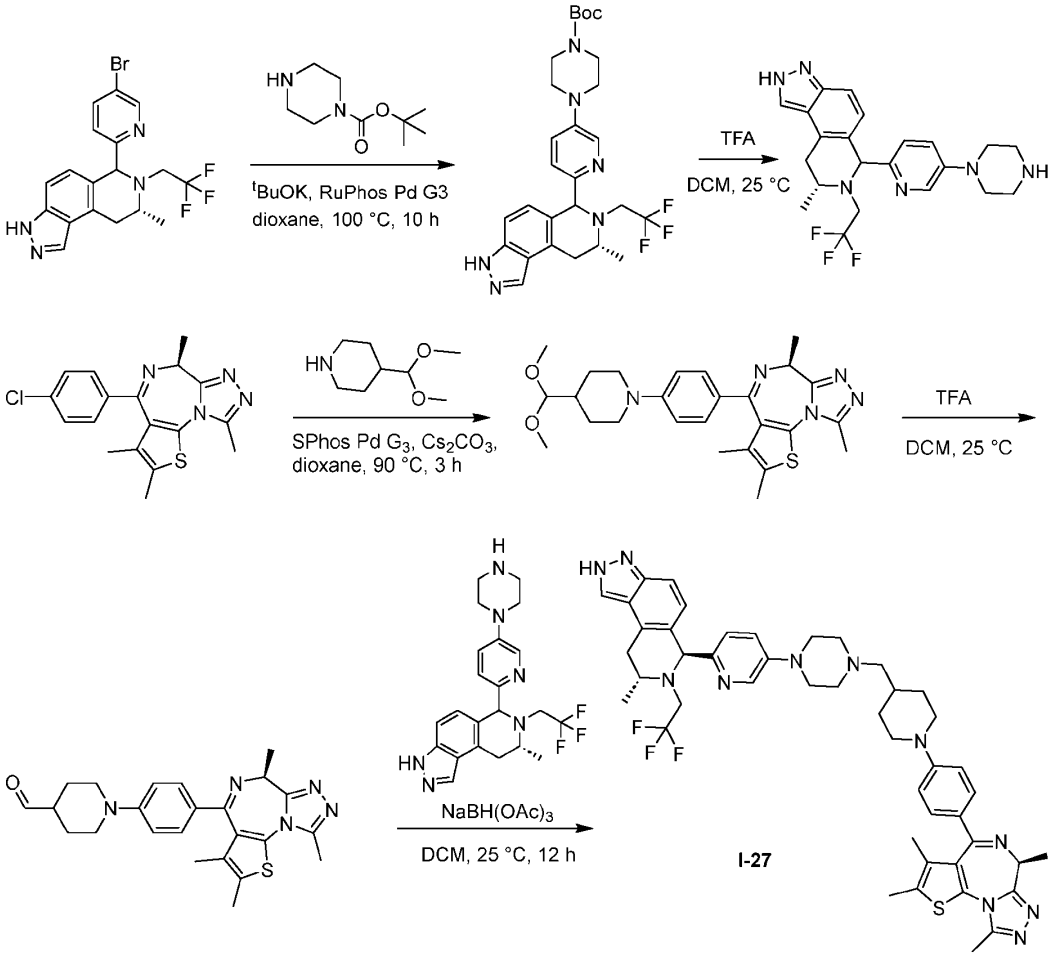
[0605] Step 3: Preparation of 2-((4-(4-((7-azaspiro[3.5]nonan-2-yl)oxy)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)methyl)oxazole. To a solution of tert-butyl 2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenoxy)-7-azaspiro[3.5]nonane-7-carboxylate (240 mg, 381 μmol, 1 *equiv*) in DCM (3 mL) was added TFA (3.68 g, 32.31 mmol, 2.40 mL, 84.65 *equiv*). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition $NaHCO_3$ (aq) (10 mL) at 25 °C, adjusted pH to 8, and then diluted with H_2O (20 mL) and extracted with EA (20 mL x 2). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-((4-(4-((7-azaspiro[3.5] nonan-2-yl)oxy)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)methyl)oxazole (200 mg, 99% yield) as a white solid.

[0606] Step 4: Preparation of (6-((tetrahydro-2H-pyran-2-yl)oxy)-2-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)-7-azaspiro [3.5]nonan-7-yl)phenyl)methanone. To a solution of 2-((4-(4-((7-azaspiro[3.5]nonan-2-yl)oxy)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)methyl)oxazole (200 mg, 378 μmol, 1 *equiv*) and (4-fluorophenyl)-[6-tetrahydropyran-2-yloxy-2-(4-tetrahydropyran-2-yloxyphenyl)benzothiophen-3-yl]methanone (201.50 mg, 378 μmol, 1 *equiv*) in DMSO (2 mL) was added Cs_2CO_3 (246.52 mg, 756 μmol, 2 *equiv*). The mixture was stirred at 100 °C for 12h. The reaction mixture was partitioned between EA (50 mL) and H_2O (50 mL). The organic phase was separated, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH, 10:1) to afford (6-((tetrahydro-2H-pyran-2-yl)oxy)-2-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)phenyl)methanone (200 mg, 50% yield) as a white solid.

[0607] Step 5: Preparation of (6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-

a][1,4]diazepin-4-yl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)phenyl)methanone (isomer 1 and isomer 2). To a solution of (6-((tetrahydro-2H-pyran-2-yl)oxy)-2-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl) benzo[b]thiophen-3-yl)(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)-7-azaspiro[3.5] nonan-7-yl)phenyl) methanone (150 mg, 144 μmol, 1 *equiv*) in MeOH (0.1 mL) was added HCl (102 mg, 2.80 mmol, 0.1 mL, 100% purity, 19.4 *equiv*) and H_2O (1 mL). The mixture was stirred at 60 °C for 0.5h. The reaction mixture was quenched by addition $NaHCO_3$ (aq) (10 mL) at 25 °C, adjust pH to 8, and then diluted with H_2O (20 mL) and extracted with EA (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: [water (FA)-ACN]; gradient: 58%-88% B over 9 min) to afford a white solid. The racemate was resolved by SFC ((s,s)-WHELK-O1 (250mm x 30mm x 10um); mobile phase: [CO_2-ACN/EtOH(0.1% NH_3H_2O)]; 65% B, isocratic elution mode) to give isomer 1 as a white solid (peak 1, 18 mg, 44% yield) and isomer 2 of (6-hydroxy -2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)-7-azaspiro[3.5] nonan-7-yl)phenyl)methanone as a white solid (peak 2, 20 mg, 49% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.73 (br d, *J*=9.2 Hz, 2 H) 8.03 (s, 1 H) 7.52 (d, *J*=8.8 Hz, 2 H) 7.31 (d, *J*=2.0 Hz, 1 H) 7.27 (br d, *J*=8.8 Hz, 2 H) 7.15 - 7.22 (m, 3 H) 7.12 (s, 1 H) 6.79 - 6.87 (m, 5 H) 6.65 - 6.71 (m, 2 H) 4.73 - 4.82 (m, 1 H) 4.61 (t, *J*=7.6 Hz, 1 H) 3.76 - 3.90 (m, 2 H) 3.25 (br d, *J*=2.8 Hz, 2 H) 2.59 (s, 3 H) 2.52 - 2.54 (m, 2 H) 2.41 (s, 5 H) 1.77 - 1.84 (m, 2 H) 1.53 - 1.65 (m, 7 H). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.68 - 9.79 (m, 2 H) 8.03 (d, *J*=0.8 Hz, 1 H) 7.52 (d, *J*=8.8 Hz, 2 H) 7.31 (d, *J*=2.0 Hz, 1 H) 7.27 (d, *J*=8.4 Hz, 2 H) 7.15 - 7.22 (m, 3 H) 7.12 (d, *J*=0.8 Hz, 1 H) 6.79 - 6.87 (m, 5 H) 6.68 (d, *J*=8.8 Hz, 2 H) 4.78 (br t, *J*=6.8 Hz, 1 H) 4.61 (t, *J*=7.6 Hz, 1 H) 3.75 - 3.92 (m, 2 H) 3.26 (dt, *J*=4.0, 2.2 Hz, 2 H) 2.59 (s, 3 H) 2.54 (s, 2 H) 2.39 - 2.45 (m, 5 H) 1.80 (br dd, *J*=12.8, 6.4 Hz, 2 H) 1.64 (s, 7 H).

EXAMPLE 28 – **Synthesis of (S)-2,3,6,9-tetramethyl-4-(4-(4-((4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (I-27)**



[0608] Step 1: Preparation of *tert*-butyl 4-(6-((8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridine-3-yl)piperazine-1-carboxylate. To a solution of (8R)-6-(5-bromopyridin-2-yl)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinoline (1.00 g, 2.35 mmol, 1.00 equiv), *tert*-butyl piperazine-1-carboxylate (1.31 g, 7.05 mmol, 3.00 equiv), potassium *tert*-butoxide (1.32 g,11.76 mmol, 5.00 equiv), [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium; dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane (393 mg, 0.47 mmol, 0.20 *equiv*) in dioxane (20 mL)

was stirred at 100 °C for 10 h under nitrogen atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=6/1 to 1/1) to give *tert*-butyl 4-(6-((8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridine-3-yl)piperazine-1-carboxylate (450 mg, 36% yield) as a yellow solid.

[0609] Step 2: Preparation of (8R)-8-methyl-6-(5-(piperazin-1-yl)pyridine-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinoline. To a solution of *tert*-butyl 4-(6-((8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridine-3-yl)piperazine-1-carboxylate (150 mg, 0.28 mmol, 1.00 *equiv*) in dichloromethane (1 mL) was added trifluoroacetic acid (767 mg, 6.73 mmol, 23.81 *equiv*). The mixture was stirred at 25 °C for 10 min. Ethyl acetate (2 mL) and saturated sodium bicarbonate solution (2 mL) were added, then the mixture was extracted with ethyl acetate (2 mL × 3). The organic layers was washed with brine (2 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (8R)-8-methyl-6-(5-(piperazin-1-yl)pyridine-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]iso quinoline (120 mg, 98% yield) as a red oil, which was used into the next step without further purification.

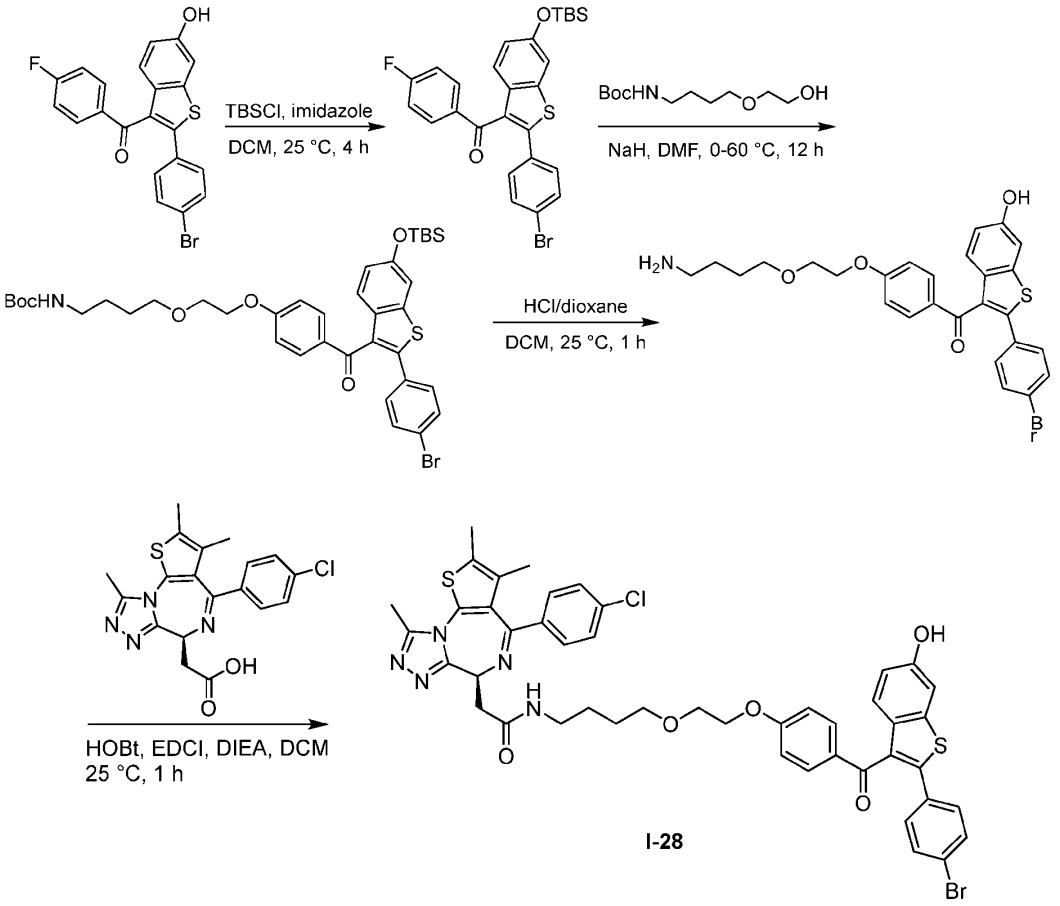
[0610] Step 3: Preparation of (S)-4-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine. A mixture of (9S)-7-(4-chlorophenyl)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$] trideca-2(6),4,7,10,12-pentaene (100 mg, 0.28 mmol, 1.00 *equiv*), 4-(dimethoxymethyl) piperidine (223 mg, 1.40 mmol, 5.00 *equiv*), dicyclohexyl-[2-(2,6-dimethoxyphenyl)phenyl] phosphane; methanesulfonate; (2-phenylanilino)palladium(1+), (22 mg, 0.03 mmol, 0.10 *equiv*) and cesium carbonate (183 mg, 0.56 mmol, 2.00 *equiv*) in dioxane (1 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 90 °C for 3 h under nitrogen atmosphere. Ethyl acetate (5 mL) and water (5 mL) were added before the mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the residue. The residue was purified by prep-TLC (dichloromethane / methanol=10 / 1) to afford (S)-4-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (100 mg, 73% yield) as a yellow oil.

[0611] Step 4: Preparation of (S)-1-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo [4,3-a][1,4]diazepin-4-yl)phenyl)piperidine-4-carbaldehyde. To a solution of (S)-4-(4-(4-

(dimethoxymethyl)piperidin-1-yl)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepine (100 mg, 0.21 mmol, 1.00 *equiv*) in dichloromethane (1 mL) was added trifluoroacetic acid (768 mg, 6.73 mmol, 32 *equiv*). The mixture was stirred at 25 °C for 10 min. The mixture was concentrated under reduced pressure to give (S)-1-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidine-4-carbaldehyde (110 mg, 96% yield, trifluoroacetate) as a yellow oil, which was used into the next step without further purification.

[0612] Step 5: Preparation of (S)-2,3,6,9-tetramethyl-4-(4-(4-((4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine. To a solution of (S)-1-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidine-4-carbaldehyde (110 mg, 0.20 mmol, 1.00 *equiv*, trifluoroacetate) in dichloromethane (2 mL) was added sodium triacetoxyborohydride (128 mg, 0.60 mmol, 3.00 *equiv*) and (8R)-8-methyl-6-(5-(piperazin-1-yl)pyridine-2-yl)-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinoline (86 mg, 0.20 mmol, 1.00 *equiv*). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated under reduced pressure to get the residue. The residue was purified by prep-TLC (dichloromethane / methanol = 10/1) to get the crude product. The crude product was purified by prep-SFC (column: DAICEL CHIRALCEL OD (250mm x 30mm x 10um); mobile phase: [CO_2-I/EtOH (0.1% NH_3H_2O)]; 40/60 isocratic elution mode) give a crude product, and then the crude product was further purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: [water(FIACN]; gradient: 10%-40% B over 8 min) to afford (S)-2,3,6,9-tetramethyl-4-(4-(4-((4-(6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)pyridin-3-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (**I-27**, 38.7 mg, 22% yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 12.98 (s, 1H), 8.14 - 8.02 (m, 2H), 7.33 - 7.19 (m, 4H), 7.10 (d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 1H), 5.00 (s, 1H), 4.12 (q, *J* = 6.2 Hz, 1H), 3.82-3.76 (m, 2H), 3.59 - 3.45 (m, 3H), 3.30 - 3.20 (m, 3H), 3.15 (s, 4H), 3.07 - 2.95 (m, 2H), 2.89 - 2.82 (m, 1H), 2.77 - 2.69 (m, 2H), 2.57 (s, 3H), 2.47 - 2.46 (m, 1H), 2.40 (s, 3H), 2.18 (d, *J* = 6.4 Hz, 2H), 1.84 (d, *J* = 6.4 Hz, 3H), 1.81-1.75 (m, 2H), 1.70 (s, 3H), 1.25 - 1.13 (m, 2H), 1.09 (d, *J* = 6.4 Hz, 3H). LC-MS: MS (ES^+): RT = 1.289 min, m/z = 848.6 $[M+H]^+$, LC-MS Method: 10.

EXAMPLE 29 – Synthesis of (S)-N-(4-(2-(4-(2-(4-bromophenyl)-6-hydroxybenzo[b] thiophene-3-carbonyl)phenoxy)ethoxy)butyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide (I-28)



I-28

[0613] Step 1: Preparation of [2-(4-bromophenyl)-6-[tert-butyl(dimethyl)silyl]oxy-benzothiophen-3-yl]-(4-fluorophenyl)methanone. To a solution of [2-(4-bromophenyl)-6-hydroxy-benzothiophen-3-yl]-(4-fluorophenyl)methanone (350 mg, 819 μmol, 1.0 *equiv*) in DCM (5 mL) was added TBSCl (185.19 mg, 1.23 mmol, 151 μL, 1.5 *equiv*) and IMIDAZOLE (66.92 mg, 983 μmol, 1.2 *equiv*). The mixture was stirred at 25 °C for 4h. The reaction mixture was partitioned between H_2O 50 mL and EtOAc (50 mL x 3). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 5/1) to afford [2-(4-bromophenyl)-6-[tert-butyl(dimethyl)silyl]oxy-benzothio phen-3-yl]-(4-fluorophenyl)methanone (300 mg, 67% yield) as a yellow solid.

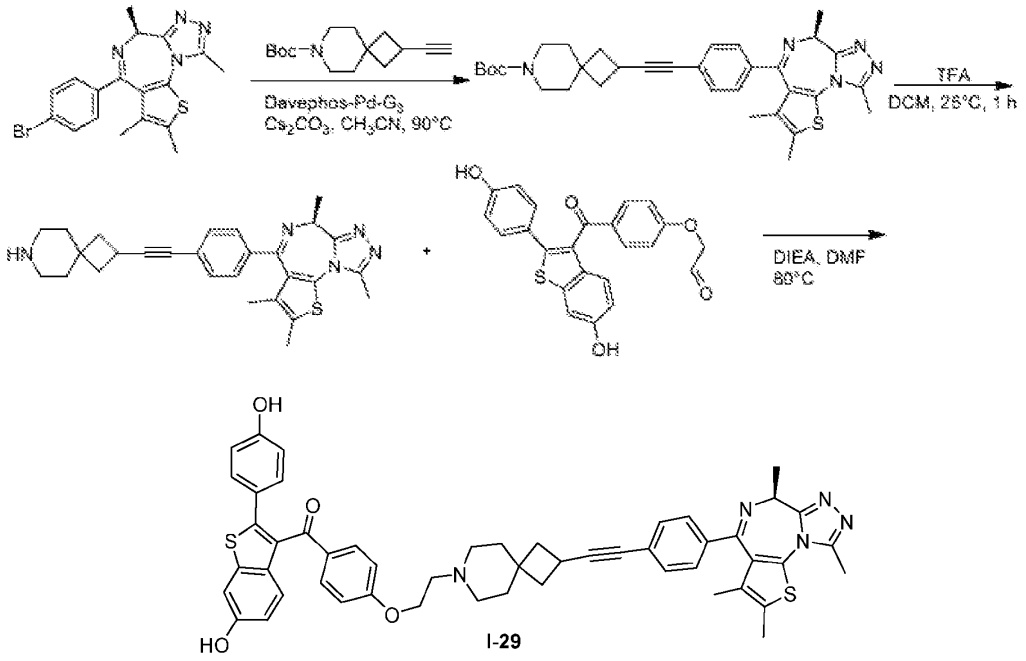
[0614] Step 2: Preparation of tert-butyl N-[4-[2-[4-[2-(4-bromophenyl)-6-hydroxy-benzothiophene-3-carbonyl]phenoxy]ethoxy]butyl]carbamate. To a solution of tert-butyl N-[4-(2-hydroxyethoxy)butyl]carbamate (193.86 mg, 831 μmol, 1.5 *equiv*) in THF (8 mL) was added NaH (44.32 mg, 1.11 mmol, 60% purity, 2 *equiv*) at 0°C under N_2. The mixture was stirred at 0°C for 1 h. Then added [2-(4-bromophenyl)-6-[tert-butyl(dimethyl)silyl]oxy-benzo thiophen-3-yl]-(4-fluorophenyl)methanone (300 mg, 554 μmol, 1 *equiv*) to the mixture at 0°C under N_2. The mixture was stirred at 60°C for 11 h. The reaction mixture was quenched by addition H_2O (2 mL) at 25 °C, and then diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1) to afford tert-butyl N-[4-[2-[4-[2-(4-bromo phenyl)-6-hydroxy-benzothiophene-3-carbonyl]phenoxy]ethoxy]butyl] carbamate (210 mg, 59% yield) as a white solid.

[0615] Step 3: Preparation of [4-[2-(4-aminobutoxy)ethoxy]phenyl]-[2-(4-bromophenyl)-6-hydroxy-benzothiophen-3-yl]methanone. To a solution of tert-butyl N-[4-[2-[4-[2-(4-bromophenyl)-6-hydroxy-benzothiophene-3-carbonyl]phenoxy]ethoxy] butyl] carbamate (190 mg, 297 μmol, 1 *equiv*) in DCM (6 mL) was added HCl/dioxane (4 M, 2 mL, 27 *equiv*). The mixture was stirred at 25 °C for 1h. The reaction mixture was quenched by addition of $NaHCO_3$ (aq) (15 mL) at 25 °C, and then diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue to afford [4-[2-(4-aminobutoxy) ethoxy] phenyl]-[2-(4-bromophenyl)-6-hydroxy-benzothiophen-3-yl]methanone (150 mg, 93% yield) as a yellow oil.

[0616] Step 4: Preparation of (S)-N-(4-(2-(4-(2-(4-bromophenyl)-6-hydroxybenzo [b]thiophene-3-carbonyl)phenoxy)ethoxy)butyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide. To a solution of [4-[2-(4-aminobutoxy)ethoxy]phenyl]-[2-(4-bromophenyl)-6-hydroxy-benzothiophen-3-yl]methanone (150 mg, 278 μmol, 1 *equiv*) and (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (111.26 mg, 278 μmol, 1 *equiv*) in DCM (5 mL) was added DIEA (143.48 mg, 1.11 mmol, 193 μL, 4.0 *equiv*), EDCI (159.61 mg, 832 μmol, 3.0 *equiv*) and HOBt (56.25 mg, 416 μmol, 1.5 *equiv*). The mixture was stirred at 25 °C for 1h. The reaction mixture was partitioned between H_2O 50 mL and EtOAc (50 mL x 3). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give

a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1). The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 62%-92% B over 9 min) to afford (S)-N-(4-(2-(4-(2-(4-bromophenyl)-6-hydroxybenzo[b]thiophene-3-carbonyl)phenoxy) ethoxy)butyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-6-yl)acetamide (**I-28**, 66.3 mg, 25% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 - 9.69 (m, 1H), 8.17 (t, *J* = 5.6 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.54 - 7.49 (m, 2H), 7.47 - 7.43 (m, 2H), 7.42 - 7.37 (m, 3H), 7.32 - 7.26 (m, 3H), 6.93 (d, J = 9.2 Hz, 2H), 6.88 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.49 (dd, *J* = 6.0, 8.4 Hz, 1H), 4.16 - 4.05 (m, 2H), 3.71 - 3.62 (m, 2H), 3.44 (s, 2H), 3.27 - 3.17 (m, 2H), 3.15 - 3.04 (m, 2H), 2.58 (s, 3H), 2.38 (s, 3H), 1.59 (s, 3H), 1.55 - 1.43 (m, 4H). LC-MS: MS (ES$^+$): RT = 1.494 min, m/z = 924.4 [M +H$^+$]. LCMS Method: 50.

EXAMPLE 30 – Synthesis of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-((4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)ethynyl)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl)methanone (I-29)



[0617] Step 1: Preparation of tert-butyl (S)-2-((4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)ethynyl)-7-azaspiro[3.5]nonane-7-carboxylate. To a solution of (S)-4-(4-bromophenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-

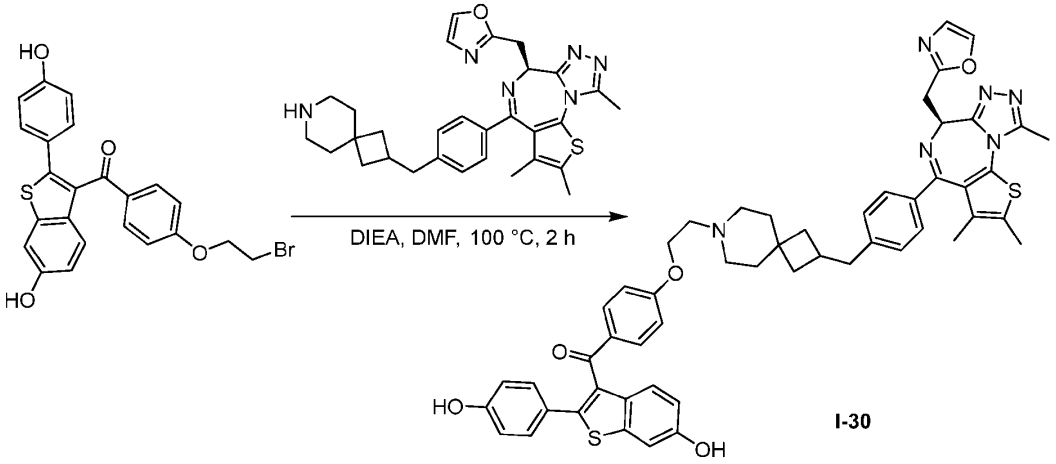
f][1,2,4]triazolo[4,3-a][1,4]diazepine (500 mg, 1.25 mmol, 1 *equiv*) and tert-butyl 2-ethynyl-7-azaspiro[3.5]nonane-7-carboxylate (777 mg, 3.11 mmol, 2.5 *equiv*) in MeCN (15 mL) was added DavePhos Pd G_3 (95 mg, 125 μmol, 0.1 *equiv*) and Cs_2CO_3 (812 mg, 2.49 mmol, 2.0 *equiv*) under N_2. The mixture was stirred at 90 °C for 2h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1) to afford tert-butyl (S)-2-((4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)ethynyl)-7-azaspiro[3.5]nonane-7-carboxylate (600 mg, 84% yield) as a white solid.

[0618] Step 2: Preparation of (S)-4-(4-((7-azaspiro[3.5]nonan-2-yl)ethynyl)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine. To a solution of tert-butyl (S)-2-((4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)ethynyl)-7-azaspiro[3.5]nonane-7-carboxylate (300 mg, 526 μmol, 1 *equiv*) in DCM (3 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL, 26 *equiv*). The mixture was stirred at 25 °C for 1h. The reaction mixture was quenched by addition $NaHCO_3$ (15 mL) at 25 °C, and then diluted with H_2O (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (S)-4-(4-((7-azaspiro[3.5]nonan-2-yl)ethynyl)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]tri azolo [4,3-a][1,4]diazepine (240 mg, 97% yield) as a yellow oil.

[0619] Step 3: Preparation of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-((4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)ethynyl)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl)methanone. To a solution of [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (60 mg, 127.84 μmol, 1 *equiv*) and (S)-4-(4-((7-azaspiro[3.5]nonan-2-yl)ethynyl)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (60.04 mg, 127 μmol, 1 *equiv*) in DMF (1.5 mL) was added DIEA (49.6 mg, 383 μmol, 66.80 μL, 3.0 *equiv*). The mixture was stirred at 80 °C for 12h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic phases dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 30%-60% B over 9 min) to afford (S)-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b] thiophen-3-yl)(4-(2-(2-((4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)ethynyl)-7-

azaspiro[3.5]nonan-7-yl)ethoxy)phenyl)methanone (**I-29**, 33.6 mg, 29% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 - 9.62 (m, 2H), 8.14 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.40 (s, 3H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.84 (*J* = 2.0, 8.8 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 2H), 4.22 (q, *J* = 6.8 Hz, 1H), 4.09 (t, *J* = 5.6 Hz, 2H), 2.59 (s, 3H), 2.54 (s, 4H), 2.39 (s, 7H), 2.17 (t, *J* = 10.0 Hz, 2H), 1.93 - 1.79 (m, 5H), 1.67 - 1.51 (m, 7H). LC-MS: MS (ES$^+$): RT = 1.960 min, m/z = 858.3 [M +H$^+$]. LCMS Method: 25.

EXAMPLE 31 – Synthesis of (S)-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzyl)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl)methanone (I-30)

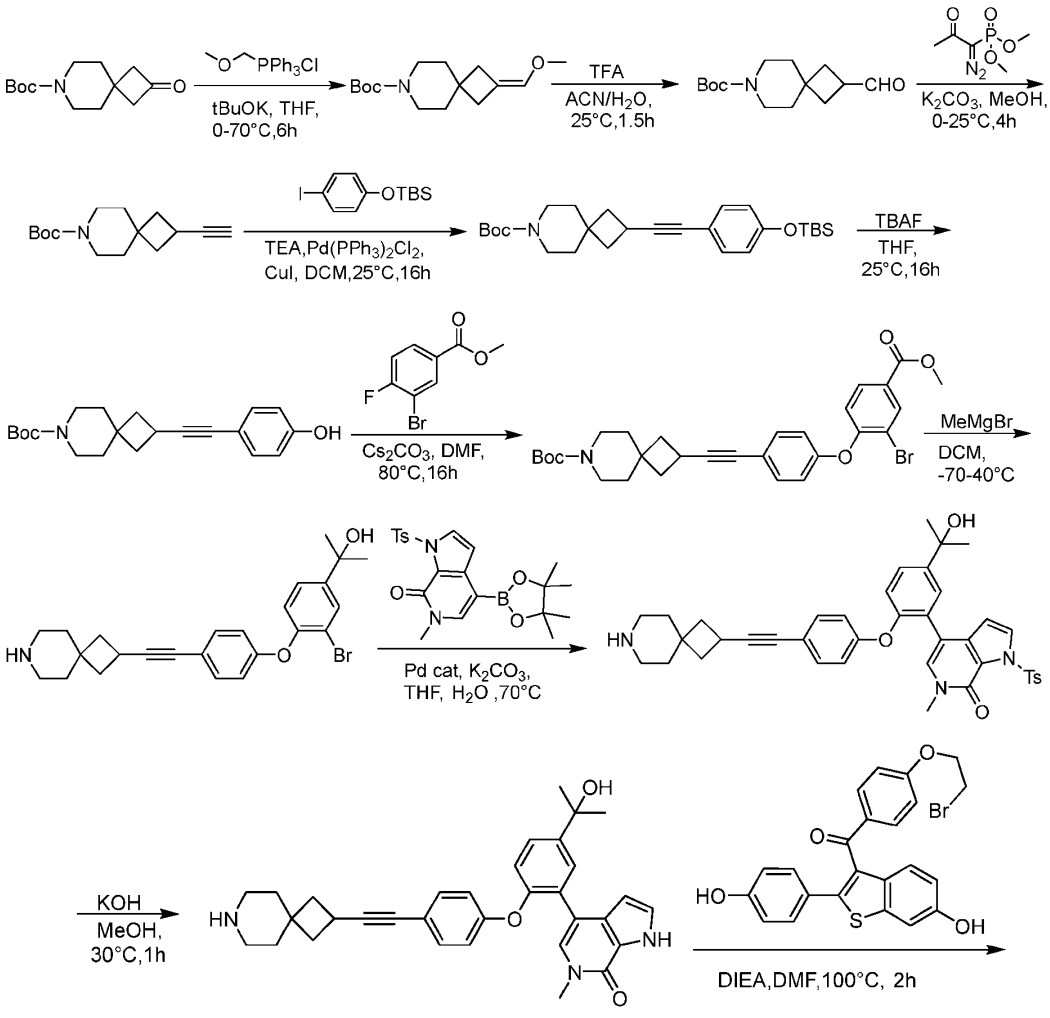


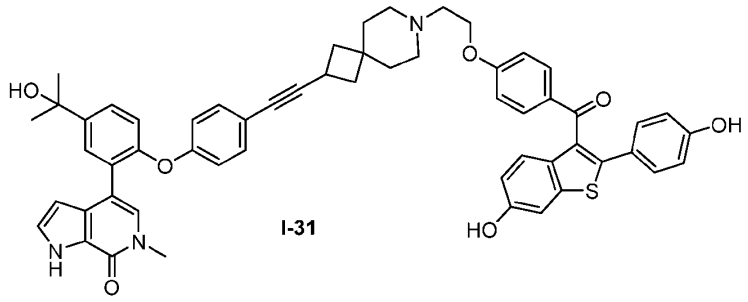
I-30

[0620] To a solution of [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl) benzothiophen-3-yl]methanone (40 mg, 85.22 μmol, 1 *equiv*) in DMF (1 mL) was added (S)-2-((4-(4-((7-azaspiro[3.5]nonan-2-yl)methyl)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4] triazolo [4,3-a][1,4]diazepin-6-yl)methyl)oxazole (44.89 mg, 85 μmol, 1 *equiv*), DIEA (27.54 mg, 213 μmol, 37 μL, 2.5 *equiv*). The mixture was stirred at 100 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water(FA)-ACN]; gradient: 23%-53% B over 10 min) to afford (S)-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophen-3-yl)(4-(2-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzyl)-7-azaspiro[3.5]nonan-7-yl)ethoxy)phenyl) methanone (**I-30**, 46.4 mg, 59% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (d, *J* = 18.4 Hz, 2H), 8.14 (s, 1H), 8.04 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 2.4 Hz, 1H),

7.27 - 7.22 (m, 3H), 7.19 - 7.14 (m, 4H), 7.13 (s, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.85 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.67 (d, *J* = 8.8 Hz, 2H), 4.65 (t, *J* = 7.6 Hz, 1H), 4.09 (d, *J* = 5.2 Hz, 2H), 3.95 - 3.75 (m, 2H), 2.76 - 2.64 (m, 4H), 2.60 (s, 3H), 2.41 (s, 6H), 2.36 - 2.30 (m, 2H), 1.77 (t, *J* = 9.6 Hz, 2H), 1.60 (s, 3H), 1.56 - 1.35 (m, 6H). LC-MS: MS (ES^+): RT = 1.978 min, m/z = 915.4 [M $+H^+$], LC-MS Method: 25.

EXAMPLE 32 – Synthesis of 4-(2-(4-((7-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo [b]thiophene-3-carbonyl)phenoxy)ethyl)-7-azaspiro[3.5]nonan-2-yl)ethynyl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (I-31)





I-31

[0621] Step 1: Preparation of tert-butyl 2-(methoxymethylene)-7-azaspiro [3.5] nonane-7-carboxylate. A mixture of methoxymethyl(triphenyl)phosphonium chloride (35.81 g, 105 mmol, 2 *equiv*) in THF (400 ml) added *t*BuOK (9.38 g, 84 mmol, 1.6 *equiv*) in THF (70 ml) at 0 °C under N_2 atmosphere , and then the mixture was stirred at 20 °C for 3 h under N_2 atmosphere. Add tert-butyl 2-oxo-7-azaspiro [3.5] nonane-7-carboxylate (12.5 g, 52 mmol, 1 *equiv*) in THF (30 ml) to the reaction mixture, then the reaction was stirred at 70 °C for 3 hours. The reaction mixture was quenched by addition H_2O (100 mL), and then extracted with EA (150 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 10/1). Compound tert-butyl 2-(methoxymethylene)-7-azaspiro [3.5] nonane-7-carboxylate (9.18 g, 65% yield) was obtained as a colorless oil.

[0622] Step 2: Preparation of tert-butyl 2-formyl-7-azaspiro [3.5] nonane-7-carboxylate. To a solution of tert-butyl 2-(methoxymethylene)-7-azaspiro [3.5] nonane-7-carboxylate (21.9 g, 81.9 mmol, 1 *equiv*) in ACN (520 ml) and H_2O (130 ml) was added TFA (7.47 g, 65.5 mmol, 4.87 ml, 0.8 *equiv*). The mixture was stirred at 25 °C for 1.5 h. TLC (PE : EA = 3 : 1) indicated Reactant 1 was consumed completely and one new spotformed. The mixture was adjusted to pH 9-10 with aqueous sodium bicarbonate solution, and then diluted extracted with EA (200 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 2-formyl-7-azaspiro [3.5] nonane-7-carboxylate (20.4 g, 98% yield) as a yellow oil which was used in the next step without further purification.

[0623] Step 3: Preparation of tert-butyl 2-ethynyl-7-azaspiro [3.5] nonane-7-carboxylate. To a stirred mixture of tert-butyl 2-formyl-7-azaspiro[3.5]nonane-7-carboxylate (10 g, 39.5 mmol, 1 *equiv*) and K_2CO_3 (10.91 g, 78.9 mmol, 2 *equiv*) in MeOH (300 ml) was added 1-diazo-1-dimethoxyphosphoryl-propan-2-one (11.37 g, 59.2 mmol, 1.5 *equiv*) in portions at 0 °C. The

reaction mixture was stirred for 4 hours at 25 °C. TLC (PE:EA = 5:1) indicated Reactant 1 was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure remove MeOH, and then diluted extracted with H_2O (80 mL) and EA (80 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether / Ethyl acetate = 1/0, 20/1) to afford tert-butyl 2-ethynyl-7-azaspiro [3.5] nonane-7-carboxylate (6.5 g, 66% yield) was obtained as a yellow oil.

[0624] Step 4: Preparation of tert-butyl 2-[2-[4-[tert-butyl (dimethyl) silyl] oxyphenyl] ethynyl]-7-azaspiro[3.5]nonane-7-carboxylate. To tert-butyl-(4-iodophenoxy)-dimethyl-silane (4.95 g, 14.81 mmol, 1 *equiv*) in DCM (60 ml) was added TEA (4.50 g, 44.42 mmol, 6.18 ml, 3 *equiv*) and $Pd(PPh_3)_2Cl_2$ (1.04 g, 1.48 mmol, 0.1 *equiv*) and CuI (423.02 mg, 2.22 mmol, 0.15 *equiv*), then, tert-butyl 2-ethynyl-7-azaspiro [3.5] nonane-7-carboxylate (4.8 g, 19.25 mmol, 1.3 *equiv*) in DCM (20 ml) was dropwise. The mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched by addition H_2O (30 mL), and then extracted with DCM (50 ml x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether / Ethyl acetate = 1/0 to 20/1) to afford tert-butyl 2-[2-[4-[tert-butyl (dimethyl) silyl] oxyphenyl]ethynyl]-7-azaspiro[3.5]nonane-7-carboxylate (6.27 g, 92% yield) as a yellow oil.

[0625] Step 5: Preparation of tert-butyl 2-[2-(4-hydroxyphenyl) ethynyl]-7-azaspiro [3.5] nonane-7-carboxylate. To a solution of tert-butyl 2-[2-[4-[tert-butyl (dimethyl) silyl] oxyphenyl]ethynyl]-7-azaspiro[3.5]nonane-7-carboxylate (6.27 g, 13.76 mmol, 1 *equiv*) in THF (60 ml) was added TBAF (1 M, 20.64 ml, 1.5 *equiv*). The mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched by addition H_2O (20 mL) and extracted with EtOAc (30ml x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 5/1) to afford tert-butyl 2-[2-(4-hydroxyphenyl) ethynyl]-7-azaspiro [3.5] nonane-7-carboxylate (4.38 g, 93% yield) as a colorless oil.

[0626] Step 6: Preparation of Compound tert-butyl 2-[2-[4-(2-bromo-4-methoxy carbonyl-phenoxy) phenyl] ethynyl]-7-azaspiro[3.5]nonane-7-carboxylate. To a solution of tert-butyl 2-[2-(4-hydroxyphenyl) ethynyl]-7-azaspiro [3.5] nonane-7-carboxylate (4.38 g, 12.83

mmol, 1 *equiv*) in DMF (100 ml) was added Cs_2CO_3 (12.54 g, 38.48 mmol, 3 *equiv*) and methyl 3-bromo-4-fluoro-benzoate (3.89 g, 16.7 mmol, 1.3 *equiv*). The mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched by addition H_2O (50 mL), and extracted with EA (100 ml x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether / Ethyl acetate = 1/0 to 5/1). Compound tert-butyl 2-[2-[4-(2-bromo-4-methoxycarbonyl-phenoxy) phenyl] ethynyl]-7-azaspiro[3.5]nonane-7-carboxylate (6.52 g, 91% yield) was obtained as a white solid.

[0627] Step 7: Preparation of 2-[4-[4-[2-(7-azaspiro [3.5] nonan-2-yl)ethynyl] phenoxy]-3-bromo-phenyl]propan-2-ol. A mixture of tert-butyl 2-[2-[4-(2-bromo-4-methoxycarbonyl-phenoxy)phenyl]ethynyl]-7-azaspiro[3.5]nonane-7-carboxylate (3 g, 5.41 mmol, 1 *equiv*) in DCM (100 ml) was degassed and purged with N_2 three times, and then the mixture was added MeMgBr (3 M, 9.02 ml, 5 *equiv*) at -70 °C dropwise under N_2 atmosphere. The resulting mixture was stirred at 40 °C for 16 hours. The reaction mixture was quenched by adding to NH_4Cl (aq) (200 mL) at 0-5 °C under N_2, and then extracted with DCM/MeOH (10:1, 100 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-[4-[4-[2-(7-azaspiro [3.5] nonan-2-yl)ethynyl]phenoxy]-3-bromo-phenyl]propan-2-ol (2.1 g, 85% yield) as a yellow gum.

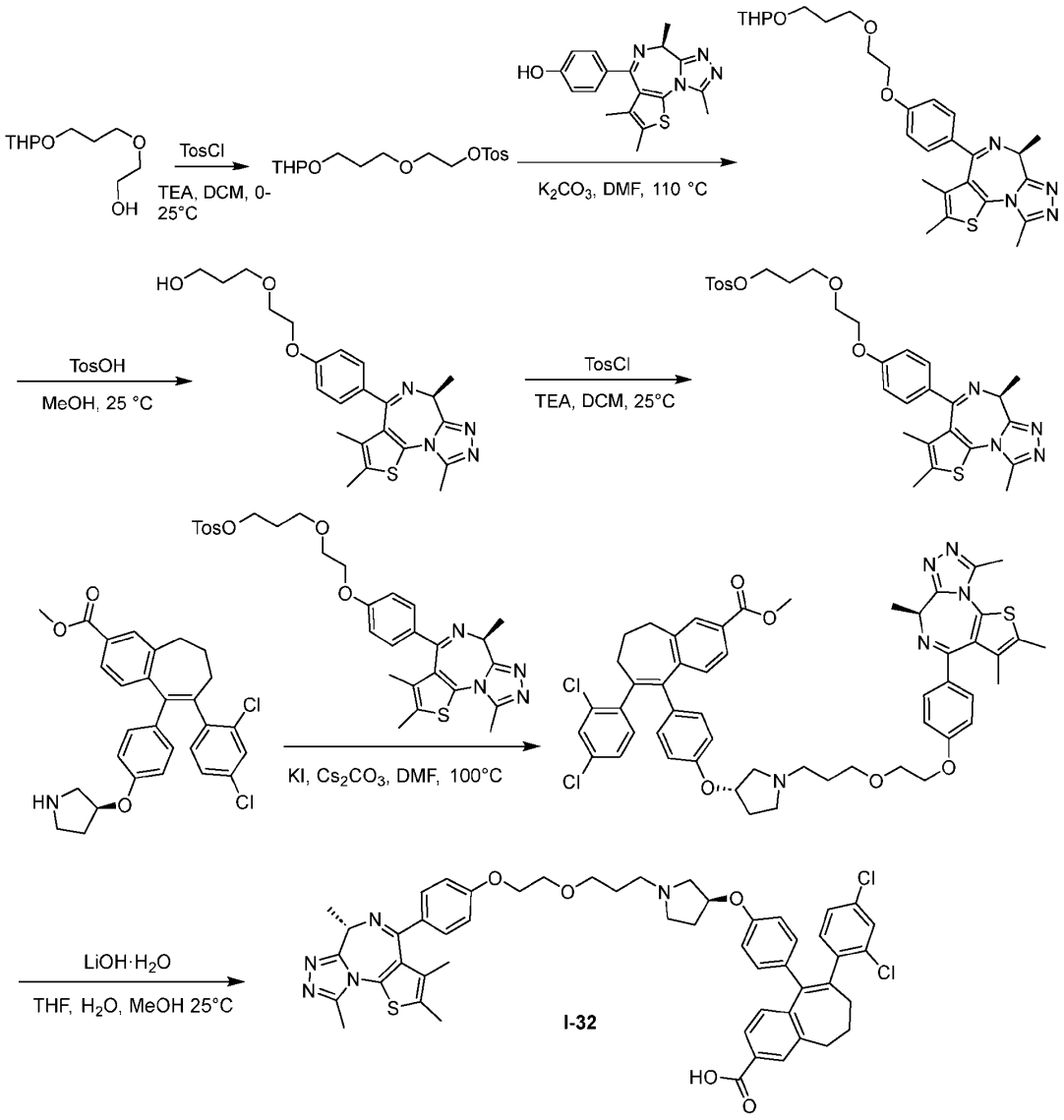
[0628] Step 8: Preparation of 4-[2-[4-[2-(7-azaspiro[3.5]nonan-2-yl)ethynyl]phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3pyridinedin-7-one. A mixture of 2-[4-[4-[2-(7-azaspiro[3.5]nonan-2-yl)ethynyl]phenoxy]-3-bromo-phenyl]propan-2-ol (2.1 g, 4.62 mmol, 1 *equiv*), 6-methyl-1-(p-tolylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3pyridinedin-7-one (1.98 g, 4.62 mmol, 1 *equiv*), K_2CO_3 (1.41 g, 10.17 mmol, 2.2 *equiv*), [2-(2-aminophenyl)phenyl]palladium[bis(1-adamantyl)-butyl-phosphane]methanesulfonate (336.57 mg, 462 μmol, 0.1 *equiv*) in THF (50 ml) and H_2O (5 ml) was degassed and purged with N_2 three times, and then the mixture was stirred at 70 °C for 16 hr under N_2 atmosphere. The mixture was concentrated to give crude 4-[2-[4-[2-(7-azaspiro[3.5]nonan-2-yl)ethynyl]phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3pyridinedin-7-one (2.7 g, 4.00 mmol, 86% yield) as a yellow oil and was used without further purification.

[0629] Step 9: Preparation of 4-[2-[4-[2-(7-azaspiro [3.5] nonan-2-yl)ethynyl] phenoxy]-5-(1-hydroxy-1-methyl-ethyl) phenyl]-6-methyl-1H-pyrrolo[2,3pyridinedin-7-one. To a

solution of 4-[2-[4-[2-(7-azaspiro[3.5]nonan-2-yl)ethynyl]phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3pyridinedin-7-one (2.7 g, 4.00 mmol, 1 *equiv*) in MeOH (120 ml) was added KOH (4.93 g, 87.89 mmol, 22 *equiv*). The mixture was stirred at 30 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 (250 x 70mm x 10 um); mobile phase: [water(FIACN]; gradient: 20%-50% B over 20 min) to give 4-[2-[4-[2-(7-azaspiro [3.5] nonan-2-yl) ethynyl] phenoxy]-5-(1-hydroxy-1-methyl-ethyl) phenyl]-6-methyl-1H-pyrrolo[pyridineyridin-7-one (1 g, 47% yield) as a white solid.

[0630] Step 10: Preparation of 4-(2-(4-((7-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)-7-azaspiro[3.5]nonan-2-yl)ethynyl) phenoxy) -5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one. To a solution of [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxy-phenyl)benzothiophen-3-yl]methanone (40 mg, 85.22 μmol, 1 *equiv*) and 4-[2-[4-[2-(7-azaspiro[3.5]nonan-2-yl)ethynyl]phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridin-7-one (44.46 mg, 85.2 μmol, 1 *equiv*) in DMF (1 ml) was added DIEA (39.98 mg, 309 μmol, 54 μL, 3.63 *equiv*). The mixture was stirred at 100 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm x 5um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 48-78% B over 9 min) to provide 4-(2-(4-((7-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)-7-azaspiro[3.5] nonan-2-yl)ethynyl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (**I-31**, 19 mg, 24% yield) as a brown gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.03 - 11.94 (m, 1H), 9.85 - 9.62 (m, 2H), 7.67 - 7.59 (m, 3H), 7.47 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.27 - 7.14 (m, 7H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.94 - 6.88 (m, 2H), 6.86 - 6.81 (m, 1H), 6.77 - 6.71 (m, 2H), 6.70 - 6.64 (m, 2H), 6.22 - 6.16 (m, 1H), 5.08 (s, 1H), 4.06 (br t, *J* = 6.0 Hz, 2H), 3.51 - 3.46 (m, 3H), 3.29 - 3.27 (m, 3H), 3.19 - 3.13 (m, 1H), 2.60 - 2.58 (m, 1H), 2.31 - 2.23 (m, 2H), 2.17 - 2.08 (m, 2H), 1.83 - 1.74 (m, 2H), 1.57 - 1.50 (m, 4H), 1.49 - 1.44 (m, 6H). LC-MS: MS (ES^+): RT = 2.057 min, m/z = 910.6 [M +H^+], LC-MS Method: 25.

EXAMPLE 33 – Synthesis of 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) propyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (I-32)



[0631] Step 1: Preparation of 2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)ethyl 4-methylbenzenesulfonate. To a solution of 2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy) ethan-1-ol (2.70 g, 13.22 mmol, 1.00 *equiv*) in dichloromethane (30 mL) was added triethylamine (4.01 g, 39.65 mmol, 3.00 *equiv*). Then was added *p*-toluenesulfonyl chloride (2.52 g, 13.22 mmol,

1.00 *equiv*) at 0 °C, and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=1/0 to 1/1) to afford 2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)ethyl 4-methylbenzenesulfonate (500 mg, 10% yield) as a yellow oil.

[0632] Step 2: Preparation of (6S)-2,3,6,9-tetramethyl-4-(4-(2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)ethoxy)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4] diazepine. A mixture of 2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)ethyl 4-methylbenzenesulfonate (444 mg, 1.24 mmol, 1.50 *equiv*), (*S*)-4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenol (280 mg, 0.83 mmol, 1.00 *equiv*), potassium carbonate (343 mg, 2.48 mmol, 3.00 *equiv*) in *N,N*-dimethylformamide (5 mL) was stirred at 110 °C for 1 h. The reaction mixture was quenched by the addition of water (20 mL), and then extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (dichloromethane/methanol = 10:1, R_f = 0.45) to afford (6*S*)-2,3,6,9-tetramethyl-4-(4-(2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)ethoxy)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (210 mg, 48% yield) as a yellow solid.

[0633] Step 3: Preparation of (S)-3-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)propan-1-ol. To a solution of (6*S*)-2,3,6,9-tetramethyl-4-(4-(2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)ethoxy)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (210 mg, 0.40 mmol, 1.00 *equiv*) in methanol (2 mL) was added tosyl chloride (6 mg, 0.04 mmol, 0.10 *equiv*) and the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (dichloromethane/methanol = 10:1) to afford (*S*)-3-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)propan-1-ol (170 mg, 96% yield) as a yellow solid.

[0634] Step 4: Preparation of (*S*)-3-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)propyl 4-methylbenzene sulfonate. To a solution of (*S*)-3-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)propan-1-ol (160 mg, 0.36 mmol, 1.00 *equiv*), *p*-toluenesulfonyl chloride (138 mg, 0.73 mmol, 2.00 *equiv*) in dichloromethane (2 mL) was added triethylamine (147 mg, 1.45 mmol, 4.00 *equiv*) and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue.

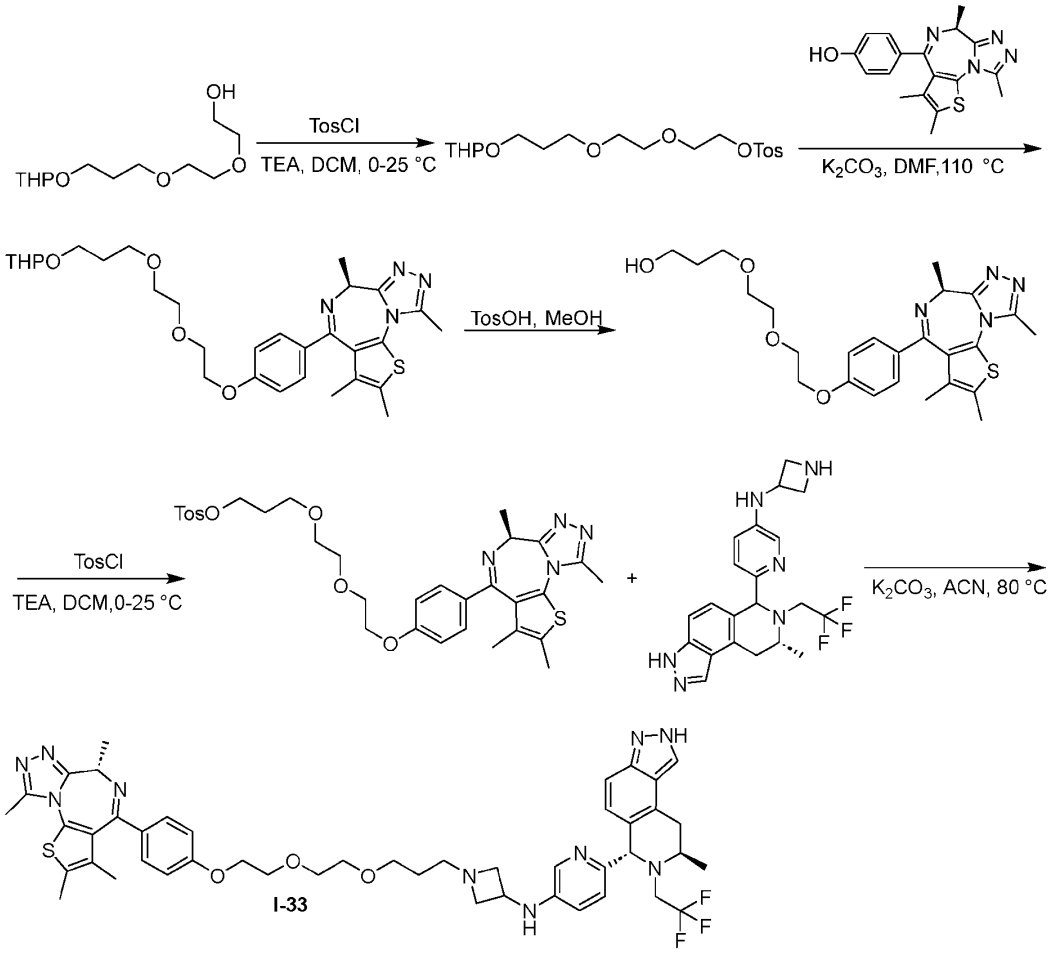
The residue was purified by prep-TLC (dichloromethane/methanol = 10:1) to afford (*S*)-3-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) propyl 4-methylbenzenesulfonate (145 mg, 67% yield) as a yellow oil.

[0635] Step 5: Preparation of methyl 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy) ethoxy) propyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate. A mixture of methyl (S)-8-(2,4-dichlorophenyl)-9-(4-(pyrrolidin-3-yloxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (51 mg, 0.10 mmol, 1.20 *equiv*), (S)-3-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)propyl 4-methylbenzenesulfonate (50 mg, 0.08 mmol, 1.00 *equiv*), potassium iodide (13 mg, 0.8 mmol, 1.00 *equiv*), cesium carbonate (82 mg, 0.25 mmol, 3.00 *equiv*) in N,N-dimethylformamide (1 mL) was stirred at 100 °C for 1 h. The reaction mixture was quenched by water (10 mL), and then extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 35%-65% B over 10 min] to afford methyl 8-(2,4-dichloro-phenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4] diazepin-4-yl)phenoxy)ethoxy)propyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7] annulene-3-carboxylate (50 mg, 63% yield) as a yellow oil.

[0636] Step 6: Preparation of 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) propyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid. To a solution of methyl 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy) ethoxy)propyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (50 mg, 0.05 mmol, 1.00 *equiv*) in tetrahydrofuran (0.2 mL), methanol (0.2 mL) and water (0.2 mL) was added lithium hydroxide (6 mg, 0.16 mmol, 3.00 *equiv*) and the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by aqueous hydrochloric acid (1 M, 5 mL), and then filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water(FA)-ACN]; gradient: 28%-58% B over 10 min] to afford 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenoxy) ethoxy)propyl)pyrrolidin-3-

yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (**I-32**, 16.82 mg, 32% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.39 - 7.34 (m, 1H), 7.09 - 6.97 (m, 2H), 6.92 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 6.57 - 6.51 (m, 2H), 4.93 - 4.74 (m, 1H), 4.21 - 4.04 (m, 3H), 3.78 (t, J = 4.4 Hz, 2H), 3.62 (t, J = 5.6 Hz, 3H), 3.44 - 3.21 (m, 1H), 3.09 - 2.85 (m, 6H), 2.68 (s, 3H), 2.41 (s, 3H), 2.32 - 2.24 (m, 4H), 2.09 (s, 3H), 1.99 - 1.94 (m, 4H), 1.71 (s, 3H). LCMS: MS (ES^+): RT = 2.014 min, m/z = 916.6 $[M+H]^+$; LC-MS Method: 25.

<u>EXAMPLE 34</u> – Synthesis of 6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)-N-(1-(3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)propyl) azetidin-3-yl)pyridin-3-amine (I-33)



[0637] Step 1: Preparation of 2-[2-(3-tetrahydropyran-2-yloxypropoxy)ethoxy]ethyl 4-methylbenzenesulfonate. To a solution of 2-(2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy) ethoxy) ethan-1-ol (1.00 g, 4.03 mmol, 1.00 *equiv*) in dichloromethane (10 mL) was added triethylamine (1.22 g, 12.08 mmol, 3.00 *equiv*) and *p*-toluenesulfonyl chloride (1.54 g, 8.05 mmol, 2.00 *equiv*) at 0 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10:1 to 1:1) to afford 2-[2-(3-tetra hydropyran-2-yloxypropoxy)ethoxy]ethyl 4-methylbenzenesulfonate (1.50 g, 92% yield) as a yellow oil.

[0638] Step 2: Preparation of (6S)-2,3,6,9-tetramethyl-4-(4-(2-(2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)ethoxy)ethoxy)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine. To a solution of 2-[2-(3-tetrahydropyran-2-yloxypropoxy)ethoxy]ethyl 4-methylbenzenesulfonate (309 mg, 0.76 mmol, 2.00 *equiv*) and (S)-4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenol (130 mg, 0.38 mmol, 1.00 *equiv*) in *N,N*-dimethylformamide (5 mL) was added potassium carbonate (159 mg, 1.15 mmol, 3.00 *equiv*). The mixture was stirred at 110 °C for 1 h. Ethyl acetate (20 mL) and water (30 mL) were added and the organic layer collected. The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the residue. The residue was purified by silica gel column chromatography (DCM/methanol = 100:1 to 10:1) to afford (6S)-2,3,6,9-tetramethyl-4-(4-(2-(2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy) ethoxy)ethoxy)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (216 mg, 98 % yield) as a yellow oil.

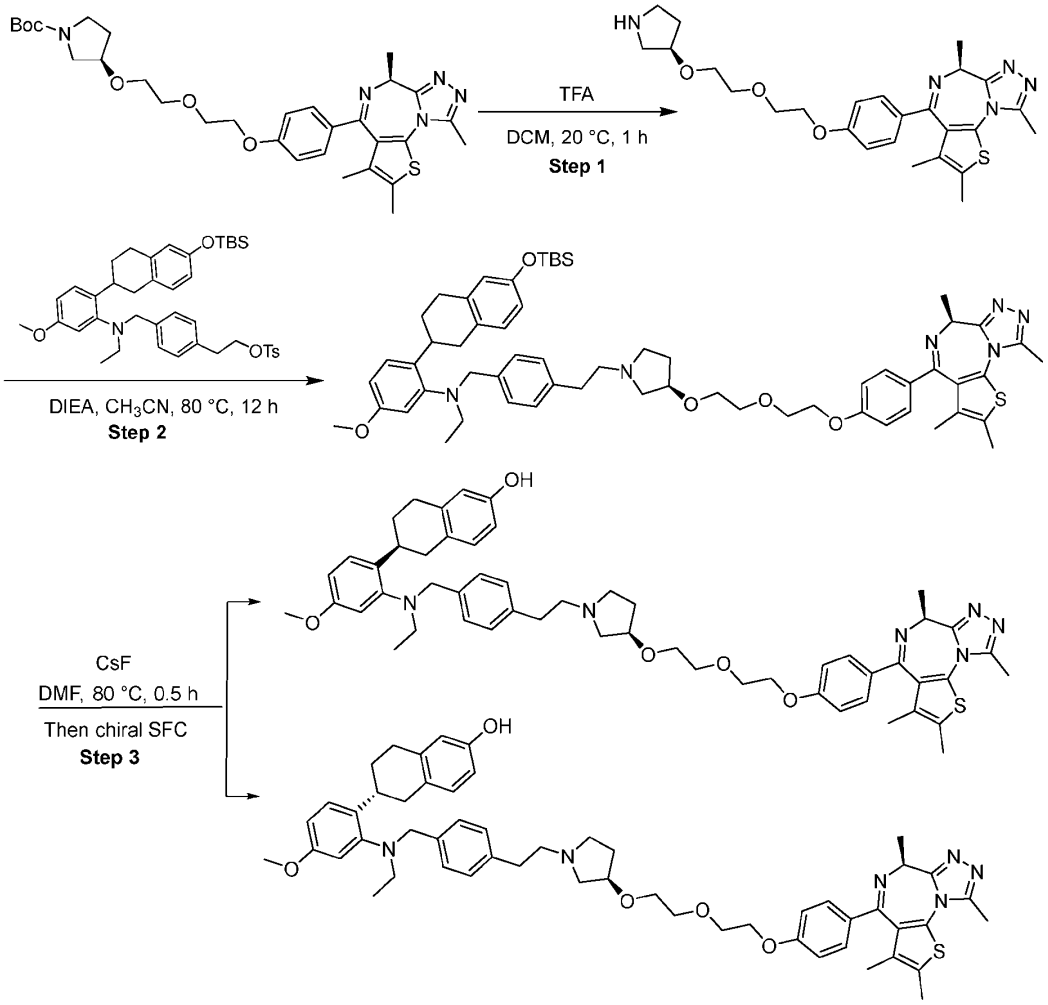
[0639] Step 3: Preparation of (S)-3-(2-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)propan-1-ol. To a solution of (6S)-2,3,6,9-tetramethyl-4-(4-(2-(2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy) ethoxy)ethoxy)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (216 mg, 0.37 mmol, 1.00 *equiv*) in methanol (2 mL) was added *p*-toluenesulfonic acid (6 mg, 0.03 mmol, 0.10 *equiv*) and the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-TLC (DCM:methanol = 10:1) to afford (S)-3-(2-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4] diazepin-4-yl)phenoxy)ethoxy)ethoxy)propan-1-ol (140 mg, 76% yield) as a yellow oil.

[0640] Step 4: Preparation of (S)-3-(2-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)propyl 4-methyl benzenesulfonate. To a solution of (S)-3-(2-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)propan-1-ol (140 mg, 0.28 mmol, 1.00 *equiv*) in dichloromethane (2 mL) was added triethylamine (87 mg, 0.86 mmol, 3.00 *equiv*). Then *p*-toluenesulfonyl chloride (82 mg, 0.43 mmol, 1.50 *equiv*) was added at 0 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-TLC (DCM / methanol = 10:1) to afford (S)-3-(2-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)propyl 4-methylbenzenesulfonate (130 mg, 70 % yield) as a yellow oil.

[0641] Step 5: Preparation of 6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo[4,3-f]isoquinolin-6-yl)-N-(1-(3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy) propyl)azetidin-3-yl)pyridin-3-amine. To a solution of (S)-3-(2-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)propyl 4-methyl-benzenesulfonate (118 mg, 0.18 mmol, 1.40 *equiv*) and N-(azetidin-3-yl)-6-[(6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-3,6,8,9-tetrahydropyrazolo[4,3-f]isoquinolin-6-yl]pyridin-3-amine (70 mg, 0.13 mmol, 1.00 *equiv*, trifluoroacetate) in acetonitrile (2 mL) was added potassium carbonate (54 mg, 0.39 mmol, 3.00 *equiv*) and potassium iodide (43 mg, 0.26 mmol, 2.00 *equiv*). The mixture was stirred at 80 °C for 1 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (dichloromethane : methanol = 10:1). The obtained residue was further purified by preparative SFC (Column: Chiralcel OD-3 50 x 4.6 mm x 3 μm; Mobile phase: Phase A for CO_2, and Phase B for IPA/acetonitrile (0.05% DEA); Gradient elution: 40% IPA+ acetonitrile (0.05% DEA) in CO_2). The obtained residue was further purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25mm x 10um; mobile phase: [water (formic acid)-acetonitrile]; gradient: 10%-40% B over 10 min) to give 6-((6S,8R)-8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-2H-pyrazolo [4,3-f]isoquinolin-6-yl)-N-(1-(3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) ethoxy)propyl)azetidin-3-yl)pyridin-3-amine (**I-33**, 30 mg, 25% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.04 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 1H), 7.01 - 6.89 (m, 3H), 6.86 - 6.74 (m, 2H), 6.21 (d, J = 6.8 Hz, 1H), 4.93 (s, 1H), 4.20 - 4.07 (m, 3H), 3.93 - 3.87 (m, 1H), 3.76 - 3.70 (m,

2H), 3.64 - 3.51 (m, 6H), 3.50 - 3.43 (m, 6H), 3.13 - 2.95 (m, 3H), 2.87 - 2.79 (m, 1H), 2.75 - 2.70 (m, 1H), 2.58 (s, 3H), 2.38 (s, 3H), 1.85 (d, J = 6.8 Hz, 3H), 1.64 (s, 3H), 1.52 - 1.42 (m, 2H), 1.08 (d, J = 6.8 Hz, 3H). LC-MS: MS (ES^+): RT = 1.215 min, m/z = 883.7 [M +H^+], LC-MS Method: 25.

EXAMPLE 35 – Synthesis of (R)-6-(2-(ethyl(4-(2-((R)-3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy) pyrrolidin-1-yl)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol and (S)-6-(2-(ethyl(4-(2-((R)-3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)pyrrolidin-1-yl)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (I-34a and I-34b).



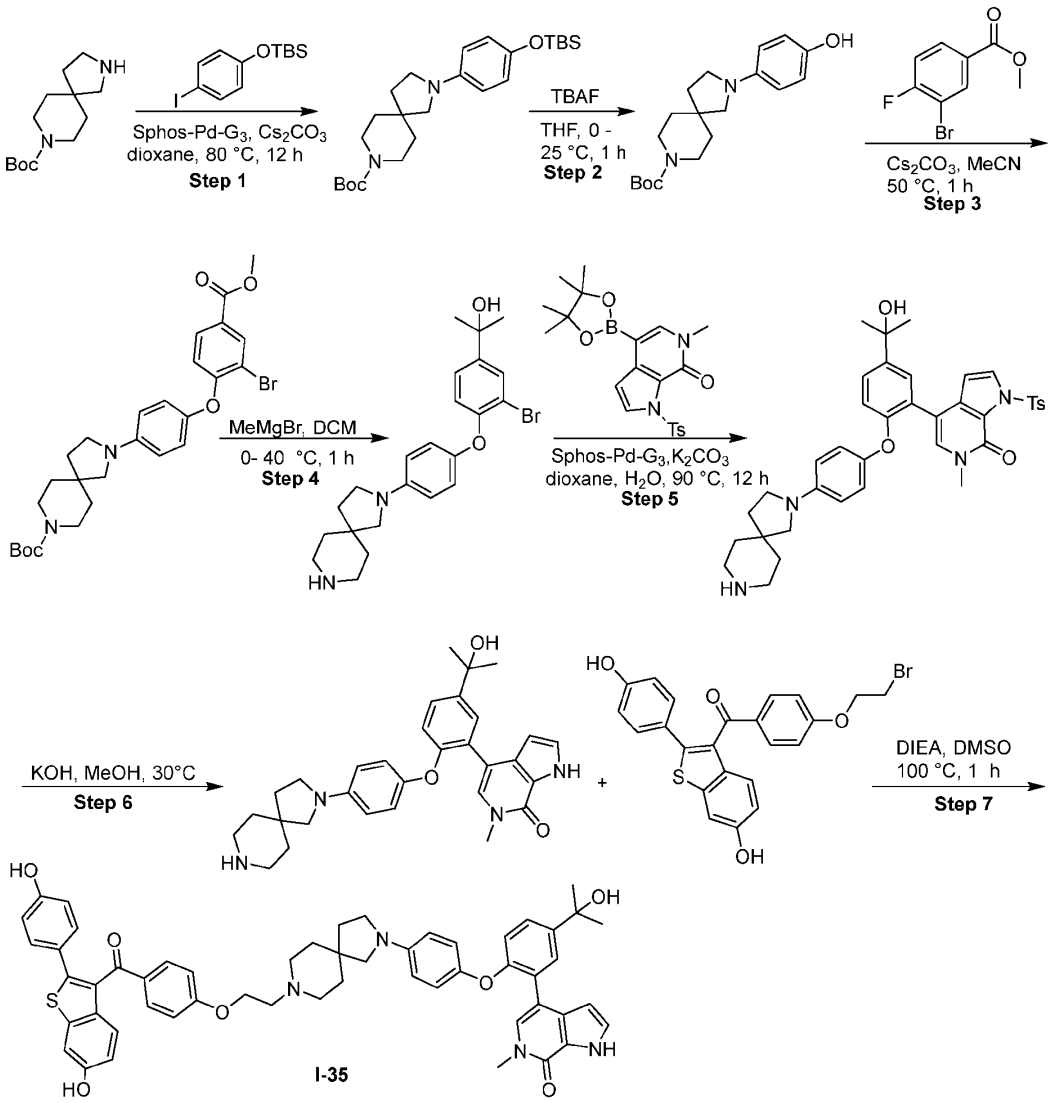
[0642] Step 1: Preparation of (S)-2,3,6,9-tetramethyl-4-(4-(2-(2-(((R)-pyrrolidin-3-yl)oxy)ethoxy)ethoxy)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine. To a solution of *tert*-butyl (R)-3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)pyrrolidine-1-carboxylate (110 mg, 0.18 mmol, 1 equiv.) in DCM (3 mL) was added TFA (5.07 g, 44 mmol, 3.30 mL, 240 equiv.). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent to afford (S)-2,3,6,9-tetramethyl-4-(4-(2-(2-(((R)-pyrrolidin-3-yl)oxy)ethoxy)ethoxy)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (92 mg, crude) as a yellow oil. LC-MS: MS (ES^+): RT = 0.384 min, m/z = 496.3 [M +H^-].

[0643] Step 2: Preparation of 2-(6-((tert-butyldimethylsilyl)oxy)-1,2,3,4-tetra hydronaphthalen-2-yl)-N-ethyl-5-methoxy-N-(4-(2-((R)-3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) ethoxy)pyrrolidin-1-yl)ethyl)benzyl)aniline. To a solution of (S)-2,3,6,9-tetramethyl-4-(4-(2-(2-(((R)-pyrrolidin-3-yl)oxy)ethoxy)ethoxy)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (92 mg, 0.18 mmol, 1 *equiv*) and 4-(((2-(6-((tert-butyldimethylsilyl)oxy)-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)(ethyl)amino)methyl)phenethyl 4-methylbenzenesulfonate (129.94 mg, 0.18 mmol, 1 *equiv*) in ACN (5 mL) was added DIEA (72 mg, 0.5 mmol, 3 *equiv*). The mixture was stirred at 80 °C for 12 hr. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM/MeOH=10/1) to afford 2-(6-((tert-butyldimethylsilyl)oxy)-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-ethyl-5-methoxy-N-(4-(2-((R)-3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f] [1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) ethoxy)pyrrolidin-1-yl)ethyl) benzyl)aniline (103 mg, 49% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.8 Hz, 2H), 7.19 - 7.12 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.92 - 6.85 (m, 3H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.69 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.64 - 6.58 (m, 2H), 4.19 - 4.08 (m, 4H), 3.98 (s, 2H), 3.86 (t, *J* = 4.8 Hz, 2H), 3.79 (s, 3H), 3.74 - 3.66 (m, 3H), 3.60 (q, *J* = 5.2 Hz, 2H), 2.94 - 2.87 (m, 3H), 2.86 - 2.76 (m, 5H), 2.76 - 2.69 (m, 4H), 2.67 (s, 3H), 2.41 (s, 3H), 2.17 - 2.06 (m, 4H), 1.96 - 1.85 (m, 1H), 1.82 - 1.70 (m, 6H), 1.26 (s, 1H), 1.00 (s, 9H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.24 - 0.19 (m, 6H). LC-MS: MS (ES+): RT = 0.493 min, m/z = 289.2 [M + H^+].

[0644] Step 3: Preparation of (R)-6-(2-(ethyl(4-(2-((R)-3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) ethoxy)pyrrolidin-

1-yl)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydro naphthalen-2-ol and (S)-6-(2-(ethyl(4-(2-((R)-3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)pyrrolidin-1-yl)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol. To a solution of 2-(6-((tert-butyldimethylsilyl)oxy)-1,2,3,4-tetrahydronaphthalen-2-yl)-N-ethyl-5-methoxy-N-(4-(2-((R)-3-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4] diazepin-4-yl)phenoxy)ethoxy)ethoxy)pyrrolidin-1-yl)ethyl)benzyl)aniline (80 mg, 0.07 mmol, 1 *equiv*) in DMF (3 mL) was added CsF (59.37 mg, 0.39 mmol, 5 *equiv*). The mixture was stirred at 80 °C for 0.5 hr. The reaction mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; gradient:26%-56% B over min) to afford a mixture of **I-34a** and **I-34b** (50 mg, 66% yield) as a white solid. The mixture was separated by SFC (column: Phenomenex-Cellulose-2 (250mm x 30mm,10um); mobile phase: [CO_2-ACN/MeOH(0.1% NH_3H_2O)]; B%:70%, isocratic elution mode) to afford **I-34a** (16.14 mg, 31% yield) as a white solid and **I-34b** (19.8 mg, 38% yield) as a white solid. ^{1}H NMR (**I-34a**) (400 MHz, DMSO-d_6) δ 7.75 - 7.64 (m, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.15 - 7.03 (m, 5H), 6.95 (d, J = 8.8 Hz, 2H), 6.84 - 6.75 (m, 2H), 6.66 (dd, J = 2.4, 8.8 Hz, 1H), 6.52 - 6.46 (m, 2H), 4.18 - 4.08 (m, 5H), 3.96 (d, J = 2.4 Hz, 3H), 3.75 - 3.71 (m, 4H), 3.70 (s, 3H), 3.55 (s, 3H), 2.89 - 2.83 (m, 4H), 2.72 (d, J = 3.6 Hz, 4H), 2.69 - 2.65 (m, 4H), 2.64 (s, 2H), 2.33 (dd, J = 1.6, 3.2 Hz, 2H), 1.94 (dd, J = 6.0, 13.2 Hz, 2H), 1.85 (d, J = 6.8 Hz, 3H), 1.64 (s, 3H), 1.29 - 1.20 (m, 2H), 0.87 (t, J = 7.2 Hz, 5H). LC-MS: MS (ES$^+$): RT = 1.395 min, m/z = 909.7 [M +H$^+$], 25. ^{1}H NMR **(I-34b)** (400 MHz, DMSO-d_6) δ 7.75 - 7.62 (m, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.15 - 7.03 (m, 5H), 6.95 (d, J = 8.8 Hz, 2H), 6.82 - 6.76 (m, 2H), 6.66 (dd, J = 2.4, 8.4 Hz, 1H), 6.52 - 6.47 (m, 2H), 4.17 - 4.08 (m, 5H), 3.96 (d, J = 2.4 Hz, 3H), 3.75 - 3.71 (m, 4H), 3.70 (s, 3H), 3.55 (s, 3H), 2.88 - 2.83 (m, 4H), 2.73 (d, J = 5.2 Hz, 4H), 2.66 (d, J = 3.6 Hz, 4H), 2.63 (s, 2H), 2.33 (d, J = 1.6 Hz, 2H), 1.97 - 1.90 (m, 2H), 1.85 (d, J = 6.4 Hz, 3H), 1.64 (s, 3H), 1.27 - 1.21 (m, 2H), 0.89 - 0.82 (m, 5H). LC-MS**:** MS (ES$^+$): RT = 1.395 min, m/z = 909.7 [M +H$^+$], Method 25.

EXAMPLE 36 – Synthesis of 4-(2-(4-(8-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b] thiophene-3-carbonyl)phenoxy)ethyl)-2,8-diazaspiro[4.5]decan-2-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (I-35).



[0645] Step 1: Preparation of tert-butyl 2-[4-[tert-butyl(dimethyl)silyl]oxyphenyl]-2,8-diazaspiro[4.5]decane-8-carboxylate. A mixture of tert-butyl 2,8-diazaspiro[4.5]decane-8-carboxylate (1 g, 4.16 mmol, 1 *equiv*), tert-butyl-(4-iodophenoxy)-dimethyl-silane (1.39 g, 4.16 mmol, 1 *equiv*), SPhos Pd G3 (227.25 mg, 291.25 μmol, 0.07 *equiv*), Cs_2CO_3 (3.39 g, 10.40 mmol, 2.5 *equiv*) in dioxane (20 mL) was degassed and purged with N_2 for 3 times, and then the

mixture was stirred at 80 °C for 12 h under N_2 atmosphere. The mixture was filtered off, filter-cake was washed by EtOAc (20 mL *3), and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (20 g SepaFlash® Silica Flash Column, Eluent of 3~10 % Ethyl acetate/Petroleum ether gradient 20 mL/min) to afford tert-butyl 2-[4-[tert-butyl(dimethyl)silyl]oxyphenyl]-2,8-diazaspiro[4.5] decane-8-carboxylate (1.2 g, 64% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 - 6.71 (m, 2H), 6.47 - 6.39 (m, 2H), 3.55 - 3.45 (m, 2H), 3.42 - 3.35 (m, 2H), 3.32 (t, 2H, J = 6.8 Hz), 3.11 (s, 2H), 1.87 (t, 2H, J = 7.2 Hz), 1.63 (s, 1H), 1.58 (s, 3H), 1.47 (s, 9H), 0.98 (s, 9H), 0.16 (s, 6H).

[0646] Step 2: Preparation of tert-butyl 2-(4-hydroxyphenyl)-2,8-diazaspiro [4.5]decane-8-carboxylate. To a solution of tert-butyl 2-[4-[tert-butyl(dimethyl)silyl] oxyphenyl]-2,8-diazaspiro[4.5]decane-8-carboxylate (1.2 g, 2.69 mmol, 1 *equiv*) in THF (20 mL) was added TBAF (1 M, 4.03 mL, 1.5 *equiv*) at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to afford tert-butyl 2-(4-hydroxy phenyl)-2,8-diazaspiro[4.5]decane-8-carboxylate (820 mg, crude) as brown solid.

[0647] Step 3: Preparation of tert-butyl 2-[4-(2-bromo-4-methoxycarbonyl-phenoxy)phenyl]-2,8-diazaspiro[4.5]decane-8-carboxylate. To a solution of tert-butyl 2-(4-hydroxyphenyl)-2,8-diazaspiro[4.5]decane-8-carboxylate (800 mg, 2.41 mmol, 1 *equiv*) in MeCN (3 mL) was added Cs_2CO_3 (1.96 g, 6.02 mmol, 2.5 *equiv*) and methyl 3-bromo-4-fluoro-benzoate (392.55 mg, 1.68 mmol, 0.7 *equiv*). The mixture was stirred at 50 °C for 1 h. The mixture was filtered, the filter-cake was washed by EtOAc (10 mL x 3), and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (20 g SepaFlash Silica Flash Column, eluent: 15~30 % ethyl acetate / petroleum ether gradient 30 mL/min) to afford tert-butyl 2-[4-(2-bromo-4-methoxycarbonyl-phenoxy) phenyl]-2,8-diazaspiro[4.5]decane-8-carboxylate (410 mg, 29% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, 1H, J = 2.4 H), 7.82 (dd, 1H, J = 2.0, 8.4 Hz), 7.02 - 6.94 (m, 2H), 6.71 (d, 1H, J = 8.8 Hz), 6.60 - 6.50 (m, 2H), 3.90 (s, 3H), 3.57 - 3.47 (m, 2H), 3.45 - 3.36 (m, 4H), 3.18 (s, 2H), 1.92 (t, 2H, J = 6.8 Hz), 1.65 - 1.59 (m, 4H), 1.48 (s, 9H). **LC-MS:** MS (ES^+): RT = 0.730 min, m/z = 545.1; 547.1 [M +H^+].

[0648] Step 4: Preparation of 2-[3-bromo-4-[4-(2,8-diazaspiro[4.5]decan-2-yl) phenoxy]phenyl]propan-2-ol. To a solution of tert-butyl 2-[4-(2-bromo-4-methoxycarbonyl - phenoxy) phenyl]-2,8-diazaspiro[4.5]decane-8-carboxylate (460 mg, 843.32 μmol, 1 *equiv*) in THF (3 mL) was added MeMgBr (3 M, 5.62 mL, 20 *equiv*) at 0 °C under an N_2 atmosphere. The

mixture was stirred at 40 °C for 1 h. The reaction mixture was quenched by adding saturated NH_4Cl (10 mL), and extracted with DCM: MeOH (10:1, 20 mL *3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-[3-bromo-4-[4-(2,8-diazaspiro[4.5]decan-2-yl)phenoxy] phenyl] propan-2-ol (220 mg, 54% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.730 min, m/z = 445.1; 447.1 [M $+H^+$].

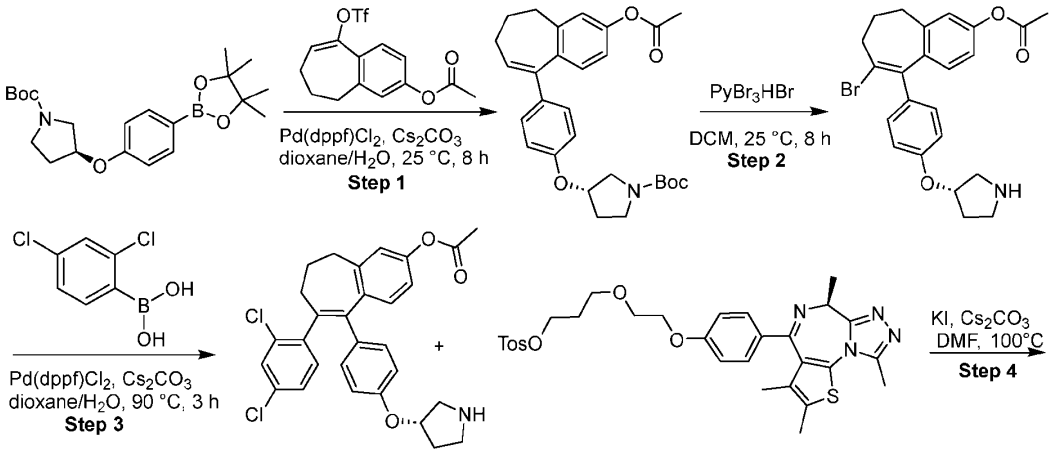
[0649] Step 5: Preparation of 4-(2-(4-(2,8-diazaspiro[4.5]decan-2-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1-tosyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one. A mixture of 2-[3-bromo-4-[4-(2,8-diazaspiro[4.5]decan-2-yl)phenoxy]phenyl]propan-2-ol (100 mg, 224.52 μmol, 1 *equiv*), 6-methyl-1-(p-tolylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-c]pyridin-7-one (96.16 mg, 224.52 μmol, 1 *equiv*), [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane;methanesulfonate (16.35 mg, 22.45 μmol, 0.1 *equiv*) and K_2CO_3 (77.58 mg, 561.30 μmol, 2.5 *equiv*) in dioxane (3 mL) and H_2O (0.3 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 90 °C for 12 h under an N_2 atmosphere. To the reaction mixture was added H_2O (10 mL) and the reaction mixture was extracted with DCM: MeOH=10:1 (10 mL *3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude desired product (105 mg) as a yellow solid.

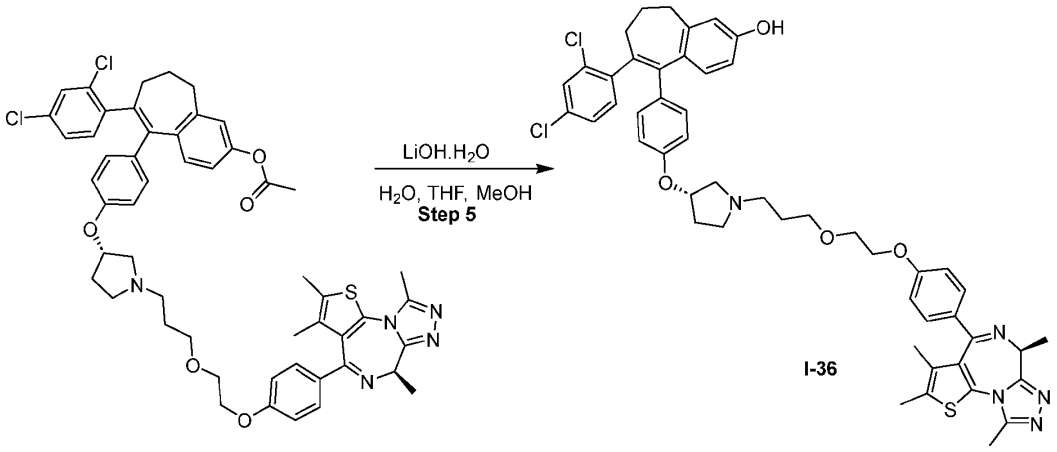
[0650] Step 6: Preparation of 4-[2-[4-(2,8-diazaspiro[4.5]decan-2-yl)phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridin-7-one. To a solution of 4-[2-[4-(2,8-diazaspiro[4.5]decan-2-yl)phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridin-7-one (100 mg, 149.96 μmol, 1 *equiv*) in MeOH (3 mL) was added KOH (168.28 mg, 3.00 mmol, 20 *equiv*). The mixture was stirred at 30 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water(FA)-ACN]; gradient: 10%-40% B over 10 min) to afford 4-[2-[4-(2,8-diazaspiro[4.5]decan-2-yl)phenoxy]-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridin-7-one (45 mg, 55% yield) as an off-white solid. LC-MS: MS (ES^+): RT = 0.890 min, m/z = 513.3 [M $+H^+$].

[0651] Step 7: Preparation of 4-(2-(4-(8-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl) benzo[b] thiophene-3-carbonyl)phenoxy)ethyl)-2,8-diazaspiro[4.5]decan-2-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one. To a solution of 4-[2-[4-(2,8-diazaspiro[4.5]decan-2-yl)phenoxy]-5-(1-hydroxy-1-methyl-

ethyl)phenyl]-6-methyl-1H-pyrrolo[2,3-c]pyridin-7-one (40 mg, 78.03 μmol, 1 *equiv*) in DMSO (0.5 mL) was added DIEA (30.25 mg, 234.08 μmol, 40.77 μL, 3 *equiv*) and [4-(2-bromoethoxy)phenyl]-[6-hydroxy-2-(4-hydroxyphenyl)benzothiophen-3-yl]methanone (36.62 mg, 78.03 μmol, 1 *equiv*). The mixture was stirred at 100 °C for 1 h. To the reaction mixture was added H_2O (20 mL), and it was 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 (SiO_2, DCM: MeOH = 10:1), and then purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water(FA)-ACN]; gradient:20%-50% B over 10 min) to afford 4-(2-(4-(8-(2-(4-(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene-3-carbonyl)phenoxy)ethyl)-2,8-diazaspiro[4.5]decan-2-yl)phenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (**I-35**, 17 mg, 23% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 10.03 - 9.51 (m, 2H), 8.20 (s, 1H), 7.65 (d, 2H, J = 8.8 Hz), 7.51 (d, 1H, J = 2.4 Hz), 7.35 - 7.30 (m, 2H), 7.28 - 7.22 (m, 3H), 7.19 - 7.14 (m, 2H), 6.92 (d, 2H, J = 7.2 Hz), 6.88 - 6.80 (m, 3H), 6.71 - 6.64 (m, 3H), 6.47 (d, 2H, J = 9.2 Hz), 6.24 (t, 1H, J = 2.4 Hz), 4.98 (s, 1H), 4.10 (t, 2H, J = 5.6 Hz), 3.55 (s, 3H), 3.23 (t, 4H, J = 6.8 Hz), 3.03 (s, 2H), 2.67 (t, 2H, J = 5.6 Hz), 2.44 - 2.38 (m, 2H), 1.79 (t, 2H, J = 6.4 Hz), 1.58 - 1.48 (m, 4H), 1.44 (s, 6H). LC-MS: MS (ES$^+$): RT = 1.917 min, m/z = 901.7 [M +H$^+$], LCMS Method: 25.

<u>EXAMPLE 37</u> – Synthesis of 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) propyl) pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-ol (I-36).





[0652] Step 1: Preparation of *tert*-butyl (S)-3-(4-(3-acetoxy-6,7-dihydro-5H-benzo[7] annulen-9-yl)phenoxy)pyrrolidine-1-carboxylate. To a solution of 9-(((trifluoro methyl)sulfonyl)oxy)-6,7-dihydro-5H-benzo[7]annulen-3-yl acetate (3.00 g, 8.56 mmol, 1.00 *equiv*), tert-butyl (S)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy) pyrrolidine-1-carboxylate (3.33 g, 8.56 mmol, 1.00 *equiv*), and cesium carbonate (5.58 g, 17.13 mmol, 2.00 *equiv*) in dioxane (24 mL) and water (6 mL) was added 1,1'-bis(diphenyl phosphino) ferrocene-palladium(II)dichloride (626 mg, 0.86 mmol, 0.10 *equiv*) and the mixture was stirred at 25 °C for 8 h under a nitrogen atmosphere. The reaction mixture was quenched with water (50 mL), and then extracted with ethyl acetate (30 mLx3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=1/0 to 3/1) to afford *tert*-butyl (S)-3-(4-(3-acetoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenoxy)pyrrolidine-1-carboxylate (3.50 g, 88% yield) as a white solid. LCMS: MS (ES+): RT = 0.758 min, m/z = 486.4 $[M+Na]^+$.

[0653] Step 2: Preparation of (S)-8-bromo-9-(4-(pyrrolidin-3-yloxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-yl acetate. A mixture of monopyidinium tribromide (379 mg, 1.19 mmol, 1.10 *equiv*) and *tert*-butyl (S)-3-(4-(3-acetoxy-6,7-dihydro-5H-benzo[7] annulen-9-yl)phenoxy)pyrrolidine-1-carboxylate (500 mg, 1.08 mmol, 1.00 *equiv*) in dichloromethane (15 mL) was stirred at 25 °C for 8 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=1/0 to 10/1) to afford (S)-8-bromo-9-(4-(pyrrolidin-3-yloxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-yl acetate (330 mg, 69% yield) as a white solid. ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.94 - 6.78 (m, 4H), 5.09 (s, 1H), 3.70 - 3.53 (m, 4H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.64 - 2.57 (m, 2H), 2.44 (dd, *J* = 6.0, 14.4 Hz, 1H), 2.38 - 2.22 (m, 7H).

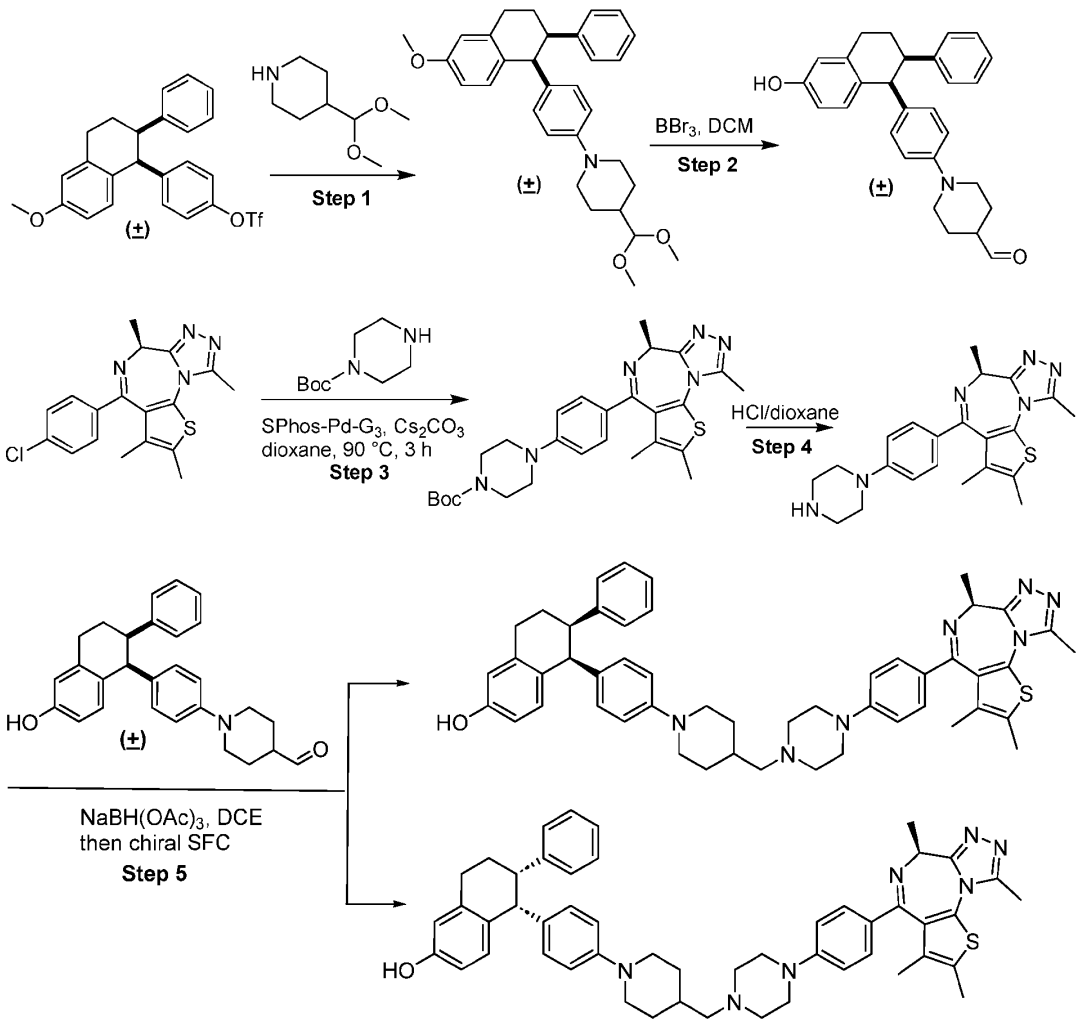
[0654] Step 3: Preparation of (S)-8-(2,4-dichlorophenyl)-9-(4-(pyrrolidin-3-yloxy) phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-yl acetate. To a solution of (S)-8-bromo-9-(4-(pyrrolidin-3-yloxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-yl acetate (330 mg, 0.74 mmol, 1.00 *equiv*), (2,4-dichlorophenyl)boronic acid (156 mg, 0.82 mmol, 1.10 *equiv*), and cesium carbonate (486 mg, 1.49 mmol, 2.00 *equiv*) in dioxane (4 mL) and water (1 mL) was added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (54 mg, 0.07 mmol, 0.10 *equiv*) and the mixture was stirred at 90 °C for 3 h under a nitrogen atmosphere. The reaction mixture was quenched with water (20 mL), and then extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (dichloromethane: methanol = 10:1) to afford (S)-8-(2,4-dichlorophenyl)-9-(4-(pyrrolidin-3-yloxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-yl acetate (320 mg, 84% yield) as a yellow solid. LCMS: MS (ES+): RT = 0.625 min, m/z = 510.1 $[M+H]^+$.

[0655] Step 4: Preparation of 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) propyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-yl acetate. A mixture of (S)-8-(2,4-dichlorophenyl)-9-(4-(pyrrolidin-3-yloxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-yl acetate (51 mg, 0.10 mmol, 1.20 *equiv*), (S)-3-(2-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)propyl 4-methyl benzenesulfonate (50 mg, 0.08 mmol, 1.00 *equiv*), potassium iodide (13 mg, 0.08 mmol, 1.00 *equiv*), and cesium carbonate (82 mg, 0.25 mmol, 3.00 *equiv*) in *N,N*-dimethylformamide (1 mL) was stirred at 100 °C for 1 h. The reaction mixture was quenched with water (10 mL), and then extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient:80%-100% B over 10 min] to afford 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno [3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)propyl) pyrrolidin-3-yl)oxy) phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-yl

acetate (50 mg, 63% yield) as a white solid. LCMS: MS (ES^+): RT = 0.656 min, m/z = 930.4 $[M+H]^+$.

[0656] Step 5: Preparation of 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) propyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-ol. To a solution of 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4] triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)propyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-yl acetate (50 mg, 0.05 mmol, 1.00 *equiv*) in water (0.2 mL), tetrahydrofuran (0.2 mL) and methanol (0.2 mL) was added lithium hydroxide (6 mg, 0.16 mmol, 3.00 *equiv*) and the mixture was stirred at 25 °C for 108 h. The reaction mixture was quenched with an aqueous hydrochloric acid solution (1M, 5 mL), and then filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Welch Xtimate C18 150 x 25mm x 5um;mobile phase: [water(FA)-ACN]; gradient:30%-60% B over 10 min] to afford 8-(2,4-dichlorophenyl)-9-(4-(((S)-1-(3-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy) propyl)pyrrolidin-3-yl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulen-3-ol (**I-36**, 22.78 mg, 42.09% yield) as a white solid. LCMS: MS (ES+): RT = 2.604 min, m/z = 888.4 $[M+H]^+$; 5-95. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 2H), 7.57 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.27 - 7.22 (m, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.4 Hz, 1H), 6.75 - 6.69 (m, 3H), 6.67 - 6.62 (m, 3H), 4.75 (t, J = 7.6 Hz, 1H), 4.17 - 4.10 (m, 3H), 4.04 (t, J = 6.0 Hz, 2H), 3.75 - 3.72 (m, 2H), 3.62 (s, 2H), 3.43 (s, 1H), 3.07 - 3.03 (m, 1H), 2.85 - 2.76 (m, 4H), 2.58 (s, 3H), 2.38 (s, 3H), 2.19 - 2.12 (m, 2H), 2.10 - 2.03 (m, 2H), 2.00 - 1.93 (m, 3H), 1.87 - 1.82 (m, 3H), 1.76 - 1.69 (m, 1H), 1.63 (s, 3H).

EXAMPLE 38 – Synthesis of (5S,6R)-6-phenyl-5-(4-(4-((4-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperazin-1-yl)methyl) piperidin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol and (5R,6S)-6-phenyl-5-(4-(4-((4-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl) phenyl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (I-37a and I-37b).



[0657] Step 1: Preparation of (±)-*cis*-4-(dimethoxymethyl)-1-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl]piperidine. A mixture of (±)-*cis*-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl] trifluoromethanesulfonate (200 mg, 0.43 mmol, 1 *equiv*), 4-(dimethoxymethyl)piperidine (103 mg, 0.64 mmol, 1.5 *equiv*), CPHOS PD G_3 (69 mg, 0.08

mmol, 0.2 *equiv*), Xantphos (75 mg, 0.12 mmol, 0.3 *equiv*) and Cs_2CO_3 (281 mg, 0.86μmol, 2 *equiv*) in dioxane (5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 95 °C for 12 h under an N_2 atmosphere. The reaction mixture was quenched by addition H_2O (50 mL), and then extracted with ethyl acetate (200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/ethyl acetate= 5:1). (±)-*cis*-4-(dimethoxymethyl)-1-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl]piperidine (150 mg, 0.31 mmol, 73% yield) was obtained as a yellow oil. LC-MS: MS (ES+): RT = 0.537 min, m/z = 472.3 [M + H^+].

[0658] Step 2: Preparation of (±)-*cis*-1-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)phenyl] piperidine -4-carbaldehyde. To a solution of (±)-*cis*-4-(dimethoxymethyl)-1-[4-(6-methoxy-2-phenyl-tetralin-1-yl)phenyl]piperidine (150.00 mg, 0.31mmol, 1 *equiv*) in DCM (2 mL) was added BBr_3 (1.30 g, 5.19 mmol, 0.5 mL, 16.32 *equiv*) at 0 °C . The mixture was stirred at 20 °C for 3 h. And then H_2O (2 mL) was added dropwise at 0°C. The resulting mixture was stirred at 20 °C for 2 hours. The reaction mixture was adjusted to pH=7~8 with aqueous $NaHCO_3$ and extracted with EA 15 mL (5 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (±)-*cis*-1-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)phenyl]piperidine-4-carbaldehyde (120 mg, 0.29 mmol, 91% yield) as a white solid. LC-MS: MS (ES+): RT = 0.471 min, m/z = 412.2 [M + H^+].

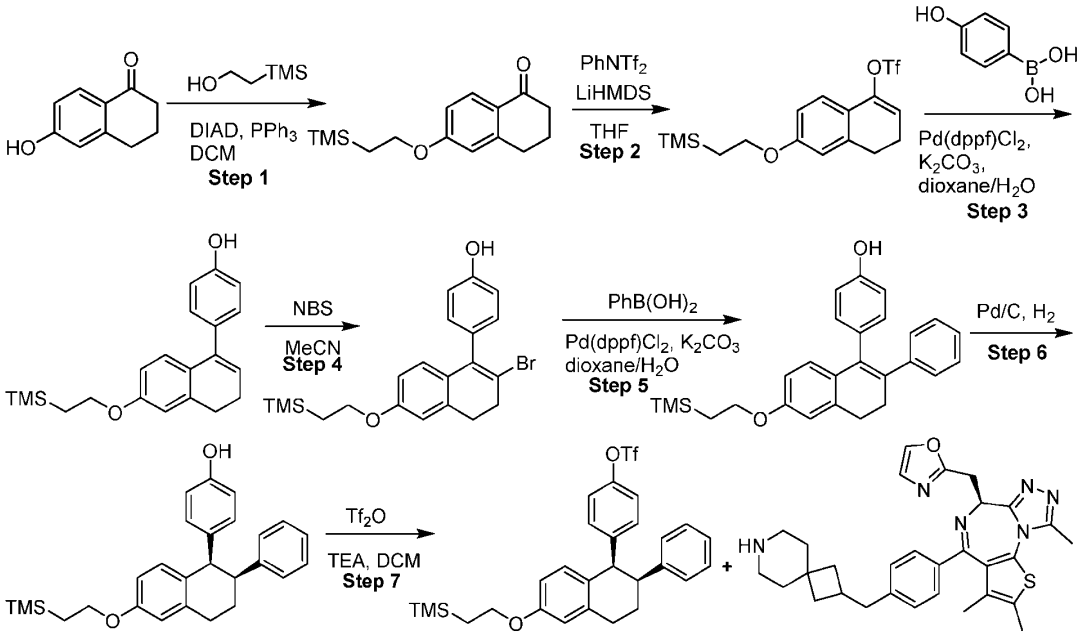
[0659] Step 3: Preparation of tert-butyl (S)-4-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperazine-1-carboxylate. A mixture of (S)-4-(4-chlorophenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (100 mg, 0.28 mmol, 1 *equiv*), tert-butyl piperazine-1-carboxylate (78 mg, 0.42 mmol, 1.5 *equiv*), SPhos Pd G_3 (21 mg, 0.02 mmol, 0.1 *equiv)*, and Cs_2CO_3 (182 mg, 0.56 mmol, 2 *equiv*) in dioxane (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 °C for 12 h under an N_2 atmosphere. The reaction mixture was partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to afford tert-butyl (S)-4-(4-(2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepin-4-yl)phenyl)piperazine-1-carboxylate (140 mg, 98% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.478 min, m/z = 507.3 [M +H^+].

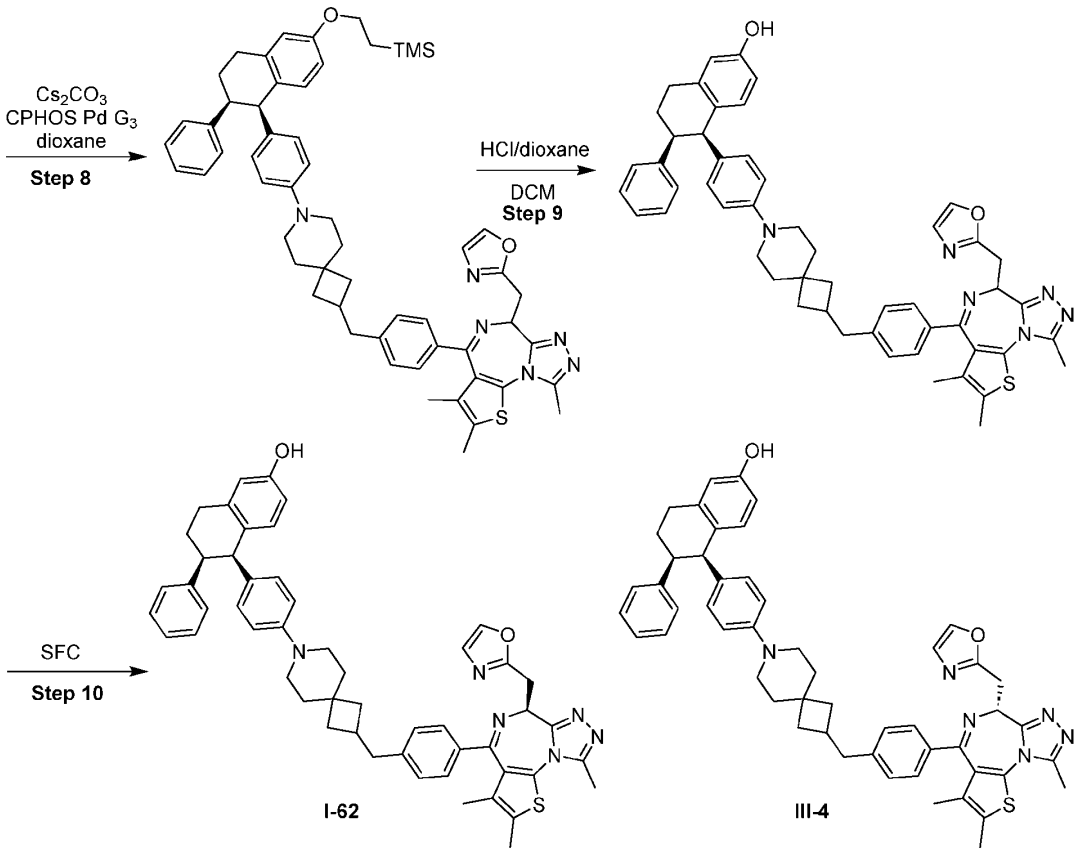
[0660] Step 4: Preparation of (S)-2,3,6,9-tetramethyl-4-(4-(piperazin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine. To a solution of tert-butyl 4-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperazine-1-carboxylate (140 mg, 0.27 mmol, 1 *equiv*) in DCM (2 mL) was added HCl/dioxane (2 M, 3.50 mL, 25.33 *equiv*). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove solvent to afford (S)-2,3,6,9-tetramethyl-4-(4-(piperazin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (120 mg, 98% yield, HCl) as a yellow solid. LC-MS: MS (ES+): RT = 0.352 min, m/z = 407.2 [M + H^+].

[0661] Step 5: Preparation of (5S,6R)-6-phenyl-5-(4-(4-((4-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperazin-1-yl)methyl) piperidin -1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol and (5R,6S)-6-phenyl-5-(4-(4-((4-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (I-37a and I-37b). To a solution of (S)-2,3,6,9-tetramethyl-4-(4-(piperazin-1-yl)phenyl)-6H-thieno[3,2-f][1,2,4]triazolo [4,3-a][1,4]diazepine (80 mg, 0.18 mmol, 1 *equiv*, HCl) in DCM (3 mL) was added NaOAc (148 mg, 1.81 mmol, 10 *equiv*) at 25°C. The mixture was stirred at 25°C for 0.5 h. Then (±)-*cis*-1-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)phenyl]piperidine-4-carbaldehyde (81 mg, 0.19 mmol, 1.1 *equiv*) and $NaBH(OAc)_3$ (57 mg, 0.27 mmol, 1.5 *equiv*) were added. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to afford 2-phenyl-1-[4-[4-[[4-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]tetralin-6-ol (40 mg, 0.04 mmol, 27% yield) as a white solid. The stereoisomeric mixture was purified by prep-HPLC (column: DAICEL CHIRALPAK AD (250mm x 30mm,10um); mobile phase: [CO_2-ACN/i-PrOH (0.1% NH_3H_2O)]; B%:70%, isocratic elution mode) to give **I-37a** (about 22% yield) as a white solid and **I-37b** (about 22% yield) as a white solid. ^{1}H NMR (peak 1): (400 MHz, CHLOROFORM-*d*) δ ppm 1.29 - 1.38 (m, 3 H) 1.56 - 1.68 (m, 2 H) 1.76 (s, 3 H) 1.83 (br d, *J*=13.6 Hz, 3 H) 2.05 - 2.09 (m, 3 H) 2.22 - 2.28 (m, 2 H) 2.41 (s, 3 H) 2.52 - 2.61 (m, 6 H) 2.66 - 2.68 (m, 3 H) 2.95 - 3.07 (m, 2 H) 3.25 (br d, *J*=2.8 Hz, 4 H) 3.50 - 3.59 (m, 2 H) 4.11 - 4.21 (m, 2 H) 6.29 (d, *J*=8.8 Hz, 2 H) 6.55 - 6.62 (m, 3 H) 6.72 (d, *J*=2.4 Hz, 1 H) 6.79 - 6.86 (m, 5 H) 7.11 - 7.18 (m, 3 H) 7.38 - 7.44 (m, 2 H) LC-MS (peak 1): MS (ES^+): RT = 1.035 min, m/z = 802.5 [M +H^+], LCMS Method

10. ^{1}H NMR (peak 2): (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 - 1.38 (m, 3 H) 1.56 - 1.69 (m, 2 H) 1.76 (s, 3 H) 1.83 (br d, *J*=14.4 Hz, 3 H) 2.08 (d, *J*=6.8 Hz, 3 H) 2.22 - 2.29 (m, 2 H) 2.41 (s, 3 H) 2.52 - 2.62 (m, 6 H) 2.67 (s, 3 H) 2.93 - 3.06 (m, 2 H) 3.25 (br d, *J*=2.0 Hz, 4 H) 3.55 (br dd, *J*=8.8, 3.2 Hz, 2 H) 4.11 - 4.21 (m, 2 H) 6.29 (d, *J*=8.8 Hz, 2 H) 6.54 - 6.60 (m, 3 H) 6.72 (d, *J*=2.4 Hz, 1 H) 6.78 - 6.87 (m, 5 H) 7.12 - 7.18 (m, 3 H) 7.39 (d, *J*=8.8 Hz, 2 H). LC-MS (peak 2): MS (ES$^+$): RT = 1.035 min, m/z = 802.5 [M +H$^+$], LCMS Method 10.

<u>EXAMPLE 39</u> – Synthesis of (5R,6S)-6-phenyl-5-(4-(2-(4-((S)-2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (I-62) and (5R,6S)-6-phenyl-5-(4-(2-(4-((R)-2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (III-4)





[0662] Step 1: Preparation of 6-(2-trimethylsilylethoxy)tetralin-1-one. To a solution of 6-hydroxytetralin-1-one (21 g, 129.48 mmol, 1 *equiv*), 2-trimethylsilylethanol (19.14 g, 161.85 mmol, 23.20 mL, 1.25 *equiv*) and PPh_3 (42.45 g, 161.85 mmol, 1.25 *equiv)* in DCM (210 mL) was added DIAD (32.73 g, 161.85 mmol, 31.38 mL, 1.25 *equiv*) at -78°C. The mixture was stirred at 40 °C for 12h. The reaction mixture was partitioned between DCM (100 mL) and H_2O (100 mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=10/1 to 3/1). 6-(2-trimethylsilylethoxy) tetralin-1-one (8.4 g, 32.01 mmol, 24% yield) was obtained as a yellow oil. LC-MS: MS (ES+): RT = 0.460 min, m/z = 265.2 [M +H^+].

[0663] Step 2: Preparation of [6-(2-trimethylsilylethoxy)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate. To a mixture of 6-(2-trimethylsilylethoxy)tetralin-1-one (10.6 g, 40.39 mmol, 1 *equiv*) in THF (100 mL) was added LiHMDS (1 M, 60.59 mL, 1.5 *equiv*) dropwise at -78 °C and the mixture was stirred at -78 °C for 1 h under an N_2 atmosphere. Then 1,1,1-

trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (15.87 g, 44.43 mmol, 1.1 *equiv*) in THF (30 mL) was added dropwise to the mixture. The mixture was stirred at 25 °C for 12 h under an N_2 atmosphere. The reaction mixture was quenched by the addition of H_2O (100 mL) at 0 °C under an N_2 atmosphere, stirred at 0 °C for 20 min and then stirred at 25 °C for 20 min. The reaction mixture was then diluted with H_2O (500 mL) and extracted with EtOAc (500 mL x 2). The combined organic layers were washed with brine (300 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=20/1 to 3/1) to afford [6-(2-trimethylsilylethoxy)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (10.5 g, 26.62 mmol, 65% yield) as a white solid. LC-MS: MS (ES+): RT = 0.718 min.

[0664] Step 3: Preparation of 4-[6-(2-trimethylsilylethoxy)-3,4-dihydronaphthalen-1-yl]phenol. A mixture of [6-(2-trimethylsilylethoxy)-3,4-dihydronaphthalen-1-yl] trifluoromethane sulfonate (6.5 g, 16.48 mmol, 1 *equiv*), (4-hydroxyphenyl)boronic acid (2.73 g, 19.77 mmol, 1.2 *equiv*), K_2CO_3 (4.55 g, 32.95 mmol, 2 *equiv*), and $Pd(dppf)Cl_2$ (1.21 g, 1.65 mmol, 0.1 *equiv*) in dioxane (65 mL) and H_2O (13 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 °C for 2 hr under an N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250 x 70mm, 10 um); mobile phase: [water (FA)-ACN]; gradient :66%-96% B over 21 min) to afford 4-[6-(2-trimethylsilylethoxy)-3,4-dihydronaphthalen-1-yl]phenol (4.1 g, 73% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.686 min, m/z = 339.2 [$M+H^+$].

[0665] Step 4: Preparation of 4-[2-bromo-6-(2-trimethylsilylethoxy)-3,4-dihydro naphthalen-1-yl]phenol. To a solution of 4-[6-(2-trimethylsilylethoxy)-3,4-dihydro naphthalen-1-yl]phenol (4.1 g, 12.11 mmol, 1 *equiv*) in MeCN (40 mL) was added NBS (2.05 g, 11.51 mmol, 0.95 *equiv)*. The mixture was stirred at 20 °C for 2 h. The reaction mixture was partitioned between EA (50 mL) and H_2O (50 mL). The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=10/1 to 3/1) to afford 4-[2-bromo-6-(2-trimethylsilylethoxy)-3,4-dihydronaphthalen-1-yl]phenol (4.3 g, 85% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.720 min.

[0666] Step 5: Preparation of 4-[2-phenyl-6-(2-trimethylsilylethoxy)-3,4-dihydronaphthalen-1-yl]phenol. A mixture of 4-[2-bromo-6-(2-trimethylsilylethoxy)-3,4-

dihydronaphthalen-1-yl]phenol (4.3 g, 10.30 mmol, 1 *equiv*), phenylboronic acid (1.51 g, 12.36 mmol, 1.2 *equiv*), K_2CO_3 (2.85 g, 20.60 mmol, 2 *equiv*), and $Pd(dppf)Cl_2$ (753.78 mg, 1.03 mmol, 0.1 *equiv*) in dioxane (50 mL) and H_2O (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 90 °C for 3 hr under an N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 30/1 to 3/1) to afford 4-[2-phenyl-6-(2-trimethylsilylethoxy)-3,4-dihydronaphthalen-1-yl]phenol (4.2 g, 98% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.793 min, m/z = 415.2 [M +H^+].

[0667] Step 6: Preparation of 4-[(1R,2S)-2-phenyl-6-(2-trimethylsilylethoxy)tetralin-1-yl]phenol. To a hydrogenation vessel filled with N_2 was added Pd/C (500 mg, 469.84 μmol, 10% purity, 4.64e-2 *equiv*), followed by 4-[2-phenyl-6-(2-trimethylsilylethoxy)-3,4-dihydronaphthalen-1-yl]phenol (4.2 g, 10.13 mmol, 1 *equiv*) in MeOH (40 mL). The suspension was degassed and purged with H_2 3 times. The mixture was stirred under H_2 (45 psi) at 25 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 150 x 40mm x 15um; mobile phase: [water (FA)-ACN]; gradient: 70%-100% B over 15 min) and SFC (column: DAICEL CHIRALPAKAD (250mm x 30mm x 10um); mobile phase: [CO_2-i-PrOH (0.1%NH_3-H_2O)]; B%: 40%, isocratic elution mode) to afford 4-[(1R,2S)-2-phenyl-6-(2-trimethylsilylethoxy)tetralin-1-yl]phenol (280 mg, 672.07 μmol, 6% yield, $[a]_D$:-287.21) as a white solid and 4-[(1S,2R)-2-phenyl-6-(2-trimethylsilylethoxy)tetralin-1-yl]phenol (280 mg, 672.07 μmol, 6% yield, $[a]_D$:+356.42) as a white solid. LC-MS: MS (ES^-): RT = 0.729 min.

[0668] Step 7: Preparation of [4-[(1R,2S)-2-phenyl-6-(2-trimethylsilylethoxy)tetralin-1-yl]phenyl] trifluoromethanesulfonate. To a solution of 4-[(1R,2S)-2-phenyl-6-(2-trimethyl silylethoxy)tetralin-1-yl]phenol (250 mg, 600.06 μmol, 1 *equiv*) in DCM (5 mL) was added Tf_2O (338.60 mg, 1.20 mmol, 198.01 μL, 2 *equiv*) and TEA (182.16 mg, 1.80 mmol, 250.56 μL, 3 *equiv*). The mixture was stirred at 25 °C for 1h. The reaction mixture was partitioned between EtOAc (30 mL) and H_2O (30 mL). The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, PE: EA = 5:1) to afford [4-[(1R,2S)-2-phenyl-6-(2-trimethylsilylethoxy) tetralin-1-yl]phenyl] trifluoromethanesulfonate (280 mg, 510.31 μmol, 85% yield) as a white solid.

[0669] Step 8: Preparation of trimethyl-[2-[(1R,2S)-2-phenyl-1-[4-[2-[[4-[4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-

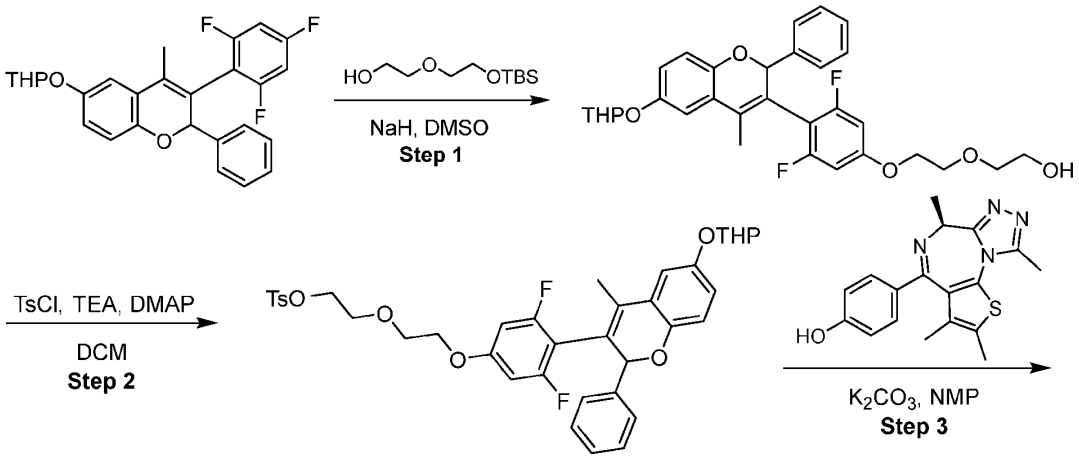
2(6),4,7,10,12-pentaen-7-yl]phenyl]methyl]-7-azaspiro[3.5]nonan-7-yl]phenyl]tetralin-6-yl]oxyethyl]silane. To a mixture of 2-[[(9S)-7-[4-(7-azaspiro[3.5]nonan-2-ylmethyl)phenyl]-4,5,13-trimethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-9-yl]methyl]oxazole (100 mg, 189.86 μmol, 1 *equiv*), [4-[(1R,2S)-2-phenyl-6-(2-trimethylsilyl ethoxy)tetralin-1-yl]phenyl] trifluoromethanesulfonate (125.01 mg, 227.84 μmol, 1.2 *equiv*), Cs_2CO_3 (185.58 mg, 569.59 μmol, 3 *equiv*), and CPHOS PD G_3 (15.31 mg, 18.99 μmol, 0.1 *equiv*) in dioxane (5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 90 °C for 12 h under an N_2 atmosphere. The reaction mixture was partitioned between EA (20 mL) and H_2O (20 mL). The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to afford trimethyl-[2-[(1R,2S)-2-phenyl-1-[4-[2-[[4-[4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]methyl]-7-azaspiro[3.5]nonan-7-yl]phenyl]tetralin-6-yl]oxyethyl]silane (80 mg, 45% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.702 min, m/z = 925.6 [M +H^+].

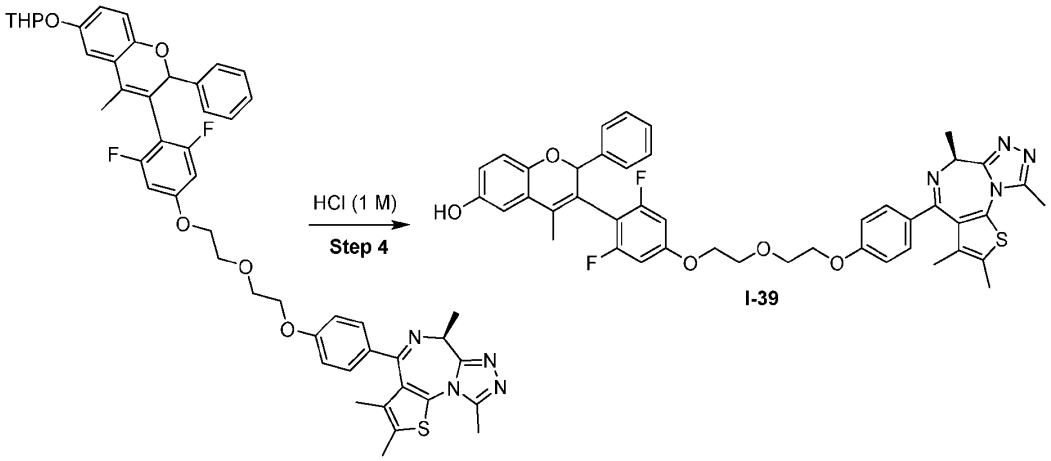
[0670] Step 9: Preparation of (1R,2S)-2-phenyl-1-[4-[2-[[4-[4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]methyl]-7-azaspiro[3.5]nonan-7-yl]phenyl]tetralin-6-ol. To a solution of trimethyl-[2-[(1R,2S)-2-phenyl-1-[4-[2-[[4-[4,5,13-trimethyl-9-(oxazol-2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]methyl]-7-azaspiro[3.5]nonan-7-yl]phenyl]tetralin-6-yl]oxyethyl]silane (30 mg, 32.42 μmol, 1 *equiv*) in DCM (3 mL) was added HCl/dioxane (4 M, 3.60 mL, 444.15 *equiv*). The mixture was stirred at 25 °C for 3 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water (FA)-ACN]; gradient: 48%-78% B over 9 min) to afford (5R,6S)-6-phenyl-5-(4-(2-(4-(2,3,9-trimethyl-6-(oxazol-2-ylmethyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (6.76 mg, 25% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.785 min, m/z = 825.5 [M +H^+].

[0671] Step 10: Preparation of I-62 and III-4. The residue from the prior step was purified by SFC (column: DAICEL CHIRALPAK IC (250mm x 30mm x 10um); mobile phase: [CO_2-ACN/EtOH (0.1% NH_3H_2O)]; B%: 75%, isocratic elution mode) to afford compounds **I-62** and **III-4**, each of the two diastereomers of (1R,2S)-2-phenyl-1-[4-[2-[[4-[4,5,13-trimethyl-9-(oxazol-

2-ylmethyl)-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]methyl]-7-azaspiro[3.5]nonan-7-yl]phenyl]tetralin-6-ol. The diastereomer that was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below), was obtained as a white solid (6.76 mg, 8.19 µmol, 25% yield, 100% purity). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.17 - 7.12 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.06 (br s, 1H), 6.84 - 6.77 (m, 3H), 6.70 (d, *J* = 2.4 Hz, 1H), 6.58 (br dd, *J* = 2.8, 8.1 Hz, 3H), 6.28 (br d, *J* = 8.4 Hz, 2H), 4.75 - 4.70 (m, 1H), 4.20 (br d, *J* = 4.4 Hz, 1H), 4.14 - 4.03 (m, 2H), 3.41 - 3.26 (m, 1H), 3.10 - 2.87 (m, 6H), 2.71 (br d, *J* = 7.6 Hz, 2H), 2.68 (s, 3H), 2.50 - 2.44 (m, 1H), 2.41 (s, 3H), 2.26 - 2.08 (m, 1H), 1.92 - 1.86 (m, 2H), 1.83 - 1.78 (m, 1H), 1.67 (s, 3H), 1.50 - 1.39 (m, 4H), 1.27 (s, 2H). LCMS (ES$^+$): RT = 2.165 min, m/z = 825.3 [M +H$^+$]; LCMS Method: 10.

<u>EXAMPLE 40</u> – Synthesis of 3-(2,6-difluoro-4-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)phenyl)-4-methyl-2-phenyl-2H-chromen-6-ol (I-39) As a Mixture of Stereoisomer I and II





[0672] Step 1: Preparation of 2-[2-[3,5-difluoro-4-(4-methyl-2-phenyl-6-tetrahydro pyran-2-yloxy-2H-chromen-3-yl)phenoxy]ethoxy]ethanol. To a solution of 2-[2-[tert-butyl(dimethyl)silyl]oxyethoxy]ethanol (97.41 mg, 0.44 mmol, 2 *equiv*) in DMSO (3 mL) was added NaH (17.68 mg, 0.4 mmol, 60% purity, 2 *equiv*) at 20 °C and the reaction mixture was stirred for 0.5 h. Then 4-methyl-2-phenyl-6-tetrahydropyran-2-yloxy-3-(2,4,6-trifluoro phenyl)-2H-chromene (100 mg, 0.2 mmol, 1 *equiv*) was added and the mixture was stirred at 60 °C for 2.5 h. The reaction mixture was quenched by the addition of water (50 mL) and then the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/1) to afford 2-[2-[3,5-difluoro-4-(4-methyl-2-phenyl-6-tetrahydropyran-2-yloxy-2H-chromen-3-yl)phenoxy] ethoxy]ethanol (52 mg, 42% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 0.645 min, m/z = 561.2 [M +Na^+].

[0673] Step 2: Preparation of 2-(2-(3,5-difluoro-4-(4-methyl-2-phenyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-2H-chromen-3-yl)phenoxy)ethoxy)ethyl 4-methylbenzenesulfonate. To a solution of 2-[2-[3,5-difluoro-4-(4-methyl-2-phenyl-6-tetrahydropyran-2-yloxy-2H-chromen-3-yl)phenoxy]ethoxy]ethanol (140 mg, 0.26 mmol, 1 *equiv*) in DCM (3 mL) was added TosCl (99.12 mg, 0.5 mmol, 2 *equiv*), DMAP (3.18 mg, 0.025 mmol, 0.1 *equiv*) and TEA (78.91 mg, 0.78 mmol, 3 *equiv*). The mixture was stirred at 20 °C for 12 hr. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum

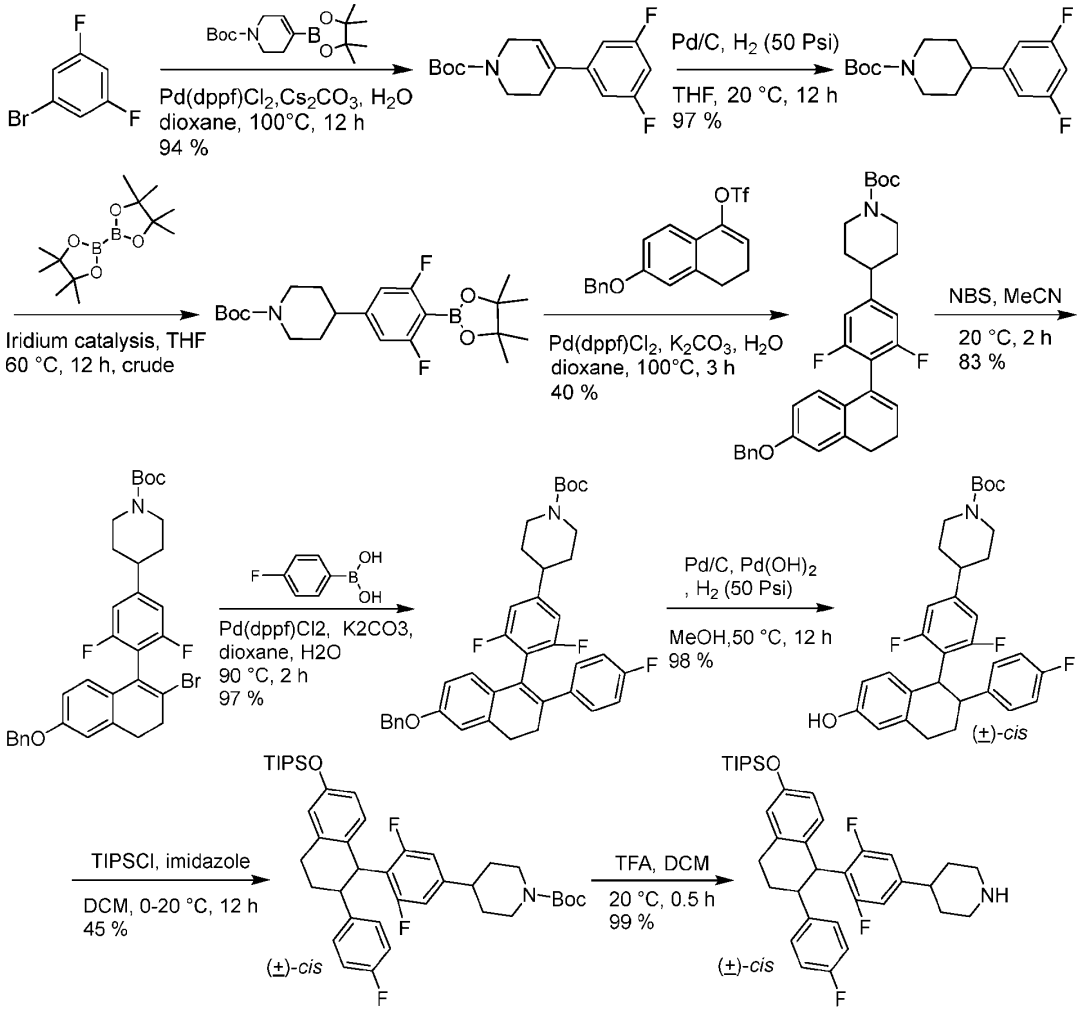
ether/ethyl acetate = 1/1) to afford 2-(2-(3,5-difluoro-4-(4-methyl-2-phenyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-2H-chromen-3-yl)phenoxy)ethoxy)ethyl 4-methylbenzenesulfonate (135 mg, 60% yield) as a yellow solid. LC-MS: MS (ES+): RT = 0.703 min, m/z = 691.3 [M - H^+].

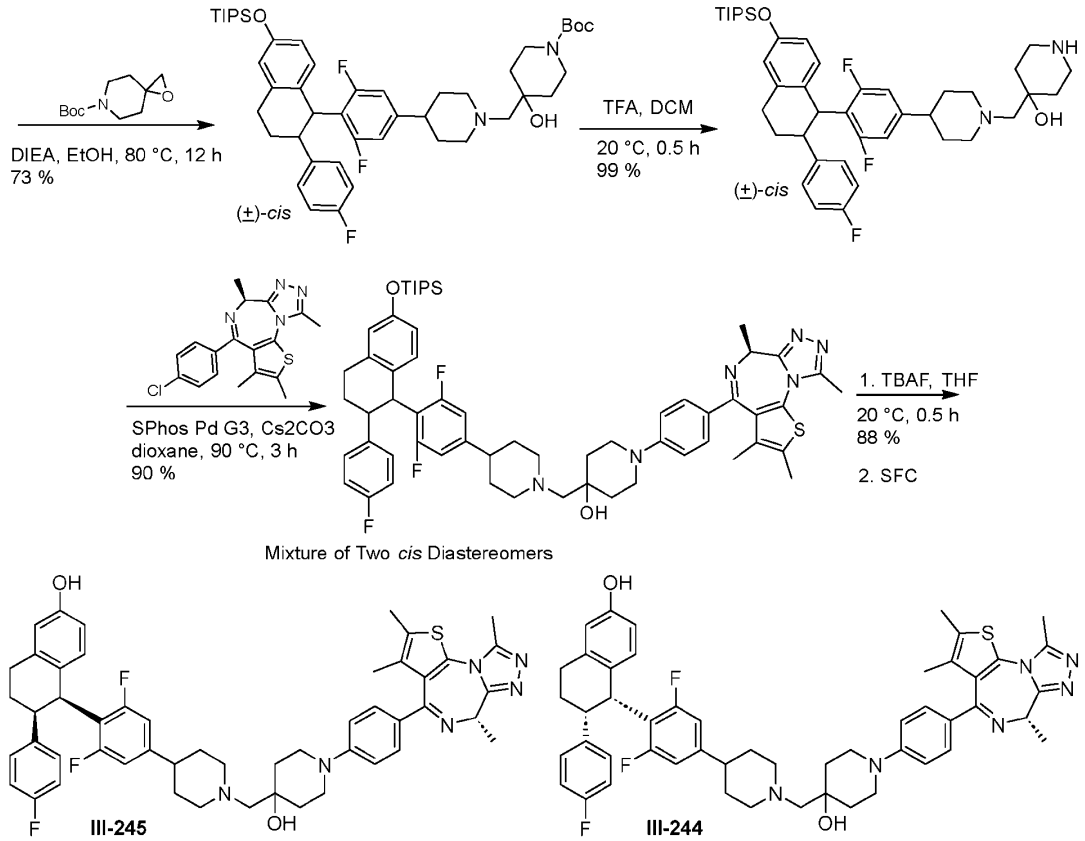
[0674] Step 3: Preparation of (6S)-4-(4-(2-(2-(3,5-difluoro-4-(4-methyl-2-phenyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-2H-chromen-3-yl)phenoxy)ethoxy)ethoxy)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine. To a solution of 2-[2-[3,5-difluoro-4-(4-methyl-2-phenyl-6-tetrahydropyran-2-yloxy-2H-chromen-3-yl)phenoxy] ethoxy]ethyl 4-methylbenzenesulfonate (150 mg, 0.21 mmol, 1 *equiv*) and 4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenol (73.28 mg, 0.21 mmol, 1 *equiv*) in DMF (3 mL) was added K_2CO_3 (89.77 mg, 0.64 mmol, 3 *equiv*). The mixture was stirred at 120 °C for 12 hr. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM/MeOH= 10/1) to afford (6S)-4-(4-(2-(2-(3,5-difluoro-4-(4-methyl-2-phenyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-2H-chromen-3-yl)phenoxy)ethoxy)ethoxy)phenyl)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (110 mg, 57% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.643 min, m/z = 859.3 [M +H^+]

[0675] Step 4: Preparation of 3-(2,6-difluoro-4-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy)phenyl)-4-methyl-2-phenyl-2H-chromen-6-ol. To a solution of (9S)-7-[4-[2-[2-[3,5-difluoro-4-(4-methyl-2-phenyl-6-tetrahydropyran-2-yloxy-2H-chromen-3-yl)phenoxy]ethoxy]ethoxy] phenyl]-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.02,6]trideca-2(6),4,7,10,12-pentaene (100 mg, 0.11 mmol, 1 equiv) in dioxane (3 mL) was added HCl (1 M, 2 mL, 17.18 equiv). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150mm x 30mm x 7um; mobile phase: [water (FA)-ACN]; gradient: 53%-83% B over 10 min) to afford 3-(2,6-difluoro-4-(2-(2-(4-((S)-2,3,6,9-tetramethyl-6H-thieno [3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenoxy)ethoxy)ethoxy) phenyl)-4-methyl-2-phenyl-2H-chromen-6-ol (**I-39**, 42.73 mg, 44% yield) as a mixture of stereoisomers, which were a white solid. ^{1}H NMR (400 MHz, DMSO-d6) 7.50 - 7.39 (m, 2H), 7.31 (t, J = 6.0 Hz, 2H), 7.24 - 7.07 (m, 4H), 7.05 - 6.98 (m, 1H), 6.92 - 6.81 (m, 3H), 6.75 - 6.66 (m, 1H), 6.49 - 6.26 (m, 2H), 6.06 - 5.86 (m, 1H), 5.35 -

5.25 (m, 1H), 4.22 - 4.11 (m, 3H), 4.10 - 3.93 (m, 4H), 3.93 - 3.80 (m, 3H), 3.75 - 3.53 (m, 2H), 2.69 (s, 3H), 2.41 (s, 3H), 2.11 (d, J = 6.4 Hz, 3H), 2.01 - 1.93 (m, 3H), 1.91 - 1.79 (m, 3H), 1.72 - 1.70 (m, 2H), 1.68 (d, J = 7.6 Hz, 2H). LC-MS: MS (ES+): RT = 2.121 min, m/z = 775.5 [M +H+]; LCMS Method: 25.

EXAMPLE 41 – Synthesis of 4-((4-(3,5-difluoro-4-((1S,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-245) and 4-((4-(3,5-difluoro-4-((1R,2R)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-244)





[0676] **Step 1:** A mixture of 1-bromo-3,5-difluoro-benzene (9 g, 46.63 mmol, 5.37 mL, 1 *equiv*), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (17.30 g, 55.96 mmol, 1.2 *equiv*), Cs_2CO_3 (45.58 g, 139.90 mmol, 3 *equiv*), and $Pd(dppf)Cl_2$ (3.41 g, 4.66 mmol, 0.1 *equiv*) in dioxane (200 mL) and H_2O (40 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, PE: EA = 3:1) to afford tert-butyl 4-(3,5-difluorophenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (13 g, 94% yield) as a yellow oil. LC-MS: MS (ES^+): RT = 0.903 min, m/z = 240.4 [M - 55]; LCMS method 5-95.

[0677] **Step 2:** A mixture of tert-butyl 4-(3,5-difluorophenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (13 g, 44. mmol, 1 *equiv*) and Pd/C (4.68 g, 4.40 mmol, 10% purity, 0.1 *equiv*) in THF (130 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 20 °C for 12 h under H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to afford tert-butyl 4-(3,5-difluorophenyl)piperidine-1-carboxylate (12.7 g, 97%

yield) as a yellow oil. LC-MS: MS (ES^+): RT = 0.922 min, m/z = 242.2 [M - 55]; LCMS method 5-95.

[0678] **Step 3:** A mixture of tert-butyl 4-(3,5-difluorophenyl)piperidine-1-carboxylate (4 g, 13.45 mmol, 1 *equiv*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.12 g, 20.18 mmol, 1.5 *equiv*), 3,4,7,8-tetramethyl-1,10-phenanthroline (317 mg, 1.35 mmol, 0.1 *equiv*), and (1Z,5Z)-cycloocta-1,5-diene;2,4-dimethyl-BLAHbicyclo[1.1.0]butane (445 mg, 672 μmol, 0.05 *equiv*) in THF (45 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated to give crude compound as a yellow solid. The crude product tert-butyl 4-[3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (5.6 g, crude) was used in the next step without further purification. LC-MS: MS (ES^+): RT = 0.993 min, m/z = 368.1 [M - 55]; LCMS method 5-95.

[0679] **Step 4:** A mixture of (6-benzyloxy-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate (4.24 g, 11.02 mmol, 1 *equiv*), tert-butyl 4-[3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (5.6 g, 13.23 mmol, 1.2 *equiv*), $Pd(dppf)Cl_2$ (806 mg, 1.10 mmol, 0.1 *equiv*), and K_2CO_3 (4.57 g, 33.07 mmol, 3 *equiv*) in dioxane (50 mL) and H_2O (12 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 3 h under N_2 atmosphere. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO2, PE : EA = 3:1) to afford tert-butyl 4-[4-(6-benzyloxy-3,4-dihydronaphthalen-1-yl)-3,5-difluoro-phenyl]piperidine-1-carboxylate (2.3 g, 39% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 1.090 min, m/z = 476.1 [M - 55]; LCMS method 5-95.

[0680] **Step 5:** To a solution of tert-butyl 4-[4-(6-benzyloxy-3,4-dihydronaphthalen-1-yl)-3,5-difluoro-phenyl]piperidine-1-carboxylate (2.3 g, 4.33 mmol, 1 *equiv*) in MeCN (20 mL) was added NBS (770 mg, 4.33 mmol, 1 *equiv*). The mixture was stirred at 20 °C for 2 h. The reaction mixture was partitioned between ethyl acetate 100 mL and water 50 mL. The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica column chromatography on silica gel (Petroleum ether: Ethyl acetate from 1/0 to 3/1) to afford tert-butyl 4-[4-(6-benzyloxy-2-bromo-3,4-dihydronaphthalen-1-yl)-3,5-difluoro-phenyl] piperidine-1-carboxylate (2.2 g, 83% yield) as a yellow oil. LC-MS: MS (ES^+): RT = 1.223 min, m/z = 554.2 [M - 55]; LCMS method 5-95.

[0681] **Step 6:** A mixture of (4-fluorophenyl)boronic acid (504 mg, 3.60 mmol, 1.1 *equiv*), tert-butyl 4-[4-(6-benzyloxy-2-bromo-3,4-dihydronaphthalen-1-yl)-3,5-difluoro-phenyl]piperidine-1-carboxylate (2 g, 3.28 mmol, 1 *equiv*), $Pd(dppf)Cl_2$ (239 mg, 327 μmol, 0.1 *equiv*), and K_2CO_3 (1.13 g, 8.19 mmol, 2.5 *equiv*) in dioxane (30 mL) and H_2O (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 2 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate from 1/0 to 3/1) to afford tert-butyl 4-[4-[6-benzyloxy-2-(4-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3,5-difluoro-phenyl]piperidine-1-carboxylate (2 g, 97% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl3) δ = 7.47-7.34 (m, 5H), 7.10-7.01 (m, 2H), 6.94-6.79 (m, 3H), 6.79-6.55 (m, 4H), 5.08 (s, 2H), 4.38-4.13 (m, 2H), 3.03 (t, J = 7.8 Hz, 2H), 2.92-2.70 (m, 4H), 2.69-2.53 (m, 1H), 1.90-1.75 (m, 2H), 1.68-1.58 (m, 2H), 1.50 (s, 9H). LC-MS: MS (ES^+): RT = 1.238 min, m/z = 526.3 [M - 100]; LCMS method 5-95.

[0682] **Step 7:** To a solution of tert-butyl 4-[4-[6-benzyloxy-2-(4-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3,5-difluoro-phenyl]piperidine-1-carboxylate (2 g, 3.20 mmol, 1 *equiv*) in MeOH (30 mL) was added Pd/C (680 mg, 639 μmol, 10% purity, 0.2 *equiv*) and $Pd(OH)_2$ (448 mg, 639 μmol, 20% purity, 0.2 *equiv*) under H_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi.) at 50 °C for 12 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate from 1/0 to 3/1) to afford (±)-*cis*-tert-butyl 4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]phenyl]piperidine-1-carboxylate (1.7 g, 98% yield) as a yellow oil. LC-MS: MS (ES^+): RT = 1.098 min, m/z = 482.3 [M - 55]; LCMS method 5-95.

[0683] **Step 8:** To a solution of (±)-*cis*-tert-butyl 4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]phenyl]piperidine-1-carboxylate (1.7 g, 3.16 mmol, 1 *equiv*) in DCM (20 mL) was added TIPSCl (1.22 g, 6.32 mmol, 1.35 mL, 2 *equiv*) and imidazole (645.81 mg, 9.49 mmol, 3 *equiv*) at 0°C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was partitioned between DCM 200 mL and water 100 mL. The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate from 1/0 to 3/1) to afford (±)-*cis*-tert-butyl 4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]phenyl]

piperidine-1 -carboxylate (1 g, 45 % yield) as a yellow oil. LC-MS: MS (ES^+): RT = 1.280 min, m/z = 594.4 [M - 100]; LCMS method 5-95.

[0684] **Step 9:** To a solution of (±)-*cis*-tert-butyl 4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]phenyl]piperidine-1-carboxylate (1 g, 1.44 mmol, 1 *equiv*) in DCM (6 mL) was added TFA (2.30 g, 20.19 mmol, 1.50 mL, 14.01 *equiv*). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was partitioned between DCM 100 mL and water 50 mL. The organic phase was separated, filtered and concentrated under reduced pressure to afford (±)-*cis*-[1-[2,6-difluoro-4-(4-piperidyl)phenyl]-2-(4-fluorophenyl)tetralin-6-yl]oxy-triisopropyl- silane (855 mg, 99 % yield) as a yellow oil. LC-MS: MS (ES^+): RT = 0.954 min, m/z = 594.4 [$M + H^+$]; LCMS method 5-95.

[0685] **Step 10:** To a solution of (±)-*cis*-[1-[2,6-difluoro-4-(4-piperidyl)phenyl]-2-(4-fluorophenyl)tetralin-6-yl]oxy-triisopropyl-silane (1.7 g, 2.86 mmol, 1 *equiv*) in EtOH (20 mL) was added DIEA (1.11 g, 8.59 mmol, 1.50 mL, 3 *equiv*) and tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (915 mg, 4.29 mmol, 1.5 *equiv*. The mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate from 1/0 to 3/1) to afford (±)-*cis*-tert-butyl 4-[[4-[3,5-difluoro-4-[2-(4-fluorophenyl) -6-triisopropylsilyloxy-tetralin-1-yl]phenyl]-1-piperidyl]methyl]-4-hydroxy-piperidine-1-carboxylate (1.7 g, 73% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.10-7.01 (m, 1H), 6.93-6.72 (m, 5H), 6.69-6.65 (m, 1H), 6.63-6.57 (m, 1H), 6.51-6.41 (m, 1H), 4.03-3.60 (m, 4H), 3.50-3.40 (m, 2H), 3.23-3.13 (m, 2H), 3.01-2.91 (m, 3H), 2.62-2.22 (m, 6H), 1.85-1.78 (m, 2H), 1.51-1.46 (m, 18H), 1.15-1.09 (m, 18H). LC-MS: MS (ES^+): RT = 1.012 min, m/z = 807.5 [$M + H^+$]; LCMS method 5-95.

[0686] **Step 11:** To a solution of (±)-*cis*-tert-butyl 4-[[4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]phenyl]-1-piperidyl]methyl]-4-hydroxy-piperidine-1-carboxylate (1 g, 1.24 mmol, 1 *equiv*) in DCM (5 mL) was added TFA (3.84 g, 33.66 mmol, 2.5 mL, 27.16 *equiv*). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was partitioned between DCM 100 mL and $NaHCO_3$ 50 mL. The organic phase was separated, filtered and concentrated under reduced pressure to afford (±)-*cis*-4-[[4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]phenyl]-1-piperidyl]methyl]piperidin-4-ol (875 mg, 99% yield) as a yellow oil. LC-MS: MS (ES^+): RT = 0.876 min, m/z = 707.2 [$M + H^+$]; LCMS method: 5-95.

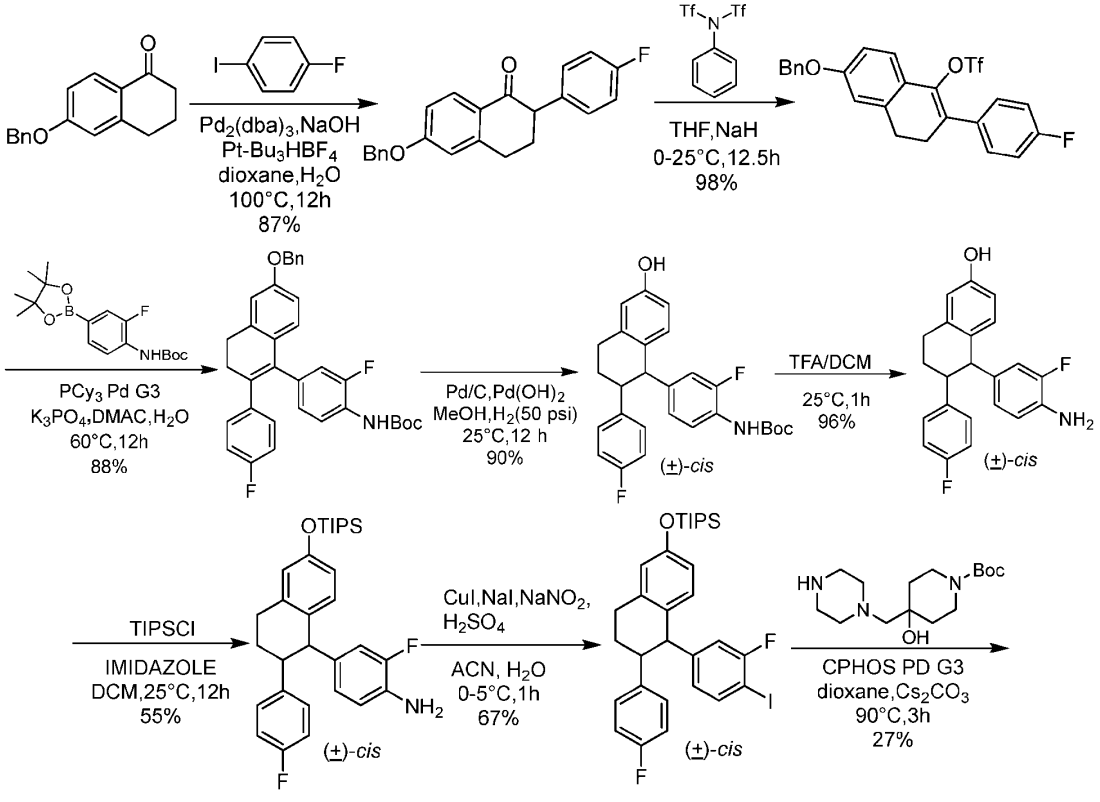
[0687] **Step 12:** A mixture of (9S)-7-(4-chlorophenyl)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaene (326 mg, 913.49 μmol, 1 *equiv*), (±)-*cis*-4-[[4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6- triisopropylsilyloxy-tetralin-1-yl]phenyl]-1-piperidyl]methyl]piperidin-4-ol (775 mg, 1.10 mmol, 1.2 *equiv*), Cs_2CO_3 (892 mg, 2.74 mmol, 3 *equiv*) and SPhos Pd G_3 (71 mg, 91 μmol, 0.1 *equiv*) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 3 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate from 1/0 to 3/1) to afford a mixture of the two *cis*-tetraline diastereomers of 4-[[4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6- triisopropylsilyloxy-tetralin-1-yl]phenyl] -1-piperidyl]methyl]-1-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperidin-4-ol (850 mg, 90 % yield) as a yellow solid. LC-MS: MS (ES^+): RT = 0.927 min, m/z = 1026.9 [M +H^+]; LCMS method 5-95.

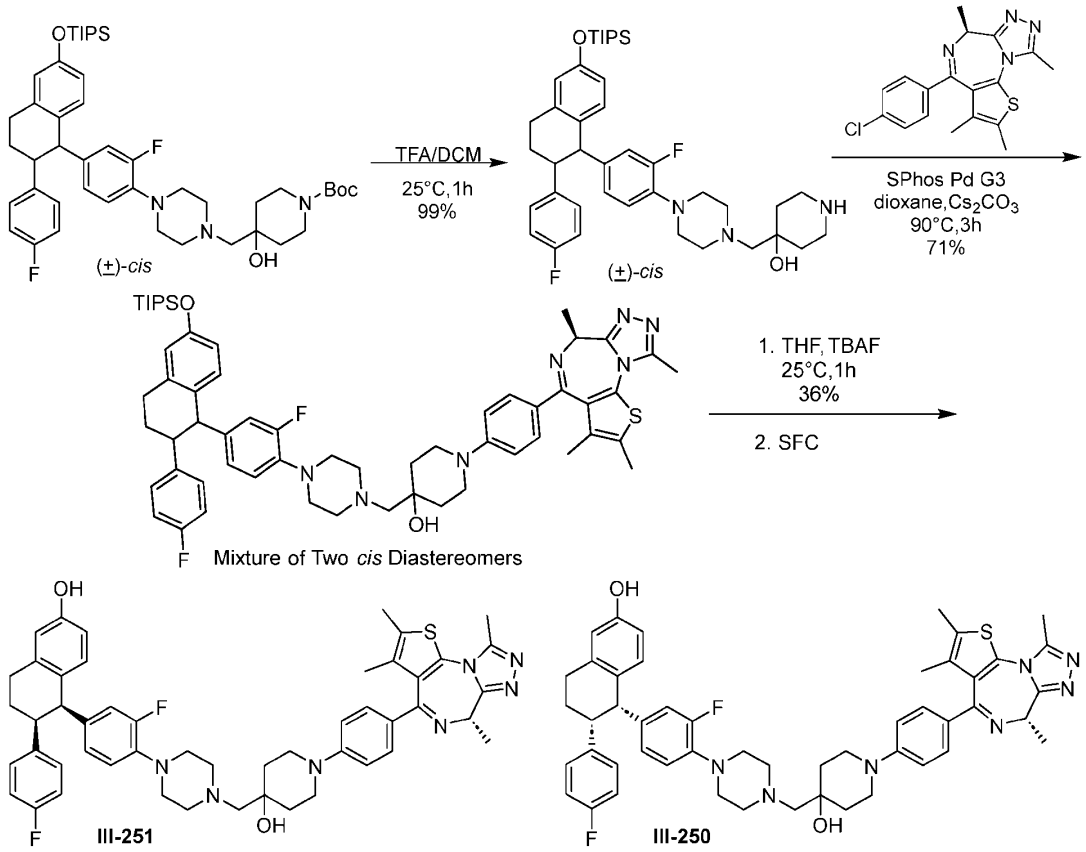
[0688] **Step 13:** To a solution of the two *cis*-tetraline diastereomers of 4-[[4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]phenyl]-1-piperidyl]methyl]-1-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperidin-4-ol (400 mg, 389 μmol, 1 *equiv*) in THF (5 mL) was added TBAF (1 M, 1.00 mL, 2.57 *equiv*). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was partitioned between EA 100 mL and water 50 mL. The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to afford a mixture of the two *cis*-tetraline diastereomers of 4-[[4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]phenyl]-1-piperidyl]methyl]-1-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperidin-4-ol (300 mg, 88 % yield) as a yellow solid. LC-MS: MS (ES^+): RT = 0.761 min, m/z = 871.3 [M +H^+]; LCMS method: 5-95.

[0689] **Step 14:** A mixture of the two *cis*-tetraline diastereomers of 4-[[4-[3,5-difluoro-4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]phenyl]-1-piperidyl]methyl]-1-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperidin-4-ol (300 mg, 344 μmol) was purified by prep-SFC (column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO2-ACN/i-PrOH (0.1% NH3H2O)]; B%:65%, isocratic elution mode) and (column: DAICEL CHIRALPAK IG (250mm*30mm, 10um); mobile phase: [CO2-ACN/EtOH(0.1% NH3H2O)]; B%:65%, isocratic elution mode) to

afford compounds **III-245** and **III-244**. The second-eluting diastereomer, which was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below), was obtained as a yellow solid (45 mg, 16 % yield). ^{1}H NMR (400 MHz, CDCl3) δ = 7.30 (d, *J* = 8.8 Hz, 2H), 6.83-6.75 (m, 4H), 6.74-6.69 (m, 3H), 6.62 (d, *J* = 2.4 Hz, 1H), 6.55-6.47 (m, 1H), 6.45-6.27 (m, 2H), 4.57 (d, *J* = 5.6 Hz, 1H), 4.07 (d, *J* = 6.8 Hz, 1H), 3.57-3.45 (m, 2H), 3.37-3.27 (m, 1H), 3.26-3.14 (m, 2H), 2.99-2.91 (m, 3H), 2.59 (s, 3H), 2.47-2.37 (m, 2H), 2.34 (s, 3H), 2.29-2.20 (m, 2H), 2.00 (d, *J* = 6.8 Hz, 3H), 1.84-1.76 (m, 2H), 1.69 (s, 3H), 1.65-1.45 (m, 10H). LC-MS: MS (ES$^+$): RT = 1.530 min, m/z = 871.3 [M + H$^+$]; LCMS method 25.

EXAMPLE 42 – Synthesis of 4-((4-(2-fluoro-4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)methyl)-1-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-251) and 4-((4-(2-fluoro-4-((1S,2R)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)methyl)-1-(4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-250)





[0690] **Step 1:** To a solution of 6-benzyloxytetralin-1-one (10 g, 39.63 mmol, 1.0 equiv) in dioxane (200 mL) and H_2O (50 mL) was added 1-fluoro-4-iodo-benzene (10.56 g, 47.56 mmol, 5.48 mL, 1.2 equiv), tritert-butylphosphonium tetrafluoroborate(2.30 g, 7.93 mmol, 0.2 equiv), $Pd_2(dba)_3$ (3.63 g, 3.96 mmol, 0.1 equiv) and NaOH (3.17 g, 79.27 mmol, 2.0 equiv). The mixture was stirred at 100 °C for 12 h. The reaction mixture was diluted with H_2O 100 mL and extracted with EA 150 mL (50 mL * 3). The combined organic layers were washed with saturated NaCl aqueous (20 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1) to give 6-benzyloxy-2-(4-fluorophenyl)tetralin-1-one (12 g, 87% yield) as a brown solid. ^1H NMR (400 MHz, CDCl3) δ 8.12-8.05 (m, 1H), 7.49-7.34 (m, 5H), 7.21-7.12 (m, 2H), 7.08-6.99 (m, 2H), 6.97-6.92 (m, 1H), 6.85-6.80 (m, 1H), 5.15 (s, 2H), 3.88-3.65 (m, 1H), 3.20-2.91 (m, 2H), 2.49-2.30 (m, 2H). LC-MS: MS (ES+): RT = 0.667 min, m/z = 347.1 [M + H+]; LCMS Method: 5-95.

[0691] **Step 2:** To a mixture of 6-benzyloxy-2-(4-fluorophenyl)tetralin-1-one (4.6 g, 13.28 mmol, 1.0 *equiv*) in THF (50 mL) was added NaH (1.06 g, 26.56 mmol, 60% purity, 2.0 *equiv*) at 0 °C for 0.5 h under N_2 atmosphere. Then 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl) methanesulfonamide (13.05 g, 36.52 mmol, 2.75 *equiv*) was added to the mixture. The mixture was stirred at 25 °C for 12.5 h under N_2 atmosphere. The reaction mixture was quenched by addition saturated NH_4Cl (20 mL) under N_2 atmosphere, and then extracted with EA (30 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, PE/EA=100/1 to 1/1) to give [6-benzyloxy-2-(4-fluorophenyl)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (10 g, 98% yield, 62% purity) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.51 (m, 3H), 7.44-7.41 (m, 5H), 7.15-7.08 (m, 2H), 6.95-6.86 (m, 2H), 5.11 (s, 2H), 3.09-2.93 (m, 2H), 2.82-2.74 (m, 2H).

[0692] **Step 3:** To a solution of [6-benzyloxy-2-(4-fluorophenyl)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (8.70 g,11.27 mmol, 1.0 *equiv*) in DMAC (225 mL) and H_2O (45 mL) was added tert-butyl N-[2-fluoro-4-(4,4,5,5-tetramethyl1,3,2-dioxaborolan-2-yl)phenyl]carbamate (3.8 g, 11.27 mmol, 1.0 *equiv*), [2-(2-aminophenyl)phenyl]-methylsulfonyloxypalladium; dichloromethane;tricyclohexylphosphane (828.41 mg, 1.13 mmol, 0.1 *equiv*) and K_3PO_4 (7.18 g, 33.81 mmol,3.0 *equiv*). The mixture was stirred at 60 °C for 12 h. The reaction mixture was diluted with H_2O 150 mL and extracted with EA (50 mL * 3). The combined organic layers were washed with saturated NaCl aqueous (50 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1) to give tert-butyl N-[4-[6-benzyloxy-2-(4-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-2-fluoro-phenyl]carbamate (5.33 g, 88% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 1.227 min, m/z = 562.3 [M + Na^+]; LCMS Method: 5-95.

[0693] **Step 4:** To a solution of tert-butyl N-[4-[6-benzyloxy-2-(4-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-2-fluorophenyl]carbamate (5.3 g, 9.82 mmol, 1.0 *equiv*) in MeOH (60 mL) was added Pd/C (500 mg, 470 μmol, 10% purity, 0.1 *equiv*) and $Pd(OH)_2$ (500 mg, 712 μmol, 20% purity, 0.1 *equiv*) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 psi) at 25 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give (±)-*cis*-tert-butyl 3-[(4-methoxycarbonylcyclohexyl)methyl]azetidine-1-carboxylate (4 g, 90% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.670 min, m/z = 474.2 [M + Na^+]; LCMS Method: 5-95.

[0694] **Step 5:** To a solution of (±)-*cis*-tert-butyl N-[2-fluoro-4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]phenyl]carbamate (2 g, 4.43 mmol, 1.0 *equiv*) in DCM (20 mL) was added TFA (3.07 g, 26.92 mmol, 2 mL, 6.08 *equiv*). The mixture was stirred at 25 °C for 1h. The reaction mixture was added $NaHCO_3$ to adjust pH > 7. To the reaction mixture was added water (2 mL) and the mixture was extracted with DCM (30 mL). The combined organic phase was washed with brine (3 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum give (±)-*cis*-1-(4-amino-3-fluoro-phenyl)-2-(4-fluorophenyl)tetralin-6-ol (1.5 g, 96 % yield) as a white oil. LC-MS: MS (ES^+): RT = 0.813 min, m/z = 352.3 [$M + H^+$]; LCMS Method: 5-95.

[0695] **Step 6:** To a solution of (±)-*cis*-1-(4-amino-3-fluoro-phenyl)-2-(4-fluorophenyl)tetralin-6-ol (1.5 g, 4.27 mmol, 1.0 *equiv*) in DCM (15 mL) was added TIPSCl (2.47 g, 12.81 mmol, 2.74 mL, 3.0 *equiv*) and imidazole (1.45 g, 21.34 mmol, 5.0 *equiv*). The mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched by addition Na_2SO_3 (5 mL) at 0 °C, and then diluted with H_2O 10 mL and extracted with EA 30 mL (10 mL * 3). The combined organic layers were washed with saturated NaCl aqueous 30mL (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1) to give (±)-*cis*-2-fluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]aniline (1.2 g, 2.36 mmol, 55% yield) as a white oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.93-6.84 (m, 2H), 6.81-6.74 (m, 4H), 6.67-6.61 (m, 1H), 6.45-6.38 (m, 1H), 6.11-6.03 (m, 1H), 5.98-5.92 (m, 1H), 4.17-4.10 (m, 1H), 3.39-3.29 (m, 1H), 3.06-2.95 (m, 2H), 2.20-2.05 (m, 1H), 1.86-1.72 (m, 1H), 1.33-1.23 (m, 3H), 1.20-1.05 (m, 18H). LC-MS: MS (ES^+): RT = 0.916 min, m/z = 508.3 [$M + H^+$]; LCMS Method: 5-95.

[0696] **Step 7:** To a solution of (±)-*cis*-2-fluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]aniline (1 g, 1.97 mmol, 1.0 *equiv*) in THF (20 mL) was added $NaNO_2$ (271.78 mg, 3.94 mmol, 2.0 *equiv*) in H_2O (1 mL).Then was added H_2SO_4 (2 M, 2.95 mL, 3.0 *equiv*) at 0-5 °C, the mixture was stirred at this temperature for 0.5 h. Then NaI (1.48 g, 9.85 mmol, 5.0 *equiv*) in H_2O (2.5 mL) was added into the mixture. Then mixture was stirred at 0-5 °C for 0.5 hr. Then the reaction mixture was added $NaHCO_3$ to adjust pH > 7. Then the reaction mixture was added water (2 mL) and was extracted with DCM (5 mL). The combined organic phase was washed with brine (3 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1) to give (±)-*cis*-[1-(3-fluoro-4-iodo-phenyl)-2-(4-fluorophenyl)tetralin-6-yl]oxy-triisopropyl-silane (820 mg, 67% yield) as a white solid. LC-MS: MS (ES^+): RT=1.280 min, m/z = 619.2 [$M + H^+$]; LCMS Method: 5-95.

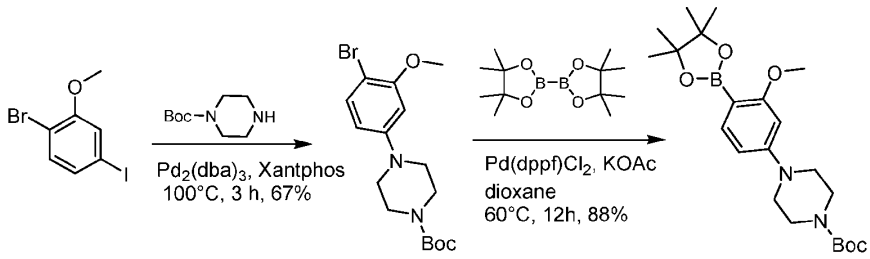
[0697] **Step 8:** To a solution of (±)-*cis*-[1-(3-fluoro-4-iodo-phenyl)-2-(4-fluorophenyl)tetralin-6-yl]oxy-triisopropyl-silane (700 mg, 1.13 mmol, 1.0 *equiv*) in dioxane (15 mL) was added tert-butyl 4-hydroxy-4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (677.60 mg, 2.26 mmol, 2.0 *equiv*), CPhos Pd G3 (182.49 mg, 226 μmol, 0.2 *equiv*) and Cs_2CO_3 (1.11 g, 3.39 mmol, 3.0 *equiv*). The mixture was stirred at 90 °C for 3h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=100/1 to 0/1) to give (±)-*cis*-tert-butyl 4-[[4-[2-fluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxytetralin-1-yl]phenyl]piperazin-1-yl]methyl]-4-hydroxy-piperidine-1-carboxylate (240 mg, 27% yield) as a white solid. LC-MS: MS (ES^+): RT = 1.073 min, m/z = 790.6 [M + H^+]; LCMS Method: 5-95.

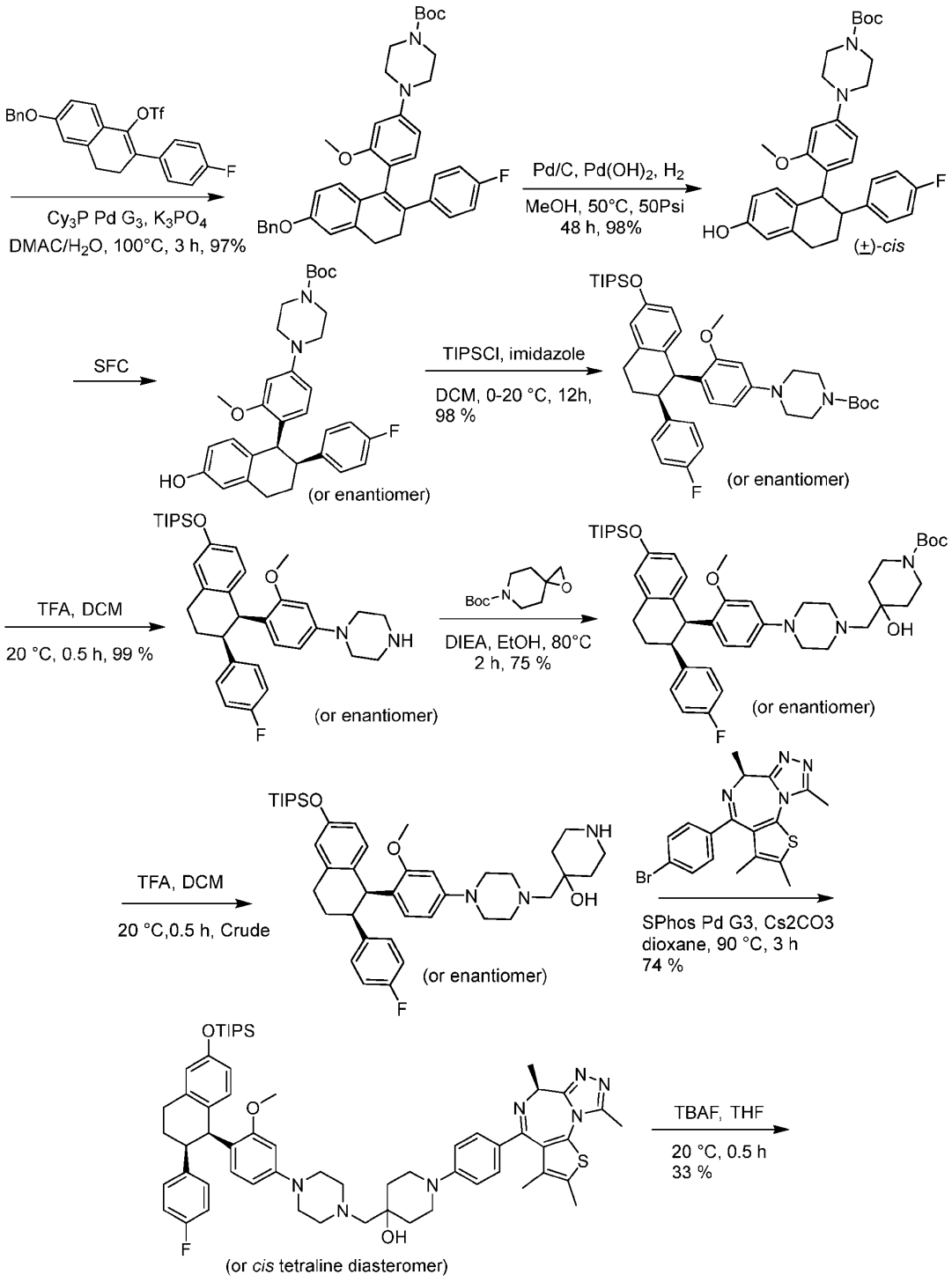
[0698] **Step 9:** To a solution of (±)-*cis*-tert-butyl 4-[[4-[2-fluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]phenyl]piperazin1-yl]methyl]-4-hydroxy-piperidine-1-carboxylate (240 mg, 304 μmol, 1.0 *equiv*) in DCM (2 mL) was added TFA (307.00 mg, 2.69 mmol, 0.2 mL, 8.86 *equiv*). The mixture was stirred at 25 °C for 1h. The reaction mixture was added $NaHCO_3$ to adjust pH > 7. To the reaction mixture was added water (2 mL) and the mixture was extracted with DCM (5 mL). The combined organic phase was washed with brine (3 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give (±)-*cis*- 4-[[4-[2-fluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1- yl]phenyl]piperazin-1-yl]methyl]piperidin-4-ol (209 mg, 99 % yield) as a white solid. LC-MS: MS (ES^+): RT = 0.711 min, m/z = 690.4 [M + H^+]; LCMS Method: 5-95.

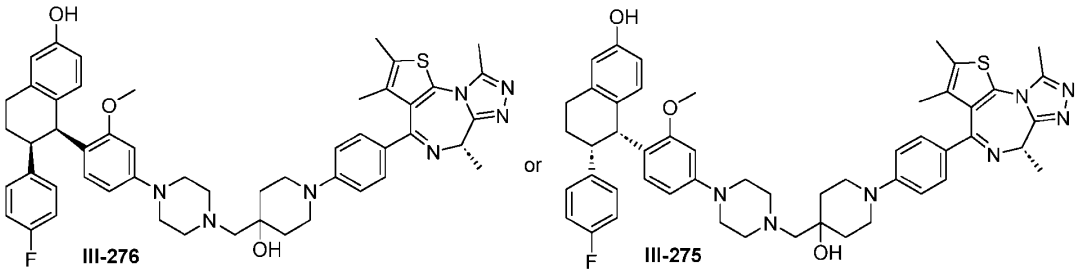
[0699] **Step 10:** To a solution of (±)-*cis*-4-[[4-[2-fluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]phenyl]piperazin-1-yl]methyl]piperidin-4-ol (209 mg, 308 μmol, 1.0 equiv) in dioxane (8 mL) was added (9S)-7-(4-chlorophenyl)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaene (110 mg, 308 μmol, 1.0 *equiv*), SPhos Pd G3 (48 mg, 63 μmol, 0.2 *equiv*) and Cs_2CO_3 (301 mg, 925 μmol, 3.0 *equiv*). The mixture was stirred at 90 °C for 3h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (SiO_2, DCM: MeOH=10:1) to give a mixture of the two *cis*-tetraline diastereomers of 4-[[4-[2-fluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxytetralin-1-yl]phenyl]piperazin-1-yl]methyl]-1-[4-[(9S)-4,5,9,13-tetramethyl-3-thia1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperidin-4-ol (210 mg, 71% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 0.703 min, m/z =1010.3 [M + H^+]; LCMS Method: 5-95.

[0700] **Step 11:** To a solution of the two *cis*-tetraline diastereomers of 4-[[4-[2-fluoro-4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]phenyl]piperazin-1-yl]methyl]-1-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperidin-4-ol (210 mg, 208 μmol, 1.0 *equiv*) in THF (1 mL) was added TBAF (1 M, 208 μL, 1.0 *equiv*). The mixture was stirred at 25 °C for 2h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (SiO2, DCM: MeOH = 10:1) and SFC (Column: Chiralcel OD-350×4.6mm I.D., 3um Mobile phase: Phase A for CO2, and Phase B for IPA+ACN(0.05%DEA); Gradient elution: 40% IPA+ACN (0.05% DEA) in CO2 Flow rate: 3mL/min; Detector: PDA; Column Temp: 35C; Back Pressure: 100Bar) to give **III-251** and **III-250**. The second-eluting diastereomer, which was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below), was obtained as a white solid (65.43 mg, 36% yield, 98.86% purity). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.35 (m, 2H), 6.95-6.82 (m, 4H), 6.81-6.70 (m, 4H), 6.65-6.49 (m, 2H), 6.17-6.06 (m, 2H), 4.19-4.10 (m, 2H), 3.3.63-3.52 (m, 2H), 3.39-3.31 (m, 1H), 3.30-3.19 (m, 2H), 3.09-2.93 (m, 6H), 2.86- 2.75 (m, 4H), 2.67 (s, 3H), 2.41 (s, 5H), 2.14-2.05 (m, 4H), 1.77 (s, 6H), 1.70-1.66 m, 2H). LCMS: MS (ES^+): RT = 1.493 min, m/z = 854.3 [$M + H^+$]. LCMS Method: 25.

EXAMPLE 43 – Synthesis of 4-((4-(4-((1S,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-276) and 4-((4-(4-((1R,2R)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-275)




BnO
OTf
F
Cy3P Pd G3, K3PO4
DMAC/H2O, 100°C, 3 h, 97%
Boc
N
O
BnO
Pd/C, Pd(OH)2, H2
MeOH, 50°C, 50Psi
48 h, 98%
HO
(±)-cis
SFC
(or enantiomer)
TIPSCl, imidazole
DCM, 0-20 °C, 12h,
98 %
TIPSO
Boc
TFA, DCM
20 °C, 0.5 h, 99 %
NH
DIEA, EtOH, 80°C
2 h, 75 %
OH
TFA, DCM
20 °C,0.5 h, Crude
Br
SPhos Pd G3, Cs2CO3
dioxane, 90 °C, 3 h
74 %
S
OTIPS
TBAF, THF
20 °C, 0.5 h
33 %
(or cis tetraline diasteromer)



[0701] **Step 1:** A mixture of tert-butyl piperazine-1-carboxylate (2.98 g, 15 mmol, 1 *equiv*), 1-bromo-4-iodo-2-methoxy-benzene (5 g, 15 mmol, 1 *equiv*), $Pd_2(dba)_3$ (1 g, 1 mmol, 0.1 *equiv*), Xantphos (924 mg, 1 mmol, 0.1 *equiv*) and Cs_2CO_3 (15 g, 47 mmol, 3 *equiv*) in DMF (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The reaction mixture was diluted with water (20 mL) and then extracted with ethyl acetate (120 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether : Ethyl acetate =10/1) to give compound tert-butyl 4-(4-bromo-3-methoxy-phenyl)piperazine-1-carboxylate (4 g, 10.8 mmol, 67 % yield) as a red solid, and used for next step directly. LC-MS: MS (ES^+): RT = 0.906 min, m/z = 371.0 [M - 100]; LCMS Method: 5-95.

[0702] **Step 2:** A mixture of tert-butyl 4-(4-bromo-3-methoxy-phenyl)piperazine-1-carboxylate (4 g, 10 mmol, 1 *equiv*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (8 g, 32 mmol, 3 *equiv*), $Pd(dppf)Cl_2$ (788 mg, 1 mmol, 0.1 *equiv*), and potassium acetate (3 g, 32 mmol, 3 *equiv*) in dioxane (80 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The reaction mixture was diluted with water (20 mL) and then extracted with ethyl acetate (60 mL × 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether : Ethyl acetate=3/1) to give compound tert-butyl 4-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (4 g, 9 mmol, 88 % yield) as a yellow solid. LC-MS: MS (ES^+): RT = 0.883 min, m/z =419.4 [M + 1]; LCMS Method: 5-95.

[0703] **Step 3:** A mixture of tert-butyl 4-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (2 g, 6 mmol, 1 *equiv*), [6-benzyloxy-2-(4-fluorophenyl)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (3 g, 6 mmol,

1 *equiv*), tricyclohexylphosphane Pd G3 (460 mg, 627 μmol, 0.1 *equiv*), K_3PO_4 (3 g, 18 mmol, 3 *equiv*) in H_2O (15 mL) and DMAC (75 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The reaction mixture was diluted with water (20 mL) and then extracted with ethyl acetate (60 mL × 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate =5/1) to give compound tert-butyl 4-[4-[6-benzyloxy-2-(4-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (3.8 g, 6 mmol, 97 % yield) as a yellow solid. LC-MS: MS (ES^+): RT = 1.058 min, m/z =621.4 [M + 1]; LCMS Method: 5-95.

[0704] **Step 4:** Palladium on carbon (1.5 g, 1 mmol, 10% purity, 0.2 *equiv*) and $Pd(OH)_2$ (1.5 g, 2 mmol, 20% purity, 0.4 *equiv*) were added into a 250 mL single-necked round bottom flask under N_2, and then MeOH (80 mL) was added at 25 °C under N_2. After addition, tert-butyl 4-[4-[6-benzyloxy-2-(4-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (3.8 g, 6 mmol, 1 *equiv*) was added under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 50 °C for 48 h. The residue was filtered and concentrated under reduced pressure to give (±)-*cis*-tert-butyl 4-[4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (3.2 g, 98 % yield) as a white solid. LC-MS: MS (ES^+): RT = 0.948 min, m/z =533.3 [M + 1]; LCMS Method: 5-95.

[0705] **Step 5:** Racemic *cis*-tert-butyl 4-[4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (500 mg, 0.938 mmol) was purified by prep-SFC (column: DAICEL CHIRALPAK AD (250mm*30mm, 10um); mobile phase: [CO_2-EtOH ($0.1\%NH_3H_2O$)]; B%: 40%, isocratic elution mode) to afford (1S,2S)- and (1R,2R)-tert-butyl 4-[4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. The faster-eluting enantiomer (146 mg, 274.10 μmol, 29.20% yield, 99% ee) was obtained as a yellow oil, and the slower-eluting enantiomer (188 mg, 37 % yield, 99% ee) was obtained as a yellow solid. LC-MS: MS (ES^-): RT = 1.025 min, m/z =533.3 [$M + H^+$]; LCMS Method: 5-95.

[0706] The following Steps 6 through 11 describe further synthetic procedures conducted on the slower-eluting enantiomer of *cis*- tert-butyl 4-[4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. This slower-eluting enantiomer produced the diastereomer of compounds **III-276** and **III-275** that was found to be the more potent inhibitor of

cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The faster-eluting enantiomer of *cis*- tert-butyl 4-[4-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate was carried through the same steps to afford the other one of compounds **III-276** and **III-275**.

[0707] **Step 6:** To a solution of tert-butyl 4-[4-(1S,2S)-[2-(4-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate or its enantiomer (188 mg, 352 μmol, 1 *equiv*) in DCM (2 mL) was added TIPSCl (136 mg, 705 μmol, 151 μL, 2 *equiv*) and imidazole (72 mg, 1.06 mmol, 3 *equiv*) at 0 °C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was partitioned between dichloromethane (100 mL) and water (50 mL). The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether: Ethyl acetate = 3:1) to afford tert-butyl 4-[4-(1S, 2S)-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate or its enantiomer (240 mg, 98 % yield) as a yellow oil. LC-MS: MS (ES^+): RT = 1.338 min, m/z =689.5 [M + 1]; LCMS Method: 5-95.

[0708] **Step 7:** To a solution of tert-butyl 4-[4-(1S,2S)-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate or its enantiomer (240 mg, 348 μmol, 1 *equiv*) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 38 *equiv*). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was partitioned between dichloromethane (100 mL) and water (50 mL). The organic phase was separated, filtered and concentrated under reduced pressure to afford [2-(1S,2S)-(4-fluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-yl]oxy-triisopropyl-silane or its enantiomer (205 mg, 99 % yield) as a yellow oil. LC-MS: MS (ES^+): RT = 1.046 min, m/z =589.5 [M + 1]; LCMS Method: 5-95.

[0709] **Step 8:** To a solution of [2-(1S,2S)-(4-fluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-yl]oxy-triisopropyl-silane or its enantiomer (180 mg, 305 μmol, 1 *equiv*) in EtOH (3 mL) was added DIEA (118 mg, 917 μmol, 159 μL, 3 *equiv*) and tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (97 mg, 458 μmol, 1.5 *equiv*). The mixture was stirred at 80 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether: Ethyl acetate = 3:1) to afford tert-butyl 4-[[4-[4-(1S,2S)-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]-3-methoxy-phenyl]piperazin-1-yl]methyl]-4-hydroxy-piperidine-1-carboxylate or its enantiomer (186 mg, 75 % yield) as a yellow oil. LC-MS: MS (ES^+): RT = 0.986 min, m/z =802.2 [M + 1]; LCMS Method: 5-95.

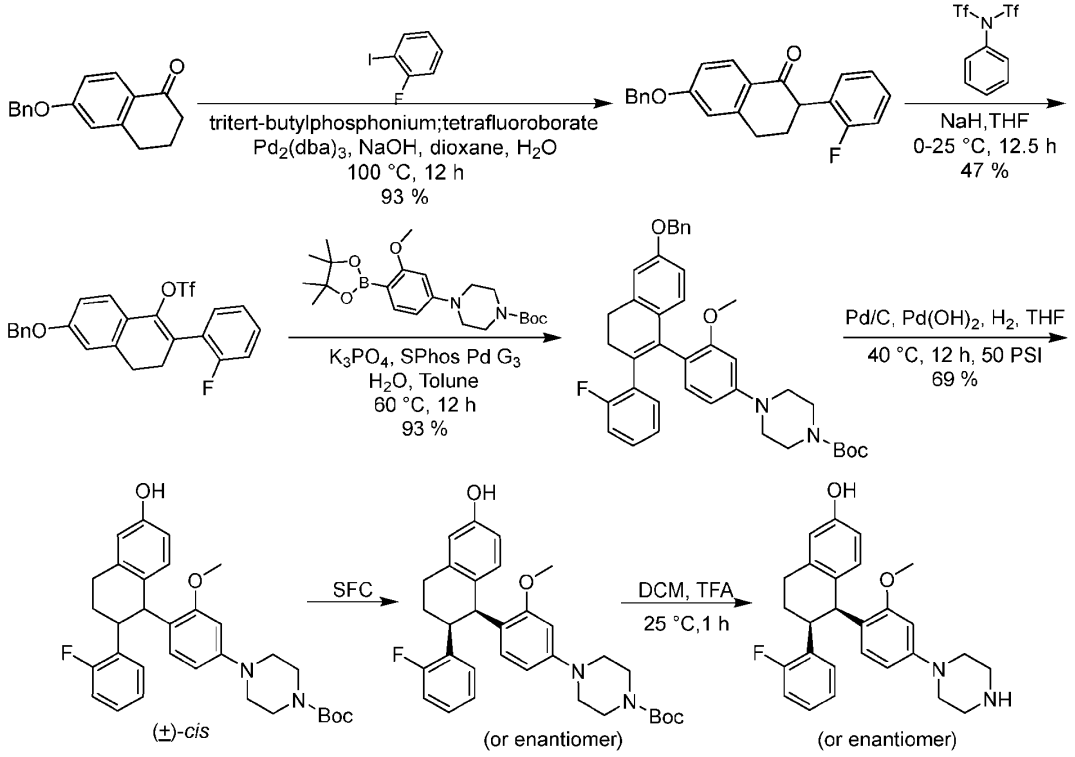
[0710] **Step 9:** To a solution of tert-butyl 4-[[4-(1S,2S)-[4-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]-3-methoxy-phenyl]piperazin-1-yl]methyl]-4-hydroxy-piperidine-1-carboxylate or its enantiomer (140 mg, 174 μmol, 1 *equiv*) in DCM (1 mL) was added TFA (2.15 g, 18.85 mmol, 1.40 mL, 107 *equiv*). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was partitioned between aqueous $NaHCO_3$ (30 mL) and dichloromethane (50 mL). The organic phase was separated, filtered and concentrated under reduced pressure to afford 4-[[4-[4-(1S,2S)-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]-3-methoxy-phenyl]piperazin-1-yl]methyl]piperidin-4-ol or its enantiomer (122 mg, 99 % yield) as a yellow oil. LC-MS: MS (ES^+): RT = 0.858 min, m/z =702.3 [M + 1]; LCMS Method: 5-95.

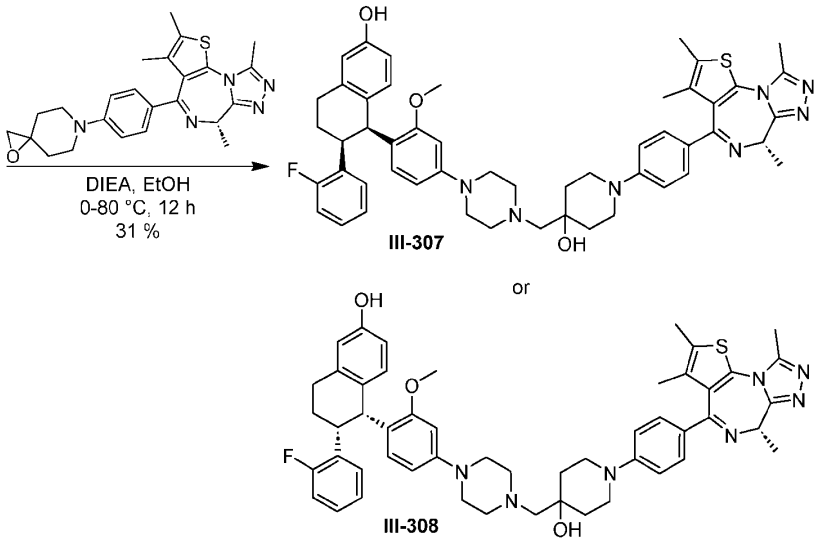
[0711] **Step 10:** A mixture of (9S)-7-(4-bromophenyl)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaene (58 mg, 144 μmol, 1 *equiv*), 4-[[4-[4-(1S,2S)-[2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]-3-methoxy-phenyl]piperazin-1-yl]methyl]piperidin-4-ol or its enantiomer (122 mg, 173 μmol, 1.2 *equiv*), SPhos Pd G_3 (16 mg, 21 μmol, 0.15 *equiv*) and Cs_2CO_3 (141 mg, 434 μmol, 3 *equiv*) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 3 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Dichloromethane: Methanol = 10:1) to afford 4-[[4-[4-[(1S,2S)- or (1R,2R)-2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]-3-methoxy-phenyl]piperazin-1-yl]methyl]-1-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperidin-4-ol (110 mg, 74 % yield) as a yellow oil. LC-MS: MS (ES^+): RT = 1.033 min, m/z =1022.6 [M + 1]; LCMS Method: 5-95.

[0712] **Step 11:** To a solution of 4-[[4-[4-[(1S,2S)- or (1R,2R)-2-(4-fluorophenyl)-6-triisopropylsilyloxy-tetralin-1-yl]-3-methoxy-phenyl]piperazin-1-yl]methyl]-1-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]piperidin-4-ol (110 mg, 107 μmol, 1 *equiv*) in THF (3 mL) was added TBAF (28 mg, 107 μmol, 0.6 mL, 1 *equiv*). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (30 mL). The organic phase was separated, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; gradient: 20%-50% B over 10 min) to afford compound **III-276** or **III-275** (32 mg, 33 % yield) as a yellow solid. ^1H NMR (400 MHz,$CDCl_3$) δ = 7.40 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 9.0

Hz, 2H), 6.82-6.76 (m, 3H), 6.76-6.69 (m, 3H), 6.59 (dd, *J* = 2.4, 8.0 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 6.32 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.09 (d, *J* = 2.0 Hz, 1H), 4.77 (d, *J* = 5.6 Hz, 1H), 4.20-4.12 (m, 1H), 3.65-3.51 (m, 2H), 3.32-3.22 (m, 3H), 3.17-3.10 (m, 7H), 3.05-2.95 (m, 2H), 2.85-2.77 (m, 4H), 2.68 (s, 3H), 2.43 (s, 5H), 2.31-2.15 (m, 2H), 2.11-2.07 (m, 3H), 1.78 (s, 3H), 1.67-1.63 (m, 4H). LC-MS: MS (ES^+): RT = 2.612 min, m/z = 866.6 [M + 1]; LCMS Method: 01.

EXAMPLE 44 – Synthesis of 4-((4-(4-((1S,2S)-2-(2-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-307) and 4-((4-(4-((1R,2R)-2-(2-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-308)





[0713] **Step 1:** To a solution of 6-benzyloxytetralin-1-one (5 g, 19 mmol, 1.0 *equiv*) and 1-fluoro-2-iodo-benzene (6.6 g, 29 mmol, 3.4 mL, 1.5 *equiv*) in dioxane (40.0 mL) and H_2O (10.0 mL) was added $Pd_2(dba)_3$ (1.8 g, 1 mmol, 0.1 *equiv*), NaOH (1.5 g, 39 mmol, 2.0 *equiv*) and tritert-butylphosphonium tetrafluoroborate (1.1 g, 3 mmol, 0.2 *equiv*) in one portion at 25 °C. Then the resulting mixture was heated to 100 °C and stirred under N_2 atmosphere for 12 h. The residue was diluted with water (10.0 mL) and extracted with ethyl acetate (20.0 mL * 3). The combined organic layers were washed with saturated aqueous NaCl solution (10.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 1/1) to give 6-benzyloxy-2-(2-fluorophenyl)tetralin-1-one (6.4 g, 93 % yield) as yellow solid. LC-MS: MS (ES^+): RT = 0.653 min, m/z = 347.1 [M + H^+]. LCMS Method: 5-95.

[0714] **Step 2:** To a mixture of 6-benzyloxy-2-(2-fluorophenyl)tetralin-1-one (6 g, 17 mmol, 1.0 *equiv*) in THF (60.0 mL) was added NaH (1.3 g, 34 mmol, 60 % purity, 2.0 *equiv*) at 0 °C for 0.5 h under N_2 atmosphere. Then 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl) methanesulfonamide (18.5 g, 51 mmol, 3.0 *equiv*) was added to the mixture. The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched with saturated aqueous NH_4Cl (50.0 mL) solution at 0 °C dropwise. And the resulting mixture was extracted with ethyl acetate (30.0 mL*3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 5/1) to give [6-benzyloxy-2-(2-fluorophenyl)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (3.9 g, 47 % yield) as white solid. ^1H NMR

(400 MHz, DMSO-d_6): δ 7.52-7.45 (m, 4H), 7.43-7.34 (m, 3H), 7.33-7.24 (m, 3H), 7.09-6.98 (m, 2H), 5.16 (s, 2H), 2.96 (s, 2H), 2.76-2.66 (m, 2H).

[0715] **Step 3:** To a solution of [6-benzyloxy-2-(2-fluorophenyl)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (2.9 g, 6 mmol, 1.0 *equiv*) and tert-butyl 4-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (2.5 g, 6 mmol, 1.0 *equiv*) in H_2O (8.0 mL) and toluene (32.0 mL) was added K_3PO_4 (3.8 g, 18 mmol, 3.0 *equiv*), SPhos Pd G_3 (472 mg, 606 μmol, 0.1 *equiv*) in one portion at 25 °C. Then the resulting mixture was heated to 60 °C and stirred under N_2 atmosphere for 12 h. The residue was diluted with water (30.0 mL) and extracted with ethyl acetate (30.0 mL * 3). The combined organic layers were washed with saturated aqueous NaCl solution (30.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 3/1) to give tert-butyl 4-[4-[6-benzyloxy-2-(2-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (3.5 g, 93 % yield) as white solid. LC-MS: MS (ES^+): RT = 0.795 min, m/z = 621.5 [M + H^+]. LCMS Method: 5-95.

[0716] **Step 4:** To a solution of tert-butyl 4-[4-[6-benzyloxy-2-(2-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (3.5 g, 5 mmol, 1.0 *equiv*) in THF (35.0 mL) was added Pd/C (6.0 g, 5 mmol, 10 % purity, 1.0 *equiv*) and $Pd(OH)_2$ (3.9 g, 5 mmol, 20 % purity, 1.0 *equiv*) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 40 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with MeOH at 25 °C for 30 min to give (±)-*cis*-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (2.1 g, 69 % yield) as white solid. LC-MS: MS (ES^-): RT =3.038 min, m/z = 533.4 [M + H^+]. LCMS Method: 5-95.

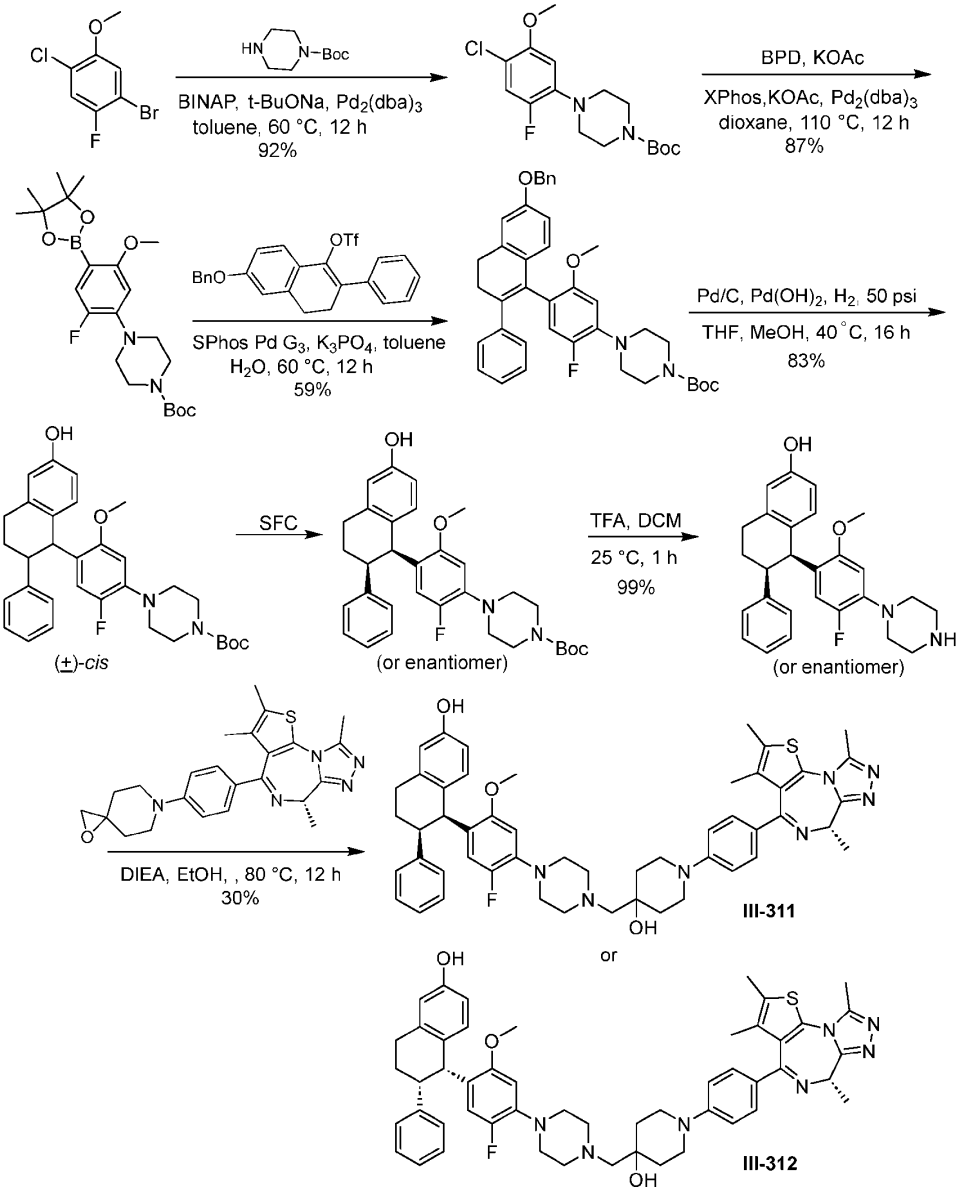
[0717] **Step 5:** Racemic *cis*-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (700 mg, 1 mmol, 1.0 *equiv*) was purified by preparative SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [CO_2-IPA(0.1% NH_3H_2O)];B%:25%, isocratic elution mode) to give (1S,2S)- and (1R,2R)-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. The slower-eluting enantiomer (340 mg) was obtained as a white solid. LC-MS: MS (ES^+): RT =0.655 min, m/z = 533.2 [M + H^+]; LCMS Method: 5-95.

[0718] The following Steps 6 and 7 describe further synthetic procedures conducted on the slower-eluting enantiomer of *cis*-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. This slower-eluting enantiomer produced the diastereomer of compounds **III-307** and **III-308** that was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The faster-eluting enantiomer of *cis*-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate was carried through the same steps to afford the other one of compounds **III-307** and **III-308**.

[0719] **Step 6:** To a solution of tert-butyl 4-[4-[(1S,2S)-2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate or its enantiomer (150 mg, 281 μmol, 1.0 *equiv*) in DCM (1.0 mL) was added TFA (307 mg, 2 mmol, 0.2 mL, 9.5 *equiv*). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to give a residue. The crude (1S,2S)-2-(2-fluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-ol or its enantiomer (121 mg, crude) as white solid was used into the next step without further purification. LC-MS: MS (ES^+): RT =0.536 min, m/z = 433.2[$M + H^+$]. LCMS Method: 5-95.

[0720] **Step 7:** To a solution of (1S,2S)-2-(2-fluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-ol or its enantiomer (121 mg, 279 μmol, 1.0 *equiv*) in EtOH (4.0 mL) was added DIEA (180 mg, 1 mmol, 243 μL, 5.0 *equiv*)and 6-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (303 mg, 699 μmol, 2.5 *equiv*) at 0 °C. The mixture was stirred at 80 °C for 12 h. The mixture was concentrated to give a residue. The residue was purified by preparative HPLC (column: Waters Xbridge C18 150*50mm*10um;mobile phase: [H_2O(10mM NH_4HCO_3)-ACN]; gradient: 58%-88% B over 11.0 min) to give compound **III-307** or **III-308** (118 mg, 47 % yield, 97 % purity) as white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 9.29-8.86 (m, 1H), 7.26 (s, 2H), 7.16-7.04 (m, 2H), 6.89 (s, 2H), 6.80-6.73 (m, 1H), 6.59-6.51 (m, 2H), 6.46-6.40 (m, 1H), 6.36-6.21 (m, 3H), 6.06 (s, 1H), 4.72 (s, 1H), 4.23 (s, 1H), 4.10 (s, 1H), 3.54-3.42 (m, 6H), 3.30 (s, 3H), 3.14 (s, 2H), 3.00 (s, 3H), 2.95 (s, 5H), 2.60 (s, 3H), 2.57 (s, 2H), 2.47 (s, 1H), 2.38 (s, 3H), 2.28 (s, 1H), 1.83 (s, 3H), 1.64 (s, 3H), 1.52 (s, 3H). LC-MS: MS (ES^+): RT = 1.779 min, m/z = 866.7[$M + H^+$]. LCMS method: 25.

EXAMPLE 45 – Synthesis of 4-((4-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-311) and 4-((4-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-312)



[0721] **Step 1:** A mixture of 1-bromo-4-chloro-2-fluoro-5-methoxy-benzene (5 g, 20.8 mmol, 1.0 *equiv*), tert-butyl piperazine-1-carboxylate (3.89 g, 20.9 mmol, 1.0 *equiv*), [1-(2-diphenylphosphanyl-1-naphthyl)-2-naphthyl]-diphenyl-phosphane (2.60 g, 4.18 mmol, 0.2 *equiv*), $Pd_2(dba)_3$ (1.91 g, 2.09 mmol, 0.1 *equiv*) and t-BuONa (4.01 g, 41.8 mmol, 2.0 *equiv*) in toluene (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The mixture was filtered and concentrated to give a residue. The residue was purified by silica column chromatography on silica gel (Petroleum ether: Ethyl acetate from 50/1 to 5/1) to give tert-butyl 4-(4-chloro-2-fluoro-5-methoxy-phenyl)piperazine-1-carboxylate (6.6 g, 92% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, J = 11.6 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 3.86 (s, 3H), 3.65-3.55 (m, 4H), 3.08-2.96 (m, 4H), 1.49 (s, 9H). LC-MS: MS (ES^+): RT = 0.684 min, m/z = 345.1 [M + H^+]. LCMS Method: 5-95.

[0722] **Step 2:** A mixture of tert-butyl 4-(4-chloro-2-fluoro-5-methoxy-phenyl)piperazine-1-carboxylate (8.5 g, 24.7 mmol, 1.0 *equiv*), BPD (12.5 g, 49.3 mmol, 2.0 *equiv*), XPhos (1.76 g, 3.70 mmol, 0.15 *equiv*), $Pd_2(dba)_3$ (1.13 g, 1.23 mmol, 0.05 *equiv*) and KOAc (7.26 g, 74.0 mmol, 3.0 *equiv*) in dioxane (100 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 12 h under N_2 atmosphere. The mixture was filtered and concentrated to give a residue. The residue was purified by silica column chromatography on silica gel (Petroleum ether: Ethyl acetate from 50/1 to 3/1) to give tert-butyl 4-[2-fluoro-5-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (9.4 g, 87% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 13.2 Hz, 1H), 6.39 (d, J = 6.8 Hz, 1H), 3.80 (s, 3H), 3.66-3.54 (m, 4H), 3.14-3.02 (m, 4H), 1.48 (s, 9H), 1.33 (s, 12H). LC-MS: MS (ES^+): RT = 0.713 min, m/z = 437.3 [M + H^+]. LCMS Method: 5-95.

[0723] **Step 3:** To a solution of tert-butyl 4-[2-fluoro-5-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (3.41 g, 7.82 mmol, 1.2 *equiv*) in toluene (40 mL) and H_2O (10 mL) and was added K_3PO_4 (4.15 g, 19.6 mmol, 3.0 *equiv*), (6-benzyloxy-2-phenyl-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate (3 g, 6.52 mmol, 1.0 *equiv*) and SPhos Pd G_3 (508 mg, 652 μmol, 0.1 *equiv*). The mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The mixture was filtered and concentrated to give a residue. The residue was purified by silica column chromatography on silica gel (Petroleum ether: Ethyl acetate from 50/1 to 5/1) to give tert-butyl 4-[4-(6-benzyloxy-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxy-phenyl]piperazine-1-carboxylate (2.4 g, 59% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.42 (m, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.36-7.30 (m, 1H), 7.15-7.08 (m, 2H),

7.08-7.01 (m, 3H), 6.85 (d, J = 1.6 Hz, 1H), 6.72-6.59 (m, 3H), 6.37 (d, J = 7.2 Hz, 1H), 5.07 (s, 2H), 3.60 (t, J = 4.8 Hz, 4H), 3.48 (s, 3H), 3.11-2.94 (m, 6H), 2.79 (m, J = 3.6, 7.6 Hz, 2H), 1.50 (s, 9H). LC-MS: MS (ES^+): RT = 0.727 min, m/z = 621.3 [M + H^+]. LCMS Method: 5-95.

[0724] **Step 4:** To a solution of tert-butyl 4-[4-(6-benzyloxy-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl] piperazine-1-carboxylate (2.4 g, 3.87 mmol, 1.0 *equiv*) in THF (24 mL) and MeOH (12 mL) was added Pd/C (1 g, 10% purity) and $Pd(OH)_2$ (1 g) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 40 °C for 16 h. The mixture was filtered and concentrated to give a residue. The crude product was triturated with PE: EA= 5/1(36 mL) at 25 ℃ for 1 h. The mixture was filtered to give (±)-*cis*-tert-butyl 4-[2-fluoro-4-(6-hydroxy-2-phenyl-tetralin-1-yl)-5-methoxy-phenyl]piperazine-1-carboxylate (1.7 g, 83% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.15-7.02 (m, 3H), 6.70-6.82 (m, 3H), 6.69 (d, J = 2.0 Hz, 1H), 6.55-6.63 (m, 1H), 6.37 (d, J = 13.6 Hz, 1H), 6.06 (d, J = 7.2 Hz, 1H), 5.34-5.14 (m, 1H), 4.81 (d, J = 5.2 Hz, 1H), 3.57 (s, 4H), 3.31 (m, J = 5.2, 11.6 Hz, 1H), 3.09-2.88 (m, 9H), 2.24 (m, J = 6.4, 12.8 Hz, 1H), 1.80-1.63 (m, 2H), 1.49 (s, 9H). LC-MS: MS (ES^+): RT = 3.255 min, m/z = 533.4 [M + H^+]. LCMS Method: 5-95.

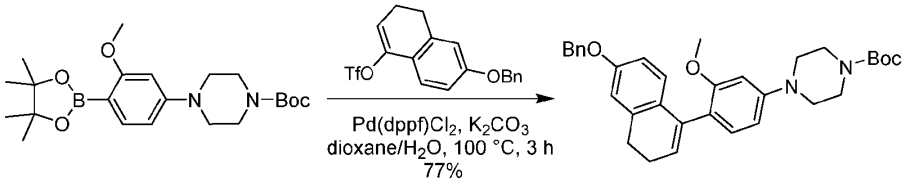
[0725] **Step 5:** Racemic *cis*-tert-butyl 4-[2-fluoro-4-(6-hydroxy-2-phenyl-tetralin-1-yl)-5-methoxy-phenyl]piperazine-1-carboxylate (700 mg, 1.31 mmol, 1.0 *equiv*) was purified by preparative SFC (column: DAICEL CHIRALCEL OD (250 mm * 30 mm, 10 um); mobile phase: [CO_2-IPA (0.1% NH_3H_2O)]; B%:55%, isocratic elution mode) to give (1S,2S)- and (1R,2R)-tert-butyl 4-[2-fluoro-4-[6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]piperazine-1-carboxylate. The faster-eluting enantiomer was isolated (340 mg, 49% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.651 min, m/z = 533.3 [M + H^+]; LCMS Method: 5-95.

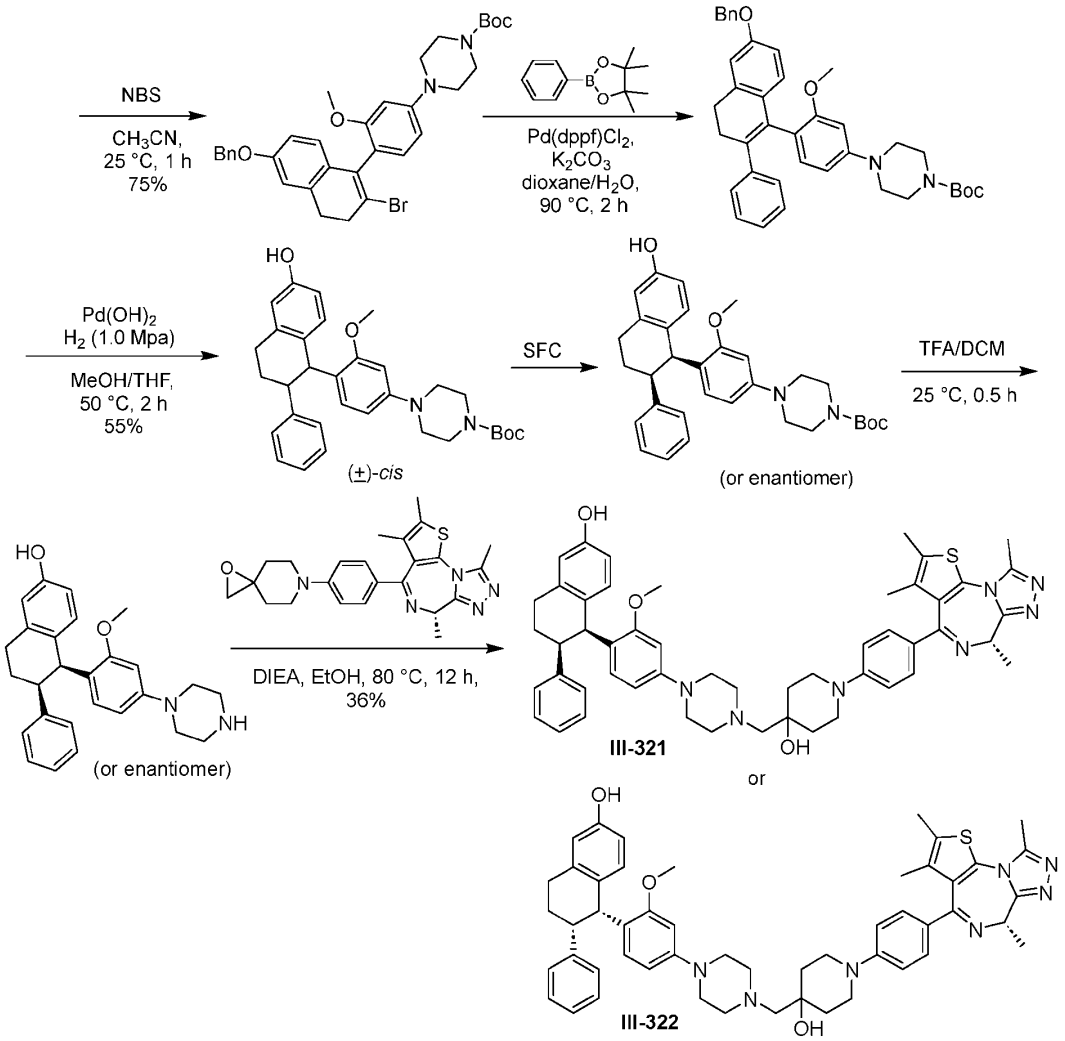
[0726] The following Steps 6 and 7 describe further synthetic procedures conducted on the faster-eluting enantiomer of *cis*-tert-butyl 4-[2-fluoro-4-(6-hydroxy-2-phenyl-tetralin-1-yl)-5-methoxy-phenyl]piperazine-1-carboxylate. This faster-eluting enantiomer produced the diastereomer of compounds **III-311** and **III-312** that was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The slower-eluting enantiomer of *cis*-tert-butyl 4-[2-fluoro-4-(6-hydroxy-2-phenyl-tetralin-1-yl)-5-methoxy-phenyl]piperazine-1-carboxylate was carried through the same steps to afford the other one of compounds **III-311** and **III-312**.

[0727] **Step 6:** To a solution of tert-butyl 4-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]piperazine-1-carboxylate or its enantiomer (150 mg, 281 μmol, 1.0 *equiv*) in DCM (1.5 mL) was added TFA (461 mg, 4.04 mmol, 0.3 mL, 14.3 *equiv*). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to give (1S,2S)-1-(5-fluoro-2-methoxy-4-piperazin-1-yl-phenyl)-2-phenyl-tetralin-6-ol or its enantiomer (120 mg, 99% yield) as a colorless oil. LC-MS: MS (ES^+): RT = 0.489 min, m/z = 433.2 [$M + H^+$]. LCMS Method: 5-95.

[0728] **Step 7:** To a solution of 6-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (241 mg, 555 μmol, 2.0 *equiv*) in EtOH (3 mL) was added DIEA (179 mg, 1.39 mmol, 0.2 mL, 5.0 *equiv*) and (1S,2S)-1-(5-fluoro-2-methoxy-4-piperazin-1-yl-phenyl)-2-phenyltetralin-6-ol or its enantiomer (120 mg, 277 μmol, 1.0 *equiv*). The mixture was stirred at 80 °C for 12 h. The mixture was concentrated to give a residue. The residue was purified by preparative HPLC (column: Waters Xbridge C_{18} 150 * 25 mm * 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 64%-94% B over 9.0 min) to give compound **III-311** or **III-312** (74 mg, 30% yield, 98% purity) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.8 Hz, 2H), 7.12-7.04 (m, 3H), 6.86 (d, *J* = 9.2 Hz, 2H), 6.81-6.74 (m, 3H), 6.69 (d, *J* = 2.4 Hz, 1H), 6.65-6.55 (m, 1H), 6.35 (d, *J* = 13.6 Hz, 1H), 6.06 (d, *J* = 7.6 Hz, 1H), 5.56-5.11 (m, 1H), 4.80 (d, *J* = 5.2 Hz, 1H), 4.15 (q, *J* = 6.8 Hz, 1H), 3.70-3.50 (m, 2H), 3.34-3.20 (m, 3H), 3.12-2.95 (m, 9H), 2.80 (d, *J* = 4.0 Hz, 4H), 2.67 (s, 3H), 2.46-2.35 (m, 5H), 2.30-2.19 (m, 1H), 2.08 (d, *J* = 6.8 Hz, 3H), 1.82-1.65 (m, 8H). LC-MS: MS (ES^+): RT = 1.796 min, m/z = 866.7 [$M + H^+$]. LCMS method: 25.

EXAMPLE 46 – Synthesis of 4-((4-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-321) and 4-((4-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-322)





[0729] **Step 1:** A mixture of tert-butyl 4-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (4.80 g, 11.4 mmol, 1.0 *equiv*), (6-benzyloxy-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate (5.29 g, 13.7 mmol, 1.2 *equiv*), K_2CO_3 (4.76 g, 34.4 mmol, 3.0 *equiv*) and $Pd(dppf)Cl_2$ (834 mg, 1.15 mmol, 0.1 *equiv*) in dioxane (80.0 mL) and H_2O (20.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 3 h under N_2 atmosphere. The mixture was filtered, and the filtrate was concentrated under reduced pressure to remove solvent and give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 3/1) to obtain compound tert-butyl 4-[4-(6-benzyloxy-3,4-dihydronaphthalen-1-yl)-3-methoxy-

phenyl]piperazine-1-carboxylate (4.88 g, 8.80 mmol, 77% yield) as a pale yellow solid. LC-MS: MS (ES^+): RT = 0.763 min, m/z = 527.3 $[M + H]^+$.

[0730] **Step 2:** To a solution of tert-butyl 4-[4-(6-benzyloxy-3,4-dihydronaphthalen-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (4.88 g, 8.80 mmol, 1.0 *equiv*) in MeCN (50.0 mL) was added NBS (1.48 g, 8.33 mmol, 0.9 *equiv*) solution in MeCN (50.0 mL) dropwise. The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition of saturated NH_4Cl (aq, 100 mL) at 0 °C, and then extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1) to obtain compound tert-butyl 4-[4-(6-benzyloxy-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (4.20 g, 6.94 mmol, 75% yield) as a colorless oil. LC-MS: MS (ES^+): RT = 0.783 min, m/z = 607.2 $[M + H]^+$.

[0731] **Step 3:** A mixture of tert-butyl 4-[4-(6-benzyloxy-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (1.40 g, 2.31 mmol, 1.0 *equiv*), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (708 mg, 3.47 mmol, 1.5 *equiv*), K_2CO_3 (799 mg, 5.78 mmol, 2.5 *equiv*) and $Pd(dppf)Cl_2$ (169 mg, 231 μmol, 0.1 *equiv*) in dioxane (10.0 mL) and H_2O (1.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 2 h under N_2 atmosphere. The reaction mixture was treated under reduced pressure to remove solvent and give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1) to obtain compound tert-butyl 4-[4-(6-benzyloxy-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (1.41 g, crude) as a pale yellow solid. LC-MS: MS (ES^+): RT = 0.800 min, m/z = 603.4 $[M + H]^+$; LCMS Method: 5-95.

[0732] **Step 4:** A solution of tert-butyl 4-[4-(6-benzyloxy-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (1.4 g) in MeOH (14.0 mL) and THF (14.0 mL) was prepared. To a fixed bed flow reactor was added 5% $Pd(OH)_2/Al_2O_3$. The H_2 back pressure regulator was adjusted to 1.0 MPa, and the flow rate of H_2 was 30 mL/min. Then the solution was pumped (0.3 mL/min) through fixed bed reactor (set at 50 °C). The flow process continued for 2 h. The resultant reaction solution was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 150 x 40mm x 15um; mobile phase: [H_2O (0.225% FA)-ACN]; gradient: 60%-90% B over 15.0 min) to obtain compound (±)-*cis*-tert-butyl 4-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate

(765 mg, 1.47 mmol, 55% yield) as a pale yellow solid. LC-MS: MS (ES^+): RT = 0.690 min, m/z = 515.3 $[M + H]^+$; LCMS Method: 5-95.

[0733] **Step 5:** The compound (±)-*cis*-tert-butyl 4-[4-(6-hydroxy-2-phenyl-tetralin-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (765 mg, 1.47 mmol, 1.0 *equiv*) was separated by Chiral SFC (column: DAICEL CHIRALCEL OD(250mm*30mm, 10um); mobile phase: [CO_2-IPA(0.1%NH_3H_2O)]; B%: 50%, isocratic elution mode; RT = 1.785 and 1.994 min.) to obtain (1S,2S)- and (1R,2R)-tert-butyl 4-[4-[6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. The faster-eluting enantiomer was isolated (282 mg, 510 μmol) as a pale yellow solid; and the slower-eluting enantiomer was isolated (301 mg, 550 μmol) as a pale yellow solid. LC-MS: MS (ES^+): RT = 0.691 min, m/z = 515.3 $[M + H]^+$ (isomer-1); 0.690 min, m/z = 515.3 $[M + H]^+$ (isomer-2); LCMS Method: 5-95.

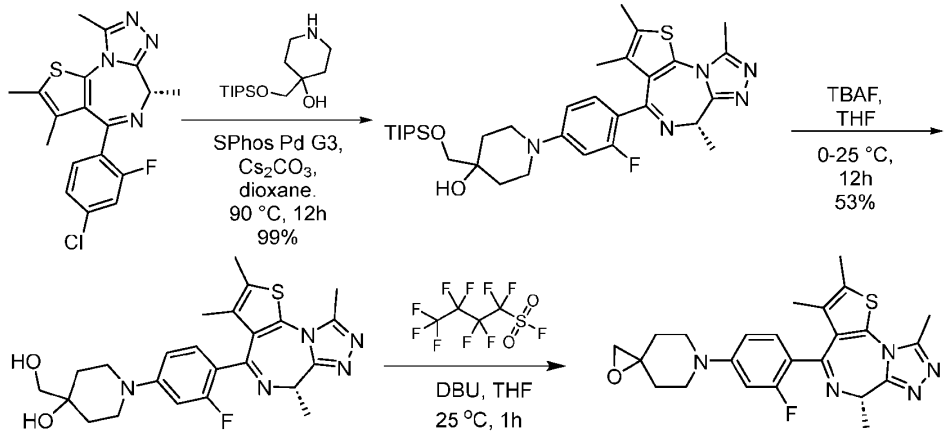
[0734] The following Steps 6 and 7 describe further synthetic procedures conducted on the faster-eluting enantiomer of *cis*-tert-butyl 4-[4-[6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. This faster-eluting enantiomer produced the diastereomer of compounds **III-321** and **III-322** that was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The slower-eluting enantiomer of *cis*-tert-butyl 4-[4-[6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate was carried through the same steps to afford the other one of compounds **III-321** and **III-322**.

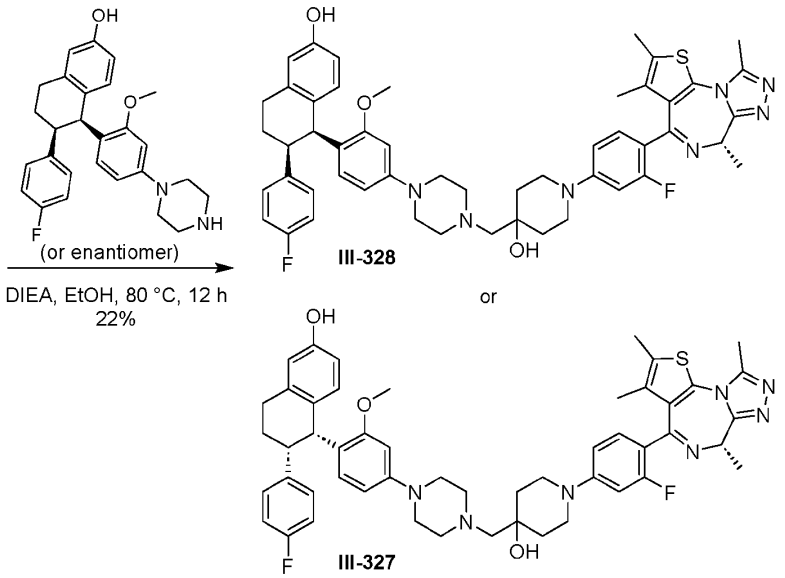
[0735] **Step 6:** To a solution of tert-butyl 4-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate or its enantiomer (100 mg, 194 μmol, 1.0 *equiv*) in DCM (1.0 mL) was added TFA (0.5 mL). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to obtain compound (1S,2S)-1-(2-methoxy-4-piperazin-1-yl-phenyl)-2-phenyl-tetralin-6-ol or its enantiomer (110 mg, crude, TFA salt) as a green oil. LC-MS: MS (ES^+): RT = 0.563 min, m/z = 415.2 $[M + H]^+$; LCMS Method: 5-95.

[0736] **Step 7:** To a solution of (1S,2S)-1-(2-methoxy-4-piperazin-1-yl-phenyl)-2-phenyl-tetralin-6-ol or its enantiomer (110 mg, 208 μmol, 1.0 *equiv*, TFA salt) and 6-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (246 mg, 250 μmol, 1.2 *equiv*) in EtOH (5.0 mL) was added DIEA (80.7 mg, 624 μmol, 109 μL, 3.0 *equiv*). The mixture was stirred at 80 °C for 12 h. The reaction mixture was treated under reduced pressure to remove solvent and give a residue.

The residue was purified by *prep*-HPLC (column: Waters Xbridge C18 150 x 25mm x 5um; mobile phase: [H_2O(10mM NH_4HCO_3)-ACN]; gradient: 53%-83% B over 15.0 min) to obtain compound **III-321** or **III-322** (65.4 mg, 74.3 μmol, 36% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 2.592 min, m/z = 848.8 $[M + H]^+$; LCMS Method: 01. ^1H NMR (400 MHz, CD_3OD) δ = 7.31 (br d, *J* = 8.4 Hz, 2 H), 7.05 - 7.00 (m, 3 H), 6.94 (br d, *J* = 8.9 Hz, 2 H), 6.75 - 6.69 (m, 2 H), 6.64 - 6.57 (m, 2 H), 6.54 - 6.41 (m, 2 H), 6.35 (dd, *J* = 1.7 Hz, 1 H), 6.15 (d, *J* = 1.7 Hz, 1 H), 4.75 (br d, *J* = 5.1 Hz, 1 H), 4.24 - 4.14 (m, 1 H), 3.60 (br dd, *J* = 4.1 Hz, 2 H), 3.28 - 3.18 (m, 3 H), 3.09 - 2.92 (m, 9 H), 2.77 - 2.66 (m, 7 H), 2.46 - 2.35 (m, 5 H), 2.34 - 2.22 (m, 1 H), 1.96 (d, *J* = 6.7 Hz, 3 H), 1.78 (dt, *J* = 3.9 Hz, 2 H).

EXAMPLE 47 – Synthesis of 1-(3-fluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(4-((1S,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-328) and 1-(3-fluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(4-((1R,2R)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-327)





[0737] **Step 1:** A mixture of (9S)-7-(4-chloro-2-fluoro-phenyl)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaene (2.1 g, 5.6 mmol, 1.0 *equiv*), 4-(triisopropylsilyloxymethyl)piperidin-4-ol (1.9 g, 6.7 mmol, 1.2 *equiv*), SPhos Pd G3 (874 mg, 1.1 mmol, 0.2 *equiv*), Cs_2CO_3 (5.5 g, 16.8 mmol, 3.0 *equiv*) in dioxane (20.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The reaction mixture was partitioned between Ethyl acetate 200 mL and H_2O 50 mL. The organic phase was separated, washed with NaCl 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The reaction mixture was filtered and concentrated under reduced pressure to give compound 1-[3-fluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(triisopropylsilyloxymethyl)piperidin-4-ol (3.5 g, 5.6 mmol, 99% yield) as a brown solid. LC-MS: MS (ES^+): RT = 0.623 min, m/z = 626.4 $[M+1]^+$. LCMS Method: 5-95.

[0738] **Step 2:** To a solution of 1-[3-fluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(triisopropylsilyloxymethyl)piperidin-4-ol (3.5 g, 5.6 mmol, 1.0 *equiv*) in THF (35 mL) was added TBAF (1.00 M, 5.6 mL, 1.0 *equiv*) at 0~25 °C .The mixture was stirred at 0~25 °C for 12 h. The reaction mixture was partitioned between Ethyl acetate 200 mL and H_2O 50 mL. The organic phase was separated, washed with NaCl 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 0/1 to Ethyl acetate : MeOH = 10:1) to

give compound 1-[3-fluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(hydroxymethyl)piperidin-4-ol (1.4 g, 3.0 mmol, 53% yield) as a yellow solid. LC-MS: MS (ES$^+$): RT = 0.478 min, m/z = 470.2 [M+1]$^+$. LCMS Method: 5-95.

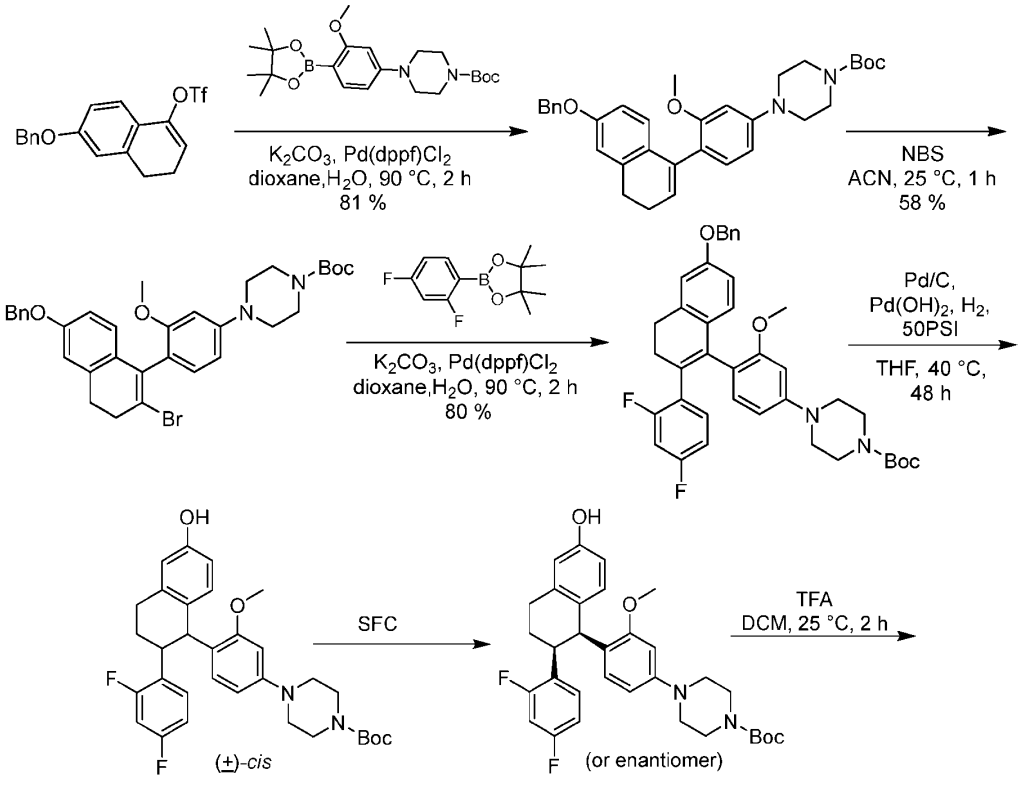
[0739] **Step 3:** To a solution of 1-[3-fluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(hydroxymethyl)piperidin-4-ol (200 mg, 426 μmol, 1.0 *equiv*) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (386 mg, 1.3 mmol, 225 μL, 3.0 *equiv*) in THF (3.0 mL) was added DBU (324 mg, 2.1 mmol, 321 μL, 5.0 *equiv*). The mixture was stirred at 25 °C for 1 h. The mixture was quenched with H_2O (10mL) and extracted with DCM 20 mL (10 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without purification. Compound 6-[3-fluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (200 mg, crude) was obtained as a brown oil. LC-MS: MS (ES$^+$): RT = 0.467 min, m/z = 452.2 [M+1]$^+$. LCMS Method: 5-95.

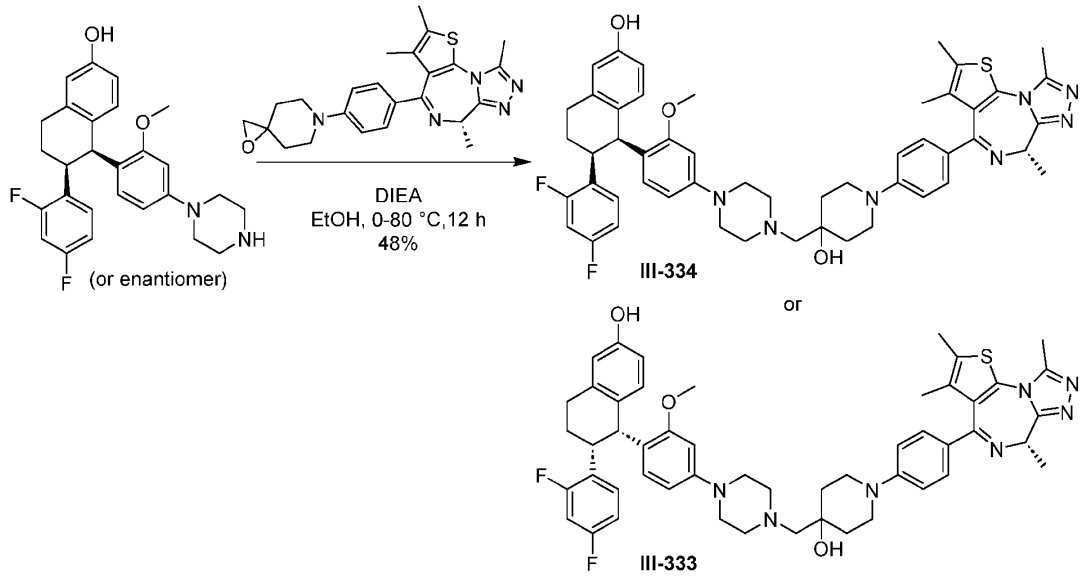
[0740] **Step 4:** To a solution of 6-[3-fluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (80.0 mg, 177 μmol, 1.0 *equiv*) and the slower-eluting enantiomer of (5S,6S)- or (5R,6R)-6-(4-fluorophenyl)-5-(2-methoxy-4-(piperazin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (76.6 mg, 177 μmol, 1.0 *equiv*; prepared as described in Example 43) in EtOH (2 mL) was added DIEA (22.9 mg, 177 μmol, 30.8 μL, 1.0 *equiv*). The mixture was stirred at 80 °C for 12 h. It was filtered. The residue was purified by *prep*-HPLC(column: Waters xbridge 150*25mm 10um;mobile phase: [H_2O(10mM NH_4HCO_3)-ACN];gradient:68-88% B over 8.0 min) (column: Phenomenex Luna C18 150*25mm*10um;mobile phase: [H_2O(0.225% FA)-ACN];gradient:3%-33% B over 10.0 min) to afford compound **III-328** or **III-327** (34.92 mg, 39.50 μmol, 22 % yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (br t, *J* = 8.9 Hz, 1H), 6.82 - 6.69 (m, 5H), 6.64 - 6.57 (m, 3H), 6.51 - 6.43 (m, 2H), 6.36 (dd, *J* = 2.1, 8.5 Hz, 1H), 6.18 (d, *J* = 2.0 Hz, 1H), 4.72 (br d, *J* = 5.4 Hz, 1H), 4.22 (q, *J* = 6.7 Hz, 1H), 3.67 - 3.57 (m, 2H), 3.25 (br d, *J* = 11.8 Hz, 3H), 3.11 (s, 3H), 3.06 (br s, 4H), 3.00 - 2.93 (m, 2H), 2.73 (br d, *J* = 4.5 Hz, 4H), 2.67 (s, 3H), 2.43 - 2.36 (m, 5H), 2.31 - 2.17 (m, 1H), 1.97 (d, *J* = 6.9 Hz, 3H), 1.81 - 1.73 (m, 2H), 1.71 - 1.60 (m, 6H). LC-MS: MS (ES+): RT = 2.674 min, m/z = 884.7 [M + H$^+$]; LCMS Method: 01. This diastereomer of compounds **III-328** and **III-327** was found to be the more potent inhibitor of cell growth of T-

Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below).

[0741] The faster-eluting enantiomer of *cis*-6-(4-fluorophenyl)-5-(2-methoxy-4-(piperazin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol was used in a similar reaction to afford the other one of compounds **III-327** and **III-328**.

EXAMPLE 48 – Synthesis of 4-((4-(4-((1S,2S)-2-(2,4-difluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-334) and 4-((4-(4-((1R,2R)-2-(2,4-difluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-333)





[0742] **Step 1:** A mixture of (6-benzyloxy-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate (1.8 g, 4.68 mmol, 1.0 *equiv*), tert-butyl 4-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (2.55 g, 6 mmol, 1.3 *equiv*), K_2CO_3 (1.62 g, 12 mmol, 2.5 *equiv*), and $Pd(dppf)Cl_2$ (171 mg, 234 μmol, 0.05 *equiv*) in dioxane (20 mL) and H_2O (4 mL) in one portion at 25 °C. Then the resulting mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 2 h under N_2 atmosphere. The residue was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 20/1) to give tert-butyl 4-[4-(6-benzyloxy-3,4-dihydronaphthalen-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (2.0 g, 81% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.53-7.30 (m, 7H), 7.15-7.07 (m, 1H), 6.84 (s, 1H), 6.67 (s, 2H), 6.63-6.51 (m, 1H), 5.93-5.95 (m, 1H), 5.06 (s, 2H), 3.77-3.56 (m, 6H), 3.30-3.15 (m, 4H), 2.92-2.80 (m, 2H), 2.47-2.36 (m, 2H), 1.52 (s, 9H). LC-MS: MS (ES^+): RT = 0.767 min, m/z = 527.3 [$M + H^+$]. LCMS method: 5-95.

[0743] **Step 2:** To a solution of tert-butyl 4-[4-(6-benzyloxy-3,4-dihydronaphthalen-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (1.80 g, 3 mmol, 1.0 *equiv*) in ACN (20 mL) was added NBS (547 mg, 3 mmol, 0.9 *equiv*). The mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 20/1) to give tert-butyl 4-[4-(6-benzyloxy-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxy-phenyl]piperazine-

1-carboxylate (1.20 g, 58% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.777 min, m/z = 605.2 [$M + H^+$]. LCMS method: 5-95.

[0744] **Step 3:** A mixture of tert-butyl 4-[4-(6-benzyloxy-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxy-phenyl]piperazine-1-carboxylate (500 mg, 826 μmol, 1.0 *equiv*), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (208 mg, 867 μmol, 1.05 *equiv*), K_2CO_3 (285 mg, 2 mmol, 2.5 *equiv*), and $Pd(dppf)Cl_2$ (30 mg, 41 μmol, 0.05 *equiv*) in dioxane (5 mL) and H_2O (0.5 mL) in one portion at 25 °C. Then the resulting mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 2 h under N_2 atmosphere. The residue was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15um;mobile phase: [H_2O(0.225% FA)-ACN]; gradient:90%-100% B over 15.0 min) to give tert-butyl 4-[4-[6-benzyloxy-2-(2,4-difluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (420 mg, 80% yield) as a white solid. LC-MS: MS (ES^+): RT =0.797 min, m/z = 639.3[$M + H^+$]. LCMS method: 5-95.

[0745] **Step 4:** Pd/C (200 mg, 10% purity), $Pd(OH)_2$ (200 mg, 10% purity) was added into a flask under N_2, tert-butyl 4-[4-[6-benzyloxy-2-(2,4-difluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (420 mg, 657 μmol, 1.0 *equiv*) in THF (4 mL) and MeOH (2 mL) was added into the mixture. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 40 °C for 48 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude (±)-*cis*-tert-butyl 4-[4-[2-(2,4-difluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (360 mg, crude) as a white solid was used into the next step without further purification. LC-MS: MS (ES^+): RT =0.682 min, m/z = 551.4[$M + H^+$]. LCMS method: 5-95.

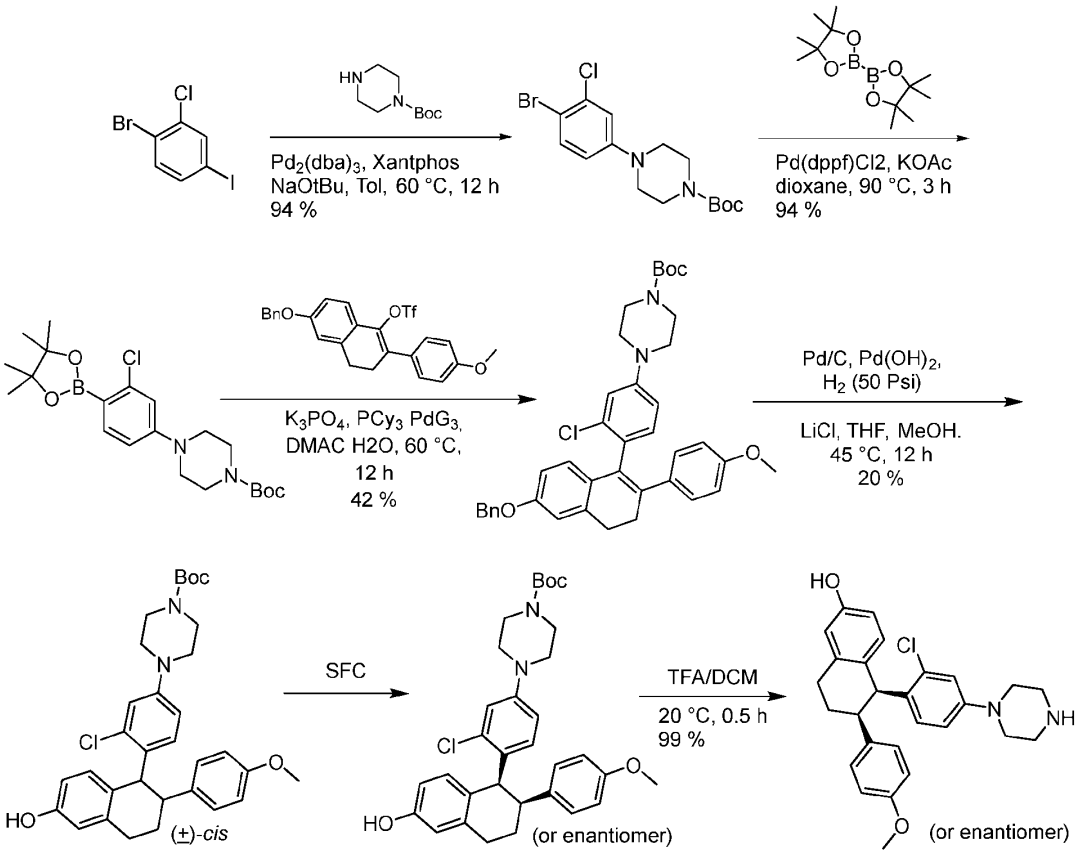
[0746] **Step 5:** The (±)-*cis*-tert-butyl 4-[4-[2-(2,4-difluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (360 mg, crude) was purified by preparative SFC (column: DAICEL CHIRALPAK AD (250mm*30mm, 10um); mobile phase: [CO_2-IPA(0.1% NH_3H_2O)];B%:35%, isocratic elution mode) to give (1S,2S)- and (1R,2R)-tert-butyl 4-[4-[2-(2,4-difluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. The slower-eluting enantiomer (150 mg, 42% yield) was obtained as a white solid. LC-MS: MS (ES^+): RT =0.689 min, m/z = 551.2 [$M + H^+$]. LCMS method: 5-95.

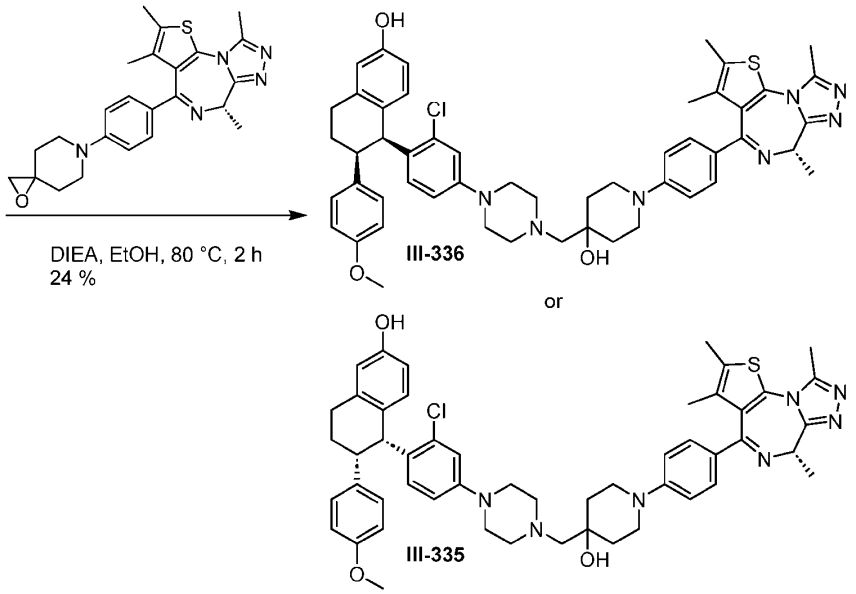
[0747] The following Steps 6 and 7 describe further synthetic procedures conducted on the slower-eluting enantiomer of *cis*-tert-butyl 4-[4-[2-(2,4-difluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. This slower-eluting enantiomer produced the diastereomer of compounds **III-333** and **III-334** that was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The faster-eluting enantiomer of *cis*-tert-butyl 4-[4-[2-(2,4-difluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate was carried through the same steps to afford the other one of compounds **III-333** and **III-334**.

[0748] **Step 6:** To a solution of tert-butyl 4-[4-[(1S,2S)-2-(2,4-difluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate or its enantiomer (150 mg, 272 μmol, 1.0 *equiv*) in DCM (1.5 mL) was added TFA (767 mg, 7 mmol, 0.5 mL, 25.0 *equiv*). The mixture was stirred at 25 °C for 2 h. The mixture was diluted with $NaHCO_3$(10 mL), then extracted with DCM (10 mL *3). The combined organic layers were washed with H_2O(10 mL *2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude (1S,2S)-2-(2,4-difluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-ol or its enantiomer (122 mg, crude) as a yellow solid was used into the next step without further purification. LC-MS: MS (ES^+): RT =0.548 min, m/z = 451.1 [$M + H^+$]. LCMS method: 5-95.

[0749] **Step 7:** To a solution of (1S,2S)-2-(2,4-difluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-ol or its enantiomer (122 mg, 271 μmol, 1.0 *equiv*) in EtOH (4 mL) was added DIEA (105 mg, 812 μmol, 141 μL, 3.0 *equiv*) and 6-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (141 mg, 325 μmol, 1.2 *equiv*) at 0 °C. The mixture was stirred at 80 °C for 12 h. The mixture was concentrated to give a residue. The residue was purified by preparative HPLC (column: Waters Xbridge C18 150*50mm*10um;mobile phase: [H_2O(10mM NH_4HCO_3)-ACN];gradient:60%-90% B over 11.0 min) to give compound **III-334** or **III-333** (114 mg, 48% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43-7.35 (m, 2H), 6.93-6.84 (m, 2H), 6.81-6.72 (m, 2H), 6.70 (s, 1H), 6.63-6.57 (m, 1H), 6.53-6.43 (m, 2H), 6.34-6.24 (m, 2H), 6.07 (s, 1H), 5.35 (s, 1H), 4.88 (s, 1H), 4.24-4.07 (m, 1H), 3.73-3.51 (m, 3H), 3.33-3.23 (m, 2H), 3.20 (s, 3H), 3.17-3.06 (m, 4H), 3.05-2.98 (m, 2H), 2.78 (br s, 4H), 2.68 (s, 3H), 2.47-2.33 (m, 5H), 2.31-2.16 (m, 1H), 2.13-2.05 (m, 3H), 1.78 (s, 3H), 1.62 (s, 6H). LC-MS: MS (ES^+): RT = 1.84 min, m/z = 884.8 [$M + H^+$]. LCMS method: 25.

EXAMPLE 49 – Synthesis of 4-((4-(3-chloro-4-((1S,2S)-6-hydroxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-336) and 4-((4-(3-chloro-4-((1R,2R)-6-hydroxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)methyl)-1-(4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-335)





[0750] **Step 1:** A mixture of tert-butyl piperazine-1-carboxylate (10 g, 53 mmol, 1 *equiv*), 1-bromo-2-chloro-4-iodo-benzene (20.45 g, 64 mmol, 1.2 *equiv*), $Pd_2(dba)_3$ (4.92 g, 5.37 mmol, 0.1 *equiv*), Xantphos (9.32 g, 16.11 mmol, 0.3 *equiv*) and NaOtBu (15.48 g, 161.07 mmol, 3 *equiv*) in Tol. (180 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica column chromatography on silica gel (Petroleum ether: Ethyl acetate from 1/0 to 3/1) to afford desired producd tert-butyl 4-(4-bromo-3-chloro-phenyl) piperazine-1-carboxylate (19 g, 94 % yield) as a yellow oil. LC-MS: MS (ES^+): RT = 0.643 min, m/z = 320.9 [M - 55]. LCMS method: 5-95.

[0751] **Step 2:** A mixture of tert-butyl 4-(4-bromo-3-chloro-phenyl)piperazine-1-carboxylate (15 g, 39.93 mmol, 1 *equiv*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (20.28 g, 79.85 mmol, 2 *equiv*), KOAc (7.84 g, 79.85 mmol, 2 *equiv*), $Pd(dppf)Cl_2$ (5.84 g, 7.99 mmol, 0.2 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (20.28 g, 79.85 mmol, 2 *equiv*) in dioxane (200 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 3 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica column chromatography on silica gel (Petroleum ether: Ethyl acetate from 1/0 to 10/1) to afford tert-butyl 4-[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (16 g, 94 % yield) as yellow oil. ^1H NMR

(400 MHz, $CDCL_3$): δ = 7.63 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.75 (dd, *J* = 2.4, 8.4 Hz, 1H), 3.60-3.57 (m, 4H), 3.24-3.21 (m, 4H), 1.50 (s, 9H), 1.36 (s, 12H). LC-MS: MS (ES^+): RT = 0.711 min, m/z = 423.1 [$M + H^+$]. LCMS method: 5-95.

[0752] **Step 3:** A mixture of [6-benzyloxy-2-(4-methoxyphenyl)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (6.54 g, 13.33 mmol, 1 *equiv*), tert-butyl 4-[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (6.2 g, 14.67 mmol, 1.1 *equiv*), tricyclohexylphosphane Pd G3 (980 mg, 1.33 mmol, 0.1 *equiv*) and K_3PO_4 (8.49 g, 40.00 mmol, 3 *equiv*) in H_2O (20 mL) and DMAC (100 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, PE: EA = 3:1) to afford tert-butyl 4-[4-[6-benzyloxy-2-(4-methoxyphenyl)-3,4-dihydronaphthalen-1-yl]-3-chloro-phenyl]piperazine-1-carboxylate (3.6 g, 42 % yield) as a yellow solid. LC-MS: MS (ES^-): RT = 0.806 min, m/z = 637.1 [$M + H^+$]. LCMS method: 5-95.

[0753] **Step 4:** To a solution of tert-butyl 4-[4-[6-benzyloxy-2-(4-methoxyphenyl)-3,4-dihydronaphthalen-1-yl]-3-chloro-phenyl]piperazine-1-carboxylate (3.45 g, 5.41 mmol, 1 *equiv*) in MeOH (15 mL) and THF (15 mL) was added LiCl (229 mg, 5.41 mmol, 110 μL, 1 *equiv*) and Pd/C (1.15 g, 1.08 mmol, 10% purity, 0.2 *equiv*) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 45 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to afford (±)-*cis*-tert-butyl 4-[3-chloro-4-[6-hydroxy-2-(4-methoxyphenyl)tetralin-1-yl]phenyl]piperazine-1-carboxylate (600 mg, 20 % yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (s, 2H), 6.98-6.85 (m, 3H), 6.80-6.74 (m, 2H), 6.64-6.58 (m, 3H), 4.13-4.06 (m, 1H), 3.67 (s, 3H), 3.54-3.46 (m, 5H), 3.06-3.01 (m, 4H), 2.86-2.80 (m, 1H), 2.58-2.51 (m, 1H), 2.33-2.25 (m, 1H), 1.94-1.89 (m, 1H), 1.41 (s, 9H). LC-MS: MS (ES^+): RT = 0.684 min, m/z = 549.2 [$M + H^+$]. LCMS method: 5-95.

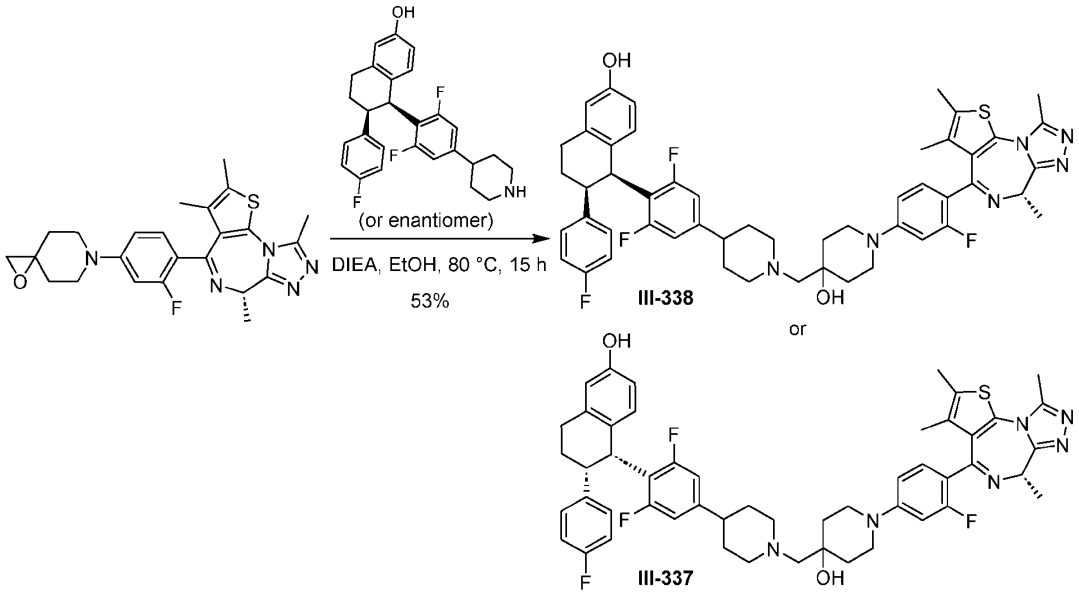
[0754] **Step 5:** Racemic *cis*-tert-butyl 4-[3-chloro-4-[6-hydroxy-2-(4-methoxyphenyl)tetralin-1-yl]phenyl]piperazine-1-carboxylate (600 mg, 1.09 mmol) was purified by prep-SFC (column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO_2-EtOH (0.1% NH3H2O)]; B%:45%, isocratic elution mode) to afford (1S,2S)- and (1R,2R)-tert-butyl 4-[3-chloro-4-[6-hydroxy-2-(4-methoxyphenyl)tetralin-1-yl]phenyl]piperazine-1-carboxylate. The slower-eluting enantiomer (238 mg, 39 % yield) was obtained as a yellow solid. LC-MS: MS (ES^+): RT = 0.682 min, m/z = 549.3 [$M + H^+$]. LCMS method: 5-95.

[0755] The following Steps 6 and 7 describe further synthetic procedures conducted on the slower-eluting enantiomer of *cis*-tert-butyl 4-[3-chloro-4-[6-hydroxy-2-(4-methoxyphenyl) tetralin-1-yl]phenyl]piperazine-1-carboxylate. This slower-eluting enantiomer produced the diastereomer of compounds **III-335** and **III-336** that was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The faster-eluting enantiomer of *cis*-tert-butyl 4-[3-chloro-4-[6-hydroxy-2-(4-methoxyphenyl) tetralin-1-yl]phenyl]piperazine-1-carboxylate was carried through the same steps to afford the other one of compounds **III-335** and **III-336**.

[0756] **Step 6:** To a solution of tert-butyl 4-[3-chloro-4-[(1S,2S)-6-hydroxy-2-(4-methoxyphenyl)tetralin-1-yl]phenyl]piperazine-1-carboxylate or its enantiomer (119 mg, 216 μmol, 1 *equiv*) in DCM (1 mL) was added TFA (767 mg, 6.73 mmol, 0.5 mL, 31.06 *equiv*). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was partitioned between $NaHCO_3$ 30 mL and DCM 50 mL. The organic phase was separated, filtered and concentrated under reduced pressure to afford desired product (1S,2S)-1-(2-chloro-4-piperazin-1-yl-phenyl)-2-(4-methoxyphenyl)tetralin-6-ol or its enantiomer (97 mg, 99 % yield) as a white solid. LC-MS: MS (ES^+): RT = 0.480 min, m/z = 449.1 [$M + H^+$]. LCMS method: 5-95.

[0757] **Step 7:** To a solution of 6-[4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (281 mg, 648 μmol, 3 *equiv*) in EtOH (3 mL) was added DIEA (83 mg, 648 μmol, 112 μL, 3 *equiv*) and (1S,2S)-1-(2-chloro-4-piperazin-1-yl-phenyl)-2-(4-methoxyphenyl)tetralin-6-ol or its enantiomer (97 mg, 216 μmol, 1 *equiv*). The mixture was stirred at 80 °C for 2 h. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um;mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 55%-85% B over 15.0 min) to afford compound **III-336** or **III-335** (46 mg, 23 % yield) as a yellow solid. ^1H NMR (400 MHz, MeOD): δ = 7.32 (d, *J* = 6.0 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.71 (s, 2H), 6.67-6.57 (m, 7H), 6.51-6.41 (m, 1H), 4.80-4.75 (m, 1H), 4.29-4.15 (m, 1H), 3.72 (s, 3H), 3.65-3.55 (m, 2H), 3.29-3.21 (m, 3H), 3.10-3.05 (m, 4H), 3.04-2.94 (m, 2H), 2.76-2.66 (m, 7H), 2.45-2.36 (m, 5H), 2.00-1.974 (m, 3H), 1.87-1.74 (m, 3H), 1.70-1.5 (m, 6H). LC-MS: MS (ES^+): RT = 2.625 min, m/z = 882.7 [$M + H^+$]. LCMS Method: 01.

EXAMPLE 50 – Synthesis of 4-((4-(3,5-difluoro-4-((1S,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-1-yl)methyl)-1-(3-fluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-338) and 4-((4-(3,5-difluoro-4-((1R,2R)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-1-yl)methyl)-1-(3-fluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)piperidin-4-ol (III-337)

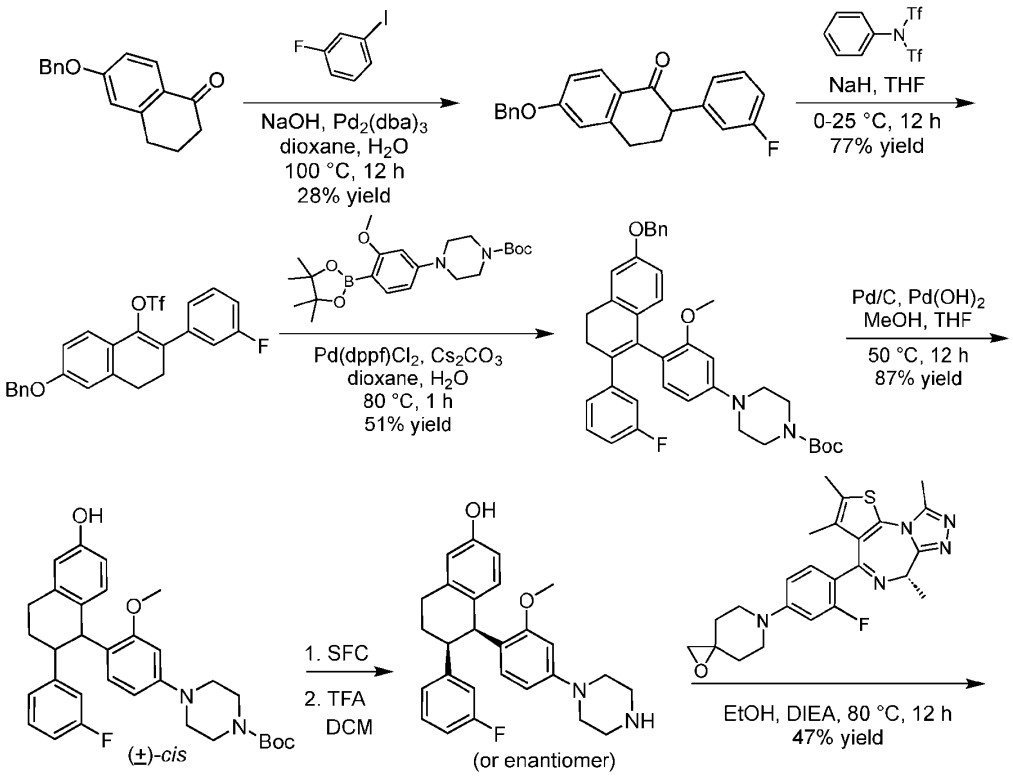


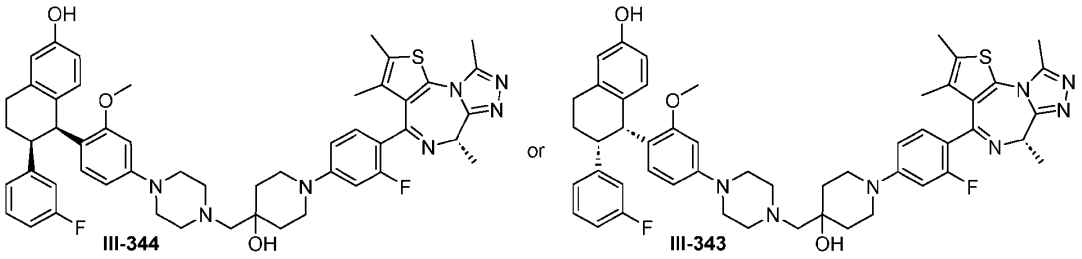
[0758] **Step 1:** To a mixture of (1S,2S)-1-[2,6-difluoro-4-(4-piperidyl)phenyl]-2-(4-fluorophenyl)tetralin-6-ol or its enantiomer (106 mg, 0.24 mmol, 1.0 *equiv*) in EtOH (5 mL) was added DIEA (156 mg, 1.21 mmol, 0.21 mL, 5.0 *equiv*) and 6-[3-fluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.0^{2,6}]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (144 mg, 0.32 mmol, 1.3 *equiv*) under N_2. The mixture was stirred at 80 °C for 15 h under N_2. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by *Prep*-HPLC (column: Waters xbridge 150 * 25 mm 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 65% - 95% B over 9.0 min) to give compound **III-338** or **III-337** (114.21 mg, 127.81 μmol, 53% yield, 99.5% purity) as a white solid. LCMS: MS(ES+): RT = 2.701 min, m/z = 889.7 [M+H+]. LCMS method: 01. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 1H), 7.28 (t, J = 8.4 Hz, 1H), 6.98 - 6.86 (m, 4H), 6.77 (dd, J_1 = 1.6 Hz, J_2= 8.8 Hz, 1H), 6.69 - 6.52 (m, 5H), 6.42 (dd, J_1= 2.0, J_2= 8.0 Hz, 1H), 4.54 (d, J = 6.0 Hz, 1H), 4.19 (s, 1H), 4.16 - 4.09 (m, 1H), 3.57 - 3.39 (m, 3H), 3.14 (t, J = 11.2 Hz, 2H), 2.95 -

2.93 (m, 4H), 2.57 (s, 3H), 2.39 - 2.29 (m, 4H), 2.25 (s, 2H), 2.22 - 2.11 (m, 3H), 1.84 (d, J = 6.8 Hz, 3H), 1.76 - 1.73 (m, 1H), 1.64 (s, 3H), 1.62 - 1.58 (m, 4H), 1.53 - 1.41 (m, 4H). This diastereomer of compounds **III-337** and **III-338** was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below).

[0759] The other enantiomer of *cis*-1-[2,6-difluoro-4-(4-piperidyl)phenyl]-2-(4-fluorophenyl)tetralin-6-ol was used in a similar reaction to afford the other one of compounds **III-337** and **III-338**.

EXAMPLE 51 – Synthesis of 1-(3-fluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(4-((1S,2S)-2-(3-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-344) and 1-(3-fluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(4-((1R,2R)-2-(3-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-343)





[0760] **Step 1:** A mixture of 6-benzyloxytetralin-1-one (8.0 g, 31.7 mmol, 1.0 *equiv*), 1-fluoro-3-iodo-benzene (8.5 g, 38.1 mmol, 4.5 mL, 1.2 *equiv*), NaOH (1.3 g, 31.7 mmol, 1.0 *equiv*), $Pd_2(dba)_3$ (2.9 g, 3.2 mmol, 0.1 *equiv*) and tritert-butylphosphonium tetrafluoroborate (1.8 g, 6.3 mmol, 0.2 *equiv*) in dioxane (80.0 mL) and H_2O (20.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The reaction mixture was partitioned between Ethyl acetate (300 mL) and H_2O (300 mL x 2). The organic phase was separated, washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Ultimate XB-NH_2 250*50mm*10um;mobile phase: [Heptane-EtOH(0.1%NH_3H_2O)];gradient:1%-30% B over 15.0 min) to give the 6-benzyloxy-2-(3-fluorophenyl)tetralin-1-one (3.1 g, 9.0 mmol, 28% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 0.703 min, m/z = 347.1 [$M + H^+$]. LCMS Method: 5-95.

[0761] **Step 2:** To a solution of 6-benzyloxy-2-(3-fluorophenyl)tetralin-1-one (3.1 g, 9.0 mmol, 1.0 *equiv*) in THF (31.0 mL) was added NaH (716 mg, 17.9 mmol, 60% purity, 2.0 *equiv*) at 0 °C under N_2, the mixture was stirred at 25 °C for 30 min, then the 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (6.4 g, 17.9 mmol, 2.0 *equiv*) was added to the mixture at 0 °C. The mixture was stirred at 25 °C for 12 h under N_2. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) solution at 0°C dropwise. And the resulting mixture was extracted with Ethyl acetate (70 mL x 3). The organic phase was separated, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 20/1) to give the [6-benzyloxy-2-(3-fluorophenyl)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (3.3 g, 6.9 mmol, 77% yield) as a white solid. LC-MS: MS (ES^+): RT = 0.736 min, m/z = 501.2 [$M + Na]^+$. LCMS Method: 5-95.

[0762] **Step 3:** A mixture of [6-benzyloxy-2-(3-fluorophenyl)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (3.0 g, 6.3 mmol, 1.0 *equiv*), tert-butyl 4-[3-methoxy-4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (3.2 g, 7.5 mmol, 1.2 *equiv*), $Pd(dppf)Cl_2$ (459 mg, 627 μmol, 0.1 *equiv*), Cs_2CO_3 (4.1 g, 12.5 mmol, 2.0 *equiv*) in dioxane (30.0 mL) and H_2O (3.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 1 h under N_2 atmosphere. The reaction mixture was partitioned between Ethyl acetate (100 mL) and H_2O (100 mL x 2). The organic phase was separated, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*10 um;mobile phase: [H_2O(0.225% FA)-ACN];gradient:70%-100% B over 22.0 min) to give the tert-butyl 4-[4-[6-benzyloxy-2-(3-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (2.0 g, 3.2 mmol, 51% yield, 99% purity) as a yellow solid. LC-MS: MS (ES^-): RT = 0.731 min, m/z = 621.3 [$M + H^+$]. LCMS Method: 5-95.

[0763] **Step 4:** Pd/C (1.0 g, 940 μmol, 10% purity, 2.92e-1 *equiv*) and $Pd(OH)_2$ (1.0 g, 1.4 mmol, 20% purity, 4.42e-1 *equiv*) was added into a 75 mL single-necked round bottom flask under N_2, and then MeOH (10.0 mL) was added at 25 °C under N_2. After addition, tert-butyl 4-[4-[6-benzyloxy-2-(3-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (2.0 g, 3.2 mmol, 1.0 *equiv*) in THF (10.0 mL) was added under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 PSI) at 50 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 10/1) to give the (±)-*cis*-tert-butyl 4-[4-[2-(3-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (1.5 g, 2.8 mmol, 87% yield) as a yellow solid. LC-MS: MS (ES^+): RT = 0.653 min, m/z = 533.2 [$M + H^+$]. LCMS Method: 5-95.

[0764] **Step 5:** The residue was purified by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm, 10um);mobile phase: [CO_2-EtOH(0.1% NH_3H_2O)];B%:45%, isocratic elution mode) to give the (1S,2S)- and (1R,2R)-tert-butyl 4-[4-[2-(3-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. The faster-eluting enantiomer (Rt = 1.195 min) was isolated (730 mg, 1.4 mmol, 49% yield) as a yellow solid, and the slower-eluting enantiomer (Rt = 1.437 min) was isolated (720 mg, 1.4 mmol, 48% yield) as a yellow solid.

[0765] The following Steps 6 and 7 describe further synthetic procedures conducted on the slower-eluting enantiomer of *cis*-tert-butyl 4-[4-[2-(3-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. This slower-eluting enantiomer produced the

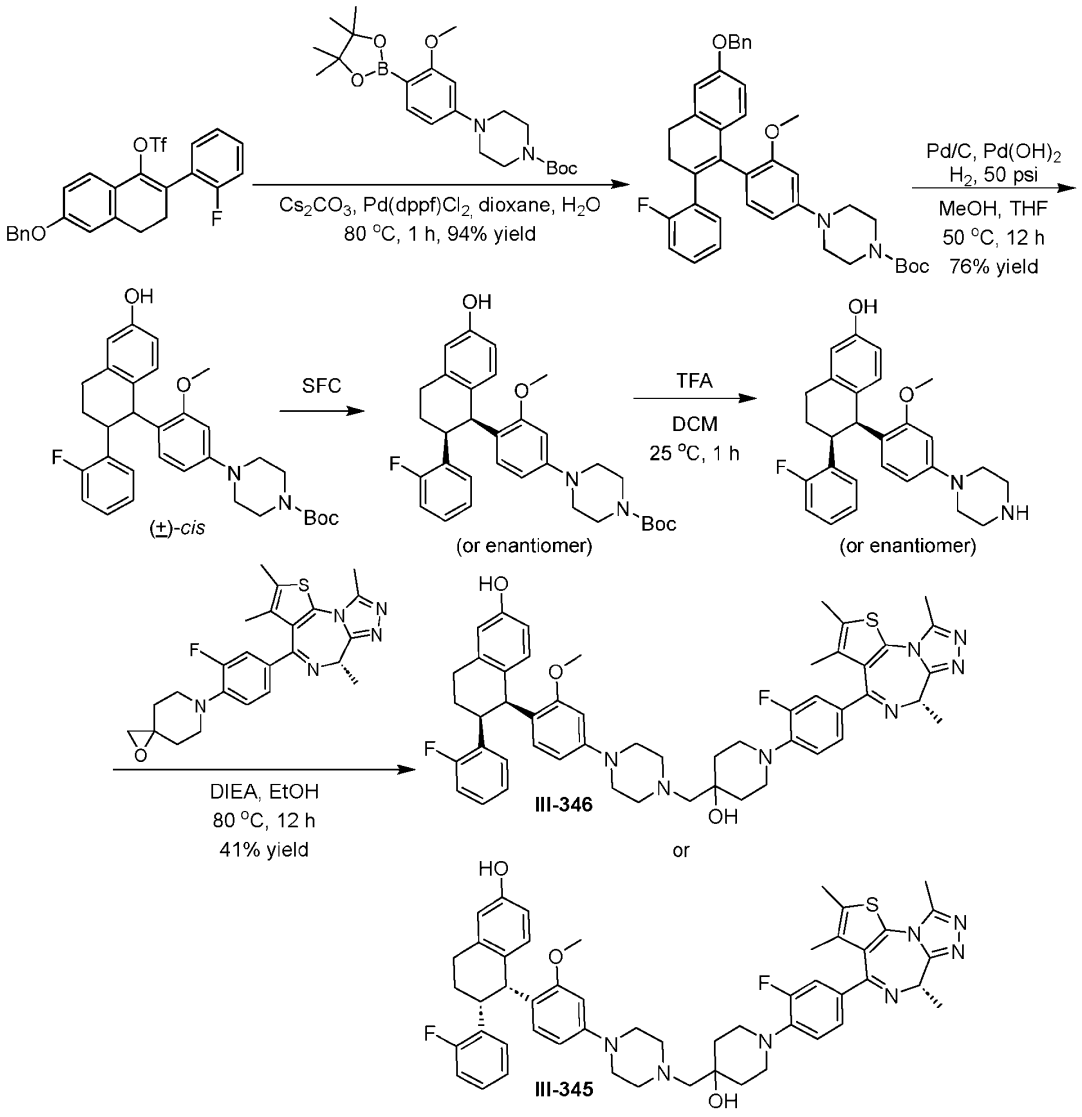
diastereomer of compounds **III-343** and **III-344** that was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The faster-eluting enantiomer of *cis*-tert-butyl 4-[4-[2-(3-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate was carried through the same steps to afford the other one of compounds **III-343** and **III-344**.

[0766] **Step 6:** To a solution of tert-butyl 4-[4-[(1S,2S)-2-(3-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate or its enantiomer (720 mg, 1.4 mmol, 1.0 *equiv*) in DCM (6.0 mL) was added TFA (2.0 mL). The mixture was stirred at 25 °C for 1 h. The reaction was added saturated aqueous $NaHCO_3$ solution to adjust the PH>7 and the reaction mixture was partitioned between DCM (80 mL) and H_2O (80 mL x 2). The organic phase was separated, washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue to give the (1S,2S)-2-(3-fluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-ol or its enantiomer (crude) as a white solid.

[0767] **Step 7:** A mixture of (1S,2S)-2-(3-fluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-ol or its enantiomer (109 mg, 252 μmol, 1.2 *equiv*), 6-[3-fluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (95 mg, 210 μmol, 1.0 *equiv*) and DIEA (136 mg, 1.1 mmol, 183 μL, 5.0 *equiv*) in EtOH (2.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um;mobile phase: [H_2O(10mM NH_4HCO_3)-ACN]; gradient: 62%-82% B over 8.0 min) to give compound **III-344** or **III-343** (90 mg, 99 μmol, 47% yield, 97% purity) as a yellow solid. LC-MS: MS (ES^+): RT = 2.655 min, m/z = 884.7 [M + H^+]. LCMS Method: 01. ^{1}H NMR: (400 MHz, CD_3OD) δ = 7.40 - 7.28 (m, 1H), 7.11 - 7.00 (m, 1H), 6.84 - 6.71 (m, 2H), 6.68 - 6.55 (m, 4H), 6.53 - 6.41 (m, 2H), 6.41 - 6.30 (m, 2H), 6.19 (d, J = 2.0 Hz, 1H), 4.76 (d, J = 5.2 Hz, 1H), 4.28 - 4.16 (m, 1H), 3.70 - 3.53 (m, 2H), 3.29 - 3.22 (m, 3H), 3.10 (s, 3H), 3.06 (s, 4H), 3.00 - 2.90 (m, 2H), 2.73 (d, J = 4.4 Hz, 4H), 2.68 (s, 3H), 2.41 - 2.34 (m, 5H), 2.30 - 2.19 (m, 1H), 1.97 (d, J = 6.8 Hz, 3H), 1.84 - 1.71 (m, 2H), 1.70 - 1.58 (m, 6H).

EXAMPLE 52 – Synthesis of 1-(2-fluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(4-((1S,2S)-2-(2-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-346) and 1-(2-fluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(4-((1R,2R)-2-(2-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-345)



[0768] **Step 1:** To a solution of [6-benzyloxy-2-(2-fluorophenyl)-3,4-dihydronaphthalen-1-yl] trifluoromethanesulfonate (3.0 g, 6.3 mmol, 1.0 *equiv*) and tert-butyl 4-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (3.7 g, 8.8 mmol, 1.4 *equiv*) in dioxane (30.0 mL) and H_2O (3.0 mL) was added Cs_2CO_3 (4.1 g, 12.5 mmol, 2.0 *equiv*) and $Pd(dppf)Cl_2$ (459 mg, 627 µmol, 0.1 *equiv*). The mixture was stirred at 80 °C for 1 h under N_2.

The resulting mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL), the H_2O phase was separated, washed twice with EtOAc (50 mL), then the organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 8/1). Compound tert-butyl 4-[4-[6-benzyloxy-2-(2-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (3.7 g, 5.9 mmol, 94% yield, 99% purity) was obtained as a white solid. LC-MS: MS (ES^+): RT = 0.733 min, m/z = 621.3 $[M+H]^+$. LCMS method: 5-95.

[0769] **Step 2:** Pd/C (1.8 g, 1.7 mmol, 10% purity, 0.3 *equiv*) and $Pd(OH)_2$ (1.8 g, 2.6 mmol, 20% purity, 0.4 *equiv*) was added into a 250 mL single-necked round bottom flask under N_2, and then THF (30.0 mL) and MeOH (30.0 mL) was added at 25 °C under N_2. After addition, tert-butyl 4-[4-[6-benzyloxy-2-(2-fluorophenyl)-3,4-dihydronaphthalen-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (3.7 g, 6.0 mmol, 1.0 *equiv*) was added under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 50 °C for 12 h. The reaction mixture was filtered and the filtrate was concentrated and then triturated with MeOH at 25°C for 8 h. Compound (±)-*cis*-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (2.4 g, 4.5 mmol, 76% yield, 99% purity) was obtained as a white solid. LC-MS: MS (ES^+): RT = 0.643 min, m/z = 533.3 $[M+H]^+$. LCMS Method: 5-95.

[0770] **Step 3:** Compound (±)-*cis*-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate (2.4 g, 4.5 mmol) was separated by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO_2-EtOH(0.1% NH_3H_2O)]; B%:30%, isocratic elution mode) to afford (1S,2S)- and (1R,2R)-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. Each of the faster-eluting and slower-eluting enantiomers were isolated as white solids (710 mg, 1.3 mmol, 47% yield, 99% purity). LC-MS: MS (ES^+): RT = 0.641 min, m/z = 533.3 $[M+H]^+$; LCMS Method: 5-95.

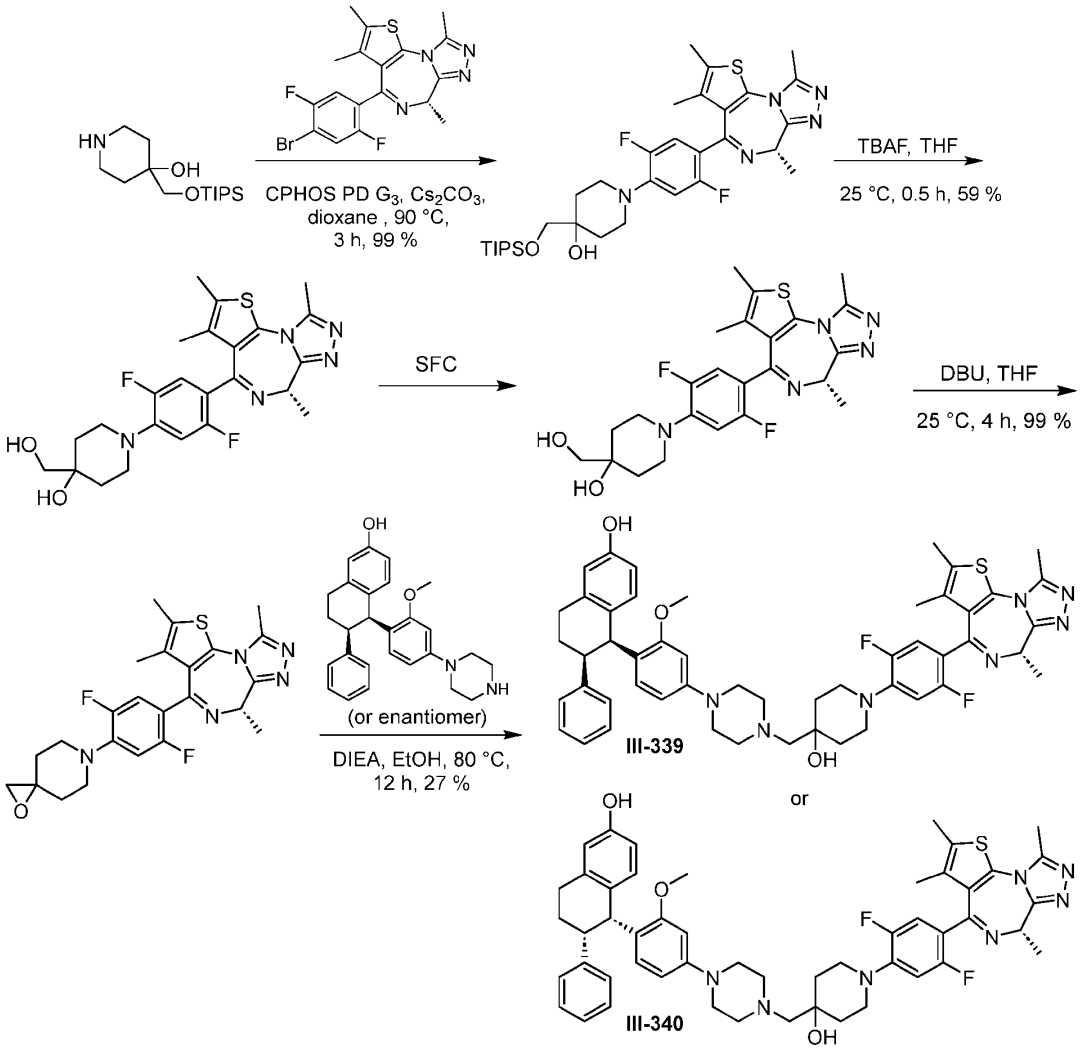
[0771] The following Steps 4 and 5 were conducted on the slower-eluting enantiomer of *cis*-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate. This slower-eluting enantiomer produced the diastereomer of compounds **III-345** and **III-346** that was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The faster-eluting enantiomer of *cis*-tert-butyl 4-[4-[2-(2-fluorophenyl)-6-hydroxy-

tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate was carried through the same step to afford the other one of compounds **III-345** and **III-346**.

[0772] **Step 4:** To a solution of tert-butyl 4-[4-[(1S,2S)-2-(2-fluorophenyl)-6-hydroxy-tetralin-1-yl]-3-methoxy-phenyl]piperazine-1-carboxylate or its enantiomer (710 mg, 1.3 mmol, 1.0 *equiv*) in DCM (9.0 mL) was added TFA (3.0 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The resulting mixture was basified with saturated aqueous $NaHCO_3$ solution to adjust pH = 8, and then diluted with DCM (30 mL) and extracted with DCM (30 mL x 2). The combined organic layers were washed with DCM (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound (1S,2S)-2-(2-fluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-ol or its enantiomer (560 mg, 1.3 mmol, 97% yield) was obtained as a yellow solid and used in the next step without further purification. LC-MS: MS (ES^+): RT = 0.843 min, m/z = 433.2 $[M+H]^+$; LCMS method: 5-95.

[0773] **Step 5:** To a solution of (1S,2S)-2-(2-fluorophenyl)-1-(2-methoxy-4-piperazin-1-yl-phenyl)tetralin-6-ol or its enantiomer (120 mg, 277 μmol, 1.3 *equiv*) and 6-[3-fluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (95 mg, 210 μmol, 1.0 *equiv*) in EtOH (3.0 mL) was added DIEA (82 mg, 631 μmol, 110 μL, 3.0 *equiv*). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove solvent and purified by prep-HPLC (column: Waters xbridge 150*25mm 10um; mobile phase: [H_2O(10mM NH_4HCO_3)-ACN];gradient:63%-83% B over 8.0 min). Compound **III-346** or **III-345** (80 mg, 87 μmol, 41% yield, 96% purity) was obtained as an off-white solid. LC-MS: MS (ES^+): RT = 2.626 min, m/z = 884.6 $[M+H]^+$; LCMS method: 01. ^1H NMR (400 MHz, CD_3OD) δ = 7.37 - 7.29 (m, 1H), 7.11 - 7.03 (m, 1H), 7.02 - 6.95 (m, 1H), 6.82 - 6.77 (m, 1H), 6.72 - 6.66 (m, 1H), 6.62 - 6.56 (m, 3H), 6.50 - 6.43 (m, 2H), 6.37 - 6.25 (m, 2H), 6.12 (d, J = 2.0 Hz, 1H), 4.26 - 4.18 (m, 1H), 3.66 - 3.56 (m, 3H), 3.29 - 3.21 (m, 2H), 3.16 - 2.88 (m, 10H), 2.74 - 2.65 (m, 7H), 2.40 - 2.26 (m, 5H), 1.97 (d, J = 6.8 Hz, 3H), 1.81 - 1.73 (m, 2H), 1.69 - 1.57 (m, 6H).

EXAMPLE 53 – Synthesis of 1-(2,5-difluoro-4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-339) and 1-(2,5-difluoro-4-((S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-340)



[0774] **Step 1:** To a solution of 4-(triisopropylsilyloxymethyl)piperidin-4-ol (2 g, 10 mmol, 1 *equiv*), (9S)-7-(4-bromo-2,5-difluoro-phenyl)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaene (3 g, 6 mmol, 1 *equiv*) in dioxane (50 mL) was added Cs_2CO_3 (6 g, 20 mmol, 3 *equiv*) and Cphos Pd G_3 (553 mg, 686 µmol, 0.1 *equiv*).

The mixture was stirred at 90 °C for 3 h. The combined organic phase was filtered and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0/1) to give compound 1-[2,5-difluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(triisopropylsilyloxymethyl)piperidin-4-ol (3 g, crude) as a white solid. LC-MS: MS (ES^+): RT = 0.733 min, m/z = 644.4 [M- 55]. LCMS Method: 5-95.

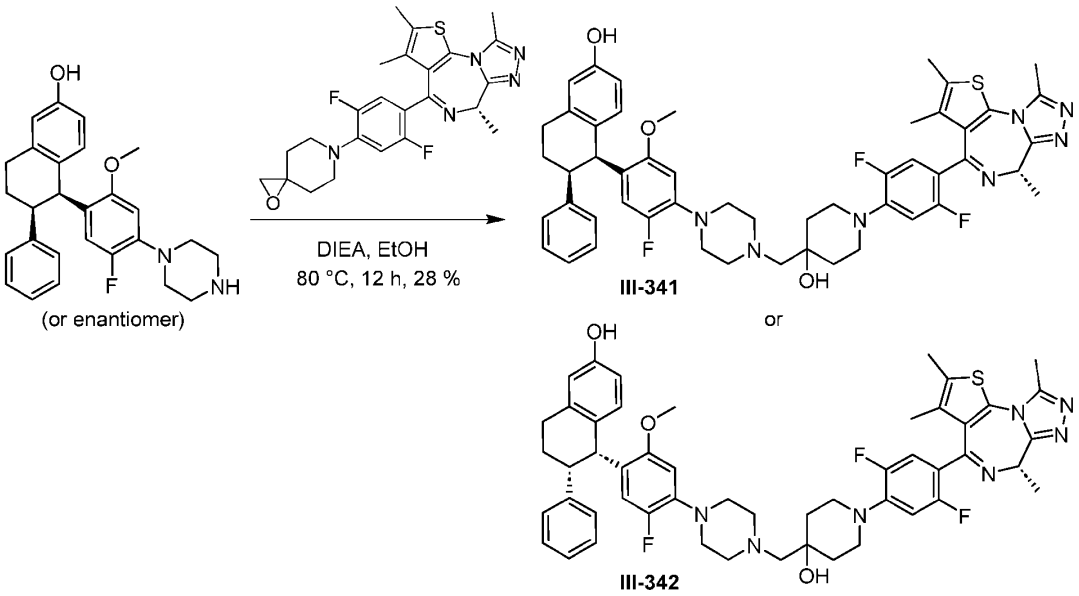
[0775] **Step 2:** To a solution of 1-[2,5-difluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(triisopropylsilyloxymethyl)piperidin-4-ol (2 g, 4 mmol, 1 *equiv*) in THF (30 mL) was added TBAF (1 M, 6 mL, 1.5 *equiv*). The mixture was stirred at 25 °C for 0.5 h. The combined organic phase was filtered and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol=10/1) to give compound 1-[2,5-difluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$] trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(hydroxymethyl)piperidin-4-ol (1 g, 2 mmol, 59 % yield) as a white solid. LC-MS: MS (ES^+): RT = 0.464 min, m/z = 488.2 [M- 100]. LCMS Method: 5-95.

[0776] **Step 3:** 1-[2,5-difluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo [8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(hydroxymethyl)piperidin-4-ol (1.3 g) was purified by prep-SFC to remove impurities, including any minor amounts of enantiomeric material (column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO_2-IPA:ACN=4:1 (0.1%NH_3H_2O)]; B%: 45%, isocratic elution mode) to give compound 1-[2,5-difluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(hydroxymethyl)piperidin-4-ol (950 mg, 1 mmol, 73 % yield) as a white solid. LC-MS: MS (ES^+): RT = 0. 481 min, m/z = 488.1 [M + 1]. LCMS Method: 5-95.

[0777] **Step 4:** To a solution of 1-[2,5-difluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-4-(hydroxymethyl)piperidin-4-ol (400 mg, 820 μmol, 1 *equiv*), 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (371 mg, 1 mmol, 216 μL, 1 *equiv*) in THF (4 mL) was added DBU (249 mg, 1 mmol, 247 μL, 2 *equiv*). The mixture was stirred at 25 °C for 1 h. The combined organic layers were filtered and concentrated in vacuum and used directly. LC-MS: MS (ES^+): RT = 0.501 min, m/z = 470.1 [M + 1]. LCMS Method: 5-95.

[0778] **Step 5:** To a solution of 6-[2,5-difluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (95 mg, 202 μmol, 1 *equiv*) and the enantiomer of *cis*-1-(2-methoxy-4-piperazin-1-yl-phenyl)-2-phenyl-tetralin-6-ol prepared in Step 6 of Example 46 (83 mg, 202 μmol, 1 *equiv*) in EtOH (2 mL) was added DIEA (78 mg, 606 μmol, 105 μL, 3 *equiv*). The mixture was stirred at 80 °C for 12 h. The combined organic layers were filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient:55%-85% B over 15.0 min) to give compound **III-339** or **III-340** (49 mg, 27% yield, 99 % purity) as a white solid. ^{1}H NMR (400 MHz, MeOD) ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.30 - 7.16 (m, 1H), 7.12 - 7.00 (m, 3H), 6.82 - 6.70 (m, 3H), 6.68 - 6.60 (m, 2H), 6.58 - 6.44 (m, 2H), 6.42 - 6.32 (m, 1H), 6.18 (d, *J* = 2.1 Hz, 1H), 4.76 (d, *J* = 5.4 Hz, 1H), 4.32 - 4.20 (m, 1H), 3.42 - 3.34 (m, 2H), 3.28 - 3.12 (m, 3H), 3.11 (d, *J* = 4.2 Hz, 4H), 3.02 (s, 5H), 2.82 - 2.72 (m, 4H), 2.68 (s, 3H), 2.48 - 2.36 (m, 5H), 2.36 - 2.24 (m, 1H), 2.00 (d, *J* = 6.8 Hz, 3H), 1.92 - 1.80 (m, 2H), 1.78 - 1.64 (m, 6H). LC-MS: MS (ES^+): RT = 2.927 min, m/z = 884.1 [M + 1]. LCMS Method: 25. This diastereomer of compounds **III-339** and **III-340** was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The other diastereomer of compounds **III-339** and **III-340** was prepared from the other enantiomer of *cis*-1-(2-methoxy-4-piperazin-1-yl-phenyl)-2-phenyl-tetralin-6-ol.

EXAMPLE 54 – Synthesis of 1-(2,5-difluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-341) and 1-(2,5-difluoro-4-((6S)-2,3,6,9-tetramethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl)-4-((4-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperazin-1-yl)methyl)piperidin-4-ol (III-342)



[0779] **Step 1:** To a solution of the enantiomer of *cis*-1-(5-fluoro-2-methoxy-4-piperazin-1-yl-phenyl)-2-phenyl-tetralin-6-ol prepared in Step 6 of Example 45 (87 mg, 201 μmol, 1 *equiv*) in EtOH (2 mL) was added DIEA (129 mg, 1.01 mmol, 175 μL, 5 *equiv*) and 6-[2,5-difluoro-4-[(9S)-4,5,9,13-tetramethyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.$0^{2,6}$]trideca-2(6),4,7,10,12-pentaen-7-yl]phenyl]-1-oxa-6-azaspiro[2.5]octane (94 mg, 201 μmol, 1 *equiv*). The mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered. The residue was purified by prep-HPLC (neutral condition; column: Waters Xbridge C18 150*25mm*5um; mobile phase: [H_2O(10mM NH_4HCO_3)-ACN]; gradient: 50%-80% B over 15.0 min) to give compound **III-341** or **III-342** (51 mg, 28 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 - 7.27 (m, 1H), 7.16 - 7.03 (m, 3H), 6.85 - 6.73 (m, 3H), 6.70 (d, *J* = 2.4 Hz, 1H), 6.62 - 6.48 (m, 2H), 6.36 (d, *J* = 13.2 Hz, 1H), 6.05 (d, *J* = 7.2 Hz, 1H), 5.70 - 5.18 (m, 1H), 4.80 (d, *J* = 5.2 Hz, 1H), 4.17 (q, *J* = 6.6 Hz, 1H), 3.41 - 3.23 (m, 4H), 3.22 - 3.05 (m, 5H), 3.04 - 2.99 (m, 2H), 2.97 (s, 3H), 2.89 - 2.75 (m, 2H), 2.68 (s, 3H), 2.54 - 2.41 (m, 1H), 2.39 (s, 3H), 2.30 - 2.20 (m, 1H), 2.09 (d, *J* = 6.8 Hz, 3H), 1.77 (s, 3H), 1.75 - 1.56 (m, 8H). LC-MS: MS (ES^+): RT = 2.962 min, m/z = 902.6 [M + H^+]. LCMS method: 01. This diastereomer of compounds **III-341** and **III-342** was found to be the more potent inhibitor of cell growth of T-Rex 293 cells having increased expression of estrogen receptor alpha protein (as described in the Example 56, below). The other diastereomer of compounds **III-339** and **III-340** was prepared from the other enantiomer of *cis*-1-(5-fluoro-2-methoxy-4-piperazin-1-yl-phenyl)-2-phenyl-tetralin-6-ol.

EXAMPLE 55 – Synthesis of Additional Compounds in Tables 2, 3, 4, and 5

[0780] All compounds in Tables 2, 3, 4, and 5 that do not have a synthetic procedure described in the preceding examples were synthesized by analogy to the procedures described above. Observed mass data (m/z values) obtained from LC/MS of the compounds is provided in Table 6, below.

TABLE 6.

Compound No.	Observed Mass (m/z)
I-34a	909.7
I-34b	909.7
I-37a or I-37b	802.5
	802.7
I-57	839.5
I-59	862.6
I-60	868.7
II-1	1234.6
II-2	1318.7
II-3	970.4
II-4	1230.7
II-5	1146.4
I-12, III-1, III-2, or III-3	869.7
	869.4
	869.4
	869.6
I-62 or III-4	825.6
	825.6
III-5 or III-6	802.7
	802.6
III-7 or III-8	775.6
	775.6
III-9 or III-10	803.7
	803.7
III-11 or III-12	842.7
	842.7
I-44 or III-13	758.4
	758.4
III-14 or III-15	758.4
	758.4
III-16 or III-17	749.6
	749.6

Compound No.	Observed Mass (m/z)
I-47 or III-18	768.8
	768.7
I-46, III-19, III-20, or III-21	835.6
	835.6
	835.6
	835.6
III-22 or III-23	800.4
	800.4
III-24 or III-25	817.7
	817.7
III-26 or III-27	817.4
	817.6
III-28	816.3
III-29	859.3
III-30	862.3
III-31	842.3
III-32	858.4
III-33	844.3
III-34	844.4
III-35	899.3
III-36	870.4
III-37	873.3
III-38	884.4
III-39	846.4
III-40	828.3
III-41	871.3
III-42	887.4
III-43	858.4
III-44	858.4
III-45	858.4
III-46	848.3
III-47	844.3

Compound No.	Observed Mass (m/z)
III-48	872.3
III-49	872.3
III-50	885.4
III-51	856.3
III-52	844.3
III-53	844.3
III-54	844.3
III-55	884.3
III-56	844.4
III-57	830.4
III-58	844.3
III-59	856.3
III-60	886.4
III-61	830.3
III-62	858.4
III-63	899.4
III-64	870.3
III-65	870.4
III-66	846.4
III-67 or III-68	774.4
	774.4
III-69 or III-70	803.4
	803.4
III-71, III-72, III-73, or III-74	869.4
	869.4
	869.4
	869.4
III-75 or III-76	816.4
	816.7
III-77a or b	843.4
III-78 or III-79	789.7
	789.7

Compound No.	Observed Mass (m/z)
III-80	788.7
III-81	846.7
III-82 or III-83	801.7
	801.7
III-84 or III-85	789.6
	789.6
III-86	817.8
III-87	842.6
III-88	842.7
III-89	774.6
III-90	760.5
III-91 or III-92	870.7
	870.7
III-93a or b	899.7
III-94a or b	803.5
III-95 or III-96	789.7
	789.7
III-97	408
III-98	773.5
III-99 or III-100	761.5
	381.3
III-101 or III-102	775.6
	775.6
III-103 or III-104	859.7
	859.6
III-105	899.7
III-106	803.7
III-107	759.7
III-108	407.9
III-109 or III-110	860.6
	860.7
III-111 or III-112	845.7
	845.7
III-113 or III-114	871.7
	871.6
III-115	787.7
III-116	773.6
III-117	759.5
III-118	818.6
III-119	816.5
III-120	759.5

Compound No.	Observed Mass (m/z)
III-121	832.7
III-122 or III-123	804.5
	804.5
III-124	841.6
III-125 or III-126	870.8
	870.7
III-127 or III-128	871.6
	871.6
III-129	787.6
III-130	831.6
III-131	842.8
III-132	801.7
III-133	843.7
III-134	857.6
III-135	857.7
III-136	844.8
III-137	801.6
III-138	774.6
III-139	788.6
III-140	885.6
III-141	774.3
III-142	788.6
III-143	886.6
III-144	819.6
III-145	816.6
III-146	844.6
III-147	844.7
III-148	773.4
III-149	884.6
III-150	827.6
III-151	860.6
III-152	817.6
III-153	817.6
III-154 or III-155	884.6
	884.6
III-156	855.6
III-157	861.4
III-158	790.4
III-159	790.3
III-160	858.6
III-161	909.6

Compound No.	Observed Mass (m/z)
III-162	910.6
III-163 or III-164	885.4
	885.4
III-165	858.4
III-166	859.4
III-167	857.4
III-168	925.7
III-169	925.6
III-170	788.4
III-171	858.6
III-172	857.4
III-173	857.4
III-174	855.4
III-175	924.5
III-176	924.5
III-177	859.6
III-178	857.4
III-179	925.5
III-180	926.5
III-181	927.7
III-182 or III-183	854.6
	854.6
III-184 or III-185	837.6
	836.6
III-186 or III-187	854.6
	854.6
III-188 or III-189	846.6
	846.6
III-190	857.7
III-191	856.6
III-192	921.3
III-193	921.6
III-194, III-195, III-196, or III-197	922.6
	922.7
	922.7
	922.6
III-198, III-199, III-200, or III-201	914.6
	914.7
	914.6
	914.6
III-202	924.8

Compound No.	Observed Mass (m/z)
III-203	861.7
III-204 or III-205	883.6
	883.6
III-206	858.7
III-207, III-208, III-209, or III-210	904.7
	904.6
	904.7
	904.7
III-211	925.7
III-212	861.7
III-213 or III-214	950.6
	949.7
III-215	869.6
III-216	869.6
III-217 or III-218	821.6
	821.6
III-219	815.5
III-220	815.6
III-221	815.7
III-222	859.4
III-223, III-224, III-225, or III-226	888.7
	888.7
	888.7
	888.7
III-227	927.7
III-228	829.7
III-229	842.6
III-230	843.8
III-231 or III-232	886.6
	886.6
III-233	842.7
III-234	841.6
III-235	859.6
III-236 or III-237	873.6
	873.6
III-238 or III-239	877.5
	877.4
III-240	831.6
III-241	831.6
III-242	814.4
III-243	814.4

Compound No.	Observed Mass (m/z)
III-244 or III-245	871.4
	871.5
III-246 or III-247	855.7
	854.3
III-248 or III-249	854.3
	855.3
III-250 or III-251	855.3
	854.5
III-252 or III-253	861.1
	861.1
III-254 or III-255	867.5
	867.2
III-256 or III-257	873.3
	873.3
III-258 or III-259	922.4
	922.3
III-260 or III-261	814.5
	813.6
III-262 or III-263	833.6
	833.6
III-264	847.6
III-265	878.4
III-266 or III-267	911.7
	911.6
III-268	831.5
III-269 or III-270	873.6
	873.6
III-271 or III-272	873.6
	873.6
III-273 or III-274	873.5
	873.6
III-275 or III-276	866.4
	866.4
III-277 or III-278	851.5
	851.6
III-279 or III-280	885.6
	885.6
III-281 or III-282	851.5
	851.6
III-283 or III-284	851.6
	851.6

Compound No.	Observed Mass (m/z)
III-285 or III-286	851.6
	851.7
III-287 or III-288	851.7
	851.6
III-289 or III-290	855.7
	855.6
III-291 or III-292	855.8
	855.6
III-293 or III-294	872.7
	873.5
III-295 or III-296	869.6
	869.5
III-297 or III-298	851.6
	851.5
III-299 or III-300	922.6
	922.6
III-301 or III-302	871.6
	872.4
III-303 or III-304	873.5
	873.4
III-305 or III-306	870.8
	870.8
III-307 or III-308	867.7
	867.7
III-309 or III-310	867.9
	867.7
III-311 or III-312	867.8
	867.8
III-313 or III-314	868.7
	869.7
III-315 or III-316	851.8
	851.7
III-317 or III-318	839.7
	839.7
III-319 or III-320	885.6
	885.7
III-321 or III-322	848.5
	849.5
III-323 or III-324	839.7
	839.8

Compound No.	Observed Mass (m/z)
III-325 or III-326	839.7
	839.7
III-327 or III-328	885.8
	884.7
III-329 or III-330	846.9
	846.8
III-331 or III-332	864.5
	865.8
III-333 or III-334	885.7
	885.8
III-335 or III-336	882.8
	883.7
III-337 or III-338	890.7
	890.7
III-339 or III-340	885.6
	885.7
III-341 or III-342	903.7
	903.7
III-343 or III-344	885.7
	885.7
III-345 or III-346	885.7
	885.7
III-347	828.3
III-348	917.7
III-349	917.8
III-350	919.8
III-351	919.7
III-352	885.6
III-353	885.6
III-354	935.7
III-355	935.7
III-356	885.8
III-357	885.7
III-358	902.7
III-359	902.7
IV-1	912.6
IV-2	928.6
IV-3	912.6
IV-4	977.6
IV-5	927.6
IV-6	911.6

Compound No.	Observed Mass (m/z)
IV-7	926.6
IV-8	951.6
IV-9	928.6
IV-10	884.6
IV-11	912.6
IV-12	911.5
IV-13	951.3
IV-14	979.4
IV-15	928.6
IV-16	859.6
IV-17	830.6
IV-18	893.6
IV-19	900.6
IV-20	865.6
IV-21	929.6
IV-22	855.6
IV-23	855.6
IV-24	882.6
IV-25	920.7
IV-26	894.5
IV-27	930.6
IV-28	877.6
IV-29	899.6
IV-30 or IV-31	995.4
	995.6
IV-32	882.6
IV-33	877.6
IV-34	912.5
IV-35	910.6
IV-36	855.6
IV-37	877.4
IV-38	902.4
IV-39	814.3
IV-40	850.2
IV-41	854.3
IV-42	870.3
IV-43	870.3
IV-44	882.3
IV-45	900.4
IV-46	899.2
IV-47	855.1

Compound No.	Observed Mass (m/z)
IV-48	896.3
IV-49	963.3
IV-50	826.6
IV-51	893.5
IV-52	928.5
IV-53	928.5
IV-54	917.6
IV-55	843.6
IV-56	916.5
IV-57	892.6
IV-58	906.6
IV-59	890.5
IV-60	978.5
IV-61	928.6
IV-62	853.6
IV-63	859.6
IV-64	932.6
IV-65	922.7
IV-66	888.4
IV-67	895.7
IV-68	925.7
IV-69	894.4
IV-70	920.6
IV-71	947.5
IV-72	909.5
V-1	961.4
V-2	945.4
V-3	933.4
V-4 or V-5	885.6
	885.6
V-6	831.6
V-7, V-8, V-9, or V-10	871.5
	871.5
	871.6
	871.6
V-11	871.4
V-12 or V-13	869.4
	869.4
V-14 or V-15	885.6
	885.6
V-16	872.6

Compound No.	Observed Mass (m/z)
V-17	872.6
V-18	870.6
V-19 or V-20	911.6
	911.7
V-21	843.6
V-22 or V-23	870.4
	870.4
V-24 or V-25	871.4
	871.4

Compound No.	Observed Mass (m/z)
V-26 or V-27	886.4
	886.4
V-28	887.4
V-29 or V-30	886.4
	886.3
V-31 or V-32	886.5
	886.6
V-33 or V-34	953.4
	953.4

Compound No.	Observed Mass (m/z)
V-35 or V-36	911.6
	911.6
V-37 or V-38	921.7
	921.7
V-39 or V-40	921.8
	921.7

EXAMPLE 56 – Cellular Growth Inhibition Assay Using T-Rex 293 Cells

[0781] Exemplary compounds were tested for the ability to inhibit the proliferation of the following types of cells: (i) a T-Rex 293 cell line having increased expression of estrogen receptor alpha protein from exposure to doxycycline and (ii) a T-Rex 293 cell line lacking increased expression of estrogen receptor alpha protein. Experimental procedures and results are provided below.

Part I – Experimental Procedure

[0782] The following types of cells were prepared for this experiment: (i) a T-Rex 293 cell line having increased expression of estrogen receptor alpha protein from exposure to doxycycline and (ii) a T-Rex 293 cell line lacking increased expression of estrogen receptor alpha protein. The ability of the test compounds to inhibit proliferation of the foregoing cell types was evaluated according to the procedures set forth below.

[0783] The doxycycline-inducible estrogen receptor alpha protein expressing cell line was established using the following protocol: T-Rex 293 cells were purchased from Invitrogen (Cat#R71007) and transfected using Lipofectamine 2000 with the wild-type estrogen receptor alpha protein sequence cloned into the pcDNA4/TO vector. Transfected cells were selected using 400 μg/mL Zeocin (Invitrogen Cat#R25001). Following selection, single clones were raised and maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% w/w Tetracycline-free fetal bovine serum (FBS) and 250 μg/mL Zeocin. Clones were analyzed for expression of estrogen receptor alpha protein in the presence and absence of 3 ng/mL doxycycline (Sigma Cat#D9891), and a single doxycycline-inducible clone (hereinafter "SC") was selected for use in downstream assays.

[0784] The SC cells were seeded on poly-D-lysine coated, black clear-bottom 384-well plates at 2500/well, in 25 µL Phenol Red Free Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% w/w charcoal-dextran treated fetal bovine serum (FBS) and 1% w/w pen-strep, with or without 3 ng/mL doxycycline. Pen-Strep is a commercially available mixture of penicillin G and streptomycin, which is used in mammalian cell culture media to prevent bacterial contamination. Phenol Red Free Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% w/w charcoal-dextran treated fetal bovine serum (FBS) and 1% w/w pen-strep, with or without 3 ng/mL doxycycline is herein referred to as Treatment Medium. Following seeding of cells in the plates, the plates were spun at 300 × g for 30 seconds, then equilibrated to room temperature for 30 minutes, and then deposited in a humidified tissue culture incubator maintained at 37 °C with 5% CO_2.

[0785] At 24 hours after seeding of the cells, dilutions of test compound were prepared in DMSO and dissolved in Treatment Medium, to achieve a final DMSO concentration of 0.5% w/w, thereby providing the Test Compound Solution. A 25 µL aliquot of the Test Compound Solution was added to cells in the well plates. An equal volume of a solution containing DMSO and Treatment Medium was used as a negative control. Following treatment of cells with Test Compound Solution or said equal volume of a solution containing DMSO and Treatment Medium, the plates were spun at 300 × g for 30 seconds, and then left in an incubator for 72 hours.

[0786] At the end of the treatment duration, cell viability was quantified with CellTiter-Glo 2.0 reagent (Promega Cat#G9243). For this purpose, plates were equilibrated to room temperature for 30 minutes, and then 25 µL of CellTiter-Glo 2.0 reagent was added to cells in the plate wells. Plates were then agitated on a shaker for two minutes at 500 rpm and subsequently incubated at room temperature for 10 minutes. Following incubation, the plates were spun at 3000 x g for 30 seconds, then sealed with an optical adhesive cover, and luminescence readings were measured with an EnVision Plate Reader (Perkin Elmer).

[0787] Data was normalized using zero luminescence for baseline. A four-parameter non-linear regression curve fit was applied to dose-response data in GraphPad Prism data analysis software to determine the half-maximal growth inhibitory concentration (GI_{50}) for each test compound.

Part II – Results

[0788] Results showing ability of exemplary compounds to inhibit the proliferation of T-Rex 293 cells having, or lacking, increased expression of estrogen receptor alpha protein are provided in Tables 7, 7-A, and 7-B, below, where columns labeled "(+) Dox TRex ERα" or "(+) Dox" refer to results in the experiment where compound was exposed to T-Rex 293 cells having increased expression of estrogen receptor alpha protein due to exposing the cells to doxycycline. Columns labeled "(-) Dox TRex ERα" or "(-) Dox" refer to results in the experiment where compound was exposed to T-Rex 293 cells lacking increased expression of estrogen receptor alpha protein. The symbol "++++" indicates a GI_{50} less than 0.05 μM. The symbol "+++" indicates a GI_{50} in the range of 0.05 μM to 0.5 μM. The symbol "++" indicates a GI_{50} in the range of greater than 0.5 μM to 2.5 μM. The symbol "+" indicates a GI_{50} greater than 2.5 μM. The symbol "N/A" indicates that no data was available.

[0789] Unless indicated otherwise, for compounds depicted in Tables 2-5 above having one or more stereogenic center(s) where stereochemistry is not defined using a dashed or wedged bond, the results reported in Tables 7, 7-A, and 7-B below are for a mixture of compounds that are diastereomers.

TABLE 7.

Compound No.	(+) Dox TRex ERα	(-) Dox TRex ERα
I-1	+++	+++
I-2	+++	+++
I-3	+++	++
I-4	++++	++
I-5	++++	++
I-6	+++	+++
I-7	+++	+++
I-8	+++	+++
I-9	++++	+++
I-10	++++	++++
I-11	++++	++++
I-13	++++	+++
I-14	+++	+
I-15	++++	++++
I-16	+	+
I-17	++	++
I-18	++++	+++
I-19	++++	+++

Compound No.	(+) Dox TRex ERα	(-) Dox TRex ERα
I-20	++++	++++
I-21	++++	+++
I-22	++++	+++
I-23	++	++
I-24	+++	+++
I-25	+++	+++
I-26	++++	+++
I-27	++++	++
I-28	+++	++
I-29	++++	++++
I-30	++++	++++
I-31	++++	+++
I-32	++++	++
I-33	++++	+
I-35	++++	++++
I-36	++	++
I-39	+++	++

TABLE 7-A.

Compound No.	(+) Dox	(-) Dox
I-34a	+++	++
I-34b	++++	++
I-37a or I-37b	+++	++
	++	++
I-57	++++	++
I-59	+++	++
I-60	+++	++
I-12, III-1, III-2, or III-3	++++	++
	+	+
	+	+
	+++	++
I-62 or III-4	+++	++
	++	+
III-5 or III-6	++++	++
	+++	++
III-7 or III-8	+++	++
	++	++
III-9 or III-10	++++	+++
	++++	+++

Compound No.	(+) Dox	(-) Dox
III-11 or III-12	++++	+++
	++++	++
I-44 or III-13	+++	++
	++	+
III-14 or III-15	+++	++
	++	++
III-16 or III-17	+++	+++
	++	++
I-47 or III-18	+++	+
	+	+
I-46, III-19, III-20, or III-21	++++	+
	+	+
	+	+
	++	+
III-22 or III-23	++++	++
	++++	+
III-24 or III-25	++++	+++
	++++	++
III-26 or III-27	++++	+++
	++++	+++

Compound No.	(+) Dox	(-) Dox
III-28	+++	+++
III-29	++++	+++
III-30	++++	+++
III-31	+	+++
III-32	++++	+++
III-33	++++	+++
III-34	++++	+++
III-35	++++	+++
III-36	++++	+++
III-37	++++	+++
III-38	++++	+++
III-39	++++	+++
III-40	+++	+++
III-41	++++	+++
III-42	++++	+++
III-43	++++	+++
III-44	+++	++
III-45	++++	+++
III-46	++++	++++
III-47	+++	+++
III-48	++++	+++
III-49	++++	+++
III-50	++++	+++
III-51	++++	+++
III-52	+++	+++
III-53	+++	+++
III-54	+++	+++
III-55	+++	++
III-56	+++	+++
III-57	+++	+++
III-58	++++	+++
III-59	++++	+++
III-60	+++	+++
III-61	++++	+++
III-62	++++	+++
III-63	++++	+++
III-64	+++	+++
III-65	++++	+++
III-66	+++	+++
III-67 or III-68	++++	++++
	+++	++

Compound No.	(+) Dox	(-) Dox
III-69 or III-70	+++	+++
	++++	+++
III-71, III-72, III-73, or III-74	+	+
	++	++
	++++	++
	++++	+++
III-75 or III-76	+++	+++
	+++	+++
III-77a or b	++++	+++
III-78 or III-79	+++	+++
	+++	+++
III-80	+++	++
III-81	+++	+
III-82 or III-83	+++	++
	+++	++
III-84 or III-85	++++	++
	+++	++
III-86	+++	++
III-87	++++	+++
III-88	++++	+++
III-89	++++	++
III-90	++	+
III-91 or III-92	+++	++
	+++	+++
III-93a or b	+++	+++
III-94a or b	++++	+++
III-95 or III-96	++++	+++
	+++	+++
III-97	++++	++
III-98	++++	++
III-99 or III-100	+++	+++
	+++	+++
III-101 or III-102	++++	+++
	+++	+++
III-103 or III-104	++++	+++
	++++	+++
III-105	++++	+++
III-106	++++	++
III-107	+++	++
III-108	++++	+++
III-109 or III-110	++++	+++
	++++	++++

Compound No.	(+) Dox	(-) Dox
III-111 or III-112	++++	+++
	+++	+++
III-113 or III-114	++++	+++
	++++	+++
III-115	+++	++
III-116	+	+
III-117	++	++
III-118	++++	++
III-119	+++	++
III-120	+	++
III-121	++	+
III-122 or III-123	++	+
	++++	++
III-124	+++	++
III-125 or III-126	++++	+++
	++++	+++
III-127 or III-128	+++	++
	++++	+++
III-129	+++	++
III-130	+++	++
III-131	++++	++
III-132	+++	++
III-133	++++	+++
III-134	++++	+++
III-135	++++	++
III-136	+	+
III-137	++	++
III-138	++	+
III-139	++	++
III-140	+++	++
III-141	+++	++
III-142	+++	+++
III-143	+	+
III-144	+++	+
III-145	++	++
III-146	++	++
III-147	+++	+++
III-148	++++	++
III-149	++++	+++
III-150	++++	++
III-151	++++	+
III-152	++++	++

Compound No.	(+) Dox	(-) Dox
III-153	++++	++
III-154 or III-155	+	+
	++++	+++
III-156	++++	++++
III-157	++++	++
III-158	++++	+++
III-159	++++	++++
III-160	++++	+++
III-161	++++	+++
III-162	++++	+++
III-163 or III-164	+	+
	++++	+++
III-165	++++	+++
III-166	++++	+++
III-167	++++	+++
III-168	++++	+++
III-169	++++	+++
III-170	++++	+++
III-171	++++	+++
III-172	++++	+++
III-173	++++	+++
III-174	++++	+++
III-175	++++	+++
III-176	++++	+++
III-177	++++	+++
III-178	++++	+++
III-179	++++	++++
III-180	++++	+++
III-181	++++	+++
III-182 or III-183	++++	++
	++++	++
III-184 or III-185	++++	+++
	++++	++
III-186 or III-187	++++	++
	++++	+++
III-188 or III-189	++++	+++
	+	+
III-190	++++	++
III-191	++++	+++
III-192	+	+
III-193	+++	++

Compound No.	(+) Dox	(-) Dox
III-194, III-195, III-196, or III-197	+	+
	+	+
	++++	+++
	++++	+++
III-198, III-199, III-200, or III-201	+	+
	+	+
	++++	+++
	+++	+++
III-202	++++	+++
III-203	++++	++
III-204 or III-205	++++	++
	+++	++
III-206	++++	++
III-207, III-208, III-209, or III-210	+	+
	+	+
	++++	+++
	++++	+++
III-211	++++	+++
III-212	++++	+++
III-213 or III-214	+	+
	++++	+++
III-215	++++	+
III-216	+	+
III-217 or III-218	++++	+++
	++++	+++
III-219	++++	+++
III-220	++++	+++
III-221	++++	+++
III-222	++++	+
III-223, III-224, III-225, or III-226	++	++
	+	+
	++++	+++
	++++	+++
III-227	++++	+
III-228	++++	++
III-229	++++	++
III-230	++++	+
III-231 or III-232	+	+
	++++	+
III-233	++++	++
III-234	++++	++
III-235	++++	++

Compound No.	(+) Dox	(-) Dox
III-236 or III-237	++++	++
	+++	++
III-238 or III-239	+++	++
	++++	+++
III-240	++++	+++
III-241	++++	+++
III-242	++++	++
III-243	++++	++
III-244 or III-245	+	+
	++++	++
III-246 or III-247	++++	++
	++++	+++
III-248 or III-249	++++	++
	+++	++
III-250 or III-251	+++	+++
	++++	++
III-252 or III-253	+++	++
	++++	++
III-254 or III-255	++++	++
	++++	++
III-256 or III-257	++++	++
	+++	++
III-258 or III-259	+++	+++
	++++	++
III-260 or III-261	++++	++
	++++	++
III-262 or III-263	+++	++
	++++	++
III-264	++++	++
III-265	+++	+
III-266 or III-267	++++	++
	+++	+
III-268	++++	++
III-269 or III-270	+++	+++
	++++	++
III-271 or III-272	+++	+++
	++++	++
III-273 or III-274	+++	+++
	++++	++
III-275 or III-276	+++	+++
	++++	++

Compound No.	(+) Dox	(-) Dox
III-277 or III-278	++++	++
	+++	++
III-279 or III-280	++++	++
	+++	++
III-281 or III-282	+++	++
	++++	+++
III-283 or III-284	+++	++
	+++	++
III-285 or III-286	+++	+++
	++++	++
III-287 or III-288	++++	++
	+++	++
III-289 or III-290	++++	++
	++++	+++
III-291 or III-292	++++	++
	+++	+++
III-293 or III-294	++++	++
	+++	+++
III-295 or III-296	++	++
	+++	++
III-297 or III-298	+++	+++
	+++	+++
III-299 or III-300	++++	+++
	++++	+++
III-301 or III-302	++	++
	+++	++
III-303 or III-304	+++	+++
	++++	++
III-305 or III-306	++++	++
	+++	++
III-307 or III-308	++++	++
	+++	+++
III-309 or III-310	+++	+++
	++++	++
III-311 or III-312	++++	++
	+++	+++
III-313 or III-314	++++	++
	+++	++
III-315 or III-316	++	++
	++++	++
III-317 or III-318	++++	+++
	+++	+++

Compound No.	(+) Dox	(-) Dox
III-319 or III-320	++++	+++
	++++	++
III-321 or III-322	++++	++
	+++	+++
III-323 or III-324	++++	++
	+++	+++
III-325 or III-326	+++	++
	++	++
III-327 or III-328	+++	+++
	++++	++
III-329 or III-330	+++	+++
	++++	+++
III-331 or III-332	++	++
	++++	+++
III-333 or III-334	+++	++
	++++	++
III-335 or III-336	+++	++
	++++	++
III-337 or III-338	+++	++
	++++	++
III-339 or III-340	++++	+
	+++	+++
III-341 or III-342	++++	+
	+++	+++
III-343 or III-344	+++	+++
	++++	++
III-345 or III-346	++++	+++
	++++	++
IV-1	++++	+
IV-2	+++	++
IV-3	++++	++
IV-4	+++	++
IV-5	++++	+
IV-6	+++	++
IV-7	+++	++
IV-8	++++	++
IV-9	++++	++
IV-10	+++	++
IV-11	++++	++
IV-12	+++	++
IV-13	++++	+++
IV-14	++++	++

Compound No.	(+) Dox	(-) Dox
IV-15	+	+
IV-16	++++	++
IV-17	++++	++
IV-18	++++	++
IV-19	++++	++
IV-20	++++	++
IV-21	++++	++
IV-22	++++	+++
IV-23	++++	+++
IV-24	++++	++
IV-25	++++	+++
IV-26	++++	++
IV-27	+++	++
IV-28	++++	++
IV-29	++++	+++
IV-30 or IV-31	++	++
	++++	+++
IV-32	++++	+++
IV-33	++++	++
IV-34	++++	+++
IV-35	++++	++
IV-36	++++	+++
IV-37	++++	++
IV-38	++++	++
IV-39	++++	+
IV-40	++++	+
IV-41	++++	+++
IV-42	++++	+++
IV-43	++++	+++
IV-44	++++	++
IV-45	++++	++++
IV-46	++++	++
IV-47	++++	++
IV-48	++++	++
IV-49	++++	++
IV-50	++++	++
IV-51	++++	++
IV-52	+++	++
IV-53	++++	++
IV-54	++++	+++
IV-55	++++	++
IV-56	++++	+++

Compound No.	(+) Dox	(-) Dox
IV-57	++++	++
IV-58	++++	++
IV-59	++++	++
IV-60	++++	+++
IV-61	++++	++
IV-62	++++	++
IV-63	++++	++
IV-64	+++	++
V-1	+++	+++
V-2	+++	++
V-3	+++	+++
V-4 or V-5	++	++
	+++	++
V-6	+++	++
V-7, V-8, V-9, or V-10	++++	+++
	++++	++
	+	++
	++	++
V-11	+++	++
V-12 or V-13	++++	+++
	+++	+++
V-14 or V-15	+++	++
	++++	+++
V-16	++	++
V-17	+++	+++
V-18	+++	+++
V-19 or V-20	++++	++
	++++	++
V-21	++++	+++
V-22 or V-23	++++	++
	++++	++
V-24 or V-25	+	+
	+	+
V-26 or V-27	++++	+++
	++++	++
V-28	++++	+++
V-29 or V-30	+++	+++
	+++	+++
V-31 or V-32	++++	+++
	++++	++
V-33 or V-34	++++	+++
	+++	+++

Compound No.	(+) Dox	(-) Dox
V-35 or V-36	++++	+++
	++++	++

TABLE 7-B.

Compound No.	(+) Dox	(-) Dox
III-347	++++	++++
III-348	++	++
III-349	++++	++
III-350	+	+
III-351	++++	+
III-352	++++	++
III-353	+++	++
III-354	+++	++
III-355	++++	++
III-356	++++	++
III-357	+++	++
III-358	++++	++
III-359	+++	++
IV-65	++++	++
IV-66	++++	++
IV-67	++++	++
IV-68	++++	++
IV-69	++++	++
IV-70	++++	++
IV-71	++++	++
IV-72	++++	++
V-37 or V-38	++++	++
	+++	+++
V-39 or V-40	+++	+++
	++++	++

EXAMPLE 57 – Cellular Growth Inhibition Assay Using MCF7 Cells

[0790] Exemplary compounds were tested for the ability to inhibit the proliferation of MCF7 cells. Experimental procedures and results are provided below.

Part I – Experimental Procedure

[0791] MCF7 cells (ATCC #HTB-22 or ECACC # 86012803) were cultured in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum, 1% pen-strep, and 0.2U/ml insulin. Cells were seeded in 25 μL of RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum, 1% pen-strep, 0.2U/ml insulin in poly-D-lysine treated, black clear-bottom 384-well plates at 225 cells/well for MCF7 cells purchased from ECACC or 1,500 cells/well for MCF7 cells purchased from ATCC. Following seeding, plates were spun at 300 × *g* for 30 seconds and cultured at 37°C with 5% CO_2 in a humidified tissue culture incubator.

[0792] At 24 hours after seeding, compounds were titrated in 100% DMSO and diluted in RPMI 1640 medium supplemented with 10% heat-inactivate fetal bovine serum, 1% pen-strep, and 0.2U/ml insulin. A 25 μL aliquot of the compound/media mixture was added to cells, bringing the total volume in each well to 50 μL. An equal volume of DMSO without compound was used as a negative control. After treatment, plates were spun at 300 × *g* for 30 seconds, then cultured at 37°C with 5% CO_2 for six days in a humidified tissue culture incubator.

[0793] On Day 6 of treatment, cell viability was quantified with CellTiter-Glo 2.0 reagent (Promega). Plates were equilibrated to room temperature for 30 minutes, then 25 μL of CellTiter-Glo 2.0 reagent was added to cells, bringing the total volume in each well to 75 μL. After reagent was added, plates were mixed on a shaker for two minutes at 500 rpm and then incubated at room temperature for 10 minutes. Following incubation, plates were spun at 3,000 x *g* for 30 seconds, sealed with an optical adhesive cover, and luminescence readings were measured with an EnVision Plate Reader.

[0794] Data was normalized to 0 luminescence for baseline. A four-parameter, non-linear regression curve fit was applied to dose-response data in GraphPad Prism data analysis software to determine the half maximal growth inhibitory concentration (GI_{50}) for each compound.

Part II – Results

[0795] Results showing ability of exemplary compounds to inhibit the proliferation of MCF7 cells purchased from ATCC are provided in Table 8-A, below. Results showing ability of exemplary compounds to inhibit the proliferation of MCF7 cells purchased from ECACC are provided in Table 8-B, below. The symbol "++++" indicates a GI_{50} less than 0.05 μM. The symbol "+++" indicates a GI_{50} in the range of 0.05 μM to 0.5 μM. The symbol "++" indicates a

GI_{50} in the range of greater than 0.5 μM to 2.5 μM. The symbol "+" indicates a GI_{50} greater than 2.5 μM.

[0796] Unless indicated otherwise, for compounds depicted in Tables 2-5 above having one or more stereogenic center(s) where stereochemistry is not defined using a dashed or wedged bond, the results reported in Tables 8-A and 8-B below are for a mixture of compounds that are diastereomers.

TABLE 8-A.

Compound No.	GI_{50}
I-1	+++
I-2	+++
I-3	+++
I-4	+++
I-5	+++
I-6	+++
I-7	+++
I-8	++++
I-9	++++
I-10	++++
I-11	++++
I-13	++++
I-14	++
I-15	++++
I-16	+++
I-17	+++
I-19	++++
I-20	++++
I-21	++++
I-22	++++
I-23	+++
I-24	++++
I-25	++++
I-26	++++
I-27	+++
I-28	+++
I-29	++++
I-30	++++
I-31	++++
I-32	+++
I-33	++++

Compound No.	GI_{50}
I-34a	+++
I-34b	+++
I-35	++++
I-36	++
I-37a or I-37b	+++
	++
I-39	+++
I-57	++++
I-59	+++
I-60	+++
II-1	++++
II-2	++++
II-3	++++
II-4	++++
II-5	++++
I-12, III-1, III-2, or III-3	++++
	++
	++
	+++
I-62 or III-4	+
	+
III-5 or III-6	++++
	+++
III-7 or III-8	+++
	+++
III-9 or III-10	+++
	+++
III-11 or III-12	+++
	+++
I-44 or III-13	++
	++

Compound No.	GI_{50}
III-14 or III-15	++
	++
III-16 or III-17	+++
	++
I-47 or III-18	++
	++
I-46, III-19, III-20, or III-21	+++
	+
	+
	++
III-22 or III-23	+++
	+++
III-24 or III-25	+++
	++++
III-26 or III-27	+++
	+++
III-28	+++
III-29	+++
III-30	+++
III-31	+++
III-32	+++
III-33	+++
III-34	+++
III-35	++++
III-36	++++
III-37	++++
III-38	++++
III-39	++++
III-40	++++
III-42	+++
III-43	+++

Compound No.	GI_{50}
III-44	+++
III-45	+++
III-46	++++
III-47	+++
III-48	++++
III-49	++++
III-50	++++
III-51	++++
III-52	+++
III-53	+++
III-54	+++
III-55	+++
III-56	+++
III-57	+++
III-58	+++
III-59	+++
III-60	+++
III-61	++++
III-62	+++
III-63	+++
III-64	+++
III-65	+++
III-66	+++
III-67 or III-68	++++
	+++
III-69 or III-70	+++
	++++
III-71, III-72, III-73, or III-74	+
	++
	++++
	+++
III-75 or III-76	+++
	+++
III-77a or b	++++
III-78 or III-79	+++
	+++
III-80	+
III-81	+++
III-82 or III-83	+++
	+++
III-84 or III-85	+++
	+++

Compound No.	GI_{50}
III-86	+++
III-87	++++
III-88	++++
III-89	+++
III-90	+++
III-91 or III-92	++++
	+++
III-93a or b	++++
III-94a or b	+++
III-95 or III-96	++++
	+++
III-97	++++
III-98	+++
III-99 or III-100	+++
	+++
III-101 or III-102	+++
	+++
III-103 or III-104	++++
	++++
III-105	++++
III-106	+++
III-107	+++
III-108	++++
III-109 or III-110	+++
	++++
III-111 or III-112	+++
	+++
III-113 or III-114	++++
	+++
III-115	+++
III-116	++
III-117	+++
III-118	+++
III-119	+++
III-120	+++
III-121	++
III-122 or III-123	++
	+++
III-124	+++
III-125 or III-126	+++
	+++

Compound No.	GI_{50}
III-127 or III-128	+++
	+++
III-129	+++
III-130	+++
III-131	+++
III-132	+++
III-133	+++
III-134	++++
III-135	++++
III-136	+
III-137	+++
III-138	++
III-139	+++
III-140	++++
III-141	+++
III-142	+++
III-143	+
III-144	++
III-145	+++
III-146	++++
III-147	+++
III-148	++++
III-149	++++
III-150	+++
III-151	++++
III-152	+++
III-153	+++
III-154 or III-155	+++
	++++
III-156	++++
III-157	+++
III-158	++++
III-159	++++
III-160	++++
III-161	++++
III-162	++++
III-163 or III-164	+++
	++++
III-165	++++
III-166	+++
III-167	++++
III-168	++++

Compound No.	GI_{50}
III-169	+++
III-170	+++
III-171	+++
III-172	+++
III-173	++++
III-174	++++
III-175	++++
III-176	++++
III-177	+++
III-178	++++
III-179	++++
III-180	++++
III-181	++++
III-182 or III-183	+++
	+++
III-184 or III-185	+++
	++++
III-186 or III-187	++++
	+++
III-188 or III-189	+++
	+++
III-190	+++
III-191	+++
III-192	+
III-193	+++
III-194, III-195, III-196, or III-197	+
	++
	++++
	+++
III-198, III-199, III-200, or III-201	+
	+
	++++
	+++
III-202	++++
III-203	++++
III-204 or III-205	+++
	+++
III-206	++++
III-207, III-208, III-209, or III-210	++
	++
	+++
	++++

Compound No.	GI_{50}
III-211	++++
III-212	++++
III-213 or III-214	+
	++++
III-215	++++
III-216	+++
III-217 or III-218	+++
	+++
III-219	+++
III-220	+++
III-221	++++
III-222	+++
III-223, III-224, III-225, or III-226	++
	+++
	+++
	++++
III-227	+++
III-228	+++
III-229	+++
III-230	+++
III-231 or III-232	++
	++++
III-233	+++
III-234	+++
III-235	++++
III-236 or III-237	++++
	+++
III-238 or III-239	+++
	++++
III-240	++++
III-241	++++
III-242	++++
III-243	++++
III-244 or III-245	+++
	++++
III-246 or III-247	++++
	+++
III-248 or III-249	++++
	+++
III-250 or III-251	+++
	++++

Compound No.	GI_{50}
III-252 or III-253	++
	++++
III-254 or III-255	+++
	+++
III-256 or III-257	++++
	+++
III-258 or III-259	+++
	++++
III-260 or III-261	+++
	+++
III-262 or III-263	+++
	++++
III-264	++++
III-265	+++
III-266 or III-267	++++
	+++
III-268	++++
III-269 or III-270	+++
	+++
III-271 or III-272	+++
	++++
III-273 or III-274	+++
	++++
III-275 or III-276	+++
	++++
III-277 or III-278	++++
	+++
III-279 or III-280	++++
	+++
III-281 or III-282	++
	++++
III-283 or III-284	+++
	+++
III-285 or III-286	+++
	++++
III-287 or III-288	+++
	+++
III-289 or III-290	++++
	+++
III-291 or III-292	++++
	+++

Compound No.	GI_{50}
III-293 or III-294	++++
	+++
III-295 or III-296	+++
	+++
III-297 or III-298	+++
	+++
III-299 or III-300	++++
	+++
III-301 or III-302	+++
	+++
III-303 or III-304	+++
	++++
III-305 or III-306	++++
	+++
III-307 or III-308	++++
	+++
III-309 or III-310	+++
	++++
III-311 or III-312	++++
	+++
III-317 or III-318	+++
	+++
III-339 or III-340	++++
	+++
III-341 or III-342	++++
	+++
III-343 or III-344	++++
	++++
III-345 or III-346	++++
	++++
III-347	++++
IV-1	+++
IV-2	+++
IV-3	+++
IV-4	++++
IV-5	+++
IV-6	+++
IV-7	+++
IV-8	++++
IV-9	++++
IV-10	+++
IV-11	+++

Compound No.	GI_{50}
IV-12	+++
IV-13	++++
IV-14	++++
IV-15	++
IV-16	++++
IV-17	++++
IV-18	++++
IV-19	+++
IV-20	++++
IV-21	+++
IV-22	++++
IV-23	++++
IV-24	++++
IV-25	++++
IV-26	++++
IV-27	+++
IV-28	++++
IV-29	++++
IV-30 or IV-31	+++
	++++
IV-32	+++
IV-33	++++
IV-34	++++
IV-35	++++
IV-36	++++
IV-37	++++
IV-38	++++
IV-39	+++
IV-40	++++
IV-41	++++
IV-42	++++
IV-43	++++
IV-44	++++
IV-45	++++
IV-46	+++
IV-47	++++
IV-48	++++
IV-49	++++
IV-50	++++
IV-51	++++
IV-52	+++
IV-53	++++

Compound No.	GI_{50}
IV-54	++++
IV-55	++++
IV-56	++++
IV-57	++++
IV-58	++++
IV-59	++++
IV-60	++++
IV-61	++++
IV-62	++++
IV-63	++++
IV-64	++++
IV-65	+++
V-1	+++
V-2	+++
V-3	+++
V-4 or V-5	+++
	+++
V-6	+++
V-7, V-8, V-9, or V-10	+++
	+++
	+++
	++
V-11	+++
V-12 or V-13	+++
	+++
V-14 or V-15	+++
	+++
V-16	+++
V-17	+++
V-18	+++
V-19 or V-20	++++
	+++
V-21	++++
V-22 or V-23	+++
	+++
V-24 or V-25	+
	+
V-26 or V-27	+++
	+++
V-28	++++
V-29 or V-30	+++
	+++

Compound No.	GI_{50}
V-31 or V-32	+++
	+++
V-33 or V-34	+++
	+++

Compound No.	GI_{50}
V-35 or V-36	++++
	+++
V-37 or V-38	++++
	+++

Compound No.	GI_{50}
V-39 or V-40	+++
	++++

TABLE 8-B.

Compound No.	GI_{50}
III-244 or III-245	+++
	++++
III-250 or III-251	+++
	++++
III-275 or III-276	+++
	++++
III-307 or III-308	++++
	+++
III-311 or III-312	++++
	++++
III-313 or III-314	+++
	+++
III-315 or III-316	+++
	++++
III-317 or III-318	++++
	+++
III-319 or III-320	+++
	++++
III-321 or III-322	++++
	+++
III-323 or III-324	++++
	+++

Compound No.	GI_{50}
III-325 or III-326	+++
	++
III-327 or III-328	+++
	++++
III-329 or III-330	+++
	++++
III-331 or III-332	++
	++++
III-333 or III-334	+++
	++++
III-335 or III-336	+++
	++++
III-337 or III-338	+++
	++++
III-339 or III-340	++++
	+++
III-341 or III-342	++++
	+++
III-343 or III-344	+++
	++++
III-345 or III-346	+++
	++++

Compound No.	GI_{50}
III-348	++
III-349	++++
III-350	+++
III-351	++++
III-352	++++
III-353	+++
III-354	+++
III-355	++++
III-356	+++
III-357	+++
III-358	++++
III-359	+++
IV-66	++++
IV-67	++++
IV-68	++++
IV-69	++++
IV-70	++++
IV-71	++++
IV-72	++++

EXAMPLE 58 – Assay for Binding Affinity to BRD4-BD1

[0797] Exemplary compounds were tested for ability to bind to BRD4-BD1. Experimental procedures and results are provided below.

Part I – Experimental Procedure

[0798] Compounds were tested using a bromoKdELECT assay. T7 phage strains displaying bromodomains were grown in parallel in 24-well blocks in an *E. coli* host derived from the BL21

strain. *E. coli* were grown to log-phase and infected with T7 phage from a frozen stock (multiplicity of infection = 0.4) and incubated with shaking at 32°C until lysis (90-150 minutes). The lysates were centrifuged (5,000 x g) and filtered (0.2μm) to remove cell debris. Streptavidin-coated magnetic beads were treated with biotinylated small molecule or acetylated peptide ligands for 30 minutes at room temperature to generate affinity resins for bromodomain assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1 % BSA, 0.05 % Tween 20, 1 mM DTT) to remove unbound ligand and to reduce nonspecific phage binding. Binding reactions were assembled by combining bromodomains, liganded affinity beads, and test compounds in 1x binding buffer (17% SeaBlock, 0.33x PBS, 0.04% Tween 20, 0.02% BSA, 0.004% Sodium azide, 7.4 mM DTT). Test compounds were prepared as 1000X stocks in 100% DMSO. Kds were determined using an 11-point 3-fold compound dilution series with one DMSO control point. All compounds for Kd measurements are distributed by acoustic transfer (non-contact dispensing) in 100% DMSO. The compounds were then diluted directly into the assays such that the final concentration of DMSO was 0.09%. All reactions performed in polypropylene 384-well plates. Each was a final volume of 0.02 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then resuspended in elution buffer (1x PBS, 0.05% Tween 20, 2 μM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The bromodomain concentration in the eluates was measured by qPCR.

Part II – Results

[0799] Results showing ability of exemplary compounds to bind to BRD4-BD1 are provided in Table 9 below. The symbol "++++" indicates a K_d less than 0.05 μM. The symbol "+++" indicates a K_d in the range of 0.05 μM to 0.5 μM. The symbol "++" indicates a K_d in the range of greater than 0.5 μM to 2.5 μM. The symbol "+" indicates a K_d greater than 2.5 μM. The symbol "N/A" indicates that no data was available.

TABLE 9.

Compound No.	K_d
I-2	+++
I-3	++++
I-5	++++

EXAMPLE 59 – Assay for Binding Affinity to BRD4-BD2

[0800] Exemplary compounds were tested for ability to bind to BRD4-BD2. Experimental procedures and results are provided below.

Part I – Experimental Procedure

[0801] Compounds were tested using a bromoKdELECT assay. T7 phage strains displaying bromodomains were grown in parallel in 24-well blocks in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage from a frozen stock (multiplicity of infection = 0.4) and incubated with shaking at 32°C until lysis (90-150 minutes). The lysates were centrifuged (5,000 x g) and filtered (0.2μm) to remove cell debris. Streptavidin-coated magnetic beads were treated with biotinylated small molecule or acetylated peptide ligands for 30 minutes at room temperature to generate affinity resins for bromodomain assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1 % BSA, 0.05 % Tween 20, 1 mM DTT) to remove unbound ligand and to reduce nonspecific phage binding. Binding reactions were assembled by combining bromodomains, liganded affinity beads, and test compounds in 1x binding buffer (17% SeaBlock, 0.33x PBS, 0.04% Tween 20, 0.02% BSA, 0.004% Sodium azide, 7.4 mM DTT). Test compounds were prepared as 1000X stocks in 100% DMSO. Kds were determined using an 11-point 3-fold compound dilution series with one DMSO control point. All compounds for Kd measurements are distributed by acoustic transfer (non-contact dispensing) in 100% DMSO. The compounds were then diluted directly into the assays such that the final concentration of DMSO was 0.09%. All reactions performed in polypropylene 384-well plates. Each was a final volume of 0.02 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then resuspended in elution buffer (1x PBS, 0.05% Tween 20, 2 μM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The bromodomain concentration in the eluates was measured by qPCR.

Part II – Results

[0802] Results showing ability of exemplary compounds to bind to BRD4-BD2 are provided in Table 10 below. The symbol "++++" indicates a K_d less than 0.05 μM. The symbol "+++" indicates a K_d in the range of 0.05 μM to 0.5 μM. The symbol "++" indicates a K_d in the range of

greater than 0.5 μM to 2.5 μM. The symbol "+" indicates a K_d greater than 2.5 μM. The symbol "N/A" indicates that no data was available.

TABLE 10.

Compound No.	K_d
I-2	++++
I-3	++++

EXAMPLE 60 – Assay for Binding Affinity to CDK1

[0803] Exemplary compounds were tested for ability to bind to CDK1. Experimental procedures and results are provided below.

Part I – Experimental Procedure

[0804] Compounds were tested using a KdELECT assay. Kinase-tagged T7 phage strains were prepared in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage and incubated with shaking at 32°C until lysis. The lysates were centrifuged and filtered to remove cell debris. The remaining kinases were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20% SeaBlock, 0.17x PBS, 0.05% Tween 20, 6 mM DTT). Test compounds were prepared as 111X stocks in 100% DMSO. Kd values were determined using an 11-point 3-fold compound dilution series with three DMSO control points. All compounds for Kd measurements are distributed by acoustic transfer (non-contact dispensing) in 100% DMSO. The compounds were then diluted directly into the assays such that the final concentration of DMSO was 0.9%. All reactions performed in polypropylene 384-well plate. Each was a final volume of 0.02 mL. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% Tween 20, 0.5 μM nonbiotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

Part II – Results

[0805] Results showing ability of exemplary compounds to bind to CDK1 are provided in Table 11 below. The symbol "++++" indicates a K_d less than 0.05 μM. The symbol "+++" indicates a K_d in the range of 0.05 μM to 0.5 μM. The symbol "++" indicates a K_d in the range of greater than 0.5 μM to 2.5 μM. The symbol "+" indicates a K_d greater than 2.5 μM. The symbol "N/A" indicates that no data was available.

TABLE 11.

Compound No.	K_d
I-40	+++
I-42	+++

INCORPORATION BY REFERENCE

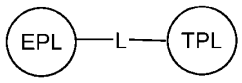
[0806] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0807] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Claims:

1. A compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

EPL is a moiety that binds to an effector protein selected from BRD4, CDK1, CDK2, or CDK9;

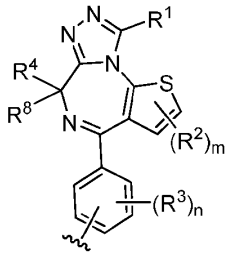
L is a linker; and

TPL is a moiety that binds to an estrogen receptor.

2. The compound of claim 1, wherein the compound is a compound of Formula I.

3. The compound of claim 1 or 2, wherein the EPL is a moiety that binds to BRD4.

4. The compound of any one of claims 1-3, wherein the EPL has the following formula:



wherein:

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

R^2 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^3 represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxyl;

R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur), -(C_{1-6} alkylene)-C(O)N(R^5)(R^6), -(C_{1-6} alkylene)-N(R^5)C(O)R^7, -(C_{1-6} alkylene)-CO_2R^7, -(C_{1-6} alkylene)-OC(O)R^7, -(C_{1-6} alkylene)-cyano, -(C_{1-6} alkylene)-O-(C_{1-6} alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl, or hydrogen; or R^4 and R^8 taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring;

R^5 and R^6 are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom;

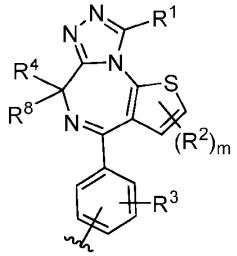
R^7 is C_{1-6} alkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

R^8 is hydrogen or C_{1-4} alkyl; and

m and n are independently 0, 1, or 2.

5. The compound of claim 4, wherein R^3 represents independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl.

6. The compound of any one of claims 1-3, wherein the EPL has the following formula:



wherein:

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

R^2 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^3 is hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxyl;

R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur), -(C_{1-6} alkylene)-C(O)N(R^5)(R^6), -(C_{1-6} alkylene)-N(R^5)C(O)R^7, -(C_{1-6} alkylene)-CO_2R^7, -(C_{1-6} alkylene)-OC(O)R^7, -(C_{1-6} alkylene)-cyano, -(C_{1-6} alkylene)-O-(C_{1-6} alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl, or hydrogen; or R^4 and R^8 taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring;

R^5 and R^6 are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or R^5 and R^6 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom;

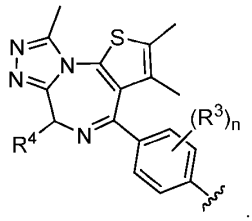
R^7 is C_{1-6} alkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

R^8 is hydrogen or C_{1-4} alkyl; and

m is 0, 1, or 2.

7. The compound of any one of claims 4-6, wherein R^1 is C_{1-4} alkyl, R^2 represents independently for each occurrence C_{1-4} alkyl, and m is 2.

8. The compound of any one of claims 4-7, wherein R^8 is hydrogen.



9. The compound of claim 4 or 5, wherein the EPL is .

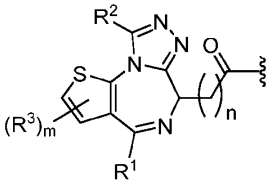
10. The compound of any one of claims 4-9, wherein R^4 is C_{1-6} alkyl.

11. The compound of any one of claims 4-9, wherein R^4 is methyl.

12. The compound of any one of claims 4-9, wherein R^4 is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

13. The compound of any one of claims 4-9, wherein R^4 is -CH_2-(oxazol-2-yl).

14. The compound of any one of claims 1-3, wherein the EPL has the following formula:



wherein:

R^1 is phenyl or 6-membered heteroaryl containing 1 or 2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the phenyl and heteroaryl are optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxyl, or C_1-C_6 alkoxy;

R^2 and R^3 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

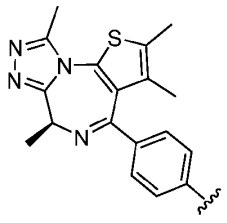
m is 0, 1, or 2; and

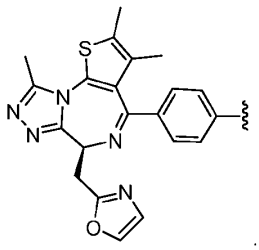
n is 0, 1, 2, 3, or 4.

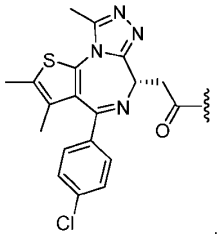
15. The compound of claim 14, wherein R^1 is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxyl, or C_1-C_6 alkoxy.

16. The compound of claim 14 or 15, wherein R^2 and R^3 are independently C_1-C_6 alkyl, and m is 2.

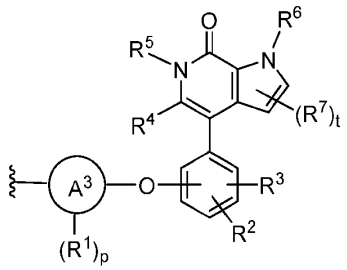
17. The compound of any one of claims 14-16, wherein n is 1.

18. The compound of claim 1 or 2, wherein the EPL is .

19. The compound of claim 1 or 2, wherein the EPL is .

20. The compound of claim 1 or 2, wherein the EPL is .

21. The compound of any one of claims 1-3, wherein the EPL has the following formula:



wherein:

R^1 represents independently for each occurrence halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^2 is hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R^3 is $-N(R^8)SO_2R^9$, $-SO_2N(R^8)_2$, $-SO_2R^9$, $-(C_{1-6}$ alkylene$)-SO_2R^9$, C_{1-6} hydroxyalkyl, or a 4-7 membered saturated carbocyclic ring in which one CH_2 is replaced with SO_2;

R^4 is hydrogen, halo, or C_{1-4} alkyl;

R^5 is C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^6 is hydrogen, C_{1-4} alkyl, or C_{3-4} cycloalkyl;

R^7 represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

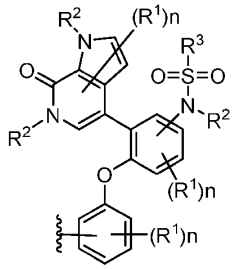
R^8 represents independently for each occurrence hydrogen or C_{1-4} alkyl; or two occurrences of R^8 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from nitrogen and oxygen; or R^8 and R^9 are taken together with their intervening atoms to a form a 5-7 membered ring containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^9 is C_{1-6} alkyl, C_{1-6} haloalkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

A^3 is phenylene, a 3-10 membered saturated monocyclic, bicyclic or spirocyclic carbocyclylene, or C_{1-6} alkylene; and

p and t are independently 0, 1, or 2.

22. The compound of any one of claims 1-3, wherein the EPL has the following formula:



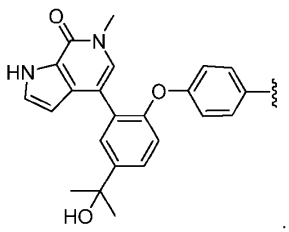
wherein:

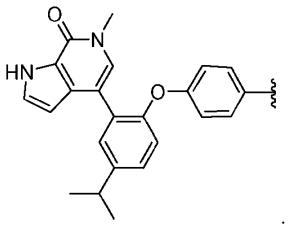
R^1 represents independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, or hydroxyl;

R^2 represents independently for each occurrence hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

n represents independently for each occurrence 0, 1, 2, or 3.

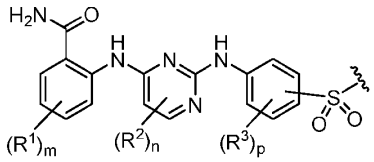
23. The compound of claim 1 or 2, wherein the EPL is .



24. The compound of claim 1 or 2, wherein the EPL is .

25. The compound of claim 1 or 2, wherein the EPL is a moiety that binds to CDK1.

26. The compound of claim 1, 2, or 25, wherein the EPL has the following formula:

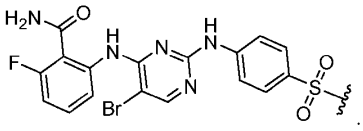


wherein:

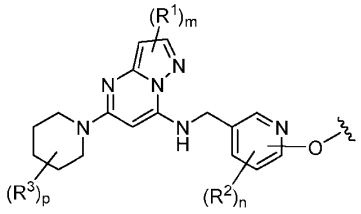
R^1, R^2 and R^3 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

m and p each represent independently 0, 1, or 2; and

n is 0, 1 or 2.

27. The compound of claim 1 or 2, wherein the EPL is .

28. The compound of claim 1, 2, or 25, wherein the EPL has the following formula:



wherein:

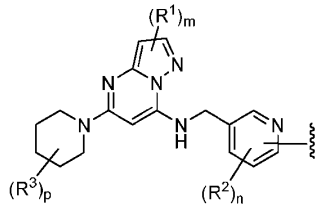
R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

29. The compound of claim 1, 2, or 25, wherein the EPL has the following formula:



wherein:

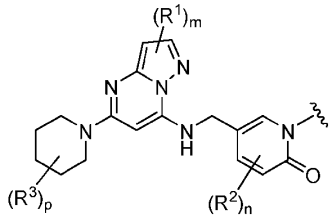
R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

30. The compound of claim 1, 2, or 25, wherein the EPL has the following formula:



wherein:

R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

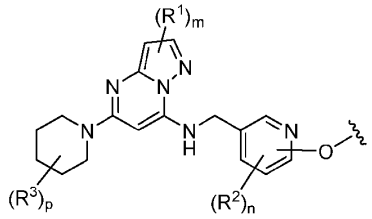
R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

31. The compound of claim 1 or 2, wherein the EPL is a moiety that binds to CDK2.

32. The compound of claim 1, 2, or 31, wherein the EPL has the following formula:



wherein:

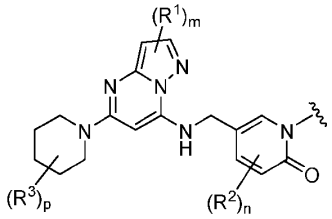
R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

33. The compound of claim 1, 2, or 31, wherein the EPL has the following formula:



wherein:

R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

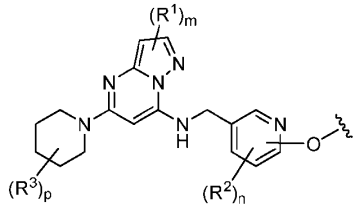
R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

34. The compound of claim 1 or 2, wherein the EPL is a moiety that binds to CDK9.

35. The compound of claim 1, 2, or 34, wherein the EPL has the following formula:



wherein:

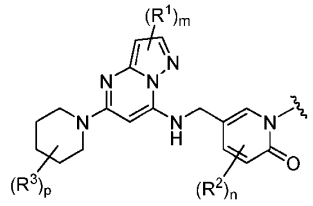
R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

36. The compound of claim 1, 2, or 34, wherein the EPL has the following formula:



wherein:

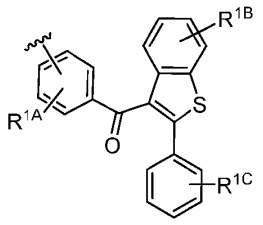
R^1 and R^2 each represent independently for each occurrence halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, or cyano;

R^3 represents independently for each occurrence C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy),

m is 0, 1, or 2; and

n and p each represent independently 0, 1, 2, or 3.

37. The compound of any one of claims 1-36, wherein the TPL is



wherein:

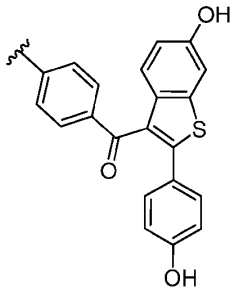
R^{1A} is hydrogen, halo, or C_{1-4} alkyl; and

R^{1B} and R^{1C} are independently hydroxyl, halo, C_{1-4} alkyl, or C_{1-4} alkoxyl.

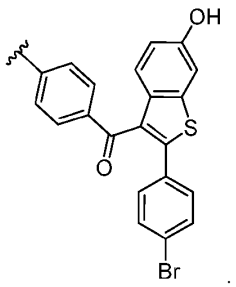
38. The compound of claim 37, wherein R^{1B} and R^{1C} are hydroxyl.

39. The compound of claim 37, wherein R^{1B} is halo, and R^{1C} is hydroxyl.

40. The compound of any one of claims 37-39, wherein R^{1A} is hydrogen.

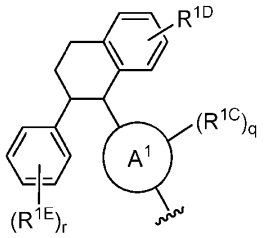
41. The compound of any one of claims 1-36, wherein the TPL is 

.

42. The compound of any one of claims 1-36, wherein the TPL is 

.

43. The compound of any one of claims 1-36, wherein the TPL is



wherein:

A^1 is phenylene or 6-membered heteroarylene containing 1 or 2 heteroatoms that are nitrogen;

R^{1C} and R^{1E} are each independently for each occurrence hydrogen, halo, C_{1-4} alkoxyl, C_{1-4} alkyl, or C_{1-4} haloalkyl;

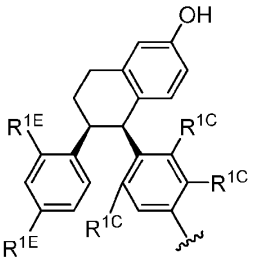
R^{1D} is hydroxyl, $-CO_2H$, or $-B(OH)_2$; and

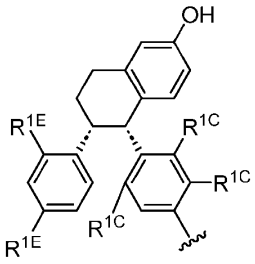
q and r are independently 0, 1, 2, or 3.

44. The compound of claim 43, wherein A^1 is *para*-phenylene, and R^{1D} is hydroxyl.

45. The compound of claim 43 or 44, wherein R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl.

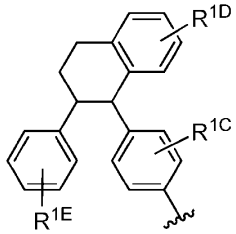
46. The compound of any one of claims 1-36, wherein the TPL is one of the following:





wherein R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl.

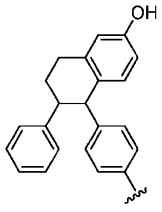
47. The compound of any one of claims 1-36, wherein the TPL is



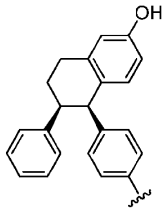
wherein:

R^{1C} and R^{1E} are independently hydrogen, halo, or C_{1-4} alkyl; and

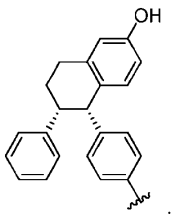
R^{1D} is hydroxyl.

48. The compound of any one of claims 1-36, wherein the TPL is 

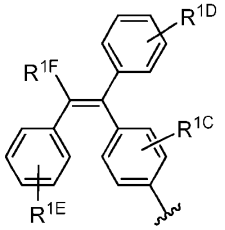
.

49. The compound of any one of claims 1-36, wherein the TPL is 

.

50. The compound of any one of claims 1-36, wherein the TPL is .

51. The compound of any one of claims 1-36, wherein the TPL is

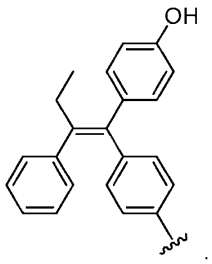


wherein:

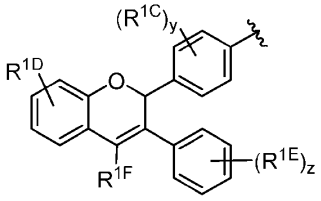
R^{1C} and R^{1E} are independently hydrogen, halo, or C_{1-4} alkyl;

R^{1D} is hydroxyl; and

R^{1F} is hydrogen or C_{1-4} alkyl.

52. The compound of any one of claims 1-36, wherein the TPL is .

53. The compound of any one of claims 1-36, wherein the TPL is



wherein:

R^{1C} represents independently for each occurrence hydrogen, halo, hydroxyl, or C_{1-4} alkyl;

R^{1D} is hydroxyl;

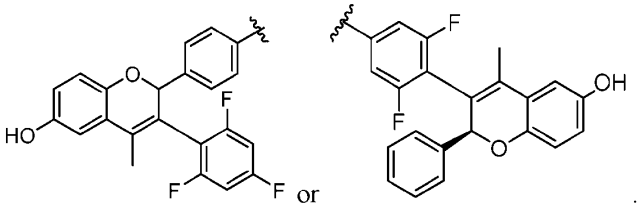
R^{1E} represents independently for each occurrence halo, hydroxyl, or C_{1-4} alkyl;

R^{1F} is hydrogen or C_{1-4} alkyl;

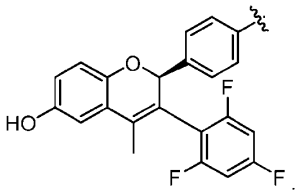
y is 1 or 2; and

z is 1, 2, or 3.

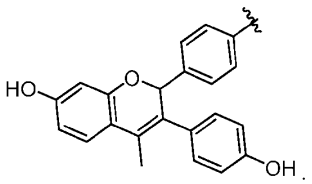
54. The compound of any one of claims 1-36, wherein the TPL is



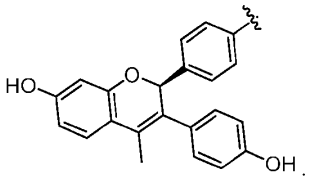
55. The compound of any one of claims 1-36, wherein the TPL is



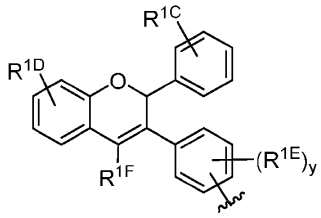
56. The compound of any one of claims 1-36, wherein the TPL is



57. The compound of any one of claims 1-36, wherein the TPL is



58. The compound of any one of claims 1-36, wherein the TPL is



wherein:

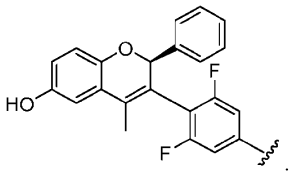
R^{1C} is hydrogen, hydroxyl, or C_{1-4} alkyl;

R^{1D} is hydroxyl;

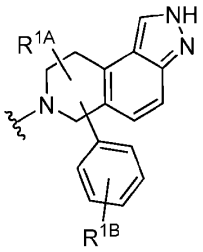
R^{1E} represents independently for each occurrence halo, hydroxyl, or C_{1-4} alkyl;

R^{1F} is hydrogen or C_{1-4} alkyl; and

y is 1, 2, or 3.

59. The compound of any one of claims 1-36, wherein the TPL is .

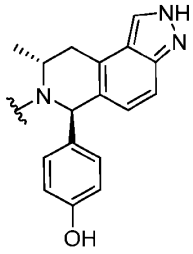
60. The compound of any one of claims 1-36, wherein the TPL is



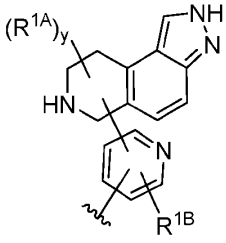
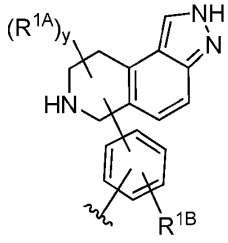
wherein:

R^{1A} is hydrogen or C_{1-4} alkyl; and

R^{1B} is -C(O)CH_3, hydroxyl, or C_{1-4} alkyl.

61. The compound of any one of claims 1-36, wherein the TPL is .

62. The compound of any one of claims 1-36, wherein the TPL is

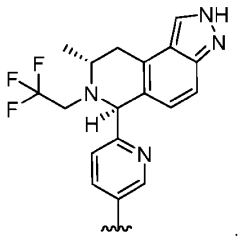
 or 

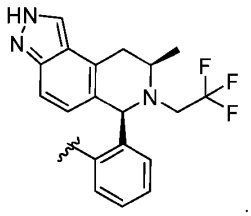
wherein:

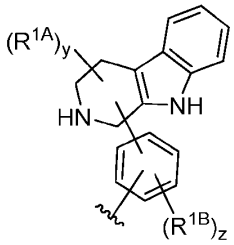
R^{1A} represents independently for each occurrence hydrogen, C_{1-4} haloalkyl, C_{1-4} alkyl, or halo;

R^{1B} is hydrogen, halo, or C_{1-4} alkyl; and

y is 1, 2, or 3.

63. The compound of any one of claims 1-36, wherein the TPL is .

64. The compound of any one of claims 1-36, wherein the TPL is .

65. The compound of any one of claims 1-36, wherein the TPL is 

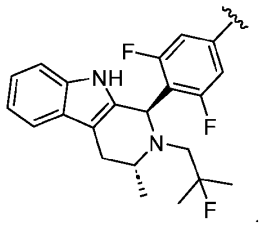
wherein:

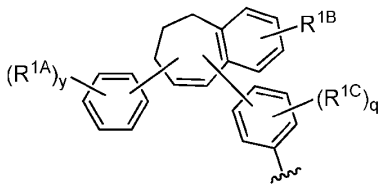
R^{1A} represents independently for each occurrence hydrogen, C_{1-4} haloalkyl, C_{1-4} alkyl, or halo;

R^{1B} represents independently for each occurrence hydrogen, halo, or C_{1-4} alkyl;

y is 1, 2, or 3; and

z is 1 or 2.

66. The compound of any one of claims 1-36, wherein the TPL is .

67. The compound of any one of claims 1-36, wherein the TPL is 

wherein:

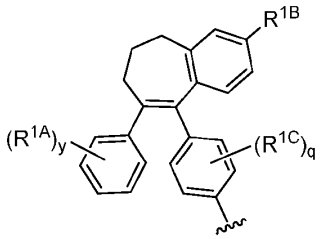
R^{1A} and R^{1C} each represents independently for each occurrence hydrogen, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^{1B} is -C(O)OH, hydrogen, halo, hydroxyl, $-B(OH)_2$, or C_{1-4} alkyl;

q is 1 or 2; and

y is 1, 2, or 3.

68. The compound of any one of claims 1-36, wherein the TPL is



wherein:

R^{1A} and R^{1C} each represents independently for each occurrence hydrogen, fluoro, chloro, methyl, or methoxy;

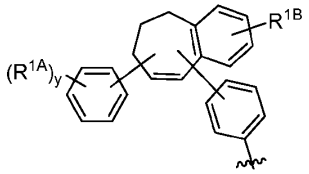
R^{1B} is -C(O)OH, -OH, or $-B(OH)_2$;

q is 1 or 2; and

y is 1, 2, or 3.

69. The compound of claim 67 or 68, wherein R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro, and R^{1C} represents independently for each occurrence hydrogen, fluoro, or methoxy.

70. The compound of any one of claims 1-36, wherein the TPL is



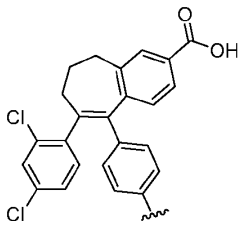
wherein:

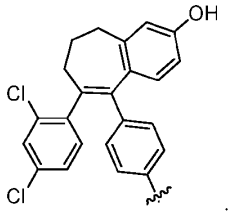
R^{1A} represents independently for each occurrence hydrogen, halo, or C_{1-4} alkyl;

R^{1B} is -C(O)OH, hydrogen, halo, hydroxyl, or C_{1-4} alkyl; and

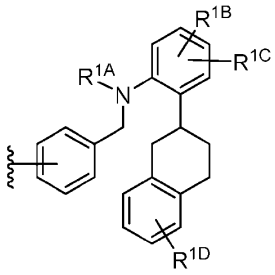
y is 1, 2, or 3.

71. The compound of any one of claims 67-70, wherein R^{1B} is -C(O)OH or -OH.

72. The compound of any one of claims 1-36, wherein the TPL is .

73. The compound of any one of claims 1-36, wherein the TPL is .

74. The compound of any one of claims 1-36, wherein the TPL is



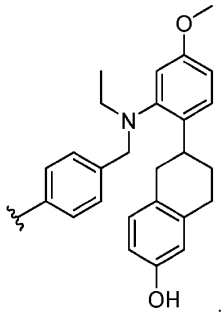
wherein:

R^{1A} is C_{1-4} alkyl;

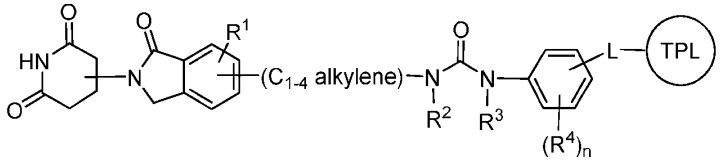
R^{1B} is C_{1-4} alkoxyl;

R^{1C} is hydrogen, halo, or C_{1-4} alkyl; and

R^{1D} is hydroxyl.

75. The compound of any one of claims 1-36, wherein the TPL is .

76. A compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is hydrogen, halo, or C_{1-4} alkyl;

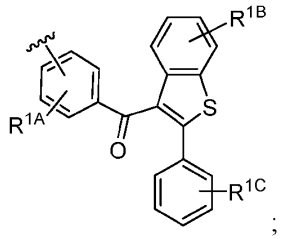
R^2 and R^3 are independently hydrogen or C_{1-4} alkyl;

R^4 represents independently for each occurrence halo, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, or C_{1-4} alkoxyl;

n is 0, 1, 2, or 3;

L is a linker; and

TPL is represented by:



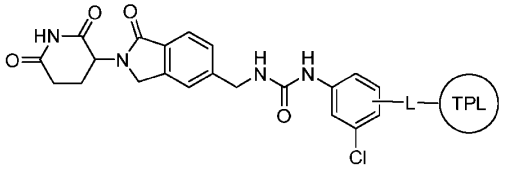
;

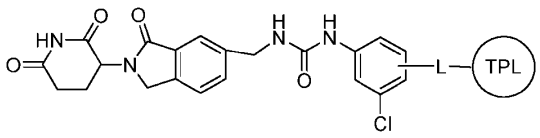
R^{1A} is hydrogen, halo, or C_{1-4} alkyl; and

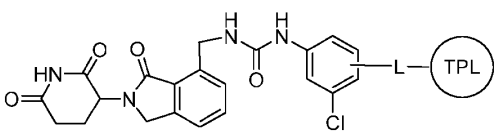
R^{1B} and R^{1C} are independently hydroxyl, halo, C_{1-4} alkyl, or C_{1-4} alkoxyl.

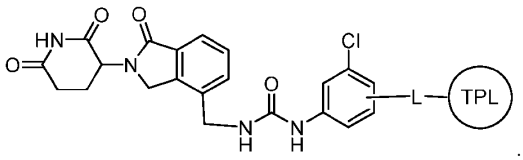
77. The compound of claim 76, wherein R^1, R^2, and R^3 are hydrogen.

78. The compound of claim 76, wherein the compound is represented by one of the following:





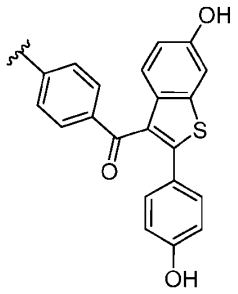




79. The compound of any one of claims 76-78, wherein R^{1A} is hydrogen.

80. The compound of any one of claims 76-79, wherein R^{1B} and R^{1C} are hydroxyl.

81. The compound of any one of claims 76-79, wherein R^{1B} is halo, and R^{1C} is hydroxyl.

82. The compound of any one of claims 76-78, wherein the TPL is 

.

83. The compound of any one of claims 1-82, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{1-60} hydrocarbon chain, wherein 0-20 methylene units of the hydrocarbon are independently replaced with -O-, -S-, -N(H)-, -N(C_{1-6} alkyl)-, -OC(O)-, -C(O)O-, -S(O)-, -S$(O)_2$-, -N(H)S$(O)_2$-, -N(C_{1-6} alkyl)S$(O)_2$-, -S$(O)_2$N(H)-, -S$(O)_2$N(C_{1-6} alkyl)-, -N(H)C(O)-, -N(C_{1-6} alkyl)C(O)-, -C(O)N(H)-, -C(O)N(C_{1-6} alkyl)-, -OC(O)N(H)-, -OC(O)N(C_{1-6} alkyl)-, -N(H)C(O)O-, -N(C_{1-6} alkyl)C(O)O-, optionally substituted 3-10 membered carbocyclyl, optionally substituted 8-11 membered spirocyclic heterocyclyl containing 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or optionally substituted 3-10 membered heterocyclyl containing 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

84. The compound of any one of claims 1-82, wherein L is a bivalent, saturated, straight or branched C_{3-30} hydrocarbon chain, wherein 0-15 methylene units of the hydrocarbon are independently replaced with -O-, -N(H)-, -N(C_{1-6} alkyl)-, -OC(O)-, -C(O)O-, -N(H)C(O)-, -N(C_{1-6} alkyl)C(O)-, -C(O)N(H)-, -C(O)N(C_{1-6} alkyl)-, 3-10 membered carbocyclyl, optionally substituted 8-11 membered spirocyclic heterocyclyl containing 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 3-10 membered heterocyclyl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

85. The compound of any one of claims 1-82, wherein L is a bivalent, saturated, straight or branched C_{3-30} hydrocarbon chain, wherein 0-15 methylene units of the hydrocarbon are independently replaced with -O-, -N(H)-, -N(C_{1-6} alkyl)-, -OC(O)-, -C(O)O-, -N(H)C(O)-, -N(C_{1-6} alkyl)C(O)-, -C(O)N(H)-, or -C(O)N(C_{1-6} alkyl)-.

86. The compound of any one of claims 1-82, wherein L has the formula –(C_{0-12} alkylene)-(optionally substituted 3-40 membered heteroalkylene)-(C_{0-12} alkylene)-.

87. The compound of any one of claims 1-82, wherein L is C_{4-14} alkylene.

88. The compound of any one of claims 1-82, wherein L is -$(CH_2)_{6-10}$-.

89. The compound of any one of claims 1-82, wherein L is -$CH_2CH_2(OCH_2CH_2)$-***, -$CH_2CH_2(OCH_2CH_2)_2$-***, -$CH_2CH_2(OCH_2CH_2)_3$-***, -$CH_2CH_2(OCH_2CH_2)_4$-***, -$CH_2CH_2(OCH_2CH_2)_5$-***, -$CH_2CH_2(OCH_2CH_2)_6$-***, -$CH_2CH_2(OCH_2CH_2)_7$-***, -$CH_2CH_2(OCH_2CH_2)_8$-***, -$CH_2CH_2(OCH_2CH_2)_9$-***, -$CH_2CH_2(OCH_2CH_2)_{10}$-***, -$CH_2CH_2(OCH_2CH_2)_{11}$-***, -$CH_2CH_2(OCH_2CH_2)_{12}$-***, -$CH_2CH_2(OCH_2CH_2)_{13}$-***, -$CH_2CH_2(OCH_2CH_2)_{14}$-***, -$CH_2CH_2(OCH_2CH_2)_{15}$-***, or -$CH_2CH_2(OCH_2CH_2)_{16-20}$-***, where *** is a point of attachment to TPL.

90. The compound of any one of claims 1-82, wherein L is -(C_{2-20} alkylene)-$(OCH_2CH_2)_{2-4}$-(C_{0-4} alkylene)-***, -(C_{2-20} alkylene)-$(OCH_2CH_2)_{5-7}$-(C_{0-4} alkylene)-***, -(C_{2-20} alkylene)-$(OCH_2CH_2)_{8-10}$-(C_{0-4} alkylene)-***, -(C_{2-20} alkylene)-$(OCH_2CH_2)_{11-13}$-(C_{0-4} alkylene)-***, -(C_{2-20} alkylene)-$(OCH_2CH_2)_{14-16}$-(C_{0-4} alkylene)-***, -(C_{2-20} alkylene)-$(OCH_2CH_2)_{17-20}$-(C_{0-4} alkylene)-***, -(C_{1-20} alkylene)-$(OCH_2CH_2)_{1-10}$-(C_{0-4} alkylene)-C(O)-***, or -(C_{1-20} alkylene)-$(OCH_2CH_2)_{11-20}$-(C_{0-4} alkylene)-C(O)-***, where *** is a point of attachment to TPL.

91. The compound of any one of claims 1-82, wherein L is -$O(CH_2CH_2O)_{2-4}$-(C_{0-4} alkylene)-***, -$O(CH_2CH_2O)_{5-7}$-(C_{0-4} alkylene)-***, -$O(CH_2CH_2O)_{8-10}$-(C_{0-4} alkylene)-***, -$O(CH_2CH_2O)_{11-13}$-(C_{0-4} alkylene)-***, -$O(CH_2CH_2O)_{14-16}$-(C_{0-4} alkylene)-***, -$O(CH_2CH_2O)_{16-20}$-(C_{0-4} alkylene)-***, -$O(CH_2CH_2O)_{2-10}$-(C_{0-4} alkylene)C(O)-***, or -$O(CH_2CH_2O)_{11-20}$-(C_{0-4} alkylene)C(O)-***, where *** is a point of attachment to TPL.

92. The compound of any one of claims 1-82, wherein L is -(C_{0-20} alkylene)-$(OCH_2CH_2)_{1-10}$-(N(C_{1-4} alkyl))-***, -(C_{0-20} alkylene)-$(OCH_2CH_2)_{11-20}$-(N(C_{1-4} alkyl))-***, -(C_{0-20} alkylene)-$(CH_2CH_2O)_{1-10}$-(C_{2-10} alkylene)-(N(C_{1-4} alkyl))-(C_{0-10} alkylene)-***, or -(C_{0-20} alkylene)-$(CH_2CH_2O)_{11-20}$-(C_{2-10} alkylene)-(N(C_{1-4} alkyl))-(C_{0-10} alkylene)-***, where *** is a point of attachment to TPL.

93. The compound of any one of claims 1-82, wherein L is -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{10-20} alkylene)-O-(C_{1-6} alkylene)-C(O)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{7-15} alkylene)-C(O)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)N(H)-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-

N(H)-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, or -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL.

94. The compound of any one of claims 1-82, wherein L is -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{10-20} alkylene)-O-(C_{1-6} alkylene)-C(O)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{7-15} alkylene)-C(O)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-(C_{2-9} alkylene)-O-(C_{1-6} alkylene)-C(O)N(H)-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-[CH_2CH_2-O-]$_{2-6}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, or -N(H)-[CH_2CH_2-O-]$_{7-15}$-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL.

95. The compound of any one of claims 1-82, wherein L is -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-C(O)-***, -N(H)-(C_{1-6} alkylene)-N(C_{1-6} alkyl)C(O)-(C_{1-6} alkylene)***, -N(H)-(C_{1-6} alkylene)-N(H)C(O)-(C_{1-6} alkylene)***, -N(H)-(C_{2-6} alkylene)-***, -N(H)-(C_{7-15} alkylene)-***, -N(C_{1-6} alkyl)-(C_{2-6} alkylene)-***, -N(C_{1-6} alkyl)-(C_{7-15} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{2-6}$-(C_{1-6} alkylene)-***, -N(H)-[(C_{2-4} alkylene)-O-]$_{7-15}$-(C_{1-6} alkylene)-***, -N(H)-(C_{1-6} alkylene)-(3-6 membered heterocycloalkylene)-(C_{1-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, -N(H)-(C_{1-6} alkylene)-(3-6 membered heterocycloalkylene)-(C_{1-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, -N(H)-(C_{2-6} alkylene)-N(H)-(C_{1-6} alkylene)-***, or -N(H)-(C_{2-6} alkylene)-N(C_{1-6} alkyl)-(C_{1-6} alkylene)-***, where *** is a point of attachment to TPL.

96. The compound of any one of claims 1-82, wherein L is -(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, -(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of hydroxyl)-(C_{0-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -(4-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -

(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{0-6} alkylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 heteroatoms selected from nitrogen)-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -O-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-(C_{0-6} alkylene)-O-***, -(C_{2-3} alkynylene)-(7-11 membered spirocyclic heterocyclyl containing 1-2 nitrogen atoms)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-***, -O-(C_{0-6} alkylene)-(5-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{1-6} alkylene)-O-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-O-***, where *** is a point of attachment to TPL.

97. The compound of any one of claims 1-82, wherein L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(4-6 membered monocyclic heterocyclyl containing 1 nitrogen atom)-(C_{0-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -N(H)-[-(C_{1-6} alkylene)-O-]$_{1-6}$-(C_{1-6} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, -N(H)-(C_{1-10} alkylene)-O-***, -N(H)-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-***, -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom, wherein the heterocyclyl is substituted with 0 or 1 occurrences of fluoro)-(C_{0-6} alkylene)-***, or -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, where *** is a point of attachment to TPL.

98. The compound of any one of claims 1-82, wherein L is -O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-O-(C_{1-6} alkylene)-(4 membered monocyclic heterocyclyl containing 1 nitrogen atom)-N(H)-***, -(C_{1-10} alkylene)-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, or -(C_{1-15} alkylene)-[-O-(C_{1-6} alkylene)-]$_{1-8}$-N(C_{1-4} alkyl)-(C_{1-6} alkylene)-O-***, where *** is a point of attachment to TPL.

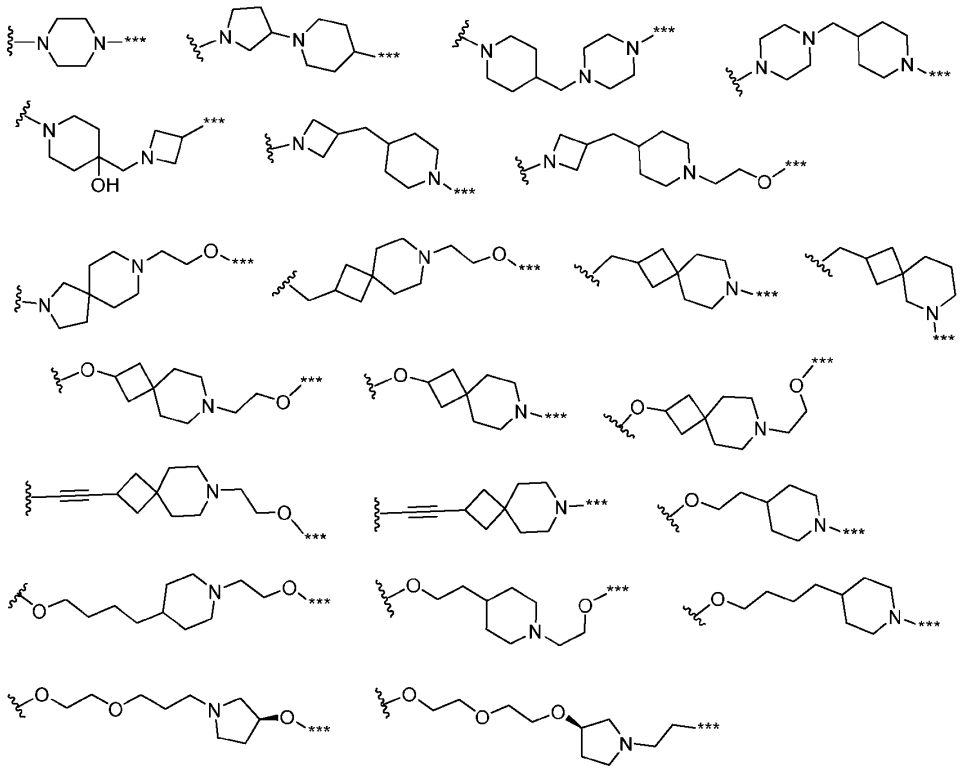
99. The compound of any one of claims 1-82, wherein L is:

(i) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***;

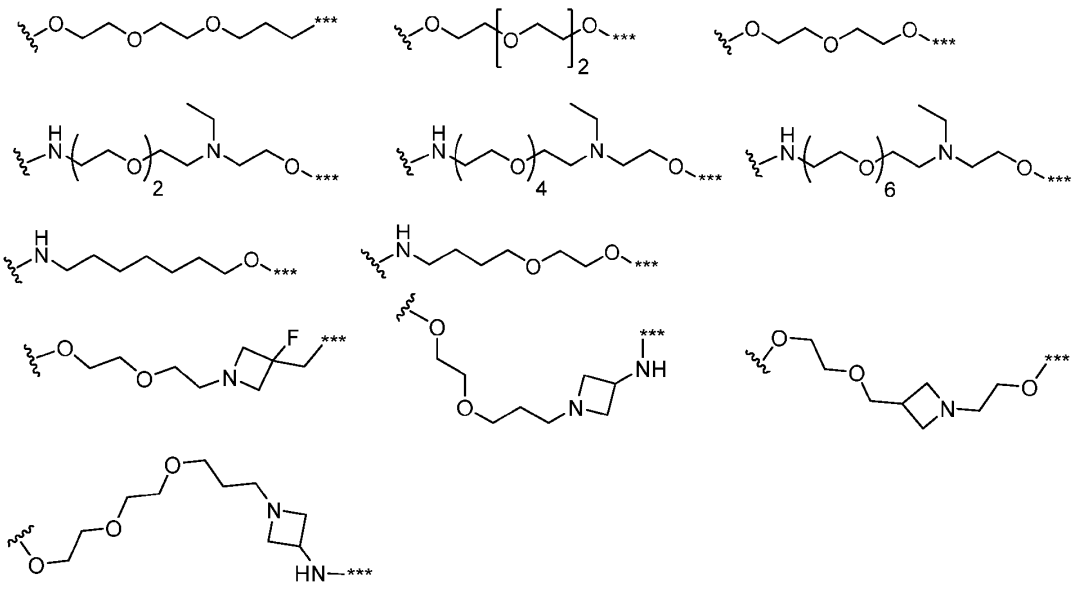
(ii) -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; or

(iii) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic ring containing 0, 1, or 2 nitrogen atoms, wherein the ring is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; wherein *** is the point of attachment to TPL.

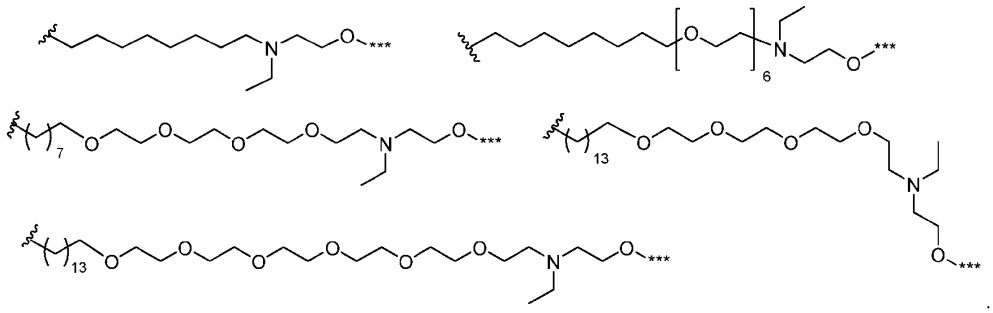
100. The compound of any one of claims 1-82, wherein L is one of the following, where *** is a point of attachment to TPL:



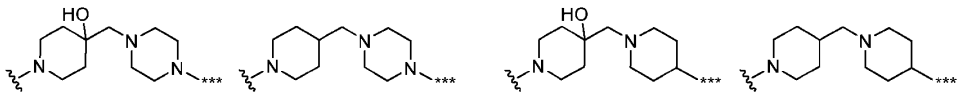
101. The compound of any one of claims 1-82, wherein L is one of the following, where *** is a point of attachment to TPL:

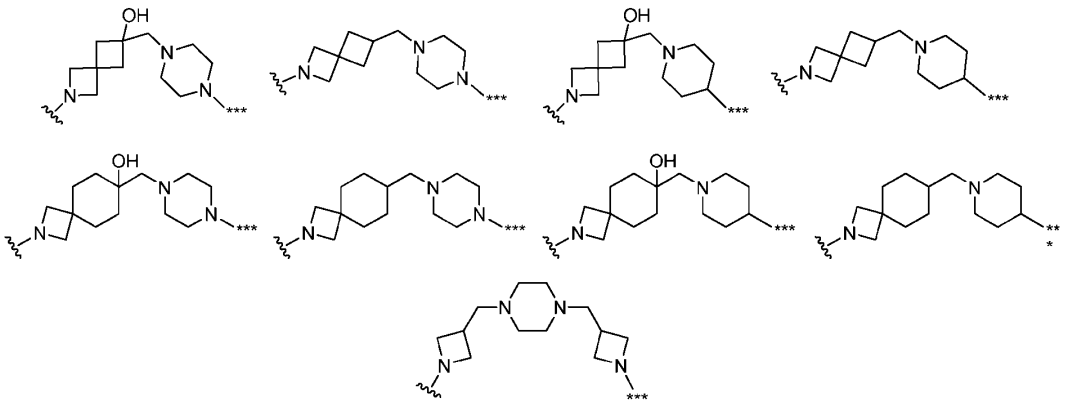


102. The compound of any one of claims 1-82, wherein L is one of the following, where *** is a point of attachment to TPL:

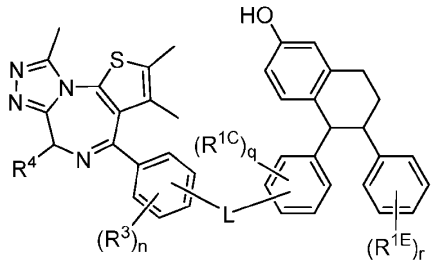


103. The compound of any one of claims 1-82, wherein L is one of the following, wherein *** is the point of attachment to TPL:





104. The compound of claim 1, wherein the compound is represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^3, R^{1C}, and R^{1E} are each independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl;

R^4 is methyl, -CH_2-(oxazolyl), or -CH_2-(thiazolyl);

L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:

(i) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-*** or

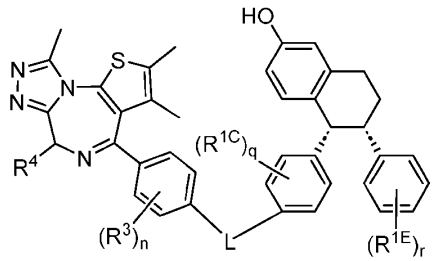
(ii) -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***; and

n, q, and r are independently 0, 1, or 2.

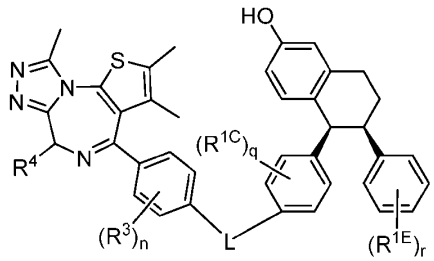
105. The compound of claim 104, wherein R^{1C} and R^{1E} are each independently for each occurrence hydrogen, fluoro, or methoxy.

106. The compound of claim 104 or 105, wherein the compound is a compound of Formula I-A.

107. The compound of claim 104 or 105, wherein the compound is represented by Formula I-A-1 or I-A-2, or a pharmaceutically acceptable salt thereof:



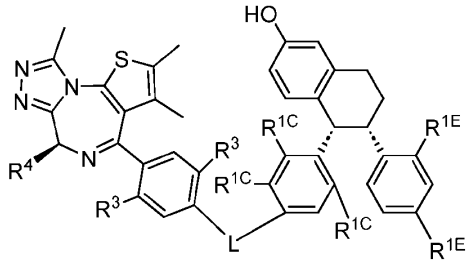
(I-A-1)



(I-A-2).

108. The compound of claim 107, wherein the compound is a compound of Formula I-A-1 or I-A-2.

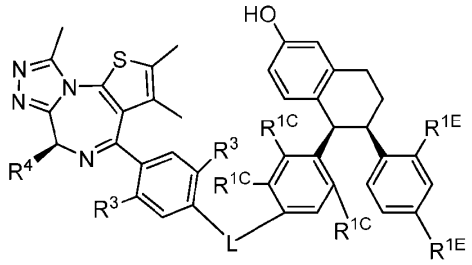
109. The compound of claim 104 or 105, wherein the compound is a compound of Formula I-A-3, or a pharmaceutically acceptable salt thereof:



(I-A-3).

110. The compound of claim 109, wherein the compound is a compound of Formula I-A-3.

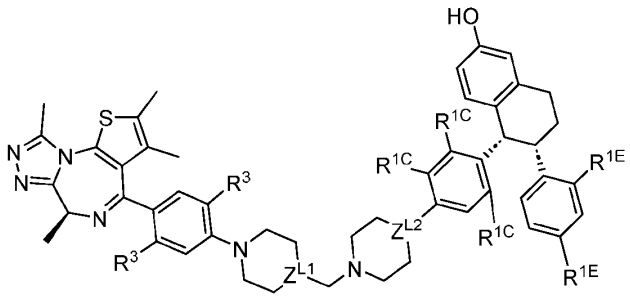
111. The compound of claim 104 or 105, wherein the compound is a compound of Formula I-A-4, or a pharmaceutically acceptable salt thereof:



(I-A-4).

112. The compound of claim 111, wherein the compound is a compound of Formula I-A-4.

113. The compound of claim 104 or 105, wherein the compound is a compound of Formula I-A-6, or a pharmaceutically acceptable salt thereof:

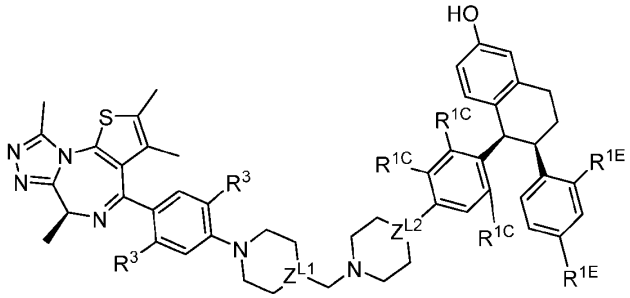


(I-A-6)

wherein Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H).

114. The compound of claim 113, wherein the compound is a compound of Formula I-A-6.

115. The compound of claim 104 or 105, wherein the compound is a compound of Formula I-A-7, or a pharmaceutically acceptable salt thereof:

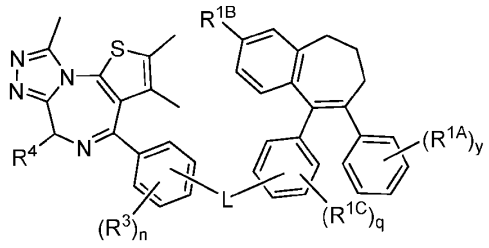


(I-A-7)

wherein Z^{L1} is C(OH) or C(H), and Z^{L2} is N or C(H).

116. The compound of claim 115, wherein the compound is a compound of Formula I-A-6 or I-A-7.

117. The compound of claim 1, wherein the compound is represented by Formula I-B:



(I-B)

or a pharmaceutically acceptable salt thereof; wherein:

R^3 represents independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl;

R^4 is methyl, -CH_2-(oxazolyl), or -CH_2-(thiazolyl);

n is 0, 1, or 2;

L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:

(i) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***,

(ii) -(7-11 membered saturated spirocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***, or

(iii) -(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms, wherein the heterocyclyl is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic ring containing 0, 1, or 2 nitrogen atoms, wherein the ring is substituted with 0 or 1 occurrence of hydroxyl or fluoro)-(C_{1-4} alkylene)-(4-6 membered saturated monocyclic heterocyclyl containing 1 or 2 nitrogen atoms)-***;

R^{1A} and R^{1C} each represents independently for each occurrence hydrogen, fluoro, chloro, methoxy, or methyl;

R^{1B} is -C(O)OH, -OH, or -$B(OH)_2$;

q is 1 or 2; and

y is 1, 2, or 3.

118. The compound of claim 117, wherein the compound is a compound of Formula I-B.

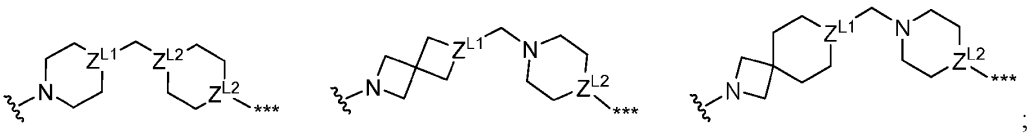
119. The compound of claim 117 or 118, wherein R^{1A} represents independently for each occurrence hydrogen, fluoro, or chloro, and R^{1C} represents independently for each occurrence hydrogen, fluoro, or methoxy.

120. The compound of any one of claims 117-119, wherein R^{1B} is -C(O)OH or -OH.

121. The compound of any one of claims 104-112 or 117-120, wherein R^4 is methyl.

122. The compound of any one of claims 104-112 or 117-120, wherein R^4 is -CH_2-(oxazol-2-yl).

123. The compound of any one of claims 104-112 or 117-122, wherein L is one of the following:

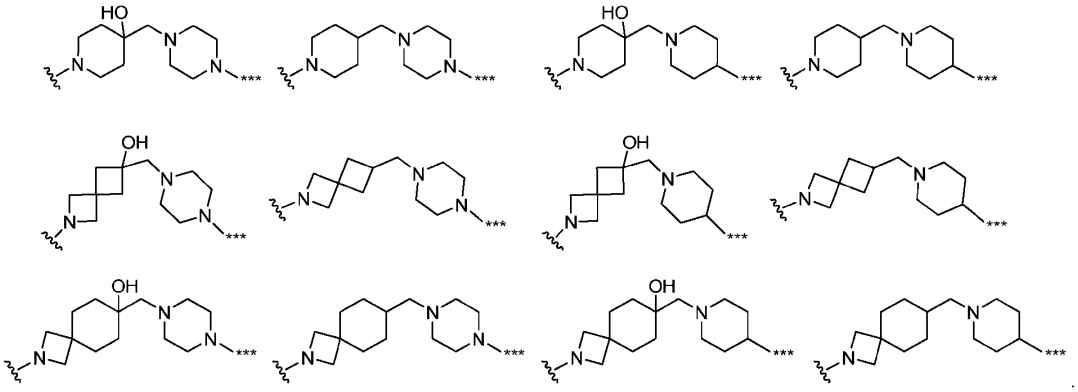

;

wherein: Z^{L1} is C(OH), C(H), C(F), or N;

Z^{L2} is independently for each occurrence N or C(H); and

*** is the point of attachment to the phenyl ring bearing R^{1C}.

124. The compound of any one of claims 104-112 or 117-122, wherein L is one of the following, wherein *** is the point of attachment to the phenyl ring bearing R^{1C}:


.

125. The compound of any one of claims 104-124, wherein R^3 represents independently for each occurrence hydrogen or fluoro.

126. A compound in Table 1, or a pharmaceutically acceptable salt thereof.

127. A compound in Table 2, or a pharmaceutically acceptable salt thereof.

128. A compound in Table 3, 4, or 5, or a pharmaceutically acceptable salt thereof.

129. A pharmaceutical composition comprising a compound of any one of claims 1-128 and a pharmaceutically acceptable carrier.

130. A method of treating cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1-128 to treat the cancer.

131. The method of claim 130, wherein the cancer is ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct cancer, gallbladder cancer, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney cancer, eye cancer, thyroid cancer, lymphoma, or leukemia.

132. The method of claim 130, wherein the cancer is breast cancer.

133. The method of any one of claims 130-132, wherein the patient is a human.

134. A method of causing death of a cancer cell, comprising contacting a cancer cell with an effective amount of a compound of any one of claims 1-128 to cause death of the cancer cell.

135. The method of claim 134, wherein the cancer cell is selected from an ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct cancer, gallbladder cancer, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney cancer, eye cancer, thyroid cancer, lymphoma, or leukemia cell.

136. The method of claim 134, wherein the cancer cell is a breast cancer cell.