PHOSPHORAMIDATE MACROCYCLE COMPOUNDS AND USES THEREOF

1. CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to International Patent Application No. PCT/CN2024/087204, filed on April 11, 2024, the entirety of which is incorporated herein by reference.

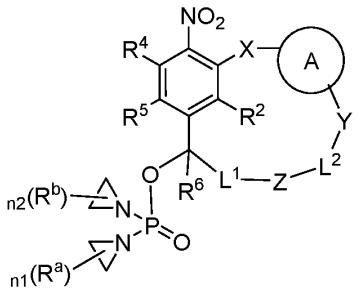
2. BACKGROUND

[0002] Aldo-keto reductase family 1 member C3 (AKR1C3) is a member of the aldo-keto reductase (AKR) superfamily, which catalyzes the conversion of aldehydes and ketones to their corresponding alcohols by using NADH and/or NADPH as cofactors. AKR1C3 was known to be overexpressed in various cancers such as prostate cancer, non-small cell lung cancer, etc. AKR1C3 is also a biomarker of NRF2 activation. Aberrant activation of NRF2 pathway, such as those caused by gain of function genetic alterations in NRF2 or loss of function genetic alterations in KEAP1 or CUL3, can lead to elevated expression of its target genes, including AKR1C3. Aberrant activation of NRF2 pathway has been implicated in various cancers and associated with poor prognosis. Novel compounds that can selectively target or utilize aberrant activation of NRF2 pathway and/or AKR1C3 are needed.

3. SUMMARY

[0003] In some embodiments, provided herein are certain phosphoramidate macrocycle compounds that can selectively inhibit the growth of cancer cells with abnormal AKR1C3 activities and/or overexpression of AKR1C3. As detailed in the Examples section herein, the tested exemplified compounds herein typically can have a lower IC_{50} value in inhibiting cancer cell growth in the absence of an AKR1C3 inhibitor compared to those observed in the presence of an AKR1C3 inhibitor. Thus, it is expected that the compounds provided herein can selectively target those cancers characterized as having abnormal AKR1C3 activity and/or an overexpressed level of AKR1C3, for example, as a result of aberrant activation of NRF2 pathway, and can have a better safety profile.

[0004] In some embodiments, provided herein is a compound of Formula (I):



(I),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein R^2, R^4, R^5, R^6, Ring A, L^1, L^2, X, Y, Z, R^a, R^b, n1, and n2 are as defined herein or elsewhere.

[0005] In some embodiments, provided herein are pharmaceutical compositions comprising a compound provided herein, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions are formulated for oral administration.

[0006] In some embodiments, provided herein are methods of treating cancer, comprising administering to a subject having the cancer a therapeutically effective amount of a compound provided herein, or a pharmaceutical composition provided herein. Also provided are uses of the compounds provided herein in the manufacture of a medicament for treating cancer, such as the cancers described herein. Also provided are uses of the compounds provided herein for treating cancer, such as the cancers described herein. Also provided are compounds provided herein for use in the treatment of cancer, such as the cancers described herein. Also provided are compounds provided herein for use in a method of treating cancer, such as the cancers described herein, wherein the method comprises administering to a subject in need thereof an effective amount of a compound provided herein. In some embodiments, the cancer is characterized as having an abnormal AKR1C3 activity and/or overexpression of AKR1C3. In some embodiments, the cancer is characterized as having an NRF2/KEAP1 pathway mutation which causes an aberrant NRF2 activation.

4. DETAILED DESCRIPTION

4.1 *Definitions*

[0007] It is meant to be understood that proper valences are maintained for all moieties and combinations thereof.

[0008] It is also meant to be understood that a specific embodiment of a variable moiety herein can be the same or different as another specific embodiment having the same identifier.

[0009] Headings and subheadings are used for convenience and/or formal compliance only, do not limit the subject technology, and are not referred to in connection with the interpretation of the description of the subject technology. Features described under one heading or one subheading may be combined, in some embodiments, with features described under other headings or subheadings. Further it is not necessarily the case that all features under a single heading or a single subheading are used together in embodiments.

[0010] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0011] As used herein, the singular form "a", "an", and "the", includes plural references unless it is expressly stated or is unambiguously clear from the context that such is not intended.

[0012] As used herein, the terms "comprising" and "including" can be used interchangeably. The terms "comprising" and "including" are to be interpreted as specifying the presence of the stated features or components as referred to, but does not preclude the presence or addition of one or more features, or components, or groups thereof. Additionally, the terms "comprising" and "including" are intended to include examples encompassed by the term "consisting of". Consequently, the term "consisting of" can be used in place of the terms "comprising" and "including" to provide for more specific embodiments.

[0013] As used herein, the term "or" is to be interpreted as an inclusive "or" meaning any one or any combination. Therefore, "A, B or C" means any of the following: "A; B; C; A and B; A and C; B and C; A, B and C". An exception to this definition will occur only when a combination of elements, functions, steps or acts are in some way inherently mutually exclusive.

[0014] The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0015] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-6}" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6}.

[0016] It should be noted that if there is a discrepancy between a depicted structure and a name for that structure, the depicted structure is to be accorded more weight.

[0017] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987. The disclosure is not intended to be limited in any manner by the exemplary listing of substituents provided herein.

[0018] As used herein, and unless otherwise specified, the term "alkyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic saturated hydrocarbon. In some embodiments, the alkyl can include one to twelve carbon atoms (*i.e.*, C_{1-12} alkyl) or the number of carbon atoms designated. In some embodiments, the alkyl group is a straight chain C_{1-10} alkyl group. In another embodiment, the alkyl group is a branched chain C_{3-10} alkyl group. In another embodiment, the alkyl group is a straight chain C_{1-6} alkyl group. In another embodiment, the alkyl group is a branched chain C_{3-6} alkyl group. In another embodiment, the alkyl group is a straight chain C_{1-4} alkyl group. For example, a C_{1-4} alkyl group includes methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and iso-butyl. As used herein, and unless otherwise specified, the term "alkylene" as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from an alkyl group. For example, non-limiting straight chain alkylene groups include -CH_2-CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-, and the like. Unless otherwise specified, an alkyl group is optionally substituted. In some embodiments, an alkyl group is unsubstituted. In some embodiments, an alkyl groups is substituted.

[0019] As used herein, and unless otherwise specified, the term "alkenyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon

containing one or more (*e.g.*, 1, 2, or 3) carbon-to-carbon double bonds. In some embodiments, the alkenyl group is a C_{2-6} alkenyl group. In another embodiment, the alkenyl group is a C_{2-4} alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, sec-butenyl, pentenyl, and hexenyl. Unless otherwise specified, an alkenyl group is optionally substituted. In some embodiments, an alkenyl group is unsubstituted. In some embodiments, an alkenyl groups is substituted.

[0020] As used herein, and unless otherwise specified, the term "alkynyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one or more (*e.g.*, 1, 2, or 3) carbon-to-carbon triple bonds. In some embodiments, the alkynyl has one carbon-carbon triple bond. In some embodiments, the alkynyl group is a C_{2-6} alkynyl group. In another embodiment, the alkynyl group is a C_{2-4} alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups. Unless otherwise specified, an alkynyl group is optionally substituted. In some embodiments, an alkynyl group is unsubstituted. In some embodiments, an alkynyl groups is substituted.

[0021] As used herein, and unless otherwise specified, the term "alkoxy" as used by itself or as part of another group refers to -O-(alkyl), wherein alkyl is as described herein. As used herein, and unless otherwise specified, the term "cycloalkoxy" as used by itself or as part of another group refers to -O-(cycloalkyl), wherein cycloalkyl as described herein.

[0022] As used herein, and unless otherwise specified, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more fluorine, chlorine, bromine and/or iodine atoms. In some embodiments, the haloalkyl is an alkyl group substituted with one, two, or three fluorine atoms. In some embodiments, the haloalkyl group is a C_{1-10} haloalkyl group. In some embodiments, the haloalkyl group is a C_{1-6} haloalkyl group. In some embodiments, the haloalkyl group is a C_{1-4} haloalkyl group.

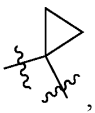
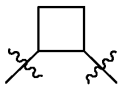
[0023] As used herein, and unless otherwise specified, the term "heteroalkyl" as used by itself or in combination with another term refers to a stable straight or branched-chain alkyl group, *e.g.*, having from 2 to 14 carbons, such as 2 to 10 carbons in the chain, wherein one or more of the carbon(s) has been replaced by a heteroatom selected from S, O, P and N, and wherein the N, P, and S atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) S, O, P and N may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. When the heteroalkyl is said to be substituted, the substituent(s) can replace one or more hydrogen atoms attached to the carbon atom(s) and/or the

heteroatom(s) of the heteroalkyl. In some embodiments, the heteroalkyl is a C_{1-4} heteroalkyl, which refers to the heteroalkyl defined herein having 1-4 carbon atoms. Examples of C_{1-4} heteroalkyl include, but are not limited to, C_4 heteroalkyl such as -CH_2-CH_2-N(CH_3)-CH_3, C_3 heteroalkyl such as -CH_2-CH_2-O-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-S-CH_2-CH_3, -CH_2-CH_2-S(O)-CH_3, and -CH_2-CH_2-S(O)$_2$-CH_3, C_2 heteroalkyl such as -CH_2-CH_2-OH, -CH_2-CH_2-NH_2, -CH_2-NH(CH_3), -and O-CH_2-CH_3, and C_1 heteroalkyl such as, -CH_2-OH, -CH_2-NH_2, and -O-CH_3. In some embodiments, the C_{1-4} heteroalkyl has 1 or 2 heteroatoms, such as those having one oxygen, one oxygen and one nitrogen, two oxygen atoms, or two nitrogen atoms. Similarly, the term "heteroalkylene" as used by itself or as part of another substituent means a multivalent (*e.g.*, divalent) radical derived from heteroalkyl, as exemplified, but not limited by, -CH_2-CH_2-O-CH_2-CH_2- and –O-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like. Unless otherwise specified, a heteroalkyl group is optionally substituted. In some embodiments, a heteroalkyl group is unsubstituted. In some embodiments, a heteroalkyl groups is substituted.

[0024] As used herein, and unless otherwise specified, the term "carbocyclyl" or "carbocyclic" as used by itself or as part of another group refers to a radical of a non–aromatic cyclic hydrocarbon group having at least 3 carbon atoms, *e.g.*, from 3 to 10 ring carbon atoms ("$C_{3–10}$ carbocyclyl"), and zero heteroatoms in the non–aromatic ring system. The carbocyclyl group can be either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. Non-limiting exemplary carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclopentenyl, and cyclohexenyl. As used herein, the term "carbocyclylene" as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from the carbocyclyl group defined herein. Unless otherwise

specified, a carbocyclyl group is optionally substituted. In some embodiments, a carbocyclyl group is unsubstituted. In some embodiments, a carbocyclyl groups is substituted.

[0025] In some embodiments, "carbocyclyl" is fully saturated, which is also referred to as "cycloalkyl". In some embodiments, the cycloalkyl can have from 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, the cycloalkyl is a monocyclic ring. As used herein, the term "cycloalkylene" as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from a cycloalkyl group, for example,

 , or  , etc.

[0026] As used herein, and unless otherwise specified, the term "heterocyclyl" or "heterocyclic" as used by itself or as part of another group refers to a radical of a 3-membered or larger, such as 3– to 14–membered, non–aromatic ring system having ring carbon atoms and at least one ring heteroatom (*e.g.*, 1, 2, 3, or 4) ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, wherein the N, P, and S atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged, or spiro ring system, such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings, and the point of attachment can be on any ring. As used herein, and unless otherwise specified, the term "heterocyclylene" as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from the heterocyclyl group defined herein. The heterocyclyl or heterocylylene can be optionally linked to the rest of the molecule through a carbon or nitrogen atom. Unless otherwise specified, a heterocyclyl group is optionally substituted. In some embodiments, a heterocyclyl group is unsubstituted. In some embodiments, a heterocyclyl groups is substituted.

[0027] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiiranyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl,

tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0028] As used herein, and unless otherwise specified, the term "aryl" as used by itself or as part of another group refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic hydrocarbon ring system (*e.g.*, having 6, 10, or 14 pi electrons shared in a cyclic array). In some embodiments, an aryl group has 6–14 ring carbon atoms ("$C_{6–14}$ aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). As used herein, and unless otherwise specified, the term "arylene" as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from the aryl group defined herein. Unless otherwise specified, an aryl group is optionally substituted. In some embodiments, an aryl group is unsubstituted. In some embodiments, an aryl groups is substituted.

[0029] As used herein, and unless otherwise specified, the term "aralkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more aryl groups, *e.g.*, substituted with one aryl group. Examples of aralkyl include benzyl, phenethyl, etc. Unless otherwise specified, an aralkyl group is optionally substituted. When an aralkyl is

said to be optionally substituted, either the alkyl portion or the aryl portion of the aralkyl can be optionally substituted.

[0030] As used herein, and unless otherwise specified, the term "heteroaryl" as used by itself or as part of another group refers to a radical of a monocyclic, bicyclic, or tricyclic 4n+2 aromatic ring system (*e.g.*, having 6 or 10 pi electrons shared in a cyclic array) having ring carbon atoms and at least one (*e.g.*, 1, 2, 3, or 4) ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur. In some embodiments, a heteroaryl group has 5–14 membered ring atoms ("5–14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. In bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, and the like), the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2–indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5–indolyl). As used herein, and unless otherwise specified, the term "heteroarylene" as used by itself or as part of another group refers to a multivalent (*e.g.*, divalent) radical derived from the heteroaryl group defined herein. Unless specified or otherwise contrary from context, when a heteroaryl group is fused to a non-aromatic ring, the resulted fused ring systems is referred to as a heterocyclyl group. Unless otherwise specified, a heteroaryl group is optionally substituted. In some embodiments, a heteroaryl group is unsubstituted. In some embodiments, a heteroaryl groups is substituted.

[0031] Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl,

isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0032] As used herein, and unless otherwise specified, the term "heteroaralkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more heteroaryl groups, *e.g.*, substituted with one heteroaryl group. Unless otherwise specified, a heteroaralkyl group is optionally substituted. When a heteroaralkyl is said to be optionally substituted, either the alkyl portion or the heteroaryl portion of the heteroaralkyl can be optionally substituted.

[0033] As used herein, and unless otherwise specified, the term "amino" refers to $–N(R^{\#})(R^{\#})$, wherein each $R^{\#}$ independently can be, but is not limited to, hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, each of which is defined herein. When a $-N(R^{\#})(R^{\#})$ group has two $R^{\#}$ other than hydrogen, they can be combined with the nitrogen atom to form a ring. In some embodiments, the ring is a 3-, 4-, 5-, 6-, 7-, or 8-membered ring. In some embodiments, one or more ring atoms are heteroatoms independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon. The term "amino" also includes N-oxide ($–N^{+}(R^{\#})(R^{\#})O^{-}$). In certain embodiments, each $R^{\#}$ or the ring formed by $-N(R^{\#})(R^{\#})$ independently may be unsubstituted or substituted with one or more substituents.

[0034] As used herein, and unless otherwise specified, an "optionally substituted" group, such as an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl groups, refers to the respective group that is unsubstituted or substituted. In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent can be the same or different at each position. In some embodiments, when substituted, the optionally substituted groups

provided herein can be substituted with 1-5 substituents. Substituents can be a carbon atom substituent, a nitrogen atom substituent, an oxygen atom substituent or a sulfur atom substituent, as applicable, each of which can be optionally isotopically labeled, such as deuterated. Two of the optional substituents can join to form a ring structure, such as an optionally substituted cycloalkyl, heterocylyl, aryl, or heteroaryl ring. Substitution can occur on any available carbon, oxygen, or nitrogen atom, and can form a spirocycle.

[0035] As used herein, and unless otherwise specified, the permissible substituents provided herein include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. The heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a cycloalkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, an aryl, or a heteroaryl, each of which can be substituted, if appropriate

[0036] Exemplary substituents include, but not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, -alkylene-aryl, -arylene-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, —OH, hydroxyalkyl, haloalkyl, —O-alkyl, —O-haloalkyl, -alkylene-O-alkyl, —O-aryl, —O-alkylene-aryl, acyl, —C(O)-aryl, halo, —NO_2, —CN, —SF_5, —C(O)OH, —C(O)O-alkyl, —C(O)O-aryl, —C(O)O—alkylene-aryl, —S(O)-alkyl, —$S(O)_2$-alkyl, —S(O)-aryl, —$S(O)_2$-aryl, —S(O)-heteroaryl, —$S(O)_2$-heteroaryl, —S-alkyl, —S-aryl, —S-heteroaryl, —S-alkylene-aryl, —S-alkylene-heteroaryl, —$S(O)_2$-alkylene-aryl, —$S(O)_2$-alkylene-heteroaryl, cycloalkyl, heterocycloalkyl, —O—C(O)-alkyl, —O—C(O)-aryl, —O—C(O)-cycloalkyl, —C(═N—CN)—NH_2, —C(═NH)—NH_2, —C(═NH)—NH(alkyl), —$N(Y_1)(Y_2)$, -alkylene-$N(Y_1)(Y_2)$, —$C(O)N(Y_1)(Y_2)$ and —$S(O)_2N(Y_1)(Y_2)$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and -alkylene-aryl.

[0037] Some examples of suitable substituents include, but not limited to, (C_1-C_8)alkyl groups, (C_2-C_8)alkenyl groups, (C_2-C_8)alkynyl groups, (C_3-C_{10})cycloalkyl groups,

halogen (F, Cl, Br or I), halogenated (C_1-C_8)alkyl groups (for example but not limited to —CF_3), —O—(C_1-C_8)alkyl groups, —OH, —S—(C_1-C_8)alkyl groups, —SH, —NH(C_1-C_8)alkyl groups, —N((C_1-C_8)alkyl)$_2$ groups, —NH_2, —C(O)NH_2, —C(O)NH(C_1-C_8)alkyl groups, —C(O)N((C_1-C_8)alkyl)$_2$, —NHC(O)H, —NHC(O) (C_1-C_8)alkyl groups, —NHC(O) (C_3-C_8)cycloalkyl groups, —N((C_1-C_8)alkyl)C(O)H, —N((C_1-C_8)alkyl)C(O)(C_1-C_8)alkyl groups, —NHC(O)NH_2, —NHC(O)NH(C_1-C_8)alkyl groups, —N((C_1-C_8)alkyl)C(O)NH_2 groups, —NHC(O)N((C_1-C_8)alkyl)$_2$ groups, —N((C_1-C_8)alkyl)C(O)N((C_1-C_8)alkyl)$_2$ groups, —N((C_1-C_8)alkyl)C(O)NH((C_1-C_8)alkyl), —C(O)H, —C(O)(C_1-C_8)alkyl groups, —CN, —NO_2, —S(O)(C_1-C_8)alkyl groups, —S(O)$_2$(C_1-C_8)alkyl groups, —S(O)$_2$N((C_1-C_8)alkyl)$_2$ groups, —S(O)$_2$NH(C_1-C_8)alkyl groups, —S(O)$_2$NH(C_3-C_8)cycloalkyl groups, —S(O)$_2$$NH_2$ groups, —NHS(O)$_2$(C_1-C_8)alkyl groups, —N((C_1-C_8)alkyl)S(O)$_2$(C_1-C_8)alkyl groups, —(C_1-C_8)alkyl-O—(C_1-C_8)alkyl groups, —O—(C_1-C_8)alkyl-O—(C_1-C_8)alkyl groups, —C(O)OH, —C(O)O(C_1-C_8)alkyl groups, NHOH, NHO(C_1-C_8)alkyl groups, —O-halogenated (C_1-C_8)alkyl groups (for example but not limited to —OCF_3), —S(O)$_2$-halogenated (C_1-C_8)alkyl groups (for example but not limited to —S(O)$_2$$CF_3$), —S-halogenated ($C_1$-$C_8$)alkyl groups (for example but not limited to —SCF_3), —(C_1-C_6) heterocycle (for example but not limited to pyrrolidine, tetrahydrofuran, pyran or morpholine), —(C_1-C_6) heteroaryl (for example but not limited to tetrazole, imidazole, furan, pyrazine or pyrazole), -phenyl, —NHC(O)O—(C_1-C_6)alkyl groups, —N((C_1-C_6)alkyl)C(O)O—(C_1-C_6)alkyl groups, —C(═NH)—(C_1-C_6)alkyl groups, —C(═NOH)—(C_1-C_6)alkyl groups, or —C(═N—O—(C_1-C_6)alkyl)-(C_1-C_6)alkyl groups.

[0038] Exemplary carbon atom substituents include, but are not limited to, deuterium, halogen, –CN, –NO_2, –N_3, hydroxyl, alkoxy, cycloalkoxy, aryloxy, amino, monoalkyl amino, dialkyl amino, amide, sulfonamide, thiol, acyl, carboxylic acid, ester, sulfone, sulfoxide, alkyl, haloalkyl, alkenyl, alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl, etc. For example, exemplary carbon atom substituents can include F, Cl, -CN, –SO_2H, –SO_3H, –OH, –$OC_{1–6}$ alkyl, –NH_2, –N($C_{1–6}$ alkyl)$_2$, –NH($C_{1–6}$ alkyl), –SH, –$SC_{1–6}$ alkyl, –C(=O)($C_{1–6}$ alkyl), –CO_2H, –CO_2($C_{1–6}$ alkyl), –OC(=O)($C_{1–6}$ alkyl), –OCO_2($C_{1–6}$ alkyl), –C(=O)NH_2, –C(=O)N($C_{1–6}$ alkyl)$_2$, –OC(=O)NH($C_{1–6}$ alkyl), –NHC(=O)($C_{1–6}$ alkyl), –N($C_{1–6}$ alkyl)C(=O)($C_{1–6}$ alkyl), –NHCO_2($C_{1–6}$ alkyl), –NHC(=O)N($C_{1–6}$ alkyl)$_2$, –NHC(=O)NH($C_{1–6}$ alkyl), –NHC(=O)NH_2, –NHSO_2($C_{1–6}$ alkyl), –SO_2N($C_{1–6}$ alkyl)$_2$, –SO_2NH($C_{1–6}$ alkyl), –SO_2NH_2,–S$O_2C_{1–6}$ alkyl, –S$O_2OC_{1–6}$ alkyl, –OS$O_2C_{1–6}$ alkyl, –S$OC_{1–6}$ alkyl, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$

carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal substituents can be joined to form =O.

[0039] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, acyl groups, esters, sulfone, sulfoxide, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two substituent groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl can be further substituted as defined herein. In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups are well known in the art and include those described in detail in *Protective Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated by reference herein. Exemplary nitrogen protecting groups include, but not limited to, those forming carbamates, such as Carbobenzyloxy (Cbz) group, p-Methoxybenzyl carbonyl (Moz or MeOZ) group, tert-Butyloxycarbonyl (BOC) group, Troc, 9-Fluorenylmethyloxycarbonyl (Fmoc) group, etc., those forming an amide, such as acetyl, benzoyl, etc., those forming a benzylic amine, such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, etc., those forming a sulfonamide, such as tosyl, Nosyl, etc., and others such as p-methoxyphenyl.

[0040] Exemplary oxygen atom substituents include, but are not limited to, acyl groups, esters, sulfonates, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl can be further substituted as defined herein. In certain embodiments, the oxygen atom substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups are well known in the art and include those described in detail in *Protective Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. Exemplary oxygen protecting groups include, but are not limited to, those forming alkyl ethers or substituted alkyl ethers, such as methyl, allyl, benzyl, substituted benzyls such as 4-methoxybenzyl, methoxylmethyl (MOM), benzyloxymethyl (BOM), 2–methoxyethoxymethyl (MEM), etc., those forming silyl ethers, such as trymethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), t-butyldimethylsilyl (TBDMS), etc., those

forming acetals or ketals, such as tetrahydropyranyl (THP), those forming esters such as formate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, etc., those forming carbonates or sulfonates such as methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts), etc.

[0041] Unless expressly stated to the contrary, combinations of substituents and/or variables are allowable only if such combinations are chemically allowed and result in a stable compound. A "stable" compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic administration to a subject).

[0042] In some embodiments, the "optionally substituted" alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkynyl, carbocyclic, carbocyclylene, cycloalkyl, cycloalkylene, alkoxy, cycloalkoxy, heterocyclyl, or heterocyclylene herein can each be independently unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from deuterium, F, Cl, -OH, oxo (as applicable), NH_2, NH(C_{1-4} alkyl), N(C_{1-4} alkyl((C_{1-4} alkyl), C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, phenyl, 5 or 6 membered heteroaryl containing 1, 2, or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein each of the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkoxy phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1, 2, or 3 substituents independently selected from deuterium, F, -OH, oxo (as applicable), C_{1-4} alkyl, fluoro-substituted C_{1-4} alkyl (*e.g.*, CF_3), C_{1-4} alkoxy and fluoro-substituted C_{1-4} alkoxy. In some embodiments, the "optionally substituted" aryl, arylene, heteroaryl or heteroarylene group herein can each be independently unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from deuterium, F, Cl, -OH, -CN, NH_2, NH(C_{1-4} alkyl), N(C_{1-4} alkyl((C_{1-4} alkyl), –S(=O)(C_{1-4} alkyl), –SO_2(C_{1-4} alkyl), C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, phenyl, 5 or 6 membered heteroaryl containing 1, 2 or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein each of the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkoxy, phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1, 2, or 3 substituents independently selected from deuterium, F, -OH, oxo (as applicable), C_{1-4} alkyl, fluoro-substituted C_{1-4} alkyl, C_{1-4} alkoxy and fluoro-substituted C_{1-4} alkoxy.

[0043] As used herein, and unless otherwise specified, the term "halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0044] As used herein, and unless otherwise specified, the term "isomer" refers to different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Atropisomers" are stereoisomers from hindered rotation about single bonds. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A mixture of a pair of enantiomers in any proportion can be known as a "racemic" mixture. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry can be specified according to the Cahn-Ingold-Prelog *R*-*S* system. When a compound is an enantiomer, the stereochemistry at each chiral carbon can be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. However, the sign of optical rotation, (+) and (-), is not related to the absolute configuration of the molecule, *R* and *S*. Certain compounds provided herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry at each asymmetric atom, as (*R*)- or (*S*)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically substantially pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers can be prepared, for example, using chiral synthons or chiral reagents, or resolved using conventional techniques.

[0045] As used herein, and unless otherwise specified, the term "enantiomeric purity" or "enantiomer purity" refers to a qualitative or quantitative measure of a purified enantiomer. The enantiomeric purity of compounds provided herein may be described in terms of enantiomeric excess (ee), which indicates the degree to which a sample contains one enantiomer in greater amounts than the other. A racemic mixture has an ee of 0%, while a single completely pure enantiomer has an ee of 100%. Examples of the enantiomeric purity include an ee of at least about 10%, at least about 12%, at least about 14%, at least about 16%, at least about 18%, at least about 20%, at least about 22%, at least about 24%, at least about 26%, at least about 28%, at least about 30%, at least about 32%, at least about 34%, at least about 36%, at least about 38%, at least about 40%, at least about 42%, at least about 44%, at least about 46%, at least about 48%, at least about 50%, at least about 52%, at least

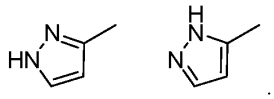
about 54%, at least about 56%, at least about 58%, at least about 60%, at least about 62%, at least about 64%, at least about 66%, at least about 68%, at least about 70%, at least about 72%, at least about 74%, at least about 76%, at least about 78%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about or at least about 99%. Similarly, "diastereomeric purity" may be described in terms of diasteriomeric excess (de), which indicates the degree to which a sample contains one diastereoisomers in greater amounts than the other(s).

[0046] As used herein, and unless otherwise specified, the term "substantially purified enantiomer" refers to a compound wherein one enantiomer has been enriched over the other, such as the other enantiomer represents less than about 20%, less than about 10%, less than about 5%, or less than about 2% of the enantiomer. In some embodiments, a substantially purified enantiomer has an enantiomeric excess of *S* enantiomer of at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about 99.9%. In some embodiments, a substantially purified enantiomer has an enantiomeric excess of *R* enantiomer of at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5% or at least about 99.9%.

[0047] "Stereoisomers" can also include E and Z isomers, or a mixture thereof, and cis and trans isomers or a mixture thereof. In certain embodiments, a compound provided herein is isolated as either the E or Z isomer. In other embodiments, a compound provided herein is a mixture of the E and Z isomers.

[0048] "Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous

solution, pyrazoles may exhibit the following isomeric forms, which are referred to as tautomers of each other:



[0049] As used herein, and unless otherwise specified, 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. As used herein, and unless otherwise specified, the term "pharmaceutically acceptable salt" includes both acid and base addition salts.

[0050] Compounds provided herein can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I. In some embodiments, compounds contain other isotopes of these and/or other atoms.

[0051] As used herein, and unless otherwise specified, the term "administration" of a compound, "administering" a compound, or other variants thereof means providing the compound to a subject in need of treatment.

[0052] As used herein, and unless otherwise specified, the term "subject" (alternatively referred to herein as "patient") refers to an animal, *e.g.*, a mammal, *e.g.*, a human, who has been the object of treatment, observation or experiment.

[0053] As used herein, and unless otherwise specified, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a compound provided herein to a subject in need of such treatment.

[0054] As used herein, and unless otherwise specified, the terms "prevent," "preventing," "prevention," and the like refer to reducing the probability of the onset of a

disease or condition, of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, developing or redeveloping a disease or condition or a recurrence of the disease or condition.

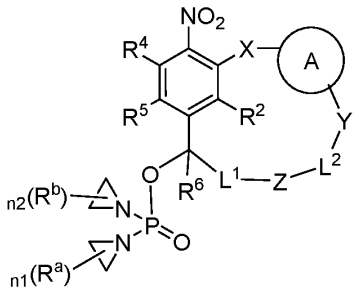
[0055] As used herein, and unless otherwise specified, the term "effective amount" refers to that amount of a compound or combination of compounds provided herein that is sufficient to effect the intended application including, but not limited to, prophylaxis or treatment of diseases. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, etc. which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells and/or tissues. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[0056] As used herein, and unless otherwise specified, the term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

4.2 *Compounds*

[0057] In some embodiments, provided herein are certain phosphoramidate macrocycle compounds. In some embodiments, the macrocycle backbone contains at least two ring structures (*e.g.*, two aromatic rings). In some embodiments, without being bound by a particular theory, the compounds provided herein are substrates of AKR1C3, which can be activated by AKR1C3, for example, to release a phosphoramidate.

[0058] In some embodiments, provided herein is a compound of Formula (I):



(I),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein:

R^2 is hydrogen, deuterium, halogen (*e.g.*, F), optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, or optionally substituted C_{1-4} alkoxy;

R^4 and R^5 are each independently hydrogen, deuterium, halogen (*e.g.*, F), optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{1-4} alkoxy, or optionally substituted 3- to 6-membered ring;

R^6 is hydrogen, deuterium, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, or optionally substituted C_{2-4} alkynyl;

X is -O-, -S-, -NR^{10}-, optionally substituted C_{1-4} alkylene, or optionally substituted C_{1-4} heteroalkylene;

Ring A is optionally substituted 3- to 10-membered ring;

L^1 is an optionally substituted C_{1-4} alkylene;

L^2 is an optionally substituted C_{1-4} alkylene;

Y is -O-, -S-, -S(O)-, -$S(O)_2$-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -$S(O)_2$-NR^{10}-, -C(O)-O-, or optionally substituted 3- to 10-membered ring;

Z is optionally substituted C_2 alkylene, optionally substituted C_2 alkenylene, C_2 alkynylene, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -$S(O)_2$-NR^{10}-, or optionally substituted 3- to 10-membered ring;

R^{10} at each occurrence is independently hydrogen, an optionally substituted C_{1-4} alkyl, or an optionally substituted 3-6 membered ring;

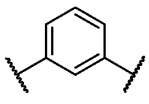
n1 is 0, 1, 2, 3, or 4;

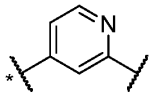
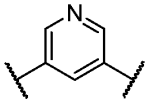
n2 is 0, 1, 2, 3, or 4;

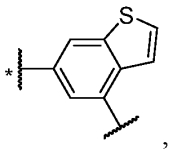
each of R^a and R^b at each occurrence is independently optionally substituted C_{1-4} alkyl or optionally substituted C_{1-4} heteroalkylene; or two instances of R^a or two instances of R^b,

together with the intervening atom(s), are joined together to form an optionally substituted 3- to 6-membered ring.

[0059] In some embodiments, Ring A is optionally substituted phenylene, optionally substituted 5- or 6-membered heteroarylene, optionally substituted 8- to 10-membered bicyclic heteroarylene, or optionally substituted 8- to 10-membered bicyclic heterocyclylene.

[0060] In some embodiments, Ring A is optionally substituted phenylene. In some embodiments, Ring A is  , which is optionally substituted.

[0061] In some embodiments, Ring A is optionally substituted 5-membered heteroarylene (*e.g.*, pyrrolylene, imidazolylene, pyrazolylene, oxazolylene, isoxazolylene, or triazolylene). In some embodiments, Ring A is optionally substituted 6-membered heteroarylene (*e.g.*, pyridinylene, pyridazinylene, pyrimidinylene, or pyrazinylene). In some embodiments, Ring A is optionally substituted pyridinylene. In some embodiments, Ring A is  , which is optionally substituted, wherein * refers to the direction of X. In some embodiments, Ring A is  , which is optionally substituted.

[0062] In some embodiments, Ring A is optionally substituted 8- to 10-membered bicyclic heteroarylene (*e.g.*, indolylene, isoindolylene, indazolylene, benzothiophenylene, benzimidazolylene, quinolinylene, or isoquinolinylene). In some embodiments, Ring A is optionally substituted phenylene fused to optionally substituted 5-membered heteroaryl. In some embodiments, Ring A is optionally substituted phenylene fused to optionally substituted 6-membered heteroaryl. In some embodiments, Ring A is optionally substituted benzothiophenylene. In some embodiments, Ring A is  , which is optionally substituted, wherein * refers to the direction of X.

[0063] In some embodiments, Ring A is optionally substituted 8- to 10-membered bicyclic heterocyclylene (*e.g.*, indolinylene, isoindolinylene, tetrahydroquinolinylene, or tetrahydroisoquinolinylene). In some embodiments, Ring A is optionally substituted phenylene fused to optionally substituted 5-membered heterocyclyl. In some embodiments,

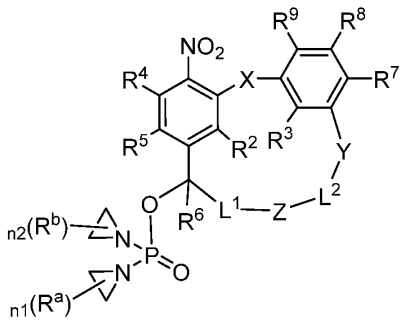
Ring A is optionally substituted phenylene fused to optionally substituted 6-membered heterocyclyl.

[0064] In some embodiments, Ring A is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each independently selected from deuterium, halogen (*e.g.*, F), CN, OH, NH_2, COOH, $CONH_2$, G^1, OG^1, SG^1, NHG^1, NG^1G^1, $C(O)G^1$, $COOG^1$, $CONHG^1$, $CONG^1G^1$, $OC(O)G^1$, $OCOOG^1$, $OCONHG^1$, $OCONG^1G^1$, $NHC(O)G^1$, $NHCOOG^1$, $NHCONHG^1$, $NHCONG^1G^1$, $NG^1C(O)G^1$, NG^1COOG^1, NG^1CONHG^1, $NG^1CONG^1G^1$, SO_2G^1, SO_2NHG^1, or $SO_2NG^1G^1$, wherein G^1 at each occurrence is independently optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, or optionally substituted 3- to 6-membered ring structure (*e.g.*, cyclopropyl, cyclobutyl, phenyl, pyrimidyl, or pyridyl), or two G^1 of an NG^1G^1 together with the nitrogen atom form an optionally substituted 4- to 8-membered heterocyclic ring.

[0065] In some embodiments, Ring A is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each independently selected from deuterium, F, Cl, CN, OH, NH_2, COOH, $CONH_2$, G^2, OG^2, NHG^2, NG^2G^2, $C(O)G^2$, $COOG^2$, $CONHG^2$, $CONG^2G^2$, SO_2G^2, SO_2NHG^2, or $SO_2NG^2G^2$, wherein G^2 at each occurrence is independently a C_{1-4} alkyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclic ring having 1-2 ring heteroatoms, phenyl, or 5- or 6-membered heteroaryl, each of which is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from deuterium, F, Cl, OH, NH_2, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} heteroalkyl having 1 or 2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or two G^2 of an NG^2G^2 together with the nitrogen atom form an optionally substituted 4- to 8-membered heterocyclic ring having 0 or 1 additional ring heteroatom.

[0066] In some embodiments, Ring A is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each independently is selected from R^3, R^7, R^8, or R^9, as described herein.

[0067] In some embodiments, the compound is a compound of Formula (II-A):



(II-A),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein:

R^3 is hydrogen, deuterium, halogen (*e.g.*, F), optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, or optionally substituted C_{1-4} alkoxy;

R^7, R^8, and R^9 are each independently hydrogen, deuterium, halogen (*e.g.*, F), CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from (i) deuterium, (ii) halogen (*e.g.*, F), (iii) CN, (iv) OH, (v) oxo, (vi) C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (vii) C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (viii) 3- to 6-membered ring optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH; or

two adjacent R^7, R^8, and R^9, together with the carbon atoms they are attached to, form a 4- to 8-membered ring, which is optionally substituted with one or more (*e.g.*, 1, 2, or 3) R^n; and

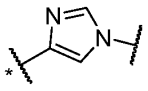
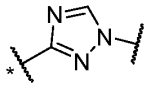
R^n at each occurrence is independently deuterium, halogen (*e.g.*, F), CN, OH, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3- to 6-membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from deuterium, F, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

[0068] In some embodiments, X is -O-. In some embodiments, X is -S-. In some embodiments, X is $-NR^{10}-$. In some embodiments, the R^{10} in X is hydrogen (*i.e.*, X is -NH-). In some embodiments, the R^{10} in X is optionally substituted C_{1-4} alkyl. In some embodiments, the R^{10} in X is methyl (*i.e.*, X is $-N(CH_3)-$). . In some embodiments, X is optionally substituted C_{1-4} alkylene (*e.g.*, $-CH_2-$). In some embodiments, X is optionally substituted C_{1-4} heteroalkylene.

[0069] In some embodiments, Y is -O-. In some embodiments, Y is -S-. In some embodiments, Y is $-NR^{10}-$. In some embodiments, Y is -NH-. In some embodiments, Y is $-N(CH_3)-$.

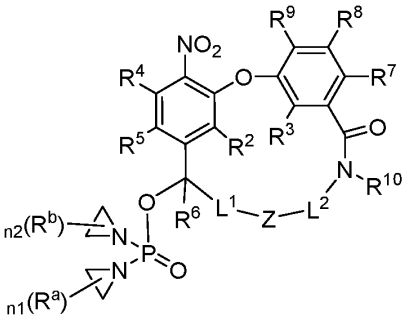
[0070] In some embodiments, Y is $-C(O)-NR^{10}-$. In some embodiments, Y is $*-C(O)-NR^{10}-$, wherein * refers to the direction toward Ring A. In some embodiments, Y is -C(O)-

NR^{10}-*, wherein * refers to the direction toward Ring A. In some embodiments, Y is -$S(O)_2$-NR^{10}-. In some embodiments, Y is *-$S(O)_2$-NR^{10}-, wherein * refers to the direction toward Ring A. In some embodiments, Y is -$S(O)_2$-NR^{10}-*, wherein * refers to the direction toward Ring A. In some embodiments, the R^{10} in Y is hydrogen. In some embodiments, the R^{10} in Y is optionally substituted C_{1-4} alkyl. In some embodiments, the R^{10} in Y is methyl.

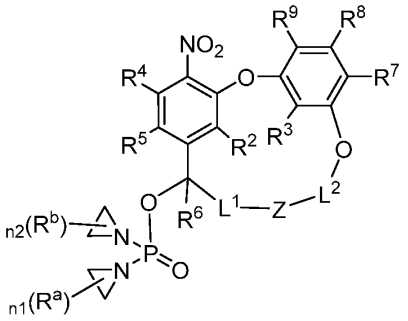
[0071] In some embodiments, Y is optionally substituted 3- to 10-membered ring (Ring B). In some embodiments, Ring B is optionally substituted 5-membered heteroarylene (*e.g.*, pyrrolylene, imidazolylene, pyrazolylene, oxazolylene, isoxazolylene, or triazolylene). In some embodiments, Ring B is optionally substituted imidazolylene. In some embodiments, Ring B is  , which is optionally substituted, wherein * refers to the direction of Ring A. In some embodiments, Ring B is optionally substituted triazolylene. In some embodiments, Ring B is  , which is optionally substituted, wherein * refers to the direction of Ring A. In some embodiments, Ring B is optionally substituted 6-membered heteroarylene (*e.g.*, pyridinylene, pyridazinylene, pyrimidinylene, or pyrazinylene). In some embodiments, Ring B is optionally substituted 3- to 8-membered heterocyclylene (*e.g.*, azetidinylene, piperidinylene, piperazinylene, or morpholinylene).

[0072] In some embodiments, Ring B is unsubstituted. In some embodiments, Ring B is substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

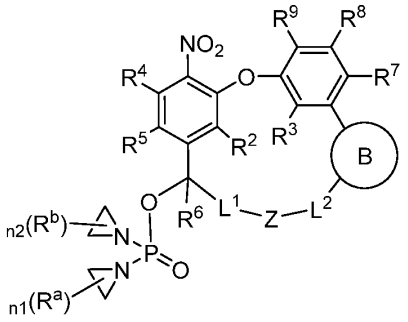
[0073] In some embodiments, the compound is a compound of Formula (III-A), (III-B), or (III-C):



(III-A),



(III-B), or



(III-C),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein Ring B is optionally substituted 3- to 10-membered ring.

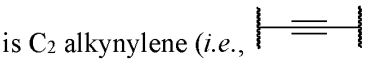
[0074] In some embodiments, L^1 is C_{1-4} alkylene optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, L^1 is C_{1-2} alkylene optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, L^1 is unsubstituted. In some embodiments, L^1 is $-CH_2-$. In some embodiments, L^1 is $-CH_2-CH_2-$.

[0075] In some embodiments, L^2 is C_{1-4} alkylene optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, L^2 is C_{1-2} alkylene optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, L^2 is unsubstituted. In some embodiments, L^2 is $-CH_2-$. In some embodiments, L^2 is $-CH_2-CH_2-$.

[0076] In some embodiments, Z is optionally substituted C_2 alkylene. In some embodiments, Z is C_2 alkylene optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, Z is unsubstituted. In some embodiments, Z is $-CH_2-CH_2-$.

[0077] In some embodiments, Z is optionally substituted C_2 alkenylene. In some embodiments, Z is C_2 alkenylene optionally substituted with one or more (*e.g.*, 1 or 2) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, Z is unsubstituted. In some embodiments, the optionally substituted C_2 alkenylene has a (Z)-configuration. In some embodiments, L^1 and

L^2 are on the same side of the double bond of the C_2 alkenylene (*i.e.*, cis-configuration with regard to L^1 and L^2). In some embodiments, Z is -CH=CH-. In some embodiments, Z is (Z)-CH=CH-.

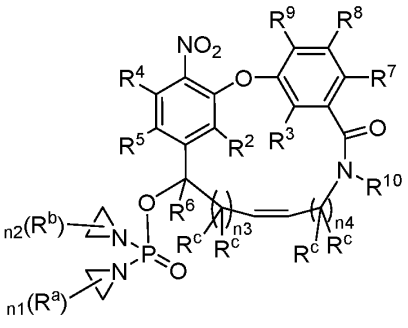
[0078] In some embodiments, Z is C_2 alkynylene (*i.e.*, ).

[0079] In some embodiments, Z is -O-. In some embodiments, Z is -S-. In some embodiments, Z is $-NR^{10}-$. In some embodiments, Z is -NH-. In some embodiments, Z is $-N(CH_3)-$.

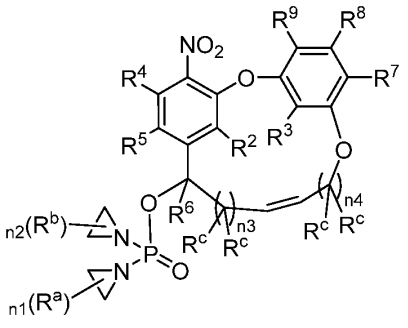
[0080] In some embodiments, Z is $-C(O)-NR^{10}-$. In some embodiments, Z is $*-C(O)-NR^{10}-$, wherein * refers to the direction toward L^1. In some embodiments, Z is $-C(O)-NR^{10}-*$, wherein * refers to the direction toward L^1. In some embodiments, Z is $-S(O)_2-NR^{10}-$. In some embodiments, Z is $*-S(O)_2-NR^{10}-$, wherein * refers to the direction toward L^1. In some embodiments, Z is $-S(O)_2-NR^{10}-*$, wherein * refers to the direction toward L^1. In some embodiments, the R^{10} in Z is hydrogen. In some embodiments, the R^{10} in Z is optionally substituted C_{1-4} alkyl. In some embodiments, the R^{10} in Z is methyl.

[0081] In some embodiments, Z is optionally substituted 3- to 10-membered ring. In some embodiments, Z is optionally substituted 5-membered heteroarylene (*e.g.*, pyrrolylene, imidazolylene, pyrazolylene, oxazolylene, isoxazolylene, or triazolylene). In some embodiments, Z is optionally substituted 6-membered heteroarylene (*e.g.*, pyridinylene, pyridazinylene, pyrimidinylene, or pyrazinylene). In some embodiments, Z is optionally substituted 3- to 8-membered heterocyclylene (*e.g.*, azetidinylene, piperidinylene, piperazinylene, or morpholinylene).

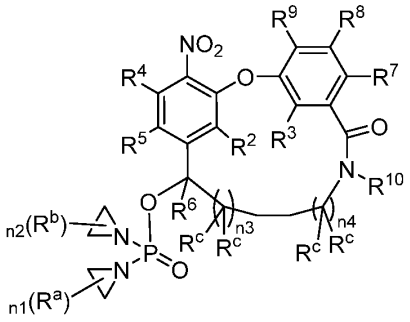
[0082] In some embodiments, the compound is a compound of Formula (IV-A), (IV-B), (IV-C), (IV-D), (IV-E), or (IV-F):



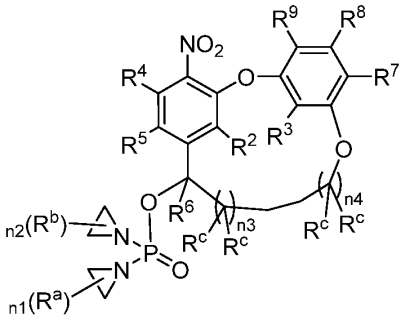
(IV-A),



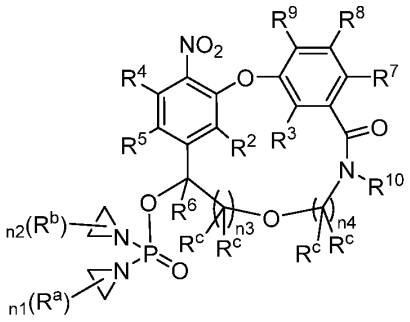
(IV-B),



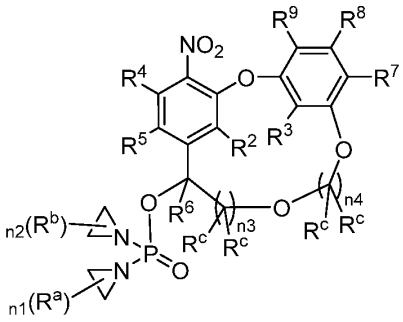
(IV-C),



(IV-D),



(IV-E), or



(IV-F),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein:

R^c at each occurrence is independently hydrogen, deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F;

n3 is 1, 2, 3, or 4; and

n4 is 1, 2, 3, or 4.

[0083] In some embodiments, n3 is 1. In some embodiments, n3 is 2. In some embodiments, n3 is 3. In some embodiments, n3 is 4.

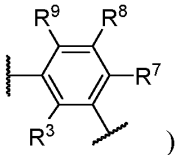
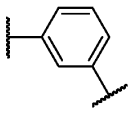
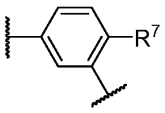
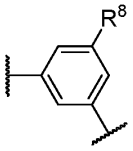
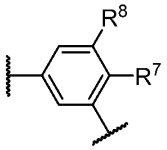
[0084] In some embodiments, n4 is 1. In some embodiments, n4 is 2. In some embodiments, n4 is 3. In some embodiments, n4 is 4.

[0085] In some embodiments, n3 is 1, and n4 is 1. In some embodiments, n3 is 1, and n4 is 2. In some embodiments, n3 is 2, and n4 is 1. In some embodiments, n3 is 2, and n4 is 2.

[0086] In some embodiments, R^c at each occurrence is hydrogen.

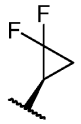
[0087] In some embodiments, R^3 is hydrogen, deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, R^3 is hydrogen.

[0088] In some embodiments, R^9 is hydrogen, deuterium, halogen (*e.g.*, F), CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from (i) deuterium, (ii) halogen (*e.g.*, F), (iii) CN, (iv) OH, (v) oxo, (vi) C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (vii) C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (viii) 3- to 6-membered ring optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH. In some embodiments, R^9 is hydrogen.

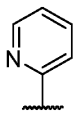
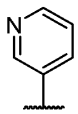
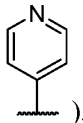
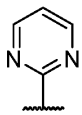
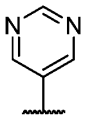
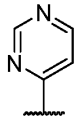
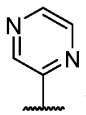
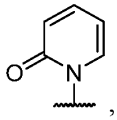
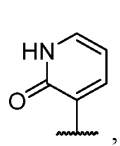
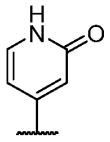
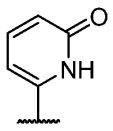
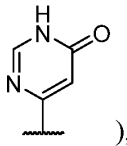
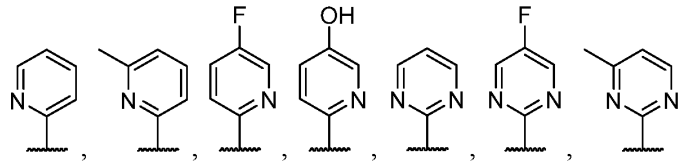
[0089] In some embodiments, the phenyl ring bearing R^3, R^7, R^8, and R^9 (*i.e.*, ) is  . In some embodiments, the phenyl ring is  . In some embodiments, the phenyl ring is  . In some embodiments, the phenyl ring is  . In some embodiments, the displayed R^7 and R^8 are not hydrogen.

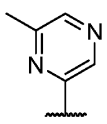
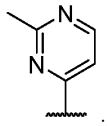
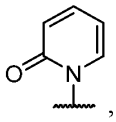
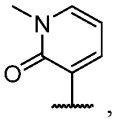
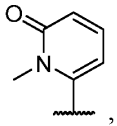
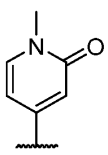
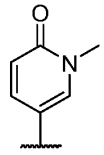
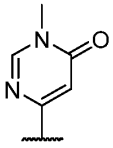
[0090] In some embodiments, R^7 is hydrogen, deuterium, halogen (*e.g.*, F), CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from (i) deuterium, (ii) halogen (*e.g.*, F), (iii) CN, (iv) OH, (v) oxo, (vi) C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (vii) C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (viii) 3- to 6-membered ring optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH.

[0091] In some embodiments, R^7 is hydrogen, deuterium, halogen (*e.g.*, F), C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is methyl. In some embodiments, R^7 is CF_3. In some embodiments, R^7 is F. In some embodiments, R^7 is methoxy.

[0092] In some embodiments, R^7 is C_{3-6} cycloalkyl, which is optionally substituted as described herein. In some embodiments, R^7 is C_{3-6} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium or F. In some embodiments, R^7 is cyclopropyl. In some embodiments, R^7 is  . In some embodiments, R^7 is  .

[0093] In some embodiments, R^7 is 6-membered heteroaryl, which is optionally substituted as described herein.

[0094] In some embodiments, R^7 is 6-membered heteroaryl having 1 or 2 ring nitrogen atoms, *e.g.*, pyridyl (*e.g.*, 2-pyridyl, 3-pyridyl, or 4-pyridyl) or pyrimidinyl. In some embodiments, the 6-membered heteroaryl is optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F or OH, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) F, or C_{3-4} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F. In some embodiments, R^7 is pyridyl (*e.g.*,  ,  , or ), pyrimidinyl (*e.g.*,  ,  , or ), or pyrazinyl (*e.g.*, ), each of which is optionally substituted with 1-2 R^j. In some embodiments, R^7 is a pyridone (*e.g.*,  ,  ,  , or ) or pyrimidinone (*e.g.*, ), each of which is optionally substituted with 1-2 R^j. In some embodiments, R^j is F, CH_3, CF_3, or propyl. In some embodiments, R^7 is  .


, or 
. In some embodiments, R^7 is 
, 
, 
, 
, 
, or 
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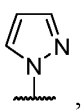
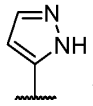
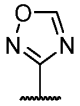
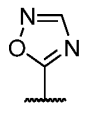
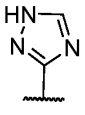
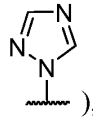
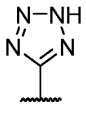
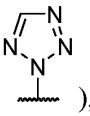
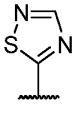
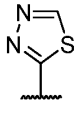
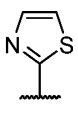
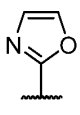
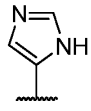
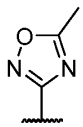
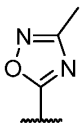
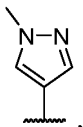
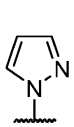
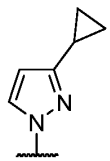
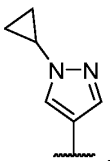
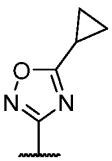
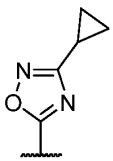
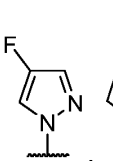
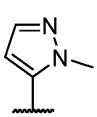
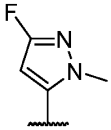
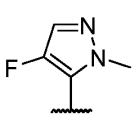
[0095] In some embodiments, R^7 is 5-membered heteroaryl, which is optionally substituted as described herein.

[0096] In some embodiments, R^7 is 5-membered heteroaryl having 1-3 ring heteroatoms, *e.g.*, pyrazole or oxadiazole. In some embodiments, the 5-membered heteroaryl is optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F or OH, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) F, or C_{3-4} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F. In some embodiments, R^7 is pyrazole (*e.g.*, 
, 
, or 
), oxadiazole (*e.g.*, 
or 
), triazole (*e.g.*, 
or 
), tetrazole (*e.g.*, 
or 
), thiadiazole (*e.g.*, 
or 
), thiazole (*e.g.*, 
), oxazole (*e.g.*, 
), or imidazole (*e.g.*, 
), each of which is optionally substituted with 1-2 R^j. In some embodiments, R^j is F, CH_3, CF_3, or cyclopropyl. In some embodiments, R^7 is 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, or 
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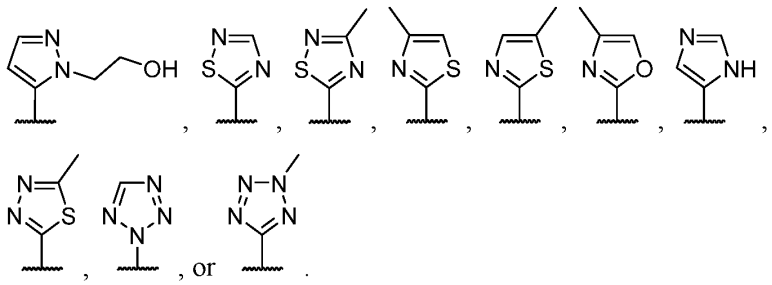
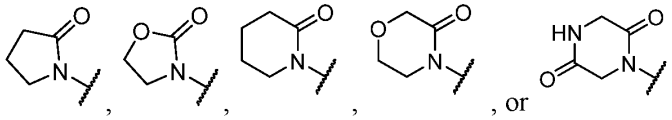
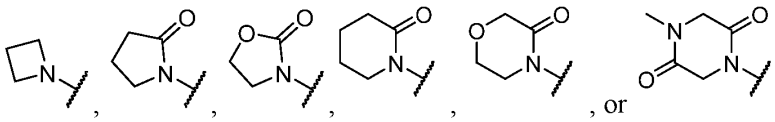
some embodiments, R^7 is 

[0097] In some embodiments, R^7 is 3- to 6-membered heterocyclyl, which is optionally substituted as described herein.

[0098] In some embodiments, R^7 is a 3- to 6-membered heterocyclyl having 1 or 2 ring heteroatoms. In some embodiments, the heterocyclyl is optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F or OH, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) F, or C_{3-4} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F. In some embodiments, R^7 is  ,  , each of which is optionally substituted with 1-2 R^j. In some embodiments, R^j is F, CH_3, CF_3, or cyclopropyl. In some embodiments, R^7 is  .

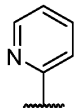
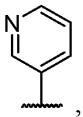
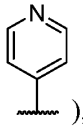
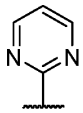
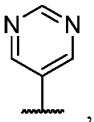
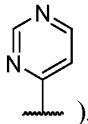
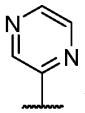
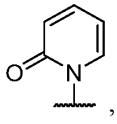
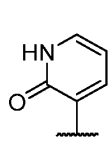
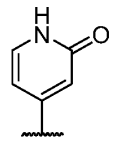
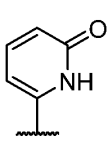
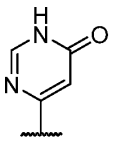
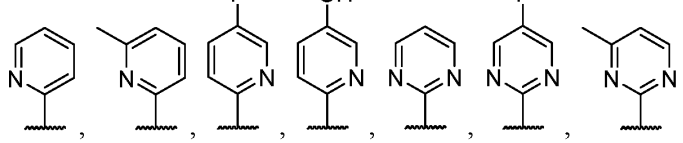
[0099] In some embodiments, R^8 is hydrogen, deuterium, halogen (*e.g.*, F), CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from (i) deuterium, (ii) halogen (*e.g.*, F), (iii) CN, (iv) OH, (v) oxo, (vi) C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (vii) C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (viii) 3- to 6-membered ring optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH.

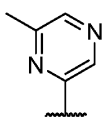
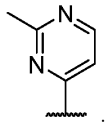
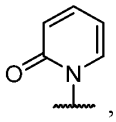
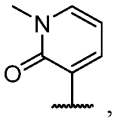
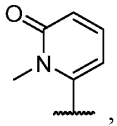
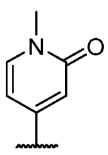
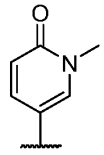
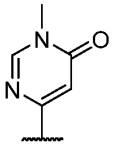
[0100] In some embodiments, R^8 is hydrogen, deuterium, halogen (*e.g.*, F), C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some

embodiments, R^8 is hydrogen. In some embodiments, R^8 is methyl. In some embodiments, R^8 is CF_3. In some embodiments, R^8 is F. In some embodiments, R^8 is methoxy.

[0101] In some embodiments, R^8 is C_{3-6} cycloalkyl, which is optionally substituted as described herein. In some embodiments, R^8 is C_{3-6} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium or F. In some embodiments, R^8 is cyclopropyl. In some embodiments, R^8 is  . In some embodiments, R^8 is  .

[0102] In some embodiments, R^8 is 6-membered heteroaryl, which is optionally substituted as described herein.

[0103] In some embodiments, R^8 is 6-membered heteroaryl having 1 or 2 ring nitrogen atoms, *e.g.*, pyridyl (*e.g.*, 2-pyridyl, 3-pyridyl, or 4-pyridyl) or pyrimidinyl. In some embodiments, the 6-membered heteroaryl is optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F or OH, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) F, or C_{3-4} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F. In some embodiments, R^8 is pyridyl (*e.g.*,  ,  , or ), pyrimidinyl (*e.g.*,  ,  , or ), or pyrazinyl (*e.g.*, ), each of which is optionally substituted with 1-2 R^j. In some embodiments, R^8 is a pyridone (*e.g.*,  ,  ,  , or ) or pyrimidinone (*e.g.*, ), each of which is optionally substituted with 1-2 R^j. In some embodiments, R^j is F, CH_3, CF_3, or propyl. In some embodiments, R^8 is  .


, or 
. In some embodiments, R^8 is 
, 
, 
, 
, 
, or 
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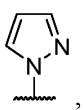
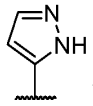
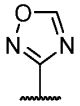
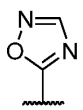
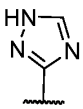
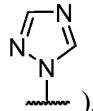
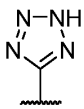
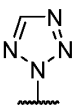
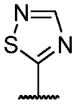
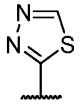
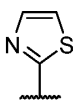
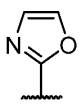
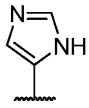
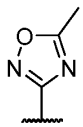
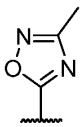
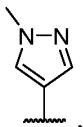
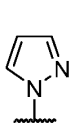
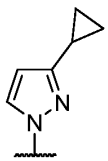
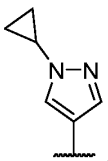
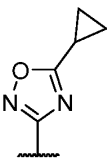
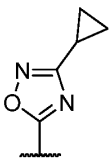
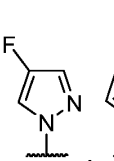
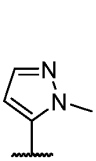
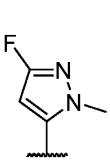
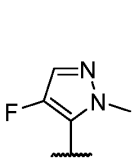
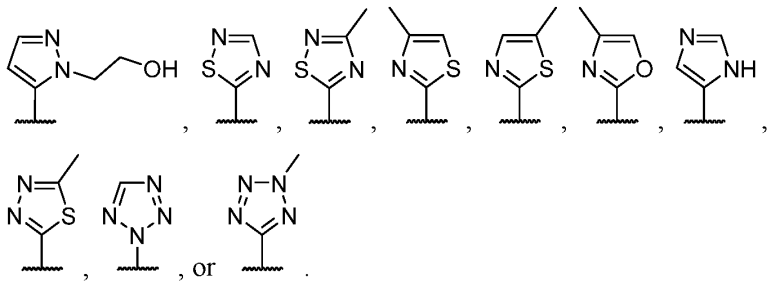
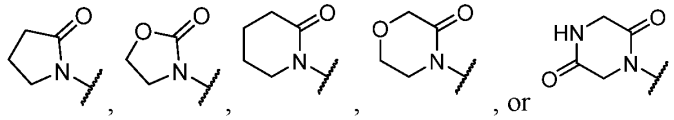
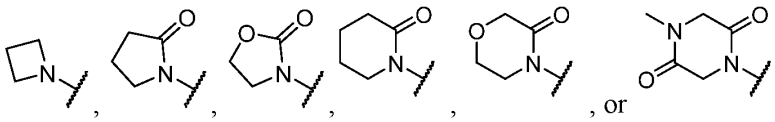
[0104] In some embodiments, R^8 is 5-membered heteroaryl, which is optionally substituted as described herein.

[0105] In some embodiments, R^8 is 5-membered heteroaryl having 1-3 ring heteroatoms, *e.g.*, pyrazole or oxadiazole. In some embodiments, the 5-membered heteroaryl is optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F or OH, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) F, or C_{3-4} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F. In some embodiments, R^8 is pyrazole (*e.g.*, 
, 
, or 
), oxadiazole (*e.g.*, 
or 
), triazole (*e.g.*, 
or 
), tetrazole (*e.g.*, 
or 
), thiadiazole (*e.g.*, 
or 
), thiazole (*e.g.*, 
), oxazole (*e.g.*, 
), or imidazole (*e.g.*, 
), each of which is optionally substituted with 1-2 R^j. In some embodiments, R^j is F, CH_3, CF_3, or cyclopropyl. In some embodiments, R^8 is 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, or 
. In

some embodiments, R^8 is  , or .

[0106] In some embodiments, R^8 is 3- to 6-membered heterocyclyl, which is optionally substituted as described herein.

[0107] In some embodiments, R^8 is a 3- to 6-membered heterocyclyl having 1 or 2 ring heteroatoms. In some embodiments, the heterocyclyl is optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F or OH, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) F, or C_{3-4} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F. In some embodiments, R^8 is  ,  , or , each of which is optionally substituted with 1-2 R^j. In some embodiments, R^j is F, CH_3, CF_3, or cyclopropyl. In some embodiments, R^8 is  , or .

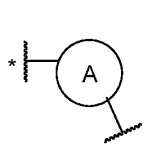
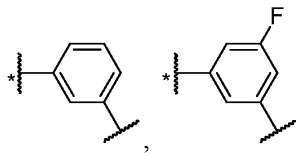
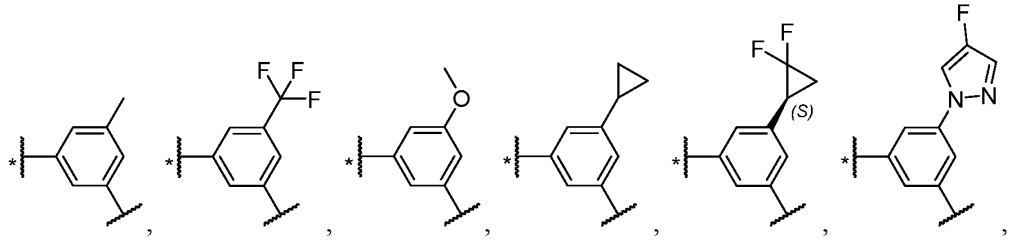
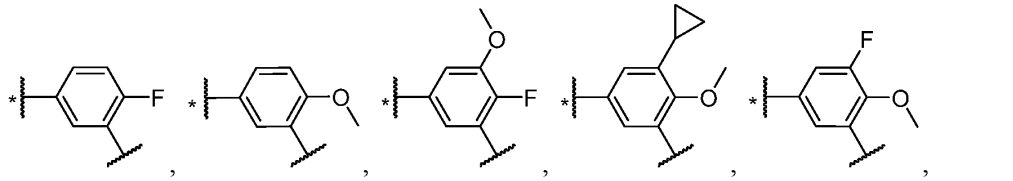
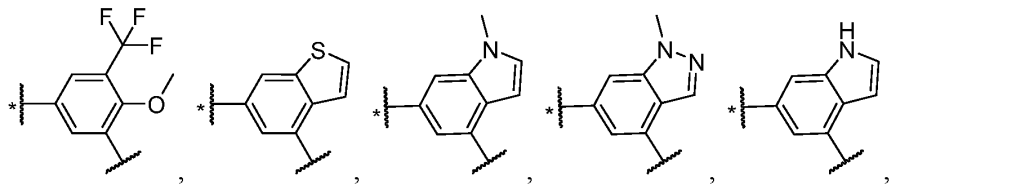
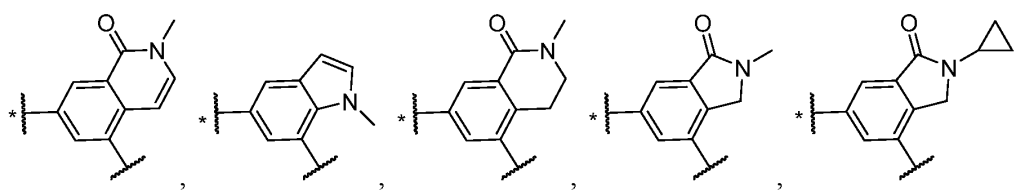
[0108] In some embodiments, R^7 is hydrogen, and R^8 is a non-hydrogen group as described herein. In some embodiments, R^7 is a non-hydrogen group as described herein, and R^8 is hydrogen.

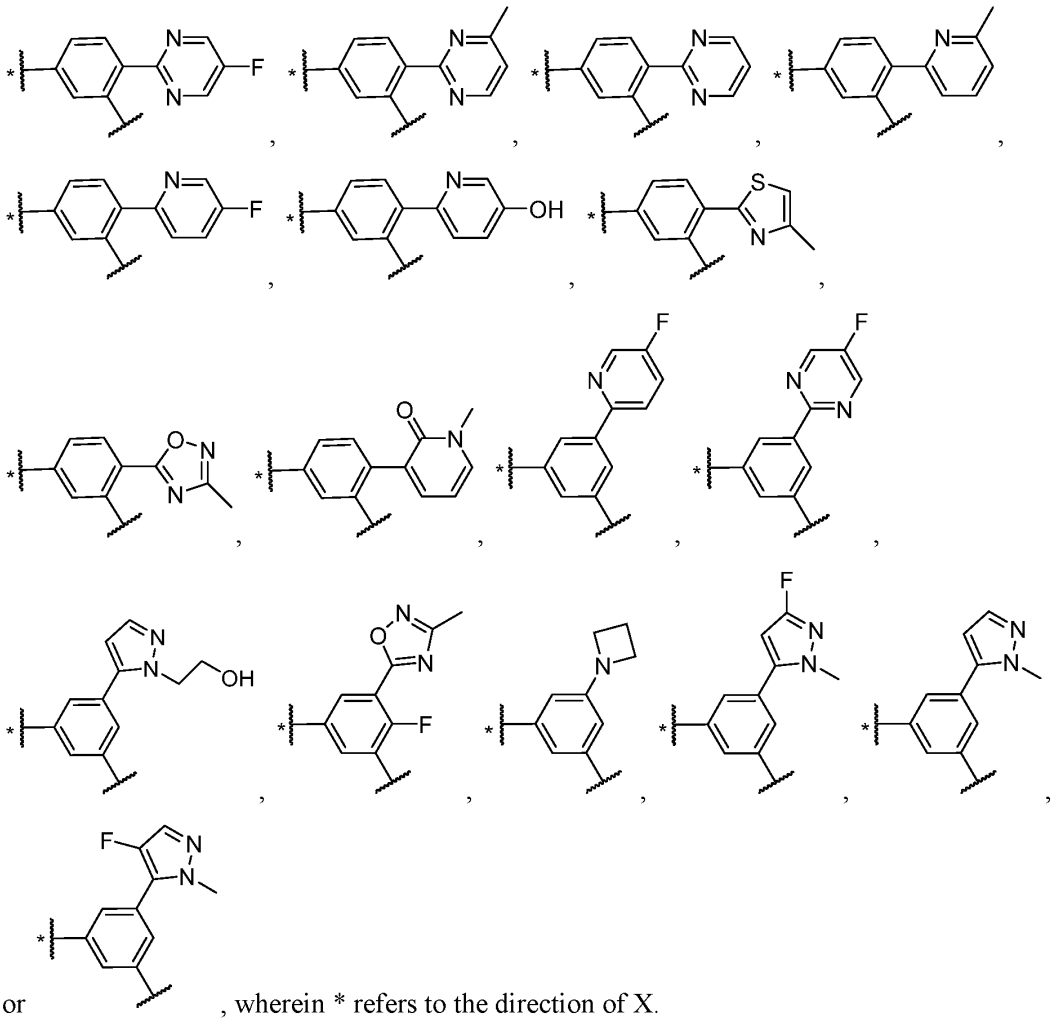
[0109] In some embodiments, R^7 and R^8, together with the carbon atoms they are attached to, form a 4- to 8-membered ring, which is optionally substituted with one or more (*e.g.*, 1, 2, or 3) R^n. In some embodiments, the formed ring is a 5-membered heteroaryl (*e.g.*, pyrrolyl, pyrazolyl, furanyl, or thiophenyl). In some embodiments, the formed ring is a 6-membered heteroaryl (*e.g.*, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl). In some embodiments, the formed ring is a 5-membered heterocyclyl (*e.g.*, pyrrolidinyl). In some embodiments, the formed ring is a 6-membered heterocyclyl (*e.g.*, piperidinyl).

[0110] In some embodiments, R^8 and R^9, together with the carbon atoms they are attached to, form a 4- to 8-membered ring, which is optionally substituted with one or more

(*e.g.*, 1, 2, or 3) R^n. In some embodiments, the formed ring is a 5-membered heteroaryl (*e.g.*, pyrrolyl, pyrazolyl, furanyl, or thiophenyl). In some embodiments, the formed ring is a 6-membered heteroaryl (*e.g.*, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl). In some embodiments, the formed ring is a 5-membered heterocyclyl (*e.g.*, pyrrolidinyl). In some embodiments, the formed ring is a 6-membered heterocyclyl (*e.g.*, piperidinyl).

[0111] In some embodiments, the formed ring (by R^7 and R^8 or by R^8 and R^9) is unsubstituted. In some embodiments, the formed ring is substituted with 1 R^n. In some embodiments, the formed ring is substituted with 2 R^n. In some embodiments, R^n at each occurrence is independently F, CN, OH, oxo, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F, or C_{3-4} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F. In some embodiments, R^n at each occurrence is independently F, CH_3, CF_3, or cyclopropyl.

[0112] In some embodiments,  is  ,  ,  ,  ,  .



or , wherein * refers to the direction of X.

[0113] In some embodiments, n1 is 0. In some embodiments, n1 is 1. In some embodiments, n1 is 2. In some embodiments, n1 is 3. In some embodiments, n1 is 4. In some embodiments, n2 is 0. In some embodiments, n2 is 1. In some embodiments, n2 is 2. In some embodiments, n2 is 3. In some embodiments, n2 is 4.

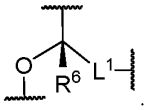
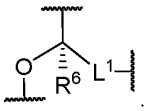
[0114] In some embodiments, both n1 and n2 are 0. In some embodiments, both n1 and n2 are 1, and R^a and R^b are same C_{1-4} alkyl (*e.g.*, methyl, ethyl, or isopropyl).

[0115] In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is deuterium. In some embodiments, R^6 is optionally substituted C_{1-4} alkyl. In some embodiments, R^6 is CH_3. In some embodiments, R^6 is CF_3.

[0116] In some embodiments, R^2 is hydrogen, deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, R^2 is hydrogen.

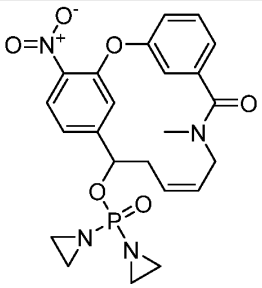
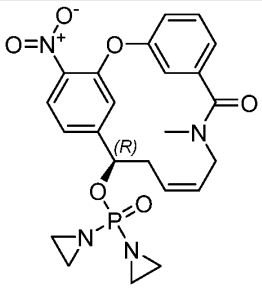
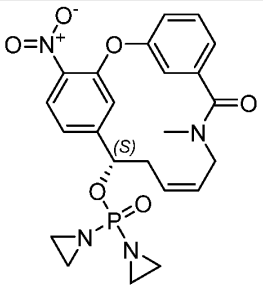
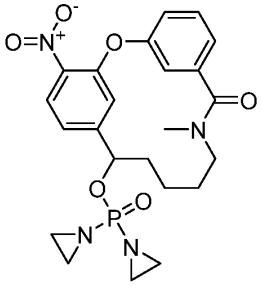
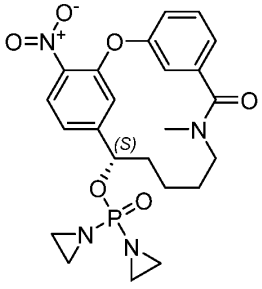
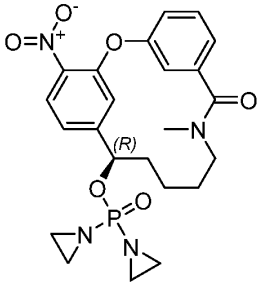
[0117] In some embodiments, R^4 is hydrogen, deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, R^4 is hydrogen.

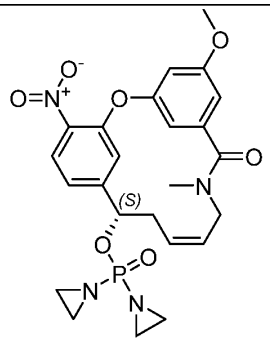
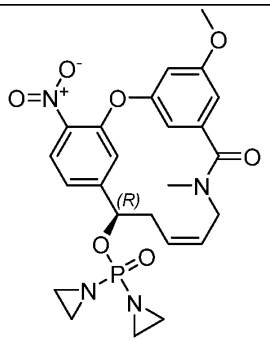
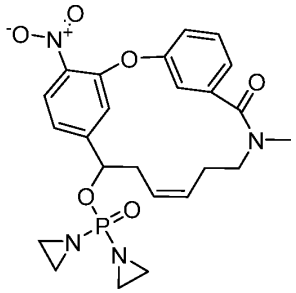
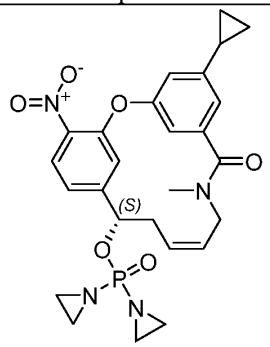
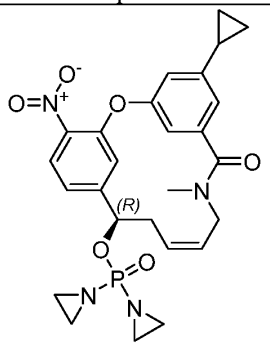
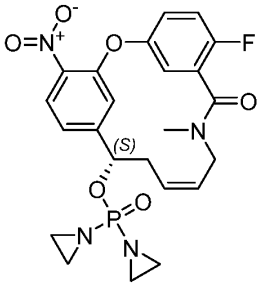
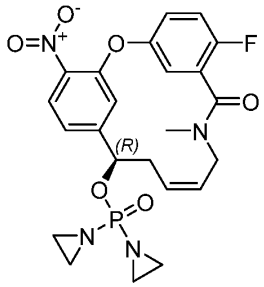
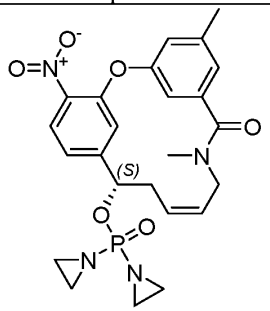
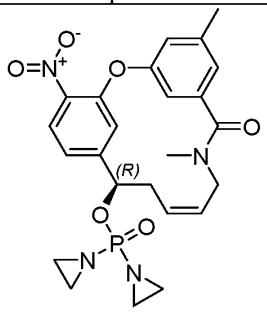
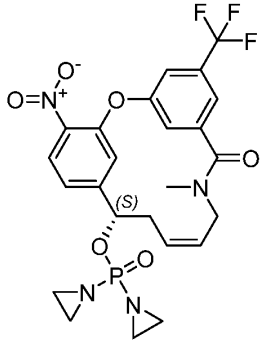
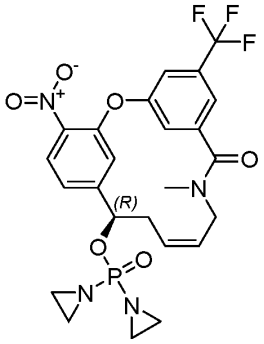
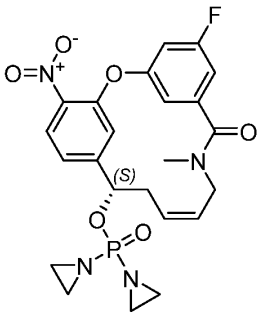
[0118] In some embodiments, R^5 is hydrogen, deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F. In some embodiments, R^5 is hydrogen.

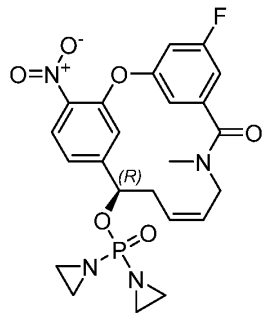
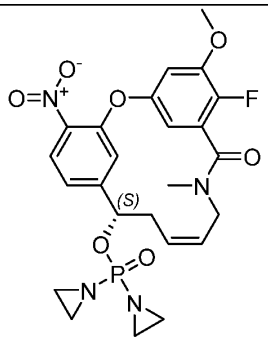
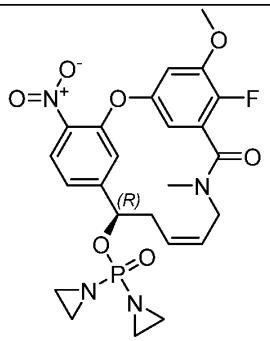
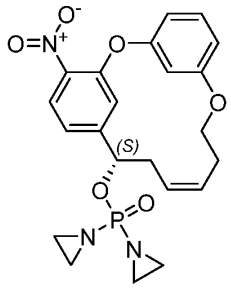
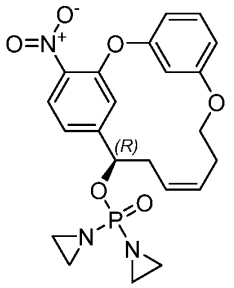
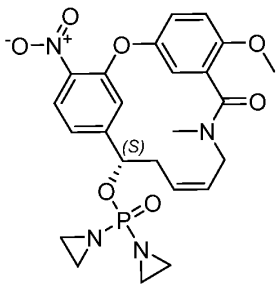
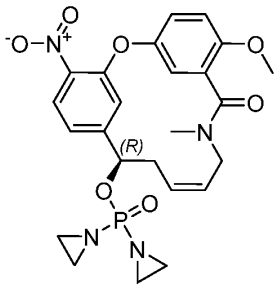
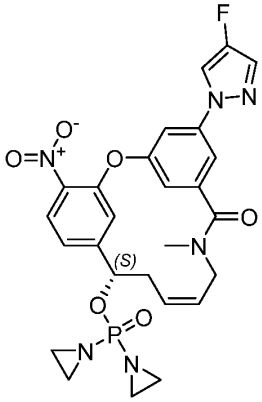
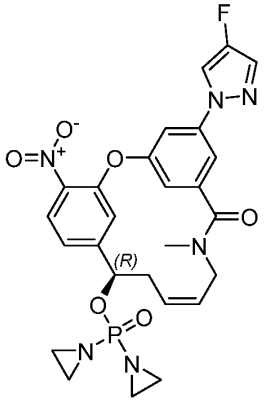
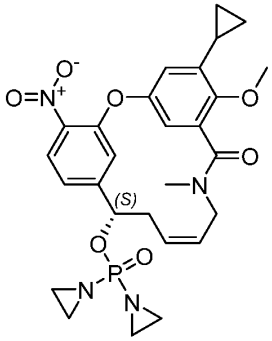
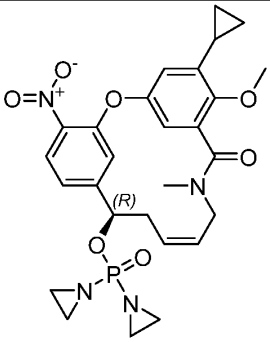
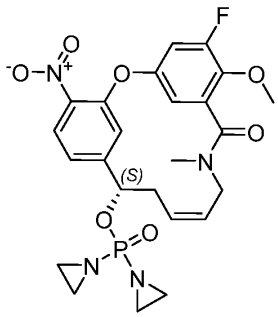
[0119] In some embodiments, the carbon connected to R^6 has configuration of  . In some embodiments, the carbon connected to R^6 has configuration of  .

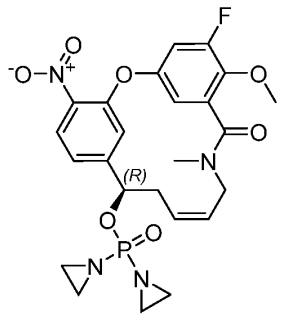
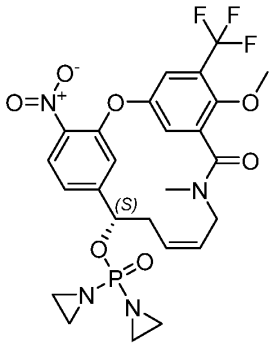
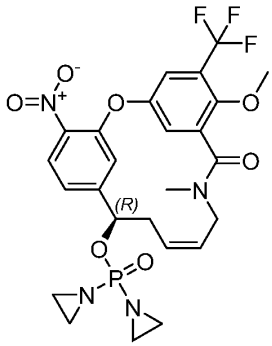
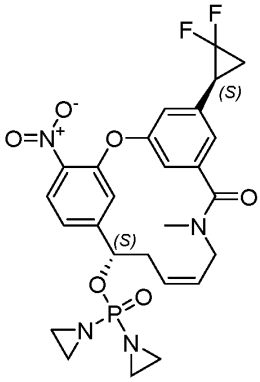
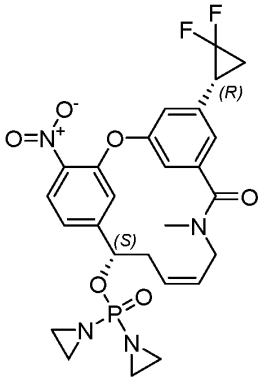
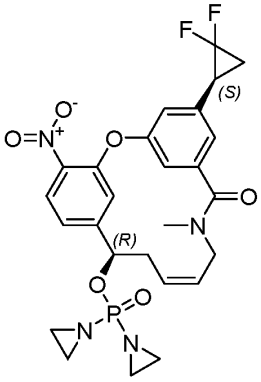
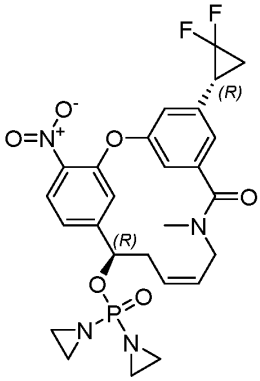
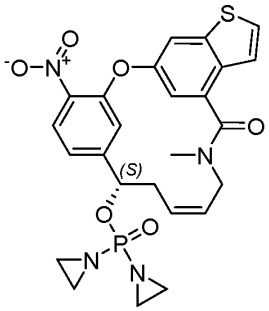
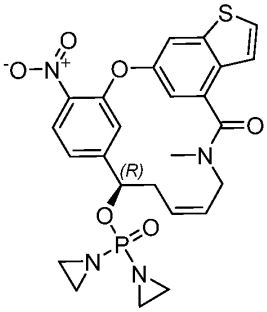
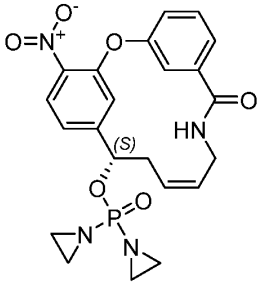
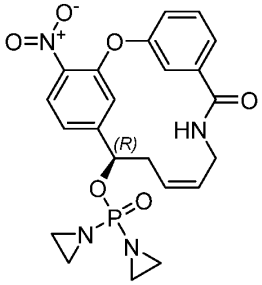
[0120] In some embodiments, the compound is a compound in Table 1, or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.

Table 1

 Compound 1	 Compound 2	 Compound 3
 Compound 4	 Compound 5	 Compound 6

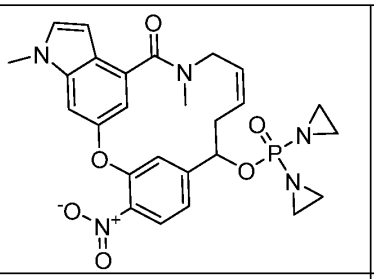
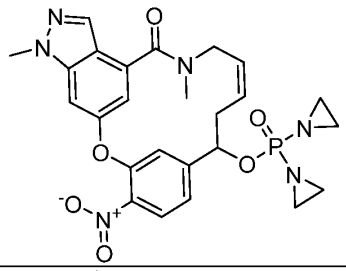
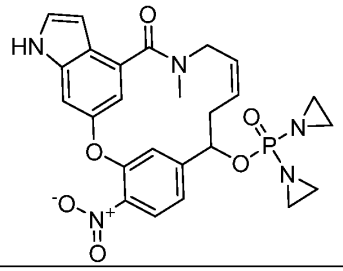
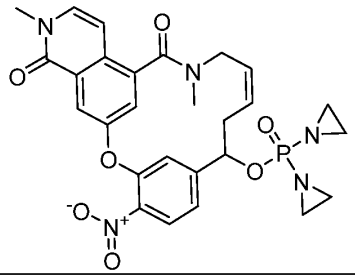
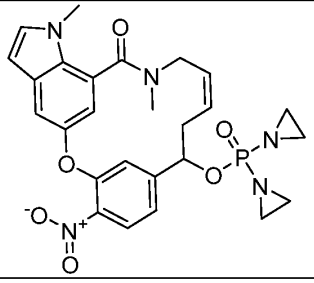
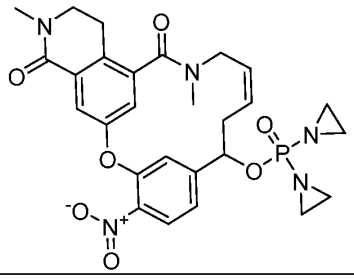
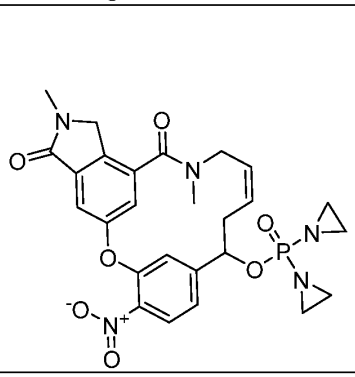
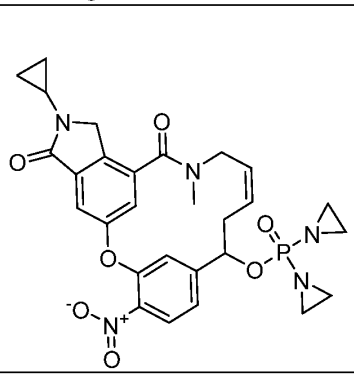
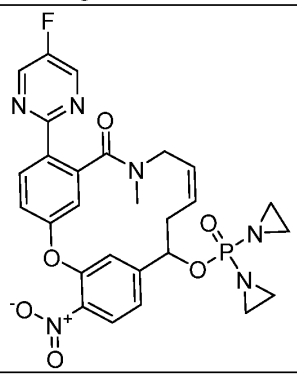
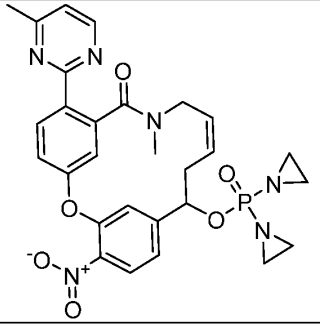
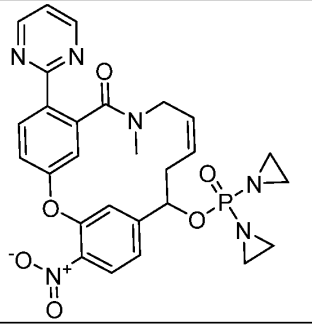
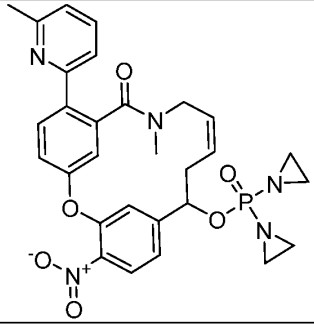
 Compound 7	 Compound 8	 Compound 9
 Compound 10	 Compound 11	 Compound 13
 Compound 14	 Compound 15	 Compound 16
 Compound 17	 Compound 18	 Compound 19

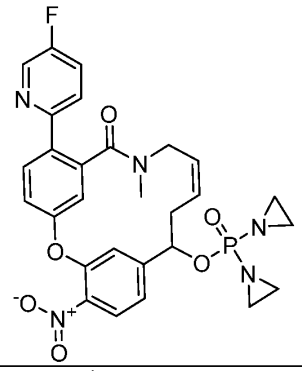
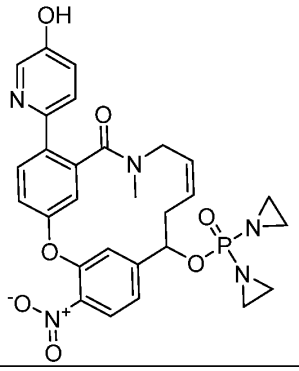
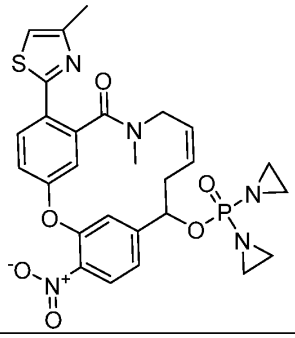
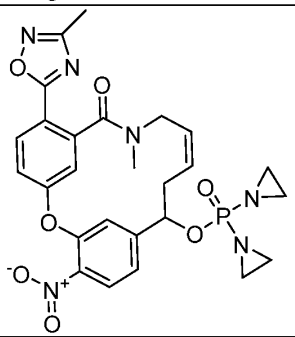
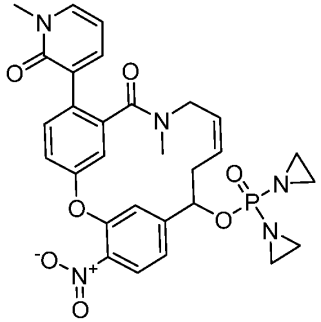
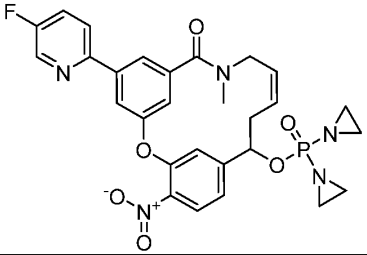
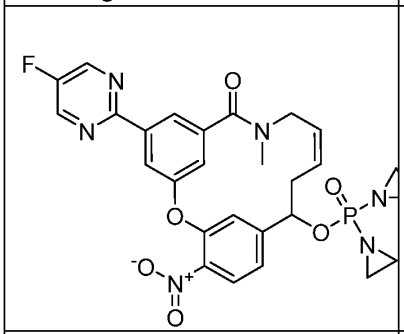
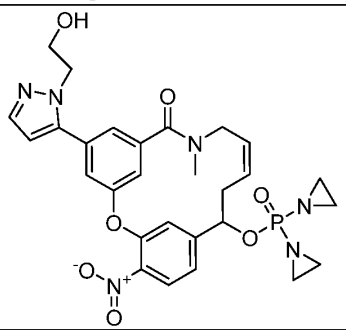
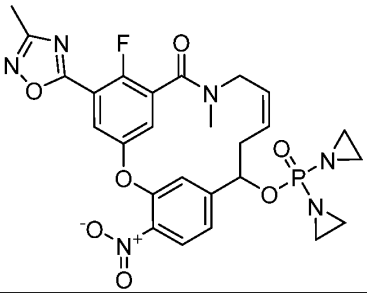
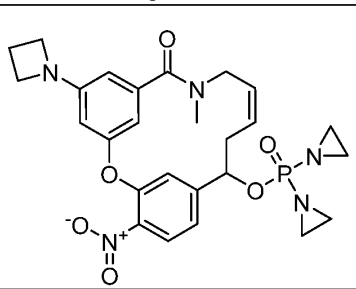
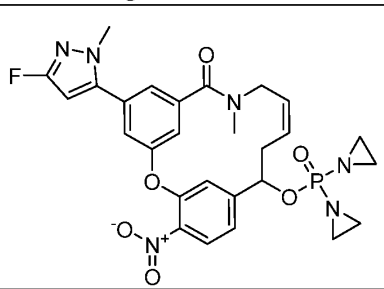
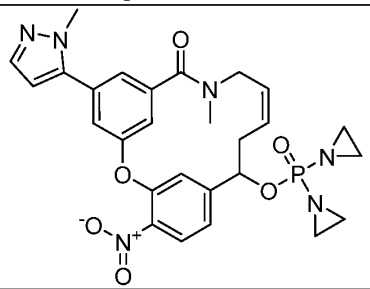
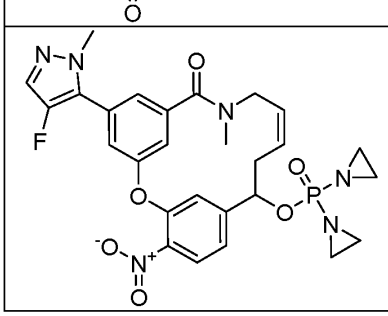
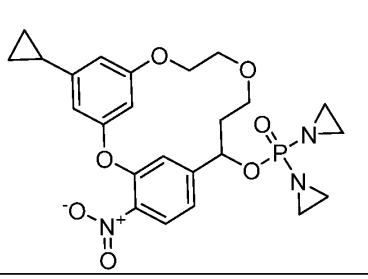
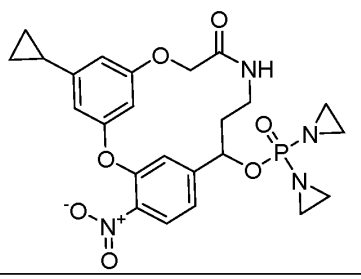
 Compound 20	 Compound 21	 Compound 22
 Compound 23	 Compound 24	 Compound 25
 Compound 26	 Compound 27	 Compound 28
 Compound 29	 Compound 30	 Compound 31

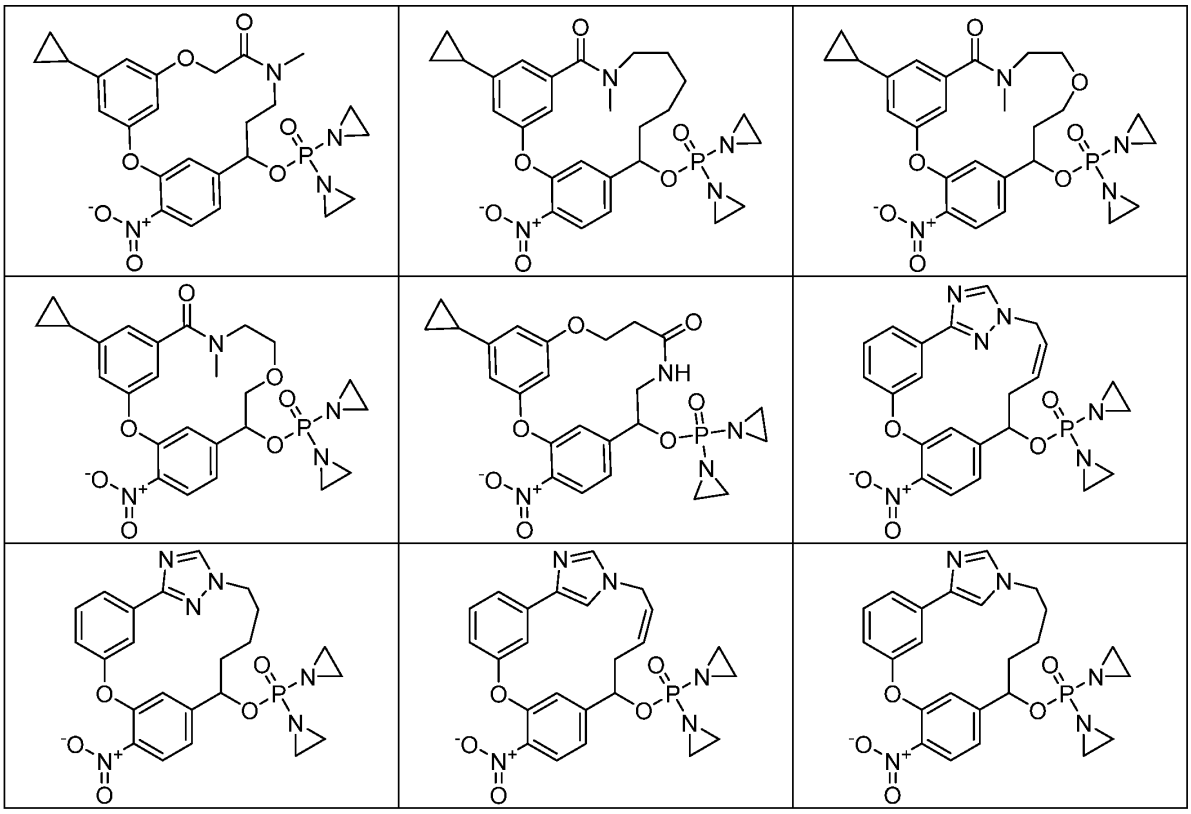
 Compound 32	 Compound 33	 Compound 34
 Compound 35	 Compound 36	 Compound 37
 Compound 38	 Compound 39	 Compound 40
 Compound 41	 Compound 42	

[0121] In some embodiments, the compound is a compound in Table 1A, or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.

Table 1A



[0122] The compounds provide herein may have a chiral center at the carbon atom bearing R^6. As described herein and unless otherwise specified, when the structure of a compound provided herein shows a wedge bond () or dash bond () at the chiral center (or R- or S-stereochemistry at the chiral center is specified in the chemical name of a compound provided herein), it means the compound is an enantiomer at the chiral center, but it does not necessarily mean the absolute stereochemistry between the two enantiomers at the chiral center has been determined. Wedge bond and dash bond are often used when two enantiomer were prepared and separated. As described herein and unless otherwise specified, when the structure of a compound provided herein shows a wavy bond () at the chiral center (or R/S-stereochemistry at the chiral center is specified in the chemical name of a compound provided herein), it means the compound is an enantiomer at the chiral center, but the stereochemistry is not specified. A wavy bond is often used when only one enantiomer was prepared. As described herein and unless otherwise specified, when the structure of a compound provided herein shows only straight bonds () at the chiral center (or the chemical name of a compound provided herein mentions (±)-mixture, racemic mixture, or does not mention stereochemistry), it means the compound is a racemic mixture at the chiral

center. A person of ordinary skill in the art can understand whether a compound is an enantiomer or a racemic mixture and/or whether the absolute stereochemistry has been determined based on the description provided herein, *e.g.*, the synthetic Examples for the compound.

[0123] Similarly, the compounds provide herein may also have one or more chiral center(s) at other places of the molecule, *e.g.*, a chiral substituent group on Ring A (*e.g.*, those in Compounds 35 to 38). As described herein and unless otherwise specified, when the structure of a compound provided herein shows a wedge bond () or dash bond () at those chiral center(s) (or R- or S-stereochemistry at those chiral center(s) is specified in the chemical name of a compound provided herein), it means the compound is an enantiomer at the chiral center, but it does not necessarily mean the absolute stereochemistry between the two enantiomers at the chiral center has been determined. A person of ordinary skill in the art can understand whether a compound is an enantiomer or a racemic mixture and/or whether the absolute stereochemistry has been determined based on the description provided herein, *e.g.*, the synthetic Examples for the compound. For example, as described herein and unless otherwise specified, when a racemic mixture at a chiral center is separated by Chiral SFC, the R/S are assigned arbitrarily to the two enantiomers at the chiral center. For another example, as described herein and unless otherwise specified, when a starting material is enantiomerically pure with regard to a chiral center, and the starting material is used to prepare a compound provided herein, the chiral center in the compound has the stereochemistry as displayed or described (unless, *e.g.*, racemization happens during the preparation).

4.3 *Pharmaceutical Compositions*

[0124] In some embodiments, provided herein is a pharmaceutical composition comprising the compound provided herein, and a pharmaceutically acceptable excipient.

[0125] Pharmaceutically acceptable excipients are known in the art. Non-limiting suitable excipients include, for example, encapsulating materials or additives such as antioxidants, binders, buffers, carriers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof. See also Remington's The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, Md., 2005; incorporated herein by reference), which discloses various excipients

used in formulating pharmaceutical compositions and known techniques for the preparation thereof.

[0126] The pharmaceutical composition provided herein can be formulated for delivery via known routes of delivery, which include but not limited to administering orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperintoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally or parenterally.

[0127] In some embodiments, the pharmaceutical composition can be formulated for oral administration. The oral formulations can be presented in discrete units, such as capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Excipients for the preparation of compositions for oral administration are known in the art. Non-limiting suitable excipients include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof.

[0128] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (such as intravenous injection or infusion, subcutaneous or intramuscular injection). The parenteral formulations can be, for example, an aqueous solution, a suspension, or an emulsion. Excipients for the preparation of parenteral formulations are known in the art. Non-limiting suitable excipients include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof.

[0129] Compounds provided herein can be used alone, in combination with each other, or in combination with one or more additional therapeutic agents, *e.g.*, in combination

with an additional anticancer therapeutic agent, such as those approved on the market, such as those approved by the U.S. Food and Drug Administration or other similar government agencies.

[0130] When used in combination with one or more additional therapeutic agents, compounds provided herein or pharmaceutical compositions provided herein can be administered to the subject either concurrently or sequentially in any order with such additional therapeutic agents. In some embodiments, the pharmaceutical composition can comprise one or more compounds provided herein and the one or more additional therapeutic agents in a single composition. In some embodiments, the pharmaceutical composition comprising one or more compounds provided herein can be included in a kit which also comprises a separate pharmaceutical composition comprising the one or more additional therapeutic agents.

[0131] The pharmaceutical composition can include various amounts of the compounds provided herein, depending on various factors such as the intended use and potency and selectivity of the compounds. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a compound provided herein. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of the compound of the present disclosure and a pharmaceutically acceptable excipient. As used herein, a therapeutically effective amount of a compound provided herein is an amount effective to treat a disease or disorder as described herein, such as a cancer described herein, which can depend on the recipient of the treatment, the disorder, condition or disease being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered.

4.4 *Method of Use*

[0132] Compounds provided herein have various utilities. For example, compounds provided herein can be used as therapeutic active substances for the treatment and/or prophylaxis of cancer, such as a cancer characterized as having abnormal AKR1C3 activity and/or overexpression of AKR1C3, for example, in an NRF2/KEAP1 mutated cancer.

[0133]

[0134] In some embodiments, provided herein is a method of treating or preventing cancer, comprising administering to a subject in need thereof a therapeutically effective amount of a compound provided herein, or a pharmaceutical composition provided herein. In

some embodiments, provided herein is a method of treating cancer, comprising administering to a subject having the cancer a therapeutically effective amount of a compound provided herein, or a pharmaceutical composition provided herein. In some embodiments, the cancer is characterized as having abnormal AKR1C3 activity and/or overexpression of AKR1C3. In some embodiments, the cancer is characterized as having abnormal AKR1C3 activity. In some embodiments, the cancer is characterized as having abnormal overexpression of AKR1C3. In some embodiments, the cancer is characterized as having abnormal AKR1C3 activity and overexpression of AKR1C3. In one embodiment, the cancer is liver cancer. In one embodiment, the cancer is lung cancer. In one embodiment, the cancer is non-small cell lung cancer. In one embodiment, the cancer is melanoma. In one embodiment, the cancer is prostate cancer, such as castration resistant prostate cancer.

[0135] In some embodiments, provided herein is a method of treating or preventing a NRF2/KEAP1 mutated cancer, comprising administering to a subject in need thereof a therapeutically effective amount of a compound provided herein, or a pharmaceutical composition provided herein. In some embodiments, provided herein is a method of treating a NRF2/KEAP1 mutated cancer, comprising administering to a subject having the cancer a therapeutically effective amount of a compound provided herein, or a pharmaceutical composition provided herein. In some embodiments, the NRF2/KAEP1 mutation results in an aberrant NRF2 activity, for example, leading to overexpression of AKR1C3. In one embodiment, the cancer is liver cancer. In one embodiment, the cancer is lung cancer. In one embodiment, the cancer is non-small cell lung cancer. In one embodiment, the cancer is melanoma. In one embodiment, the cancer is prostate cancer, such as castration resistant prostate cancer.

[0136] In some embodiments, the types of cancer suitable to be treated with the methods provided herein is selected from the group consisting of a cancer of the adrenal gland, bone, brain, breast, bronchi, colon and/or rectum, gallbladder, head and neck, kidneys, larynx, liver, lung, neural tissue, pancreas, prostate, parathyroid, skin, stomach, and thyroid; and acute and chronic lymphocytic and granulocytic tumors, adenocarcinoma, adenoma, basal cell carcinoma, cervical dysplasia and in situ carcinoma, Ewing's sarcoma, epidermoid carcinomas, giant cell tumor, glioblastoma multiforma, hairy-cell tumor, intestinal ganglioneuroma, hyperplastic corneal nerve tumor, islet cell carcinoma, Kaposi's sarcoma, leiomyoma, leukemias, lymphomas, malignant carcinoid, malignant melanomas, malignant hypercalcemia, marfanoid habitus tumor, medullary carcinoma, metastatic skin carcinoma, mucosal neuroma, myeloma, mycosis fungoides, neuroblastoma, osteo sarcoma, osteogenic

and other sarcoma, ovarian tumor, pheochromocytoma, polycythermia vera, primary brain tumor, small-cell lung tumor, squamous cell carcinoma of both ulcerating and papillary type, hyperplasia, seminoma, soft tissue sarcoma, retinoblastoma, rhabdomyo sarcoma, renal cell tumor, topical skin lesion, veticulum cell sarcoma, and Wilm's tumor. In some embodiments, the cancer is liver cancer, non-small cell lung cancer, melanoma, renal cell carcinoma, or prostate cancer. In any of the embodiments described herein, the cancer can be characterized as having an abnormal AKR1C3 activity/AKR1C3 overexpression, which for example, may be caused by a NRF2/KEAP1 mutation. In one embodiment, the cancer is liver cancer. In one embodiment, the cancer is non-small cell lung cancer. In one embodiment, the cancer is melanoma. In one embodiment, the cancer is prostate cancer, such as castration resistant prostate cancer.

[0137] In some embodiments, the method comprises first determining the AKR1C3 reductase level of the cancer, such as by methods using an AKR1C3 antibody, and then administering a therapeutically effective amount of a compound provided herein or a pharmaceutical composition provided herein to the subject if the AKR1C3 level is equal to or greater than a predetermined value, for example, if the AKR1C3 level is greater than the AKR1C3 level in a control healthy cell.

[0138] In some embodiments, the method comprises prior to administration, determining an intratumoral AKR1C3 reductase level in a sample isolated from the cancer subject and selecting the subject for the therapy if the AKR1C3 level is equal to or greater than a predetermined level, for example, if the AKR1C3 level is greater than the AKR1C3 level in a control healthy cell.

[0139] AKR1C3 levels can be measured following methods known to the ordinarily skilled artisan. In some embodiments, provided herein is a kit comprising a means for isolating a sample from a patient and determining an intratumoral AKR1C3 reductase level of the cancer in the sample using an AKR1C3 antibody; and a means for determining whether a compound provided herein or a pharmaceutical composition provided herein should be administered.

[0140] In some embodiments, the administering in the methods provided herein is orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperintoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally, or parenterally. In some embodiments, the administering is orally. In some embodiments, the administering is a parenteral injection, such as an intravenous injection.

[0141] Compounds provided herein can be used as a monotherapy or in a combination therapy. In some embodiments according to the methods described herein, one or more compounds of the present disclosure can be administered as the only active ingredient(s). In some embodiments according to the methods described herein, one or more compounds of the present disclosure can also be co-administered with an additional therapeutic agent, such as additional anticancer agents described herein, either concurrently or sequentially in any order, to the subject in need thereof. The additional therapeutic agent can typically be an additional anticancer therapeutic agent, such as any of those approved on the market, such as those approved by the U.S. Food and Drug Administration or other similar government agencies.

5. EXAMPLES

[0142] The various starting materials, intermediates, and compounds provided herein can be isolated and purified where appropriate using techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Characterization of these compounds can be performed using conventional methods such as by melting point, mass spectrum, nuclear magnetic resonance, and various other spectroscopic analyses. The abbreviations used in the Examples section should be understood as having their ordinary meanings in the art unless specifically indicated otherwise or obviously contrary from context. The examples are illustrative only and do not limit the claimed invention in any way.

[0143] Exemplary embodiments of steps for performing the synthesis of products described herein are described in greater detail infra. Some of the Examples discussed herein can be prepared by separating from the corresponding racemic mixtures. As would be understood by a person of ordinary skill in the art, the compounds described in the Examples section immediately prior to the chiral separation step, *e.g.*, by supercritical fluid chromatography (SFC), exist in racemic and/or stereoisomeric mixture forms. It should be understood that the enantiomeric excesses ("ee") reported for these examples are only representative from the exemplified procedures herein and not limiting; those skilled in the art would understand that such enantiomers with a different ee, such as a higher ee, can be obtained in view of the description provided herein.

Table of Abbreviations

ACN	acetonitrile
aq.	aqueous

B_2pin_2	bis(pinacolato)diboron
Boc	tert-butyloxycarbonyl
Cbz	carbonylbenzyloxy
CDI	carbonyldiimidazole
Cpd	Compound
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPBT	(3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one)
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	*N,N*-diisopropylethylamine
DMAP	*N,N*-dimethylpyridin-4-amine
DMC	dimethyl carbonate
DMEDA	*N,N'*-dimethylethylenediamine
DMF	dimethylformamide
DMP	1,1-bis(acetyloxy)-3-oxo-3H-1λ^5,2-benziodaoxol-1-yl acetate
DMSO	dimethyl sulfoxide
DMT	dimercaptotriazine
DPPA	{[azido(phenoxy)phosphoryl]oxy}benzene
EA	Ethyl acetate
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq	equivalent or equivalents
FA	formic acid
h	hour or hours
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
LCMS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
mCPBA	*meta*-chloroperbenzoic acid
min	minute or minutes
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromosuccinimide
NCS	1-chloropyrrolidine-2,5-dione
NMI	*N*-methylimidazole
NMR	nuclear magnetic resonance
Pbf	2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PE/Pet Ether	petroleum ether

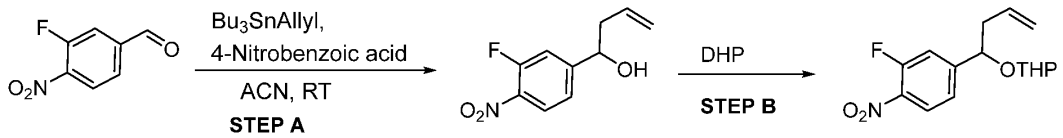
Py	pyridine
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
RT	room temperature
T3P	propanephosphonic anhydride
TBAF	Tetrabutylammonium fluoride
TCFH	*N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	Trimethylsilyl chloride
TMSI	Trimethylsilyl iodide
TFA	trifluoroacetic acid
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XantPhos Pd G4	(6-diphenylphosphanyl-10H-phenoxazin-4-yl)-diphenylphosphane;methanesulfonic acid;N-methyl-2-phenylaniline;palladium
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhos Pd G3	dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphane;methanesulfonate;palladium;2-phenylaniline

Analytical Instrumentation and Purification

[0144] NMR Instrument Details: Varian 400MHz, Probe-1: Auto XID, Probe 2: ATB.

[0145] LCMS Instrument Details: Shimadzu LCMS-2010EV system coupled to SPD-M20A PDA and ELS detectors. Softa model 400.

Preparation of KI



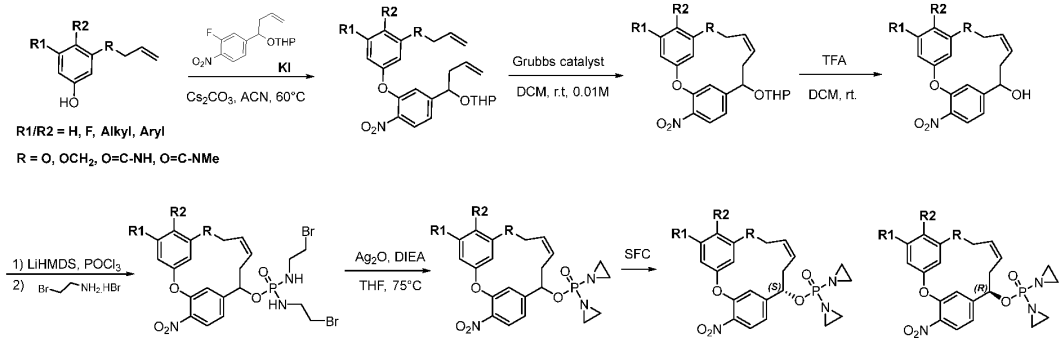
KI

[0146] STEP A: To a solution of 3-fluoro-4-nitrobenzaldehyde (500 mg, 2.96 mmol, 1.0 eq.) and 4-nitrobenzoic acid (0.31 mL, 2.96 mmol, 1.0 eq.) in acetonitrile (10 mL) was added allyltributylstannane (1.1 mL, 3.55 mmol, 1.2 eq.). The resulting mixture was stirred at room temperature overnight. After completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-(3-fluoro-4-nitrophenyl)but-3-en-1-ol

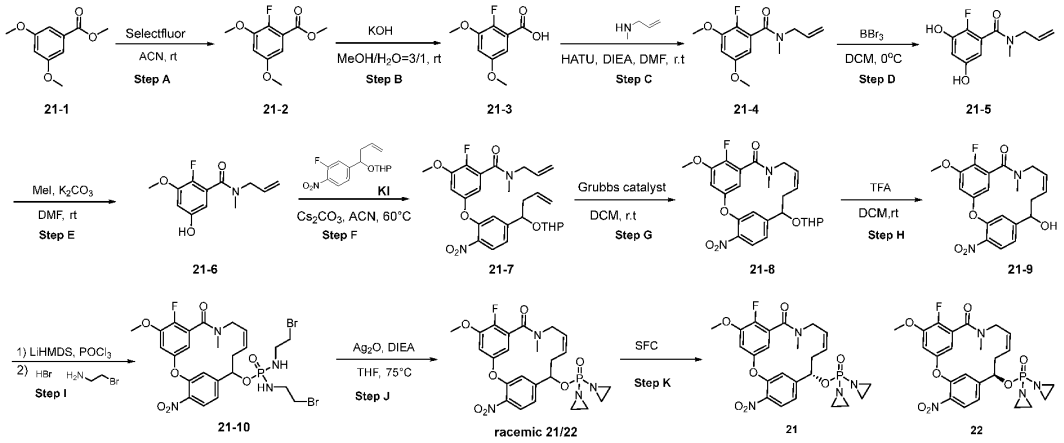
(480 mg, 2.27 mmol, 77%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.93 (m, 1H), 7.27 (dd, J = 11.8, 1.4 Hz, 1H), 7.21 (d, J = 0.7 Hz, 1H), 5.80 -5.60 (m, 1H), 5.20-5.06 (m, 2H), 4.76 (dd, J = 8.0, 4.5 Hz, 1H), 2.55-2.46 (m, 1H), 2.43-2.29 (m, 1H), 2.27-2.12 (m, 1H).

[0147] STEP B: To a stirred mixture of 1-(3-fluoro-4-nitrophenyl)but-3-en-1-ol (10 g, 47.351 mmol) in MeCN (100 mL) were added DHP (11.93 g, 142.052 mmol) and PPTS (1.19 g, 4.735 mmol). The resulting mixture was stirred at 50°C for overnight. The reaction mixture was poured into water and then extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to afford 2-((1-(3-fluoro-4-nitrophenyl)but-3-en-1-yl)oxy)tetrahydro-2H-pyran (12 g, 41 mmol, 85%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, J = 8.0 Hz, 1H), 7.37 – 7.23 (m, 2H), 5.84 – 5.70 (m, 1H), 5.26 – 5.15 (m, 2H), 4.89 – 4.79 (m, 1H), 2.62 – 2.52 (m, 1H), 2.49 – 2.39 (m, 1H).

The general route



Example 1: Preparation of Compound 21 and Compound 22



[0148] STEP A: To a stirred solution of 21-1 (25 g, 127.421 mmol) in ACN (300 mL) was added Selectfluor (81.25 g, 229.358 mmol) in batches at 0°C under N_2 for 10 mins. The reaction was stirred at 0°C for 20 mins. Then the mixture was warmed to room temperature and stirred for 48 hours. The reaction was 50% complete detected by LC-MS. The reaction mixture was poured into 300 mL of the sodium carbonate solution and then extracted with EtOAc (300 mL * 2). The combined organic layers were washed with sodium carbonate solution (200 mL * 2), water (200 mL), brine (100mL), dried over anhydrous Na_2SO_4 and concentrated. Purified with flash column (PE/EA=20/1) to give 21-2 (8 g, 37.350 mmol, 29.31%) as a white solid. LCMS (ESI): m/z = 215.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 – 6.87 (m, 1H), 6.71 (dd, J = 6.6, 3.0 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -141.70 (s).

[0149] STEP B: To a stirred solution of 21-2 (3 g, 14.006 mmol) in MeOH (25 mL) and H_2O (10 mL) was added KOH (2.36 g, 42.019 mmol). The reaction was stirred at room temperature for 18 hours. The reaction was complete detected by LC-MS. The reaction mixture was neutralized with HCl solution (4 N, 11 mL) under ice bath and then extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give 21-3 (2.6 g, 12.989 mmol, 92.74%) as a white solid. LCMS (ESI): m/z = 201.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 13.32 (s, 1H), 6.93 (dd, J = 6.7, 3.0 Hz, 1H), 6.82 (dd, J = 4.5, 3.2 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H). ^{19}F NMR (376 MHz, DMSO) δ -143.30 (s).

[0150] STEP C: To a stirred solution of 21-3 (2.7 g, 13.489 mmol) and TEA (4.09 g, 40.466 mmol) in DMF (30 mL) was added HATU (6.15 g, 16.186 mmol). The reaction was stirred at room temperature for 10 mins. methyl(prop-1-en-3-yl)amine (1.15 g, 16.186 mmol) was added to the reaction and stirred at room temperature for 60 mins. The reaction was complete detected by LC-MS. The reaction mixture was quenched with water (100 mL) and then extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated, the residue was purified by flash column (PE/EA= 5/1-2/1) to give 21-4 (3.2 g, 12.635 mmol, 93.67%) as a colorless oil. LCMS (ESI): m/z = 254.1 $[M+H]^+$.

[0151] STEP D: To a stirred solution of 21-4 (3.3 g, 13.030 mmol) in DCM (50 mL) was dropwise added boron tribromide (2.5 mL, 26.059 mmol) at 0°C under N_2. The reaction was stirred at 0°C for 5 hours. The reaction was complete detected by LC-MS. The reaction mixture was quenched with water (10 mL) at 0°C, and then extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine, dried over anhydrous

Na_2SO_4 and concentrated. Purified with flash column to give 21-5 (2.6 g, 11.544 mmol, 88.60%). LCMS (ESI): m/z = 226.0 $[M+H]^+$.

[0152] STEP E: To a mixture of 21-5 (2.6 g, 11.544 mmol) in DMF (30 mL) and K_2CO_3 (1.60 g, 11.544 mmol) were added CH_3I (1.47 g, 10.390 mmol) at 25°C. The reaction was stirred at 25°C for 18 hours. The reaction was 80% conv. detected by LC-MS. The reaction mixture was quenched with ice water (150 mL), then extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Purified with flash column (PE/EA=1/1) to give 21-6 (1.5 g, 6.270 mmol, 54.31%) which was confirmed by NOE. LCMS (ESI): m/z = 240.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 9.66 (d, J = 6.9 Hz, 1H), 6.66 – 6.50 (m, 1H), 6.26 – 6.08 (m, 1H), 5.89 – 5.60 (m, 1H), 5.31 – 5.01 (m, 2H), 4.06 (d, J = 5.0 Hz, 1H), 3.80 (d, J = 4.4 Hz, 3H), 3.76 (d, J = 5.1 Hz, 1H), 2.85 (d, J = 54.0 Hz, 3H).

[0153] STEP F: To a mixture of 21-6 (1.5 g, 6.270 mmol) and KI (1.94 g, 6.583 mmol) in ACN (20 mL) were added Cs_2CO_3 (4.09 g, 12.539 mmol) at 25°C. The reaction was stirred at 60°C for 3 hours. The reaction was 100% conv. detected by LC-MS. The reaction mixture was filtered. The combined organic layers were concentrated. Purified with flash column (PE/EA=3/1-2/1) to give 21-7 (3 g, 5.830 mmol, 92.99%). LCMS (ESI): m/z = 515.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 1H), 7.27 – 7.15 (m, 1H), 7.13 – 6.98 (m, 1H), 6.81 – 6.68 (m, 1H), 6.54 – 6.39 (m, 1H), 5.88 – 5.58 (m, 2H), 5.32 – 4.95 (m, 4H), 4.81 – 4.35 (m, 2H), 4.14 (d, J = 5.8 Hz, 1H), 3.94 – 3.89 (m, 0.5H), 3.87 (s, 3H), 3.79 (d, J = 5.1 Hz, 1H), 3.57 – 3.25 (m, 1.5H), 2.95 (d, J = 61.7 Hz, 3H), 2.61 – 2.34 (m, 2H), 1.84 – 1.45 (m, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -142.11 (d, J = 20.1 Hz), -142.54 (d, J = 27.3 Hz).

[0154] STEP G: To the solution of 21-7 (3 g, 5.830 mmol) in DCM (200 mL) were added Grubbs 2nd catalyst (0.49 g, 0.583 mmol) at 25°C under N_2. The reaction was stirred at rt. for 63 hours. The reaction was 100% conv. detected by LC-MS. The reaction mixture was filtered. The combined organic layers were concentrated. Purified with flash column (PE/EA=3/1-2/1) to give 21-8 (1.7 g, 3.494 mmol, 59.86%). LCMS (ESI): m/z = 487.0 $[M+H]^+$.

[0155] STEP H: To a stirred solution of 21-8 (600 mg, 1.233 mmol) in DCM (10 mL) was added TFA (2 mL, 26.925 mmol) at rt. The reaction was stirred at rt for 0.5 hour. The reaction was complete detected by LC-MS. The reaction mixture was concentrated, purified with flash column (PE/EA=2/1-1/1) to give 21-9 (400 mg, 0.995 mmol, 80.6%), LCMS (ESI): m/z = 403.1$[M+H]^+$.

[0156] STEP I: To a stirred solution of 21-9 (400 mg, 0.994 mmol) in THF (80 mL) was dropwise added LiHMDS (2.982 mL) at -40°C under N_2. The mixture was stirred at -40°C for 1 h. Then the solution of POCl3 (0.185 mL, 1.988 mmol) in THF (0.3 mL) was dropwise added to the reaction at -55°C for 0.5 mins. The mixture was stirred at -55°C for 1 h. Then 2-Bromoethylamine hydrobromide (1222.07 mg, 5.965 mmol) was added to the reaction and TEA (1.658 mL, 11.929 mmol) was dropwise added to the reaction at -55°C for 0.1 min. The mixture was stirred at -55°C for 10 min, at room temperature for 1h. The reaction was complete, product was detected by LC-MS. The reaction was quenched by saturated ammonium chloride solution (10 mL), diluted with water (40 mL), extracted by EA(20 mL*2), the EA layer was concentrated and the residue was purified by reversed-phase column (50% ACN in water) to give 21-10 (60 mg, 0.086 mmol, 8.69%) as a white solid. LCMS (ESI): m/z = 694.9 $[M+H]^+$.

[0157] STEP J: To a stirred solution of 21-10 (60 mg, 0.086 mmol) in THF (10 mL) was added DIEA (111.48 mg, 0.864 mmol) and silver oxide (200.27 mg, 0.864 mmol) at rt. under N_2. The mixture was stirred at 70°C for 18 hs. The reaction was complete, product was detected by LC-MS. The reaction was filtered by diatomite, concentrated, and the residue was purified by reversed-phase column (50% ACN in water) to give racemic 21/22 (30 mg, 0.056 mmol, 65.20%) as a white solid. LCMS (ESI): m/z = 533.1 $[M+H]^+$.

[0158] STEP K: racemic 21/22 (40 mg) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

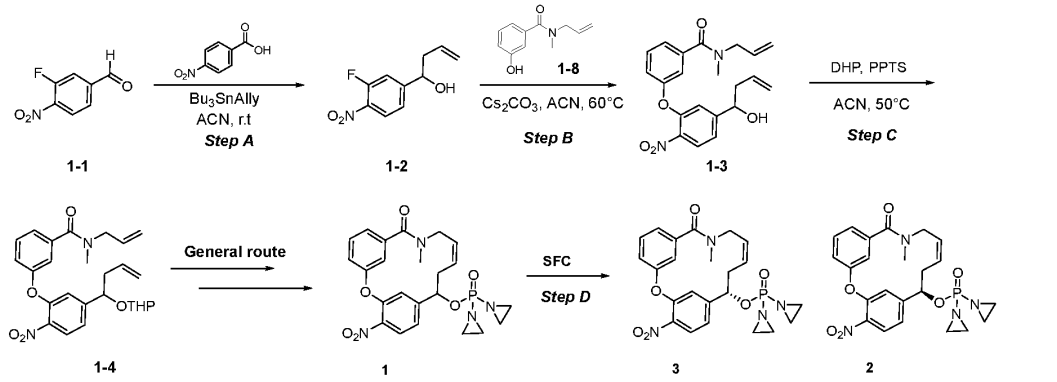
[0159] Isomer 1 (Compound 21, 13 mg, 0.024 mmol, 28.39%); Retention time: 2.429 min, >99% ee. LC-MS (ESI): m/z 533.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.65 – 7.30 (m, 1H), 7.10 (s, 1H), 6.95 (dd, J = 6.5, 2.5 Hz, 1H), 5.98 – 5.88 (m, 1H), 5.84 – 5.20 (m, 3H), 3.96 (s, 3H), 3.95 – 3.55 (m, 2H), 3.04 (s, 3H), 3.03 – 2.76 (m, 1H), 2.46 – 1.94 (m, 9H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -143.98 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.65 (s).

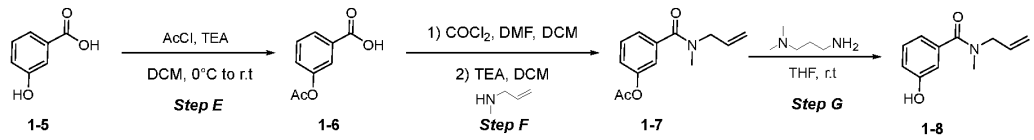
[0160] Isomer 2 (Compound 22, 13 mg, 0.024 mmol, 28.39%); Retention time: 3.662 min, >99% ee. LC-MS (ESI): m/z 533.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.65 – 7.30 (m, 1H), 7.10 (s, 1H), 6.95 (dd, J = 6.5, 2.5 Hz, 1H), 5.98 – 5.88 (m, 1H), 5.84 – 5.20 (m, 3H), 3.96 (s, 3H), 3.95 – 3.55 (m, 2H), 3.04 (s, 3H), 3.03 – 2.76 (m, 1H), 2.46 – 1.94 (m, 9H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -143.98 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.65 (s).

[0161] Analytical method: Column: CHIRALPAK C-IG 100*4.6mm 5um. Mobile phase: A: CO_2 B: MeOH (0.05% DEA v/v) Gradient: 8 min B 40 %. Flow rate: 2.0 mL/min. Back pressure: 10 MP. Column temperature: 40°C.

[0162] SFC method: Instrument: Waters Thar 80 preparative SFC, Column: ChiralPak C-IG, 250×30mm I.D., 5 μm, Mobile phase: A for CO_2 and B for MEOH (0.1% 7mol/L NH3 in MeOH), Gradient: B 40 %, Flow rate: 40 mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 11 min, Eluted time: 2h.

Example 2: Preparation of Compound 1, Compound 2, and Compound 3





[0163] STEP A: To a solution of 1-1 (1, 500 mg, 2.96 mmol, 1.0 eq.) and 4-nitrobenzoic acid (0.31 mL, 2.96 mmol, 1.0 eq.) in acetonitrile (10 mL) was added tributyl(prop-2-enyl)-λ4- stannane (1.10 mL, 3.55 mmol, 1.2 eq.). The resulting mixture was stirred at room temperature overnight. After completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-2 (480 mg, 2.27 mmol, 77%) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04-7.93 (m, 1H), 7.27 (dd, J = 11.8, 1.4 Hz, 1H), 7.21 (d, J = 0.7 Hz, 1H), 5.80 -5.60 (m, 1H), 5.20-5.06 (m, 2H), 4.76 (dd, J = 8.0, 4.5 Hz, 1H), 2.55-2.46 (m, 1H), 2.43-2.29 (m, 1H), 2.27-2.12 (m, 1H).

[0164] STEP B: To a solution of 1-2 (1.4 g, 6.63 mmol, 1.0 eq.), and 1-8 (11, 1.65 g, 8.62 mmol, 1.3 eq.) in acetonitrile (30 mL) was added Cs_2CO_3 (4.32 g, 13.3 mmol, 2.0 eq.).

The resulting mixture was stirred at 60 °C for 1.5 hrs. After completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (40 mL x 2). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-3 (1.96 g, 5.13 mmol, 77%) as a colorless oil. LC-MS (ESI): m/z = 383.1 $[M+H]^+$.

[0165] STEP C: To a solution of 1-3 (3, 1.96 g, 5.13 mmol, 1.0 eq.) and 3,4-dihydro-2H-pyran (1.41 mL, 15.4 mmol, 3.0 eq.) in acetonitrile (30 mL) was added pyridin-1-ium 4-methylbenzenesulfonate (0.13 g, 0.51 mmol, 0.1 eq.). The resulting mixture was stirred at 50 °C overnight. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-4 (2.23 g, 4.78 mmol, 93%) as a light yellow oil. LC-MS (ESI): m/z = 467.2 $[M+H]^+$.

[0166] STEP D: Compound 1 (80 mg, 0.14 mmol) was prepared from 1-4 using the general route. LCMS (ESI): m/z = 485.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.92 (m, 1H), 7.51 – 7.45 (m, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 7.06 (s, 1H), 6.46 (s, 1H), 5.72 – 5.60 (m, 1H), 5.54 – 5.44 (m, 1H), 5.40 – 5.30 (m, 1H), 3.90 – 3.70 (m, 2H), 3.01 (s, 3H), 2.82 – 2.68 (m, 1H), 2.61 – 2.47 (m, 1H), 2.25 – 2.01 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.25 (s).

[0167] Compound 1 was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

[0168] Isomer 1: (Compound 3, 15.2 mg, 0.031 mmol, 43.43%) Retention time: 3.377 min, >99% ee. LC-MS (ESI): m/z = 485.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.92 (m, 1H), 7.51 – 7.45 (m, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 7.06 (s, 1H), 6.46 (s, 1H), 5.72 – 5.60 (m, 1H), 5.54 – 5.44 (m, 1H), 5.40 – 5.30 (m, 1H), 3.90 – 3.70 (m, 2H), 3.01 (s, 3H), 2.82 – 2.68 (m, 1H), 2.61 – 2.47 (m, 1H), 2.25 – 2.01 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.25 (s).

[0169] Isomer 2: (Compound 2, 13.7 mg, 0.028 mmol, 39.14%). Retention time: 4.481 min, >99% ee. LC-MS (ESI): m/z = 485.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 1H), 7.48 (M, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.21 (m, 1H), 7.04 (s, 1H), 6.46 (s, 1H), 5.70 – 5.60 (m, 1H), 5.59 – 5.42 (m, 1H), 5.42 – 5.28 (m, 1H), 3.89 – 3.71 (m, 2H), 3.01 (s, 3H), 2.81 – 2.68 (m, 1H), 2.59 – 2.46 (m, 1H), 2.23 – 2.02 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.25 (s).

[0170] Analytical method: Column: CHIRALPAK C-IG 100*4.6mm 5um; Mobile phase: A for CO_2 and B for MeOH (0.05% DEA v/v); Gradient: @ 40% B; Flow rate: 2.0 mL/min; Column temperature: 40°C.

[0171] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC, Column: ChirChiralPak C-IG, 250×30mm I.D., 5μmalPak IA, 250×20mm I.D., 5μm, Mobile phase: A for CO_2 and B for MEOH+0.1%NH3H_2O, Gradient: B 40%, Flow rate: 65mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 5.2min, Eluted time: 2 h.

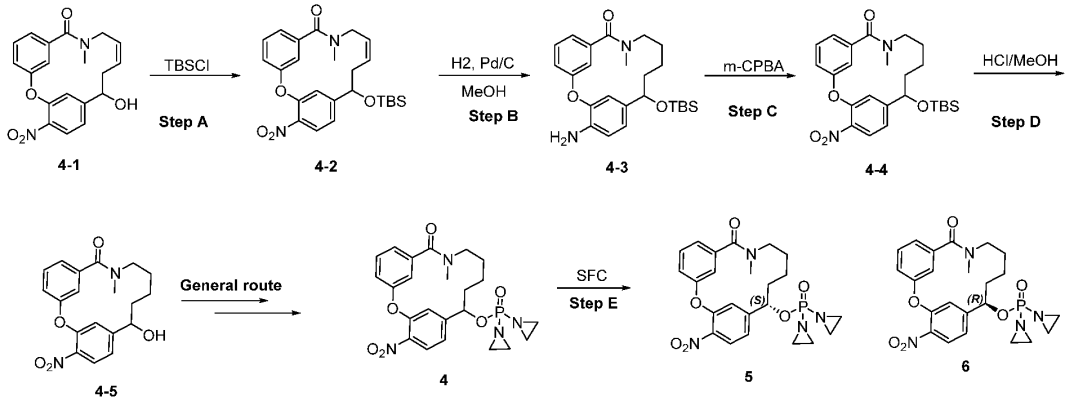
[0172] STEP E: To a solution of 1-5 (8, 6.73 mL, 72.4 mmol, 1.0 eq.) and TEA (30.2 mL, 217 mmol, 1.0 eq.) in DCM (200 mL) was added acetyl chloride (6.2 mL, 86.9 mmol, 1.0 eq.) dropwise. The resulting mixture was warmed up to room temperature and stirred for 1 hr. After completion, the reaction mixture was diluted with H_2O (200 mL) and extracted with DCM (200 mL x 2) and. The aqueous layer was acidified carefully with NaHCO3 (aq.) until the pH was adjusted to pH = 2. The resulting precipitate was collected by filtration. The wet cake was lyophilized to give 1-6 (9, 7 g, 38.9 mmol, 54%) as a white solid. LCMS (ESI): m/z = 181.1 $[M+H]^+$.

[0173] STEP F: To a solution of 1-6 (9, 2 g, 11.1 mmol, 1.0 eq.) and DMF (two drops) in DCM (30 mL) was added oxalyl chloride (1.43 mL, 16.7 mmol, 1.5 eq.) at 0°C. The resulting mixture was stirred at 0°C for 1 hr. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure acid chloride had been formed completely. After completion, the excess oxalyl chloride and solvent were removed under reduced pressure. The residue was re-dissolved in anhydrous DCM (20 mL), then added to a mixture of N-methylprop-2-en-1-amine (0.95 g, 13.3 mmol, 1.2 eq.) and triethylamine (4.63 mL, 33.3 mmol, 3.0 eq.) in anhydrous DCM (10 mL) at 0°C. The reaction was allowed to warm to room temperature, and stirred for an additional 0.5 hrs. The reaction progress was monitored by LCMS, and after completion, the reaction was quenched by adding H_2O (40 mL), and extracted with DCM (40 mL x 2). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-7 (10, 1.8 g, 7.72 mmol, 70%) as a colorless oil. LCMS (ESI): m/z = 234.1 $[M+H]^+$.

[0174] STEP G: To a solution of 1-7 (10, 500 mg, 2.14 mmol, 1.0 eq.) in THF (10 mL) was added N1,N1-dimethylpropane-1,3-diamine (0.59 mL, 5.36 mmol, 2.5 eq.).The resulting mixture was stirred at room temperature for 2 hrs. After completion, the reaction

was diluted with H_2O (30 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined and washed with HCl (20 mL, 1N), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 1-8 (11, 320 mg, 1.67 mmol, 78%) as a colorless oil. LCMS (ESI): m/z = 192.0 $[M+H]^+$.

Example 3: Preparation of Compound 4, Compound 5, and Compound 6



[0175] STEP A: A reaction is that stirred 4-1 (440 mg, 1.242 mmol), tert-butyldimethylsilyl chloride (0.54 mL, 3.104 mmol), TEA (0.52 mL, 3.725 mmol) and DBU (0.56 mL, 3.725 mmol) in DMF (8 mL) at room temperature for 2h. Then the reaction solution was added water (80 mL). The aqueous phase was extracted with EA (20 mL×3). After drying the organic phase with anhydrous sodium sulfate, the organic phase was concentrated and dried. The residue was purified by column chromatography on silica gel eluted with PE/EA (0~40%) to give 4-2 (546 mg, 1.072 mmol, 86.33%) as a yellow semi-solid. LCMS (ESI): m/z = 469.1 $[M+H]^+$.

[0176] STEP B: 4-2 (200 mg, 0.427 mmol) was dissolved in MeOH (10 mL), Pd/C 10% (0.044 mL, 0.427 mmol) was added, stirred at rt for overnight under H_2. The rection was completed. The mixture was filtered through a pad of Celite and the filter cake was washed with MeOH (10 mL×2). The combined filtrates were concentrated to dryness to give 4-3 (80 mg, 0.182 mmol, 42.54%) as white solid. LCMS (ESI): m/z = 441.2 $[M+H]^+$.

[0177] STEP C: 4-3 (140 mg, 0.318 mmol) was dissolved in 1,2-dichloroethane (5 mL), m-CPBA (0.587 mL, 1.906 mmol) was added, stirred at rt for overnight. The reaction was extracted with DCM (10 mL*2) and H_2O (15 mL), DCM layer was concentrated and purified by silica gel chromatography to give 4-4 (75 mg, 0.159 mmol, 50.16%) as pale yellow oil. LCMS (ESI): m/z = 471.3 $[M+H]^+$.

[0178] STEP D: 4-4 (110 mg, 0.234 mmol) was dissolved in HCl/MeOH (3 mL, 9.000 mmol), stirred at rt for 2hours. Desired product was detected. the reaction was concentrated and purified by silica gel chromatography to give 4-5 (70 mg, 0.196 mmol, 84.04%) as white solid. LCMS (ESI): m/z = 357.2 $[M+H]^+$.

[0179] STEP E: Compound 4 (33 mg, 0.068 mmol, 73.30%) was prepared from 4-5 using the general route as white solid. LCMS (ESI): m/z = 487.2 $[M+H]^+$. ^1H NMR(400 MHz, $CDCl_3$) δ8.02 (d, J = 8.4 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.40 – 7.29 (m, 2H), 7.24 (d, J = 7.6 Hz, 1H), 7.21 – 7.18 (m, 1H), 6.41 (s, 1H), 5.60 – 5.51 (m, 1H), 3.05 – 2.94 (m, 1H), 2.92 (s, 3H), 2.89 – 2.77 (m, 1H), 2.22 – 2.00 (m, 9H), 1.99 – 1.87 (m, 1H), 1.55 – 1.42 (m, 1H), 1.31 – 1.12 (m, 2H), 1.11 – 0.94 (m, 1H).

[0180] Compound 4 (38 mg, 0.078 mmol) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

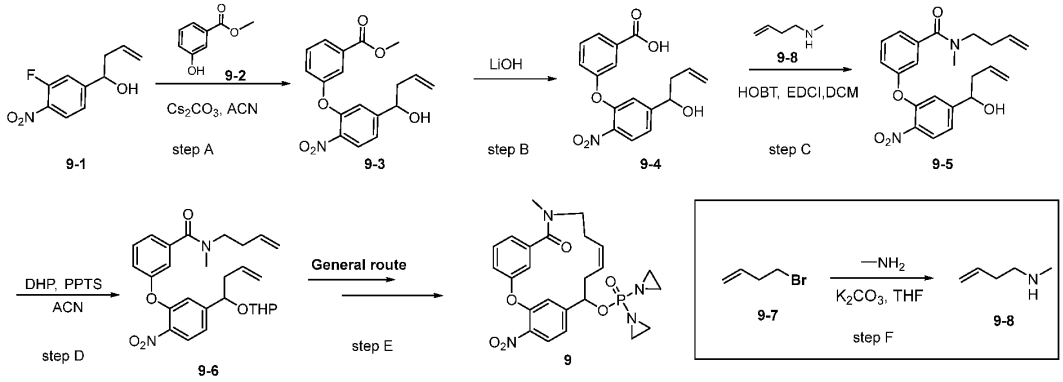
[0181] Isomer 1 (Compound 5, 10.5 mg, 0.022 mmol, 27.63%); Retention time: 3.146min, >99% ee. LC-MS (ESI): m/z 487.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.26 – 7.18 (m, 2H), 6.41 (s, 1H), 5.56 (t, J = 7.0 Hz, 1H), 3.10 – 2.73 (m, 5H), 2.23 – 1.99 (m, 9H), 1.98 – 1.85 (m, 1H), 1.53 – 1.42 (m, 1H), 1.24 – 1.13 (m, 2H), 1.10 – 0.96 (m, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.98 (s).

[0182] Isomer 2 (Compound 6, 12.1 mg, 31.8%); Retention time: 3.974 min, > 99% *ee*. LC-MS (ESI): *m/z* 487.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.43 (m, 1H), 7.41 – 7.29 (m, 2H), 7.26 – 7.17 (m, 2H), 6.41 (s, 1H), 5.56 (t, *J* = 7.0 Hz, 1H), 3.05 – 2.78 (m, 5H), 2.21 – 1.99 (m, 9H), 1.98 – 1.87 (m, 1H), 1.52 – 1.42 (m, 1H), 1.24 – 1.12 (m, 2H), 1.10 – 0.99 (m, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.98 (s).

[0183] Analytical method: Column: CHIRALPAK C-IG 100*4.6mm 5um; Mobile phase: A for CO_2 and MeOH (0.05% DEA v/v); Gradient: 40% B; Flow rate: 2.0 mL/min; Column temperature: 40 °C.

[0184] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC , Column: ChiralPak C-IG, 250×21.2 mm I.D., 5 μm, Mobile phase: A for CO_2 and B for 0.1% 7mol/L NH3 in MeOH, Gradient: B 40%, Flow rate:40mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 5.6min, Eluted time: 2 h.

Example 4: Preparation of Compound 9



[0185] STEP A: To a stirred mixture of 9-1 (2.0 g, 9.479 mmol) in MeCN (8 mL) were added 9-2 (1.73 g, 11.374 mmol) and Cs_2CO_3 (6.16 g, 18.957 mmol). The resulting mixture was stirred at r.t for overnight. TLC indicated (PE/EtOAc 3:1) the complete consumption of starting material. The reaction mixture was poured into water and then extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to afford methyl 9-3 (2 g, 5.831 mmol, 61.52%) as a yellow solid. LCMS (ESI): *m/z* = 687.0 $[2M+H]^+$.

[0186] STEP B: To solution of 9-3 (2 g, 5.825 mmol) in water (30 mL) and THF (10 mL) was added lithium hydroxide (0.73 g, 17.476 mmol). The mixture was stirred at rt for 2 hr. The reaction was completed by LC-MS analysis. The mixture was filtered and concentrated. The residue was purified by C18 column chromatography (A: H_2O, B: ACN, 50-60%B) to give 9-4 (1.8 g, 5.466 mmol, 93.83%) as a yellow solid. LCMS (ESI): *m/z* = 659.0 $[2M+H]^+$.

[0187] STEP C: To solution of 9-4 (300 mg, 0.911 mmol), EDCI (29.11 mg, 0.152 mmol) and N-methylbut-3-en-1-amine (0.897 mL, 7.240 mmol) in DCM (15 mL) was added HOBt (20.52 mg, 0.152 mmol) and TEA (0.021 mL, 0.152 mmol). The mixture was stirred at RT for 2 hr. The reaction was completed by LC-MS. The mixture was filtered and concentrated. The mixture was diluted with water and extracted with EtOAc (80 mL*3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (eluent: PE/EA=3/7) to give 9-5 (350 mg, 0.883 mmol, 96.91%) as a white liquid. LCMS (ESI): *m/z* = 397.0 $[M+H]^+$.

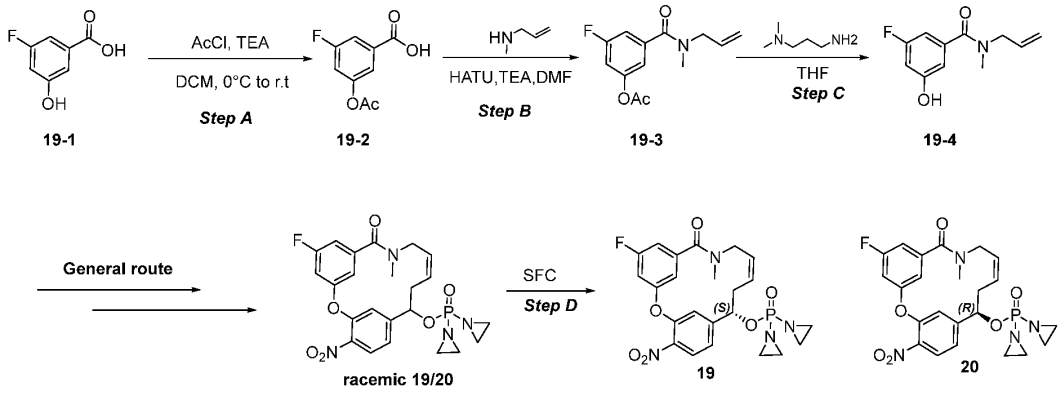
[0188] STEP D: To a solution of 9-5 (350 mg, 0.883 mmol) and 3,4-dihydro-2H-pyran (0.24 mL, 2.649 mmol, 3.0 eq.) in acetonitrile (3 mL) was added pyridin-1-ium 4-

methylbenzenesulfonate (23 mg, 0.088 mmol, 0.1 eq.). The resulting mixture was stirred at 50 °C overnight. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford 9-6 (370 mg, 0.771 mmol, 87%) as a light yellow oil. LC-MS (ESI): m/z = 480.2 $[M+H]^+$.

[0189] STEP E: Compound 9 was prepared from 9-6 using the general route. LC-MS (ESI): m/z 499.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.36 (d, J = 6.6 Hz, 1H), 7.28 (s, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.83 (s, 1H), 6.55 (s, 1H), 5.41 – 5.24 (m, 2H), 5.05 – 4.91 (m, 1H), 3.34 – 3.24 (m, 2H), 3.05 (s, 3H), 2.63 – 2.34 (m, 3H), 2.26 – 1.94 (m, 9H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.62 (s).

[0190] STEP F: To solution of 9-7 (1 g, 7.407 mmol) and K_2CO_3 (1.02 g, 7.407 mmol) in THF (50 mL) was added methylamine (37.037 mL, 74.074 mmol, 2M in THF) at -78°C. The mixture was stirred at rt for overnight under N_2. LCMS indicated that the reaction was completed. The mixture was concentrated under 15°C give crude 9-8. The crude was used directly as the next step. LCMS (ESI): *m/z* = 86.1 $[M+H]^+$.

Example 5: Preparation of Compound 19 and Compound 20



[0191] Step A: To a solution of 19-1 (3.351 mL, 32.029 mmol) and TEA (4.452 mL, 32.029 mmol) in DCM (30 mL) was added acetyl chloride (2.743 mL, 38.434 mmol) dropwise. The resulting mixture was warmed up to room temperature and stirred for 1 hr. After completion, the reaction mixture was diluted with H_2O (200 mL) and extracted with DCM (200 mL x 2), the organic phase was concentrated and dried to get the product 19-2 (5 g, 25.233 mmol, 78.78%) (crude) and used the next step directly. LC-MS (ESI): m/z = 197.1$[M-H]^-$.

[0192] step B: A solution of 19-2 (1400.00 mg, 7.065 mmol), N-methylprop-2-en-1-amine (1004.98 mg, 14.131 mmol), HATU (3223.84 mg, 8.478 mmol) and TEA (2.946 mL, 21.196 mmol) in DMF (20 mL) was stirred at room temperature for 16 hours. After

completed, LCMS showed raw material was consumed completely. The mixture was concentrated to afford the product 19-3 (1.5 g, 5.970 mmol, 84.50%) (crude) and used the next step directly. LC-MS (ESI): m/z = 252.1 $[M+H]^+$.

[0193] Step C: A mixture of 19-3 (1700 mg, 6.766mmol) and 3-(dimethylamino)propan-1-amine (2.1 mL, 16.915 mmol) in DMF (30 mL) was stirred at room temperature for 3hours. After completed, the reaction solution was added water (80 mL×3). The aqueous phase was extracted with EA (50 mL×3). After drying the organic phase with anhydrous sodium sulfate, concentrated and the residue was purified by column chromatography on silica gel eluted with PE/EA (40~80%) to give 19-4 (1.2 g, 5.736 mmol, 84.77%). LC-MS (ESI): m/z = 210.1$[M+H]^+$.

[0194] Step D: Racemic 19/20 (74 mg, 0.147 mmol, prepared from 19-4 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

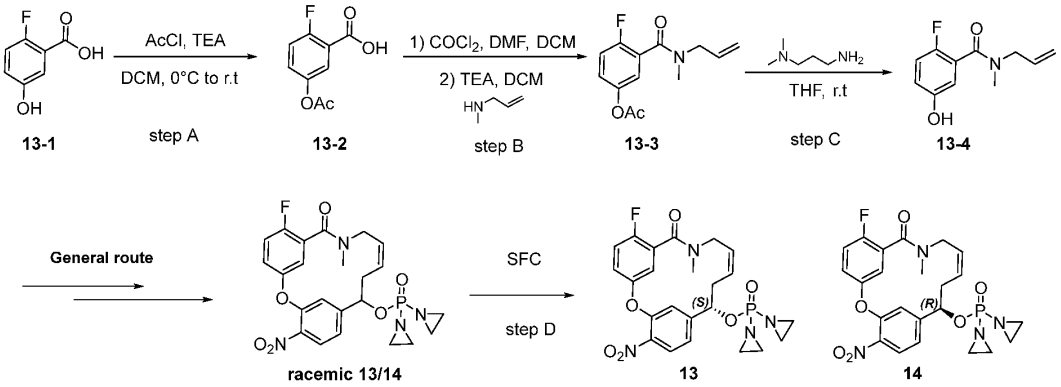
[0195] Isomer 1 (Compound 19, 34.4 mg, 46.5%); Retention time: 2.868 min, >99% ee. LC-MS (ESI): m/z = 503.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.08 (s, 1H), 7.07 – 7.02 (m, 1H), 7.01 – 6.97 (m, 1H), 6.24 (s, 1H), 5.73 – 5.65 (m, 1H), 5.57 – 5.45 (m, 1H), 5.40 – 5.27 (m, 1H), 3.91 – 3.73 (m, 2H), 3.00 (s, 3H), 2.81 – 2.71 (m, 1H), 2.61 – 2.50 (m, 1H), 2.22 – 2.05 (m, 8H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.30 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.23 (s).

[0196] Isomer 2 (Compound 20, 30.9 mg, 41.7%); Retention time: 3.258 min, >99% ee. LC-MS (ESI): m/z = 503.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.08 (s, 1H), 7.07 – 7.02 (m, 1H), 7.01 – 6.96 (m, 1H), 6.24 (s, 1H), 5.73 – 5.66 (m, 1H), 5.57 – 5.46 (m, 1H), 5.38 – 5.30 (m, 1H), 3.90 – 3.72 (m, 2H), 3.00 (s, 3H), 2.81 – 2.72 (m, 1H), 2.60 – 2.51 (m, 1H), 2.22 – 2.05 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.23 (s).

[0197] Analytical method: Column: ChiralCel OD, 100*4.6mm I.D., 3um, Mobile phase: A for CO_2 and B for ethanol (0.05% DEA), Gradient: 8 min @B 20%, Flow rate: 2.5 mL/min, Back pressure: 100 bar, Column temperature: 35°C.

[0198] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC , Column: ChiralCel OD, 250×21.2 mm I.D., 5 μm, Mobile phase: A for CO_2 and B for ETOH+0.1%MEA, Gradient: B 17%, Flow rate:40mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 5min, Eluted time: 2 h.

Example 6: Preparation of Compound 13 and Compound 14



[0199] STEP A: To solution of 13-1 (5 g, 32.029 mmol) in DCM (80 mL) was added acetyl chloride (2.51 g,32.029 mmol) and TEA (3.24 g, 32.029 mmol) at 0°C. The mixture was stirred at rt. for 1 hour under N_2. The reaction was complete detected by LC-MS, HPLC. The mixture was concentrated in vacuum and the residue was adjusted to pH=2~3 with HCl (2M), extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel to give 13-2 as a colorless liquid (3.2 g, 16.149 mmol, 50.42%). LCMS (ESI): *m/z* = 199.1 $[M+H]^+$.

[0200] STEP B: To a stirred solution of 13-2 (1 g, 5.047 mmol) in DCM (20 mL) was dropwise added oxalyl chloride (0.96 g, 7.570 mmol) via springe at rt under N_2 for 1 h. The mixture was filtered and concentrated give the crude. To a stirred solution of the crude in DCM (20 mL) was dropwise added methyl(prop-1-en-3-yl)amine (0.43 g, 6.056 mmol) at rt. TEA (1.53 g, 15.140 mmol) was added dropwise into the above mixture at rt. Then stirred the mixture for 1h. The reaction was complete detected by LCMS. The reaction mixture was quenched with saturated NH_4Cl solution and then extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel (A: dichloromethane, B: methanol, 10% B) to afford 13-3 (1.2 g, 4.776 mmol, 94.64%) as a yellow oil. LCMS (ESI): *m/z* = 252.0 $[2M+H]^+$.

[0201] STEP C: To a solution of 13-3 (1.2 g, 4.776 mmol) in THF (20 mL) was added 3-(dimethylamino)propan-1-amine (1.44 g, 9.552 mmol). The resulting mixture was stirred at room temperature for 2 hrs. After completion, the reaction was diluted with H_2O (30 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined and washed with HCl (20 mL, 1N), dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure. The residue was purified by flash column chromatography on silica gel to 13-4 (500 mg, 2.390 mmol, 50.04%) as a colorless oil. LCMS (ESI): *m/z* = 210.1 $[M+H]^+$.

[0202] STEP D: racemic 13/14 (30 mg, 0.06 mmol, prepared from 13-4 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

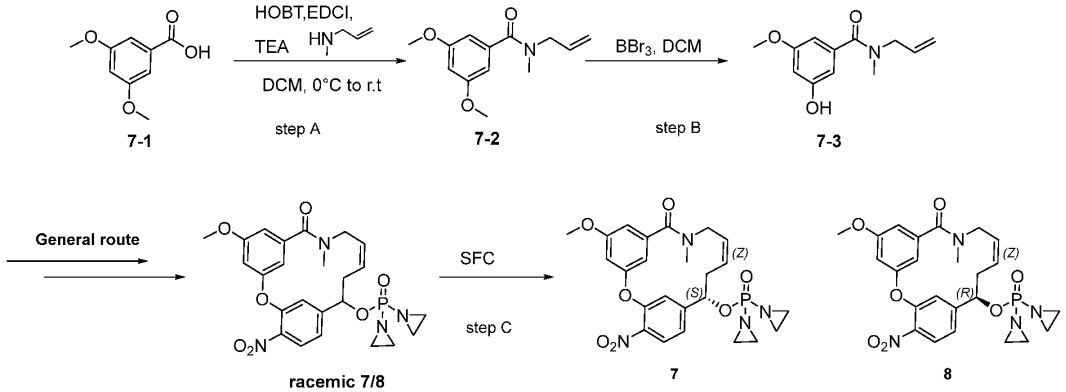
[0203] Isomer 1 (Compound 13, 7.6 mg, 25%); Retention time: 4.479 min, >99% *ee*. LC-MS (ESI): *m/z* 503.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 8.15 – 8.05 (m, 1H), 7.51 – 7.35 (m, 3H), 7.01 (s, 1H), 6.43 (s, 1H), 5.55 – 5.30 (m, 3H), 3.85 – 3.71 (m, 2H), 3.62 – 3.52 (m, 2H), 2.92 (s, 3H), 2.13 – 1.97 (m, 8H). ^{19}F NMR (376 MHz, DMSO) δ -123.99 (s). ^{31}P NMR (162 MHz, DMSO) δ 30.22 (s).

[0204] Isomer 2 (Compound 14, 8.1 mg, 27%); Retention time: 7.870 min, 90% *ee*. LC-MS (ESI): m/z 503.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 8.15 – 8.05 (m, 1H), 7.51 – 7.35 (m, 3H), 7.01 (s, 1H), 6.43 (s, 1H), 5.55 – 5.30 (m, 3H), 3.85 – 3.71 (m, 2H), 3.62 – 3.52 (m, 2H), 2.92 (s, 3H), 2.13 – 1.97 (m, 8H). ^{19}F NMR (376 MHz, DMSO) δ -124.00 (s). ^{31}P NMR (162 MHz, DMSO) δ 30.22 (s).

[0205] Analytical method: Column: 2: CHIRALPAK C-IG 100*4.6mm 5um; Mobile phase: A for CO_2 and B for IPA and 0.1% 7mol/L NH3 in MeOH; Gradient: B 50 %; Flow rate: 1.8 mL/min; Column temperature: 40 °C.

[0206] SFC Method: Instrument: Waters Thar 80 preparative SFC , Column: ChiralPak C-IG, 250×30 mm I.D., 5 μm, Mobile phase: A: CO_2 B: IPA (0.05% DEA v/v), Flow rate: 40mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 30min, Eluted time: 2 h.

Example 7: Preparation of Compound 7 and Compound 8



[0207] STEP A: To a solution of 7-1 (4.006 mL, 27.445 mmol,1 eq), HOBT (89.01 mg, 0.659 mmol, 1.2 eq) and EDCI (126.3 mg, 0.659 mmol, 1.2 eq) in DMF (5

mL) were added methyl(prop-1-en-3-yl)amine (58.56 mg, 0.823 mmol, 1.5 eq) and TEA (0.114 mL, 0.823 mmol, 1.5 eq), stirred at 20°C for 18 hr. Then the reaction solution was diluted with H_2O and extracted by EA. The organic layer was separated, washed with brine, and concentrated in vacuo. The residue was concentrated by vacuum to give 7-2 (6.0 g, 27.117 mmol, 98.80%) as a yellow solid. LCMS (ESI): *m/z* = 236.0 $[M+H]^+$.

[0208] STEP B: To a solution of 7-2 (5.5 g, 23.376 mmol, 1 eq) in DCM (30 mL) was added BBr_3 (2.652 mL, 28.052 mmol, 1.2 eq) and then stirred at 20°C for 3 hr. The reaction solution was quenched with saturated $NaHCO_3$ solution and extracted by DCM. The organic layer was separated, washed with brine, and concentrated in vacuo. The residue was concentrated by C18 column to give 7-3 (1.2 g, 5.423 mmol, 23.20%) as a yellow solid. LCMS (ESI): *m/z* = 222.0 $[M+H]^+$.

[0209] STEP C: Racemic 7/8 (60 mg, 0.117 mmol, prepared from 7-3 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

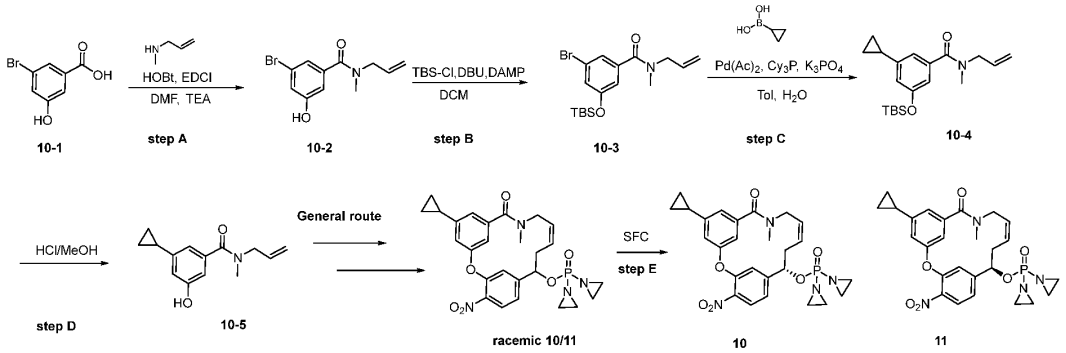
[0210] Isomer 1 (Compound 7, 21.4 mg, 0.025 mmol, 16.25%); Retention time: 1.447 min, 100 % ee. LC-MS (ESI): m/z 515.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.86 (m, 1H), 7.32 – 7.27 (m, 1H), 7.07 (s, 1H), 6.86 (s, 1H), 6.79 (s, 1H), 6.02 (s, 1H), 5.76 – 5.59 (m, 1H), 5.57 – 5.45 (m, 1H), 5.42 – 5.28 (m, 1H), 3.95 – 3.73 (m, 5H), 3.07 – 2.93 (m, 3H), 2.84 – 2.62 (m, 1H), 2.62 – 2.44 (m, 1H), 2.29 – 2.00 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.21 (s).

[0211] Isomer 2 (Compound 8, 21.4 mg, 0.024 mmol, 15.63%); Retention time: 1.974 min, 100% ee. LC-MS (ESI): m/z 515.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.84 (m, 1H), 7.37 – 7.27 (m, 1H), 7.07 (s, 1H), 6.89 – 6.74 (m, 2H), 6.02 (s, 1H), 5.74 – 5.58 (m, 1H), 5.56 – 5.40 (m, 1H), 5.40 – 5.24 (m, 1H), 3.91 – 3.71 (m, 5H), 3.09 – 2.90 (m, 3H), 2.84 – 2.62 (m, 1H), 2.62 – 2.44 (m, 1H), 2.30 – 2.00 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.21 (s).

[0212] Analytical method: Retention time: Method 1: Column: CHIRALPAK IH 100*4.6mm 5um; Mobile phase: A for CO_2 and B for MeOH (0.05% DEA v/v) Gradient: 8 min @ B 30%; Flow rate: 2.5 mL/min; Column temperature: 40°C.

[0213] SFC Method: Instrument: Waters Thar 80 preparative SFC ; Column: ChiralPak IH, 250×30 mm I.D., 5 μm; Mobile phase: A for CO_2 and B for 0.1% 7mol/L NH3 in MeOH; Gradient: B 30%; Flow rate: 40 mL/min; Back pressure: 100 bar; Column temperature: 35°C; Wavelength: 220 nm ; Cycle-time: 10 min; Eluted time: 2 h.

Example 8: Preparation of Compound 10 and Compound 11



[0214] STEP A: To a solution of 10-1 (2.5 g, 11.520 mmol, 1.0 eq) in DMF (30 mL) was added HOBt (1.87 g, 13.824 mmol, 1.2 eq) and EDCI (2.65 g, 13.824 mmol, 1.2 eq) at 0°C, and the mixture was stirred at 0°C for 15 min. methyl(prop-2-enyl)amine (1.23 g, 17.280 mmol, 1.5 eq) and TEA (2.4 mL, 17.280 mmol, 1.5 eq) was added into the mixture and stirred 25°C for 12 hrs. LCMS showed that the reaction was completed, quenched with H_2O (200 mL), extracted with EA (70 mL x 3), the organic solution was dried over Na_2SO_4, filtered, the solution was concentrated under vacuum, the crude product was purified by silica gel column [EA:PE=30%-60%] to give 10-2 (3.1 g, 11.476 mmol, 99.62%) as a yellow oil. LCMS (ESI): *m/z* = 270.1 $[M+H]^+$.

[0215] STEP B: To a solution of 10-2 (3.1 g, 11.476 mmol, 1.0 eq) and DMAP (0.03 g, 0.230 mmol, 0.02 eq) in DCM (40 mL) was added TBSCI (2.585 mL, 14.919 mmol, 1.3 eq) and DBU (2.229 mL, 14.919 mmol, 1.3 eq) at 25°C, the mixture was stirred at 25°C for 2 hrs. LCMS showed that the reaction was completed. quenched with H_2O (100 mL), extracted with DCM (50 mL x 3), the organic solution was dried over Na_2SO_4, filtered, concentrated under vacuum, the crude product was purified by silica gel column [EA:PE=0%-40%], give 10-3 (4.0 g, 10.406 mmol, 90.68%) as a yellow oil. LCMS (ESI): m/z = 386.1 $[M+H]^+$.

[0216] STEP C: To a solution of 10-3 (3.5 g, 9.105 mmol, 1.0 eq) and cyclopropylboronic acid (1.02 g, 11.837 mmol, 1.3 eq) in toluene (50 mL) and H_2O (10 mL) was added $Pd(OAc)_2$ (0.10 g, 0.455 mmol,0.05), tricyclohexylphosphane (0.26 g, 0.911 mmol,0.1 eq) and K_3PO_4 (5.80 g, 27.316 mmol,3.0 eq) at 25°C under N_2 atmosphere. The mixture was heated to 100°C and stirred at 100°C for 12 hrs. under N_2 atmosphere. LCMS showed that the reaction was completed, quenched with H_2O (200 mL), extracted with EA (50 mL x 3), the organic solution was dried over Na_2SO_4, filtered, the solution was concentrated under vacuum, the crude product was purified by silica gel column

[EA:PE=20%-40%], give 10-4 (1.3 g, 3.762 mmol, 41.32%) as a colorless oil. LCMS (ESI): *m/z* = 346.2 $[M+H]^+$.

[0217] STEP D: To a solution of 10-4 (1.3 g, 3.762 mmol, 1.0 eq) in MeOH (10 mL) was added 4M HCl/MeOH (10 mL) at 25°C, and stirred at 25°C for 2 hrs. LCMS showed that the reaction was completed and desired product was found. Then the mixture was concentrated under reduced pressure, the crude product was purified by silica gel column [EA:PE=0%-70%] to give 10-5 (820 mg, 3.545 mmol, 94.24%) as a yellow oil. LCMS (ESI): *m/z* = 232.1 $[M+H]^+$.

[0218] STEP E: Racemic 10/11 (220 mg, prepared from 10-5 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

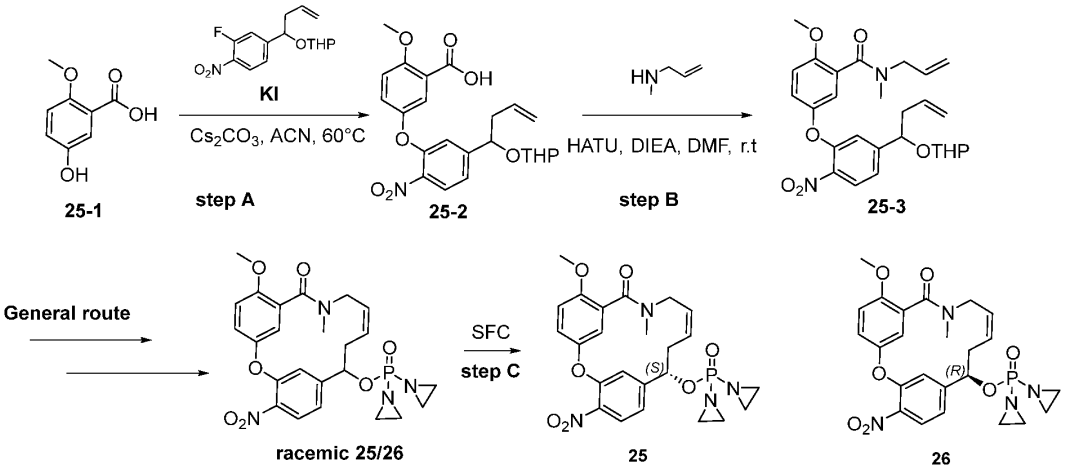
[0219] Isomer 1 (Compound 10, 80 mg, 36%); Retention time: 2.946 min, >99% ee. LC-MS (ESI): m/z 525.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.26 – 7.23 (m, 1H), 7.06 – 7.03 (m, 1H), 7.01 – 6.98 (m, 1H), 6.96 – 6.94 (m, 1H), 6.23 – 6.20 (m, 1H), 5.69 – 5.61 (m, 1H), 5.54 – 5.44 (m, 1H), 5.38 – 5.30 (m, 1H), 3.89 – 3.69 (m, 2H), 2.99 (s, 3H), 2.80 – 2.48 (m, 2H), 2.21 – 2.01 (m, 8H), 1.99 – 1.91 (m, 1H), 1.10 – 1.00 (m, 2H), 0.86 – 0.74 (m, 2H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.21 (s).

[0220] Isomer 2 (Compound 11, 80 mg, 36%); Retention time: 3.473 min, >99% ee. LC-MS (ESI): m/z 525.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.26 – 7.25 (m, 1H), 7.06 – 7.03 (m, 1H), 7.00 – 6.98 (m, 1H), 6.97 – 6.93 (m, 1H), 6.24 – 6.18 (m, 1H), 5.69 – 5.61 (m, 1H), 5.54 – 5.44 (m, 1H), 5.39 – 5.29 (m, 1H), 3.88 – 3.68 (m, 2H), 2.99 (s, 3H), 2.80 – 2.47 (m, 2H), 2.22 – 2.00 (m, 9H), 1.97 – 1.90 (m, 1H), 1.08 – 0.99 (m, 2H), 0.83 – 0.78 (m, 2H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.21 (s).

[0221] Analytical method: Column: 2: CHIRALPAK IH 100*4.6mm 5um; Mobile phase: A for CO_2 and B for ethanol (0.05%DEA); Gradient: 8 min @ 20% B; Flow rate: 2.5 mL/min; Column temperature: 40°C.

[0222] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC , Column: ChiralCel OD, 250×21.2mm I.D., 5μm, Mobile phase: A for CO_2 and B for 0.1% 7mol/L NH3 in EtOH, Gradient: B 20%, Flow rate:40mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 254 nm, Cycle-time: 10.8 min, Eluted time: 4 h.

Example 9: Preparation of Compound 25 and Compound 26



[0223] STEP A: To a solution of 25-1 (0.95 g, 5.650 mmol,1.0 eq) and KI (1.67 g, 5.650 mmol,1.0 eq) in ACN (15 mL)was added Cs_2CO_3 (3.68 g, 11.299 mmol, 2.0 eq). The reaction was stirred at 60°C for 1 hrs. LC-MS showed the reaction was complete. The reaction was cooled to room temperature and purified by C18 column to give 25-2 (1.45 g, 3.270 mmol, 57.88%) as a yellow solid. LCMS (ESI): *m/z* = 466.1 $[M+Na]^+$; 442.1$[M-H]^-$.

[0224] STEP B: To a solution of 25-2 (1.2 g, 2.706 mmol,1.0 eq) in DMF (20 mL) was added HOBt (0.40 g, 2.977 mmol,1.1 eq) and EDCI (0.57 g, 2.977 mmol, 1.1 eq) at 25°C and stirred at 25°C for 10 min. methyl(prop-1-en-3-yl)amine (0.21 g, 2.977 mmol, 1.1 eq) was added into mixture and stirred at 25°C for 30 min. LCMS showed that the reaction was completed, quenched with H_2O (200 mL), extracted with EA (30 mL x 3), the organic solution was dried over Na_2SO_4, filtered, the solution was concentrated under vacuum, the crude product was purified by silica gel column [DCM: MeOH=0%-10%], give 25-3 (1.0 g, 2.014 mmol, 74.42%) as a yellow oil. LCMS (ESI): *m/z* = 497.2 $[M+H]^+$.

[0225] STEP C: Racemic 25/26 (90 mg, prepared from 25-3 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

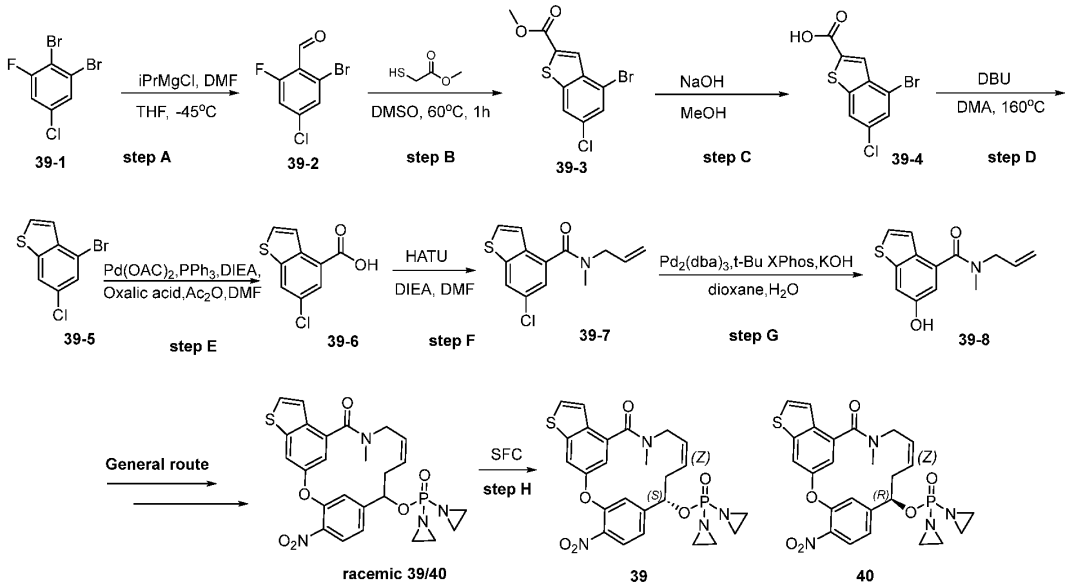
[0226] Isomer 1 (Compound 25, 41 mg, 45%); Retention time: 3.490 min, >99% ee. LC-MS (ESI): m/z 515.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.83 (m, 1H), 7.43 – 7.37 (m, 1H), 7.27 – 7.23 (m, 1H), 7.04 – 6.91 (m, 2H), 6.56 – 6.45 (m, 1H), 6.45 (s, 1H), 5.77 – 5.45 (m, 1H), 5.44 – 5.15 (m, 2H), 3.87 (d, J = 8.2 Hz, 3H), 3.70 – 3.58 (m, 1H), 3.04 (d, J = 9.2 Hz, 3H), 2.94 (t, J = 16.6 Hz, 1H), 2.38 – 1.92 (m, 10H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.71 (s), 30.72 (s).

[0227] Isomer 2 (Compound 26, 45 mg, 50%); Retention time: 5.176 min, 98.7% ee. LC-MS (ESI): m/z 515.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.85 (m, 1H), 7.44 – 7.36 (m, 1H), 7.26 – 7.21 (m, 1H), 7.05 – 6.92 (m, 2H), 6.55 – 6.45 (m, 1H), 6.45 (s, 1H), 5.74 – 5.47 (m, 1H), 5.44 – 5.13 (m, 2H), 3.87 (d, J = 8.3 Hz, 3H), 3.72 – 3.61 (m, 1H), 3.04 (d, J = 9.2 Hz, 3H), 3.00 – 2.86 (m, 1H), 2.39 – 1.92 (m, 10H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.69 (s), 30.71 (s).

[0228] Analytical method: Column: ChiralPak IC, 100*4.6mm I.D., 3um; Mobile phase: A for CO_2 and B for ethanol (0.05%DEA); Gradient: 8 min @ 50% B; Flow rate: 1.8 mL/min; Column temperature: 35 °C.

[0229] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC , Column: ChiralPak IC, 250×20mm I.D., 5μm, Mobile phase: A for CO_2 and B for MEOH, Gradient: B 50%, Flow rate:60mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 25 min, Eluted time: 4 h.

Example 10: Preparation of Compound 39 and Compound 40



[0230] STEP A: To a stirred solution of 39-1 (25 g, 86.703 mmol,1.0 eq) in N-hexane (120 mL) and THF (70 mL) was added i-Pr-MgCl (95.4 mL, 95.374 mmol) at -40°C for 30 min, DMF (34.9 mL, 433.516 mmol) was added into mixture, the mixture was stirred at -40°C for 20 min. LCMS showed that the reaction was completed. 2N HCl (250 mL) was added to the solution, the solution was extracted with EA (150 mL x 3), the organic solution was dried over Na_2SO_4, the solids were filtered out, the solution was concentrated under

vacuum, the crude product was purified by silica gel column [EA:PE=0%-5%] to give 39-2 (14 g, 58.960 mmol, 68.00%) as a white solid.

[0231] STEP B: To a solution of 39-2 (16 g, 67.383 mmol, 1.0 eq) in DMSO (300 mL) was added TEA (9.4 mL, 67.383 mmol, 2.0 eq) at 25°C and stirred at 25 -°C for 30 min. methyl sulfanylacetate (14.30 g, 134.765 mmol, 2.0 eq) was added into mixture at 25°C. After the additional, the mixture was heated to 60°C and stirred at 60 °C for 12 hrs. LCMS showed that the reaction was completed. quenched with H_2O (800 mL), extracted with EA (70 mL x 3), the organic solution was dried over Na_2SO_4, filtered, the solution was concentrated under vacuum. The crude product was purified by silica gel column [EA:PE=0%-20%] to give 39-3 (10 g, 32.726 mmol, 48.57%) as a yellow solid. LCMS (ESI): m/z = 305 $[M+H]^+$.

[0232] STEP C: To a solution of 39-3 (9 g, 29.453 mmol, 1.0 eq) in MeOH (100 mL) was added NaOH (3.53 g, 88.359 mmol,3.0 eq) at 25°C and the resulting mixture was heated to 60°C stirred at 60 °C for 3 hrs. After completion, the reaction mixture was added with HCl (2 N) until the pH was adjusted to pH = 4-5. The resulting mixture was diluted with H_2O (300 mL) and extracted with DCM (80 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The crude product was purified by silica gel column [EA:PE=40%-60%] to give 39-4 (5.1 g, 17.493 mmol, 59.39%) as a yellow solid. LCMS (ESI): m/z =291 $[M+H]^+$.

[0233] STEP D: To a solution of 39-4 (5.1 g, 17.493 mmol,1.0 eq) in DMA (100 mL) was added DBU (13.32 g, 87.467 mmol, 5.0 eq) at 25 °C, the mixture was heated 160°C and stirred at 160°C for 24 hrs. LCMS showed that the reaction was completed and desired product was found. H_2O (300 mL) was added to the solution, the solution was extracted with EA (80 mL x 3), the organic solution was dried with Na_2SO_4, the solids were filtered out, the solution was concentrated under vacuum, the crude product was purified by silica gel column [EA:PE=0%-2%] to give 39-5 (3 g, 12.120 mmol, 69.28%) as a white solid. LCMS (ESI): m/z = 245 $[M-H]^-$.

[0234] STEP E: To a solution of 39-5 (1400 mg, 5.656 mmol,1.0 eq), Pd(OAc)2 (253.96 mg, 1.131 mmol, 0.2 eq), PPh_3 (890 mg, 3.394 mmol, 0.6 eq), oxalic acid (2240 mg, 24.886 mmol, 4.4 eq), DIEA (3947 mg, 30.542 mmol, 5.4 eq) and Ac_2O (2136 mg, 20.927 mmol, 3.7 eq) in DMF (30 mL), stirred at 100 °C for overnight under N_2,the mixture was add H_2O (100 ml) adjusted PH to 9 with K_2CO_3, extracted with EA (40mL*2) and discarded, the water layer was adjusted PH to 1~2 with HCl(12 N), extracted with EA (40 mL*3), the EA

layer was washed with brine (40 mL*2) and dried over Na_2SO_4, concentrated to give 39-6 (620 mg, 2.916 mmol, 51.55%) as white solid. LCMS (ESI):*m/z* = 211 $[M-H]^-$.

[0235] STEP F: To a solution of 39-6 (500 mg, 2.351 mmol, 1.0 eq), methyl(prop-2-enyl)amine (250 mg, 3.527 mmol, 1.5 eq), HATU (1072 mg, 2.822 mmol, 1.2 eq) and DIEA (911.71 mg, 7.054 mmol, 3.0 eq) in DMF (10 mL), stirred at rt for 1 hour. The reaction was purified by C18 column to give 39-7 (550 mg, 2.070 mmol, 88.02%) as colorless oil. LCMS (ESI): *m/z* = 266.1 $[M+H]^+$.

[0236] STEP G: To a solution of 39-7 (500 mg, 1.881 mmol,1.0 eq), $Pd_2(dba)_3$ (172mg, 0.188 mmol, 1.0 eq), ^{t}BuXPhos (159 mg, 0.376 mmol, 0.2 eq) and KOH (147mg, 2.634 mmol, 1.4 eq) in dioxane (50 mL) and H_2O (10 mL), stirred at 100°C for overnight. The mixture was purified by C18 column to give 39-8 (400 mg, 1.617 mmol, 85.96%) as white solid. LCMS (ESI): *m/z* = 467.3 $[M+H]^+$.

[0237] STEP H: Racemic 39/40 (60 mg, prepared from 39-8 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

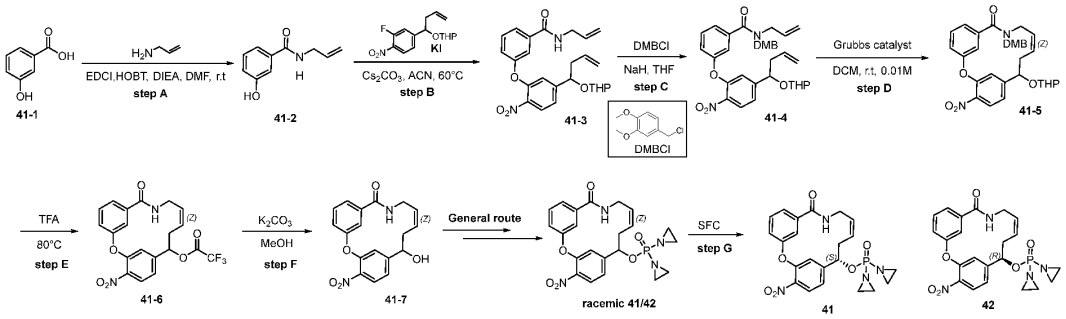
[0238] Isomer 1 (Compound 39, 12 mg, 20%); Retention time: 1.678 min, >99% ee. LC-MS (ESI): m/z 541.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.94 (m, 1H), 7.86 – 7.77 (m, 1H), 7.57 – 7.44 (m, 1H), 7.36 – 7.31 (m, 1H), 7.27 – 7.26 (m, 2H), 7.05 – 6.81 (m, 1H), 6.79 – 6.53 (m, 1H), 5.71 – 5.53 (m, 1H), 5.48 – 5.07 (m, 2H), 3.87 – 3.66 (m, 2H), 3.14 (d, J = 26.6 Hz, 3H), 2.88 – 2.38 (m, 2H), 2.23 – 2.01 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.18 (s), 30.60 (s).

[0239] Isomer 2 (Compound 40, 7 mg, 12%); Retention time: 3.148 min, 98.5% ee. LC-MS (ESI): m/z 541.4 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.89 (m, 1H), 7.85 – 7.71 (m, 1H), 7.56 – 7.42 (m, 1H), 7.39 – 7.30 (m, 1H), 7.29 – 7.24 (m, 2H), 7.07 – 6.83 (m, 1H), 6.62 – 6.45 (m, 1H), 5.69 – 5.50 (m, 1H), 5.46 – 5.21 (m, 2H), 3.94 – 3.61 (m, 2H), 3.11 (s, 3H), 2.89 – 2.33 (m, 2H), 2.28 – 1.95 (m, 9H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.17 (s).

[0240] Analytical method: Column: 3: CHIRALPAK IH 5um 4.6*100mm; Mobile phase: A for CO_2 and B for ethanol (0.05%DEA); Gradient: 8 min @ 40% B; Flow rate: 2.0 mL/min; Column temperature: 40°C.

[0241] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC , Column: ChiralPak IH, 150×20mm I.D., 5μm, Mobile phase: A for CO_2 and B for MEOH+0.1%NH3H_2O, Gradient: B 40%, Flow rate:40mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 10 min, Eluted time: 2 h.

Example 11: Preparation of Compound 41 and Compound 42



[0242] STEP A: A solution of 41-1 (5 g, 36.200 mmol, 1.0 eq.), prop-2-en-1-amine (2.48 g, 43.440 mmol, 1.2 eq.), EDCI (10.41 g, 54.301 mmol, 1.5 eq.), HOBT (7.34 g, 54.301 mmol, 1.5 eq.) and DIEA (18 mL, 108.601 mmol, 3.0 eq.) in DMF (50 mL) at room temperature. the mixture was stirred for 4h. After completion, the reaction mixture was quenched with aq. NH_4Cl (20 mL) at 0°C, the aqueous layer was extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure, the residue was purified by flash chromatography to give 41-2 (5 g, 28.217 mmol, 77.95%) as a white solid. LCMS (ESI): m/z = 178.2 $[M+H]^+$.

[0243] STEP B: A solution of KI (1.8 g, 6.095 mmol, 1.0 eq.), 41-2 (1.30 g, 7.314 mmol, 1.2 eq.) and Cs_2CO_3 (3.97 g, 12.191 mmol, 2.0 eq.) in ACN (30 mL) was heated at 60°C and stirred for 1h. After completion, the reaction mixture was cooled to room temperature, filtered through a short pad of Celite®, the filtrate was diluted with EtOAc (50 mL), washed with brine (50 mL), dried over Na_2SO_4, concentrated under reduced pressure, the residue was purified by flash chromatography to give 41-3 (2.5 g, 5.525 mmol, 90.64%) as a white solid. LCMS (ESI): m/z = 453.2 $[M+H]^+$.

[0244] STEP C: To a solution of 41-3 (2.87 g, 6.342 mmol, 1.0 eq.) in THF (10 mL) was added NaH (0.51 g, 12.685 mmol, 2.0 eq.) at 0°C, after 30 min, 3,4-dimethoxybenzyl chloride (2.37 g, 12.685 mmol, 2.0 eq.) was added into the reaction, and the resulting mixture was allowed warm to room temperature and stirred for 1h. After completion, the reaction was quenched by the addition of water (20 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 41-4 (1.04 g, 1.727 mmol, 27.23%) as a colorless oil. LCMS (ESI): m/z = 603.3 $[M+H]^+$.

[0245] STEP D: A solution of 41-4 (1.04 g, 1.727 mmol, 1.0 eq.) and Grubbs 2nd catalyst (0.15 g, 0.173 mmol, 0.1 eq.) in DCM (50 mL) under N_2, the mixture was stirred at

room temperature for overnight. After completion, the reaction mixture was concentrated under reduced pressure, the residue was purified by flash chromatography to give 41-5 (700 mg, 1.219 mmol, 70.59%) as a white solid. LCMS (ESI): m/z = 437.1 $[M+H]^+$.

[0246] STEP E: A solution of 41-5 (500 mg, 0.871 mmol, 1.0 eq.) in TFA (10 mL) was hated 80°C and stirred for overnight. After completion, the reaction mixture was concentrated under reduced pressure, the residue was purified by flash chromatography to give 41-6 (300 mg, 0.688 mmol, 78.96%) as a white solid. LCMS (ESI): m/z = 437.1 $[M+H]^+$.

[0247] STEP F: A solution of 41-6 (300 mg, 0.688 mmol, 1.0 eq.) and K_2CO_3 (190.04 mg, 1.375 mmol, 2.0 eq.) in MeOH (5 mL) was stirred at RT for 1h. After completion, the reaction mixture was cooled to room temperature, filtered through a short pad of Celite®, the filtrate was diluted with EtOAc (30 mL), washed with brine (30 mL), dried over Na_2SO_4, concentrated under reduced pressure, the residue was purified by flash chromatography to give 41-7 (130 mg, 0.382 mmol, 55.56%) as a white solid. LCMS (ESI): m/z = 341.1 $[M+H]^+$.

[0248] STEP G: Racemic 41/42 (50 mg, prepared from 41-7 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

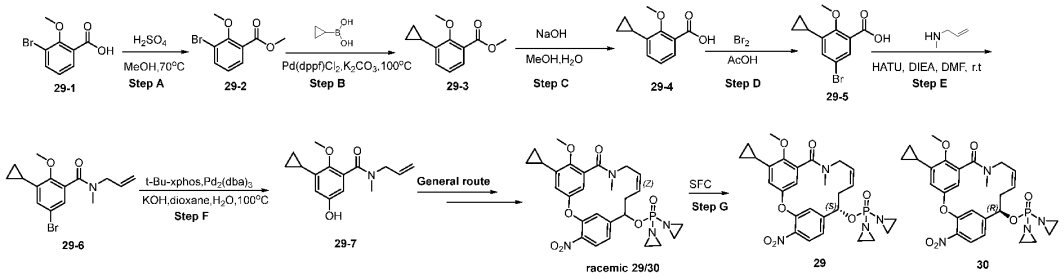
[0249] Isomer 1 (Compound 41, 14.3 mg, 0.024 mmol, 28.6%); Retention time: 2.438 min, >99% ee. LC-MS (ESI): m/z = 471.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.93 (m, 1H), 7.59 – 7.48 (m, 1H), 7.42 – 7.33 (m, 1H), 7.32 – 7.28 (m, 2H), 7.11 (s, 1H), 6.74 – 6.51 (m, 1H), 6.51 – 6.38 (m, 1H), 5.72 – 5.62 (m, 1H), 5.54 – 5.44 (m, 1H), 5.38 – 5.21 (m, 1H), 3.84 – 3.67 (m, 2H), 2.80 – 2.63 (m, 1H), 2.61 – 2.44 (m, 1H), 2.24 – 2.03 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.20 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.65 (s).

[0250] Isomer 2 (Compound 42, 16 mg, 0.024 mmol, 32.0%); Retention time: 3.594 min, >99% ee. LC-MS (ESI): m/z = 471.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.93 (m, 1H), 7.59 – 7.48 (m, 1H), 7.42 – 7.33 (m, 1H), 7.32 – 7.28 (m, 2H), 7.11 (s, 1H), 6.74 – 6.51 (m, 1H), 6.51 – 6.38 (m, 1H), 5.72 – 5.62 (m, 1H), 5.54 – 5.44 (m, 1H), 5.38 – 5.21 (m, 1H), 3.84 – 3.67 (m, 2H), 2.80 – 2.63 (m, 1H), 2.61 – 2.44 (m, 1H), 2.24 – 2.03 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.20 (s).

[0251] Analytical method: Column: ChiralPak C-IH, 100×4.6mm I.H., 5μm; Mobile phase: A for CO_2 and B for methanol (0.05%DEA); Gradient: 8 min @ 40% B; Flow rate: 2 mL/min; Column temperature: 40 °C.

[0252] SFC method: Instrument: SHIMADZU PREP SOLUTION SFC, Column: ChiralPak IH, 250×20mm I.D., 5μm, Mobile phase: A for CO_2 and B for MEOH(0.1% 7mol/L NH3 in MeOH), Gradient: B 40%, Flow rate: 40 mL/min, Back pressure: 100 bar, Column temperature: 30°C, Wavelength:220nm, Cycle-time:10 min, Eluted time: 2 h.

Example 12: Preparation of Compound 29 and Compound 30



[0253] STEP A: To a solution of 29-1 (2.5 g, 10.8 mmol) in 50 mL of methanol was added dropwise con. sulfuric acid (5 mL) and the mixture was stirred at reflux overnight. The reaction is quenched in a saturated $NaHCO_3$ saturated solution and the aqueous phase was extracted with DCM (x 3). The residue was purified by flash column chromatography on silica gel to afford methyl 29-2 (2.4 g, 9.8 mmol, 90.4 %). ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 6H), 7.04 (t, J = 7.9 Hz, 1H), 7.70 - 7.77 (m, 2H).

[0254] STEP B: A solution of methyl 29-2 (1 g, 4.080 mmol), cyclopropylboranediol (0.35 g, 4.080mmol), K_3PO_4 (551.23 mg, 2.597 mmol), tricyclohexyl phosphine (46.30 mg, 0.130 mmol), $Pd(OAc)_2$ (14.58 mg, 0.065 mmol) in toluene (10 mL) was added H_2O (2 mL), the reaction mixture was stirred at 110°C under N_2 overnight. The mixture was poured into ice water, extracted with DCM (50ml), the combined organic layers washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography to give 29-3 (0.6 g.2.9 mmol,72.5%) as a white solid. LCMS (ESI): *m/z* = 207 $[M+H]^+$.

[0255] STEP C: A solution of 29-3 (2 g, 9.697 mmol) in MeOH (10 mL) was added NaOH solution (5 mL, 2M), the reaction mixture was stirred at 50°C for 4 hours. The reaction mixture wasadded3mol/l HCl to Ph =3~4, extracted with EA (50ml), the combined organic layers washed with brine, dried over Na_2SO_4.filtered and concentrated to give 29-4 (1.8 g, 9.365 mmol, 96.57%) as a whited solid. LCMS (ESI): *m/z* = 193 $[M+H]^+$.

[0256] STEP D: A solution of 29-4 (150 mg, 0.780 mmol) in AcOH (10 mL) was added Br_2 (249 mg, 1.561 mmol), the mixture was stirred at room for 3 hours. The mixture was poured into ice water, extracted with DCM (50ml), the combined organic layers washed

with brine, dried over Na_2SO_4, filtered and concentrated. the crude product was purified by silica gel chromatography to give 29-5 (100 mg, 0.369 mmol, 47.27%) as a white solid. LCMS (ESI): *m/z* = 271 $[M+H]^+$.

[0257] STEP E: A solution of 29-5 (1.5 g, 5.533 mmol), methyl(prop-2-enyl)amine (0.79 g,11.066 mmol), HATU (365 mg, 0.959 mmol), and DIEA (191 mg, 1.475 mmol) in DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was purity with prep-HPLC to give 29-6 (1.2 g, 3.701 mmol, 66.90%) as a white solid. LCMS (ESI): *m/z* = 324 $[M+H]^+$.

[0258] STEP F: A solution of 29-6 (1.2 g, 3.701 mmol), t-Bu-XPhos (0.16 g, 0.370 mmol), $Pd_2(dba)_3$ (0.34 g, 0.370 mmol), KOH (0.29 g, 5.181 mmol), H_2O (1 mL) in dioxane (5 mL), the reaction mixture was stirred at 100°C under N_2 overnight. The mixture was poured into ice water, extracted with DCM (50ml), the combined organic layers washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography to give 29-7 (800 mg, 3.061 mmol, 82.71%) as a white solid. LCMS (ESI): *m/z* = 262 $[M+H]^+$.

[0259] STEP G: Racemic 29/30 (80 mg, 0.14 mmol, prepared from 29-7 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

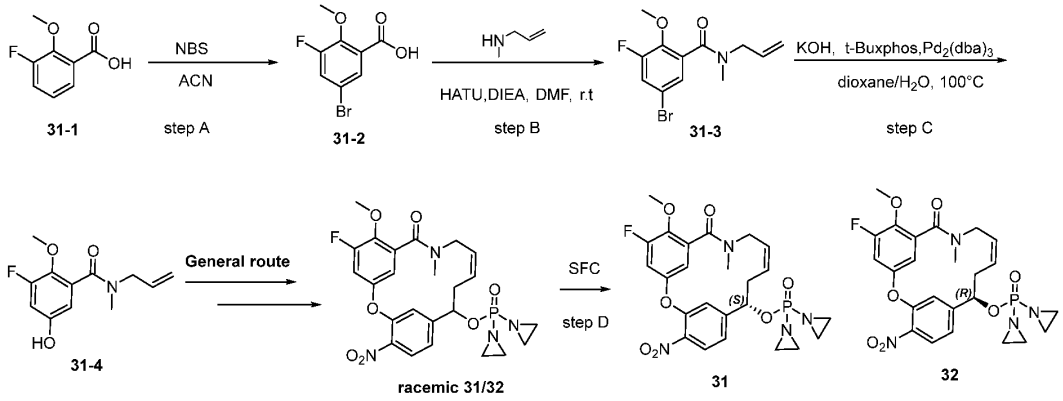
[0260] Isomer 1 (Compound 29, 30.1 mg, 37.6%); Retention time:2.64 min, >99% ee. LC-MS (ESI): m/z 555.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00-7.87 (m, 1H), 7.42 & 7.08 – 6.95 (m, 1H),7.08 – 6.95& 6.73 (m, 1H), 6.56 (s, 1H), 6.16 (d, J = 3.0 Hz, 1H), 5.80 – 5.12 (m, 3H), 4.00 – 3.78 (m, 4H), 3.74 – 3.58(m, 1H), 3.04 (d, J = 8.1 Hz, 3H), 2.99-2.91 (m, 1H), 2.39 – 1.90 (m, 10H), 1.10 (d, J = 7.0 Hz, 2H), 0.92-0.85 (m, 1H), 0.78 – 0.60 (m, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.69 (s)&30.77(s).

[0261] Isomer 2 (Compound 30, 29.2 mg, 36.5%); Retention time:3.952 min, 94.6% ee. LC-MS (ESI): m/z 555.2 $[M+H]^+$; ^1H NMR(400 MHz, $CDCl_3$) δ 8.00-7.87 (m, 1H), 7.42 & 7.08 – 6.95 (m, 1H),7.08 – 6.95& 6.73 (m, 1H), 6.56 (s, 1H), 6.16 (d, J = 3.0 Hz, 1H), 5.80 – 5.12 (m, 3H), 4.00 – 3.78 (m, 4H), 3.74 – 3.58(m, 1H), 3.04 (d, J = 8.1 Hz, 3H), 2.99-2.91 (m, 1H),, 2.39 – 1.90 (m, 10H), 1.10 (d, J = 7.0 Hz, 2H), 0.92-0.85 (m, 1H), 0.78 – 0.60 (m, 1H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.68 (s)&30.76(s).

[0262] Analytical method: Column: CHIRALPAK C-IG 5um 4.6*100mm; Mobile phase: A: CO_2, B: MEOH+0.05%DEA; Gradient: B 40%; Flow rate: 2.0 mL/min; Column temperature: 40°C.

[0263] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC, Column: ChiralPak C-IG, 250×20mm I.D., 5μm, Mobile phase: A for CO_2 and B for MEOH+0.01MEA, Gradient: B 40%, Flow rate:40mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 9min, Eluted time: 2 h.

Example 13: Preparation of Compound 31 and Compound 32



[0264] STEP A: To a solution of 31-1 (2.0 g, 11.755 mmol, 1 eq.) in AcOH (30 mL) was added Br_2 (5 mL, 11.755 mmol, 1 eq.) dropwise at 0°C. The reaction was stirred at 20°C for 18 hr. then the reaction solution was quenched by saturated sodium thiosulfate solution (1 mL), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluted (PE/EA=5/1) to give 31-2 (2.4 g, 9.637 mmol, 81.98%) as a yellow oil. LCMS (ESI): m/z = 247.0[M-H]$^-$.

[0265] STEP B: To a solution of 31-2 (600 mg, 2.409 mmol,1 eq), HATU (1374 mg, 3.614 mmol, 1.5 eq.) and DIEA (1246 mg, 9.637 mmol, 4 eq.) in DMF (15 mL) was added methyl(prop-1-en-3-yl)amine (206 mg, 2.891 mmol,1.2 eq) at rt., and stirred for 18 hr. LCMS showed that the reaction was consumed and the desired product was formed, the reaction solution was extracted with EA (5 mL x 2), the combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, after filtration, the organic layer was concentrated under reduced pressure to give an oil. The oil was purified by silica gel chromatography eluted (PE/EA= 10/1) to give 31-3 (680 mg, 2.251 mmol, 93.42%) as a yellow oil. LCMS (ESI): m/z = 303.0 [M+H]$^+$.

[0266] STEP C: To a solution of 31-3 (600 mg, 1.986 mmol), KOH (111.43 mg, 1.986 mmol, 1.0 eq.) in dioxane (15 mL) /H_2O (3 mL) was added $Pd_2(dba)_3$ (161 mg, 0.1986 mmol, 0.1 eq.) and t-BuXPhos (167 mg, 0.3972 mmol, 0.2 eq.), the mixture was stirred at 100°C for 18 hr. The reaction solution was extracted with EA (30 mL x 2), the combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, after filtration, the

organic layer was concentrated under reduced pressure to give an oil. The oil was purified by silica gel chromatography eluted (PE/EA= 1/1) to give 31-4 (400 mg, 2.090 mmol, 84.19%) as a solid. LCMS (ESI): *m/z* = 240.0 $[M+H]^+$.

[0267] STEP D: Racemic 31/32 (110 mg, 0.207 mmol, prepared from 31-4 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

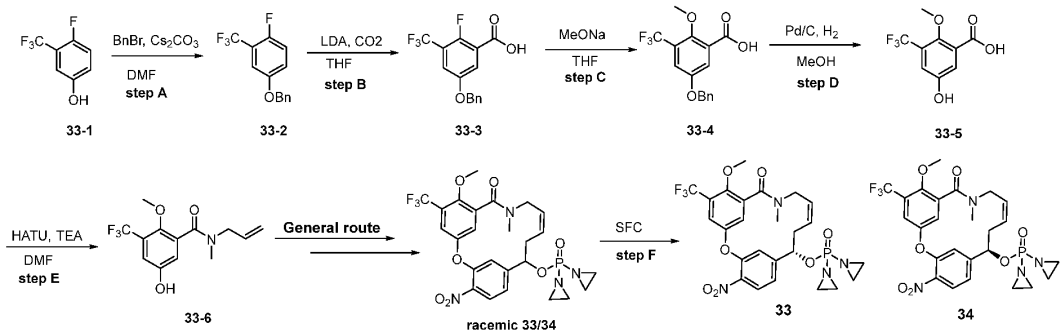
[0268] Isomer 1 (Compound 31, 37 mg, 0.069 mmol, 24.13%); Retention time: 1.237 min, 100 % ee. LC-MS (ESI): m/z 533.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.87 (m, 1H), 7.55 – 7.41 (m, 0.4 H), 7.14 – 7.09 (m, 0.6H), 7.09 – 6.56 (m, 2H), 6.14 (s, 1H), 5.81 – 5.48 (m, 1H), 5.43 – 5.15 (m, 2H), 4.01 – 3.91 (m, 3H), 3.91 – 3.61 (m, 2H), 3.08 – 2.87 (m, 4H), 2.40 – 1.95 (m, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.02 (s), -125.05 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.59 (s), 30.79 (s).

[0269] Isomer 2 (Compound 32, 37 mg, 0.069 mmol, 24.13%); Retention time: 1.909 min, 100% ee. LC-MS (ESI): m/z 533.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.86 (m, 1H), 7.53 – 7.44 (m, 0.4H), 7.13 – 7.09 (m, 0.6H), 7.09 – 6.60 (m, 2H), 6.13 (s, 1H), 5.81 – 5.46 (m, 1H), 5.44 – 5.17 (m, 2H), 4.02 – 3.92 (m, 3H), 3.91 – 3.62 (m, 2H), 3.07 – 2.90 (m, 4H), 2.37 – 1.98 (m, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.02 (s), -125.05 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.59 (s), 30.79 (s).

[0270] Analytical method: Method 1: Column: ChiralPak AD, 100¡Á4.6mm I.D., 3um; Mobile phase: A for CO_2 and B for ethanol (0.05% DEA); Gradient: 8 min @ B 30%; Flow rate: 2.5 mL/min; Column temperature: 35°C.

[0271] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC ; Column: ChiralPak AD, 250×30mm I.D., 5μm; Mobile phase: A for CO_2 and B for ETOH+0.01MEA; Gradient: B 30%; Flow rate:60mL/min; Back pressure: 100 bar; Column temperature: 35°C; Wavelength: 220 nm ; Cycle-time: 6.5min; Eluted time: 2 h.

Example 14: Preparation of Compound 33 and Compound 34



[0272] Step A: The mixture of 33-1 (3 g, 16.657 mmol), (bromomethyl)benzene (2.378 mL,19.989 mmol) and Cs_2CO_3 (10.85 g, 33.315 mmol) in DMF (40 mL) was stirred at room temperature for 16h. Then the reaction was quenched by water (200 mL), extracted with EA (80 mL×5), dried over anhydrous sodium sulfate, the organic phase was concentrated and the residue was purified by column chromatography on silica gel eluted with PE/EA (3~5%) to give 33-2 (3.8 g, 14.062 mmol, 84.42%) as a colorless oil.

[0273] Step B: To a stirred solution of 33-2 (3 g, 11.102 mmol) in THF (10 mL) was dropwise added LDA THF complex (13.877 mL, 27.754 mmol, 2M) at -65°C under N_2 for 1h. Introducing CO_2 into the reaction solution at -65°C for 1h, then warmed the mixture back to room temperature, stirred at rt. for 1h. The reaction was complete detected by LC-MS. The reaction mixture was quenched with saturated NH_4Cl solution and then extracted with EA (30 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluted with PE/EA (30~80%) to afford 33-3 (1.1 g, 3.501 mmol, 31.53%) as yellow solid. LC-MS (ESI): m/z = 313.1 $[M-H]^-$.

[0274] Step C: To a solution of 33-3 (818 mg, 2.603 mmol) in THF (8 mL) was added sodium methanolate (421.86 mg, 7.809 mmol) at rt., then the reaction was stirred at 70°C for 16hrs. The reaction was complete detected by LC-MS. Then the reaction solution was added water (50 mL×2). The aqueous phase was extracted with EA (80 mL×3). After drying the organic phase with anhydrous sodium sulfate, the organic phase was concentrated and the residue was purified by C18 column chromatography (A: NH_4HCO_3, B: MeCN, 30-50% B) to give 33-4 (820 mg, 2.513 mmol, 96.55%) as white solid. LC-MS (ESI): m/z = 327.0 $[M+H]^+$.

[0275] Step D: To a solution of 33-4 (850 mg, 2.605 mmol) in THF (30 mL) was added Pd/C 10% (85 mg, 0.799 mmol) and stirred for 16h at room temperature under H_2. After completed, the mixture was filtered with diatomite and concentrated. The residue was purified by C18 column chromatography (A: NH_4HCO_3, B: ACN, 40-50%B) to give the 33-5 (521 mg, 2.206 mmol, 84.69%) as yellow solid. LC-MS (ESI): m/z = 235.1 $[M-H]^-$.

[0276] Step E: To a solution of 33-5 (520 mg, 2.202 mmol), methyl(prop-1-en-3-yl)amine (313.21 mg, 4.404 mmol) and TEA (0.918 mL, 6.606 mmol) in DMF (6 mL) was added HATU (1004.74 mg, 2.642 mmol) and stirred at rt. for 2hr. The reaction was completed detected by LC-MS. Then the reaction solution was added water (40 mL×1). The aqueous phase was extracted with EA (60 mL×2), dried over anhydrous sodium sulfate, concentrated, the residue was purified by column chromatography on silica gel eluted with

PE/EA (0~40%) to give 33-6 (354 mg, 1.224 mmol, 55.58%) as colorless semi-solid. LCMS (ESI): m/z = 290.2 $[M+H]^+$.

[0277] Step F: Racemic 33/34 (12 mg, 0.021 mmol, prepared from 33-6 using the general route) was further separated by Chiral SFC to give:

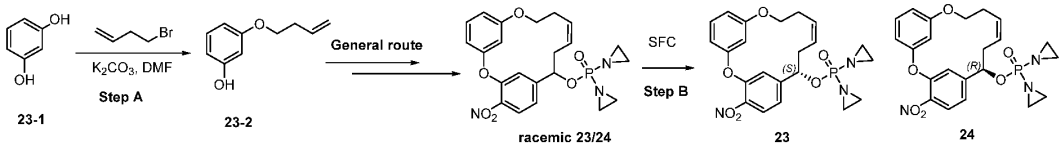
[0278] Isomer 1 (Compound 33, 5.4 mg, 45%); Retention time: 1.549 min, >99% ee. LC-MS (ESI): m/z = 583.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.89 (m, 1H), 7.60 – 7.53 (m, 1H), 7.53 – 7.47 (m, 0.5H), 7.13 – 7.06 (m, 0.5H), 7.02 – 6.53 (m, 2H), 5.80 – 5.44 (m, 1H), 5.42 – 5.17 (m, 2H), 4.01 – 3.90 (m, 3H), 3.89 – 3.65 (m, 2H), 3.11 – 2.91 (m, 4H), 2.29 – 1.99 (m, 9H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.52 – -61.66 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.27 (d, J = 133.7 Hz).

[0279] Isomer 2 (Compound 34, 4.6 mg, 38.3%); Retention time: 2.327 min, > 99% ee. LC-MS (ESI): m/z = 583.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.89 (m, 1H), 7.59 – 7.53 (m, 1H), 7.52 – 7.47 (m, 0.5H), 7.13 – 7.05 (m, 0.5H), 7.03 – 6.52 (m, 2H), 5.81 – 5.45 (m, 1H), 5.43 – 5.15 (m, 2H), 3.98 – 3.92 (m, 3H), 3.87 – 3.66 (m, 2H), 3.08 – 2.92 (m, 4H), 2.37 – 1.97 (m, 9H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.46 – -61.66 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.69 (s), 30.87 (s).

[0280] Analytical method: Column: CHIRALPAK IA 5um 4.6*100mm; Mobile phase: A for CO_2 and B for MeOH (0.05% DEA v/v); Gradient: 30% B; Flow rate: 2.0 mL/min; Column temperature: 40°C.

[0281] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC , Column: ChiralPak IA, 250×30mm I.D., 5μm, Mobile phase: A for CO_2 and B for IPA+0.01MEA, Gradient: B 30%, Flow rate:60mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 6 min, Eluted time: 2 h.

Example 15: Preparation of Compound 23 and Compound 24



[0282] STEP A: To a stirred suspension of 23-1 (7.874 mL, 90.818 mmol) and 4-bromobut-1-ene (9.218 mL, 90.818 mmol) in DMF (100 mL) was added K_2CO_3 (25.10 g, 181.637 mmol) at rt. Then the mixture was stirred at RT for 2 days. Then the product was extracted with EtOAc. Combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting mixture was filtered and the filtrate was

purified by silica gel column (PE/EA= 1/1) to give 23-2 (3.3 g, 20.097 mmol, 22.13%) as yellow solid. LCMS (ESI): m/z = 165.2 $[M+H]^+$.

[0283] STEP B: racemic 23/24 (60 mg, 0.13 mmol, prepared from 23-2 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

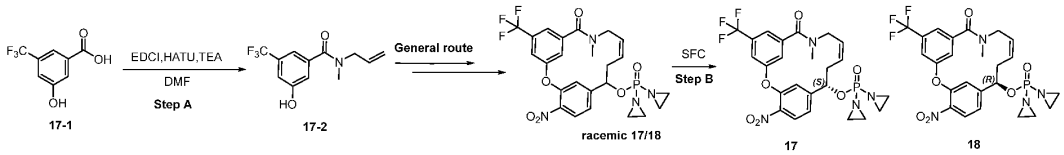
[0284] Isomer 1 (Compound 23, 26 mg, 43%); Retention time: 1.998 min, >99% ee. LCMS(ESI): m/z 458.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.91 (m, 1H), 7.42 – 7.27 (m, 2H), 7.07 (s, 1H), 6.90 – 6.79 (m, 1H), 6.73 – 6.66 (m, 1H), 6.25 (s, 1H), 5.68 – 5.58 (m, 1H), 5.42 – 5.28 (m, 2H), 4.17 – 4.04 (m, 2H), 2.90 – 2.67 (m, 2H), 2.47 – 2.30 (m, 2H), 2.23 – 2.07 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.44 (s).

[0285] Isomer 2 (Compound 24, 26 mg, 43%); Retention time: 2.721 min, >99% ee. LCMS(ESI): m/z 458.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.91 (m, 1H), 7.42 – 7.27 (m, 2H), 7.07 (s, 1H), 6.90 – 6.79 (m, 1H), 6.73 – 6.66 (m, 1H), 6.25 (s, 1H), 5.68 – 5.58 (m, 1H), 5.42 – 5.28 (m, 2H), 4.17 – 4.04 (m, 2H), 2.90 – 2.67 (m, 2H), 2.47 – 2.30 (m, 2H), 2.23 – 2.07 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.44 (s).

[0286] Analytical method: Column: CHIRALPAK C-IG 100*4.6mm 5um. Mobile phase: A for CO_2 and B for MeOH (0.05% DEA v/v). Gradient: 8 min B 40 %. Flow rate: 2.0 mL/min. Back pressure: 10 MPa. Column temperature: 40°C.

[0287] SFC Method: Instrument: Waters Thar 80 preparative SFC, Column: ChiralPak C-IG, 250×30mm I.D., 5 μm, Mobile phase: A for CO_2 and B for MEOH (0.1% 7mol/L NH3 in MeOH), Gradient: B 40 %, Flow rate: 40 mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 7 min, Eluted time:2 h.

Example 16: Preparation of Compound 17 and Compound 18



[0288] STEP A: To a solution of 17-1 (3 g, 14.555 mmol) in DMF (30 mL) was added EDCI (3.35 g, 17.466 mmol) and HATU (6.64 g, 17.466 mmol) at 0°C, the reaction was stirred at 20 min. methyl(prop-2-enyl)amine (1.55 g, 21.832 mmol) and TEA (3.035 mL, 21.832 mmol) was added into the mixture. The reaction was stirred at room temperature overnight. LCMS showed the reaction was complete. The mixture was added H_2O (30 mL) and extracted with EtOAc (3*20 mL). The separated organic layer was washed with brine and dried over Na_2SO_4.The organic layer was evaporated to afford the crude product. The

crude product was purified by flash chromatography (silica gel, 0~50% EtOAc in PE) to give 17-2 (2 g, 7.715 mmol, 53.01%) as an oil. LC-MS (ESI): m/z 260 $[M+H]^+$.

[0289] STEP B: Racemic 17/18 (80 mg, 0.14 mmol, prepared from 17-2 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

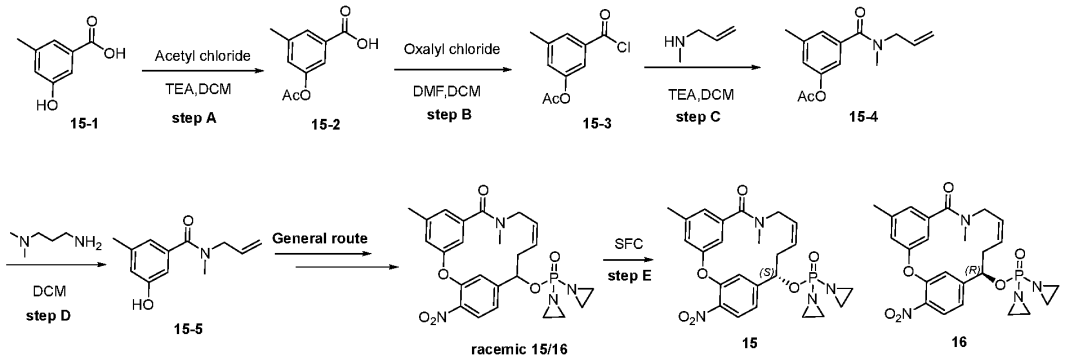
[0290] Isomer 1 (Compound 17, 34 mg, 43%); Retention time: 2.641 min, >99% ee. LC-MS (ESI): m/z 553.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 1H), 7.57 (s, 1H), 7.53 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.07 (s, 1H), 6.62 (s, 1H), 5.77 – 5.65 (m, 1H), 5.60 – 5.47 (m, 1H), 5.42 – 5.30 (m, 1H), 3.91 – 3.73 (m, 2H), 3.02 (s, 3H), 2.85 – 2.70 (m, 1H), 2.61 – 2.48 (m, 1H), 2.25 – 2.05 (m, 8H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.25 (s).

[0291] Isomer 2 (Compound 18, 34 mg, 43%); Retention time: 2.837 min, 90% ee. LC-MS (ESI): m/z 553.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 1H), 7.57 (s, 1H), 7.53 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.07 (s, 1H), 6.62 (s, 1H), 5.77 – 5.65 (m, 1H), 5.60 – 5.47 (m, 1H), 5.42 – 5.30 (m, 1H), 3.91 – 3.73 (m, 2H), 3.02 (s, 3H), 2.85 – 2.70 (m, 1H), 2.61 – 2.48 (m, 1H), 2.25 – 2.05 (m, 8H).

[0292] Analytical method: ChiralPak IC, 100¡Á4.6mm I.D., 3um, Mobile phase: A for CO_2 and B for methanol (0.05%DEA), Gradient: 8 min @B 30%, Flow rate: 2.5 mL/min, Back pressure: 100 bar, Column temperature: 35°C.

[0293] SFC Method: Instrument: Waters Thar 80 preparative SFC, Column: ChiralPak IA, 250×20mm I.D., 5μm. Mobile phase: A for CO_2 and B for IPA (0.1% 2mol/L NH3 in MeOH). Gradient: B 20%. Flow rate:40 mL/min. Back pressure: 100 bar. Column temperature: 35°C. Wavelength:220 nm. Run time:20 min. Cycle-time: 20 min. Eluted time:3 h.

Example 17: Preparation of Compound 15 and Compound 16



[0294] STEP A: To a solution of 15-1 (3.707 mL, 29.576 mmol) and TEA (12.333 mL, 88.728 mmol) in DCM (100 mL), then the solution was cooled to 0 °C, acetyl chloride (2.533 mL, 35.491 mmol) was dropwise, stirred at RT for 1 hour. The reaction mixture was extracted with (200 mL x 2) and H_2O (200 mL). The H_2O layer was adjusted pH to 2. The resulting precipitate was collected by filtration. The precipitate was dried by vacuum freeze drying to give 15-2 (2.5 g, 12.874 mmol, 43.53%) as white solid. LCMS (ESI): *m/z* = 195 $[M+H]^+$.

[0295] STEP B: To a solution of 15-2 (2 g, 10.299 mmol) and DMF (0.1 mL) in DCM (20 mL) was added oxalyl chloride (2.211 mL, 25.748 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour. The reaction was monitored by pipetting out a small amount of crude sample and quenching it with MeOH to ensure acid chloride had been formed completely. After completion, the excess oxalyl chloride and solvent were removed under reduced pressure to give 15-3 (2 g, 9.406 mmol, 91.33%) as white solid. LCMS (ESI): *m/z* = 213 $[M+H]^+$.

[0296] STEP C: The 15-3 (2 g, 9.406 mmol) was re-dissolved in anhydrous DCM (20 mL), then added to a mixture of methyl(prop-1-en-3-yl)amine (1.354 mL, 14.109 mmol) and TEA (3.922 mL, 28.218 mmol) in anhydrous DCM (20 mL) at 0 °C. The reaction was allowed to warm to room temperature, and stirred for an additional 1 hour to give 15-4 (1.9 g, 7.683 mmol, 81.68%) as white solid. LCMS (ESI): *m/z* = 248 $[M+H]^+$.

[0297] STEP D: To a solution of 15-4 (1.9 g, 7.683 mmol) and 3-(dimethylamino)propan-1-amine (2.423 mL, 19.208 mmol) in DCM (20 mL), stirred at RT for 1 hour. The reaction liquid was concentrated and purified by silica gel chromatography to give 15-5 (1.5 g, 7.308 mmol, 95.11%) as white solid. LCMS (ESI): *m/z* = 206 $[M+H]^+$.

[0298] STEP E: racemic 15/16 (60 mg, 0.12 mmol, prepared from 15-5 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

[0299] Isomer 1 (Compound 15, 12.7 mg, 21%); Retention time: 3.372 min, 97.981% ee. LC-MS (ESI): m/z 499.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 8.10 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.20 (s, 2H), 6.98 (s, 1H), 6.12 (s, 1H), 5.65 (s, 1H), 5.57 – 5.47 (m, 1H), 5.45 – 5.30 (m, 1H), 3.86 – 3.64 (m, 2H), 3.31 – 3.25 (m, 2H), 2.86 (s, 3H), 2.38 (s, 3H), 2.16 – 1.90 (m, 8H). ^{31}P NMR (162 MHz, DMSO) δ 30.01 (s).

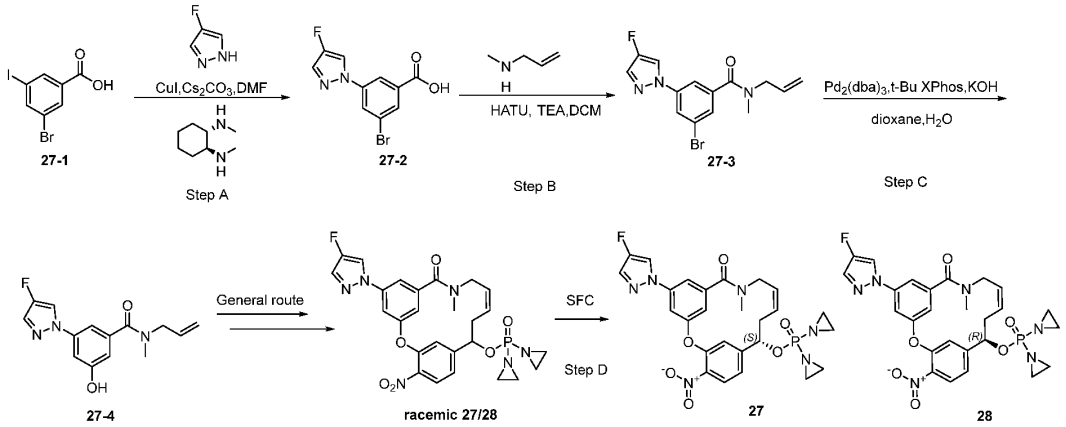
[0300] Isomer 2 (Compound 16, 23.1 mg, 38%); Retention time: 4.042min, 96.165% ee. LC-MS (ESI): m/z 499.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 8.10 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.20 (s, 2H), 6.98 (s, 1H), 6.13 (s, 1H), 5.72 – 5.59 (m, 1H),

5.57 – 5.47 (m, 1H), 5.46 – 5.34 (m, 1H), 3.86 – 3.65 (m, 2H), 3.48 – 3.41 (m, 2H), 2.86 (s, 3H), 2.38 (s, 3H), 2.13 – 1.95 (m, 8H). ^{31}P NMR (162 MHz, DMSO) δ 30.01 (s).

[0301] Analytical method: Column: CHIRALPAK IH 100*4.6mm 5um; Mobile phase: A for CO_2 and B for ethanol (0.05%DEA); Gradient: 8 min @ 20% B; Flow rate: 2.5 mL/min; Column temperature: 40 °C.

[0302] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC, Column: ChiralPak C-IG, 250×30mm I.D., 5μm, Mobile phase: A for CO_2 and B for ETOH+0.1%MEA, Gradient: B 30%, Flow rate: 40mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 3.5min, Eluted time: 2 h.

Example 18: Preparation of Compound 27 and Compound 28



[0303] STEP A: To a solution of 27-1 (4500 mg, 13.765 mmol), 4-fluoro-1H-pyrazole (1777.11 mg, 20.647 mmol), methyl[(1S,2S)-2-(methylamino)cyclohexyl]amine (391.61 mg, 2.753 mmol), CuI (629.16 mg, 3.304 mmol) and K_2CO_3 (8560.35 mg, 61.942 mmol) in DMF (20 mL), stirred at 110°C for overnight. After completion, the mixture was extracted with EtOAc (20 mL x 2) and the organic phase was washed with water (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 27-2 (3500 mg, 12.278 mmol, 89.20%) as black semisolid. LCMS (ESI): *m/z* = 286 $[M+H]^+$.

[0304] STEP B: To a solution of 27-2 (3.5 g, 12.278 mmol), methyl(prop-1-en-3-yl)amine (1.75 g, 24.556 mmol), HATU (5.60 g, 14.733 mmol) and TEA (5.120 mL, 36.833 mmol) in DMF (20 mL), stirred at RT for 1hour. After completion, the mixture was concentrated under reduced pressure. The reaction was concentrated and purified by silica gel chromatography on silica gel eluted with PE/EA(20~30%) to give 27-3 (1.827 g, 5.402 mmol, 44.00%) as yellow oil. LCMS (ESI): *m/z* = 339 $[M+H]^+$.

[0305] STEP C: To a solution of 27-3 (1900 mg, 5.618 mmol), $Pd_2(dba)_3$ (514.49 mg, 0.562 mmol), t-Bu XPhos (357.87 mg, 0.843 mmol) and KOH (409.82 mg, 7.304 mmol) in dioxane (20 mL) and H_2O (4 mL), stirred at 80°C for overnight. After completion, the mixture was concentrated under reduced pressure. The reaction was concentrated and purified by silica gel chromatography on silica gel eluted with PE/EA(50~60%) to give 27-4 (300 mg, 1.090 mmol, 19.40%) as colorless oil. LCMS (ESI): *m/z* = 276 $[M+H]^+$.

[0306] STEP E: Racemic 27/28 (140 mg, 0.24 mmol, prepared from 27-4 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

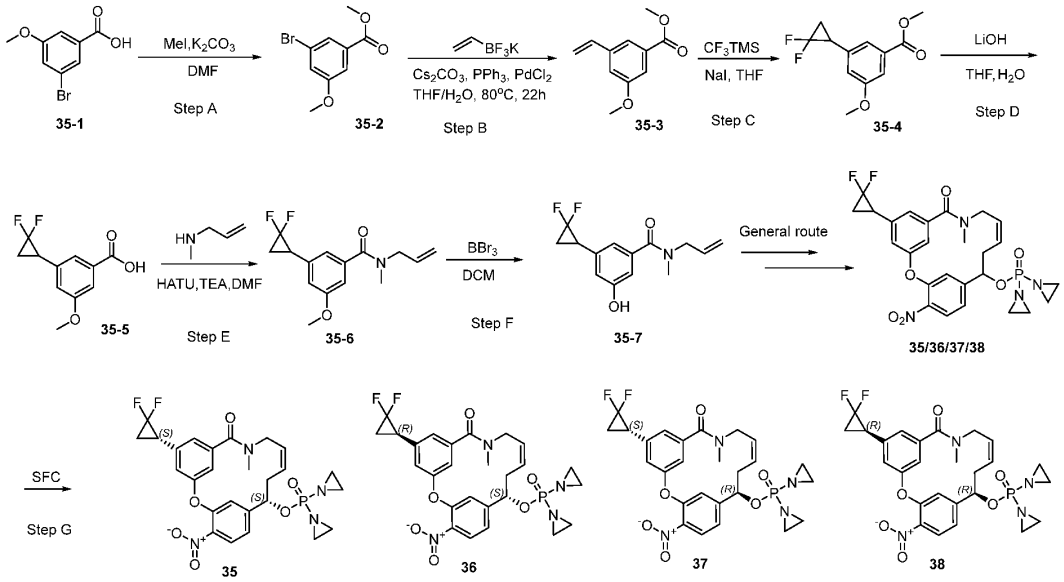
[0307] Isomer 1 (Compound 27, 41.0 mg, 29%); Retention time: 3.457 min, >99% ee. LC-MS (ESI): m/z 569.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 4.8 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.62 (d, J = 4.2 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.37 – 7.30 (m, 1H), 7.08 (s, 1H), 6.36 – 6.32 (m, 1H), 5.74 – 5.64 (m, 1H), 5.56 – 5.48 (m, 1H), 5.40 – 5.32 (m, 1H), 3.92 – 3.76 (m, 2H), 3.02 (s, 3H), 2.82 – 2.69 (m, 1H), 2.63 – 2.49 (m, 1H), 2.23 – 2.04 (m, 8H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -173.55 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.12 (s).

[0308] Isomer 2 (Compound 28, 45.9 mg, 32%); Retention time: 4.590 min, 98.971% ee. LC-MS (ESI): m/z 569.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 4.8 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.62 (d, J = 4.2 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.37 – 7.30 (m, 1H), 7.08 (s, 1H), 6.36 – 6.32 (m, 1H), 5.74 – 5.64 (m, 1H), 5.56 – 5.48 (m, 1H), 5.40 – 5.32 (m, 1H), 3.92 – 3.76 (m, 2H), 3.02 (s, 3H), 2.82 – 2.69 (m, 1H), 2.63 – 2.49 (m, 1H), 2.23 – 2.04 (m, 8H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -173.55 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.12 (s).

[0309] Analytical method: Column: CHIRALPAK AS 3um 4.6*100mm; Mobile phase: A for CO_2 and B for MeOH (0.05%DEA); Gradient: 8 min @ 20% B; Flow rate: 2.0 mL/min; Column temperature: 40 °C.

[0310] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC , Column: ChiralPak AS, 250×20mm I.D., 5μm, Mobile phase: A for CO_2 and B for MEOH+0.1%NH_3H_2O, Gradient: B 20%, Flow rate:40mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 7min, Eluted time: 2 h.

Example 19: Preparation of Compound 35, Compound 36, Compound 37, and Compound 38



[0311] STEP A: To a solution of 35-1 (3 g, 12.985 mmol), iodomethane (2.108 mL, 25.970 mmol) and K_2CO_3 (5.38 g, 38.954 mmol) in DMF (20 mL), stirred at RT for overnight. After completion, the reaction solution was partitioned between EA (50 mL x 2) and H_2O (100 mL). The combined organic layers were washed with an aqueous solution of NaCl (100 mL) and then organic layers was concentrated under reduced pressure. The reaction was concentrated and purified by silica gel chromatography on silica gel eluted with PE/EA(0~10%) to give 35-2 (2.8 g, 11.425 mmol, 87.99%) as colorless oil. LCMS (ESI): m/z = 246 $[M+H]^+$.

[0312] STEP B: To a solution of 35-2 (2.8 g, 11.425 mmol), potassium vinyltrifluoroborate (227.85 mg, 1.701 mmol), $PdCl_2$ (0.10 g, 0.571 mmol), PPh_3 (0.18 g, 0.686 mmol) and Cs_2CO_3 (11.17 g, 34.276 mmol) in H_2O (3 mL) and THF (27 mL), stirred at 80°C for overnight. After completion, the mixture was concentrated under reduced pressure. The reaction was concentrated and purified by silica gel chromatography on silica gel eluted with PE/EA (0~10%) to give 35-3 (2.1 g, 10.926 mmol, 95.63%) as colorless oil. LCMS (ESI): m/z = 193 $[M+H]^+$.

[0313] STEP C: To a solution of 35-3 (1.5 g, 7.805 mmol), NaI (5.848 g, 39.02 mmol) and trimethyl(trifluoromethyl)silane (11.097 g, 78.04 mmol) in THF (10 mL), stirred at 170°C for 1 hour (microwave). Desired product was detected, conv 100%. After completion, the mixture was concentrated under reduced pressure. The reaction was

concentrated and purified by silica gel chromatography on silica gel eluted with PE/EA(0~10%) to give 35-4 (1.2 g, 4.953 mmol, 63.49%) as colorless oil. LCMS (ESI): *m/z* = 243 $[M+H]^+$.

[0314] STEP D: To a solution of 35-4 (1.1 g, 4.543 mmol) and LiOH (1.143 g, 27.247 mmol) in THF (20 mL) and H_2O (5 mL), stirred at RT for overnight. After completion, the mixture was concentrated under reduced pressure. The residue was purified by C18 column chromatography (A: FA, B: AcN, 40~50 %B) to give 35-5 (900 mg, 3.945 mmol, 88.79%) as white solid. LCMS (ESI): *m/z* = 224 $[M+H]^+$.

[0315] STEP E: To a solution of 35-5 (900 mg, 3.944 mmol), methyl(prop-2-enyl)amine (561.01 mg, 7.888 mmol), HATU (1.799 g, 4.733 mmol) and TEA (7.126 mL, 51.273 mmol) in DMF (10 mL), stirred at RT for 1 hour. Desired product was detected, conv 100%. After completion, the reaction solution was partitioned between EA (20 mL x 2) and H_2O (50 mL). The combined organic layers were washed with an aqueous solution of NaCl (40 mL) and then organic layers was concentrated under reduced pressure. the mixture was concentrated under reduced pressure. The reaction was concentrated and purified by silica gel chromatography on silica gel eluted with PE/EA(30~40%) to give 35-6 (200 mg, 0.711 mmol, 95.43%) as colorless oil. LCMS (ESI): *m/z* = 282 $[M+H]^+$.

[0316] STEP F: To a solution of 35-6 (1 g, 3.555 mmol) and tribromoborane (13.358 mg, 53.324 mmol) in DCM (20 mL), stirred at RT for overnight. Desired product was detected, conv 100%. After completion, the mixture was concentrated under reduced pressure. The reaction was concentrated and purified by silica gel chromatography on silica gel eluted with PE/EA(30~40%) to give 35-7 (900 mg, 3.367 mmol, 94.72%) as colorless oil. LCMS (ESI): *m/z* = 267 $[M+H]^+$.

[0317] STEP G: mixture of 35/36/37/38 (150 mg, 0.268 mmol, prepared from 35-7 using the general route) was further separated by Chiral SFC to give (R/S were assigned arbitrarily, S= front peak, R = back peak):

[0318] Isomer 1 (Compound 35, 17.4 mg, 11.6%); Retention time: 5.396 min, >99% *ee*. M LC-MS (ESI): *m/z* 561.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.20 – 7.15 (m, 1H), 7.13 (s, 1H), 7.07 (s, 1H), 6.41 – 6.30 (m, 1H), 5.74 – 5.62 (m, 1H), 5.57 – 5.46 (m, 1H), 5.39 – 5.31 (m, 1H), 3.89 – 3.72 (m, 2H), 3.00 (s, 3H), 2.85 – 2.69 (m, 2H), 2.55 (s, 1H), 2.23 – 2.04 (m, 8H), 1.96 – 1.86 (m, 1H), 1.76 – 1.68 (m, 1H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -125.69 (d, *J* = 155.2 Hz), -141.66 (d, *J* = 155.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.22 (s).

[0319] Isomer 2 (Compound 36, 21.2 mg, 14.13%); Retention time: 5.801 min, >99% *ee*. LC-MS (ESI): *m/z* 561.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 1H), 7.33 – 7.28 (m, 1H), 7.20 – 7.16 (m, 1H), 7.14 – 7.09 (m, 1H), 7.09 – 7.04 (m, 1H), 6.39 – 6.32 (m, 1H), 5.73 – 5.61 (m, 1H), 5.55 – 5.47 (m, 1H), 5.41 – 5.30 (m, 1H), 3.89 – 3.72 (m, 2H), 3.03 (d, *J* = 27.2 Hz, 3H), 2.84 – 2.70 (m, 2H), 2.56 (s, 1H), 2.24 – 2.03 (m, 8H), 1.96 – 1.86 (m, 1H), 1.76 – 1.68 (m, 1H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -125.69 (d, *J* = 155.3 Hz), -141.92 (t, *J* = 82.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.21 (s).

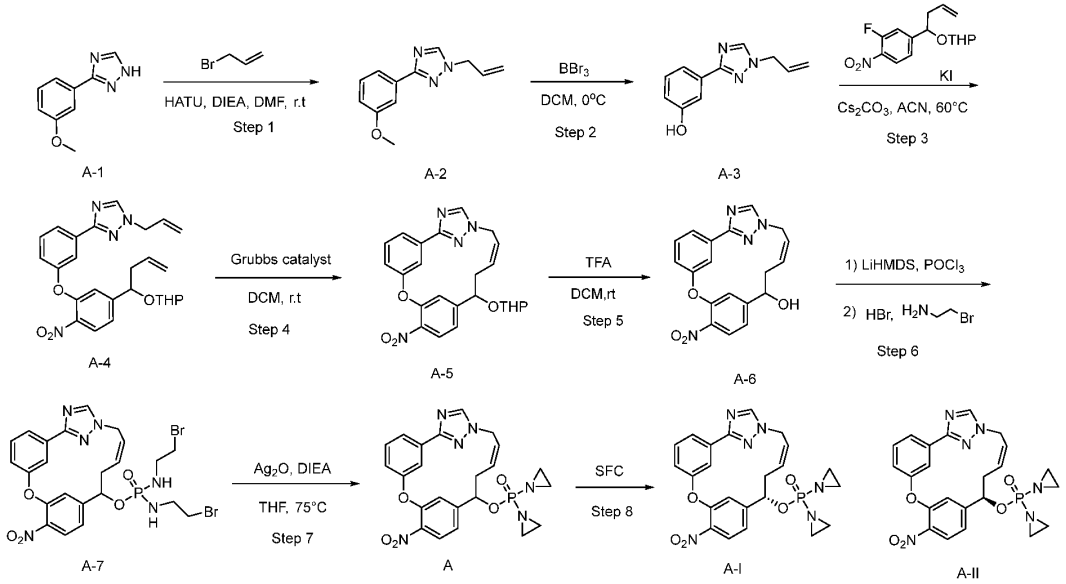
[0320] Isomer 3 (Compound 37, 21.4 mg, 14.27%); Retention time: 6.238 min, 97.902% *ee*. LC-MS (ESI): *m/z* 561.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 1H), 7.33 – 7.28 (m, 1H), 7.19 – 7.16 (m, 1H), 7.13 – 7.10 (m, 1H), 7.08 – 7.04 (m, 1H), 6.39 – 6.33 (m, 1H), 5.72 – 5.62 (m, 1H), 5.55 – 5.47 (m, 1H), 5.39 – 5.32 (m, 1H), 3.88 – 3.73 (m, 2H), 3.00 (s, 3H), 2.84 – 2.71 (m, 2H), 2.60 – 2.48 (m, 1H), 2.22 – 2.03 (m, 8H), 1.96 – 1.86 (m, 1H), 1.76 – 1.68 (m, 1H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -125.70 (d, *J* = 155.2 Hz), -141.84 (d, *J* = 155.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.21 (s).

[0321] Isomer 4 (Compound 38, 24.6 mg, 16.40%); Retention time: 6.758 min, >99% *ee*. LC-MS (ESI): *m/z* 561.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 1H), 7.32 – 7.28 (m, 1H), 7.19 – 7.15 (m, 1H), 7.15 – 7.11 (m, 1H), 7.09 – 7.04 (m, 1H), 6.38 – 6.31 (m, 1H), 5.72 – 5.62 (m, 1H), 5.55 – 5.48 (m, 1H), 5.39 – 5.31 (m, 1H), 3.89 – 3.72 (m, 2H), 3.07 – 2.99 (m, 3H), 2.86 – 2.71 (m, 2H), 2.62 – 2.47 (m, 1H), 2.22 – 2.04 (m, 8H), 1.96 – 1.86 (m, 1H), 1.76 – 1.68 (m, 1H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -125.69 (d, *J* = 155.1 Hz), -141.67 (d, *J* = 154.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.22 (s).

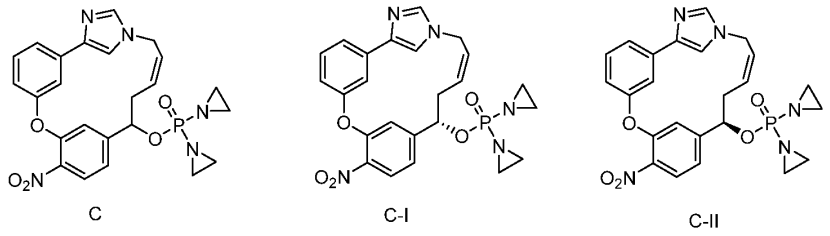
[0322] Analytical method: Column: CHIRALPAK IB 3um 4.6*100mm; Mobile phase: A for CO_2 and B for IPA (0.05% DEA v/v); Gradient: 8 min @ 20% B; Flow rate: 2.0 mL/min; Column temperature: 40 °C.

[0323] SFC Method: Instrument: SHIMADZU PREP SOLUTION SFC , Column: ChiralPak AD, 250×20mm I.D., 5μm, Mobile phase: A for CO_2 and B for IPA+0.1%$NH3H_2O$, Gradient: B 40%, Flow rate:40mL/min, Back pressure: 100 bar, Column temperature: 35°C, Wavelength: 220 nm, Cycle-time: 20min, Eluted time: 4 h.

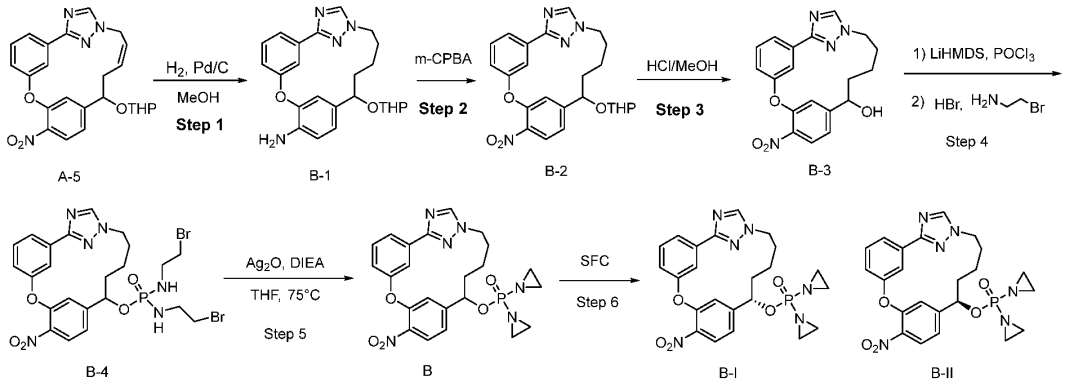
Example A: Preparation of Compound A, Compound A-I, and Compound A-II



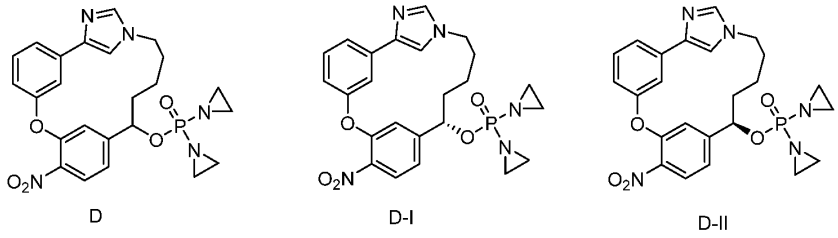
[0324] Compound C and its enantiomers are prepared in similar way to the procedures described for Example A:



Example B: Preparation of Compound B, Compound B-I, and Compound B-II



[0325] Compound D and its enantiomers are prepared in similar way to the procedures described for Example B:



Biological Example 1. In vitro human cancer cell line cytotoxicity assay

[0326] IC_{50} values in nanomolar reported here were derived from *in vitro* proliferation assay data in non-small cell lung cancer cell line H460. Specifically, exponentially growing cells were seeded at density of $3x10^3$ cells per well in 96-well plate and incubated at 37 °C in 5% CO_2, 95% air and 100% relative humidity for 24 hours before adding compounds. Compounds were solubilized in 100% DMSO at 10mM. Compounds were added to the plate using Tecan D300e® digital Dispenser. After drug addition, the plates were incubated for an additional 72 hours at 37 °C in 5% CO_2, 95% air and 100% relative humidity. At the end of the incubation, cell viability was quantified with CellTiter-Glo® assay. The drug concentration resulting in growth inhibition of 50% (IC_{50}) was calculated using CDD Vault tool.

[0327] To further confirm that compounds were activated by human AKR1C3, H460 proliferation assay were also performed in the presence of 3uM ASP9521, an AKR1C3 specific inhibitor. ASP9521 were added to the plates 4 hours prior to the addition of compounds.

[0328] Selected results according to this example are shown in the Tables below:

Compound No.	**CTG H460: Avg IC_{50} (nM) [Assay Condition: DMSO]**	**CTG H460: Avg IC_{50} (nM) [Assay Condition: ASP9521]**	**Compound No.**	**CTG H460: Avg IC_{50} (nM) [Assay Condition: DMSO]**	**CTG H460: Avg IC_{50} (nM) [Assay Condition: ASP9521]**
1	B	> 27092.5	23	C	8637.6
2	B	8977.7	24	D	4387.8
3	C	> 100000	25	B	> 100000
4	B	> 12315.1	26	A	3205.3
5	C	5560	27	B	27023.7
6	B	11064.7	28	B	8751.1
7	B	10583.9	29	D	> 100000
8	C	5179.6	30	B	> 100000
9	B	19527.6	31	A	6226.3
10	A	2817.4	32	B	7330
11	A	2723.3	33	D	> 100000
13	C	> 100000	34	B	> 100000
14	B	> 100000	35	A	874.7
15	B	> 100000	36	A	825.5

16	D	> 100000	37	A	912.3
17	C	> 100000	38	A	168
18	C	> 100000	39	A	2198.8
19	C	> 100000	40	B	> 9790.7
20	C	> 100000	41	B	> 11240.5
21	D	> 100000	42	D	> 100000
22	C	> 3100.0			

CTG H460: Avg IC_{50} (nM) [Assay Condition: DMSO]

A: $IC_{50} < 10$ nM;

B: 10 nM $\leq IC_{50} < 50$ nM;

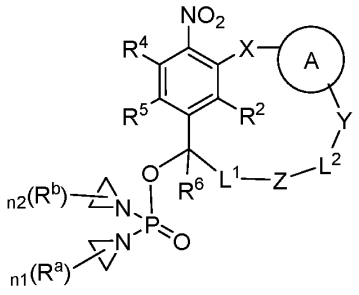
C: 50 nM $\leq IC_{50} < 200$ nM;

D: $IC_{50} \geq 200$ nM

[0329] A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the descriptions in the embodiments and examples provided herein are intended to illustrate but not limit the scope of invention described in the claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein:

R^2 is hydrogen, deuterium, halogen (*e.g.*, F), optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, or optionally substituted C_{1-4} alkoxy;

R^4 and R^5 are each independently hydrogen, deuterium, halogen (*e.g.*, F), optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{1-4} alkoxy, or optionally substituted 3- to 6-membered ring;

R^6 is hydrogen, deuterium, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, or optionally substituted C_{2-4} alkynyl;

X is -O-, -S-, -NR^{10}-, optionally substituted C_{1-4} alkylene, or optionally substituted C_{1-4} heteroalkylene;

Ring A is optionally substituted 3- to 10-membered ring;

L^1 is an optionally substituted C_{1-4} alkylene;

L^2 is an optionally substituted C_{1-4} alkylene;

Y is -O-, -S-, -S(O)-, -$S(O)_2$-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -$S(O)_2$-NR^{10}-, -C(O)-O-, or optionally substituted 3- to 10-membered ring;

Z is optionally substituted C_2 alkylene, optionally substituted C_2 alkenylene, C_2 alkynylene, -O-, -S-, -S(O)-, -$S(O)_2$-, -NR^{10}-, -C(O)-, -C(O)-NR^{10}-, -$S(O)_2$-NR^{10}-, or optionally substituted 3- to 10-membered ring;

R^{10} at each occurrence is independently hydrogen, an optionally substituted C_{1-4} alkyl, or an optionally substituted 3-6 membered ring;

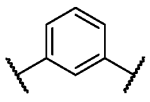
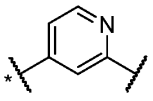
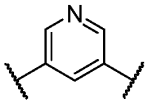
n1 is 0, 1, 2, 3, or 4;

n2 is 0, 1, 2, 3, or 4;

each of R^a and R^b at each occurrence is independently optionally substituted C_{1-4} alkyl or optionally substituted C_{1-4} heteroalkylene; or two instances of R^a or two instances of R^b, together with the intervening atom(s), are joined together to form an optionally substituted 3- to 6-membered ring.

2. The compound of claim 1, wherein Ring A is optionally substituted phenylene, optionally substituted 5- or 6-membered heteroarylene, optionally substituted 8- to 10-membered bicyclic heteroarylene, or optionally substituted 8- to 10-membered bicyclic heterocyclylene.

3. The compound of claim 2, wherein Ring A is optionally substituted phenylene.

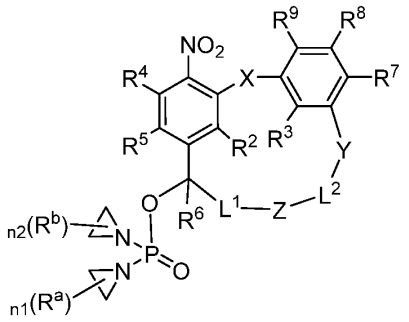
4. The compound of claim 2, wherein Ring A is  ,  , or  , each of which is optionally substituted, wherein * refers to the direction of X.

5. The compound of any one of claims 1 to 4, wherein Ring A is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each independently selected from deuterium, halogen (*e.g.*, F), CN, OH, NH_2, COOH, $CONH_2$, G^1, OG^1, SG^1, NHG^1, NG^1G^1, $C(O)G^1$, $COOG^1$, $CONHG^1$, $CONG^1G^1$, $OC(O)G^1$, $OCOOG^1$, $OCONHG^1$, $OCONG^1G^1$, $NHC(O)G^1$, $NHCOOG^1$, $NHCONHG^1$, $NHCONG^1G^1$, $NG^1C(O)G^1$, NG^1COOG^1, NG^1CONHG^1, $NG^1CONG^1G^1$, SO_2G^1, SO_2NHG^1, or $SO_2NG^1G^1$, wherein G^1 at each occurrence is independently optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, or optionally substituted 3- to 6-membered ring structure (*e.g.*, cyclopropyl, cyclobutyl, phenyl, pyrimidyl, or pyridyl), or two G^1 of an NG^1G^1 together with the nitrogen atom form an optionally substituted 4- to 8-membered heterocyclic ring.

6. The compound of any one of claims 1 to 4, wherein Ring A is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents each independently selected from deuterium, F, Cl, CN, OH, NH_2, COOH, $CONH_2$, G^2, OG^2, NHG^2, NG^2G^2, $C(O)G^2$, $COOG^2$, $CONHG^2$, $CONG^2G^2$, SO_2G^2, SO_2NHG^2, or $SO_2NG^2G^2$, wherein G^2 at each occurrence is independently a C_{1-4} alkyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclic ring having 1-2 ring heteroatoms, phenyl, or 5- or 6-membered heteroaryl, each of which is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from deuterium, F, Cl, OH, NH_2, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4}

heteroalkyl having 1 or 2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, or two G^2 of an NG^2G^2 together with the nitrogen atom form an optionally substituted 4- to 8-membered heterocyclic ring having 0 or 1 additional ring heteroatom.

7. The compound of claim 1, which is a compound of Formula (II-A):



(II-A),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein:

R^3 is hydrogen, deuterium, halogen (*e.g.*, F), optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, or optionally substituted C_{1-4} alkoxy;

R^7, R^8, and R^9 are each independently hydrogen, deuterium, halogen (*e.g.*, F), CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from (i) deuterium, (ii) halogen (*e.g.*, F), (iii) CN, (iv) OH, (v) oxo, (vi) C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (vii) C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH, (viii) 3- to 6-membered ring optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium, F, or OH; or

two adjacent R^7, R^8, and R^9, together with the carbon atoms they are attached to, form a 4- to 8-membered ring, which is optionally substituted with one or more (*e.g.*, 1, 2, or 3) R^n; and

R^n at each occurrence is independently deuterium, halogen (*e.g.*, F), CN, OH, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3- to 6-membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3- to 6-membered ring is optionally substituted with one or more (*e.g.*, 1, 2, or 3) substituents independently selected from deuterium, F, OH, C_{1-4} alkyl optionally substituted with one or

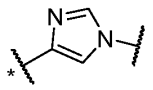
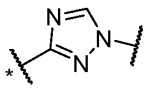
more (*e.g.*, 1, 2, or 3) deuterium or F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

8. The compound of any one of claims 1 to 7, wherein X is -O-.

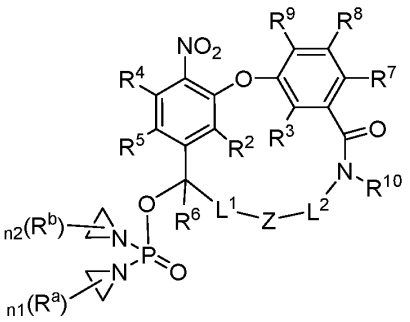
9. The compound of any one of claims 1 to 8, wherein Y is *-C(O)-NR^{10}-, wherein * refers to the direction toward Ring A.

10. The compound of any one of claims 1 to 8, wherein Y is -O-.

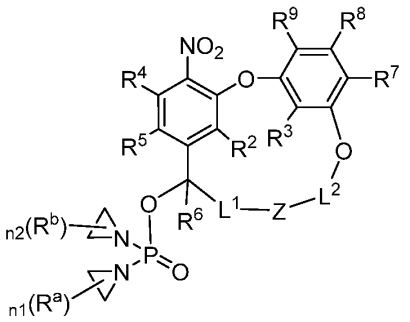
11. The compound of any one of claims 1 to 8, wherein Y is optionally substituted 5- or 6-membered heteroarylene or optionally substituted 3- to 8-membered heterocyclylene.

12. The compound of claim 11, wherein Y s  or  , each of which is optionally substituted, wherein * refers to the direction of Ring A.

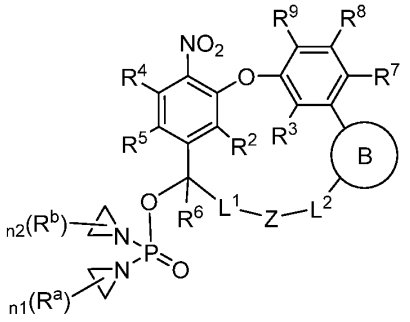
13. The compound of claim 7, which is a compound of Formula (III-A), (III-B), or (III-C):



(III-A),



(III-B), or



(III-C),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein Ring B is optionally substituted 3- to 10-membered ring.

14. The compound of any one of claims 1 to 13, wherein L^1 is C_{1-2} alkylene optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

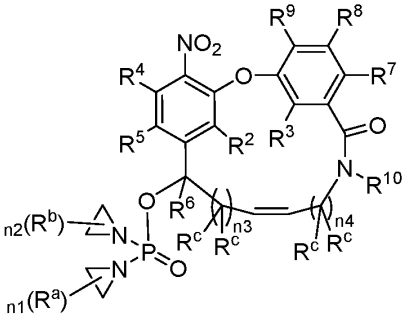
15. The compound of any one of claims 1 to 14, wherein L^2 is C_{1-2} alkylene optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

16. The compound of any one of claims 1 to 15, wherein Z is C_2 alkylene optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

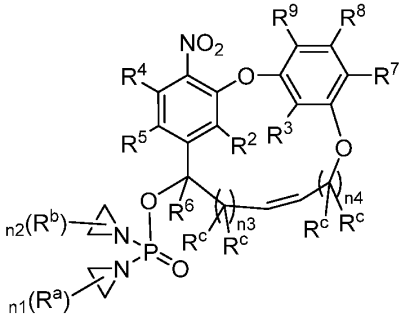
17. The compound of any one of claims 1 to 15, wherein Z is C_2 alkenylene optionally substituted with one or more (*e.g.*, 1 or 2) deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F.

18. The compound of any one of claims 1 to 15, wherein Z is -O-.

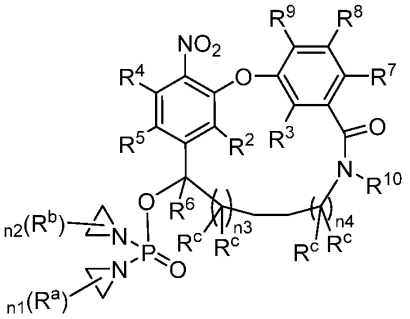
19. The compound of claim 13, which is a compound of Formula (IV-A), (IV-B), (IV-C), (IV-D), (IV-E), or (IV-F):



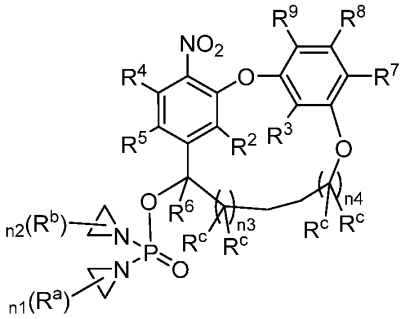
(IV-A),



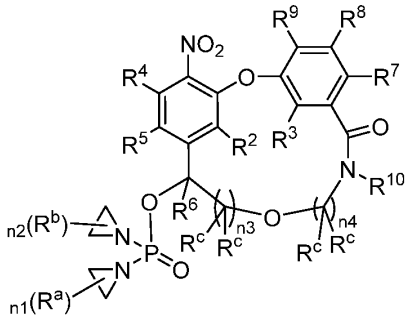
(IV-B),



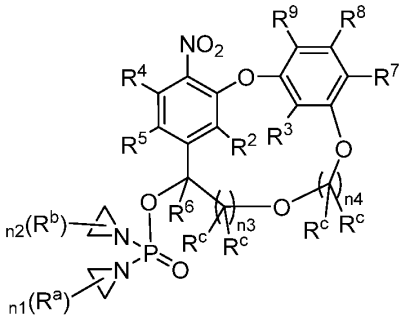
(IV-C),



(IV-D),



(IV-E), or



(IV-F),

or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof, wherein:

R^c at each occurrence is independently hydrogen, deuterium, halogen (*e.g.*, F), or C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F;

n3 is 1, 2, 3, or 4; and

n4 is 1, 2, 3, or 4.

20. The compound of claim 19, wherein n3 is 1.

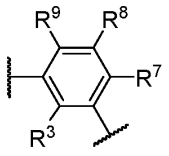
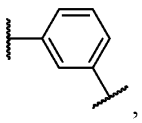
21. The compound of claim 19 or 20, wherein n4 is 1.

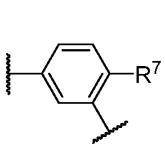
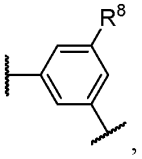
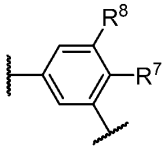
22. The compound of claim 19 or 20, wherein n4 is 2.

23. The compound of any one of claims 19 to 22, wherein R^c at each occurrence is hydrogen.

24. The compound of any one of claims 7 to 23, wherein R^3 is hydrogen.

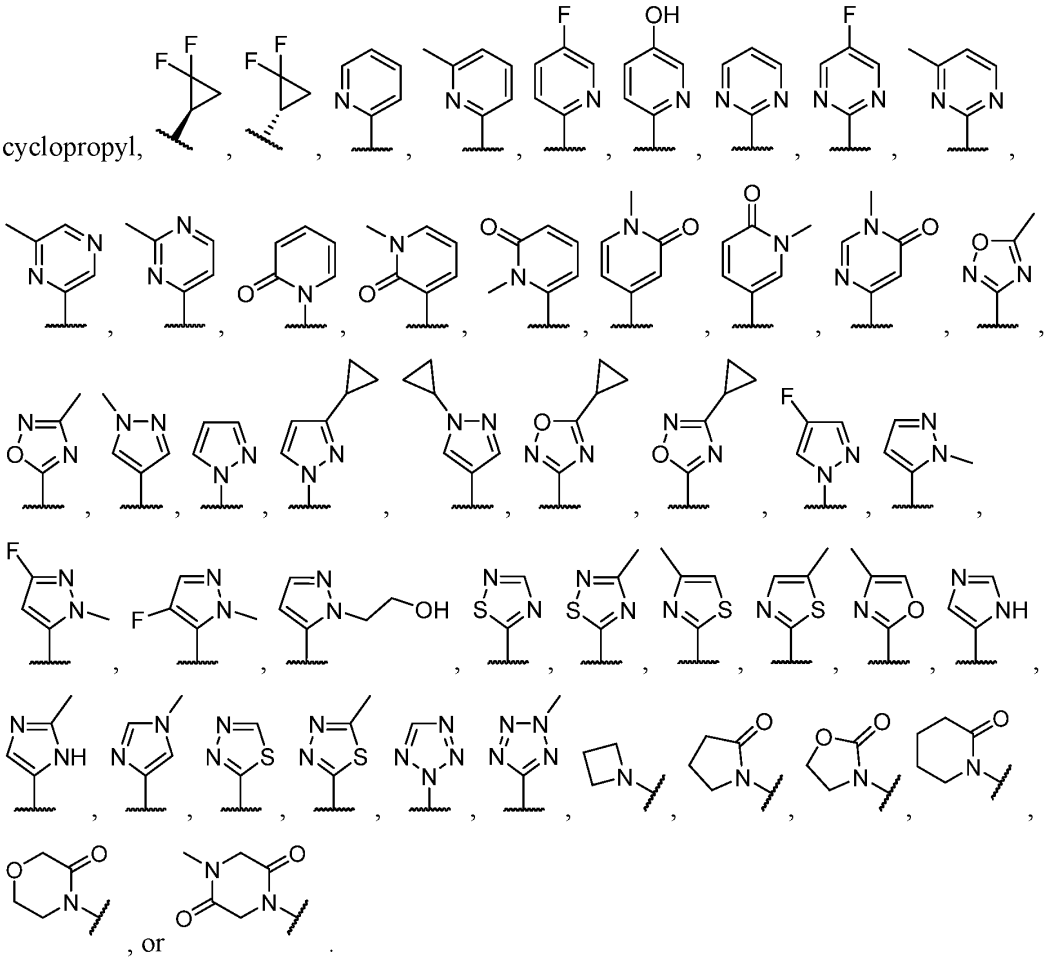
25. The compound of any one of claims 7 to 24, wherein R^9 is hydrogen.

26. The compound of any one of claims 7 to 23, wherein  is  ,

 ,  , or  .

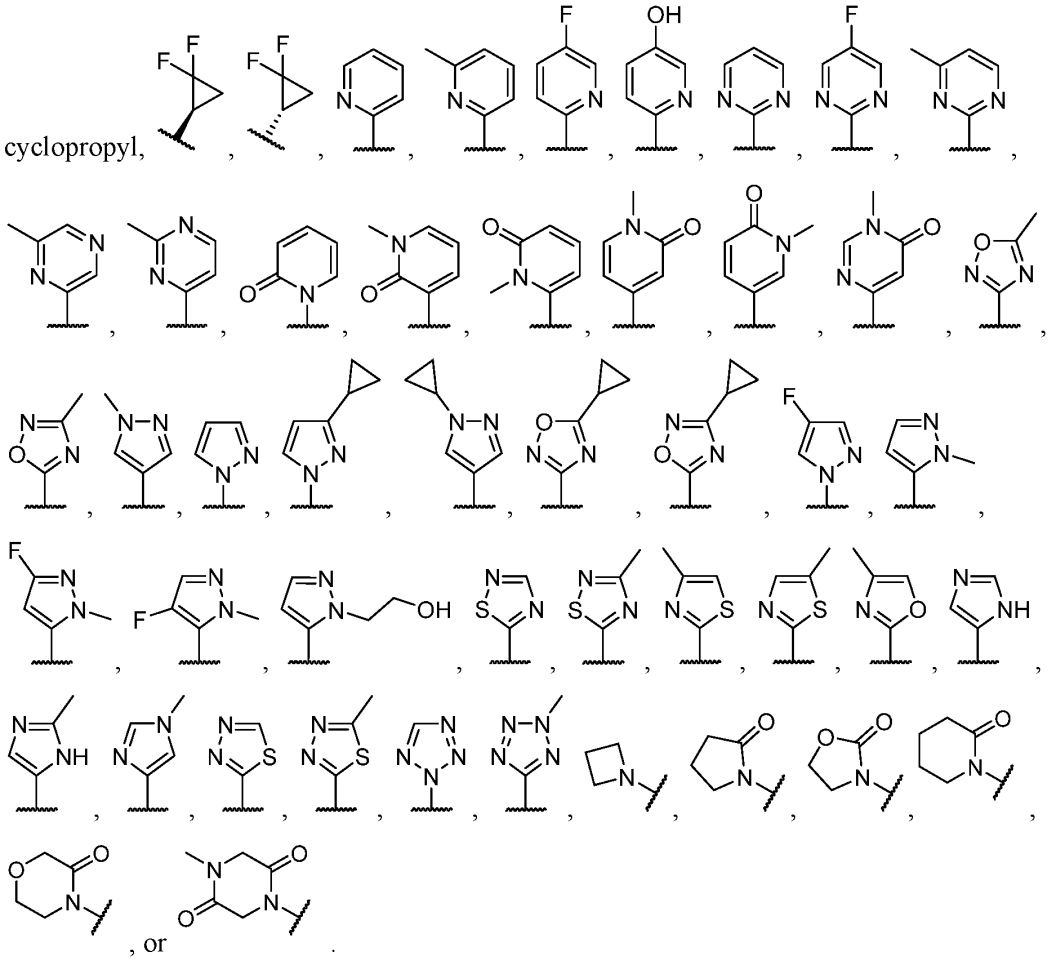
27. The compound of any one of claims 7 to 26, wherein R^7 is hydrogen, deuterium, halogen (*e.g.*, F), C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, C_{1-4} alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3)

deuterium or F, C_{3-6} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium or F, 5- or 6-membered heteroaryl optionally substituted with 1-2 R^j, or 3- to 6-membered heterocyclyl optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F or OH, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) F, or C_{3-4} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F.

28. The compound of claim 27, wherein R^7 is hydrogen, CH_3, CF_3, F, methoxy, cyclopropyl,  , or .

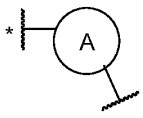
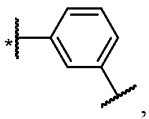
29. The compound of any one of claims 7 to 28, wherein R^8 is hydrogen, deuterium, halogen (*e.g.*, F), C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, C_{1-4} alkoxy optionally substituted with one or more (*e.g.*, 1, 2, or 3) deuterium or F, C_{3-6} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, 3, or 4) deuterium or F, 5- or 6-membered heteroaryl optionally substituted with 1-2 R^j, or 3- to 6-

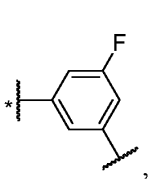
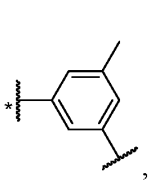
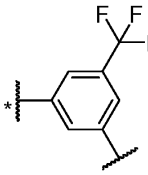
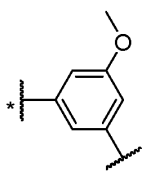
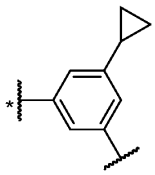
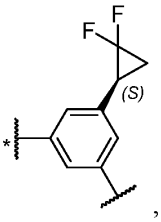
membered heterocyclyl optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F or OH, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with one or more (*e.g.*, 1, 2, or 3) F, or C_{3-4} cycloalkyl optionally substituted with one or more (*e.g.*, 1, 2, or 3) F.

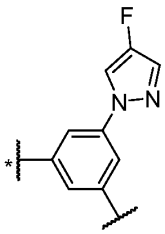
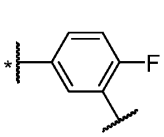
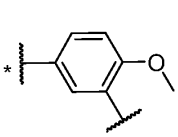
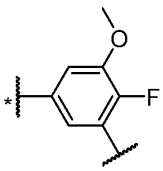
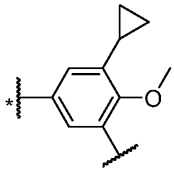
30. The compound of claim 29, wherein R^8 is hydrogen, CH_3, CF_3, F, methoxy, cyclopropyl,  , or .

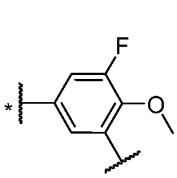
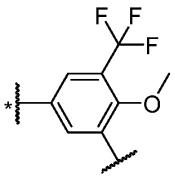
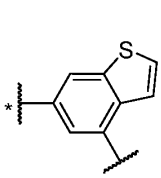
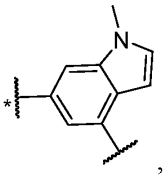
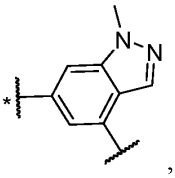
31. The compound of any one of claims 7 to 26, wherein R^7 and R^8, together with the carbon atoms they are attached to, form a 4- to 8-membered ring, which is optionally substituted with one or more (*e.g.*, 1, 2, or 3) R^n.

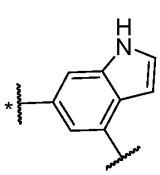
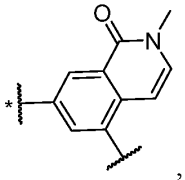
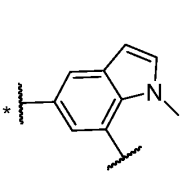
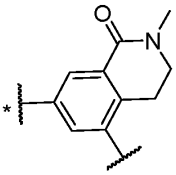
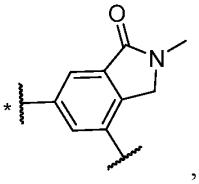
32. The compound of claim 31, wherein R^7 and R^8, together with the carbon atoms they are attached to, form a 5-membered heteroaryl, which is optionally substituted with one or more (*e.g.*, 1, 2, or 3) R^n.

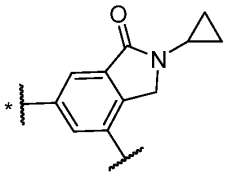
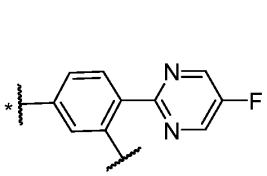
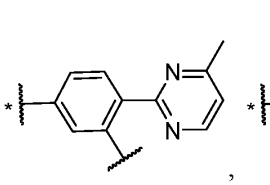
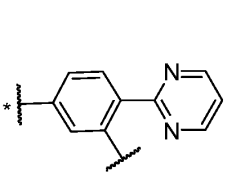
33. The compound of any one of claims 1 to 32, wherein  is  ,

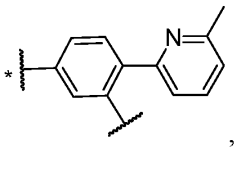
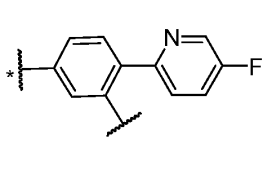
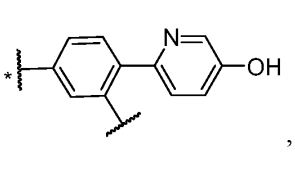
 ,  ,  ,  ,  ,  ,

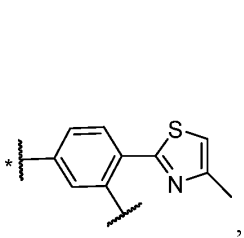
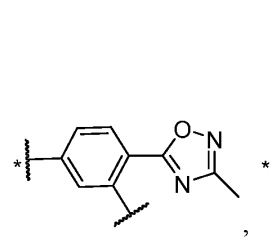
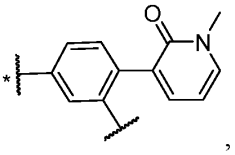
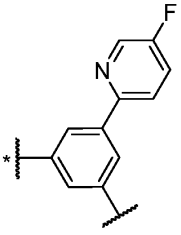
 ,  ,  ,  ,  ,

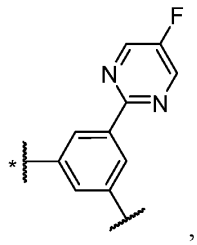
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,  ,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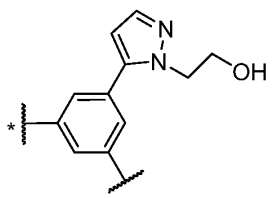
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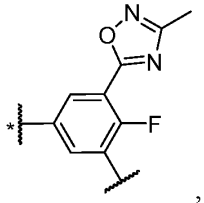
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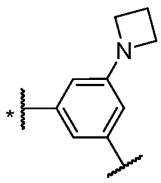
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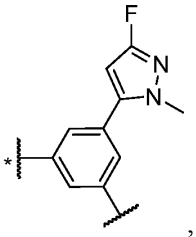
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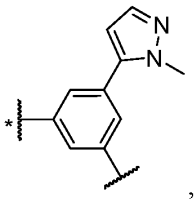

, or

, wherein * refers to the direction of X.

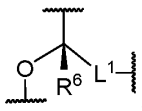
34. The compound of any one of claims 1 to 33, wherein both n1 and n2 are 0.

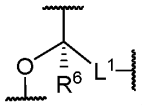
35. The compound of any one of claims 1 to 34, wherein R^6 is hydrogen, deuterium, CH_3, or CF_3.

36. The compound of any one of claims 1 to 35, wherein R^4 is hydrogen.

37. The compound of any one of claims 1 to 36, wherein R^5 is hydrogen.

38. The compound of any one of claims 1 to 37, wherein R^2 is hydrogen.

39. The compound of any one of claims 1 to 38, wherein the carbon connected to R^6 has configuration of  .

40. The compound of any one of claims 1 to 38, wherein the carbon connected to R^6 has configuration of  .

41. A compound in Table 1 or Table 1A, or a stereoisomer, a mixture of stereoisomers, isotopologue, or pharmaceutically acceptable salt thereof.

42. A pharmaceutical composition comprising the compound of any one of claims 1 to 41, and a pharmaceutically acceptable excipient.

43. A method of treating cancer, comprising administering to a subject having the cancer a therapeutically effective amount of the compound of any one of claims 1 to 41, or the pharmaceutical composition of claim 42.

44. The method of claim 43, wherein the cancer is selected from the group consisting of a cancer of the adrenal gland, bone, brain, breast, bronchi, colon and/or rectum, gallbladder, head and neck, kidneys, larynx, liver, lung, neural tissue, pancreas, prostate, parathyroid, skin, stomach, and thyroid; and acute and chronic lymphocytic and granulocytic tumors, adenocarcinoma, adenoma, basal cell carcinoma, cervical dysplasia and in situ carcinoma, Ewing's sarcoma, epidermoid carcinomas, giant cell tumor, glioblastoma multiforma, hairy-cell tumor, intestinal ganglioneuroma, hyperplastic corneal nerve tumor, islet cell carcinoma, Kaposi's sarcoma, leiomyoma, leukemias, lymphomas, malignant carcinoid, malignant melanomas, malignant hypercalcemia, marfanoid habitus tumor, medullary carcinoma, metastatic skin carcinoma, mucosal neuroma, myeloma, mycosis fungoides, neuroblastoma, osteo sarcoma, osteogenic and other sarcoma, ovarian tumor, pheochromocytoma, polycythermia vera, primary brain tumor, small-cell lung tumor, squamous cell carcinoma of both ulcerating and papillary type, hyperplasia, seminoma, soft tissue sarcoma, retinoblastoma, rhabdomyo sarcoma, renal cell tumor, topical skin lesion, veticulum cell sarcoma, and Wilm's tumor.

45. The method of claim 43, wherein the cancer is liver cancer, non-small cell lung cancer, melanoma, renal cell carcinoma, or prostate cancer.

46. The method of any one of claims 43 to 45, wherein the cancer is characterized as having abnormal AKR1C3 activity and/or overexpression of AKR1C3.