



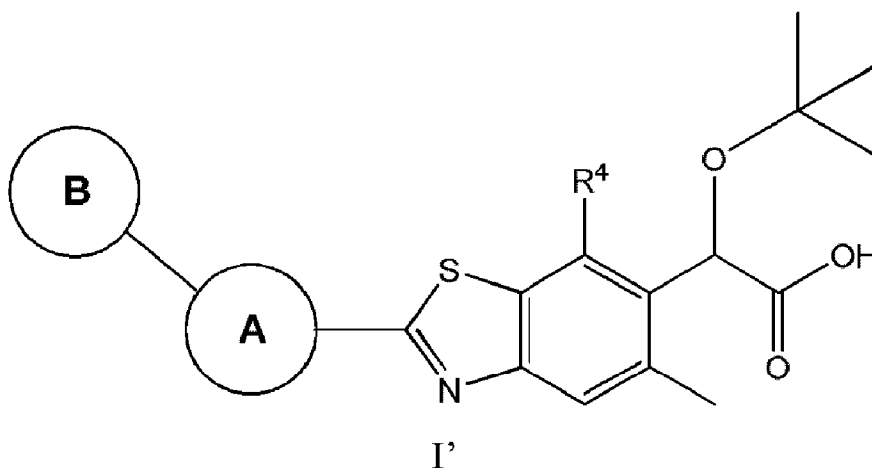
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(54) Titre : DERIVES D'ACIDE BENZOTHAZOL-6-YL ACETIQUE ET LEUR UTILISATION DANS LE TRAITEMENT D'UNE INFECTION PAR LE VIH
(54) Title: BENZOTHAZOL-6-YL ACETIC ACID DERIVATIVES AND THEIR USE FOR TREATING AN HIV INFECTION



(57) **Abrégé/Abstract:**

Compounds disclosed herein including compounds of formula (I') and salts thereof are provided. Pharmaceutical compositions comprising compounds disclosed herein, processes for preparing compounds disclosed herein, intermediates useful for preparing

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compounds disclosed herein and therapeutic methods for treating an HIV infection using compounds disclosed herein are also provided.

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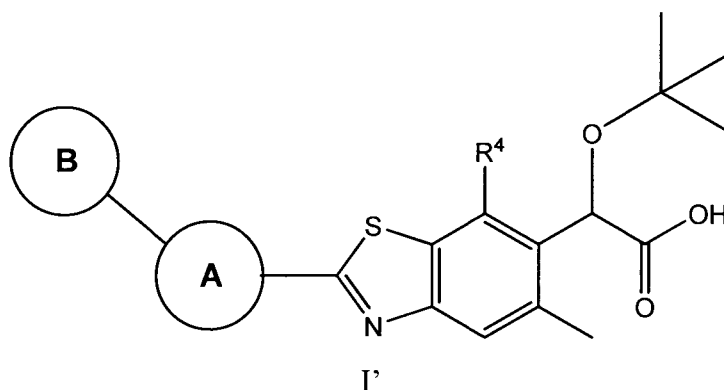
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(54) Title: BENZOTHAZOL-6-YL ACETIC ACID DERIVATIVES AND THEIR USE FOR TREATING AN HIV INFECTION



(57) Abstract: Compounds disclosed herein including compounds of formula (I') and salts thereof are provided. Pharmaceutical compositions comprising compounds disclosed herein, processes for preparing compounds disclosed herein, intermediates useful for preparing compounds disclosed herein and therapeutic methods for treating an HIV infection using compounds disclosed herein are also provided.

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
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BENZOTHIAZOL-6-YL ACETIC ACID DERIVATIVES AND THEIR USE FOR TREATING AN HIV INFECTION

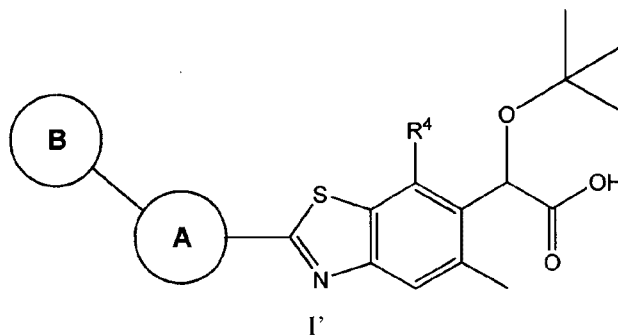
Background of the Invention

5 Human immunodeficiency virus (HIV) infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant
10 strains have limited their usefulness (Palella, et al *N. Engl. J. Med.* (1998) 338:853-860; Richman, D. D. *Nature* (2001) 410:995-1001).

Accordingly, there is a need for new agents that inhibit the replication of HIV. There is also a need for agents that are directed against alternate sites in the viral life cycle including agents that target the integrase enzyme. There is also a need for new agents with appropriate levels of
15 metabolic stability.

Summary

Compounds and methods for the treatment of an HIV infection are disclosed. Accordingly, one embodiment provides a compound of formula I':



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wherein:

R⁴ is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups each independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl,

(C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo;

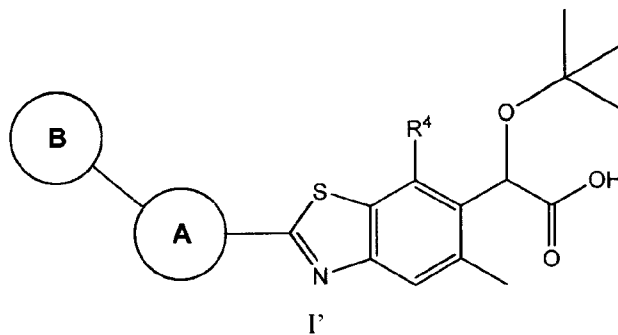
A is phenyl, monocyclic heteroaryl or monocyclic heterocycle, wherein any phenyl, monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle wherein bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups;

each Z^{1a} is independently selected from halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, (C₁-C₃)haloalkyl, (C₃-C₇)carbocycle, heterocycle, -O(C₁-C₃)alkyl, -O(C₂-C₃)alkenyl, -O(C₂-C₃)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle and heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C₁-C₆)alkyl;

each Z^{1b} is independently selected from halo, CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, heteroaryl, heterocycle, aryl(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle and heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C₁-C₆)alkyl; and

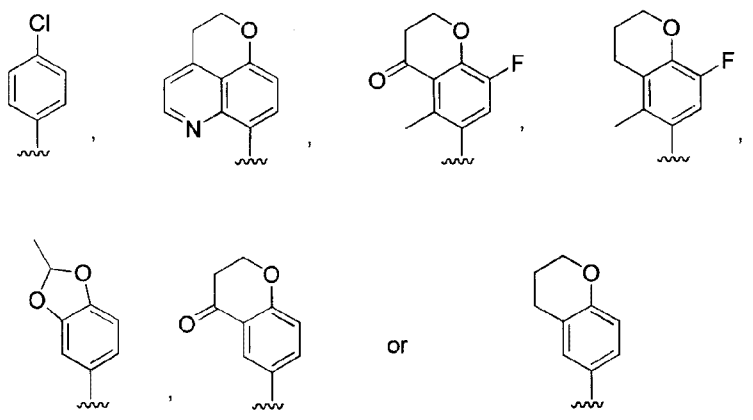
R_a, R_b, R_c and R_d are each independently H or (C₁-C₆)alkyl; or a salt thereof.

One embodiment provides a compound of formula I':



wherein:

R⁴ is:



A is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridinyl-2(1H)-one, tetrahydropyrimidin-2(1H)-one, imidazolidinyl-2-one, pyrrolidinyl-2-one, pyrrolidinyl, pyridazinyl, thiazolyl, pyrazin-2(1H)-one, piperazinyl-2-one, piperazinyl, imidazolyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl or piperidinyl, wherein any phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridinyl-2(1H)-one, tetrahydropyrimidin-2(1H)-one, imidazolidinyl-2-one, pyrrolidinyl-2-one, pyrrolidinyl, pyridazinyl, thiazolyl, pyrazin-2(1H)-one, piperazinyl-2-one, piperazinyl, imidazolyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl or piperidinyl of A is optionally substituted with one to five Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one to five Z^{1b} groups; or A and B together form a (C₉-C₁₄)bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle, wherein (C₉-C₁₄)bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one to five Z^{1b} groups;

each Z^{1a} is independently selected from halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, (C₁-C₃)haloalkyl, (C₃-C₇)carbocycle, heterocycle, -O(C₁-C₃)alkyl, -O(C₂-C₃)alkenyl, -O(C₂-C₃)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle and heterocycle of Z^{1a} is optionally substituted with one to five halogen or (C₁-C₆)alkyl;

each Z^{1b} is independently selected from halo, CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, heteroaryl, heterocycle, aryl(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle and heterocycle of Z^{1b} is optionally substituted with one to five halogen or (C₁-C₆)alkyl; and

R_a, R_b, R_c and R_d are each independently H or (C₁-C₆)alkyl;

wherein each heteroaryl is a single aromatic ring of from 1 to 6 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur or is a portion of

a multiple condensed ring system comprising 2 or 3 rings; and wherein each heterocycle is a single saturated or partially unsaturated ring of from 1 to 6 carbon atoms and 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur or is a portion of a multiple condensed ring system comprising 2 or 3 rings;

5 or a pharmaceutically acceptable salt thereof.

One embodiment provides a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of formula I, I' etc.) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10 One embodiment provides methods for treating the proliferation of the HIV virus, treating AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human), comprising administering a compound disclosed herein (e.g., a compound of formula I, I' etc.), or a pharmaceutically acceptable salt thereof, to the mammal.

One embodiment provides methods for treating an HIV infection in a mammal (e.g., a human) comprising administering a compound disclosed herein (e.g., a compound of formula I, I' etc.), or a pharmaceutically acceptable salt thereof, to the mammal.

One embodiment provides methods for treating an HIV infection in a mammal (e.g., a human) comprising administering to the mammal in need thereof a therapeutically effective

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amount of a compound disclosed herein (e.g., a compound of formula I, I' etc.), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof.

One embodiment provides a compound disclosed herein (e.g., a compound of formula I, I' etc.), or a pharmaceutically acceptable salt thereof for use in medical therapy (e.g., for use in treating the proliferation of the HIV virus or AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human)).

One embodiment provides a compound disclosed herein (e.g., a compound of formula I, I' etc.), or a pharmaceutically acceptable salt thereof for use in medical therapy (e.g., for use in treating an HIV infection in a mammal (e.g., a human)).

One embodiment provides a compound disclosed herein (e.g., a compound of formula I, I' etc.), or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating the proliferation of the HIV virus or AIDS or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human).

One embodiment provides a compound disclosed herein (e.g., a compound of formula I, I' etc.), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of the proliferation of the HIV virus or AIDS or for use in the therapeutic treatment of delaying the onset of AIDS or ARC symptoms.

One embodiment provides a compound disclosed herein (e.g., a compound of formula I, I' etc.), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating an HIV infection in a mammal (e.g., a human).

One embodiment provides a compound disclosed herein (e.g., a compound of formula I, I' etc.) or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection in a mammal (e.g., a human).

One embodiment provides a pharmaceutical composition comprising a compound of formula I' as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

One embodiment provides the use of the pharmaceutical composition as defined herein for treating an HIV infection in a mammal.

One embodiment provides a pharmaceutical composition as described herein for use in treating an HIV infection in a mammal.

One embodiment provides the use of a compound of formula I' as defined herein, or a pharmaceutically acceptable salt thereof, for treating an HIV infection in a mammal.

One embodiment provides a compound of formula I' as described herein, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection in a mammal.

One embodiment provides a compound of formula I' as described herein, or a pharmaceutically acceptable salt thereof, for use in combination with one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof for the prophylactic or therapeutic treatment of an HIV infection in a mammal.

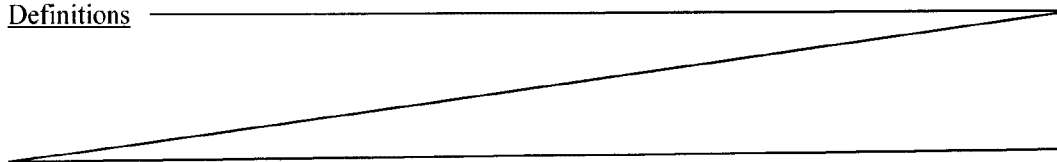
One embodiment provides a compound of formula I' as described herein, or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment of an HIV infection in a mammal.

One embodiment provides a compound of formula I' as described herein, or a pharmaceutically acceptable salt thereof, for use in combination with one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof for the prophylactic or therapeutic treatment of an HIV infection in a mammal.

One embodiment provides processes and intermediates disclosed herein that are useful for preparing compounds disclosed herein or salts thereof.

Detailed Description

Definitions



Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings.

When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

- 5 “Alkyl” is hydrocarbon containing normal, secondary or tertiary atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e.*, (C₁-C₂₀)alkyl), 1 to 10 carbon atoms (*i.e.*, (C₁-C₁₀)alkyl), 1 to 8 carbon atoms (*i.e.*, (C₁-C₈)alkyl) or 1 to 6 carbon atoms (*i.e.*, (C₁-C₆)alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃), 2-propyl (*i*-Pr, *i*-propyl, -CH(CH₃)₂), 1-
10 butyl (n-Bu, n-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, -CH₂CH(CH₃)₂), 2-butyl (s-Bu, s-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, -C(CH₃)₃), 1-pentyl (n-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl
15 (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-
20 CH(CH₃)C(CH₃)₃, and octyl (-CH₂)₇CH₃). “Alkyl” also refers to a saturated, branched or straight chain hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkyl group can have 1 to 10 carbon atoms (*i.e.*, (C₁-C₁₀)alkyl), or 1 to 6 carbon atoms (*i.e.*, (C₁-C₆)alkyl) or 1-3 carbon atoms (*i.e.*, (C₁-C₃)alkyl). Typical alkyl radicals include, but are not
25 limited to, methylene (-CH₂-), 1,1-ethyl (-CH(CH₃)-), 1,2-ethyl (-CH₂CH₂-), 1,1-propyl (-CH(CH₂CH₃)-), 1,2-propyl (-CH₂CH(CH₃)-), 1,3-propyl (-CH₂CH₂CH₂-), 1,4-butyl (-CH₂CH₂CH₂CH₂-), and the like.

The term “halo” or “halogen” as used herein refers to fluoro, chloro, bromo and iodo.

- The term “haloalkyl” as used herein refers to an alkyl as defined herein, wherein one or
30 more hydrogen atoms are each replaced by a halo substituent. For example, a (C₁-C₆)haloalkyl is a (C₁-C₆)alkyl wherein one or more of the hydrogen atoms have been replaced by a halo substituent. Such a range includes one halo substituent on the alkyl group to complete halogenation of the alkyl group.

The term "aryl" as used herein refers to a single aromatic ring or a bicyclic or multicyclic ring. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Aryl includes a phenyl radical or an ortho-fused bicyclic or multicyclic radical having about 9 to 14 atoms in which at least one ring is aromatic (e.g., an aryl fused to one or more aryl or carbocycle). Such bicyclic or multicyclic rings may be optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups on any carbocycle portion of the bicyclic or multicyclic ring. It is to be understood that the point of attachment of a bicyclic or multicyclic radical, as defined above, can be at any position of the ring including an aryl or a carbocycle portion of the ring. Exemplary aryl groups include, but are not limited to, phenyl, indenyl, naphthyl, 1, 2, 3, 4-tetrahydronaphthyl, anthracenyl, and the like.

"Arylalkyl" refers to an alkyl radical as defined herein in which one of the hydrogen atoms bonded to a carbon atom is replaced with an aryl radical as described herein (*i.e.*, an aryl-alkyl- moiety). The alkyl group of the "arylalkyl" is typically 1 to 6 carbon atoms (*i.e.* aryl(C₁-C₆)alkyl). Arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 1-phenylpropan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl and the like.

The term "heteroaryl" as used herein refers to a single aromatic ring or a multiple condensed ring. The term includes single aromatic rings of from about 1 to 6 carbon atoms and about 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the rings. The sulfur and nitrogen atoms may also be present in an oxidized form provided the ring is aromatic. Such rings include but are not limited to pyridyl, pyrimidinyl, oxazolyl or furyl. The term also includes multiple condensed ring systems (e.g., ring systems comprising 2 or 3 rings) wherein a heteroaryl group, as defined above, can be fused with one or more heteroaryls (e.g., naphthyridinyl), carbocycles (e.g., 5,6,7,8-tetrahydroquinolyl) or aryls (e.g., indazolyl) to form a multiple condensed ring. Such multiple condensed rings may be optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups on the carbocycle portions of the condensed ring. It is to be understood that the point of attachment of a heteroaryl multiple condensed ring, as defined above, can be at any position of the ring including a heteroaryl, aryl or a carbocycle portion of the ring. Exemplary heteroaryls include but are not limited to pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxalyl, quinazolyl, 5,6,7,8-tetrahydroisoquinolinyl, benzofuranyl, benzimidazolyl, thianaphthenyl, pyrrolopyridinyl and pyrazolopyridinyl.

The term "N-heteroaryl" refers to a heteroaryl that contains at least one nitrogen atom within the ring system.

The term "heterocyclyl" or "heterocycle" as used herein refers to a single saturated or partially unsaturated ring or a multiple condensed ring. The term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6 or 7-membered ring) from about 1 to 6 carbon atoms and from about 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The ring may be substituted with one or more (e.g., 1, 2 or 3) oxo groups and the sulfur and nitrogen atoms may also be present in their oxidized forms. Such rings include but are not limited to azetidiny, tetrahydrofuranyl or piperidiny. The term also includes multiple condensed ring systems (e.g., ring systems comprising 2 or 3 rings) wherein a heterocycle group (as defined above) can be connected to two adjacent atoms (fused heterocycle) with one or more heterocycles (e.g., decahydronaphthyridiny), heteroaryls (e.g., 1,2,3,4-tetrahydronaphthyridiny), carbocycles (e.g., decahydroquinoly) or aryls. It is to be understood that the point of attachment of a heterocycle multiple condensed ring, as defined above, can be at any position of the ring including a heterocycle, heteroaryl, aryl or a carbocycle portion of the ring. Exemplary heterocycles include, but are not limited to aziridiny, azetidiny, pyrrolidiny, piperidiny, homopiperidiny, morpholiny, thiomorpholiny, piperaziny, tetrahydrofuranyl, dihydrooxazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,2,3,4-tetrahydroquinoly, benzoxazinyl, dihydrooxazolyl, chromanyl, 1,2-dihydropyridiny, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, tetrahydropyrimidinyl-2-one, imidazolidinyl-2-one, pyrrolidinyl-2-one, 2,3-dihydropyrano[4,3,2-de]quinolonyl, 2,5-benzo[d][1,3]dioxolyl and chromanyl-4-one.

The term "bridged-heterocycle" as used herein refers to a 4, 5, 6, 7 or 8-membered heterocycle as defined herein connected at two non-adjacent atoms of the 4, 5, 6, 7 or 8-membered heterocycle with one or more (e.g., 1 or 2) 3, 4, 5 or 6-membered heterocycles or (C₃-C₇)carbocycles as defined herein. Such bridged-heterocycles include bicyclic and tricyclic ring systems (e.g., 2-azabicyclo[2.2.1]heptane and 4-azatricyclo[4.3.1.1^{3,8}]undecane).

The term "spiro-heterocycle" as used herein refers to a 3, 4, 5, 6, 7 or 8-membered heterocycle as defined herein connected to one or more (e.g., 1 or 2) single atoms of the 3, 4, 5, 6, 7 or 8-membered heterocycle with one or more (e.g., 1 or 2) 3, 4, 5, 6-membered heterocycles or a (C₃-C₇)carbocycles as defined herein. Such spiro-heterocycles include bicyclic and tricyclic ring systems (e.g., 1,4-dioxaspiro[4.5]dec-7-enyl).

The term "macroheterocycle" as used herein refers to a saturated or partially unsaturated 8, 9, 10, 11 or 12-membered ring comprising about 5 to 11 carbon atoms and about 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring which may be optionally fused at two adjacent atoms of the macroheterocycle to one or more (e.g., 1, 2

or 3) aryls, carbocycles, heteroaryls or heterocycles. The macroheterocycle may be substituted with one or more (e.g., 1, 2 or 3) oxo groups and the sulfur and nitrogen atoms may also be present in their oxidized forms.

“Heteroarylalkyl” refers to an alkyl radical as defined herein in which one of the
5 hydrogen atoms bonded to a carbon atom is replaced with a heteroaryl radical as described herein (*i.e.*, a heteroaryl-alkyl- moiety). The alkyl group of the “heteroarylalkyl” is typically 1 to 6 carbon atoms (*i.e.*, heteroaryl(C₁-C₆)alkyl). Heteroarylalkyl groups include, but are not limited to heteroaryl-CH₂-, heteroaryl-CH(CH₃)-, heteroaryl-CH₂CH₂-, 2-(heteroaryl)ethan-1-yl, and the like, wherein the “heteroaryl” portion includes any of the heteroaryl groups described
10 above. One skilled in the art will also understand that the heteroaryl group can be attached to the alkyl portion of the heteroarylalkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. Examples of heteroarylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heteroaryls such as thiazolylmethyl, 2-thiazolylethan-1-yl,
15 imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heteroaryls such as pyridinylmethyl, pyridizylmethyl, pyrimidinylmethyl, pyrazinylmethyl, etc.

“Heterocyclalkyl” refers to an alkyl radical as defined herein in which one of the
20 hydrogen atoms bonded to a carbon atom is replaced with a heterocyclalkyl radical as described herein (*i.e.*, a heterocyclalkyl- moiety). The alkyl group of the “heterocyclalkyl” is typically 1 to 6 carbon atoms (*i.e.* heterocyclalkyl(C₁-C₆)alkyl). Typical heterocyclalkyl groups include, but are not limited to heterocyclalkyl-CH₂-, heterocyclalkyl-CH(CH₃)-, heterocyclalkyl-CH₂CH₂-, 2-(heterocyclalkyl)ethan-1-yl, and the like, wherein the “heterocyclalkyl” portion includes any of the heterocyclalkyl groups described above. One skilled in the art will also understand that
25 the heterocyclalkyl group can be attached to the alkyl portion of the heterocyclalkyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. Examples of heterocyclalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as tetrahydrofuranylmethyl and pyrrolidinylmethyl, etc., and 6-membered sulfur, oxygen, and/or
30 nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, etc.

The term “carbocycle” or “carbocyclalkyl” refers to a saturated (*i.e.*, cycloalkyl) or partially unsaturated (e.g., cycloalkenyl, cycloalkadienyl, etc.) ring having 3 to 7 carbon atoms as a monocycle or a mutlicyclic ring system. In one embodiment the carbocycle is a monocycle

comprising 3-6 ring carbons (i.e. (C₃-C₆)carbocycle). Carbocycle includes multicyclic carbocycles having 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle provided that the largest single ring of a multicyclic carbocycle is 7 carbon atoms. The term "spiro-bicyclic carbocycle" refers to a carbocycle bicyclic ring system wherein the
5 rings of the bicyclic ring system are connected to a single carbon atom (e.g., spiropentane, spiro[4,5]decane, spiro[4.5]decane, etc). The term "fused-bicyclic carbocycle" refers to a carbocycle bicyclic ring system wherein the rings of the bicyclic ring system are connected to two adjacent carbon atoms such as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system (e.g., decahydronaphthalene, norsabinane,
10 norcarane). The term "bridged-bicyclic carbocycle" refers to a carbocycle bicyclic ring system wherein the rings of the bicyclic ring system are connected to two non-adjacent carbon (e.g., norbornane, bicyclo[2.2.2]octane, etc). The "carbocycle" or "carbocyclyl" may be optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-
15 enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl and 1-cyclohex-3-enyl.

The term "halocarbocycle" as used herein refers to a carbocycle as defined herein, wherein one or more hydrogen atoms are each replaced by a halo substituent. For example, (C₃-C₇)halocarbocycle is a (C₃-C₇)carbocycle wherein one or more of the hydrogen atoms have been
20 replaced by a halo substituent. Such a range includes one halo substituent on the carbocycle group to complete halogenation of the carbocycle group.

The term "macrocarbocycle" as used herein refers to a saturated or partially unsaturated 8, 9, 10, 11 or 12-membered ring comprising 8 to 12 carbon atoms which may be optionally fused at two adjacent atoms of the macrocarbocycle to one or more (e.g., 1, 2 or 3) aryls,
25 carbocycles, heteroaryls or heterocycles. The macrocarbocycle may be substituted with one or more (e.g., 1, 2 or 3) oxo groups.

"Carbocyclylalkyl" refers to an alkyl radical as defined herein in which one of the hydrogen atoms bonded to a carbon atom is replaced with a carbocyclyl radical as described herein (*i.e.*, a carbocyclyl-alkyl- moiety). The alkyl group of the "carbocyclylalkyl" is typically
30 1 to 6 carbon atoms (*i.e.* carbocyclyl(C₁-C₆)alkyl). Typical carbocyclyl alkyl groups include, but are not limited to carbocyclyl-CH₂-, carbocyclyl-CH(CH₃)-, carbocyclyl-CH₂CH₂-, 2-(carbocyclyl)ethan-1-yl, and the like, wherein the "carbocyclyl" portion includes any of the carbocyclyl groups described above.

It is to be understood that when a variable is substituted, for example, as described by the phrase “(C₁-C₆)alkyl, either alone or as part of a group, is optionally substituted”, the phrase means that the variable (C₁-C₆)alkyl can be substituted when it is alone and that it can also be substituted when the variable “(C₁-C₆)alkyl” is part of a larger group such as for example an aryl(C₁-C₆)alkyl or a -(C₁-C₆)alkyl-SO₂-(C₁-C₆)alkyl-(C₃-C₇)carbocycle group. Similarly, when stated, other variables (e.g., (C₁-C₆)alkenyl, (C₁-C₆)alkynyl, aryl, heteroaryl, heterocycle, etc.) can also be substituted “either alone or as part of a group.”

It is to be understood that certain variables of formula I, that connect two chemical groups may be oriented in either direction. Thus, for the X group of formula I (e.g., O, -C(O)-, -C(O)O-, -S-, -S(O)-, -SO₂-, -(C₁-C₆)alkylO-, -(C₁-C₆)alkylC(O)-, -(C₁-C₆)alkylC(O)O-, -(C₁-C₆)alkylS-, -(C₁-C₆)alkylS(O)- and -(C₁-C₆)alkylSO₂-) certain values of X that are not symmetric can be oriented in either direction. For example, the -C(O)O-, can be oriented as either -C(O)O- or -OC(O)-, relative to the groups it connects.

It is to be understood that the nitrogen that is included in the core of the compound of formula I or formula I' can be present in an oxidized form. For example, the thiazole nitrogen of either G¹ or G² of formula I can be an N-oxide. Accordingly, the invention includes a compound of formula I or formula I' (as defined in the summary of the invention) or a salt or N-oxide thereof.

One skilled in the art will recognize that substituents and other moieties of the compounds disclosed herein should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds disclosed herein which have such stability are contemplated as falling within the scope of the present invention.

The modifier “about” used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity).

The term “chiral” refers to molecules which have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner.

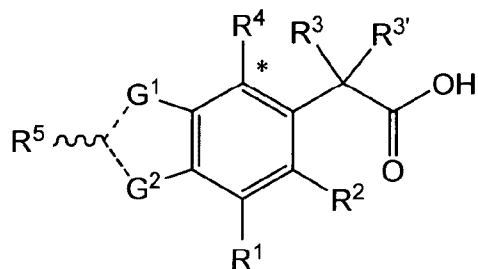
The term “stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

“Diastereomer” refers to a stereoisomer with two or more centers or axes of chirality and whose molecules are not mirror images of one another. Diastereomers typically have different physical properties, *e.g.*, melting points, boiling points, spectral properties, and reactivities.

Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

“Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

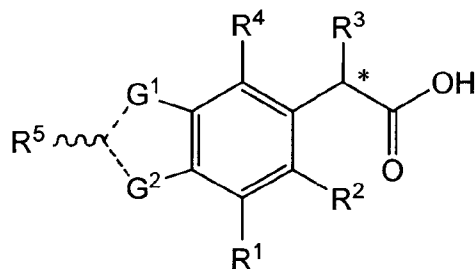
- 5 Certain compounds of the invention can exist as atropisomers. For example, it has been discovered that atropisomers exist for certain substituents at the R^4 position of compounds of the invention (e.g., compounds of formula I, I' and related formulas described herein) as marked by an asterisk in the formula below.



- 10 The chirality that results from the atropisomers at the asterisk position is a feature of certain compounds of the invention. Accordingly, the invention includes all atropisomers of compounds of the invention including mixtures of atropisomers and well as mixtures that are enriched in an atropisomer as well as single atropisomers, which mixtures or compounds possess the useful properties described herein.

- 15 In one embodiment, the compounds of the invention are greater than 50% a single atropisomer for the R^4 substituent at the asterisk position. In one embodiment, the compounds of the invention are at least 60% a single atropisomer for the R^4 substituent at the asterisk position. In another embodiment, the compounds of the invention are at least 70% a single atropisomer for the R^4 substituent at the asterisk position. In another embodiment, the
- 20 compounds of the invention are at least 80% a single atropisomer for the R^4 substituent at the asterisk position. In another embodiment, the compounds of the invention are at least 90% a single atropisomer for the R^4 substituent at the asterisk position. In another embodiment, the compounds of the invention are at least 95% a single atropisomer for the R^4 substituent at the asterisk position. In one embodiment the stereochemistry for the R^4 substituent at the carbon
- 25 marked with an asterisk as shown above for a compound of the invention (e.g., compounds of formula I or formula I') is the (R) stereochemistry. In another embodiment the stereochemistry for the R^4 substituent at the carbon marked with an asterisk as shown above for a compound of the invention (e.g., compounds of formula I or formula I') is the (S) stereochemistry.

For certain compounds of the invention the stereochemistry at the carbon bearing the R³ substituent of compounds of the invention (e.g., compounds of formula I or formula I') as marked by an asterisk in the formula below is another aspect of the invention.



In one embodiment the stereochemistry at the carbon marked with an asterisk as shown in the formula above for a compound of the invention is the (S) stereochemistry. In another embodiment the stereochemistry at the carbon marked with an asterisk as shown in the formula above for a compound of the invention is the (R) stereochemistry.

In one embodiment, the compounds of the invention are greater than 50% a stereoisomer for the carbon at the asterisk position. In another embodiment, the compounds of the invention are at least 60% a single stereoisomer for the carbon at the asterisk position. In another embodiment, the compounds of the invention are at least 70% a single stereoisomer for the carbon at the asterisk position. In another embodiment, the compounds of the invention are at least 80% a single stereoisomer for the carbon at the asterisk position. In another embodiment, the compounds of the invention are at least 90% a single stereoisomer for the carbon at the asterisk position. In another embodiment, the compounds of the invention are at least 95% a single stereoisomer for the carbon at the asterisk position.

It is to be understood that for compounds disclosed herein when a bond is drawn in a non-stereochemical manner (e.g. flat) the atom to which the bond is attached includes all stereochemical possibilities. It is also to be understood that when a bond is drawn in a stereochemical manner (e.g. bold, bold-wedge, dashed or dashed-wedge) the atom to which the stereochemical bond is attached has the stereochemistry as shown unless otherwise noted.

The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, and/or inhibiting the disease or condition, and/or eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have

the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes (D and L) or (R and S) are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning
5 that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no
10 stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Protecting Groups

15 In the context of the present disclosure, protecting groups include prodrug moieties and chemical protecting groups.

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g., Protective Groups*
20 *in Organic Chemistry*, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991.

Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity,
25 lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic
30 degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are

removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, *e.g.*, alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group “PG” will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. Protecting groups do not need to be, and generally are not, the same if the compound is substituted with multiple protecting groups. In general, protecting groups will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for –OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include “ether- or ester-forming groups”. Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) (“Greene”). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994). In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene.

Stereoisomers

The compounds of the invention may have chiral centers, *e.g.*, chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the
5 compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic
10 mixtures can be separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, *e.g.*, acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting
15 material.

The compounds described herein can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible
20 tautomeric forms are within the scope of the invention.

Salts and Hydrates

Examples of pharmaceutically acceptable salts of the compounds described herein include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1-C_4
25 alkyl). Pharmaceutically acceptable salts of a nitrogen atom or an amino group include for example salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, hydrobromic, sulfuric, phosphoric and sulfamic acids.
30 Pharmaceutically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1-C_4 alkyl group).

For therapeutic use, salts of active ingredients of the compounds disclosed herein will typically be pharmaceutically acceptable, *i.e.* they will be salts derived from a physiologically

acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a compound of disclosed herein. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

5 Metal salts can be prepared by reacting the metal hydroxide with a compound disclosed herein. Examples of metal salts which are prepared in this way are salts containing Li^+ , Na^+ , and K^+ . A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

10 In addition, salts may be formed from acid addition of certain organic and inorganic acids, *e.g.*, HCl , HBr , H_2SO_4 , H_3PO_4 or organic sulfonic acids, to basic centers, such as amines. Finally, it is to be understood that the compositions herein comprise compounds disclosed herein in their un-ionized, as well as zwitterionic form, and combinations with water as in hydrates. In one embodiment the hydrates include a compound disclosed herein with stoichiometric amounts of water.

15 Certain embodiments provide salts of the compounds disclosed herein with one or more amino acids. Any of the natural or unnatural amino acids are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, *e.g.*, lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

20

Isotopes

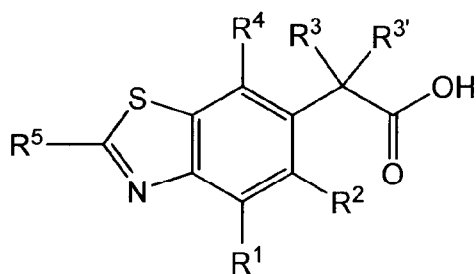
It is understood by one skilled in the art that this invention also includes any compound claimed that may be enriched at any or all atoms above naturally occurring isotopic ratios with one or more isotopes such as, but not limited to, deuterium (^2H or D). As a non-limiting
25 example, a $-\text{CH}_3$ group may be substituted with $-\text{CD}_3$.

Specific values listed below for radicals, substituents, and ranges in the embodiments of the invention are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

30

Compounds of formula I.

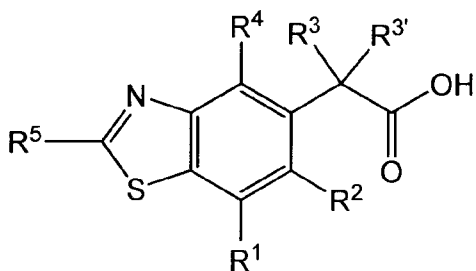
A specific group of compounds of formula I are compounds of formula Ia:



Ia

or a salt thereof.

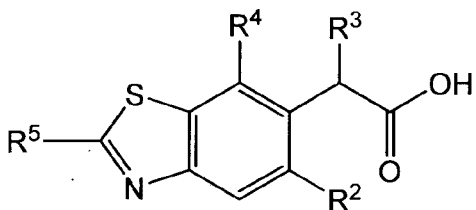
Another specific group of compounds of formula I are compounds of formula Ib:



Ib

or a salt thereof.

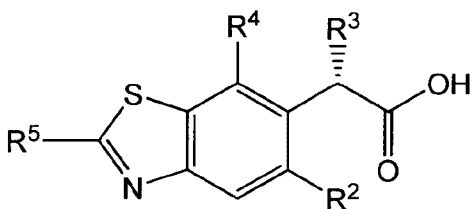
Another specific group of compounds of formula I are compounds of formula Ic:



Ic

wherein R³ is-O(C₁-C₆)alkyl or a salt thereof.

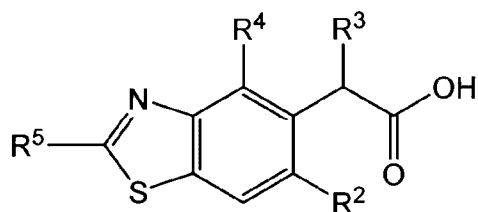
Another specific group of compounds of formula I are compounds of formula Ic':



Ic'

wherein R³ is-O(C₁-C₆)alkyl or a salt thereof.

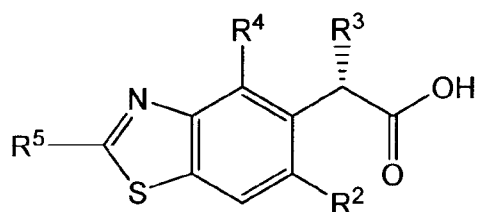
Another specific group of compounds of formula I are compounds of formula Id:



Id

wherein R³ is-O(C₁-C₆)alkyl, or a salt thereof.

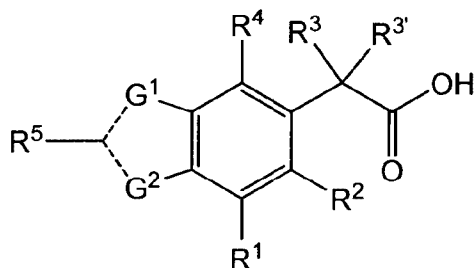
5 Another specific group of compounds of formula I are compounds of formula Id':



Id'

wherein R³ is-O(C₁-C₆)alkyl, or a salt thereof.

Another specific group of compounds of formula I are compounds of formula Ie:



Ie

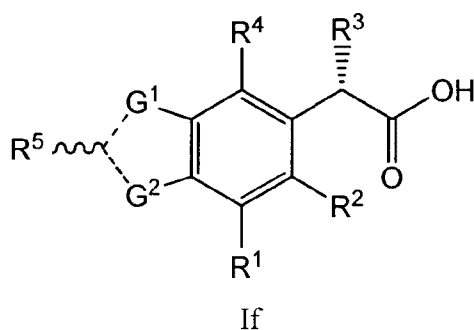
wherein:

15 G¹ is S; G² is N; the dashed bond connected to G¹ is a single bond and the dashed bond connected to G² is a double bond; or

G¹ is N; G² is S; the dashed bond connected to G¹ is a double bond and the dashed bond connected to G² is a single bond;

or a salt thereof.

Another specific group of compounds of formula I are compounds of formula If:



or a salt thereof.

Specific embodiments of the invention (e.g., embodiments) and specific values listed below are embodiments and values for compounds of formula I including all of the compounds of sub-formulas of formula I (e.g., the compounds of formulas Ia, Ib, Ic, Ic', Id, Id', Ie, If, Ia100-1a145, etc.) and for compounds of formulas I' and subformulas of I' (e.g., formula Ia'). It is to be understood that two or more of the values listed herein below may be combined with one another.

A specific group of compounds of formula I are compounds wherein at least one of R^1 , R^2 , R^3 , $R^{3'}$ or R^4 is selected from R^{1b} , R^{2b} , R^{3b} , $R^{3b'}$ or R^{4b} .

Another specific group of compounds of formula I are compounds wherein at least two of R^1 , R^2 , R^3 , $R^{3'}$ or R^4 is selected from R^{1b} , R^{2b} , R^{3b} , $R^{3b'}$ or R^{4b} .

Another specific group of compounds of formula I are compounds wherein at least three of R^1 , R^2 , R^3 , $R^{3'}$ or R^4 is selected from R^{1b} , R^{2b} , R^{3b} , $R^{3b'}$ or R^{4b} .

Another specific group of compounds of formula I are compounds wherein at least four of R^1 , R^2 , R^3 , $R^{3'}$ or R^4 is selected from R^{1b} , R^{2b} , R^{3b} , $R^{3b'}$ or R^{4b} .

Another specific group of compounds of formula I are compounds wherein all five of R^1 , R^2 , R^3 , $R^{3'}$ or R^4 is selected from R^{1b} , R^{2b} , R^{3b} , $R^{3b'}$ or R^{4b} .

Another specific group of compounds of formula I are compounds wherein R^1 , R^2 , R^3 , $R^{3'}$ and R^4 are R^{1b} , R^{2b} , R^{3b} , $R^{3b'}$ and R^{4b} .

A specific value for R^1 is H.

Another specific value for R^1 is H or halo.

Another specific value for R^1 is H or F.

A specific value for $R^{3'}$ is H.

A specific value for R^3 is R^{3b} .

A specific value for R^{3b} is $-\text{OC}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{OC}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl-O-C(O)-NH}_2$, $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl-O-C(O)-N}(\text{CH}_3)_2$ or $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl-O-C(O)-NH(phenyl)}$.

Another specific value for R^{3b} is $-(\text{C}_1\text{-C}_6)\text{alkylOH}$ or $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl-O-C(O)-NR}_d\text{R}_d$.

Another specific value for R^3 is R^{3a} .

A specific value for R^{3a} is (C_1-C_6) alkyl, (C_2-C_6) alkenyl or $-O(C_1-C_6)$ alkyl wherein any (C_1-C_6) alkyl or (C_2-C_6) alkenyl of R^{3a} is optionally substituted with one or more groups selected from $-O(C_1-C_6)$ alkyl, halo, oxo and $-CN$.

5 Another specific value for R^{3a} is $-OC(CH_3)_3$.

A specific value for $R^{3'}$ is $R^{3b'}$.

A specific value for $R^{3b'}$ is (C_1-C_6) alkyl or $-O(C_1-C_6)$ alkyl.

A specific value for $R^{3'}$ is $R^{3a'}$.

A specific value for $R^{3a'}$ is H.

10 A specific value for R^3 is (C_1-C_6) alkyl, (C_2-C_6) alkenyl or $-O(C_1-C_6)$ alkyl, wherein any (C_1-C_6) alkyl or (C_2-C_6) alkenyl of R^{3a} is optionally substituted with one or more groups selected from $-O(C_1-C_6)$ alkyl, halo, oxo and $-CN$.

Another specific value for R^3 is (C_1-C_6) alkyl, (C_2-C_6) alkenyl or $-O(C_1-C_6)$ alkyl, wherein the (C_1-C_6) alkyl, (C_2-C_6) alkenyl or $-O(C_1-C_6)$ alkyl is branched.

15 A specific value for R^3 is $-OC(CH_3)_3$.

A specific group of compounds of formula I are compounds wherein R^{3b} and $R^{3b'}$ together with the carbon to which they are attached form a (C_3-C_7) carbocycle or heterocycle; wherein the (C_3-C_7) carbocycle or heterocycle is optionally substituted with one or more Z^1 groups.

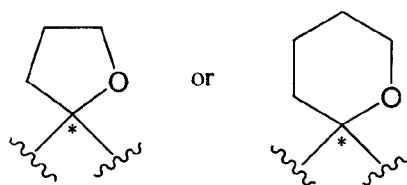
20 Another specific group of compounds of formula I are compounds wherein R^{3b} and $R^{3b'}$ together with the carbon to which they are attached form a (C_3-C_7) carbocycle or a 4, 5 or 6-membered heterocycle; wherein the (C_3-C_6) carbocycle or the 4, 5 or 6-membered heterocycle is optionally substituted with one or more Z^1 groups.

25 Another specific group of compounds of formula I are compounds wherein R^{3b} and $R^{3b'}$ together with the carbon to which they are attached form a (C_4-C_6) carbocycle or a 5 or 6-membered heterocycle; wherein the (C_4-C_6) carbocycle or the 5 or 6-membered heterocycle is optionally substituted with one or more Z^1 groups.

30 Another specific group of compounds of formula I are compounds wherein R^{3b} and $R^{3b'}$ together with the carbon to which they are attached form a 5 or 6-membered heterocycle; wherein the 5 or 6-membered heterocycle is optionally substituted with one or more Z^1 group.

Another specific group of compounds of formula I are compounds wherein R^{3b} and $R^{3b'}$ together with the carbon to which they are attached form a tetrahydropyran or tetrahydrofuran optionally substituted with one or more Z^1 groups.

Another specific group of compounds of formula I are compounds wherein R^{3b} and $R^{3b'}$ together with the carbon to which they are attached form:

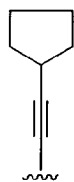


each of which is optionally substituted with one or more Z^1 groups; and wherein “*” denotes the point of attachment to the carbon of the compound of formula I.

A specific value for R^4 is R^{4b} .

A specific value for R^{4b} is (C_1-C_6) alkyl, (C_2-C_6) alkenyl or (C_2-C_6) alkynyl; wherein (C_1-C_6) alkyl, (C_2-C_6) alkenyl or (C_2-C_6) alkynyl are each optionally substituted with one or more Z^1 groups.

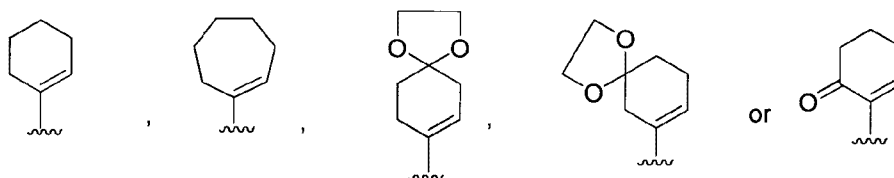
Another specific value for R^{4b} is:



optionally substituted with one or more Z^1 groups.

Another specific value for R^{4b} is (C_3-C_7) carbocycle; wherein (C_3-C_7) carbocycle is optionally substituted with one or more Z^1 groups; or wherein two Z^1 groups together with the atom or atoms to which they are attached optionally form a (C_3-C_6) carbocycle or 5-6-membered heterocycle.

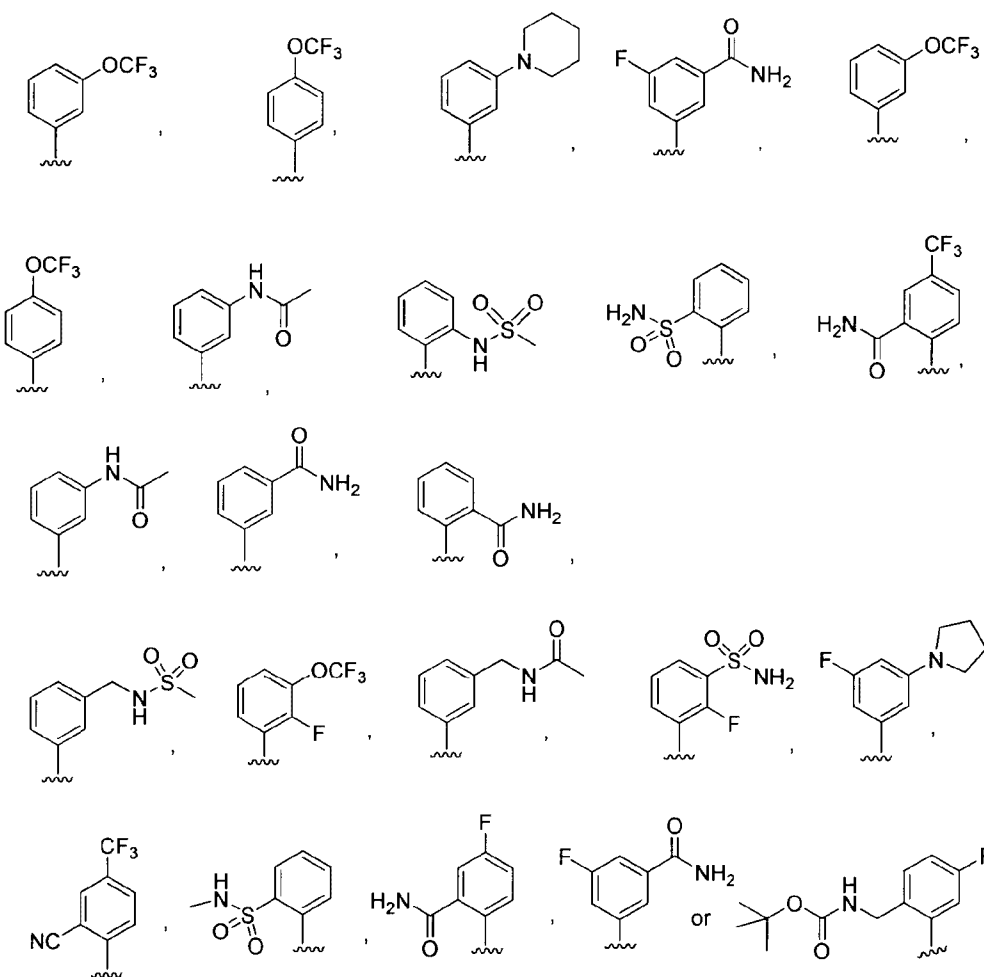
Another specific value for R^{4b} is:



each of which is optionally substituted with one or more Z^1 groups.

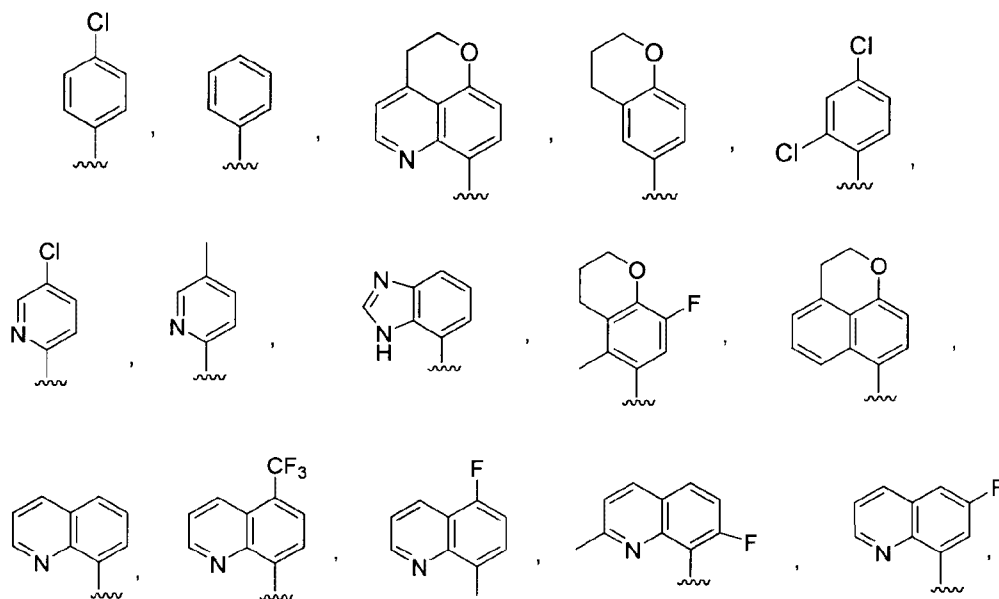
Another specific value for R^{4b} is aryl, heterocycle or heteroaryl; wherein aryl, heterocycle and heteroaryl are each independently substituted with one or more Z^7 groups and optionally substituted with one or more Z^1 groups.

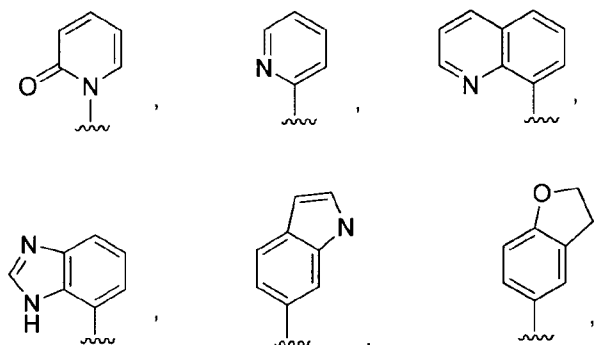
Another specific value for R^{4b} is:



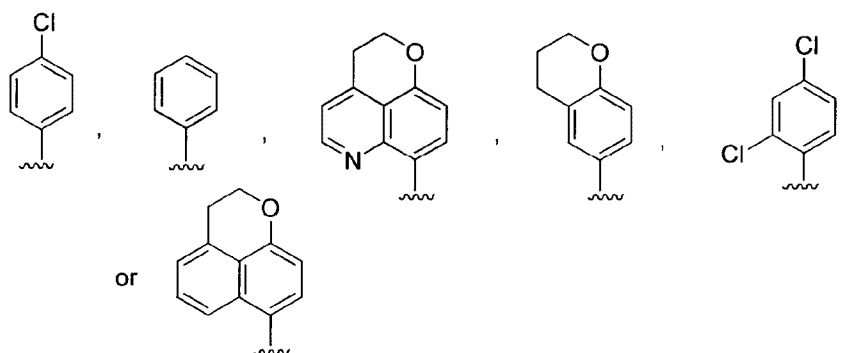
Another specific value for R^4 is R^{4a} .

A specific value for R^{4a} is:

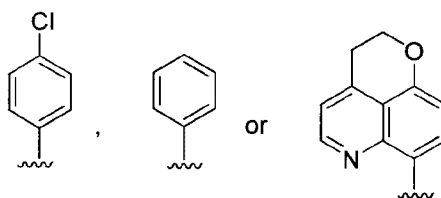




Another specific value for R^{4a} is:



Another specific value for R^{4a} is:



5

A specific value for R^4 is selected from:

- a) aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups each independently selected from halo, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, $-(C_1-C_6)$ alkyl- (C_3-C_7) cycloalkyl, -OH, $-O(C_1-C_6)$ alkyl, -SH, $-S(C_1-C_6)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl and $-N((C_1-C_6)alkyl)_2$, wherein (C_1-C_6) alkyl is optionally substituted with hydroxy, $-O(C_1-C_6)$ alkyl, cyano or oxo; and
- b) aryl, heteroaryl, spiro-, fused-, or bridged-heterocycle; wherein aryl, heteroaryl, or spiro-, fused-, or bridged-heterocycle are each independently substituted with one or more Z^7 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups.

15

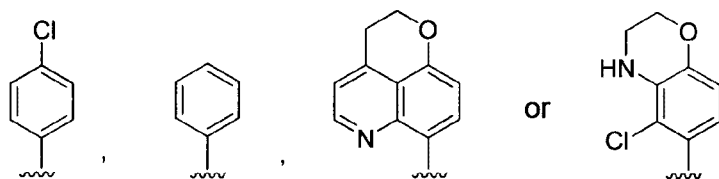
Another specific value for R^4 is selected from:

a) aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups each independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, -NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo; and

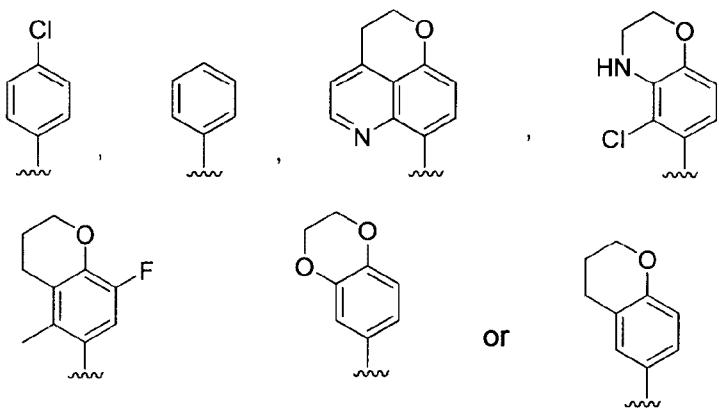
b) aryl and heteroaryl, wherein aryl and heteroaryl are each independently substituted with one or more Z^7 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups.

Another specific value for R^4 is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups each independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, -NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo.

Another specific value for R^4 is:



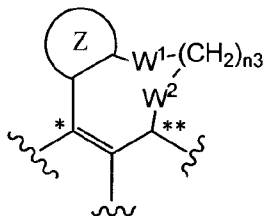
Another specific value for R^4 is:



A specific group of compounds of formula I are compounds wherein R^4 and R^3 together with the atoms to which they are attached form a macroheterocycle or a macrocarbocycle wherein any macroheterocycle or macrocarbocycle of R^4 and R^3 together with the atoms to which they are attached may be optionally substituted with one or more Z^1 groups; and $R^{3'}$ is H, (C₁-C₆)alkyl or -O(C₁-C₆)alkyl.

Another specific group of compounds of formula I are compounds wherein R^4 and R^3 together with the atoms to which they are attached form a macroheterocycle or a macrocarbocycle wherein any macroheterocycle or macrocarbocycle of R^4 and R^3 together with the atoms to which they are attached may be optionally substituted with one or more Z^1 groups; and R^3 is H.

Another specific group of compounds of formula I are compounds wherein R^4 and R^3 together with the atoms to which they are attached form the macroheterocycle or a macrocarbocycle which is further fused to a Z group;



wherein:

Z is aryl, heteroaryl or (C_3-C_6) carbocycle;

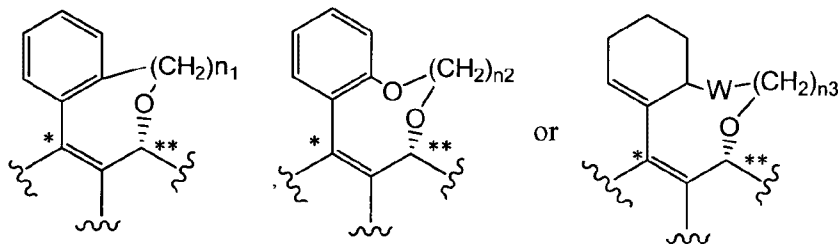
n_3 is 2, 3 or 4;

W^1 and W^2 are each independently O, NH or CH_2 ; and

wherein “*” denotes the R^4 point of attachment of the macroheterocycle or

macrocarbocycle to the compound of formula I and “**” denotes the R^3 point of attachment of the macroheterocycle or macrocarbocycle to the compound of formula I; and wherein the macroheterocycle or a macrocarbocycle is optionally substituted with one or more Z^1 groups.

Another specific group of compounds of formula I are compounds wherein, R^4 and R^3 together with the atoms to which they are attached form the macroheterocycle:



wherein:

wherein:

n_1 is 3 or 4; n_2 is 2, 3 or 4; n_3 is 2, 3 or 4; W is O, NH or $N(C_1-C_4)$ alkyl; and wherein

“*” denotes the R^4 point of attachment of the macroheterocycle to the compound of formula I

and “**” denotes the R^3 point of attachment of the macroheterocycle to the compound of formula

I; and wherein the macroheterocycle or a macrocarbocycle is optionally substituted with one or more Z^1 groups.

A specific value for R^2 is R^{2b} .

Another specific value R^2 is R^{2a} .

5 A specific value for R^{2a} is H, halo or $-CH_3$.

Another specific value for R^{2a} is Cl.

A specific value for R^2 is halo, H or (C_1-C_6) alkyl.

Another specific value for R^2 is halo, H or $-CH_3$.

Another specific value for R^2 is H or $-CH_3$.

10 Another specific value for R^2 is H or (C_1-C_6) alkyl.

Another specific value for R^2 is (C_1-C_6) alkyl.

Another specific value for R^2 is $-CH_3$.

Another specific value for R^5 is R^{5a} .

A specific value for R^{11} is aryl.

15 Another specific value for R^{11} is carbocycle or aryl.

Another specific value for R^{11} is carbocycle.

A specific value for R^9 is H or (C_1-C_6) alkyl.

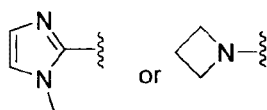
A specific value for R^{10} is H or (C_1-C_6) alkyl.

Another specific value for R^9 is H, (C_1-C_6) alkyl or $-C(=O)-R^{11}$.

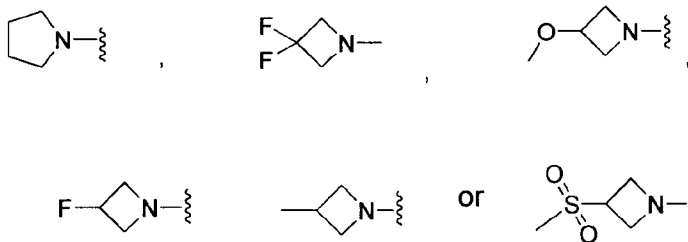
20 Another specific value for R^{10} is H, (C_1-C_6) alkyl or $-C(=O)-R^{11}$.

A value for Z^9 is "each Z^9 is independently selected from $-(C_1-C_6)$ alkyl, $-O(C_1-C_6)$ alkyl".

In one embodiment of R^5 does not include:

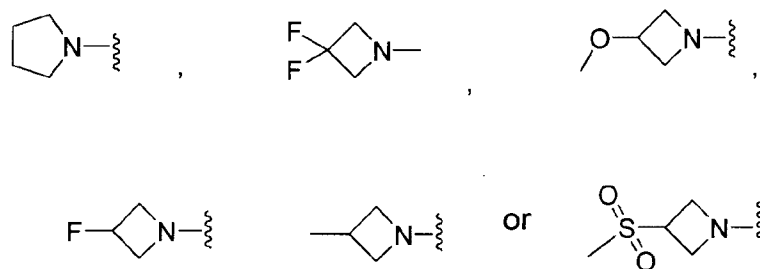


A specific value for R^5 is:



25

In one embodiment R^5 does not include:



In one embodiment the compounds of the invention do not include compounds 35, 36, 50, 51, 52, 53, 54, 55, 56, 57, 58, 76, and 89.

A specific group of compounds of formula I are compounds wherein R^{4b} is selected from;

- a) (C₁-C₆)alkyl, (C₂-C₆)alkenyl and (C₂-C₆)alkynyl, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl or (C₂-C₆)alkynyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;
- b) (C₃-C₁₄)carbocycle, wherein (C₃-C₁₄)carbocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;
- c) Spiro-heterocycle or bridged-heterocycle, wherein spiro-heterocycle or bridged-heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups; and
- d) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each independently substituted with one or more Z⁷ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups.

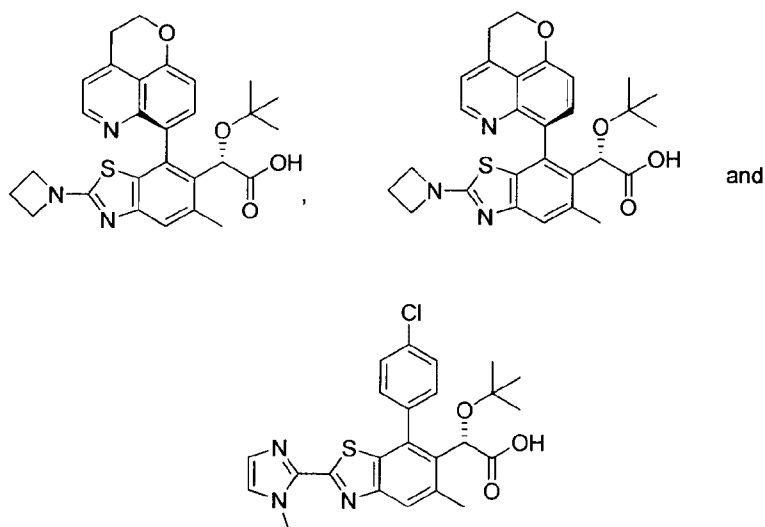
Another specific group of compounds of formula I are compounds wherein R^{4b} is selected from;

- a) (C₁-C₆)alkyl, (C₂-C₆)alkenyl and (C₂-C₆)alkynyl, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl or (C₂-C₆)alkynyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;
- b) (C₃-C₁₄)carbocycle, wherein (C₃-C₁₄)carbocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups; wherein two Z¹ groups together with the atom or atoms to which they are attached optionally form a (C₃-C₇)carbocycle or heterocycle; and
- c) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z⁷ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups.

Another specific group of compounds of formula I are compounds wherein R^{4b} is selected from;

- a) (C_1-C_6) alkyl, (C_2-C_6) alkenyl and (C_2-C_6) alkynyl, wherein any (C_1-C_6) alkyl, (C_2-C_6) alkenyl or (C_2-C_6) alkynyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;
- b) (C_3-C_{14}) carbocycle, wherein (C_3-C_{14}) carbocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and
- c) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^7 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups.

In one embodiment, the compounds of the invention do not include the compounds selected from:



and salts thereof.

- 15 A specific value for R^5 is selected from:

- a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z^{11} groups;
- b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and
- c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups.

- 25 A specific group of compounds of formula I are compounds wherein:
 R^5 is selected from:

a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z^{11} groups;

b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and

c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

and

10 $R^{3'}$ is H.

Another specific group of compounds of formula I are compounds wherein:

R^5 is selected from:

a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z^{11} groups;

15 b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and

c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

20 $R^{3'}$ is H; R^1 is H; and

R^2 is H or (C₁-C₆)alkyl.

Another specific group of compounds of formula I are compounds wherein:

R^5 is selected from:

25 a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z^{11} groups;

b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and

30 c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

$R^{3'}$ is H; R^1 is H;

R^2 is H or (C₁-C₆)alkyl; and

R³ is -O(C₁-C₆)alkyl.

A specific value for R⁵ is selected from:

- a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z¹¹ groups; and
- 5 b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups.

A specific group of compounds of formula I are compounds wherein:

R⁵ is selected from:

- 10 a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z¹¹ groups; and
- b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;
- 15 and

R^{3'} is H.

Another specific group of compounds of formula I are compounds wherein:

R⁵ is selected from:

- 20 a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z¹¹ groups; and
- b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;

R^{3'} is H; R¹ is H; and

25 R² is H or (C₁-C₆)alkyl.

Another specific group of compounds of formula I are compounds wherein:

R⁵ is selected from:

- a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z¹¹ groups; and
- 30 b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;

R^{3'} is H; R¹ is H;

R² is H or (C₁-C₆)alkyl; and

R³ is -O(C₁-C₆)alkyl.

Another specific value for R⁵ is aryl, heteroaryl, heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;

5 Another specific group of compounds of formula I are compounds wherein:

R⁵ is selected from aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups; and

R^{3'} is H.

10 Another specific group of compounds of formula I are compounds wherein:

R⁵ is selected from aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;

R^{3'} is H; R¹ is H; and

15 R² is H or (C₁-C₆)alkyl.

Another specific group of compounds of formula I are compounds wherein

R⁵ is selected from aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;

20 R^{3'} is H; R¹ is H;

R² is H or (C₁-C₆)alkyl; and

R³ is -O(C₁-C₆)alkyl.

Another specific value for R⁵ is selected from:

a) aryl, wherein aryl is optionally substituted with one or more (e.g., 1, 2 or 3) Z¹¹ groups;

b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups; and

c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups.

Another specific group of compounds of formula I are compounds wherein:

R⁵ is selected from:

a) aryl, wherein aryl is optionally substituted with one or more (e.g., 1, 2 or 3) Z^{11} groups;

b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl are heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and

c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and

10 $R^{3'}$ is H.

Another specific group of compounds of formula I are compounds wherein:

R^5 is selected from:

a) aryl, wherein aryl is optionally substituted with one or more (e.g., 1, 2 or 3) Z^{11} groups;

15 b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl are heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and

c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

$R^{3'}$ is H; R^1 is H; and

R^2 is H or (C_1-C_6) alkyl.

Another specific group of compounds of formula I are compounds wherein:

R^5 is selected from:

25 a) aryl, wherein aryl is optionally substituted with one or more (e.g., 1, 2 or 3) Z^{11} groups;

b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl are heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and

30 c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

$R^{3'}$ is H; R^1 is H;

R^2 is H or (C_1-C_6) alkyl; and

R³ is -O(C₁-C₆)alkyl.

Another specific value for R⁵ is selected from:

- a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z¹¹ groups;
- 5 b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups; and
- c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally
- 10 substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;

each Z¹¹ is independently selected from Z¹⁰, -C(=O)-NH₂, -C(=O)-NH(C₁-C₄)alkyl, -C(=O)-N((C₁-C₄)alkyl)₂, -C(=O)-aryl, -C(=O)-heterocycle and -C(=O)-heteroaryl;

wherein each Z¹⁰ is independently selected from:

- i) halo, oxo, thioxo, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -O(C₁-C₆)haloalkyl, -SH, -S(C₁-C₆)alkyl, -SO(C₁-C₆)alkyl, -SO₂(C₁-C₆)alkyl, -NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂;
- 15 ii) (C₁-C₆)alkyl substituted with -OH, -O-(C₁-C₆)haloalkyl, or -O-(C₁-C₆)alkyl; and
- 20 iii) aryl, heterocycle and heteroaryl, which aryl, heterocycle and heteroaryl is optionally substituted with halo, (C₁-C₆)alkyl or COOH; and

each Z¹¹ is independently selected from Z¹⁰, -C(=O)-NH₂, -C(=O)-NH(C₁-C₄)alkyl, -C(=O)-N((C₁-C₄)alkyl)₂, -C(=O)-aryl, -C(=O)-heterocycle and -C(=O)-heteroaryl.

25 Another specific group of compounds of formula I are compounds wherein:

R⁵ is selected from:

- a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z¹¹ groups;
- b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are
- 30 each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups; and
- c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;

R^{3'} is H;

each Z¹⁰ is independently selected from:

- i) halo, oxo, thioxo, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -O(C₁-C₆)haloalkyl, -SH, -S(C₁-C₆)alkyl, -SO(C₁-C₆)alkyl, -SO₂(C₁-C₆)alkyl, -NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂;
- ii) (C₁-C₆)alkyl substituted with -OH, -O-(C₁-C₆)haloalkyl, or -O-(C₁-C₆)alkyl; and
- iii) aryl, heterocycle and heteroaryl, which aryl, heterocycle and heteroaryl is optionally substituted with halo, (C₁-C₆)alkyl or COOH; and

each Z¹¹ is independently selected from Z¹⁰, -C(=O)-NH₂, -C(=O)-NH(C₁-C₄)alkyl, -C(=O)-N((C₁-C₄)alkyl)₂, -C(=O)-aryl, -C(=O)-heterocycle and -C(=O)-heteroaryl.

Another specific group of compounds of formula I are compounds wherein:

R⁵ is selected from:

- a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z¹¹ groups;
- b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups; and
- c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z¹ groups;

R^{3'} is H; R¹ is H;

R² is H or (C₁-C₆)alkyl;

each Z¹⁰ is independently selected from:

- i) halo, oxo, thioxo, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -O(C₁-C₆)haloalkyl, -SH, -S(C₁-C₆)alkyl, -SO(C₁-C₆)alkyl, -SO₂(C₁-C₆)alkyl, -NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂;
- ii) (C₁-C₆)alkyl substituted with -OH, -O-(C₁-C₆)haloalkyl, or -O-(C₁-C₆)alkyl; and
- iii) aryl, heterocycle and heteroaryl, which aryl, heterocycle and heteroaryl is optionally substituted with halo, (C₁-C₆)alkyl or COOH; and

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each Z^{11} is independently selected from Z^{10} , $-C(=O)-NH_2$, $-C(=O)-NH(C_1-C_4)alkyl$, $-C(=O)-N((C_1-C_4)alkyl)_2$, $-C(=O)-aryl$, $-C(=O)-heterocycle$ and $-C(=O)-heteroaryl$.

Another specific group of compounds of formula I are compounds wherein:

R^5 is selected from:

- 5 a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g., 1, 2 or 3) Z^{11} groups;
- b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and
- 10 c) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

$R^{3'}$ is H; R^1 is H;

R^2 is H or $(C_1-C_6)alkyl$;

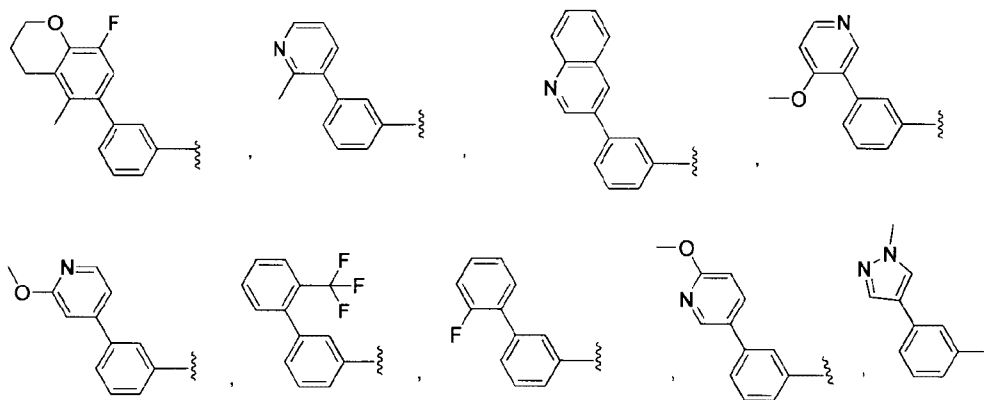
15 R^3 is $-O(C_1-C_6)alkyl$;

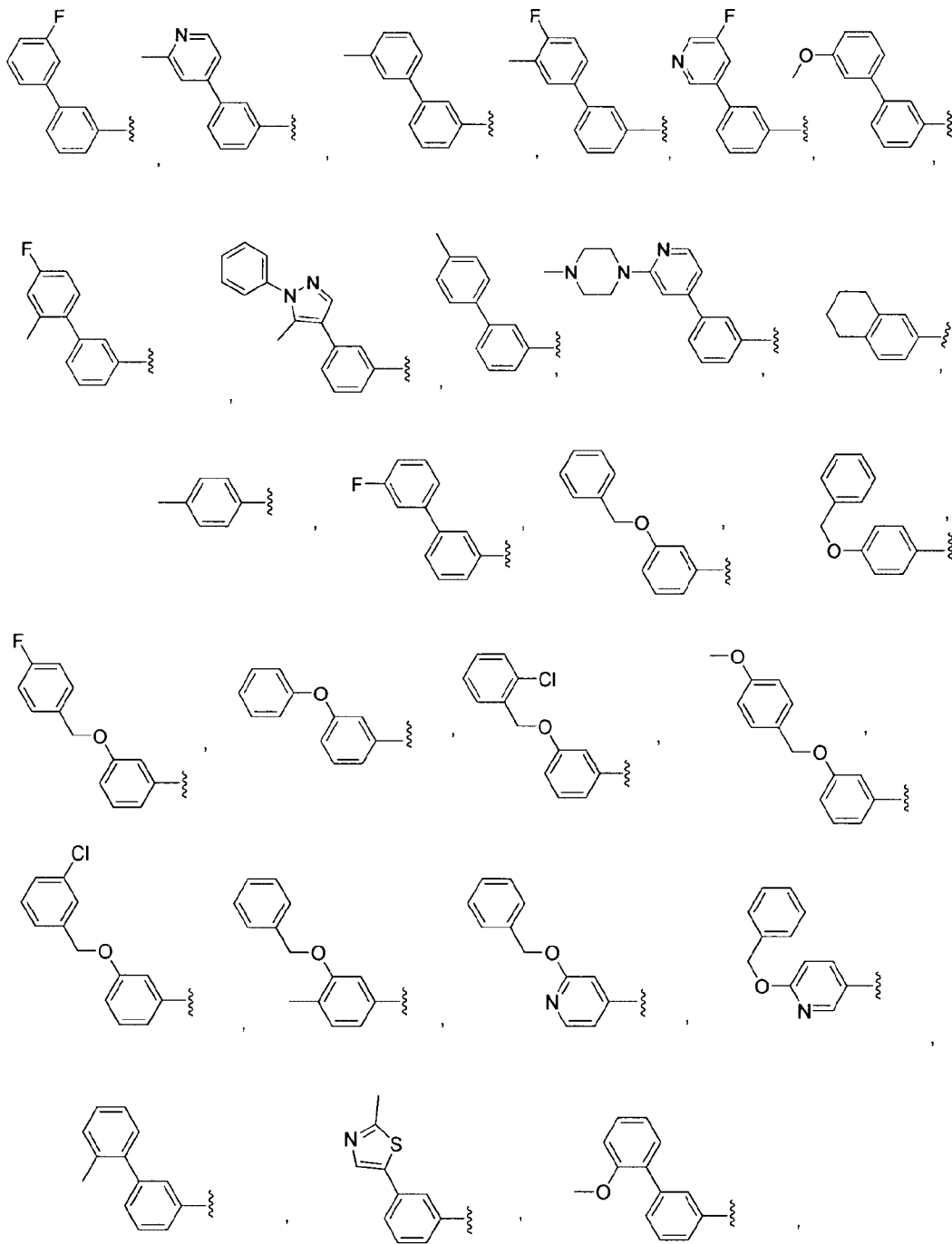
each Z^{10} is independently selected from:

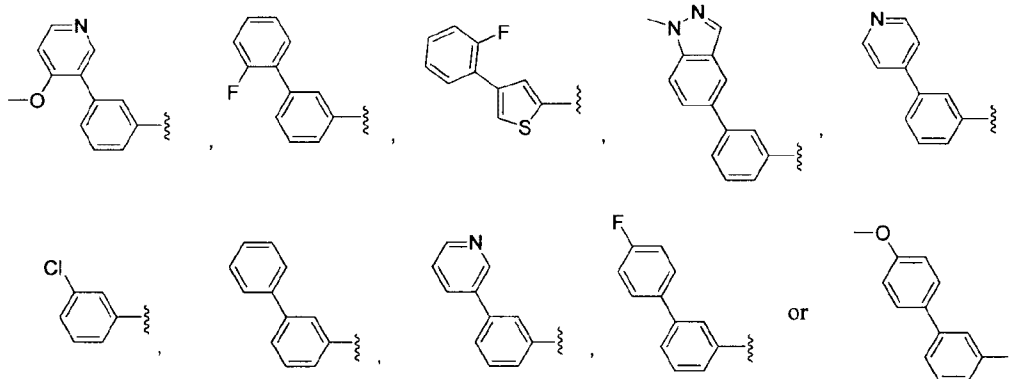
- i) halo, oxo, thioxo, $(C_2-C_6)alkenyl$, $(C_1-C_6)haloalkyl$, $(C_3-C_7)cycloalkyl$, $(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl$ -, $-OH$, $-O(C_1-C_6)alkyl$, $-O(C_1-C_6)haloalkyl$, $-SH$, $-S(C_1-C_6)alkyl$, $-SO(C_1-C_6)alkyl$, $-SO_2(C_1-C_6)alkyl$, $-NH_2$, $-NH(C_1-C_6)alkyl$ and $-N((C_1-C_6)alkyl)_2$;
- 20 ii) $(C_1-C_6)alkyl$ substituted with $-OH$, $-O-(C_1-C_6)haloalkyl$, or $-O-(C_1-C_6)alkyl$; and
- iii) aryl, heterocycle and heteroaryl, which aryl, heterocycle and heteroaryl is optionally substituted with halo, $(C_1-C_6)alkyl$ or $COOH$; and

each Z^{11} is independently selected from Z^{10} , $-C(=O)-NH_2$, $-C(=O)-NH(C_1-C_4)alkyl$, $-C(=O)-N((C_1-C_4)alkyl)_2$, $-C(=O)-aryl$, $-C(=O)-heterocycle$ and $-C(=O)-heteroaryl$.

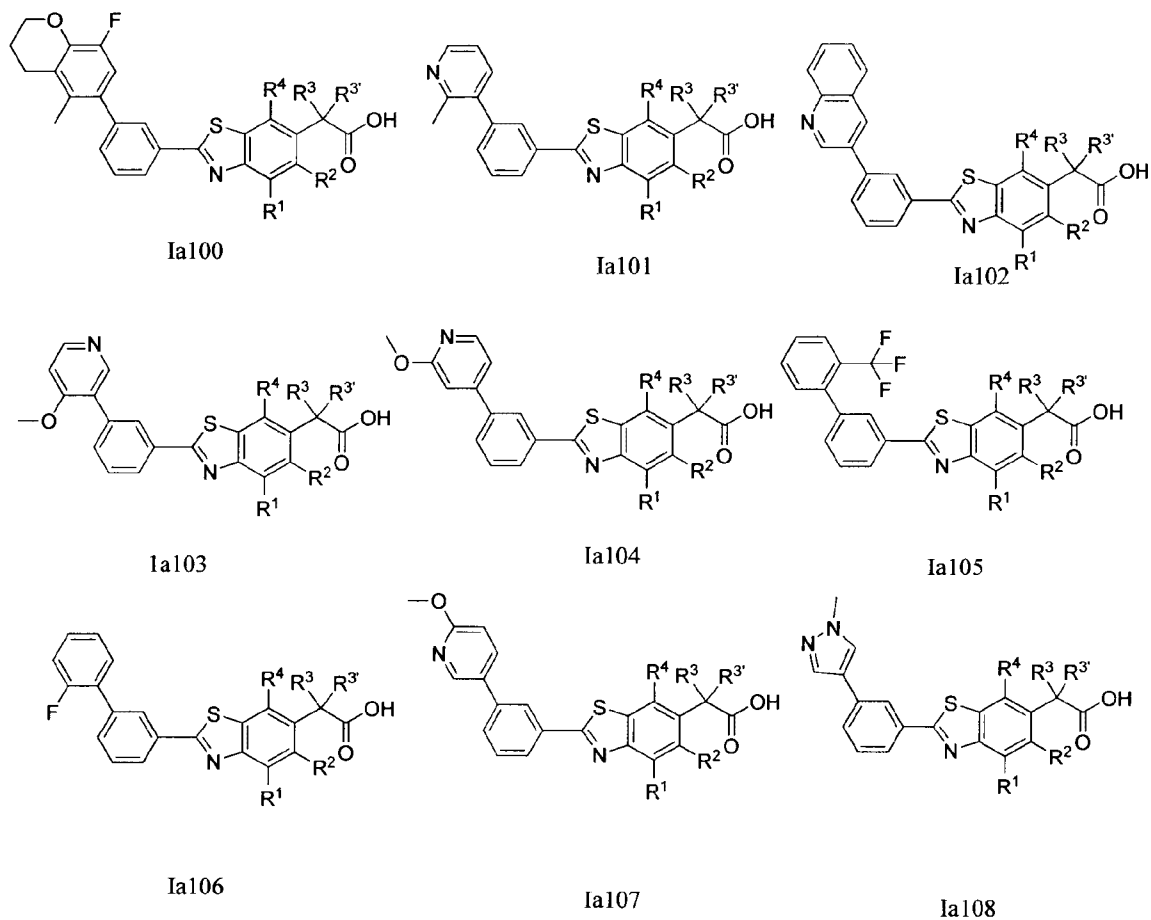
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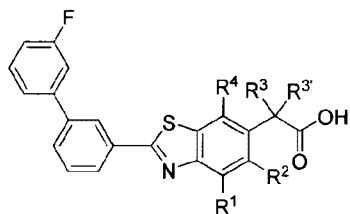




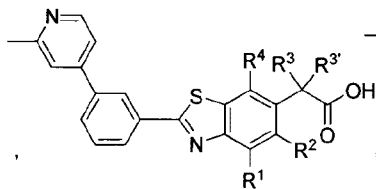


In one embodiment of the invention the compound of formula I is selected from a compound of formulas Ia100-Ia145 (e.g., compounds Ia100, Ia101, Ia102, Ia103, Ia104, Ia105, Ia106, Ia107, Ia108, Ia109, Ia110, Ia111, Ia112, Ia113, Ia114, Ia115, Ia116, Ia117, Ia118, Ia119, Ia120, Ia121, Ia122, Ia123, Ia124, Ia125, Ia126, Ia127, Ia128, Ia129, Ia130, Ia131, Ia132, Ia133, Ia134, Ia135, Ia136, Ia137, Ia138, Ia139, Ia140, Ia141, Ia142, Ia143, Ia144, Ia145):

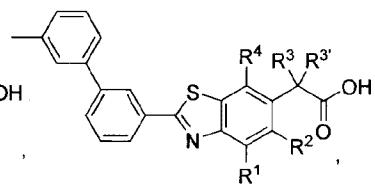




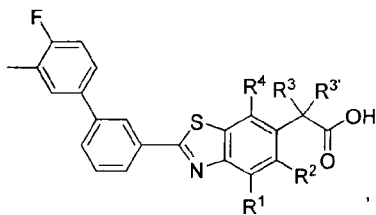
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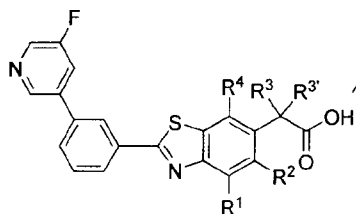
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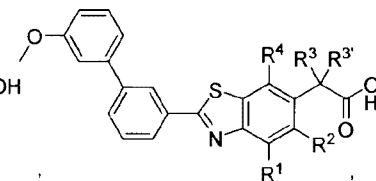
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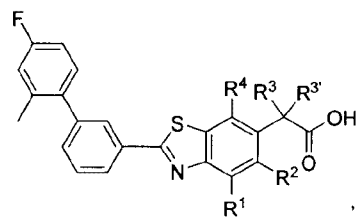
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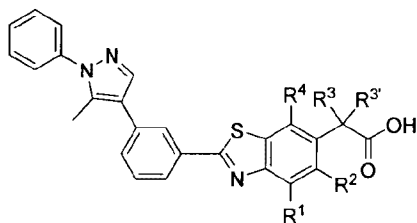
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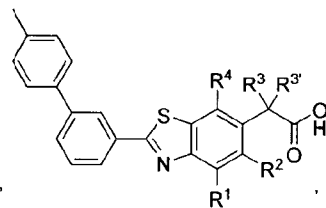
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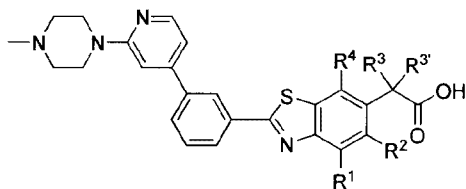
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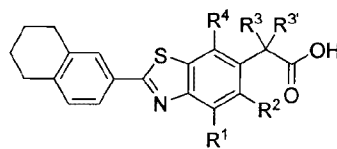
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Ia117



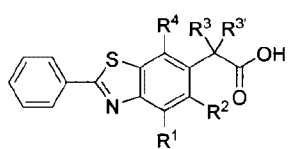
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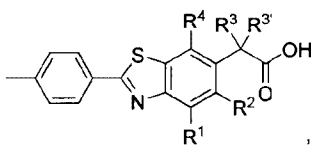
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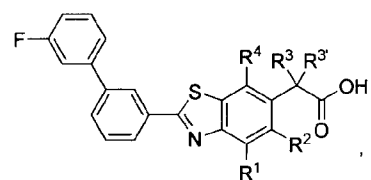
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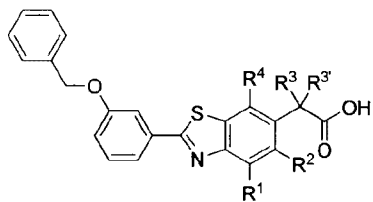
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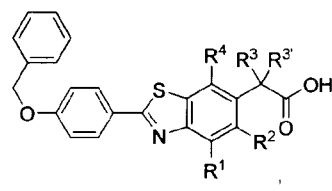
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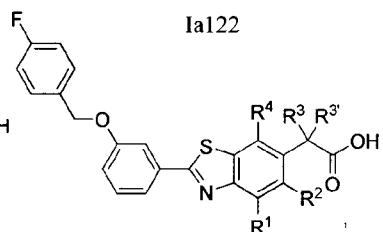
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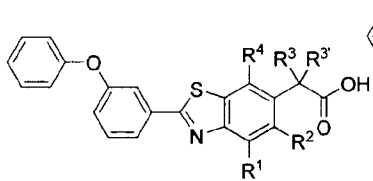
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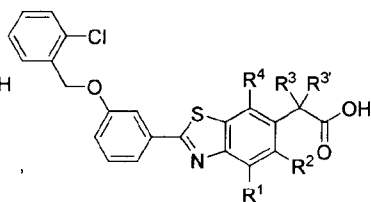
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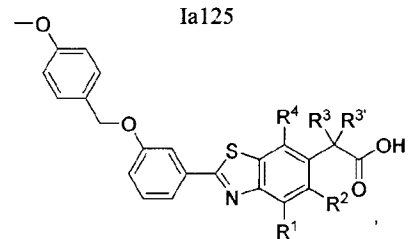
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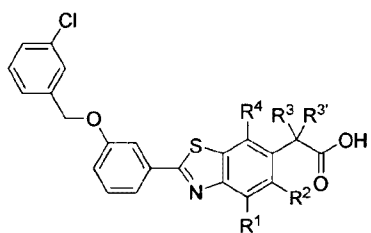
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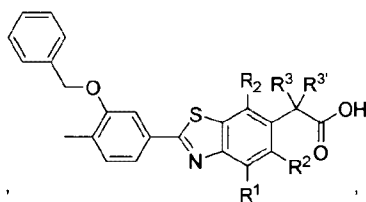
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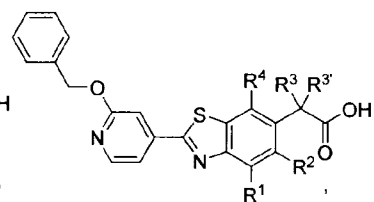
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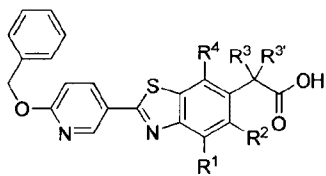
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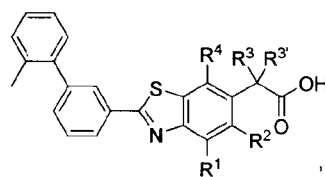
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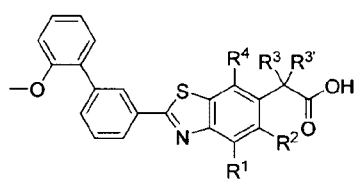
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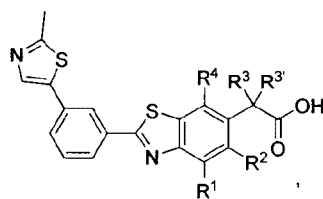
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Ia133



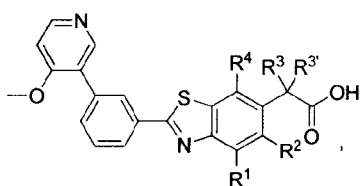
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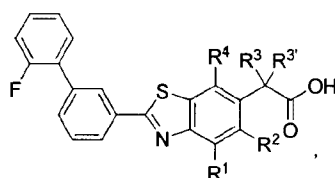
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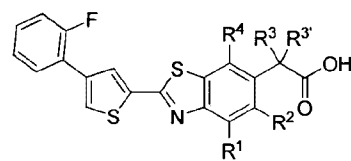
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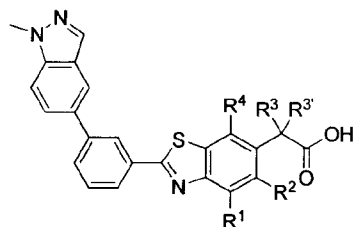
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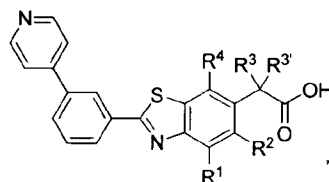
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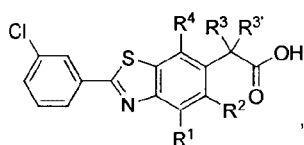
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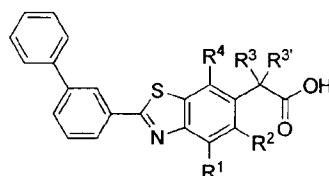
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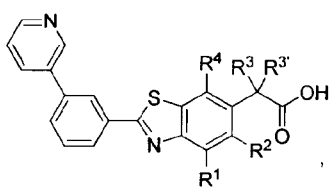
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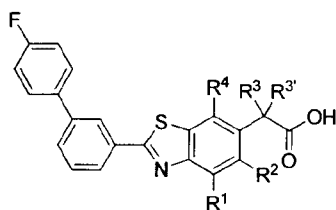
Ia141



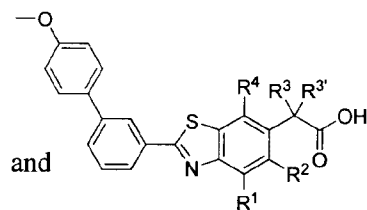
Ia142



Ia143



Ia144

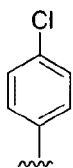


Ia145

and salts thereof.

In one embodiment, the compounds of formula I are selected from the compounds of formulas Ia100-Ia145 wherein:

- 5 R^1 is H; R^2 is methyl, $R^{3'}$ is H; R^3 is -OtBu; and
 R^4 is:

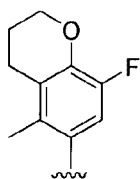


and salts thereof.

- 10 In another embodiment, the compounds of formula I are selected from the compounds of formulas Ia100-Ia145 wherein:

R^1 is H; R^2 is methyl, $R^{3'}$ is H; R^3 is -OtBu; and

R⁴ is:

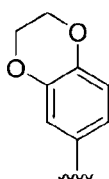


and salts thereof.

In another embodiment, the compounds of formula I are selected from the compounds of
5 formulas Ia100-Ia145 wherein:

R¹ is H; R² is methyl, R^{3'} is H; R³ is -OtBu; and

R⁴ is:

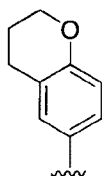


and salts thereof.

10 In another embodiment of the invention, the compounds of formula I are selected from the compounds of formulas Ia100-Ia145 wherein:

R¹ is H; R² is methyl, R^{3'} is H; R³ is -OtBu; and

R⁴ is:

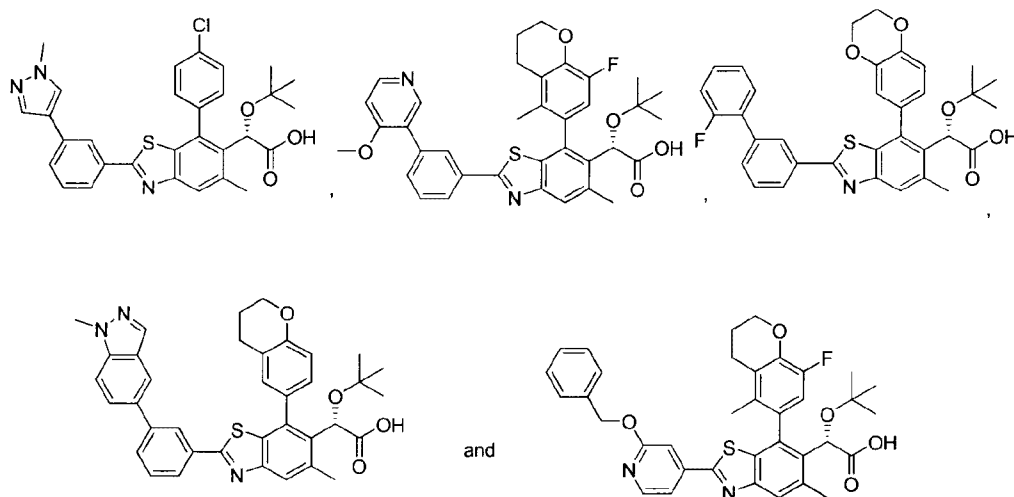


15 and salts thereof.

In one embodiment of the invention the compounds of formula I are selected from the compounds of formulas Ia100-Ia145 wherein R^{3'} is H; R³ is -O(C₁-C₆)alkyl and the stereochemistry of the carbon bearing the R³ (-O(C₁-C₆)alkyl) group is (S).

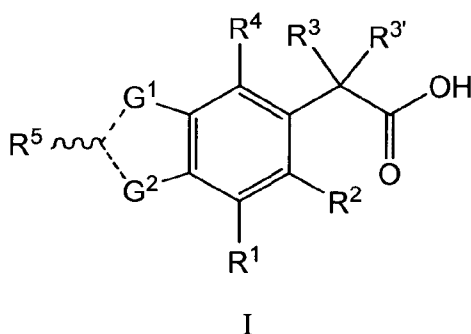
In another embodiment of the invention the compounds of formula I are selected from
20 the compounds of formulas Ia100-Ia145 wherein R^{3'} is H; R³ is -O(C₁-C₆)alkyl and the stereochemistry of the carbon bearing the R³ (-O(C₁-C₆)alkyl) group is (R).

In one embodiment of the invention, the compounds of formula I are selected from:



and salts thereof.

In one embodiment, the invention provides a compound of formula I:



wherein:

G^1 is S, G^2 is N, the dashed bond connected to G^1 is a single bond, the dashed bond connected to G^2 is a double bond, and the wavy bond connected to R^5 is a single bond; or

G^1 is N, G^2 is S, the dashed bond connected to G^1 is a double bond, the dashed bond connected to G^2 is a single bond, and the wavy bond connected to R^5 is a single bond;

R^1 is R^{1a} or R^{1b} ;

R^2 is R^{2a} or R^{2b} ;

R^3 is R^{3a} or R^{3b} ;

$R^{3'}$ is $R^{3a'}$ or $R^{3b'}$;

R^4 is R^{4a} or R^{4b} ;

R^{1a} is selected from:

a) halo;

b) R^{11} , $-C(=O)-R^{11}$, $-C(=O)-O-R^{11}$, $-O-R^{11}$, $-S-R^{11}$, $-S(O)-R^{11}$, $-SO_2-R^{11}$, $-(C_1-C_6)alkyl-R^{11}$, $-(C_1-C_6)alkyl-C(=O)-R^{11}$, $-(C_1-C_6)alkyl-C(=O)-O-R^{11}$, $-(C_1-C_6)alkyl-O-R^{11}$, $-(C_1-C_6)alkyl-S-R^{11}$, $-(C_1-C_6)alkyl-S(O)-R^{11}$ and $-(C_1-C_6)alkyl-SO_2-R^{11}$, wherein each R^{11} is

independently selected from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, aryl, heterocycle and heteroaryl, wherein aryl, heterocycle or heteroaryl are each optionally substituted with one or more (e.g. 1, 2 or 3) Z¹¹ groups; and

- c) -N(R⁹)R¹⁰, -C(=O)-N(R⁹)R¹⁰, -O-C(=O)-N(R⁹)R¹⁰, -SO₂-N(R⁹)R¹⁰,
 5 -(C₁-C₆)alkyl-N(R⁹)R¹⁰, -(C₁-C₆)alkyl-C(=O)-N(R⁹)R¹⁰, -(C₁-C₆)alkyl-O-C(=O)-N(R⁹)R¹⁰ and
 -(C₁-C₆)alkyl-SO₂-N(R⁹)R¹⁰, wherein each R⁹ is independently selected from H, (C₁-C₆)alkyl
 and (C₃-C₇)cycloalkyl, and each R¹⁰ is independently selected from R¹¹, -(C₁-C₆)alkyl-R¹¹, -SO₂-
 R¹¹, -C(=O)-R¹¹, -C(=O)OR¹¹ and -C(=O)N(R⁹)R¹¹, wherein each R¹¹ is independently selected
 10 from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, aryl,
 heterocycle and heteroaryl;

R^{1b} is selected from:

- a) -(C₁-C₆)alkyl-O-(C₁-C₆)alkyl-(C₃-C₇)carbocycle, -(C₁-C₆)alkyl-S-(C₁-
 C₆)alkyl-(C₃-C₇) carbocycle, -(C₁-C₆)alkyl-S(O)-(C₁-C₆)alkyl-(C₃-C₆) carbocycle, -(C₁-C₆)alkyl-
 SO₂-(C₁-C₆)alkyl-(C₃-C₇)carbocycle, -(C₁-C₆)alkyl-SO₂-(C₁-C₆)alkyl-Z¹³, -C(O)-(C₁-C₆)alkyl-
 15 Z¹³, -O-(C₁-C₆)alkyl-Z¹³, -S-(C₁-C₆)alkyl-Z¹³, -S(O)-(C₁-C₆)alkyl-Z¹³, -SO₂-(C₁-C₆)alkyl-Z¹³,
 -(C₁-C₆)alkyl-Z¹⁴, -(C₁-C₆)alkyl-C(O)-(C₁-C₆)alkyl-Z¹³, -(C₁-C₆)alkyl-C(O)-O(C₁-C₆)alkyl-Z¹³,
 -(C₁-C₆)alkyl-O-(C₁-C₆)alkyl-Z¹³, -(C₁-C₆)alkyl-S-(C₁-C₆)alkyl-Z¹³, -(C₂-
 C₆)alkenyl-(C₁-C₆)haloalkyl, -(C₂-C₆)alkynyl-(C₁-C₆)haloalkyl, -(C₃-C₇)halocarbocycle,-
 NR_aSO₂NR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl, -(C₂-C₆)alkenyl-(C₃-
 20 C₇)carbocycle, -(C₂-C₆)alkenyl-aryl, -(C₂-C₆)alkenyl-heteroaryl, -(C₂-C₆)alkenyl-heterocycle,
 -(C₂-C₆)alkynyl-(C₃-C₇)carbocycle, -(C₂-C₆)alkynyl-aryl, -(C₂-C₆)alkynyl-heteroaryl
 -(C₂-C₆)alkynyl-heterocycle, -(C₃-C₇)carbocycle-Z¹ or -(C₁-C₆)haloalkyl-Z³, wherein any
 (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, aryl or
 heteroaryl, either alone or as part of a group, is optionally substituted with one or more (e.g. 1, 2,
 25 3, 4 or 5) Z¹ groups;

- b) spiro-bicyclic carbocycle, fused-bicyclic carbocycle and bridged-bicyclic
 carbocycle, wherein any spiro-bicyclic carbocycle, fused-bicyclic carbocycle or bridged-bicyclic
 carbocycle is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups, or wherein
 two Z¹ groups together with the atom or atoms to which they are attached optionally form a
 30 carbocycle or heterocycle wherein the carbocycle or heterocycle is optionally substituted with
 one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;

- c) (C₁-C₆)alkyl, wherein (C₁-C₆)alkyl is substituted with one or more (e.g. 1, 2, 3, 4
 or 5) Z² groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;

d) $-X(C_1-C_6)$ alkyl, $-X(C_1-C_6)$ haloalkyl, $-X(C_2-C_6)$ alkenyl, $-X(C_2-C_6)$ alkynyl and $-X(C_3-C_7)$ carbocycle, wherein $-X(C_1-C_6)$ alkyl and $-X(C_1-C_6)$ haloalkyl are each independently substituted with one or more Z^3 groups and optionally substituted with one or more Z^1 groups, and wherein $-X(C_2-C_6)$ alkenyl, $-X(C_2-C_6)$ alkynyl and $-X(C_3-C_7)$ carbocycle, are each

5 independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^4 groups and optionally substituted with one or more Z^1 groups;

e) aryl, heteroaryl, heterocycle, $-X$ aryl, $-X$ heteroaryl and $-X$ heterocycle; wherein aryl heteroaryl and heterocycle, either alone or as part of a group, are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one
10 or more Z^1 groups;

f) (C_1-C_6) haloalkyl, (C_3-C_7) carbocycle, (C_2-C_6) alkenyl, and (C_2-C_6) alkynyl, wherein (C_1-C_6) haloalkyl, (C_3-C_7) carbocycle, (C_2-C_6) alkenyl and (C_2-C_6) alkynyl are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^6 groups and optionally substituted with one or more Z^1 groups;

15 g) $-NR_eR_f$, $-C(O)NR_eR_f$, $-OC(O)NR_eR_f$, $-SO_2NR_eR_f$, $-(C_1-C_6)$ alkyl- NR_eR_f , $-(C_1-C_6)$ alkyl $C(O)-NR_eR_f$, $-(C_1-C_6)$ alkyl-O- $C(O)-NR_eR_f$ and $-(C_1-C_6)$ alkyl- $SO_2NR_eR_f$, wherein each (C_1-C_6) alkyl, as part of a group, is independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^6 groups and optionally substituted with one or more Z^1 groups; and

h) nitro and cyano;

20 R^{2a} is selected from:

a) halo;

b) R^{11} , $C(=O)-R^{11}$, $-C(=O)-O-R^{11}$, $-O-R^{11}$, $-S-R^{11}$, $-S(O)-R^{11}$, $-SO_2-R^{11}$, $-(C_1-C_6)$ alkyl- R^{11} , $-(C_1-C_6)$ alkyl- $C(=O)-R^{11}$, $-(C_1-C_6)$ alkyl- $C(=O)-O-R^{11}$, $-(C_1-C_6)$ alkyl-O- R^{11} , $-(C_1-C_6)$ alkyl-S- R^{11} , $-(C_1-C_6)$ alkyl-S(O)- R^{11} and $-(C_1-C_6)$ alkyl- SO_2-R^{11} , wherein each R^{11} is
25 independently selected from H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, aryl and heterocycle and heteroaryl, wherein aryl, heterocycle or heteroaryl are each optionally substituted with one or more (e.g. 1, 2 or 3) Z^{11} groups; and

c) $-N(R^9)R^{10}$, $-C(=O)-N(R^9)R^{10}$, $-O-C(=O)-N(R^9)R^{10}$, $-SO_2-N(R^9)R^{10}$, $-(C_1-C_6)$ alkyl- $N(R^9)R^{10}$, $-(C_1-C_6)$ alkyl- $C(=O)-N(R^9)R^{10}$, $-(C_1-C_6)$ alkyl-O- $C(=O)-N(R^9)R^{10}$, and $-(C_1-C_6)$ alkyl-
30 $SO_2-N(R^9)R^{10}$, wherein each R^9 is independently selected from H, (C_1-C_6) alkyl and (C_3-C_7) cycloalkyl, wherein each R^{10} is independently selected from R^{11} , $-(C_1-C_6)$ alkyl- R^{11} , $-SO_2-R^{11}$, $-C(=O)-R^{11}$, $-C(=O)OR^{11}$ and $-C(=O)N(R^9)R^{11}$, wherein each R^{11} is independently selected from H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, aryl, heterocycle and heteroaryl;

R^{2b} is selected from:

- a) -(C₁-C₆)alkyl-O-(C₁-C₆)alkyl-(C₃-C₇)carbocycle, -(C₁-C₆)alkyl-S-(C₁-C₆)alkyl-(C₃-C₇)carbocycle, -(C₁-C₆)alkyl-S(O)-(C₁-C₆)alkyl-(C₃-C₇)carbocycle, -(C₁-C₆)alkyl-SO₂-(C₁-C₆)alkyl-(C₃-C₇)carbocycle, -(C₂-C₆)alkenyl-(C₁-C₆)haloalkyl, -(C₂-C₆)alkynyl-(C₁-C₆)haloalkyl, -(C₁-C₆)alkyl-SO₂-(C₁-C₆)alkyl-Z¹³, -C(O)-(C₁-C₆)alkyl-Z¹³, -O-(C₁-C₆)alkyl-Z¹³, -S-(C₁-C₆)alkyl-Z¹³, -S(O)-(C₁-C₆)alkyl-Z¹³, -SO₂-(C₁-C₆)alkyl-Z¹³, -(C₁-C₆)alkyl-Z¹⁴, -(C₁-C₆)alkyl-C(O)-(C₁-C₆)alkyl-Z¹³, -(C₁-C₆)alkyl-C(O)-O-(C₁-C₆)alkyl-Z¹³, -(C₁-C₆)alkyl-O-(C₁-C₆)alkyl-Z¹³, -(C₁-C₆)alkyl-S-(C₁-C₆)alkyl-Z¹³, -(C₃-C₇)halocarboxycle, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl,
- 10 -(C₂-C₆)alkenyl-(C₃-C₇)carbocycle, -(C₂-C₆)alkenyl-aryl, -(C₂-C₆)alkenyl-heteroaryl, -(C₂-C₆)alkenyl-heterocycle, -(C₂-C₆)alkynyl-(C₃-C₇)carbocycle, -(C₂-C₆)alkynyl-aryl, -(C₂-C₆)alkynyl-heteroaryl, -(C₂-C₆)alkynyl-heterocycle, -(C₃-C₇)carbocycle-Z¹ or -(C₁-C₆)haloalkyl-Z³, wherein any (C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, aryl or heteroaryl, either alone or as part of a group, is optionally
- 15 substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;
- b) spiro-bicyclic carbocycle, fused-bicyclic carbocycle and bridged-bicyclic carbocycle, wherein any spiro-bicyclic carbocycle, fused-bicyclic carbocycle or bridged-bicyclic carbocycle is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups, wherein two Z¹ groups together with the atom or atoms to which they are attached optionally form a
- 20 (C₃-C₇)carbocycle or heterocycle wherein the (C₃-C₆)carbocycle or heterocycle is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;
- c) (C₁-C₆)alkyl, wherein (C₁-C₆)alkyl is substituted with one or more Z² groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;
- d) -X(C₁-C₆)alkyl, -X(C₁-C₆)haloalkyl, -X(C₂-C₆)alkenyl, -X(C₂-C₆)alkynyl and
- 25 -X(C₃-C₇)carbocycle, wherein -X(C₁-C₆)alkyl and X(C₁-C₆)haloalkyl are each independently substituted with one or more Z³ groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups, and wherein -X(C₂-C₆)alkenyl, -X(C₂-C₆)alkynyl and -X(C₃-C₇)carbocycle are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z⁴ groups and optionally substituted with one or more Z¹ groups;
- 30 e) aryl, heteroaryl, heterocycle, -Xaryl, -Xheteroaryl and -Xheterocycle, wherein aryl heteroaryl and heterocycle, either alone or as part of a group, are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z⁵ groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;

f) (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, (C₂-C₆)alkenyl, and (C₂-C₆)alkynyl, wherein (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, (C₂-C₆)alkenyl and (C₂-C₆)alkynyl are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z⁶ groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;

5 g) -NR_eR_f, -C(O)NR_eR_f, -OC(O)NR_eR_f, -SO₂NR_eR_f, -(C₁-C₆)alkyl-NR_eR_f, -(C₁-C₆)alkylC(O)-NR_eR_f, -(C₁-C₆)alkyl-O-C(O)-NR_eR_f and -(C₁-C₆)alkyl-SO₂NR_eR_f, wherein each (C₁-C₆)alkyl, as part of a group, is independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z⁶ groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups; and

h) nitro and cyano;
10 or R¹ and R² together with the atoms to which they are attached form a 5 or 6-membered carbocycle or a 4, 5, 6 or 7-membered heterocycle, wherein the 5 or 6-membered carbocycle or a 4, 5, 6 or 7-membered heterocycle are optionally substituted with one or more Z¹ groups;

or R¹ and R² together with the atoms to which they are attached form a 5 or 6-membered carbocycle or a 4, 5, 6 or 7-membered heterocycle, wherein the 5 or 6-membered carbocycle or a
15 4, 5, 6 or 7-membered heterocycle are each independently substituted with one or more (e.g. 1, 2 or 3) Z⁷ or Z⁸ groups, or wherein when two Z⁷ groups are on same atom the two Z⁷ groups together with the atom to which they are attached optionally form a (C₃-C₇)carbocycle or 4, 5 or 6-membered heterocycle;

R^{3a} is (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl,
20 -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-aryl, -(C₁-C₆)alkyl-heterocycle, -(C₁-C₆)alkyl-heteroaryl, -O(C₁-C₆)alkyl, -O(C₁-C₆)haloalkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -O(C₃-C₇)cycloalkyl, -Oaryl, -O(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -O(C₁-C₆)alkyl-aryl, -O(C₁-C₆)alkyl-heterocycle and -O(C₁-C₆)alkyl-heteroaryl, wherein any (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl,
25 -(C₁-C₆)alkyl-aryl, -(C₁-C₆)alkyl-heterocycle, -(C₁-C₆)alkyl-heteroaryl, -O(C₁-C₆)alkyl, -O(C₁-C₆)haloalkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -O(C₃-C₇)cycloalkyl, -Oaryl, -O(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -O(C₁-C₆)alkyl-aryl, -O(C₁-C₆)alkyl-heterocycle or -O(C₁-C₆)alkyl-heteroaryl of R^{3a} is optionally substituted with one or more (e.g. 1, 2 or 3) groups selected from (C₁-C₆)alkyl, -O(C₁-C₆)alkyl, halo, oxo and -CN; and

30 R^{3a'} is H;

R^{3b} is -(C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, -(C₁-C₆)alkylOH, -(C₁-C₆)alkyl-O-(C₁-C₆)alkyl-Z¹², -(C₁-C₆)alkyl-O-(C₂-C₆)alkenyl-Z¹², -(C₂-C₆)alkyl-O-(C₂-C₆)alkynyl-Z¹², -(C₁-C₆)alkyl-S-(C₁-C₆)alkyl-Z¹², -(C₁-C₆)alkyl-S-(C₂-C₆)alkenyl-Z¹², -(C₂-C₆)alkyl-S-(C₂-C₆)alkynyl-Z¹², -(C₁-C₆)alkyl-S(O)-(C₁-C₆)alkyl-Z¹², -(C₁-C₆)alkyl-S(O)-(C₂-C₆)alkenyl-Z¹²,

- (C₂-C₆)alkyl-S(O)-(C₂-C₆)alkynyl-Z¹², -(C₁-C₆)alkyl-SO₂-(C₁-C₆)alkyl-Z¹², -(C₁-C₆)alkyl-SO₂-(C₂-C₆)alkenyl-Z¹², -(C₂-C₆)alkyl-SO₂-(C₂-C₆)alkynyl-Z¹², -(C₂-C₆)alkyl-NR_aR_b,
 -(C₂-C₆)alkylOC(O)-NR_cR_d, -(C₂-C₆)alkyl-NR_a-C(O)-OR_b, -(C₂-C₆)alkyl-NR_a-C(O)-NR_aR_b,
 -(C₁-C₆)alkyl-SO₂(C₁-C₆)alkyl, -(C₁-C₆)alkyl-SO₂NR_cR_d, -(C₁-C₆)alkyl-NR_aSO₂NR_cR_d,
 5 -(C₁-C₆)alkyl-NR_aSO₂O(C₃-C₇)carbocycle, -(C₁-C₆)alkyl-NR_aSO₂Oaryl,
 -(C₁-C₆)alkyl-NR_a-SO₂-(C₁-C₆)alkyl, -(C₁-C₆)alkyl-NR_a-SO₂-(C₁-C₆)haloalkyl,
 -(C₁-C₆)alkyl-NR_a-SO₂-(C₂-C₆)alkenyl, -(C₁-C₆)alkyl-NR_a-SO₂-(C₂-C₆)alkynyl,
 -(C₁-C₆)alkyl-NR_a-SO₂-(C₃-C₇)carbocycle, -(C₁-C₆)alkyl-NR_a-SO₂-(C₃-C₇)halocarbocycle,
 -(C₁-C₆)alkyl-NR_a-SO₂-aryl, -(C₁-C₆)alkyl-NR_a-SO₂-heteroaryl,
 10 -(C₁-C₆)alkyl-NR_a-SO₂-heterocycle, -O(C₁-C₆)alkyl-NR_aR_b, -O(C₁-C₆)alkylOC(O)-NR_cR_d,
 -O(C₁-C₆)alkyl-NR_a-C(O)-OR_b, -O(C₁-C₆)alkyl-NR_a-C(O)-NR_aR_b,
 -O(C₁-C₆)alkyl-NR_a-SO₂-(C₁-C₆)alkyl, -O(C₁-C₆)alkyl-NR_a-SO₂-(C₁-C₆)haloalkyl,
 -O(C₁-C₆)alkyl-NR_a-SO₂-(C₂-C₆)alkenyl, -O(C₁-C₆)alkyl-NR_a-SO₂-(C₂-C₆)alkynyl,
 -O(C₁-C₆)alkyl-NR_a-SO₂-(C₃-C₇)carbocycle, -O(C₁-C₆)alkyl-NR_a-SO₂-(C₃-C₇)halocarbocycle,
 15 -O(C₁-C₆)alkyl-NR_a-SO₂-aryl, -O(C₁-C₆)alkyl-NR_a-SO₂-heteroaryl,
 -O(C₁-C₆)alkyl-NR_a-SO₂-heterocycle, -O(C₁-C₆)alkyl-NR_a-SO₂-NR_aR_b,
 -O(C₁-C₆)alkyl-NR_a-SO₂-(C₃-C₇)carbocycle, -O(C₁-C₆)alkyl-NR_a-SO₂-(C₃-C₇)halocarbocycle,
 -O(C₁-C₆)alkyl-NR_a-SO₂-aryl, -O(C₁-C₆)alkyl-NR_aSO₂NR_cR_d, -O(C₁-C₆)alkyl-NR_aSO₂O(C₃-C₇)carbocycle,
 -O(C₁-C₆)alkyl-NR_aSO₂Oaryl, -Oheteroaryl, -Oheterocycle, -Sheteroaryl,
 20 -Sheterocycle, -S(O)heteroaryl, -S(O)heterocycle, -SO₂heteroaryl or -SO₂heterocycle, wherein
 any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, aryl, (C₃-C₇)carbocycle, heteroaryl or
 heterocycle of R^{3b}, either alone or as part of a group, is optionally substituted with one or more
 (e.g. 1, 2, 3, 4 or 5) Z¹ groups; and
 R^{3b'} is H, (C₁-C₆)alkyl or -O(C₁-C₆)alkyl; or
 25 R^{3b} and R^{3b'} together with the carbon to which they are attached form a heterocycle or
 (C₃-C₇)carbocycle, which heterocycle or (C₃-C₇)carbocycle of R^{3b} and R^{3b'} together with the
 carbon to which they are attached is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5)
 Z¹ groups;
 R^{4a} is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and
 30 heteroaryl of R^{4a} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) groups each
 independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl,
 -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, -NH₂, -NH(C₁-C₆)alkyl
 and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo;

R^{4b} is selected from;

a) (C₁-C₆)alkyl, (C₂-C₆)alkenyl and (C₂-C₆)alkynyl, wherein (C₁-C₆)alkyl, (C₂-C₆)alkenyl or (C₂-C₆)alkynyl are each optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;

5 b) (C₃-C₁₄)carbocycle, wherein (C₃-C₁₄)carbocycle is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups, or wherein two Z¹ groups together with the atom or atoms to which they are attached optionally form a (C₃-C₇)carbocycle or heterocycle;

c) Spiro-heterocycle or bridged-heterocycle, wherein spiro-heterocycle or bridged-heterocycle is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups, or
10 wherein two Z¹ groups together with the atom or atoms to which they are attached optionally form a (C₃-C₇)carbocycle or heterocycle; and

d) aryl, heteroaryl, spiro- heterocycle, fused- heterocycle, or bridged-heterocycle, wherein aryl, heteroaryl, spiro- heterocycle, fused- heterocycle and bridged-heterocycle are each independently substituted with one or more Z⁷ groups and optionally substituted with one or
15 more (e.g. 1, 2, 3, 4 or 5) Z¹ groups; or

R⁴ and R³ together with the atoms to which they are attached form a macroheterocycle or a macrocarbocycle, wherein any macroheterocycle or macrocarbocycle of R⁴ and R³ together with the atoms to which they are attached may be optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups; and R^{3b'} is H or (C₁-C₆)alkyl, -O(C₁-C₆)alkyl;

20 R⁵ is selected from:

a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g. 1, 2 or 3) Z¹¹ groups;

b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z⁵ groups and optionally
25 substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups; and

c) aryl, heteroaryl, heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups.

each X is independently selected from O, -C(O)-, -C(O)O-, -S-, -S(O)-, -SO₂-, -(C₁-C₆)alkylO-, -(C₁-C₆)alkylC(O)-, -(C₁-C₆)alkylC(O)O-, -(C₁-C₆)alkylS-, -(C₁-C₆)alkylS(O)- and
30 -(C₁-C₆)alkylSO₂-;

each Z¹ is independently selected from halo, -NO₂, -OH, =NOR_a, -SH, -CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl, heterocycle, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-

C₆alkynyl, -O(C₁-C₆)haloalkyl, -O(C₃-C₇)carbocycle, -O(C₃-C₇)halocarbocycle, -Oaryl, -Oheteroaryl, -Oheterocycle, -S(C₁-C₆)alkyl, -S(C₂-C₆)alkenyl, -S(C₂-C₆)alkynyl, -S(C₁-C₆)haloalkyl, -S(C₃-C₇)carbocycle, -S(C₃-C₇)halocarbocycle, -Saryl, -Sheteroaryl, -Sheterocycle, -S(O)(C₁-C₆)alkyl, -S(O)(C₂-C₆)alkenyl, -S(O)(C₂-C₆)alkynyl, -S(O)(C₁-C₆)haloalkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₃-C₇)halocarbocycle, -SO₂(C₁-C₆)alkyl, -S(O)aryl, -S(O)carbocycle, -S(O)heteroaryl, -S(O)heterocycle, -SO₂(C₂-C₆)alkenyl, -SO₂(C₂-C₆)alkynyl, -SO₂(C₁-C₆)haloalkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarbocycle, -SO₂aryl, -SO₂heteroaryl, -SO₂heterocycle, -SO₂NR_cR_d, -NR_cR_d, -NR_aC(O)R_a, -NR_aC(O)OR_b, -NR_aC(O)NR_cR_d, -NR_aSO₂R_b, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl, -OS(O)₂R_a, -C(O)R_a, -C(O)OR_b, -C(O)NR_cR_d, and -OC(O)NR_cR_d, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -(C₃-C₇)halocarbocycle, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl or heterocycle of Z¹, either alone or as part of a group, is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) halogen, -OH, -OR_b, -CN, -NR_aC(O)₂R_b, -heteroaryl, -heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or -S(O)₂NR_cR_d;

each Z² is independently selected from -NO₂, -CN, spiro-heterocycle, bridge-heterocycle, spiro-bicyclic carbocycle, bridged-bicyclic carbocycle, NR_aSO₂(C₃-C₇)carbocycle, -NR_aSO₂aryl, -NR_aSO₂heteroaryl, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle and -NR_aSO₂Oaryl;

each Z³ is independently selected from -NO₂, -CN, -OH, oxo, =NOR_a, thioxo, aryl, heterocycle, heteroaryl, (C₃-C₇)halocarbocycle, -O(C₁-C₆)alkyl, -O(C₃-C₇)carbocycle, -O(C₃-C₇)halocarbocycle, -Oaryl, -Oheterocycle, -Oheteroaryl, -S(C₁-C₆)alkyl, -S(C₃-C₇)carbocycle, -S(C₃-C₇)halocarbocycle, -Saryl, -Sheterocycle, -Sheteroaryl, -S(O)(C₁-C₆)alkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₃-C₇)halocarbocycle, -S(O)aryl, -S(O)heterocycle, -S(O)heteroaryl, -SO₂(C₁-C₆)alkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarbocycle, SO₂aryl, -SO₂heterocycle, -SO₂heteroaryl, -NR_aR_b, -NR_aC(O)R_b, -C(O)NR_cR_d, -SO₂NR_cR_d, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle and -NR_aSO₂Oaryl;

each Z⁴ is independently selected from halogen, -(C₁-C₆)alkyl, (C₃-C₇)carbocycle, -(C₁-C₆)haloalkyl, -NO₂, -CN, -OH, oxo, =NOR_a, thioxo, -aryl, -heterocycle, -heteroaryl, -(C₃-C₇)halocarbocycle, -O(C₁-C₆)alkyl, -O(C₃-C₇)carbocycle, -O(C₃-C₇)halocarbocycle, -Oaryl, -Oheterocycle, -Oheteroaryl, -S(C₁-C₆)alkyl, -S(C₃-C₇)carbocycle, -S(C₃-C₇)halocarbocycle, -Saryl, -Sheterocycle, -Sheteroaryl, -S(O)(C₁-C₆)alkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₃-C₇)halocarbocycle, -S(O)aryl, -S(O)heterocycle, -S(O)heteroaryl, -SO₂(C₁-C₆)alkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarbocycle, SO₂aryl, -SO₂heterocycle, -SO₂heteroaryl, -NR_aR_b,

-NR_aC(O)R_a, -C(O)NR_cR_d, -SO₂NR_cR_d, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle and -NR_aSO₂Oaryl;

each Z⁵ is independently selected from -NO₂, -CN, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl, -NR_aSO₂(C₁-C₆)alkyl, -NR_aSO₂(C₂-C₆)alkenyl, -NR_aSO₂(C₂-C₆)alkynyl, -NR_aSO₂(C₃-C₇)carbocycle, -NR_aSO₂(C₃-C₇)halocarbocycle, -NR_aSO₂aryl, -NR_aSO₂heteraryl, -NR_aSO₂heteroaryl, -NR_aSO₂heterocycle, -NR_aC(O)alkyl, -NR_aC(O)alkenyl, -NR_aC(O)alkynyl, -NR_aC(O)(C₃-C₇)carbocycle, -NR_aC(O)(C₃-C₇)halocarbocycle, -NR_aC(O)aryl, -NR_aC(O)heteroaryl, -NR_aC(O)heterocycle, -NR_aC(O)NR_cR_d and -NR_aC(O)OR_b;

each Z⁶ is independently selected from -NO₂, -CN, -NR_aR_a, NR_aC(O)R_b, -C(O)NR_cR_d, (C₃-C₇)halocarbocycle, aryl, heteroaryl, heterocycle, -Oaryl, -Oheteroaryl, -Oheterocycle, -O(C₃-C₇)halocarbocycle, -O(C₁-C₆)alkyl, -O(C₃-C₇)carbocycle, -O(C₁-C₆)haloalkyl, -Saryl, -Sheteroaryl, -Sheterocycle, -S(C₃-C₇)halocarbocycle, -S(C₁-C₆)alkyl, -S(C₃-C₇)carbocycle, -S(C₁-C₆)haloalkyl, -S(O)aryl, -S(O)heteroaryl, -S(O)heterocycle, -S(O)(C₃-C₇)halocarbocycle, -S(O)(C₁-C₆)alkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₁-C₆)haloalkyl, -SO₂aryl, -SO₂heteroaryl, -SO₂heterocycle, -SO₂(C₁-C₆)alkyl, -SO₂(C₁-C₆)haloalkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarbocycle, -SO₂NR_cR_d, -NR_aSO₂(C₃-C₇)halocarbocycle, -NR_aSO₂aryl, -NR_aSO₂heteraryl, -NR_aSO₂heteroaryl, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle and -NR_aSO₂Oaryl, wherein any aryl, of Z⁶, either alone or as part of a group, is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) halogen, -OH, -O(C₁-C₆)alkyl, -CN or -(C₁-C₆)alkyl;

each Z⁷ is independently selected from -NO₂, =NOR_a, -CN, -(C₁-C₆)alkyl-Z¹², -(C₂-C₆)alkenyl-Z¹², -(C₂-C₆)alkenylOH, -(C₂-C₆)alkynyl-Z¹², -(C₂-C₆)alkynyl-OH, -(C₁-C₆)haloalkyl-Z¹², -(C₁-C₆)haloalkylOH, -(C₃-C₇)carbocycle-Z¹², -(C₃-C₇)carbocycleOH, -(C₃-C₇)halocarbocycle, -(C₁-C₆)alkylNR_cR_d, -(C₁-C₆)alkylNR_aC(O)R_a, -(C₁-C₆)alkylNR_aSO₂R_a, aryl, heteroaryl, heterocycle, -O(C₁-C₆)alkyl-Z¹², -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -O(C₁-C₆)haloalkyl, -O(C₃-C₇)carbocycle, -O(C₃-C₇)halocarbocycle, -Oaryl, -O(C₁-C₆)alkylNR_cR_d, -O(C₁-C₆)alkylNR_aC(O)R_a, -O(C₁-C₆)alkylNR_aSO₂R_a, -Oheteroaryl, -Oheterocycle, -S(C₁-C₆)alkyl-Z¹², -S(C₂-C₆)alkenyl, -S(C₂-C₆)alkynyl, -S(C₁-C₆)haloalkyl, -S(C₃-C₇)carbocycle, -S(C₃-C₇)halocarbocycle, -S(C₁-C₆)alkylNR_cR_d, -S(C₁-C₆)alkylNR_aC(O)R_a, -S(C₁-C₆)alkylNR_aSO₂R_a, -Saryl, -Sheteroaryl, -Sheterocycle, -S(O)(C₁-C₆)alkyl, -S(O)(C₂-C₆)alkenyl, -S(O)(C₂-C₆)alkynyl, -S(O)(C₁-C₆)haloalkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₃-C₇)halocarbocycle, -SO₂(C₁-C₆)alkyl, -S(O)(C₁-C₆)alkylNR_cR_d, -S(O)(C₁-C₆)alkylNR_aC(O)R_a, -S(O)(C₁-C₆)alkylNR_aSO₂R_a, -S(O)aryl, -S(O)heteroaryl, -S(O)heterocycle, -SO₂(C₁-C₆)alkyl, -SO₂(C₂-C₆)alkenyl, -SO₂(C₂-C₆)alkynyl, -SO₂(C₁-C₆)haloalkyl, -SO₂(C₃-C₇)carbocycle,

-SO₂(C₃-C₇)halocarboxy, -SO₂aryl, -SO₂heteroaryl, -SO₂heterocycle, -SO₂(C₁-C₆)alkylNR_cR_d, -SO₂(C₁-C₆)alkylNR_aC(O)R_a, -SO₂(C₁-C₆)alkylNR_aSO₂R_a, -SO₂NR_cR_d, -NR_aC(O)OR_b, -NR_aC(O)NR_cR_d, -NR_aSO₂R_b, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl, -OS(O)₂R_a, -C(O)NR_cR_d, and -OC(O)NR_cR_d, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, (C₃-C₇)halocarboxy, aryl, heteroaryl or heterocycle of Z⁷, either alone or as part of a group, is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) halogen, -OH, -OR_b, -CN, -NR_aC(O)₂R_b, heteroaryl, heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or -S(O)₂NR_cR_d,

each Z⁸ is independently selected from -NO₂ or -CN;

10 each Z¹⁰ is independently selected from

i) halo, oxo, thio, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -O(C₁-C₆)haloalkyl, -SH, -S(C₁-C₆)alkyl, -SO(C₁-C₆)alkyl, -SO₂(C₁-C₆)alkyl, -NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂;

15 ii) (C₁-C₆)alkyl optionally substituted with -OH, -O-(C₁-C₆)haloalkyl, or -O-(C₁-C₆)alkyl; and

iii) aryl, heterocycle and heteroaryl, which aryl, heterocycle and heteroaryl is optionally substituted with halo, (C₁-C₆)alkyl or COOH;

each Z¹¹ is independently selected from Z¹⁰, -C(=O)-NH₂, -C(=O)-NH(C₁-C₄)alkyl, -C(=O)-N((C₁-C₄)alkyl)₂, -C(=O)-aryl, -C(=O)-heterocycle and -C(=O)-heteroaryl;

20 each Z¹² is independently selected from -NO₂, =NOR_a, thio, aryl, heterocycle, heteroaryl, (C₃-C₇)halocarboxy, (C₃-C₇)carbocycle, -O(C₃-C₇)carbocycle, -O(C₃-C₇)halocarboxy, -Oaryl, -Oheterocycle, -Oheteroaryl, -S(C₁-C₆)alkyl, -S(C₃-C₇)carbocycle, -S(C₃-C₇)halocarboxy, -Saryl, -Sheterocycle, -Sheteroaryl, -S(O)(C₁-C₆)alkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₃-C₇)halocarboxy, -S(O)aryl, -S(O)heterocycle, -S(O)heteroaryl, -SO₂(C₁-C₆)alkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarboxy, SO₂aryl, -SO₂heterocycle, -SO₂heteroaryl, -NR_aR_a, -NR_aC(O)R_b, -C(O)NR_cR_d, -SO₂NR_cR_d, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle and -NR_aSO₂Oaryl;

25 each Z¹³ is independently selected from -NO₂, -OH, =NOR_a, -SH, -CN, (C₃-C₇)halocarboxy, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -O(C₁-C₆)haloalkyl, -O(C₃-C₇)carbocycle, -O(C₃-C₇)halocarboxy, -Oaryl, -Oheteroaryl, -Oheterocycle, -S(C₁-C₆)alkyl, -S(C₂-C₆)alkenyl, -S(C₂-C₆)alkynyl, -S(C₁-C₆)haloalkyl, -S(C₃-C₇)carbocycle, -S(C₃-C₇)halocarboxy, -Saryl, -Sheteroaryl, -Sheterocycle, -S(O)(C₁-C₆)alkyl, -S(O)(C₂-C₆)alkenyl, -S(O)(C₂-C₆)alkynyl, -S(O)(C₁-C₆)haloalkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₃-C₇)halocarboxy, -S(O)aryl, -S(O)heteroaryl, -S(O)heterocycle, -SO₂(C₁-C₆)alkyl, -SO₂(C₂-C₆)alkenyl, -SO₂(C₂-C₆)alkynyl, -SO₂(C₁-C₆)haloalkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarboxy, -SO₂aryl, -SO₂heterocycle, -SO₂heteroaryl, -NR_aR_a, -NR_aC(O)R_b, -C(O)NR_cR_d, -SO₂NR_cR_d, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle and -NR_aSO₂Oaryl;

- C₆alkenyl, -SO₂(C₂-C₆)alkynyl, -SO₂(C₁-C₆)haloalkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarbocycle, -SO₂aryl, -SO₂heteroaryl, -SO₂heterocycle, -SO₂NR_cR_d, -NR_cR_d, -NR_aC(O)R_a, -NR_aC(O)OR_b, -NR_aC(O)NR_cR_d, -NR_aSO₂R_b, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl, -OS(O)₂R_a, -C(O)R_a, -C(O)OR_b, -C(O)NR_cR_d, and
- 5 -OC(O)NR_cR_d, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)halocarbocycle, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl or heterocycle of Z¹³, either alone or as part of a group, is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) halogen, -OH, -OR_b, -CN, -NR_aC(O)₂R_b, -heteroaryl, -heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle, or -S(O)₂NR_cR_d;
- 10 each Z¹⁴ is independently selected from -NO₂, =NOR_a, -CN, -(C₃-C₇)halocarbocycle, -O(C₃-C₇)halocarbocycle, -S(C₃-C₇)halocarbocycle, -S(O)(C₃-C₇)halocarbocycle, -SO₂(C₃-C₇)halocarbocycle, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl, -OS(O)₂R_a, wherein any -(C₃-C₇)halocarbocycle of Z¹⁴, either alone or as part of a group, is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) halogen, -OH, -OR_b, -CN, -NR_aC(O)₂R_b,
- 15 heteroaryl, -heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle, or -S(O)₂NR_cR_d;
- each Z¹⁵ is independently selected from aryl, heteroaryl, heterocycle, -Oaryl, -Oheteroaryl, -Oheterocycle, -O(C₁-C₆)alkyl-aryl, -O(C₁-C₆)alkyl-heteroaryl, -O(C₁-C₆)alkyl-heterocycle, wherein aryl, heteroaryl and heterocycle are each independently
- 20 substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹⁶ groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups, and wherein any -Oaryl, -Oheteroaryl, -Oheterocycle, -O(C₁-C₆)alkyl-aryl, -O(C₁-C₆)alkyl-heteroaryl or -O(C₁-C₆)alkyl-heterocycle is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;
- each Z¹⁶ is independently selected from -NO₂, -OH, =NOR_a, -SH, -CN, (C₂-C₆)alkenyl,
- 25 (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl, heterocycle, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -O(C₁-C₆)haloalkyl, -O(C₃-C₇)carbocycle, -O(C₃-C₇)halocarbocycle, -Oaryl, -Oheteroaryl, -Oheterocycle, -S(C₁-C₆)alkyl, -S(C₂-C₆)alkenyl, -S(C₂-C₆)alkynyl, -S(C₁-C₆)haloalkyl, -S(C₃-C₇)carbocycle, -S(C₃-C₇)halocarbocycle, -Saryl, -Sheteroaryl, -Sheterocycle, -S(O)(C₁-C₆)alkyl, -S(O)(C₂-C₆)alkenyl,
- 30 -S(O)(C₂-C₆)alkynyl, -S(O)(C₁-C₆)haloalkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₃-C₇)halocarbocycle, -SO₂(C₁-C₆)alkyl, -S(O)aryl, -S(O)carbocycle, -S(O)heteroaryl, -S(O)heterocycle, -SO₂(C₂-C₆)alkenyl, -SO₂(C₂-C₆)alkynyl, -SO₂(C₁-C₆)haloalkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarbocycle, -SO₂aryl, -SO₂heteroaryl, -SO₂heterocycle, -SO₂NR_cR_d, -NR_cR_d, -NR_aC(O)R_a, -NR_aC(O)OR_b, -NR_aC(O)NR_cR_d, -NR_aSO₂R_b,

-NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl, -OS(O)₂R_a, -C(O)R_a, -C(O)OR_b,
 -C(O)NR_cR_d, and -OC(O)NR_cR_d, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl,
 -(C₃-C₇)halocarbocycle, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl or
 heterocycle of Z¹⁶, either alone or as part of a group, is optionally substituted with one or more
 5 (e.g. 1, 2, 3, 4 or 5) halogen, (C₁-C₆)alkyl, -OH, -OR_b, -CN, -NR_aC(O)₂R_b, heteroaryl,
 heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or -S(O)₂NR_cR_d;

each R_a is independently H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl,
 (C₃-C₇)carbocycle, heterocycle, aryl, aryl(C₁-C₆)alkyl-, heteroaryl or heteroaryl(C₁-C₆)alkyl-,
 wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl,
 10 or heteroaryl of R_a, either alone or as part of a group, is optionally substituted with one or more
 (e.g. 1, 2, 3, 4 or 5) halogen, OH or cyano;

each R_b is independently (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl,
 (C₃-C₇)carbocycle, heterocycle, aryl, aryl(C₁-C₆)alkyl-, heteroaryl or heteroaryl(C₁-C₆)alkyl-,
 wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl,
 15 or heteroaryl of R_b, either alone or as part of a group, is optionally substituted with one or more
 (e.g. 1, 2, 3, 4 or 5) halogen, OH and cyano;

R_c and R_d are each independently selected from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl,
 (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, aryl, aryl(C₁-C₆)alkyl-, heterocycle, heteroaryl or
 heteroaryl(C₁-C₆)alkyl-, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl,
 20 (C₃-C₇)carbocycle, heterocycle, aryl, or heteroaryl of R_c or R_d, either alone or as part of a group,
 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) halogen, OH or cyano; or R_c and
 R_d together with the nitrogen to which they are attached form a heterocycle, wherein any
 heterocycle of R_c and R_d together with the nitrogen to which they are attached is optionally
 substituted with one or more (e.g. 1, 2, 3, 4 or 5) halogen, OH or cyano;

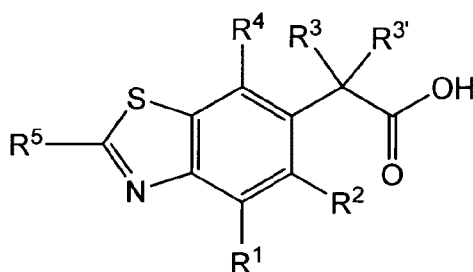
each R_e is independently selected from -OR_a, (C₁-C₆)alkyl or (C₃-C₇)carbocycle, wherein
 (C₁-C₆)alkyl and (C₃-C₇)carbocycle are each independently substituted with one or more (e.g. 1,
 2, 3, 4 or 5) Z⁶ groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹
 groups; (C₂-C₆)haloalkyl, (C₂-C₆)alkenyl and (C₂-C₆)alkynyl, wherein any (C₂-C₆)haloalkyl,
 (C₂-C₆)alkenyl or (C₂-C₆)alkynyl is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5)
 30 Z₁ groups; and aryl, heterocycle and heteroaryl wherein aryl, heterocycle and heteroaryl are each
 independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z₅ groups;

each R_f is independently selected from -R_g, -OR_a, -(C₁-C₆)alkyl-Z⁶, -SO₂R_g, -C(O)R_g,
 C(O)OR_g and -C(O)NR_cR_g; and

each R_g is independently selected from (C_1-C_6) alkyl, (C_3-C_7) carbocycle (C_1-C_6) haloalkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, aryl, heterocycle and heteroaryl, wherein any (C_1-C_6) alkyl, (C_3-C_7) carbocycle (C_1-C_6) haloalkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, aryl, heterocycle or heteroaryl of R_g is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z_1 groups;

or a salt thereof.

In one embodiment, the invention provides a compound of formula Ia:



Ia

wherein:

R^1 is H;

R^2 is (C_1-C_6) alkyl;

R^3 is $-O(C_1-C_6)$ alkyl;

$R^{3'}$ is H;

R^4 is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R^4 is optionally substituted with one or more groups each independently selected from halo, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_1-C_6) haloalkyl, (C_3-C_7) cycloalkyl, $-(C_1-C_6)$ alkyl- (C_3-C_7) cycloalkyl, $-OH$, $-O(C_1-C_6)$ alkyl, $-SH$, $-S(C_1-C_6)$ alkyl, NH_2 , $-NH(C_1-C_6)$ alkyl and $-N((C_1-C_6)alkyl)_2$, wherein (C_1-C_6) alkyl is optionally substituted with hydroxy, $-O(C_1-C_6)$ alkyl, cyano or oxo;

R^5 is selected from:

a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{11} groups;

b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups; and

c) aryl, heteroaryl, and heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups;

each Z^1 is independently selected from halo, $-\text{NO}_2$, $-\text{OH}$, $=\text{NOR}_a$, $-\text{SH}$, $-\text{CN}$, $(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_2-\text{C}_6)\text{alkenyl}$, $(\text{C}_2-\text{C}_6)\text{alkynyl}$, $(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $(\text{C}_3-\text{C}_7)\text{carbocycle}$, $(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, aryl, heteroaryl, heterocycle, $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{O}(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{O}(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{O}(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{O}(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{Oaryl}$, $-\text{Oheteroaryl}$, $-\text{Oheterocycle}$, $-\text{S}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{S}(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{S}(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{S}(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{S}(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{S}(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{Saryl}$, $-\text{Sheteroaryl}$, $-\text{Sheterocycle}$, $-\text{S}(\text{O})(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{S}(\text{O})(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{S}(\text{O})(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{S}(\text{O})(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{S}(\text{O})(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{S}(\text{O})(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{S}(\text{O})\text{aryl}$, $-\text{S}(\text{O})\text{carbocycle}$, $-\text{S}(\text{O})\text{heteroaryl}$, $-\text{S}(\text{O})\text{heterocycle}$, $-\text{SO}_2(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{SO}_2(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{SO}_2(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{SO}_2(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{SO}_2(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{SO}_2\text{aryl}$, $-\text{SO}_2\text{heteroaryl}$, $-\text{SO}_2\text{heterocycle}$, $-\text{SO}_2\text{NR}_c\text{R}_d$, $-\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{C}(\text{O})\text{R}_a$, $-\text{NR}_a\text{C}(\text{O})\text{OR}_b$, $-\text{NR}_a\text{C}(\text{O})\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{SO}_2\text{R}_b$, $-\text{NR}_a\text{SO}_2\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{SO}_2\text{O}(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{NR}_a\text{SO}_2\text{Oaryl}$, $-\text{OS}(\text{O})_2\text{R}_a$, $-\text{C}(\text{O})\text{R}_a$, $-\text{C}(\text{O})\text{OR}_b$, $-\text{C}(\text{O})\text{NR}_c\text{R}_d$, and $-\text{OC}(\text{O})\text{NR}_c\text{R}_d$, wherein any $(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_2-\text{C}_6)\text{alkenyl}$, $(\text{C}_2-\text{C}_6)\text{alkynyl}$, $(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $(\text{C}_3-\text{C}_7)\text{carbocycle}$, $(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, aryl, heteroaryl or heterocycle of Z^1 , either alone or as part of a group, is optionally substituted with one or more halogen, $-\text{OH}$, $-\text{OR}_b$, $-\text{CN}$, $-\text{NR}_a\text{C}(\text{O})_2\text{R}_b$, heteroaryl, heterocycle, $-\text{Oheteroaryl}$, $-\text{Oheterocycle}$, $-\text{NHheteroaryl}$, $-\text{NHheterocycle}$ or $-\text{S}(\text{O})_2\text{NR}_c\text{R}_d$;

each Z^5 is independently selected from $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}_a\text{SO}_2\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{SO}_2\text{O}(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{NR}_a\text{SO}_2\text{Oaryl}$, $-\text{NR}_a\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{NR}_a\text{SO}_2(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{NR}_a\text{SO}_2(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{NR}_a\text{SO}_2(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{NR}_a\text{SO}_2(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{NR}_a\text{SO}_2\text{aryl}$, $-\text{NR}_a\text{SO}_2\text{heteraryl}$, $-\text{NR}_a\text{SO}_2\text{heteroaryl}$, $-\text{NR}_a\text{SO}_2\text{heterocycle}$, $-\text{NR}_a\text{C}(\text{O})\text{alkyl}$, $-\text{NR}_a\text{C}(\text{O})\text{alkenyl}$, $-\text{NR}_a\text{C}(\text{O})\text{alkynyl}$, $-\text{NR}_a\text{C}(\text{O})(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{NR}_a\text{C}(\text{O})(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{NR}_a\text{C}(\text{O})\text{aryl}$, $-\text{NR}_a\text{C}(\text{O})\text{heteroaryl}$, $-\text{NR}_a\text{C}(\text{O})\text{heterocycle}$, $-\text{NR}_a\text{C}(\text{O})\text{NR}_c\text{R}_d$ and $-\text{NR}_a\text{C}(\text{O})\text{OR}_b$;

each Z^{10} is independently selected from

i) halo, oxo, thioxo, $(\text{C}_2-\text{C}_6)\text{alkenyl}$, $(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $(\text{C}_3-\text{C}_7)\text{cycloalkyl}$, $(\text{C}_3-\text{C}_7)\text{cycloalkyl}-(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{SH}$, $-\text{S}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{SO}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1-\text{C}_6)\text{alkyl}$ and $-\text{N}((\text{C}_1-\text{C}_6)\text{alkyl})_2$;

ii) $(\text{C}_1-\text{C}_6)\text{alkyl}$ optionally substituted with one or more $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{haloalkyl}$, or $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$; and

iii) aryl, heterocycle and heteroaryl, which aryl, heterocycle and heteroaryl is optionally substituted with one or more halo, $(\text{C}_1-\text{C}_6)\text{alkyl}$ or COOH ;

each Z^{11} is independently selected from Z^{10} , $-\text{C}(=\text{O})-\text{NH}_2$, $-\text{C}(=\text{O})-\text{NH}(\text{C}_1-\text{C}_4)\text{alkyl}$, $-\text{C}(=\text{O})-\text{N}((\text{C}_1-\text{C}_4)\text{alkyl})_2$, $-\text{C}(=\text{O})-\text{aryl}$, $-\text{C}(=\text{O})-\text{heterocycle}$ and $-\text{C}(=\text{O})-\text{heteroaryl}$;

each Z^{15} is independently selected from aryl, heteroaryl, heterocycle, $-\text{Oaryl}$,

-Oheteroaryl, -Oheterocycle, -O(C₁-C₆)alkyl-aryl, -O(C₁-C₆)alkyl-heteroaryl, -O(C₁-C₆)alkyl-heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more Z¹⁶ groups and optionally substituted with one or more Z¹ groups, and wherein any -Oaryl, -Oheteroaryl, -Oheterocycle, -O(C₁-C₆)alkyl-aryl, -O(C₁-C₆)alkyl-heteroaryl or -O(C₁-C₆)alkyl-heterocycle is optionally substituted with one or more Z¹ groups;

each Z¹⁶ is independently selected from -NO₂, -OH, =NOR_a, -SH, -CN, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl, heterocycle, aryl(C₁-C₆)alkyl-, -O(C₁-C₆)alkyl-, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -O(C₁-C₆)haloalkyl, -O(C₃-C₇)carbocycle, -O(C₃-C₇)halocarbocycle, -Oaryl, -Oheteroaryl, -Oheterocycle, -S(C₁-C₆)alkyl-, -S(C₂-C₆)alkenyl, -S(C₂-C₆)alkynyl, -S(C₁-C₆)haloalkyl, -S(C₃-C₇)carbocycle, -S(C₃-C₇)halocarbocycle, -Saryl, -Sheteroaryl, -Sheterocycle, -S(O)(C₁-C₆)alkyl-, -S(O)(C₂-C₆)alkenyl, -S(O)(C₂-C₆)alkynyl, -S(O)(C₁-C₆)haloalkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₃-C₇)halocarbocycle, -SO₂(C₁-C₆)alkyl-, -S(O)aryl, -S(O)carbocycle, -S(O)heteroaryl, -S(O)heterocycle, -SO₂(C₂-C₆)alkenyl, -SO₂(C₂-C₆)alkynyl, -SO₂(C₁-C₆)haloalkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarbocycle, -SO₂aryl, -SO₂heteroaryl, -SO₂heterocycle, -SO₂NR_cR_d, -NR_cR_d, -NR_aC(O)R_a, -NR_aC(O)OR_b, -NR_aC(O)NR_cR_d, -NR_aSO₂R_b, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl, -OS(O)₂R_a, -C(O)R_a, -C(O)OR_b, -C(O)NR_cR_d, and -OC(O)NR_cR_d, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)halocarbocycle, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl or heterocycle of Z¹⁶, either alone or as part of a group, is optionally substituted with one or more halogen, (C₁-C₆)alkyl, -OH, -OR_b, -CN, -NR_aC(O)₂R_b, -heteroaryl, -heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or -S(O)₂NR_cR_d;

each R_a is independently H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, aryl(C₁-C₆)alkyl-, heteroaryl or heteroaryl(C₁-C₆)alkyl-, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, or heteroaryl of R_a, either alone or as part of a group, is optionally substituted with one or more halogen, OH or cyano;

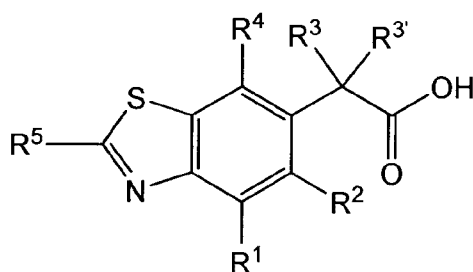
each R_b is independently (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, aryl(C₁-C₆)alkyl-, heteroaryl or heteroaryl(C₁-C₆)alkyl-, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, or heteroaryl of R_b, either alone or as part of a group, is optionally substituted with one or more halogen, OH and cyano; and

R_c and R_d are each independently selected from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, aryl, aryl(C₁-C₆)alkyl-, heterocycle, heteroaryl or heteroaryl(C₁-C₆)alkyl-, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, or heteroaryl of R_c or R_d , either alone or as part of a group, is optionally substituted with one or more halogen, OH or cyano; or R_c and R_d together with the nitrogen to which they are attached form a heterocycle, wherein any such heterocycle is optionally substituted with one or more halogen, OH or cyano;

or a salt thereof;

provided R^5 is not azetidiny or 1-methyl-imidazo-2-yl.

In one embodiment, the invention provides a compound of formula Ia:



Ia

wherein:

R^1 is H;

R^2 is (C₁-C₆)alkyl;

R^3 is -O(C₁-C₆)alkyl;

$R^{3'}$ is H;

R^4 is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R^4 is optionally substituted with one or more groups each independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo;

R^5 is selected from:

a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g. 1, 2 or 3) Z^{11} groups;

b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^5 groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups; and

c) aryl, heteroaryl, heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{15} groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups;

each Z^1 is independently selected from halo, $-\text{NO}_2$, $-\text{OH}$, $=\text{NOR}_a$, $-\text{SH}$, $-\text{CN}$, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl, heterocycle, $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{O}(\text{C}_2\text{-C}_6)\text{alkenyl}$, $-\text{O}(\text{C}_2\text{-C}_6)\text{alkynyl}$, $-\text{O}(\text{C}_1\text{-C}_6)\text{haloalkyl}$, $-\text{O}(\text{C}_3\text{-C}_7)\text{carbocycle}$, $-\text{O}(\text{C}_3\text{-C}_7)\text{halocarbocycle}$, $-\text{Oaryl}$, $-\text{Oheteroaryl}$, $-\text{Oheterocycle}$, $-\text{S}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{S}(\text{C}_2\text{-C}_6)\text{alkenyl}$, $-\text{S}(\text{C}_2\text{-C}_6)\text{alkynyl}$, $-\text{S}(\text{C}_1\text{-C}_6)\text{haloalkyl}$, $-\text{S}(\text{C}_3\text{-C}_7)\text{carbocycle}$, $-\text{S}(\text{C}_3\text{-C}_7)\text{halocarbocycle}$, $-\text{Saryl}$, $-\text{Sheteroaryl}$, $-\text{Sheterocycle}$, $-\text{S}(\text{O})(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{S}(\text{O})(\text{C}_2\text{-C}_6)\text{alkenyl}$, $-\text{S}(\text{O})(\text{C}_2\text{-C}_6)\text{alkynyl}$, $-\text{S}(\text{O})(\text{C}_1\text{-C}_6)\text{haloalkyl}$, $-\text{S}(\text{O})(\text{C}_3\text{-C}_7)\text{carbocycle}$, $-\text{S}(\text{O})(\text{C}_3\text{-C}_7)\text{halocarbocycle}$, $-\text{SO}_2(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{S}(\text{O})\text{aryl}$, $-\text{S}(\text{O})\text{carbocycle}$, $-\text{S}(\text{O})\text{heteroaryl}$, $-\text{S}(\text{O})\text{heterocycle}$, $-\text{SO}_2(\text{C}_2\text{-C}_6)\text{alkenyl}$, $-\text{SO}_2(\text{C}_2\text{-C}_6)\text{alkynyl}$, $-\text{SO}_2(\text{C}_1\text{-C}_6)\text{haloalkyl}$, $-\text{SO}_2(\text{C}_3\text{-C}_7)\text{carbocycle}$, $-\text{SO}_2(\text{C}_3\text{-C}_7)\text{halocarbocycle}$, $-\text{SO}_2\text{aryl}$, $-\text{SO}_2\text{heteroaryl}$, $-\text{SO}_2\text{heterocycle}$, $-\text{SO}_2\text{NR}_c\text{R}_d$, $-\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{C}(\text{O})\text{R}_a$, $-\text{NR}_a\text{C}(\text{O})\text{OR}_b$, $-\text{NR}_a\text{C}(\text{O})\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{SO}_2\text{R}_b$, $-\text{NR}_a\text{SO}_2\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{SO}_2\text{O}(\text{C}_3\text{-C}_7)\text{carbocycle}$, $-\text{NR}_a\text{SO}_2\text{Oaryl}$, $-\text{OS}(\text{O})_2\text{R}_a$, $-\text{C}(\text{O})\text{R}_a$, $-\text{C}(\text{O})\text{OR}_b$, $-\text{C}(\text{O})\text{NR}_c\text{R}_d$, and $-\text{OC}(\text{O})\text{NR}_c\text{R}_d$, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)halocarbocycle, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl or heterocycle of Z^1 , either alone or as part of a group, is optionally substituted with one or more halogen, $-\text{OH}$, $-\text{OR}_b$, $-\text{CN}$, $-\text{NR}_a\text{C}(\text{O})_2\text{R}_b$, heteroaryl, heterocycle, $-\text{Oheteroaryl}$, $-\text{Oheterocycle}$, $-\text{NHheteroaryl}$, $-\text{NHheterocycle}$ or $-\text{S}(\text{O})_2\text{NR}_c\text{R}_d$;

each Z^5 is independently selected from $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}_a\text{SO}_2\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{SO}_2\text{O}(\text{C}_3\text{-C}_7)\text{carbocycle}$, $-\text{NR}_a\text{SO}_2\text{Oaryl}$, $-\text{NR}_a\text{SO}_2(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{NR}_a\text{SO}_2(\text{C}_2\text{-C}_6)\text{alkenyl}$, $-\text{NR}_a\text{SO}_2(\text{C}_2\text{-C}_6)\text{alkynyl}$, $-\text{NR}_a\text{SO}_2(\text{C}_3\text{-C}_7)\text{carbocycle}$, $-\text{NR}_a\text{SO}_2(\text{C}_3\text{-C}_7)\text{halocarbocycle}$, $-\text{NR}_a\text{SO}_2\text{aryl}$, $-\text{NR}_a\text{SO}_2\text{heteraryl}$, $-\text{NR}_a\text{SO}_2\text{heteroaryl}$, $-\text{NR}_a\text{SO}_2\text{heterocycle}$, $-\text{NR}_a\text{C}(\text{O})\text{alkyl}$, $-\text{NR}_a\text{C}(\text{O})\text{alkenyl}$, $-\text{NR}_a\text{C}(\text{O})\text{alkynyl}$, $-\text{NR}_a\text{C}(\text{O})(\text{C}_3\text{-C}_7)\text{carbocycle}$, $-\text{NR}_a\text{C}(\text{O})(\text{C}_3\text{-C}_7)\text{halocarbocycle}$, $-\text{NR}_a\text{C}(\text{O})\text{aryl}$, $-\text{NR}_a\text{C}(\text{O})\text{heteroaryl}$, $-\text{NR}_a\text{C}(\text{O})\text{heterocycle}$, $-\text{NR}_a\text{C}(\text{O})\text{NR}_c\text{R}_d$ and $-\text{NR}_a\text{C}(\text{O})\text{OR}_b$;

each Z^{10} is independently selected from

i) halo, oxo, thioxo, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl-, $-\text{OH}$, $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{O}(\text{C}_1\text{-C}_6)\text{haloalkyl}$, $-\text{SH}$, $-\text{S}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{SO}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{SO}_2(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1\text{-C}_6)\text{alkyl}$ and $-\text{N}((\text{C}_1\text{-C}_6)\text{alkyl})_2$;

ii) (C₁-C₆)alkyl optionally substituted with one or more $-\text{OH}$, $-\text{O}(\text{C}_1\text{-C}_6)\text{haloalkyl}$, or $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$; and

iii) aryl, heterocycle and heteroaryl, which aryl, heterocycle and heteroaryl is optionally substituted with one or more halo, (C₁-C₆)alkyl or COOH ;

each Z^{11} is independently selected from Z^{10} , $-C(=O)-NH_2$, $-C(=O)-NH(C_1-C_4)alkyl$, $-C(=O)-N((C_1-C_4)alkyl)_2$, $-C(=O)-aryl$, $-C(=O)-heterocycle$ and $-C(=O)-heteroaryl$;

each Z^{15} is independently selected from aryl, heteroaryl, heterocycle, -Oaryl, -Oheteroaryl, -Oheterocycle, $-O(C_1-C_6)alkyl-aryl$, $-O(C_1-C_6)alkyl-heteroaryl$, $-O(C_1-$

5 $C_6)alkyl-heterocycle$, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more Z^{16} groups and optionally substituted with one or more Z^1 groups, and wherein any -Oaryl, -Oheteroaryl, -Oheterocycle, $-O(C_1-C_6)alkyl-aryl$, $-O(C_1-$ $C_6)alkyl-heteroaryl$ or $-O(C_1-C_6)alkyl-heterocycle$ is optionally substituted with one or more Z^1 groups;

10 each Z^{16} is independently selected from $-NO_2$, $-OH$, $=NOR_a$, $-SH$, $-CN$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_1-C_6)haloalkyl$, $(C_3-C_7)carbocycle$, $(C_3-C_7)halocarbocycle$, aryl, heteroaryl, heterocycle, $aryl(C_1-C_6)alkyl-$, $-O(C_1-C_6)alkyl$, $-O(C_2-C_6)alkenyl$, $-O(C_2-C_6)alkynyl$, $-O(C_1-$ $C_6)haloalkyl$, $-O(C_3-C_7)carbocycle$, $-O(C_3-C_7)halocarbocycle$, -Oaryl, -Oheteroaryl, -Oheterocycle, $-S(C_1-C_6)alkyl$, $-S(C_2-C_6)alkenyl$, $-S(C_2-C_6)alkynyl$, $-S(C_1-C_6)haloalkyl$, $-S(C_3-$
15 $C_7)carbocycle$, $-S(C_3-C_7)halocarbocycle$, -Saryl, -Sheteroaryl, -Sheterocycle, $-S(O)(C_1-C_6)alkyl$, $-S(O)(C_2-C_6)alkenyl$, $-S(O)(C_2-C_6)alkynyl$, $-S(O)(C_1-C_6)haloalkyl$, $-S(O)(C_3-C_7)carbocycle$, $-S(O)(C_3-C_7)halocarbocycle$, $-SO_2(C_1-C_6)alkyl$, $-S(O)aryl$, $-S(O)carbocycle$, $-S(O)heteroaryl$, $-S(O)heterocycle$, $-SO_2(C_2-C_6)alkenyl$, $-SO_2(C_2-C_6)alkynyl$, $-SO_2(C_1-C_6)haloalkyl$, $-SO_2(C_3-$ $C_7)carbocycle$, $-SO_2(C_3-C_7)halocarbocycle$, $-SO_2aryl$, $-SO_2heteroaryl$, $-SO_2heterocycle$,
20 $-SO_2NR_cR_d$, $-NR_cR_d$, $-NR_aC(O)R_a$, $-NR_aC(O)OR_b$, $-NR_aC(O)NR_cR_d$, $-NR_aSO_2R_b$, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3-C_7)carbocycle$, $-NR_aSO_2Oaryl$, $-OS(O)_2R_a$, $-C(O)R_a$, $-C(O)OR_b$, $-C(O)NR_cR_d$, and $-OC(O)NR_cR_d$, wherein any $(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_3-C_7)halocarbocycle$, $(C_3-C_7)carbocycle$, $(C_3-C_7)halocarbocycle$, aryl, heteroaryl or heterocycle of Z^{16} , either alone or as part of a group, is optionally substituted with one or more
25 halogen, $(C_1-C_6)alkyl$, $-OH$, $-OR_b$, $-CN$, $-NR_aC(O)_2R_b$, -heteroaryl, -heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or $-S(O)_2NR_cR_d$;

each R_a is independently H, $(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_3-C_7)carbocycle$, heterocycle, aryl, $aryl(C_1-C_6)alkyl-$, heteroaryl or heteroaryl $(C_1-C_6)alkyl-$, wherein any $(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_3-C_7)carbocycle$, heterocycle, aryl, or heteroaryl of R_a , either alone or as part of a group, is optionally substituted with one or more
30 halogen, OH or cyano;

each R_b is independently $(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_3-C_7)carbocycle$, heterocycle, aryl, $aryl(C_1-C_6)alkyl-$, heteroaryl or heteroaryl $(C_1-C_6)alkyl-$, wherein any $(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_3-C_7)carbocycle$, heterocycle, aryl,

or heteroaryl of R_b, either alone or as part of a group, is optionally substituted with one or more halogen, OH and cyano; and

R_c and R_d are each independently selected from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, aryl, aryl(C₁-C₆)alkyl-, heterocycle, heteroaryl or
 5 heteroaryl(C₁-C₆)alkyl-, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, or heteroaryl of R_c or R_d, either alone or as part of a group, is optionally substituted with one or more halogen, OH or cyano; or R_c and R_d together with the nitrogen to which they are attached form a heterocycle, wherein any heterocycle of R_c and R_d together with the nitrogen to which they are attached is optionally substituted with one or more
 10 halogen, OH or cyano;
 or a salt thereof;
 provided R⁵ is not azetidiny1 or 1-methyl-imidazo-2-yl.

In one embodiment, the invention provides a compound of formula Ia:

wherein:

15 R¹ is H;
 R² is (C₁-C₆)alkyl;
 R³ is -O(C₁-C₆)alkyl;
 R^{3'} is H;

R⁴ is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and
 20 heteroaryl of R⁴ is optionally substituted with one or more groups each independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo;

25 R⁵ is selected from:

a) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each optionally substituted with one or more (e.g. 1, 2 or 3) Z¹¹ groups;
 b) aryl, heteroaryl and heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z⁵ groups and optionally
 30 substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups; and
 c) aryl, heteroaryl, heterocycle, wherein aryl, heteroaryl and heterocycle, are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹⁵ groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z¹ groups;

each Z^1 is independently selected from halo, $-\text{NO}_2$, $-\text{OH}$, $=\text{NOR}_a$, $-\text{SH}$, $-\text{CN}$, $(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_2-\text{C}_6)\text{alkenyl}$, $(\text{C}_2-\text{C}_6)\text{alkynyl}$, $(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $(\text{C}_3-\text{C}_7)\text{carbocycle}$, $(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, aryl, heteroaryl, heterocycle, $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{O}(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{O}(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{O}(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{O}(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{Oaryl}$, $-\text{Oheteroaryl}$, $-\text{Oheterocycle}$, $-\text{S}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{S}(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{S}(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{S}(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{S}(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{S}(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{Saryl}$, $-\text{Sheteroaryl}$, $-\text{Sheterocycle}$, $-\text{S}(\text{O})(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{S}(\text{O})(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{S}(\text{O})(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{S}(\text{O})(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{S}(\text{O})(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{S}(\text{O})(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{S}(\text{O})\text{aryl}$, $-\text{S}(\text{O})\text{carbocycle}$, $-\text{S}(\text{O})\text{heteroaryl}$, $-\text{S}(\text{O})\text{heterocycle}$, $-\text{SO}_2(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{SO}_2(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{SO}_2(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{SO}_2(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{SO}_2(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{SO}_2\text{aryl}$, $-\text{SO}_2\text{heteroaryl}$, $-\text{SO}_2\text{heterocycle}$, $-\text{SO}_2\text{NR}_c\text{R}_d$, $-\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{C}(\text{O})\text{R}_a$, $-\text{NR}_a\text{C}(\text{O})\text{OR}_b$, $-\text{NR}_a\text{C}(\text{O})\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{SO}_2\text{R}_b$, $-\text{NR}_a\text{SO}_2\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{SO}_2\text{O}(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{NR}_a\text{SO}_2\text{Oaryl}$, $-\text{OS}(\text{O})_2\text{R}_a$, $-\text{C}(\text{O})\text{R}_a$, $-\text{C}(\text{O})\text{OR}_b$, $-\text{C}(\text{O})\text{NR}_c\text{R}_d$, and $-\text{OC}(\text{O})\text{NR}_c\text{R}_d$, wherein any $(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_2-\text{C}_6)\text{alkenyl}$, $(\text{C}_2-\text{C}_6)\text{alkynyl}$, $(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $(\text{C}_3-\text{C}_7)\text{carbocycle}$, $(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, aryl, heteroaryl or heterocycle of Z^1 , either alone or as part of a group, is optionally substituted with one or more halogen, $-\text{OH}$, $-\text{OR}_b$, $-\text{CN}$, $-\text{NR}_a\text{C}(\text{O})_2\text{R}_b$, heteroaryl, heterocycle, $-\text{Oheteroaryl}$, $-\text{Oheterocycle}$, $-\text{NHheteroaryl}$, $-\text{NHheterocycle}$ or $-\text{S}(\text{O})_2\text{NR}_c\text{R}_d$;

each Z^5 is independently selected from $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}_a\text{SO}_2\text{NR}_c\text{R}_d$, $-\text{NR}_a\text{SO}_2\text{O}(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{NR}_a\text{SO}_2\text{Oaryl}$, $-\text{NR}_a\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{NR}_a\text{SO}_2(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{NR}_a\text{SO}_2(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{NR}_a\text{SO}_2(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{NR}_a\text{SO}_2(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{NR}_a\text{SO}_2\text{aryl}$, $-\text{NR}_a\text{SO}_2\text{heteraryl}$, $-\text{NR}_a\text{SO}_2\text{heteroaryl}$, $-\text{NR}_a\text{SO}_2\text{heterocycle}$, $-\text{NR}_a\text{C}(\text{O})\text{alkyl}$, $-\text{NR}_a\text{C}(\text{O})\text{alkenyl}$, $-\text{NR}_a\text{C}(\text{O})\text{alkynyl}$, $-\text{NR}_a\text{C}(\text{O})(\text{C}_3-\text{C}_7)\text{carbocycle}$, $-\text{NR}_a\text{C}(\text{O})(\text{C}_3-\text{C}_7)\text{halocarbocycle}$, $-\text{NR}_a\text{C}(\text{O})\text{aryl}$, $-\text{NR}_a\text{C}(\text{O})\text{heteroaryl}$, $-\text{NR}_a\text{C}(\text{O})\text{heterocycle}$, $-\text{NR}_a\text{C}(\text{O})\text{NR}_c\text{R}_d$ and $-\text{NR}_a\text{C}(\text{O})\text{OR}_b$;

each Z^{10} is independently selected from

i) halo, oxo, thioxo, $(\text{C}_2-\text{C}_6)\text{alkenyl}$, $(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $(\text{C}_3-\text{C}_7)\text{cycloalkyl}$, $(\text{C}_3-\text{C}_7)\text{cycloalkyl}-(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{haloalkyl}$, $-\text{SH}$, $-\text{S}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{SO}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1-\text{C}_6)\text{alkyl}$ and $-\text{N}((\text{C}_1-\text{C}_6)\text{alkyl})_2$;

ii) $(\text{C}_1-\text{C}_6)\text{alkyl}$ optionally substituted with one or more $-\text{OH}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{haloalkyl}$, or $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$; and

iii) aryl, heterocycle and heteroaryl, which aryl, heterocycle and heteroaryl is optionally substituted with halo, $(\text{C}_1-\text{C}_6)\text{alkyl}$ or COOH ;

each Z^{11} is independently selected from Z^{10} , $-\text{C}(=\text{O})-\text{NH}_2$, $-\text{C}(=\text{O})-\text{NH}(\text{C}_1-\text{C}_4)\text{alkyl}$, $-\text{C}(=\text{O})-\text{N}((\text{C}_1-\text{C}_4)\text{alkyl})_2$, $-\text{C}(=\text{O})-\text{aryl}$, $-\text{C}(=\text{O})-\text{heterocycle}$ and $-\text{C}(=\text{O})-\text{heteroaryl}$;

each Z^{15} is independently selected from aryl, heteroaryl, heterocycle, $-\text{Oaryl}$,

-Oheteroaryl, -Oheterocycle, -O(C₁-C₆)alkyl-aryl, -O(C₁-C₆)alkyl-heteroaryl, -O(C₁-C₆)alkyl-heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more Z¹⁶ groups and optionally substituted with one or more Z¹ groups, and wherein any -Oaryl, -Oheteroaryl, -Oheterocycle, -O(C₁-C₆)alkyl-aryl, -O(C₁-C₆)alkyl-heteroaryl or -O(C₁-C₆)alkyl-heterocycle is optionally substituted with one or more Z¹ groups;

each Z¹⁶ is independently selected from -NO₂, -OH, =NOR_a, -SH, -CN, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl, heterocycle, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -O(C₁-C₆)haloalkyl, -O(C₃-C₇)carbocycle, -O(C₃-C₇)halocarbocycle, -Oaryl, -Oheteroaryl, -Oheterocycle, -S(C₁-C₆)alkyl, -S(C₂-C₆)alkenyl, -S(C₂-C₆)alkynyl, -S(C₁-C₆)haloalkyl, -S(C₃-C₇)carbocycle, -S(C₃-C₇)halocarbocycle, -Saryl, -Sheteroaryl, -Sheterocycle, -S(O)(C₁-C₆)alkyl, -S(O)(C₂-C₆)alkenyl, -S(O)(C₂-C₆)alkynyl, -S(O)(C₁-C₆)haloalkyl, -S(O)(C₃-C₇)carbocycle, -S(O)(C₃-C₇)halocarbocycle, -SO₂(C₁-C₆)alkyl, -S(O)aryl, -S(O)carbocycle, -S(O)heteroaryl, -S(O)heterocycle, -SO₂(C₂-C₆)alkenyl, -SO₂(C₂-C₆)alkynyl, -SO₂(C₁-C₆)haloalkyl, -SO₂(C₃-C₇)carbocycle, -SO₂(C₃-C₇)halocarbocycle, -SO₂aryl, -SO₂heteroaryl, -SO₂heterocycle, -SO₂NR_cR_d, -NR_cR_d, -NR_aC(O)R_a, -NR_aC(O)OR_b, -NR_aC(O)NR_cR_d, -NR_aSO₂R_b, -NR_aSO₂NR_cR_d, -NR_aSO₂O(C₃-C₇)carbocycle, -NR_aSO₂Oaryl, -OS(O)₂R_a, -C(O)R_a, -C(O)OR_b, -C(O)NR_cR_d, and -OC(O)NR_cR_d, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)halocarbocycle, (C₃-C₇)carbocycle, (C₃-C₇)halocarbocycle, aryl, heteroaryl or heterocycle of Z¹⁶, either alone or as part of a group, is optionally substituted with one or more halogen, (C₁-C₆)alkyl, -OH, -OR_b, -CN, -NR_aC(O)₂R_b, -heteroaryl, -heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or -S(O)₂NR_cR_d;

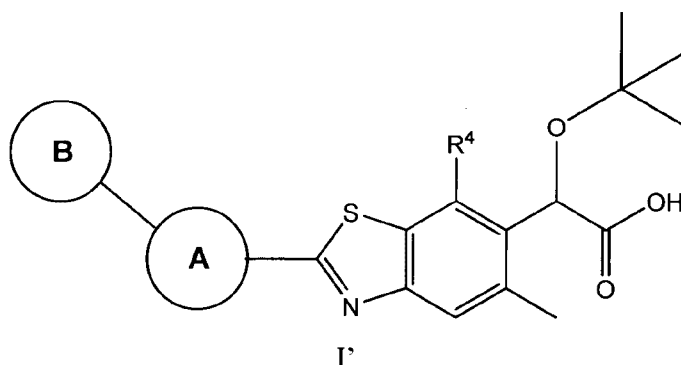
each R_a is independently H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, aryl(C₁-C₆)alkyl-, heteroaryl or heteroaryl(C₁-C₆)alkyl-, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, or heteroaryl of R_a, either alone or as part of a group, is optionally substituted with one or more halogen, OH or cyano;

each R_b is independently (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, aryl(C₁-C₆)alkyl-, heteroaryl or heteroaryl(C₁-C₆)alkyl-, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, or heteroaryl of R_b, either alone or as part of a group, is optionally substituted with one or more halogen, OH and cyano; and

R_c and R_d are each independently selected from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, aryl, aryl(C₁-C₆)alkyl-, heterocycle, heteroaryl or heteroaryl(C₁-C₆)alkyl-, wherein any (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)carbocycle, heterocycle, aryl, or heteroaryl of R_c or R_d , either alone or as part of a group, is optionally substituted with one or more halogen, OH or cyano; or R_c and R_d together with the nitrogen to which they are attached form a heterocycle, wherein any heterocycle of R_c and R_d together with the nitrogen to which they are attached is optionally substituted with one or more halogen, OH or cyano;

or a salt thereof.

In one embodiment, the invention provides a compound of formula I':



wherein:

R^4 is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R^4 is optionally substituted with one or more groups each independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo;

A is phenyl, monocyclic heteroaryl or monocyclic heterocycle, wherein any phenyl, monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle wherein bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more Z^{1b} groups;

each Z^{1a} is independently selected from halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, (C₁-C₃)haloalkyl, (C₃-C₇)carbocycle, heterocycle, -O(C₁-C₃)alkyl, -O(C₂-C₃)alkenyl, -O(C₂-C₃)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b, and -C(O)NR_cR_d, wherein any (C₃-

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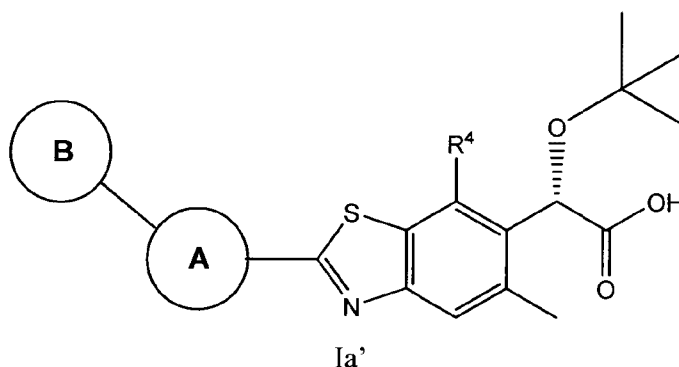
C₇)carbocycle or heterocycle of Z^{1a}, either alone or as part of a group, is optionally substituted with one or more halogen or (C₁-C₆)alkyl;

each Z^{1b} is independently selected from halo, CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, heteroaryl, heterocycle, aryl(C₁-C₆)alkyl-,
 5 -OH, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b, and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle or heterocycle of Z^{1b}, either alone or as part of a group, is optionally substituted with one or more halogen or (C₁-C₆)alkyl; and

R_a, R_b, R_c and R_d are each independently H or (C₁-C₆)alkyl;

or a salt thereof.

10 A specific group of compounds of formula I' are compounds of formula Ia':



or a pharmaceutically acceptable salt thereof.

In one embodiment, the invention provides a compound of formula I':

15 wherein:

R⁴ is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups each independently selected from halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, NH₂, -NH(C₁-
 20 C₆)alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo;

A is phenyl, monocyclic heteroaryl or monocyclic heterocycle, wherein any phenyl, monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl,
 25 heteroaryl or heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle, wherein bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups;

each Z^{1a} is independently selected from halo, (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_3-C_7) carbocycle, heterocycle, $-O(C_1-C_3)$ alkyl, $-NR_cR_d$, $-NR_aC(O)R_a$, $-C(O)OR_b$ and $-C(O)NR_cR_d$, wherein any (C_3-C_7) carbocycle and heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C_1-C_6) alkyl;

5 each Z^{1b} is independently selected from halo, CN, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_3-C_7) carbocycle, heteroaryl, heterocycle, aryl (C_1-C_6) alkyl-, $-OH$, $-O(C_1-C_6)$ alkyl, $-NR_cR_d$, $-NR_aC(O)R_a$, $-C(O)OR_b$ and $-C(O)NR_cR_d$, wherein any (C_3-C_7) carbocycle and heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C_1-C_6) alkyl; and

R_a , R_b , R_c and R_d are each independently H or (C_1-C_6) alkyl;

10 or a salt thereof.

Specific embodiments of the invention (e.g., embodiments) and specific values listed below are embodiments and values for compounds of formula I' and subformulas of formula I' (e.g., formula Ia'). It is to be understood that two or more of the values listed herein below may be combined with one another.

15 A specific value for A is phenyl, monocyclic heteroaryl or monocyclic heterocycle wherein any phenyl, monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is phenyl, monocyclic N-heteroaryl or monocyclic heterocycle wherein any phenyl, monocyclic N-heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

25 Another specific value for A is monocyclic heteroaryl or monocyclic heterocycle, wherein any monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is monocyclic N-heteroaryl or monocyclic heterocycle, wherein any monocyclic N-heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is monocyclic heteroaryl, wherein monocyclic heteroaryl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle,

wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is monocyclic N-heteroaryl, wherein monocyclic N-heteroaryl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is monocyclic heterocycle, wherein monocyclic heterocycle is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is pyridinyl, pyrimidinyl, pyrazinyl, pyridinyl-2-one, tetrahydropyrimidinyl-2-one, imidazolidinyl-2-one, pyrrolidinyl-2-one or pyrrolidinyl, wherein pyridinyl, pyrimidinyl, pyrazinyl, pyridinyl-2-one, tetrahydropyrimidinyl-2-one, imidazolidinyl-2-one, pyrrolidinyl-2-one or pyrrolidinyl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is pyridinyl, pyrimidinyl or pyrazinyl wherein pyridinyl, pyrimidinyl or pyrazinyl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is pyridinyl, wherein pyridinyl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is pyridin-4-yl, wherein pyridin-4-yl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

Another specific value for A is pyridinyl-2-one, tetrahydropyrimidinyl-2-one, imidazolidinyl-2-one, pyrrolidinyl-2-one or pyrrolidinyl, wherein pyridinyl-2-one, tetrahydropyrimidinyl-2-one, imidazolidinyl-2-one, pyrrolidinyl-2-one or pyrrolidinyl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

A specific group of compounds of formula I' are compounds wherein A is not substituted with Z^{1a} .

A specific value for B is phenyl, pyridinyl, pyrazolyl, pyrimidinyl, indazolyl, pyrazolopyridine or benzimidazolyl, wherein any phenyl, pyridinyl, pyrazolyl, pyrimidinyl, indazolyl, pyrazolopyridine or benzimidazolyl of B is optionally substituted with one or more Z^{1b} groups.

- 5 Another specific value for B is phenyl or indazolyl, wherein any phenyl or indazolyl of B is optionally substituted with one or more Z^{1b} groups.

A specific group of compounds of formula I' are compounds wherein A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle, wherein bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more Z^{1b} groups.

- 10 Another specific group of compounds of formula I' are compounds wherein A and B together form a bicyclic heteroaryl, wherein bicyclic heteroaryl is optionally substituted with one or more Z^{1b} groups.

- Another specific group of compounds of formula I' are compounds wherein A and B together form a pyrrolopyridinyl, pyrazolopyridine or indazolyl, wherein pyrrolopyridinyl or indazolyl is optionally substituted with one or more Z^{1b} groups.
- 15

Another specific value for A is phenyl, wherein phenyl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

A specific value for Z^{1a} is halo.

- 20 Another specific value for Z^{1a} is fluoro or chloro.

Another specific value for B is phenyl, pyridinyl, pyrazolyl, pyrimidinyl, indazolyl or pyrazolopyridine, wherein any phenyl, pyridinyl, pyrazolyl, pyrimidinyl, indazolyl or pyrazolopyridine of B is optionally substituted with one or more Z^{1b} groups.

- A specific group of compounds of formula I' are compounds wherein each Z^{1b} is independently selected from methyl, isobutyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, N-methylpiperazinyl, morpholinyl, tetrazolyl, -OCH₃, t-butyl, -C(O)OH, -NH₂, -N(CH₃)₂, -OH, -C(O)NH₂, benzyl and CN.
- 25

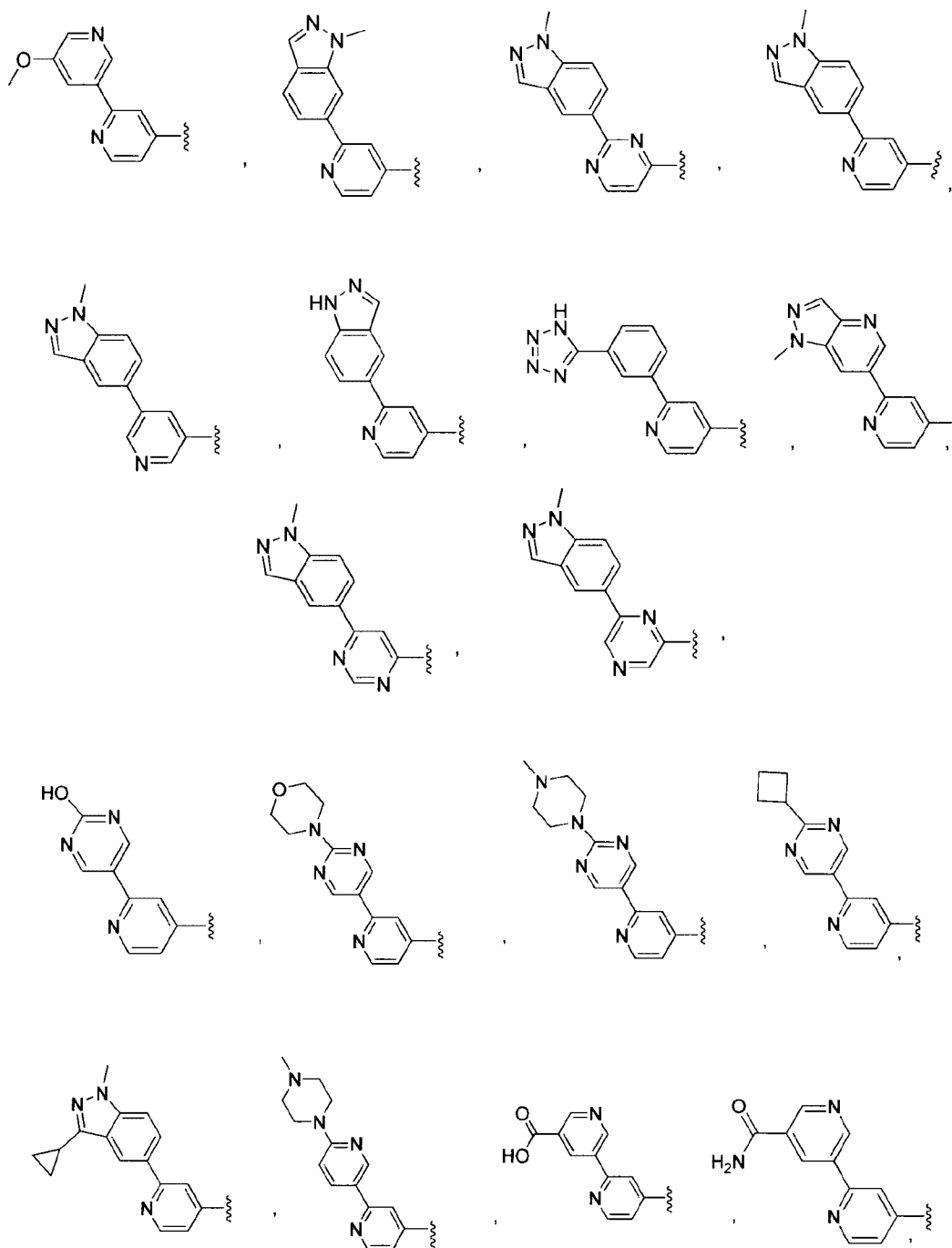
- Another specific group of compounds of formula I' are compounds wherein each Z^{1b} is independently selected from methyl, cyclopropyl, cyclobutyl, N-methylpiperazinyl, morpholinyl, tetrazolyl, -OCH₃, -C(O)OH, -OH, -C(O)NH₂, NH₂ and CN.
- 30

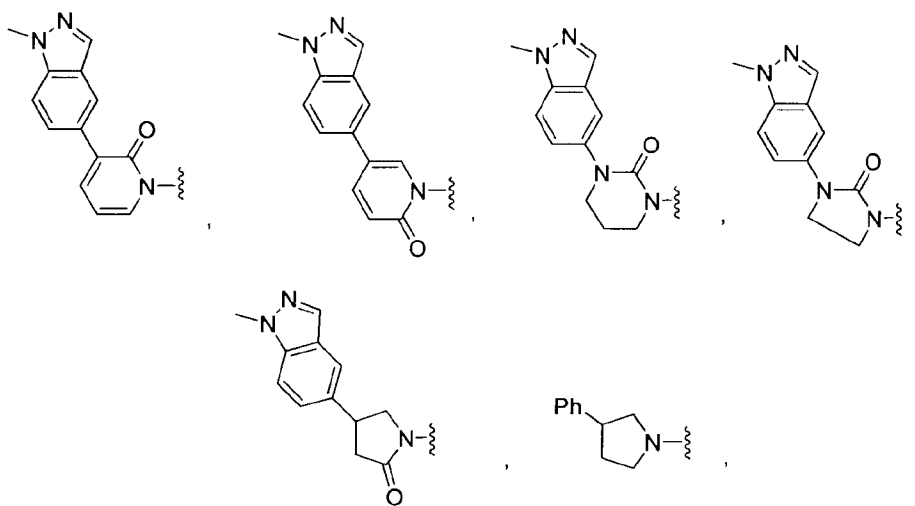
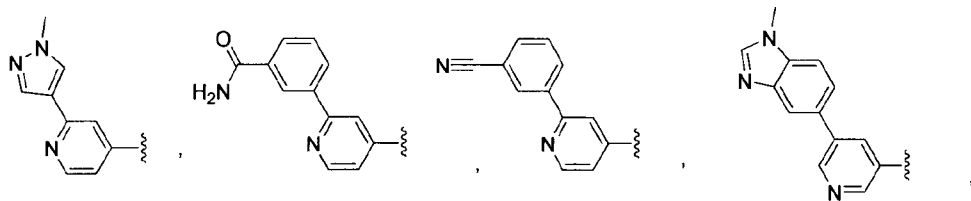
Another specific group of compounds of formula I' are compounds wherein each Z^{1b} is independently selected from methyl, cyclopropyl, cyclobutyl, N-methylpiperazinyl, morpholinyl, tetrazolyl, -OCH₃, -C(O)OH, -OH, -C(O)NH₂ and CN.

Another specific group of compounds of formula I' are compounds wherein each Z^{1b} is independently selected from methyl and NH_2 .

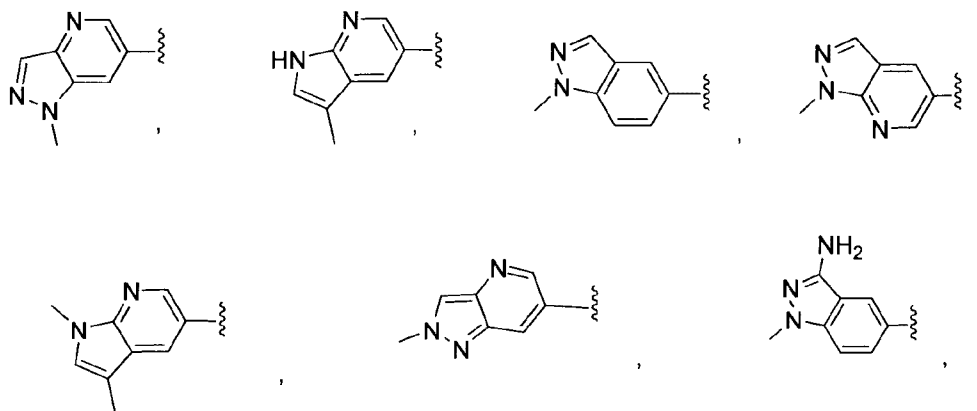
Another specific group of compounds of formula I' are compounds wherein each Z^{1b} is independently selected from methyl, isobutyl, isopropyl, cyclopentyl, N-methylpiperazinyl, 5 - OCH_3 , t-butyl, $-N(CH_3)_2$, $-OH$ and benzyl.

A specific group of compounds of formula I' are compounds wherein A-B is selected from:



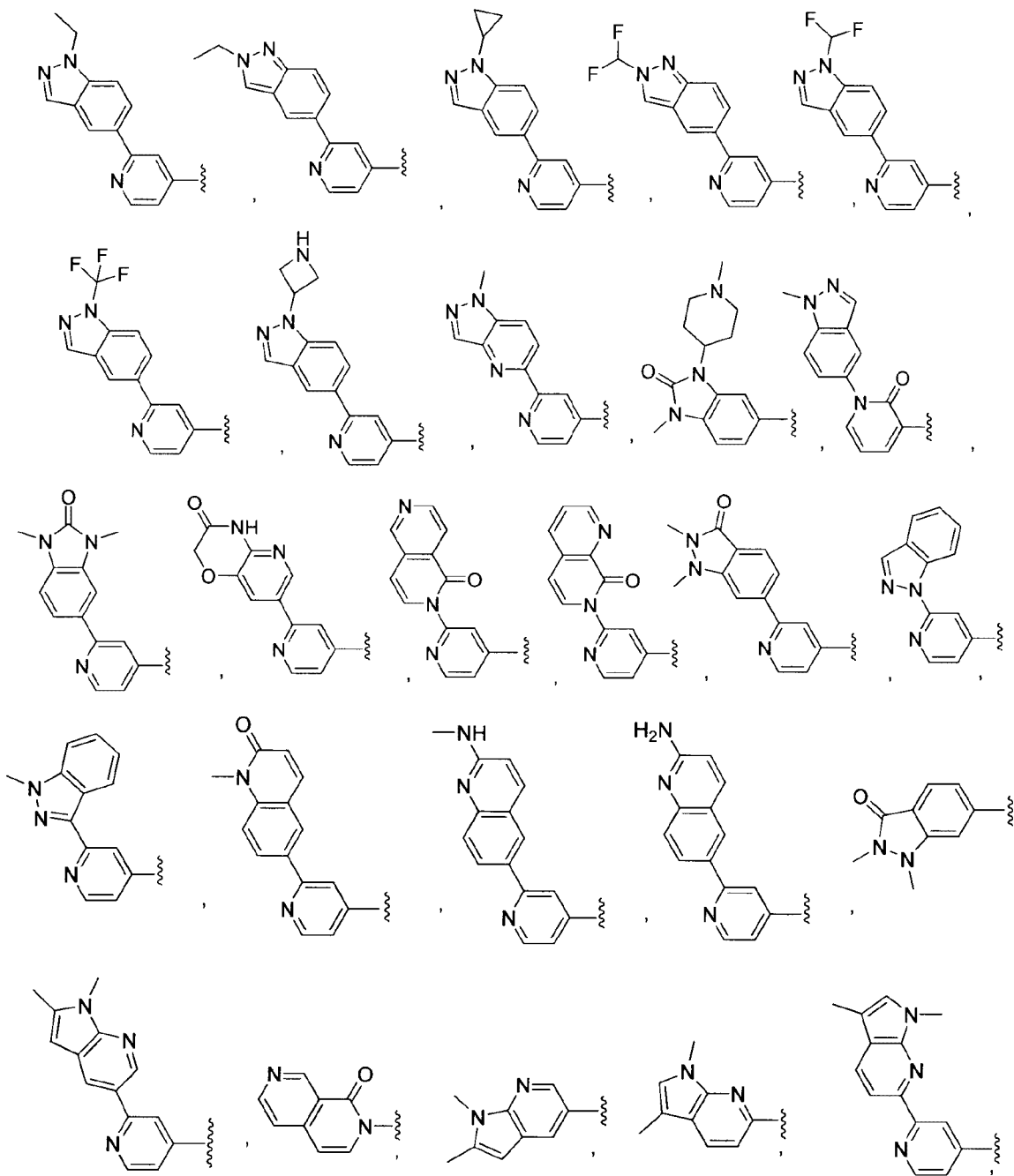


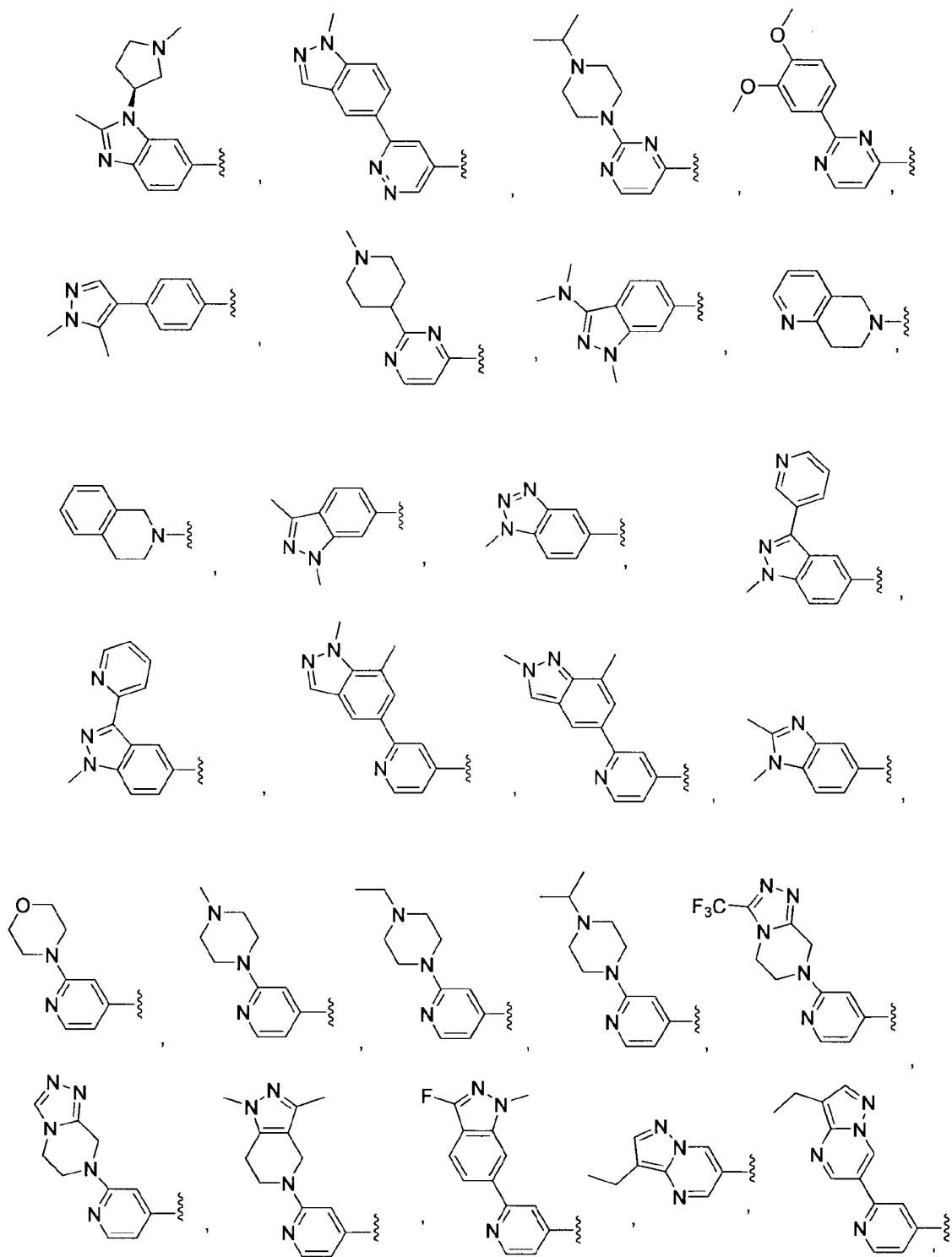
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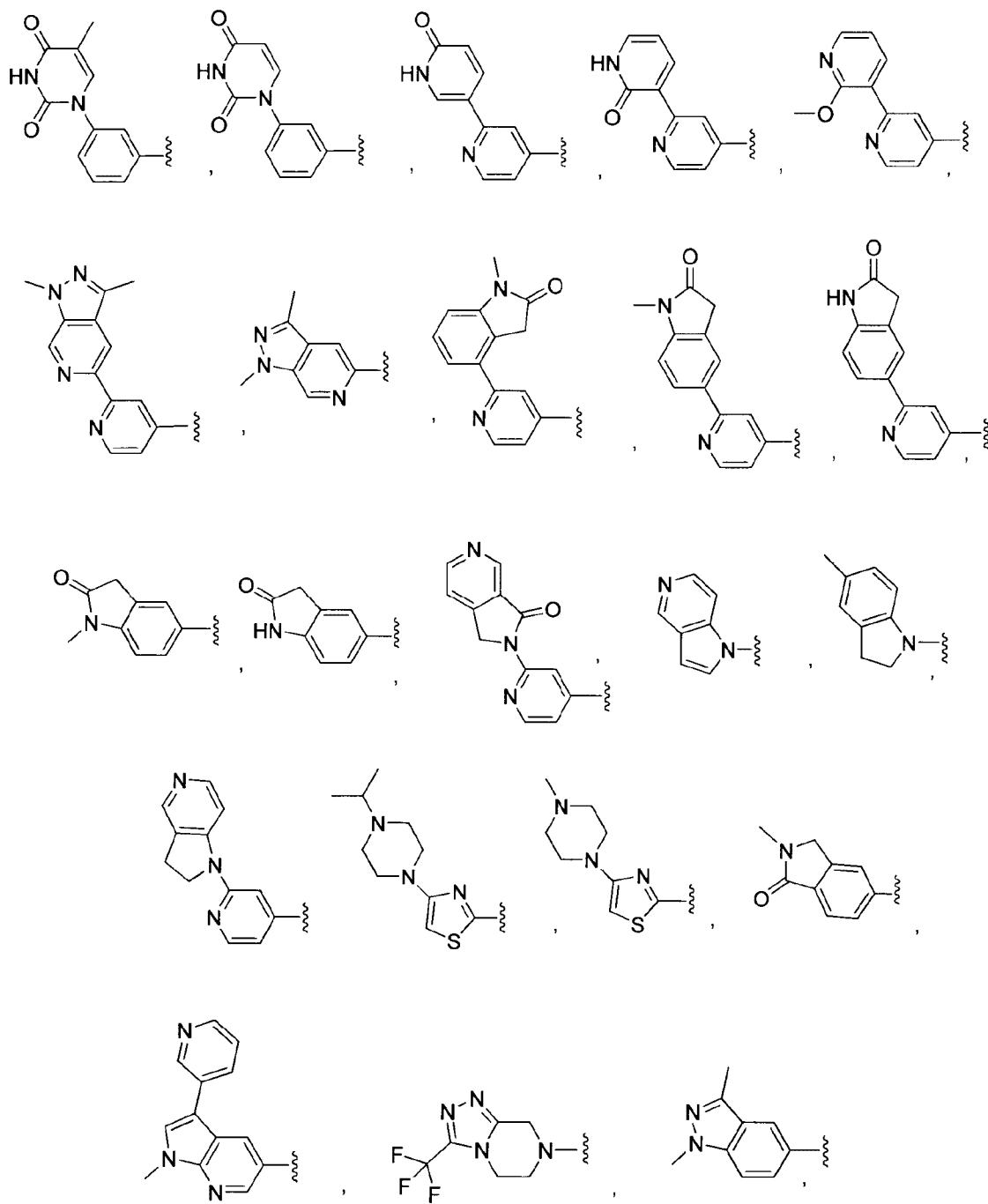


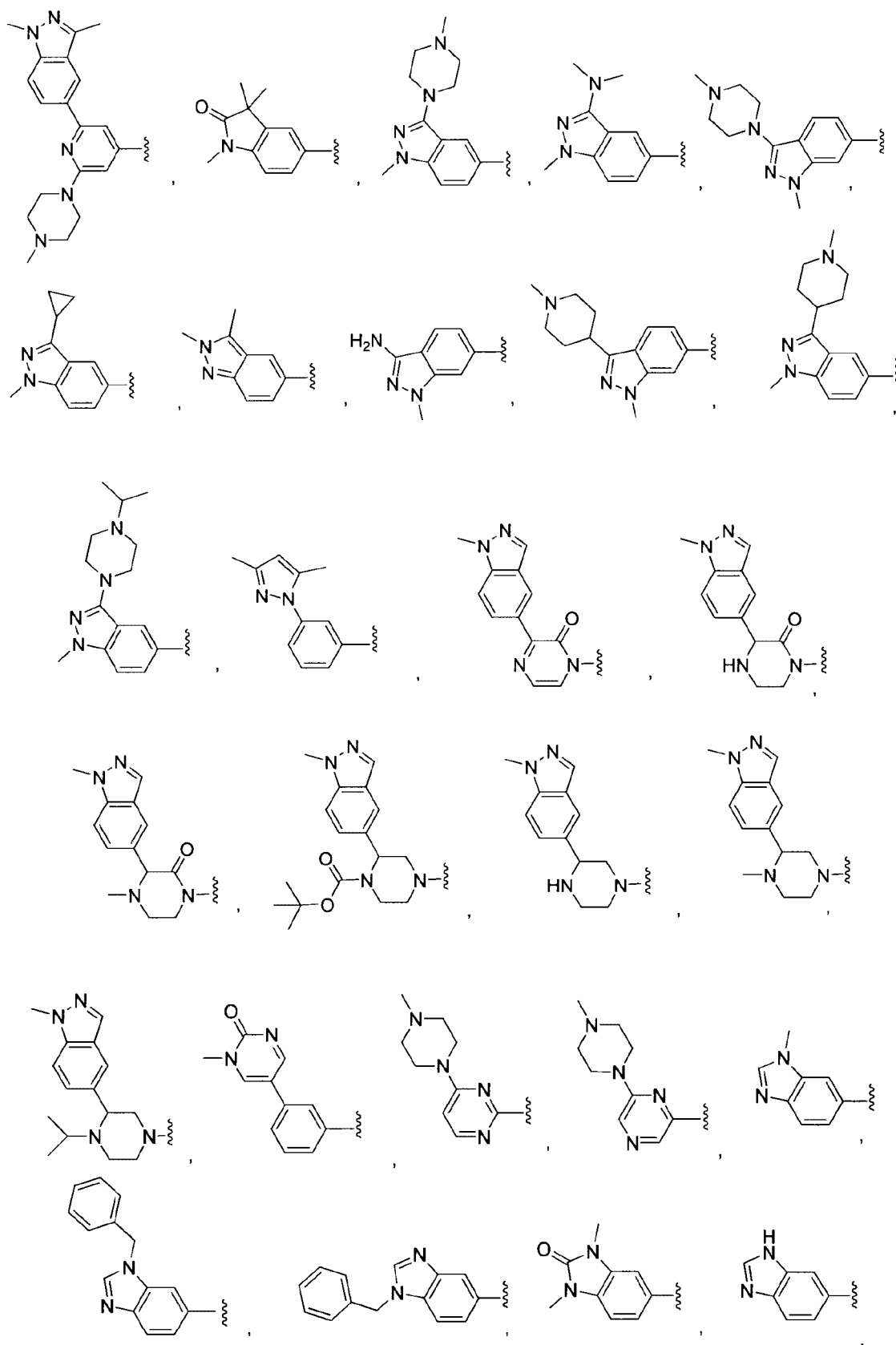


A specific group of compounds of formula I' are compounds wherein A-B is selected from:



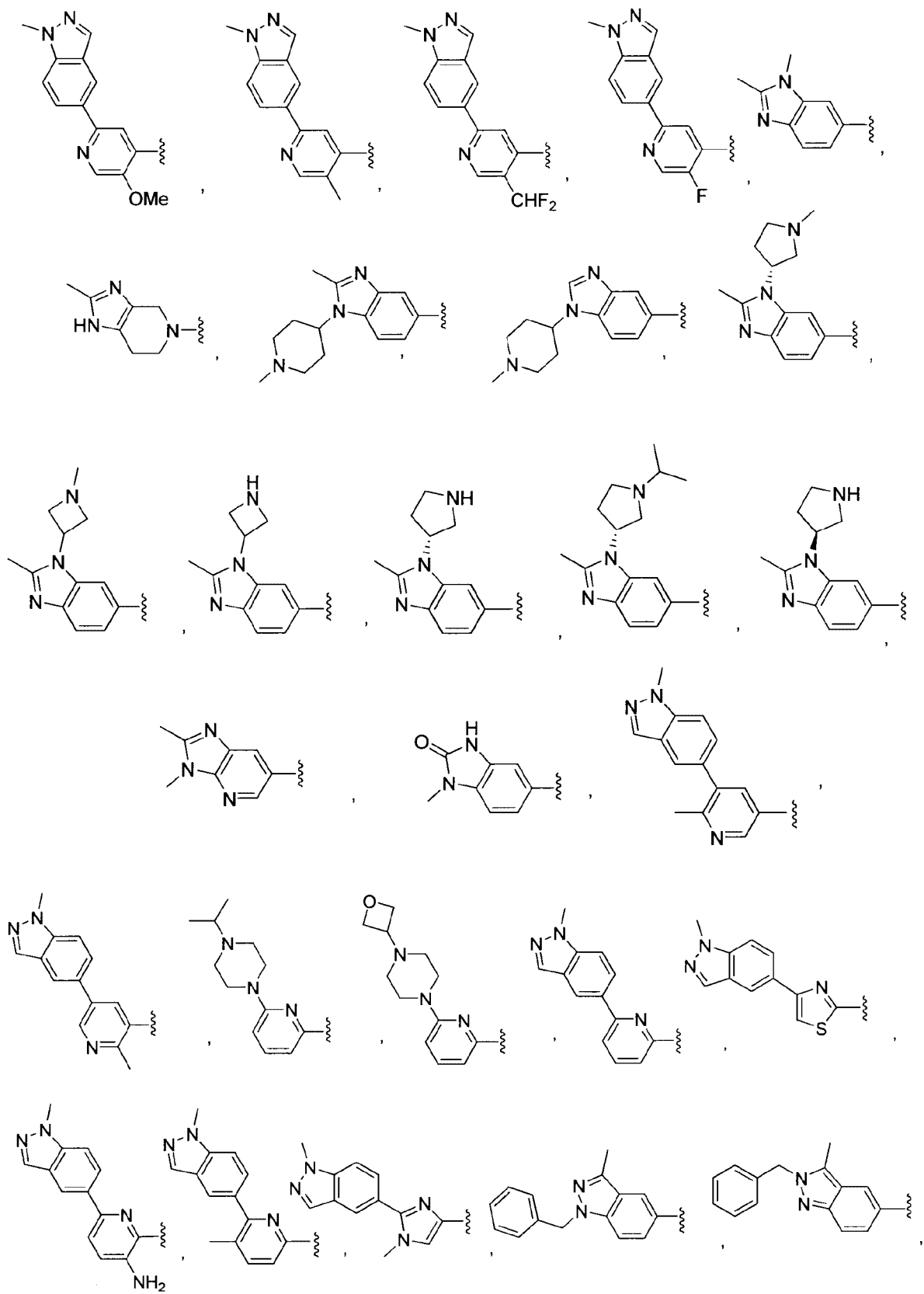


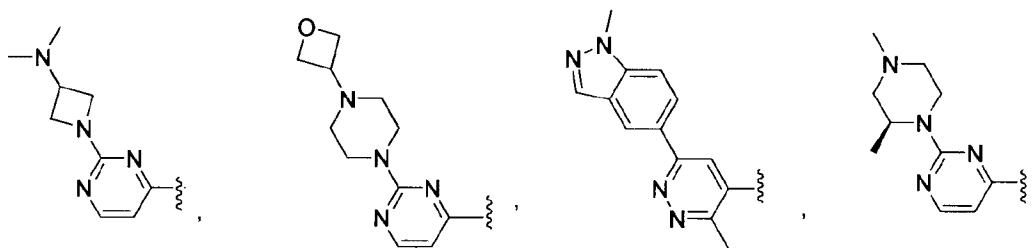
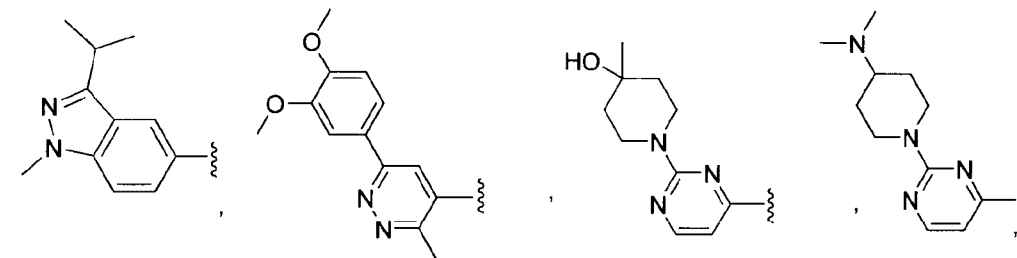
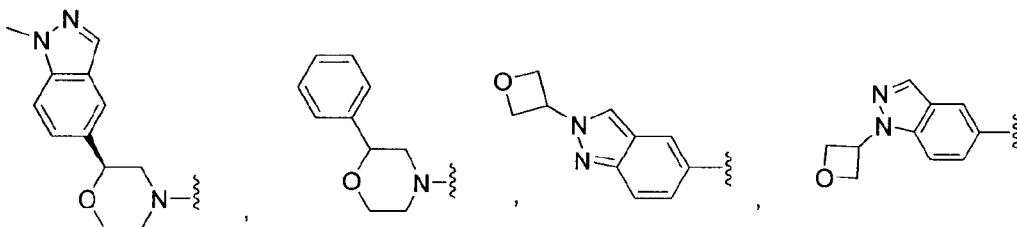
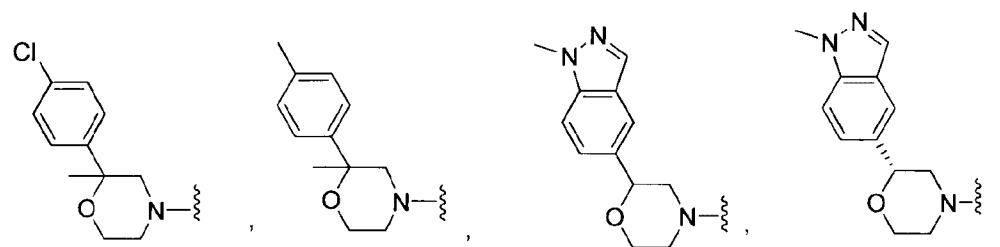
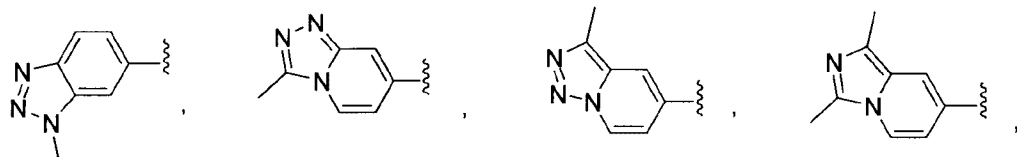




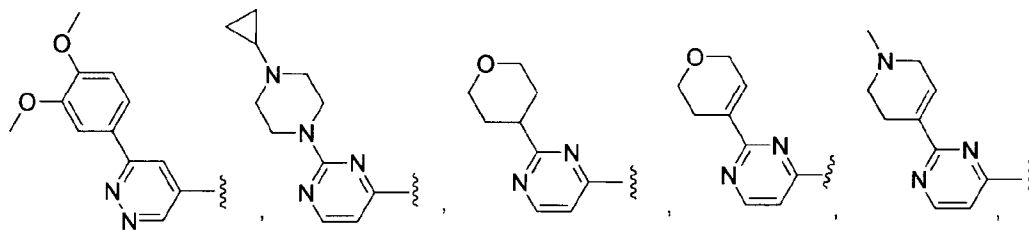
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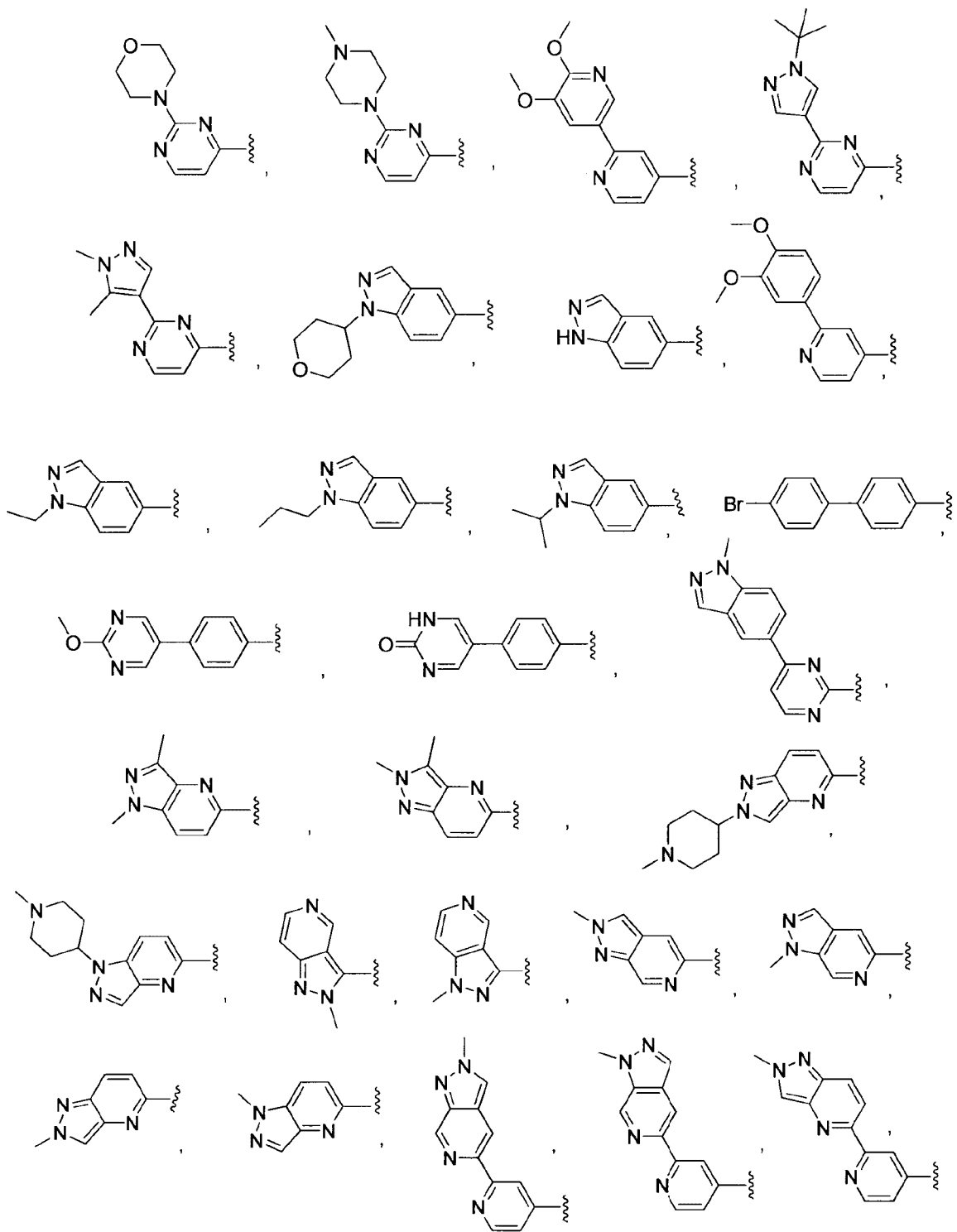
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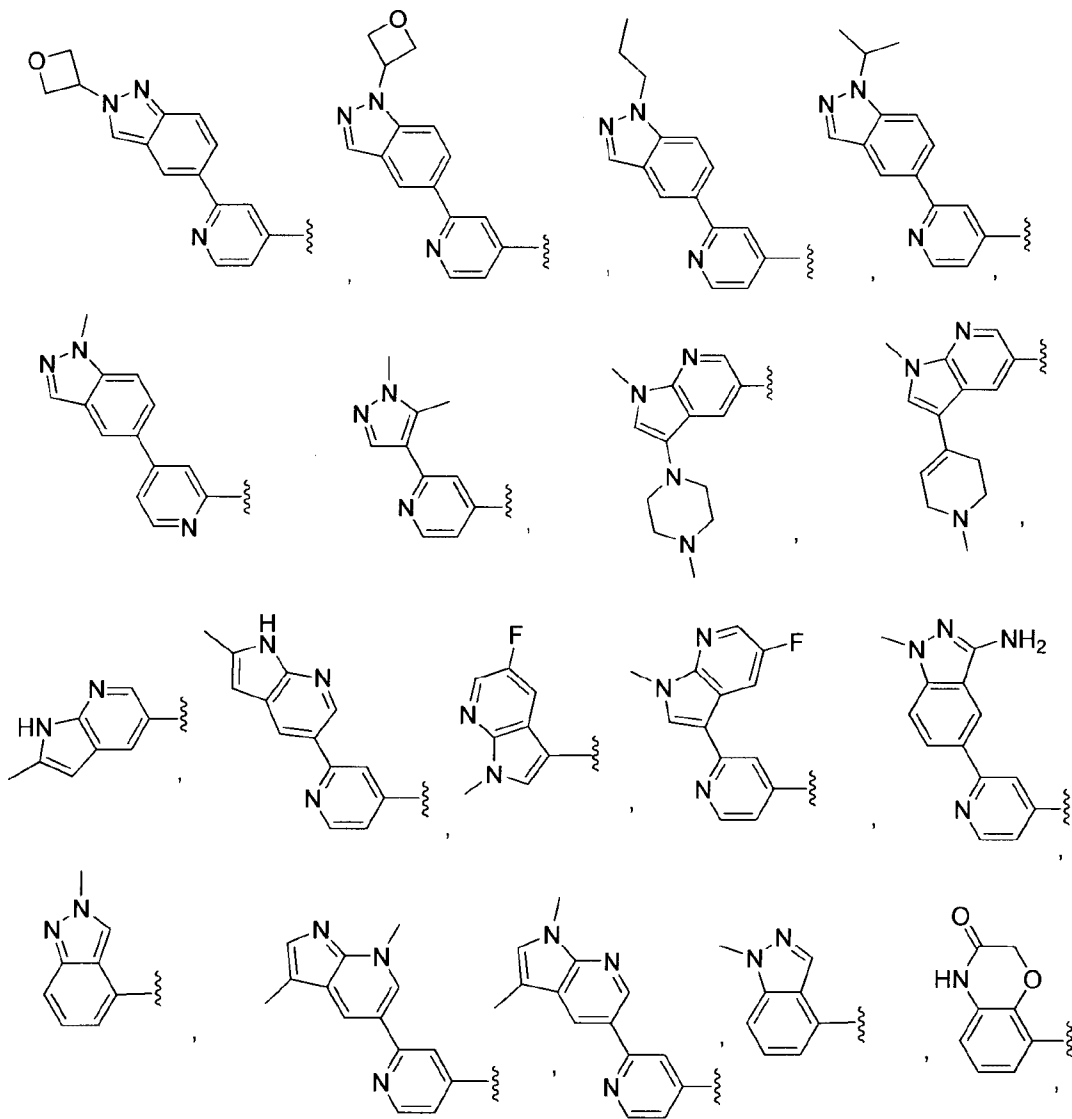




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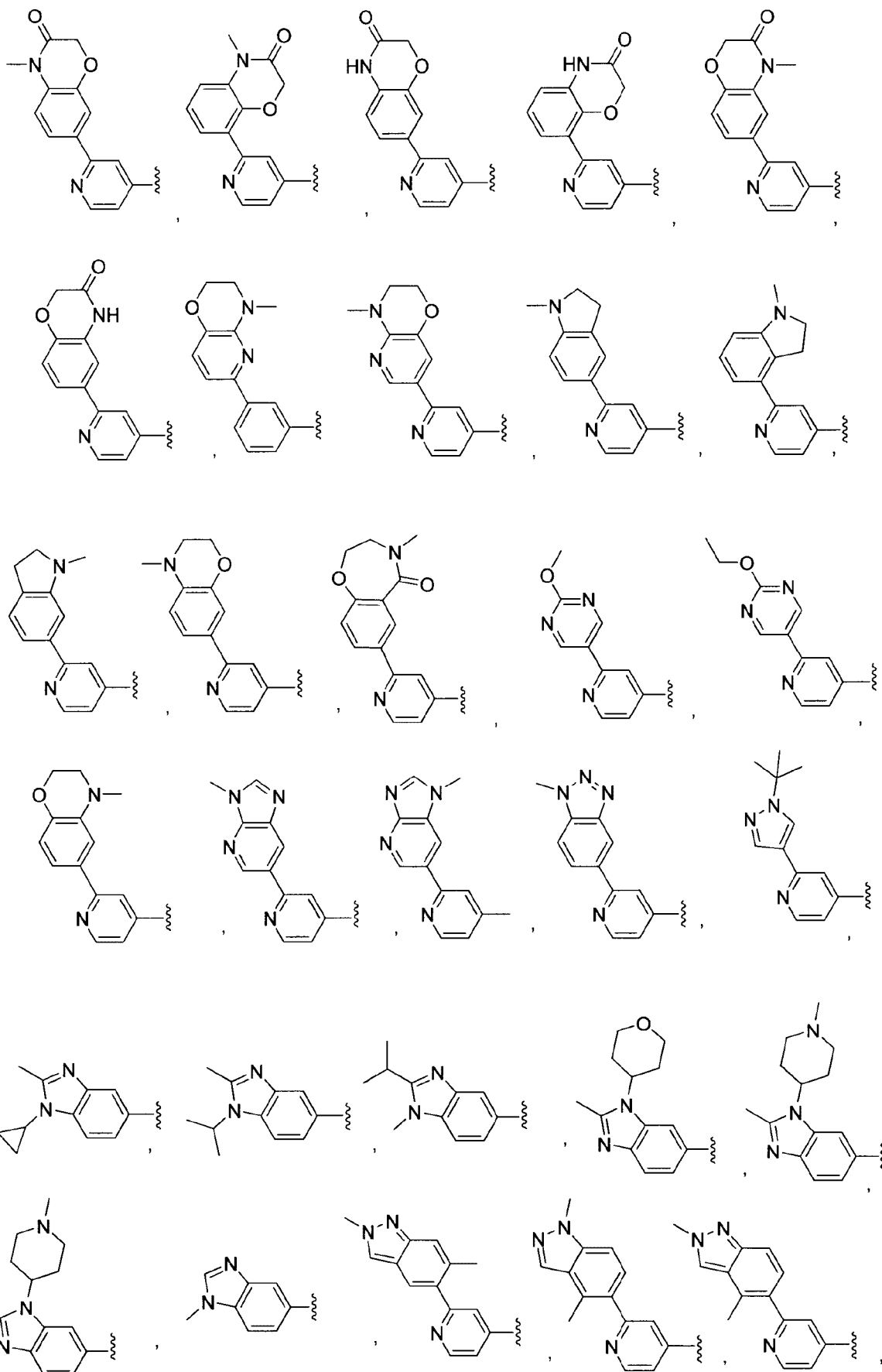


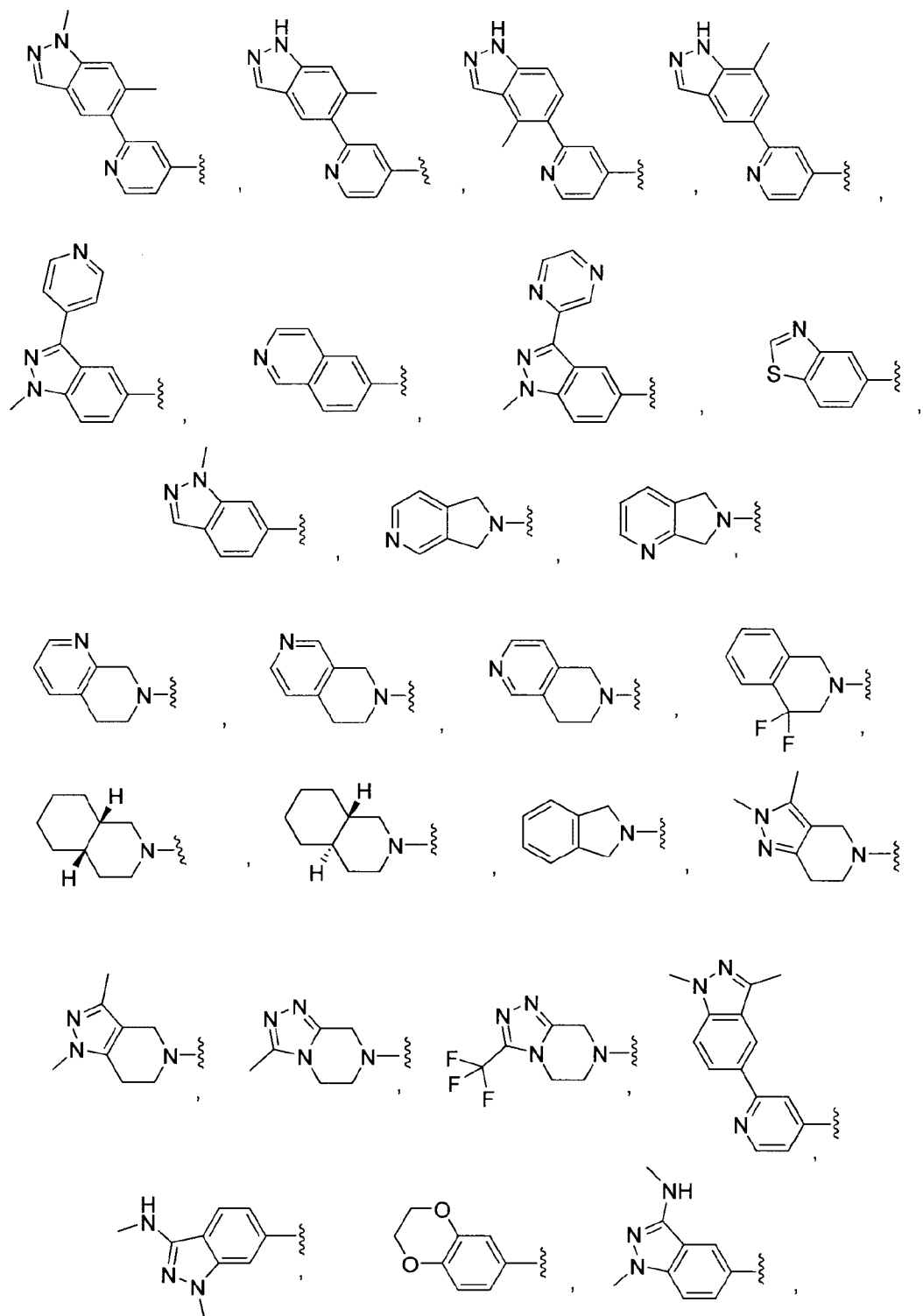




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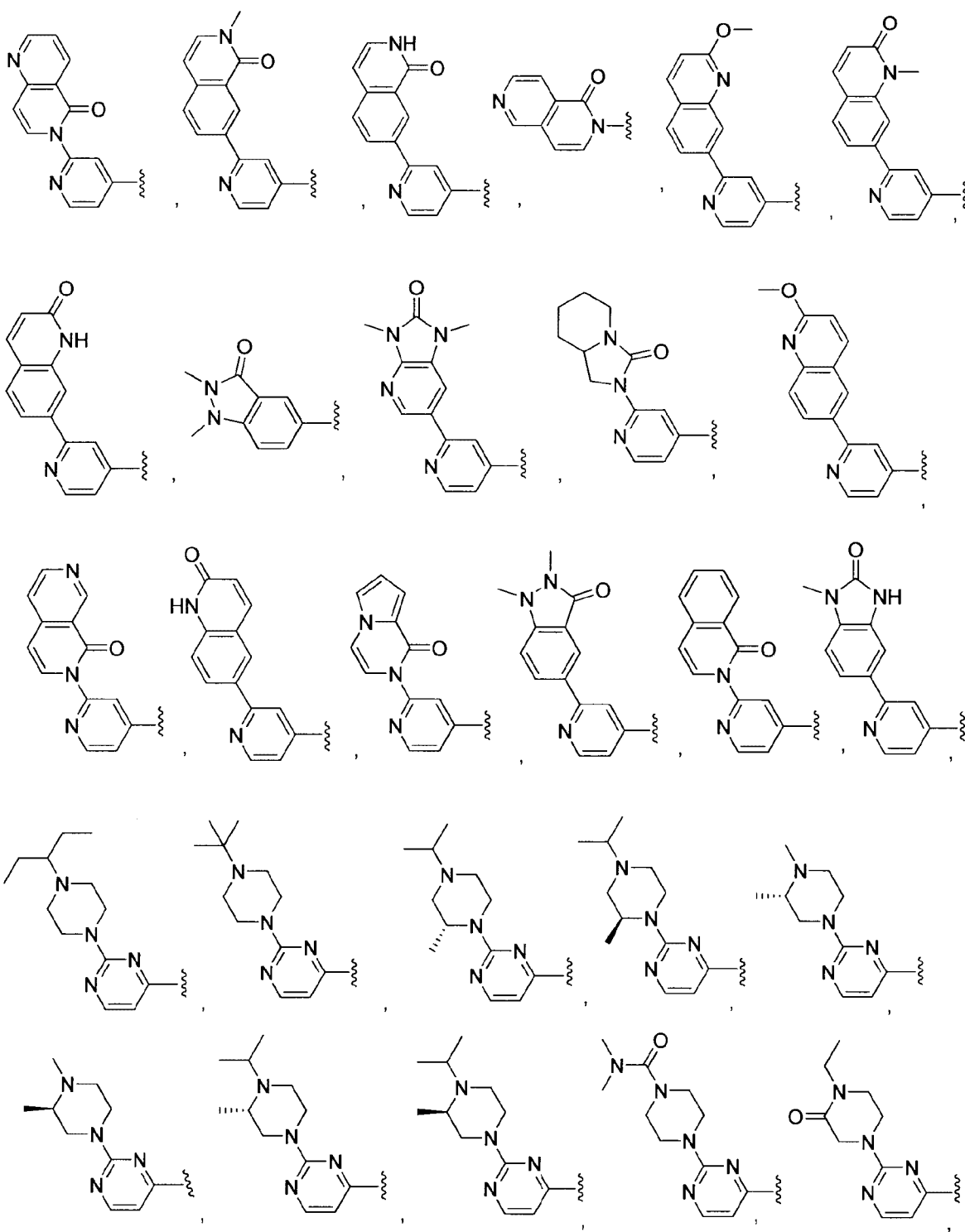
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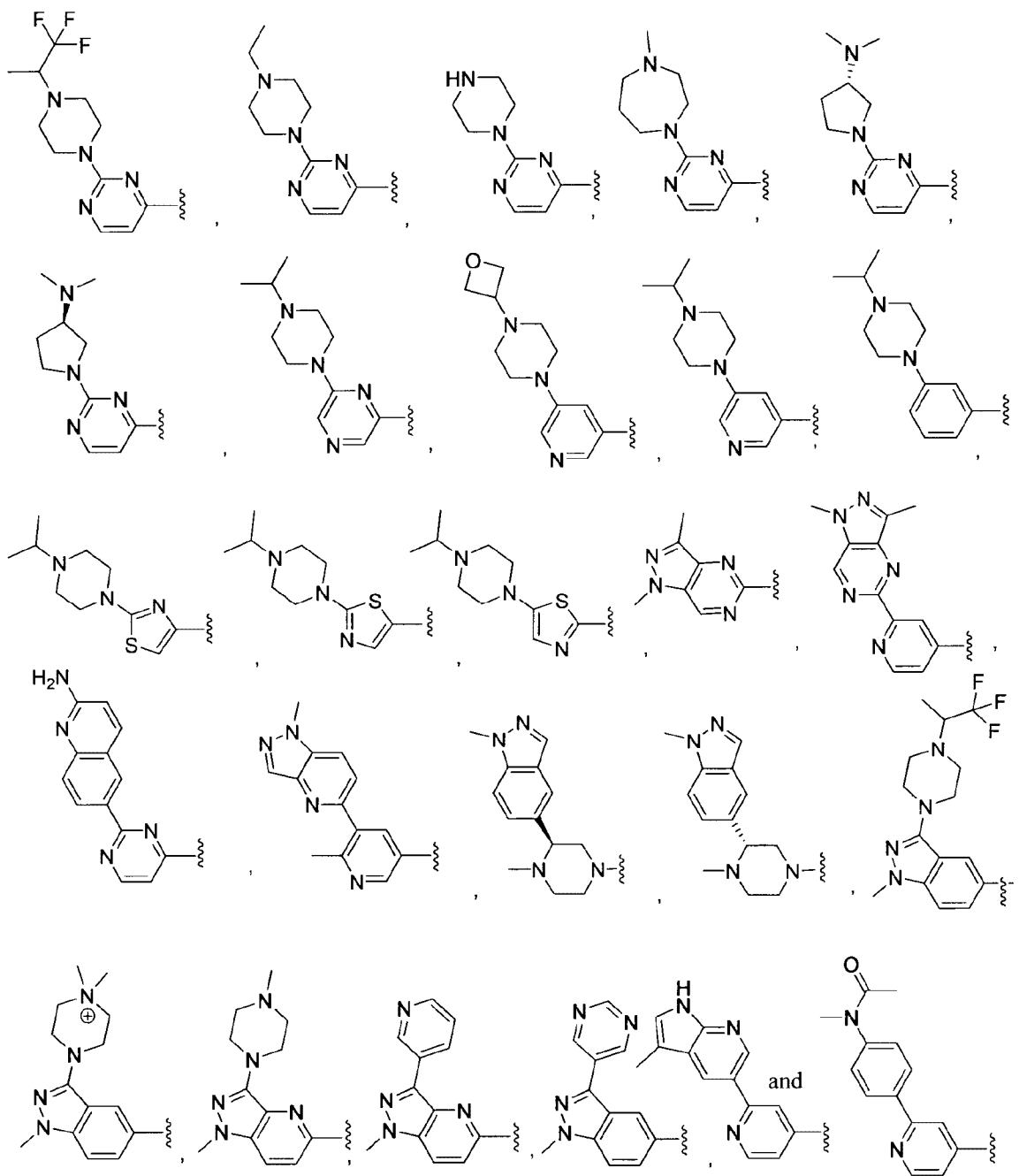




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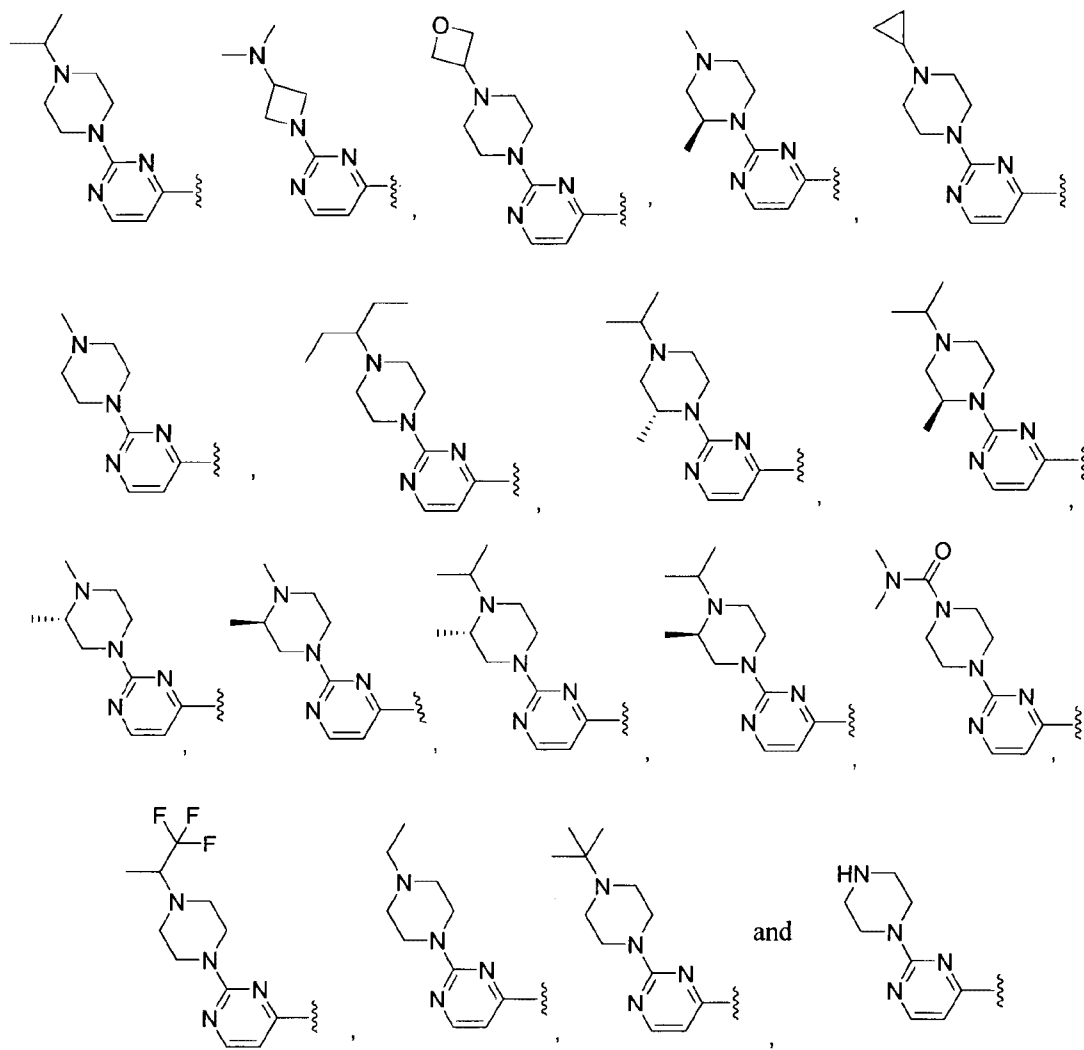


A specific group of compounds of formula I' are compounds wherein A-B is selected

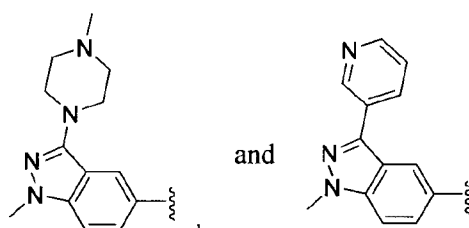
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5 A specific group of compounds of formula I' are compounds wherein A-B is selected from:



A specific value for R^4 is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R^4 is optionally substituted with one or more halo or (C₁-C₆)alkyl.

10 Another specific value for R^4 is selected from aryl and heterocycle, wherein any aryl and heterocycle of R^4 is optionally substituted with one or more chloro, fluoro or methyl.

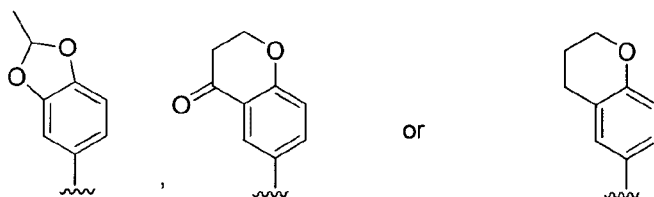
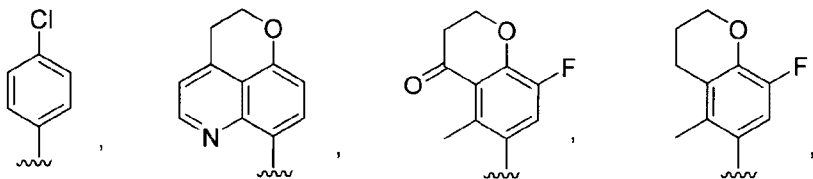
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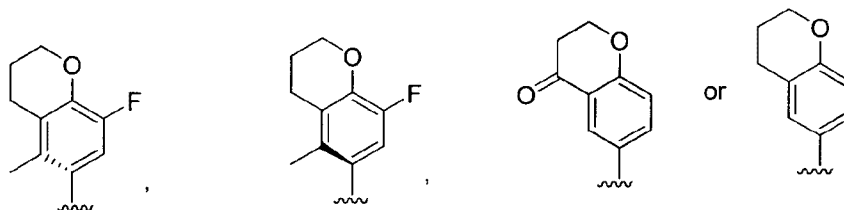
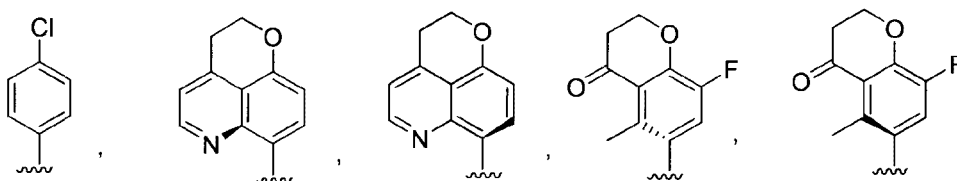
Another specific value for R^4 is phenyl, wherein phenyl is optionally substituted with one or more halo or (C_1-C_6) alkyl.

Another specific value for R^4 is phenyl wherein phenyl is optionally substituted with one or more chloro, fluoro or methyl.

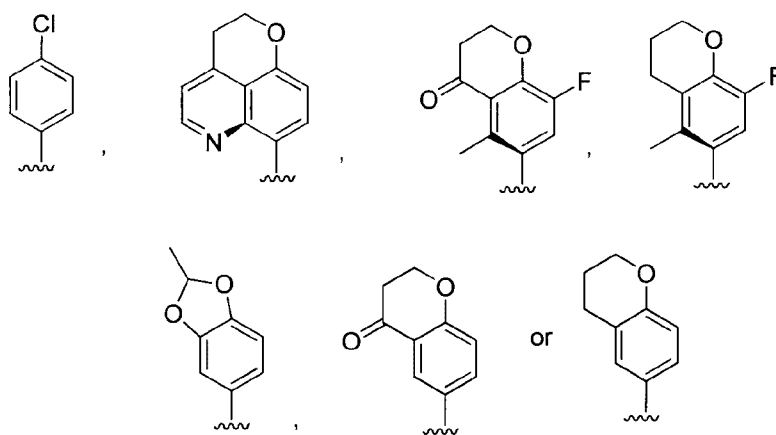
5 A specific value for R^4 is:



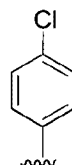
Another specific value for R^4 is:



10 Another specific value for R^4 is:



A specific value for R^4 is:



One embodiment provides a specific group of compounds of formula I' wherein the configuration of the R^3 group of formula I' is the (S) stereochemistry.

One embodiment provides a specific group of compounds of formula I' wherein the configuration of the $-OC(CH_3)_3$ group as shown in formula I' is the (S) stereochemistry.

A specific group or compounds of formula I' are compounds wherein

R^4 is selected from phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle, wherein any phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle of R^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from selected from halo and (C_1-C_6) alkyl;

A is phenyl, 5-6 membered monocyclic heteroaryl or 3-7 membered monocyclic heterocycle, wherein any phenyl, 5-6 membered monocyclic heteroaryl or 3-7 membered monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle, wherein any phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-12 membered bicyclic heterocycle, wherein any 8-11

membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups;

each Z^{1a} is independently selected from halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, (C₁-C₃)haloalkyl, (C₃-C₇)carbocycle, 3-7 membered monocyclic heterocycle, -O(C₁-C₃)alkyl, -O(C₂-C₃)alkenyl, -O(C₂-C₃)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle or 3-7 membered monocyclic heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C₁-C₆)alkyl;

each Z^{1b} is independently selected from halo, CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, 5-6 membered monocyclic heteroaryl, 7-12 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle, 6-11 membered bicyclic heterocycle, phenyl(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C₁-C₆)alkyl; and

R_a, R_b, R_c and R_d are each independently H or (C₁-C₆)alkyl; or a salt thereof.

A specific value for R⁴ is selected from phenyl, bicyclic aryl, monocyclic heterocycle, bicyclic heterocycle, tricyclic heterocycle, monocyclic heteroaryl, bicyclic heteroaryl and tricyclic heteroaryl, wherein any phenyl, bicyclic aryl, monocyclic heterocycle, bicyclic heterocycle, tricyclic heterocycle, monocyclic heteroaryl, bicyclic heteroaryl and tricyclic heteroaryl of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and (C₁-C₆)alkyl.

A specific value for R⁴ is selected from phenyl, bicyclic aryl, monocyclic heterocycle, bicyclic heterocycle, tricyclic heterocycle, monocyclic heteroaryl, bicyclic heteroaryl and tricyclic heteroaryl, wherein any phenyl, bicyclic aryl, monocyclic heterocycle, bicyclic heterocycle, tricyclic heterocycle, monocyclic heteroaryl, bicyclic heteroaryl and tricyclic heteroaryl of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and methyl.

A specific value for R⁴ is selected from phenyl, bicyclic heterocycle and tricyclic heterocycle, wherein any phenyl, bicyclic heterocycle and tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, NH₂, -NH(C₁-

C₆alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo.

5 A specific value for R⁴ is selected from phenyl, bicyclic heterocycle and tricyclic heterocycle, wherein any phenyl, bicyclic heterocycle and tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and (C₁-C₆)alkyl.

10 A specific value for R⁴ is selected from phenyl, bicyclic heterocycle and tricyclic heterocycle, wherein any phenyl, bicyclic heterocycle and tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and methyl.

A specific value for R⁴ is selected from phenyl, bicyclic heterocycle and tricyclic heterocycle, wherein any phenyl, bicyclic heterocycle and tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from fluoro, chloro or methyl.

15 A specific value for R⁴ is selected from phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle, wherein any phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo.

25 A specific value for R⁴ is selected from phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle, wherein any phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from selected from halo and (C₁-C₆)alkyl.

A specific value for R⁴ is selected from phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle, wherein any phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and methyl.

30 A specific value for R⁴ is selected from phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle, wherein any phenyl, 9-10 membered bicyclic heterocycle and 12-13 membered tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from fluoro, chloro or methyl.

A specific value for R⁴ is selected from phenyl, 9-10 membered bicyclic heterocycle and 13 membered tricyclic heterocycle, wherein any phenyl, 9-10 membered bicyclic heterocycle and 13 membered tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from selected from halo and (C₁-C₆)alkyl.

5 A specific value for R⁴ is selected from phenyl, 9-10 membered bicyclic heterocycle and 13 membered tricyclic heterocycle, wherein any phenyl, 9-10 membered bicyclic heterocycle and 13 membered tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and methyl.

A specific value for R⁴ is selected from phenyl, 9-10 membered bicyclic heterocycle and
10 13 membered tricyclic heterocycle, wherein any phenyl, 9-10 membered bicyclic heterocycle and 13 membered tricyclic heterocycle of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from fluoro, chloro or methyl.

A specific value for R⁴ is selected from phenyl, 2,3-dihydropyrano[4,3,2-de]quinolinyl, chromanyl-4-one, chromanyl and 2-methylbenzo[d][1,3]dioxolyl wherein any phenyl, 2,3-
15 dihydropyrano[4,3,2-de]quinolinyl, chromanyl-4-one, chromanyl and 2-methylbenzo[d][1,3]dioxolyl of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and (C₁-C₆)alkyl.

A specific value for R⁴ is selected from phenyl, 2,3-dihydropyrano[4,3,2-de]quinolinyl, chromanyl-4-one, chromanyl and 2-methylbenzo[d][1,3]dioxolyl wherein any phenyl, 2,3-
20 dihydropyrano[4,3,2-de]quinolinyl, chromanyl-4-one, chromanyl and 2-methylbenzo[d][1,3]dioxolyl of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and methyl.

A specific value for R⁴ is selected from phenyl, 2,3-dihydropyrano[4,3,2-de]quinolinyl, chromanyl-4-one, chromanyl and 2-methylbenzo[d][1,3]dioxolyl wherein any phenyl, 2,3-
25 dihydropyrano[4,3,2-de]quinolinyl, chromanyl-4-one, chromanyl and 2-methylbenzo[d][1,3]dioxolyl of R⁴ is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from fluoro, chloro and methyl.

A specific value for R⁴ is phenyl, wherein phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and (C₁-C₆)alkyl.

30 A specific value for R⁴ is phenyl, wherein phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and methyl.

A specific value for R⁴ is phenyl, wherein phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from fluoro and chloro.

A specific value for R⁴ is phenyl, wherein phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) chloro.

A specific group of compounds of formula I' include compounds wherein A is phenyl, monocyclic heteroaryl or monocyclic heterocycle, wherein any phenyl, monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle bicyclic, wherein any bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is phenyl, monocyclic heteroaryl or monocyclic heterocycle, wherein any phenyl, monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle, or bicyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle bicyclic wherein any bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is phenyl, 5-6 membered monocyclic heteroaryl or 3-7 membered monocyclic heterocycle, wherein any phenyl, 5-6 membered monocyclic heteroaryl or 3-7 membered monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle, wherein any phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle bicyclic, wherein any 8-11 membered bicyclic

aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is phenyl, monocyclic heteroaryl or monocyclic heterocycle, wherein any phenyl, monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is phenyl, monocyclic heteroaryl or monocyclic heterocycle, wherein any phenyl, monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle, or bicyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is phenyl, 5-6 membered monocyclic heteroaryl or 3-7 membered monocyclic heterocycle, wherein any phenyl, 5-6 membered monocyclic heteroaryl or 3-7 membered monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle, wherein any phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is monocyclic N-heteroaryl or monocyclic heterocycle, wherein any monocyclic N-heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle of B is optionally

substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle bicyclic, wherein any bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

5 A specific group of compounds of formula I' include compounds wherein A is monocyclic N-heteroaryl or monocyclic heterocycle, wherein any monocyclic N-heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle, or bicyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle of B is optionally substituted
10 with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle bicyclic, wherein any bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

15 A specific group of compounds of formula I' include compounds wherein A is 5-6 membered monocyclic N-heteroaryl or 3-7 membered monocyclic heterocycle, wherein any 5-6 membered monocyclic N-heteroaryl or 3-7 membered monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7
20 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle, wherein any phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered
25 bicyclic heterocycle bicyclic, wherein any 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is monocyclic N-heteroaryl or monocyclic heterocycle, wherein any monocyclic N-heteroaryl or
30 monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl,

monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is monocyclic N-heteroaryl or monocyclic heterocycle, wherein any monocyclic N-heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle, or bicyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is 5-6 membered monocyclic N-heteroaryl or 3-7 membered monocyclic heterocycle, wherein any 5-6 membered monocyclic N-heteroaryl or 3-7 membered monocyclic heterocycle of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle, wherein any phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is monocyclic N-heteroaryl, wherein any monocyclic N-heteroaryl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle bicyclic, wherein any bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is monocyclic N-heteroaryl, wherein any monocyclic N-heteroaryl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b}

groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle bicyclic, wherein any bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is 5-6
 5 membered monocyclic N-heteroaryl, wherein any 5-6 membered monocyclic N-heteroaryl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle, wherein any phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11
 10 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together form a 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle bicyclic, wherein any 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle is optionally
 15 substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is monocyclic N-heteroaryl, wherein any monocyclic N-heteroaryl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle
 20 or tricyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, tricyclic heteroaryl, monocyclic heterocycle, bicyclic heterocycle or tricyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is monocyclic N-heteroaryl, wherein any monocyclic N-heteroaryl of A is optionally substituted
 25 with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle, or bicyclic heterocycle, wherein any phenyl, bicyclic aryl, monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

30 A specific group of compounds of formula I' include compounds wherein A is 5-6 membered monocyclic N-heteroaryl, wherein any 5-6 membered monocyclic N-heteroaryl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle,

wherein any phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

5 A specific group of compounds of formula I' include compounds wherein A is 5-6 membered monocyclic N-heteroaryl, wherein any 5-6 membered monocyclic N-heteroaryl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is 3-7 membered monocyclic heterocycle, wherein any 3-7 membered monocyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups; or A and B together
10 form a 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle, wherein any 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A is 5-6
15 membered monocyclic N-heteroaryl, wherein any 5-6 membered monocyclic N-heteroaryl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups, and B is 3-7 membered monocyclic heterocycle, wherein any 3-7 membered monocyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

In one embodiment a monocyclic N-heteroaryl includes monocyclic heteroaryls which
20 include one or two nitrogens in the monocyclic ring and which may optionally include one oxygen or one sulfur in the monocyclic ring.

In one embodiment a monocyclic N-heteroaryl includes monocyclic heteroaryls which include one or two nitrogens in the monocyclic ring.

In one embodiment a N-heteroaryl includes heteroaryls which include one or two
25 nitrogens in the heteroary ring and which may optionally include one oxygen or one sulfur in the heteroaryl ring.

A specific value for A is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridinyl-2(1H)-one, tetrahydropyrimidin-2(1H)-one, imidazolidinyl-2-one, pyrrolidinyl-2-one, pyrrolidinyl, pyridazinyl, thiazolyl, pyrazin-2(1H)-one, piperazinyl-2-one, piperazinyl, imidazolyl,
30 morpholinyl, 1,2,3,6-tetrahydropyridinyl or piperidinyl, wherein any phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridinyl-2(1H)-one, tetrahydropyrimidin-2(1H)-one, imidazolidinyl-2-one, pyrrolidinyl-2-one, pyrrolidinyl, pyridazinyl, thiazolyl, pyrazin-2(1H)-one, piperazinyl-2-one, piperazinyl, imidazolyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl or piperidinyl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

A specific value for A is 5-6 membered monocyclic N-heteroaryl, wherein any 5-6 membered monocyclic N-heteroaryl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

A specific value for A is 6 membered monocyclic N-heteroaryl, wherein any 6 membered monocyclic N-heteroaryl of A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

A specific value for A is pyridinyl or pyrimidinyl, wherein pyridinyl, or pyrimidinyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

A specific value for A is pyridinyl, pyrimidinyl, pyrazinyl or pyridizynyl wherein the pyridinyl, pyrimidinyl, pyrazinyl or pyradizynyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

A specific value for A is pyrimidinyl wherein the pyrimidinyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups.

A specific value for B is selected from phenyl, pyridinyl, indazolyl, pyrazolo[4,3-b]pyridinyl, pyrimidinyl, pyrazolyl, benzo[d]imidazolyl, indazolyl, 1H-benzo[d]imidazolyl-2(3H)-one, 2H-pyrido[3,2-b][1,4]oxazinyl-3(4H)-one, 2,6-naphthyridin-1(2H)-one, 1,7-naphthyridinyl-8(7H)-one, 1H-indazolyl-3(2H)-one, quinolinyl-2(1H)-one, quinolinyl, pyrrolo[2,3-b]pyridinyl, pyrrolidinyl, piperazinyl, phenyl, imidazolyl, piperidinyl, morpholinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrimidinyl-2,4(1H,3H)-dionyl, pyridinyl-2(1H)-one, 1H-pyrazolo[3,4-c]pyridinyl, indolinyl-2-one, 1H-pyrrolo[3,4-c]pyridinyl-3(2H)-one, 2,3-dihydro-1H-pyrrolo[3,2-c]pyridinyl, pyrazolyl, pyrimidinyl-2(1H)-one, azetidyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, 1,2,3,6-tetrahydropyridine, 1H-pyrazolo[3,4-b]pyridinyl, 2H-benzo[b][1,4]oxazinyl-3(4H)-one, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazinyl, indolinyl, 3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one, 3H-imidazo[4,5-b]pyridinyl and 1H-benzo[d][1,2,3]triazolyl, wherein any phenyl, pyridinyl, indazolyl, pyrazolo[4,3-b]pyridinyl, pyrimidinyl, pyrazolyl, benzo[d]imidazolyl, indazolyl, 1H-benzo[d]imidazolyl-2(3H)-one, 2H-pyrido[3,2-b][1,4]oxazinyl-3(4H)-one, 2,6-naphthyridin-1(2H)-one, 1,7-naphthyridinyl-8(7H)-one, 1H-indazolyl-3(2H)-one, quinolinyl-2(1H)-one, quinolinyl, pyrrolo[2,3-b]pyridinyl, pyrrolidinyl, piperazinyl, phenyl, imidazolyl, piperidinyl, morpholinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrimidinyl-2,4(1H,3H)-dionyl, pyridinyl-2(1H)-one, 1H-pyrazolo[3,4-c]pyridinyl, indolinyl-2-one, 1H-pyrrolo[3,4-c]pyridinyl-3(2H)-one, 2,3-dihydro-1H-pyrrolo[3,2-c]pyridinyl, pyrazolyl, pyrimidinyl-2(1H)-one, azetidyl, tetrahydro-2H-pyranyl,

3,6-dihydro-2H-pyran-2-yl, 1,2,3,6-tetrahydropyridine, 1H-pyrazolo[3,4-b]pyridin-2-yl, 2H-benzo[b][1,4]oxazin-3(4H)-one, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-5(2H)-one, 3H-imidazo[4,5-b]pyridin-2-yl, and 1H-benzo[d][1,2,3]triazol-4-yl of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b}

5 groups.

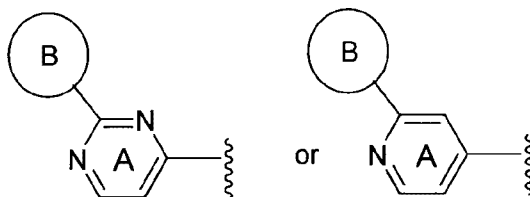
A specific value for B is 3-7 membered monocyclic heterocycle, wherein any 3-7 membered monocyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific value for B is 4-7 membered monocyclic heterocycle, wherein any 4-7 membered monocyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific value for B is 4-6 membered monocyclic heterocycle, wherein any 4-6 membered monocyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

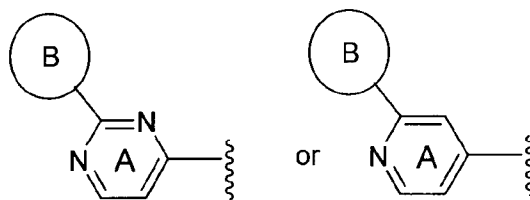
A specific value for B is piperazinyl or azetidynyl, wherein any piperazinyl or azetidynyl of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group or compounds of formula I' include compounds wherein A-B is:



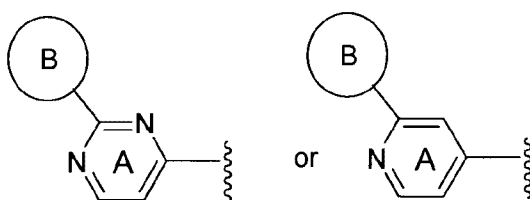
wherein A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups and B is phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle, wherein any phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A-B is:



wherein A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups and B is 3-7 membered monocyclic heterocycle wherein any 3-7 membered monocyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

5 A specific group of compounds of formula I' include compounds wherein A-B is:



wherein B is azetidinyI or piperazinyl, wherein any azetidinyI or piperazinyl of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

10 A specific group of compounds of formula I' are compounds wherein wherein A and B together form a pyrrolopyridinyl, pyrazolopyridine or indazolyl, wherein the pyrrolopyridinyl, pyrazolopyridine or indazolyl is optionally substituted with one or more Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle, wherein the bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more (e.g.,
15 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A and B together form a 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle, wherein the 8-11 membered bicyclic aryl, 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle is optionally substituted with one or
20 more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A and B together form a 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle, wherein the 7-11 membered bicyclic heteroaryl or 6-11 membered bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A and B together form a 7-11 membered bicyclic heteroaryl, wherein the 7-11 membered bicyclic heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

5 A specific group of compounds of formula I' include compounds wherein A and B together form a 9-10 membered bicyclic heteroaryl or 9-11 membered bicyclic heterocycle bicyclic wherein the 9-10 membered bicyclic heteroaryl or 9-11 membered bicyclic heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

10 A specific group of compounds of formula I' include compounds wherein A and B together form a 9-10 membered bicyclic heteroaryl, wherein the 9-10 membered bicyclic heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' include compounds wherein A and B together form a 9-10 membered bicyclic heteroaryl, wherein the 9-10 membered bicyclic heteroaryl includes 1-4 nitrogen atoms, and wherein the 9-10 membered bicyclic heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

15 A specific group of compounds of formula I' include compounds wherein A and B together form a 9-10 membered bicyclic heteroaryl, wherein the 9-10 membered bicyclic heteroaryl includes 2 or 3 nitrogen atoms, and wherein the 9-10 membered bicyclic heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

20 A specific group of compounds of formula I' include compounds wherein A and B together form an indazolyl, wherein the indazolyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' are compounds wherein wherein A and B together form a pyrazolo[4,3-b]pyridinyl, pyrrolo[2,3-b]pyridinyl, indazolyl, pyrazolo[3,4-b]pyridinyl, 2,7-naphthyridinyl-1(2H)-one, benzoimidazolyl, benzo[1,2,3]triazolyl, pyrazolo[3,4-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrazolo[4,3-c]pyridinyl, isoquinolinyl, benzothiazolyl, 1H-pyrazolo[4,3-d]pyrimidinyl or 2,6-naphthyridin-1(2H)-one, wherein the pyrazolo[4,3-b]pyridinyl, pyrrolo[2,3-b]pyridinyl, indazolyl, pyrazolo[3,4-b]pyridinyl, 2,7-naphthyridinyl-1(2H)-one, benzoimidazolyl, benzo[1,2,3]triazolyl, pyrazolo[3,4-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrazolo[4,3-c]pyridinyl, isoquinolinyl, benzothiazolyl, 1H-pyrazolo[4,3-d]pyrimidinyl or 2,6-naphthyridin-1(2H)-one is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

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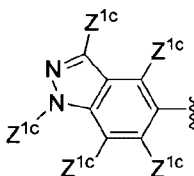
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A specific group of compounds of formula I' are compounds wherein wherein A and B together form a 1H-benzo[d]imidazolyl-2(3H)-one, 1H-indazolyl-3(2H)-one, 5,6,7,8-tetrahydro-1,6-naphthyridinyl, 1,2,3,4-tetrahydroisoquinolinyl, indolinyl-2-one, isoindolinyl-1-one, indolinyl, 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 2H-benzo[b][1,4]oxazinyl-3(4H)-one, 5,6,7,8-tetrahydro-1,7-naphthyridinyl, 2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl, 1,2,3,4-tetrahydro-2,7-naphthyridinyl, 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl, 1,2,3,4-tetrahydro-2,6-naphthyridinyl, decahydroisoquinolinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridinyl, isoindolinyl or 2,3-dihydrobenzo[b][1,4]dioxinyl, wherein the 1H-benzo[d]imidazolyl-2(3H)-one, 1H-indazolyl-3(2H)-one, 5,6,7,8-tetrahydro-1,6-naphthyridinyl, 1,2,3,4-tetrahydroisoquinolinyl, indolinyl-2-one, isoindolinyl-1-one, indolinyl, 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 2H-benzo[b][1,4]oxazinyl-3(4H)-one, 5,6,7,8-tetrahydro-1,7-naphthyridinyl, 2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl, 1,2,3,4-tetrahydro-2,7-naphthyridinyl, 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl, 1,2,3,4-tetrahydro-2,6-naphthyridinyl, decahydroisoquinolinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridinyl, isoindolinyl or 2,3-dihydrobenzo[b][1,4]dioxinyl, is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

A specific group of compounds of formula I' are compounds wherein wherein A and B together form a pyrazolo[4,3-b]pyridinyl, pyrrolo[2,3-b]pyridinyl, indazolyl, pyrazolo[3,4-b]pyridinyl, 2,7-naphthyridinyl-1(2H)-one, benzoimidazolyl, benzo[1,2,3]triazolyl, pyrazolo[3,4-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrazolo[4,3-c]pyridinyl, isoquinolinyl, benzothiazolyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2,6-naphthyridin-1(2H)-one, 1H-benzo[d]imidazolyl-2(3H)-one, 1H-indazolyl-3(2H)-one, 5,6,7,8-tetrahydro-1,6-naphthyridinyl, 1,2,3,4-tetrahydroisoquinolinyl, indolinyl-2-one, isoindolinyl-1-one, indolinyl, 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 2H-benzo[b][1,4]oxazinyl-3(4H)-one, 5,6,7,8-tetrahydro-1,7-naphthyridinyl, 2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl, 1,2,3,4-tetrahydro-2,7-naphthyridinyl, 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl, 1,2,3,4-tetrahydro-2,6-naphthyridinyl, decahydroisoquinolinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridinyl, isoindolinyl or 2,3-dihydrobenzo[b][1,4]dioxinyl, wherein the pyrazolo[4,3-b]pyridinyl, pyrrolo[2,3-b]pyridinyl, indazolyl, pyrazolo[3,4-b]pyridinyl, 2,7-naphthyridinyl-1(2H)-one, benzoimidazolyl, benzo[1,2,3]triazolyl, pyrazolo[3,4-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrazolo[4,3-c]pyridinyl, isoquinolinyl, benzothiazolyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2,6-naphthyridin-1(2H)-one, 1H-benzo[d]imidazolyl-2(3H)-one,

1H-indazolyl-3(2H)-one, 5,6,7,8-tetrahydro-1,6-naphthyridinyl, 1,2,3,4-tetrahydroisoquinolinyl, indolinyl-2-one, isoindolinyl-1-one, indolinyl, 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 2H-benzo[b][1,4]oxazinyl-3(4H)-one, 5,6,7,8-tetrahydro-1,7-naphthyridinyl, 2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl, 1,2,3,4-tetrahydro-2,7-naphthyridinyl, 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl, 1,2,3,4-tetrahydro-2,6-naphthyridinyl, decahydroisoquinolinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridinyl, isoindolinyl or 2,3-dihydrobenzo[b][1,4]dioxinyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

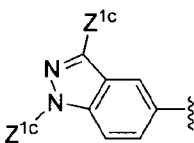
A specific group of compounds of formula I' include compounds wherein A-B is:



10

wherein each Z^{1c} is H or Z^{1b} .

A specific group of compounds of formula I' include compounds wherein A-B is:



wherein each Z^{1c} is H or Z^{1b} .

15

A specific value for each Z^{1a} is halo, (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_3-C_7) carbocycle, 3-7 membered monocyclic heterocycle, $-O(C_1-C_3)$ alkyl, $-O(C_2-C_3)$ alkenyl, $-O(C_2-C_3)$ alkynyl, $-NR_cR_d$, $-NR_aC(O)R_a$, $-C(O)OR_b$, and $-C(O)NR_cR_d$, wherein any (C_3-C_7) carbocycle or 3-7 membered monocyclic heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C_1-C_6) alkyl.

20

A specific value for Z^{1a} is halo, (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, $-O(C_1-C_3)$ alkyl or $-C(O)OR_b$.

25

A specific value for each Z^{1b} is independently selected from halo, CN, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_3-C_7) carbocycle, heteroaryl, heterocycle, aryl (C_1-C_6) alkyl-, $-OH$, $-O(C_1-C_6)$ alkyl, $-NR_cR_d$, $-C(O)OR_b$, and $-C(O)NR_cR_d$, wherein any (C_3-C_7) carbocycle or heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C_1-C_6) alkyl.

A specific value for Z^{1b} is halo, CN, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_3-C_7) carbocycle, monocyclic heteroaryl, monocyclic heterocycle, phenyl (C_1-C_6) alkyl-, $-OH$, $-O(C_1-C_6)$ alkyl, $-NR_cR_d$, $-C(O)OR_b$ and $-C(O)NR_cR_d$, wherein any (C_3-C_7) carbocycle or monocyclic heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C_1-C_6) alkyl.

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A specific value for Z^{1b} is halo, CN, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, 5-6 membered monocyclic heteroaryl, 3-7 membered monocyclic heterocycle, aryl(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -NR_cR_d, -C(O)OR_b or -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle or 5-6 membered monocyclic heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C₁-C₆)alkyl.

A specific value for each Z^{1b} is (C₁-C₆)alkyl, heteroaryl, heterocycle or -NR_cR_d, wherein any heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C₁-C₆)alkyl.

A specific value for Z^{1b} is (C₁-C₆)alkyl, monocyclic heteroaryl, monocyclic heterocycle or -NR_cR_d, wherein any monocyclic heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C₁-C₆)alkyl.

A specific value for Z^{1b} is (C₁-C₆)alkyl, 5-6 membered monocyclic heteroaryl, 3-7 membered monocyclic heterocycle or -NR_cR_d, wherein any 5-6 membered monocyclic heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or (C₁-C₆)alkyl.

A specific value for Z^{1b} is methyl, isopropyl, -N(CH₃)₂, oxetanyl, pyridinyl, N-methylpiperazinyl.

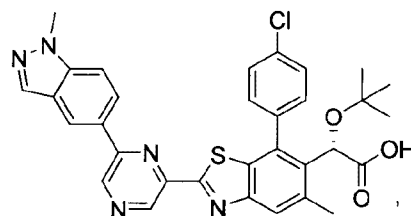
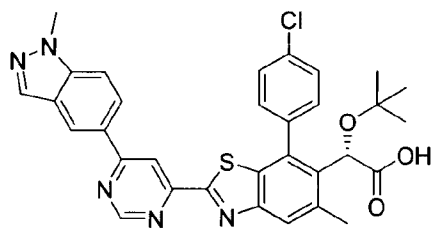
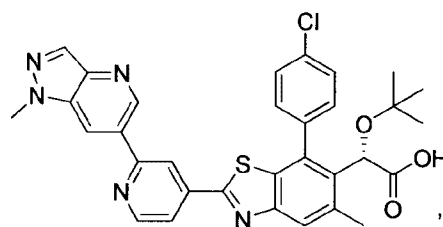
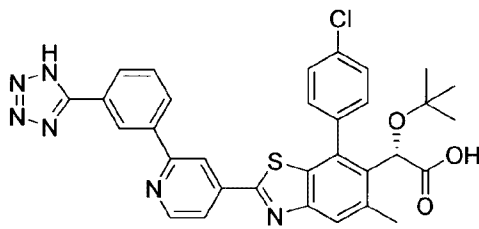
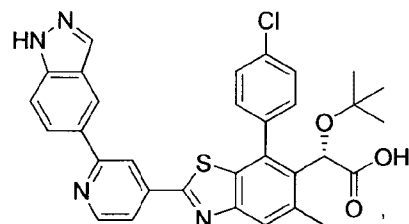
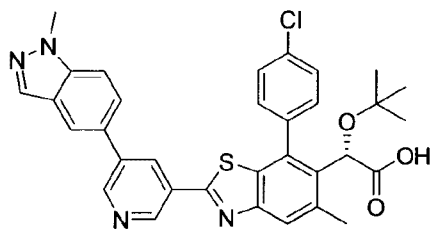
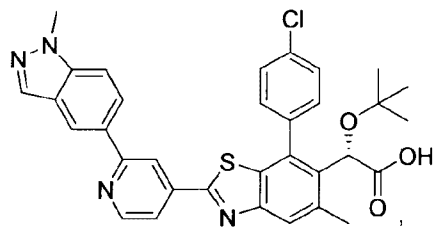
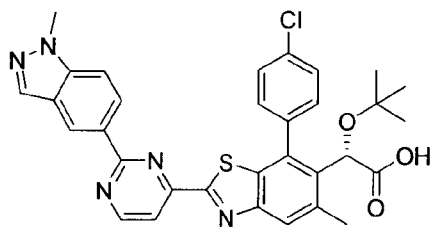
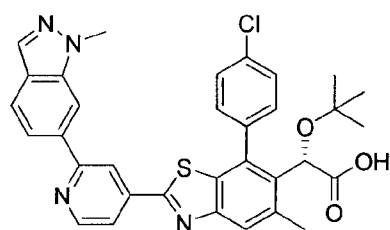
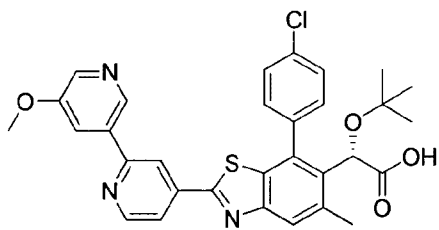
A specific value for Z^{1b} is methyl, pyridinyl or N-methylpiperazinyl.

A specific value for Z^{1b} is isopropyl, -N(CH₃)₂ or oxetanyl.

In one embodiment a compound is selected from:

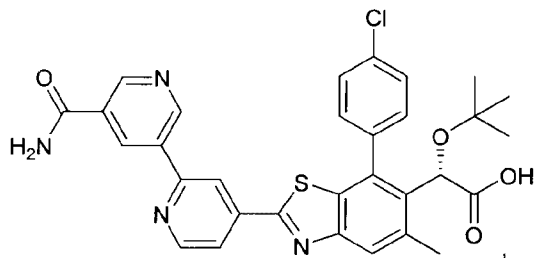
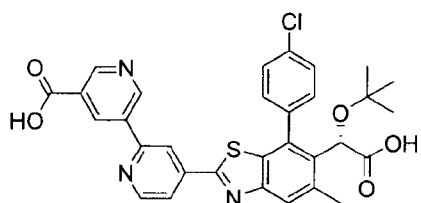
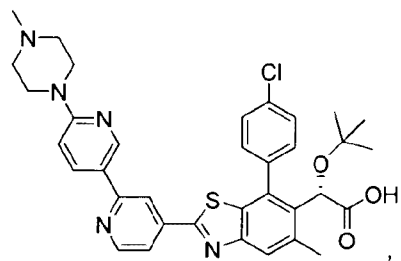
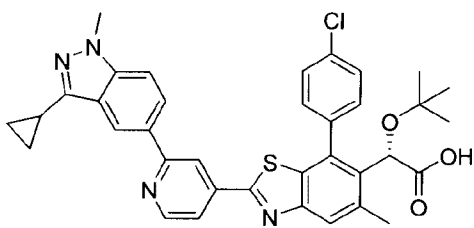
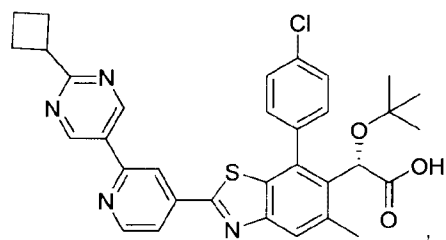
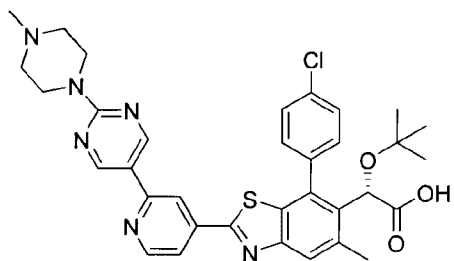
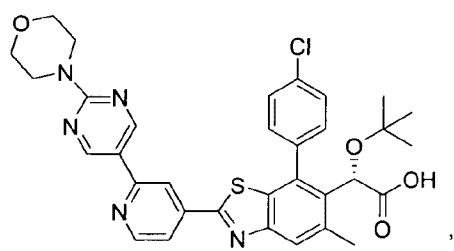
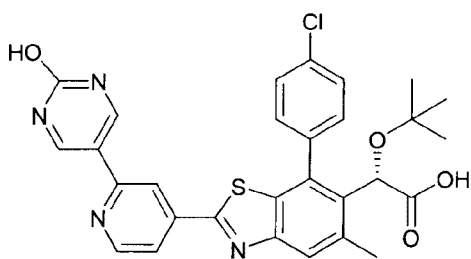
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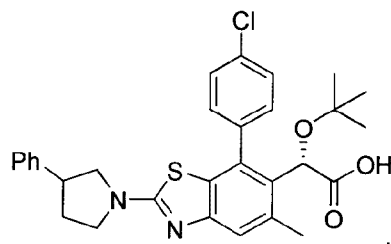
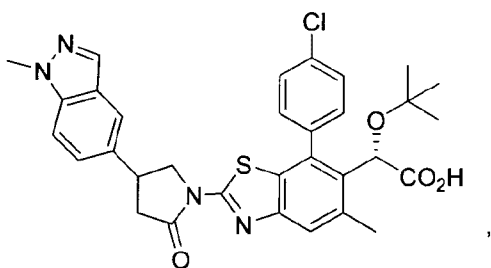
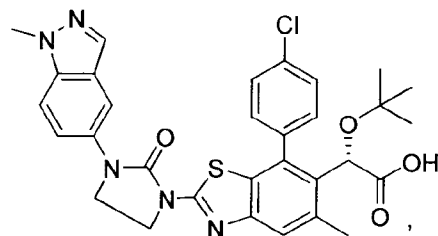
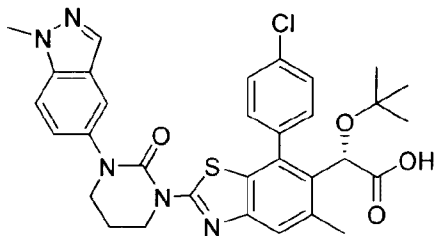
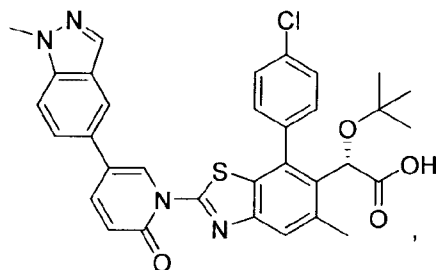
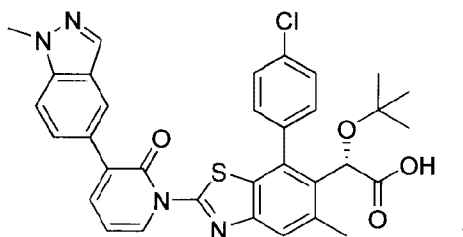
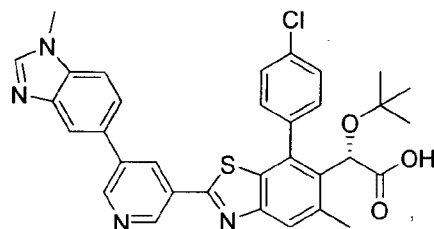
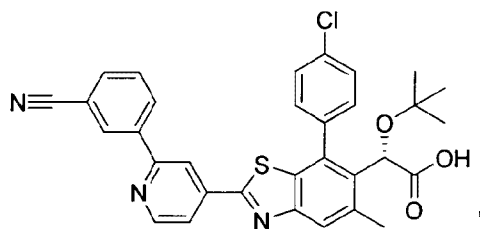
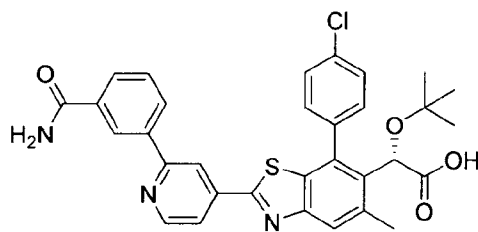
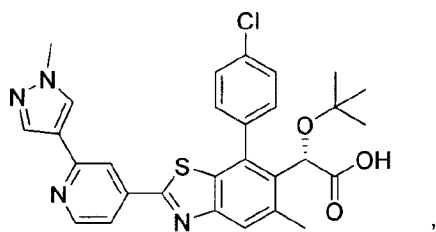
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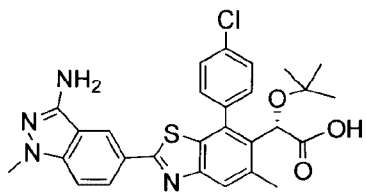
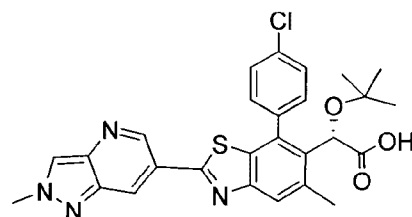
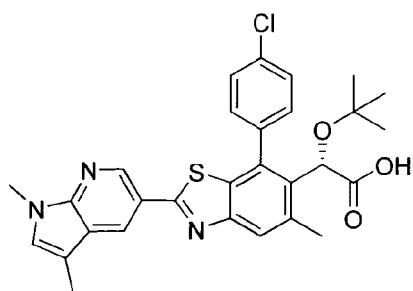
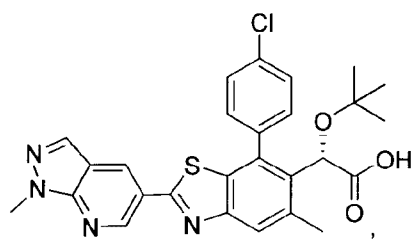
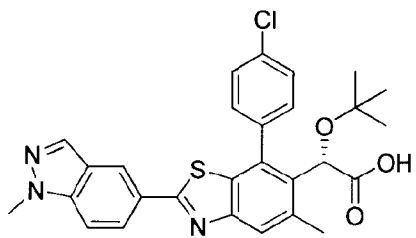
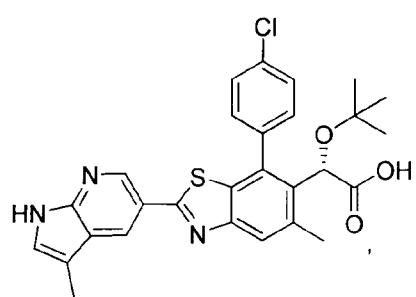
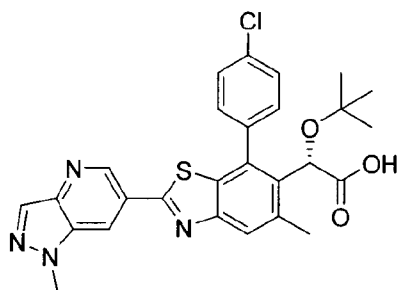
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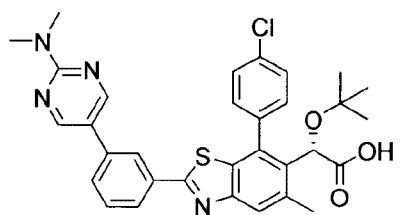
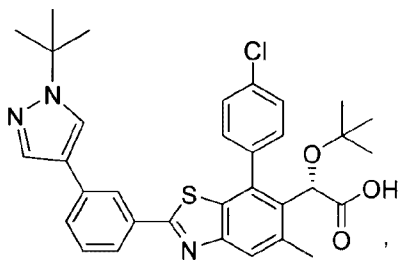
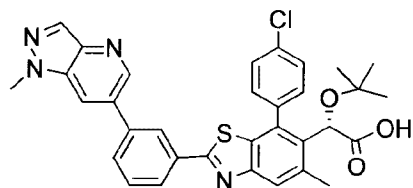
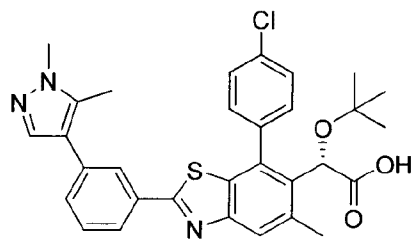
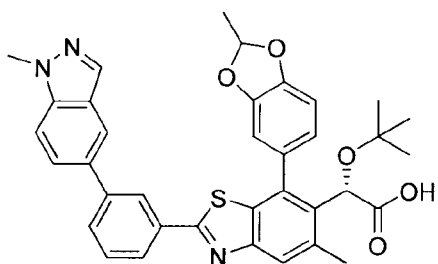
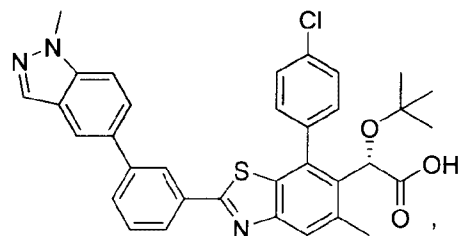
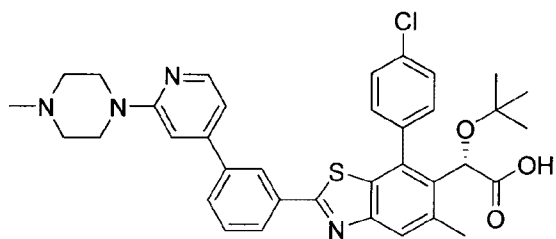
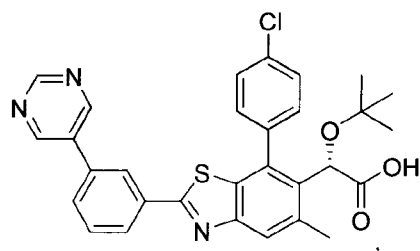
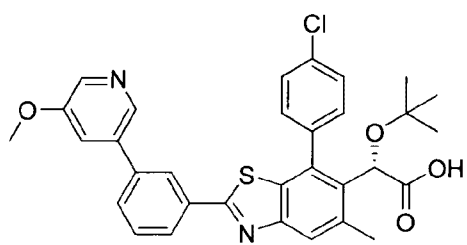


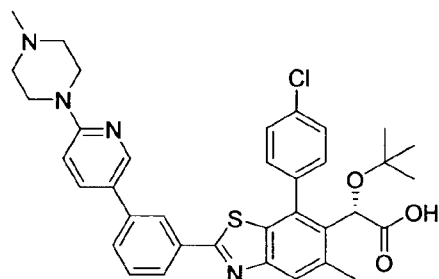
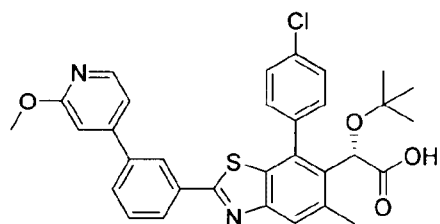
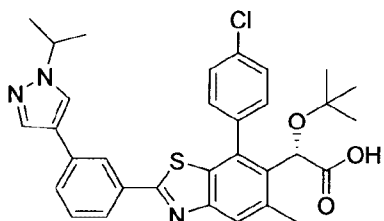
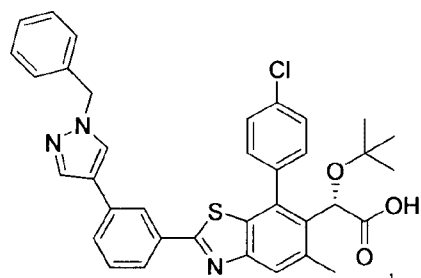
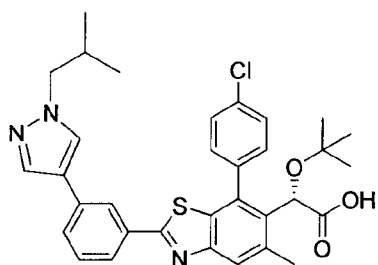
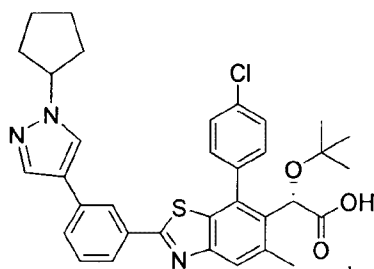
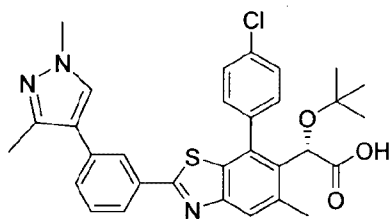
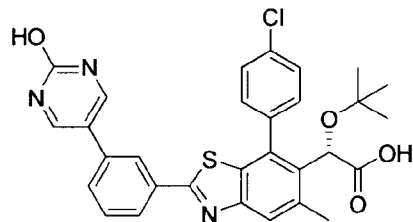
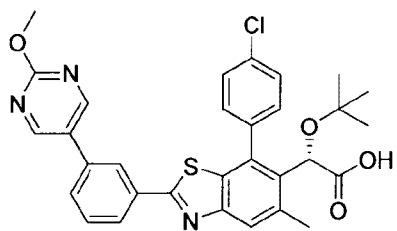


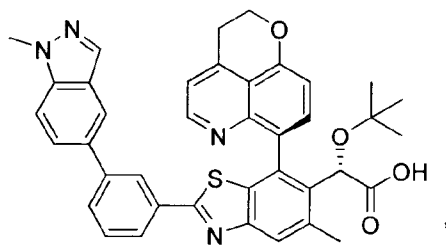
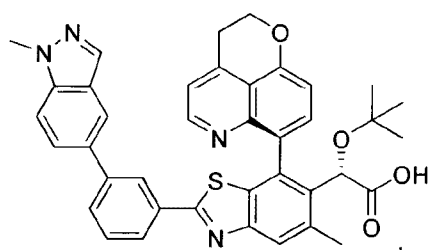
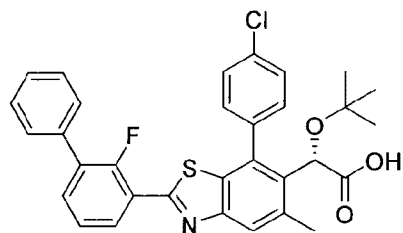
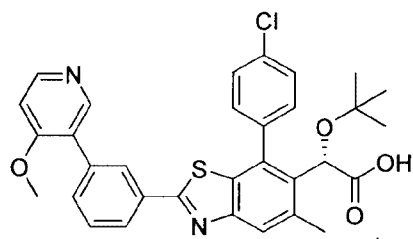
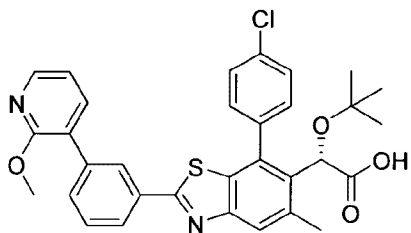
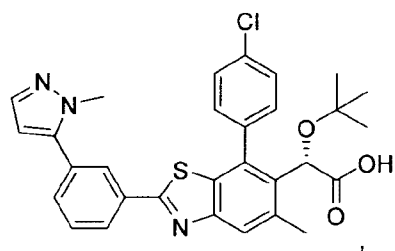
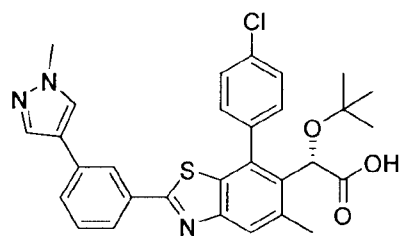
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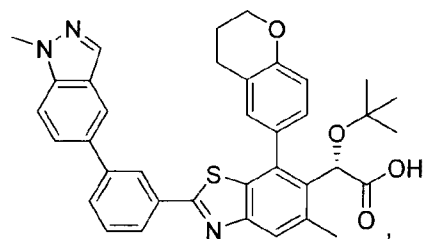
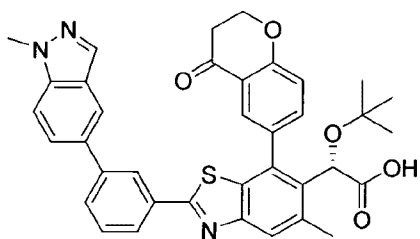
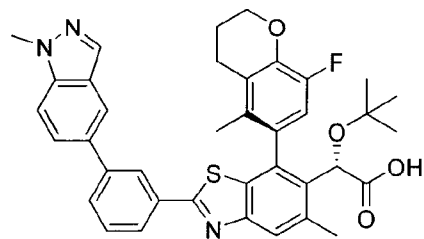
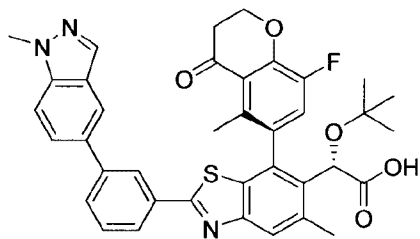
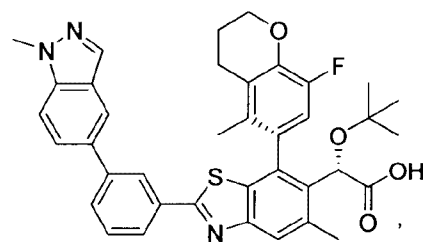
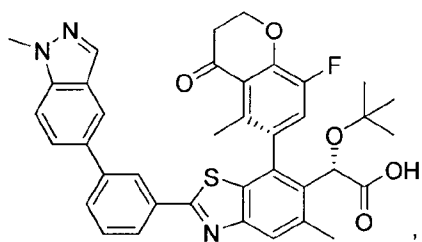




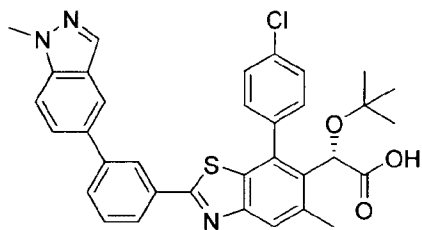


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and

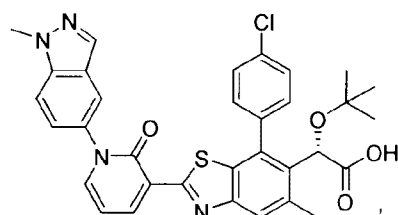
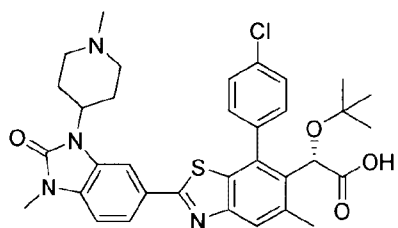
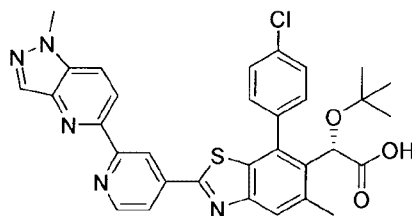
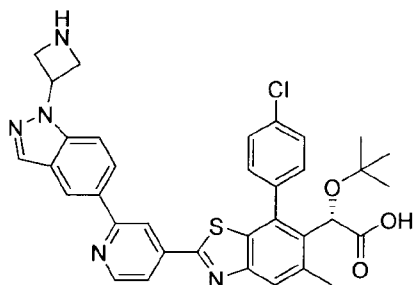
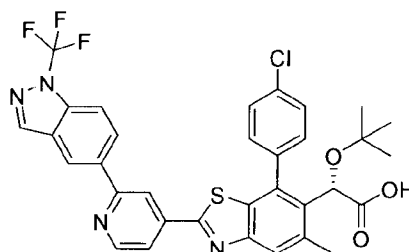
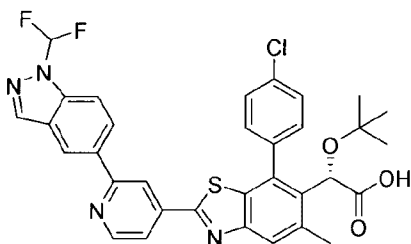
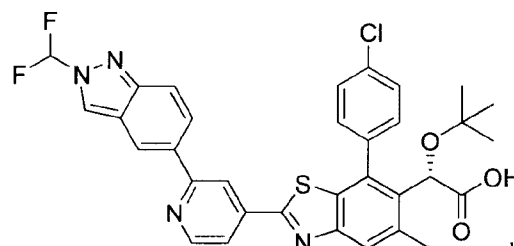
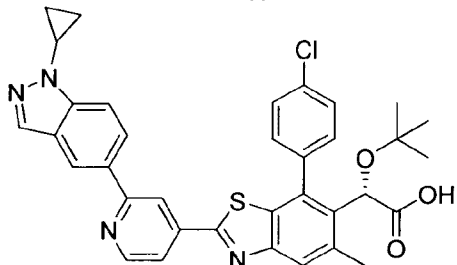
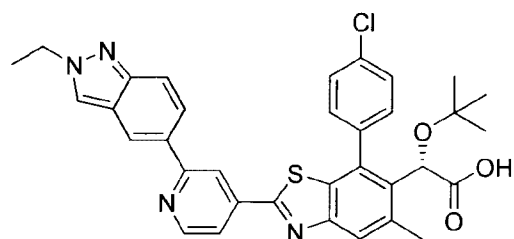
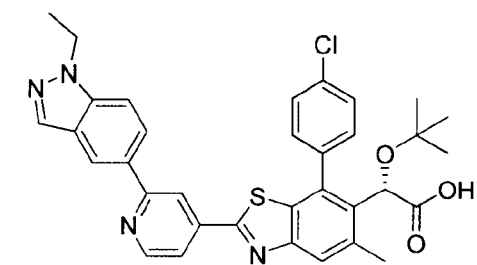


and salts thereof.

In one embodiment a compound is selected from:

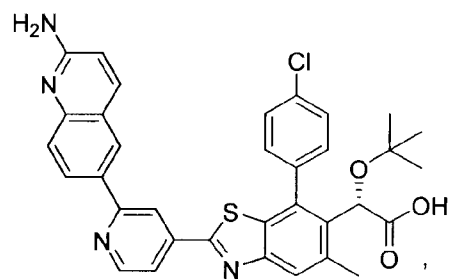
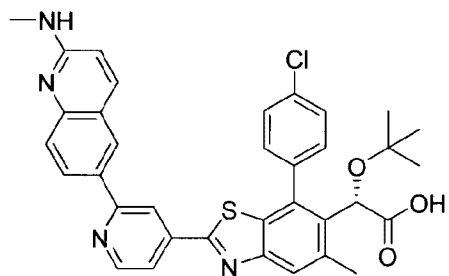
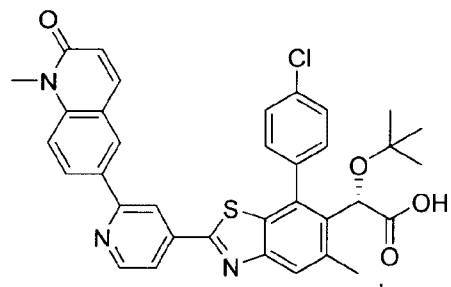
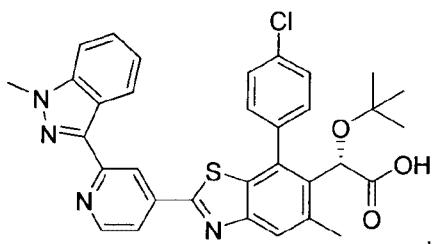
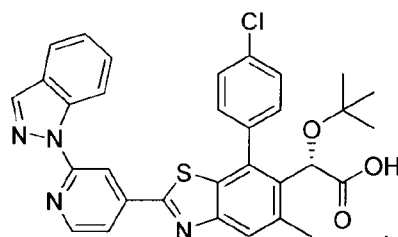
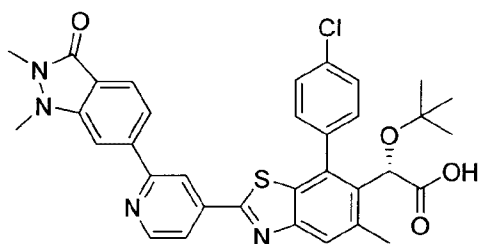
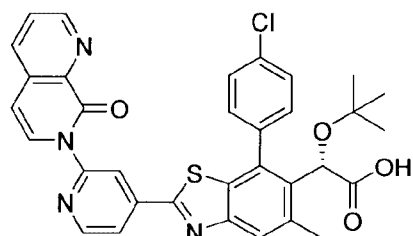
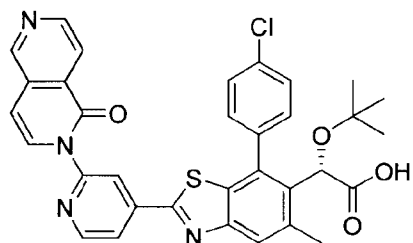
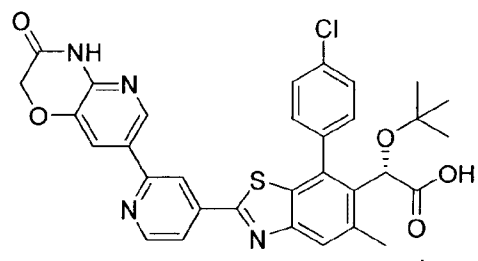
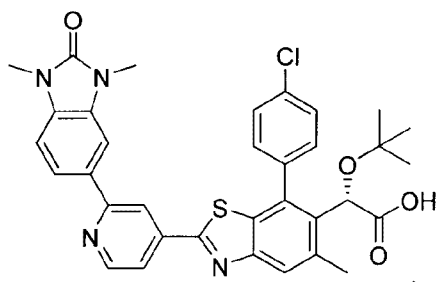
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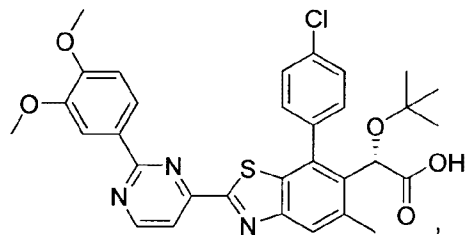
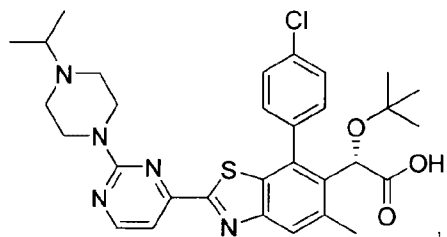
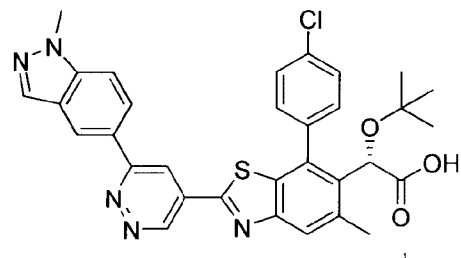
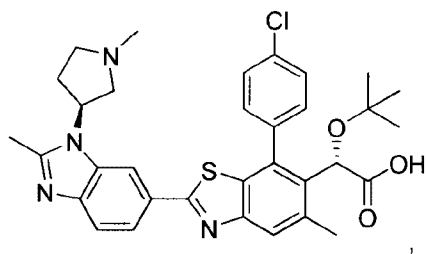
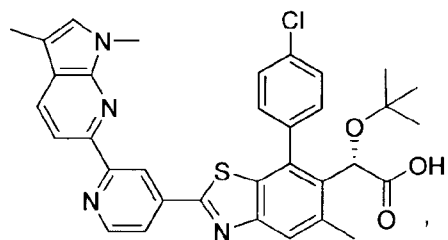
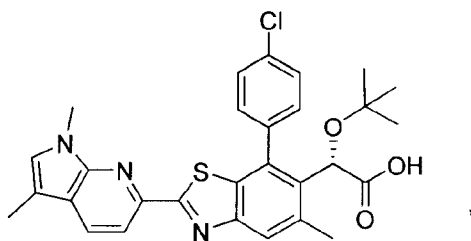
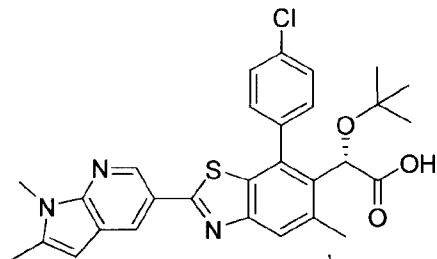
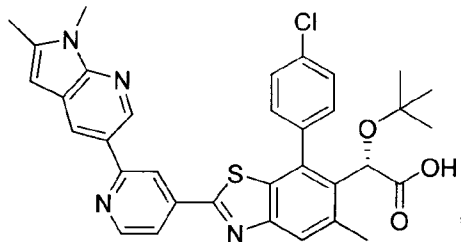
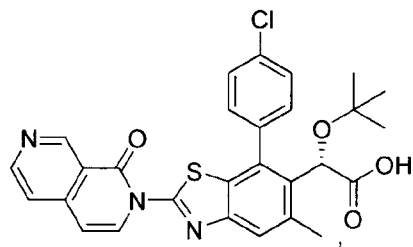
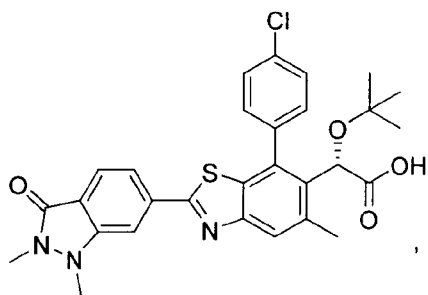
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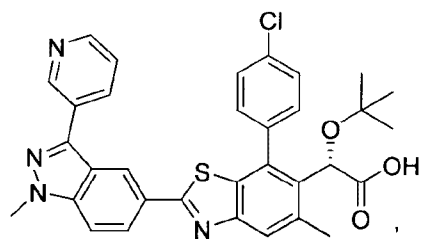
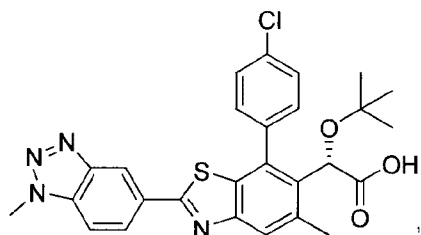
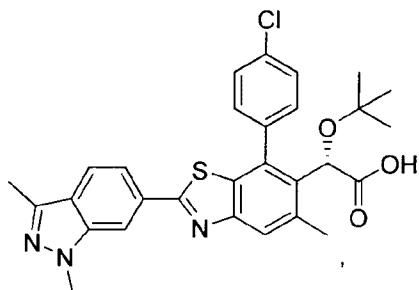
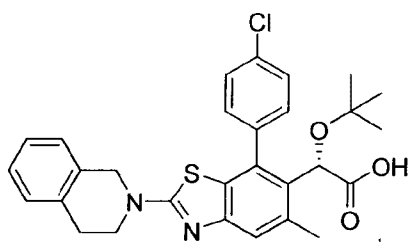
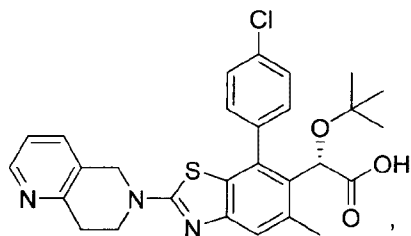
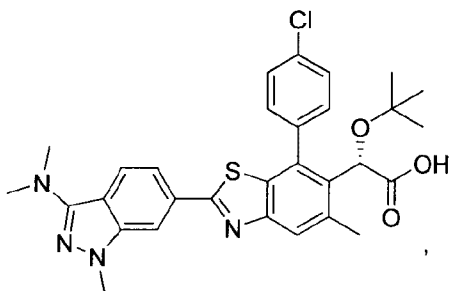
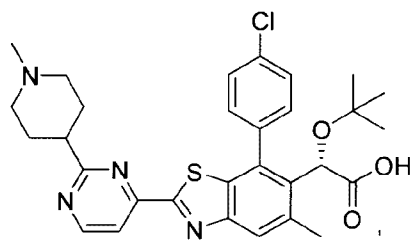
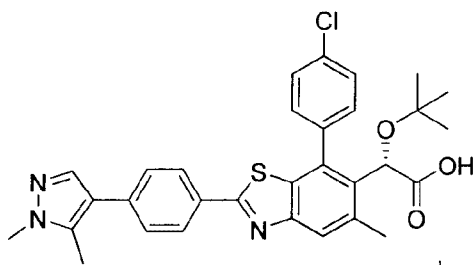
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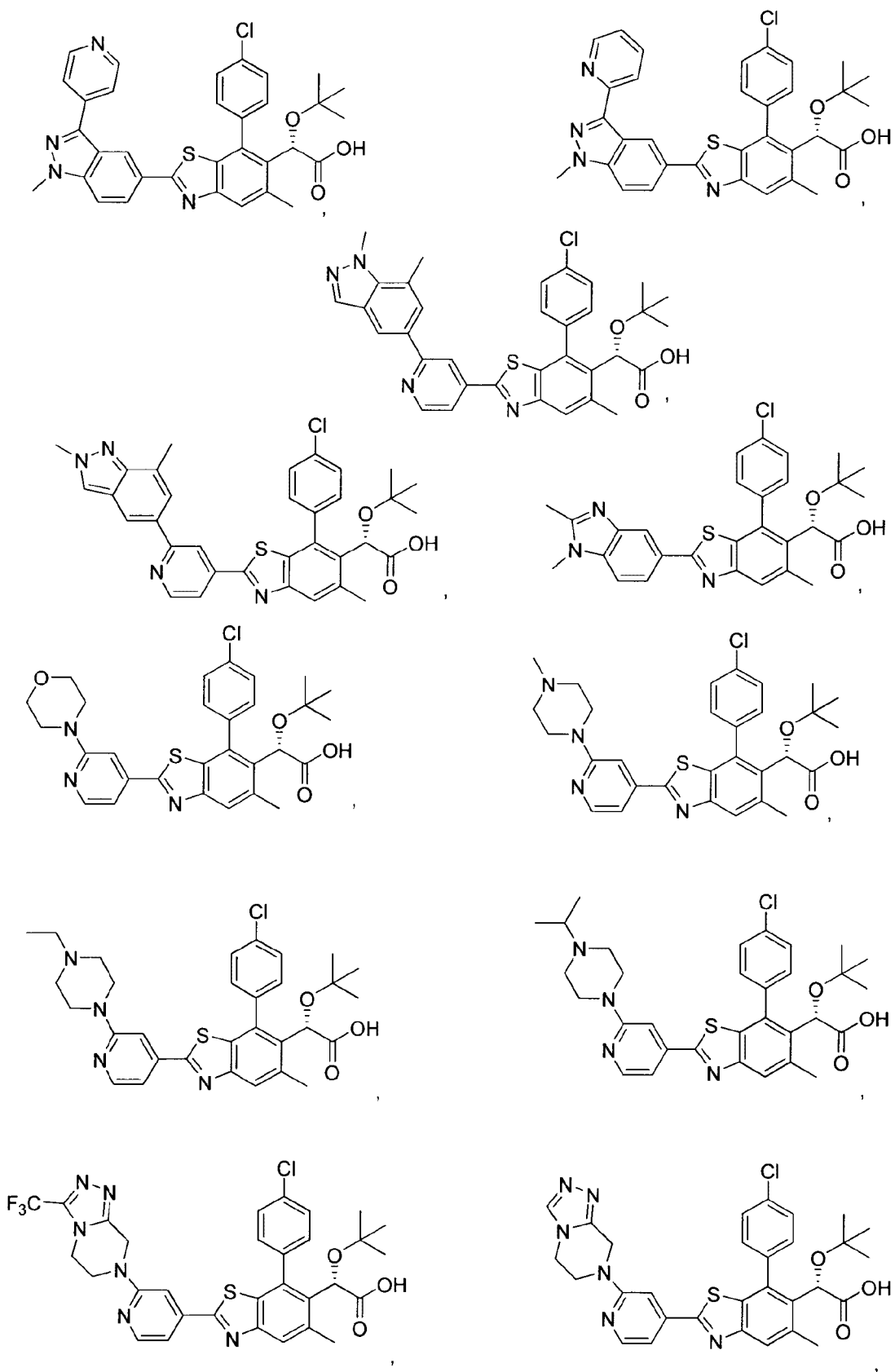


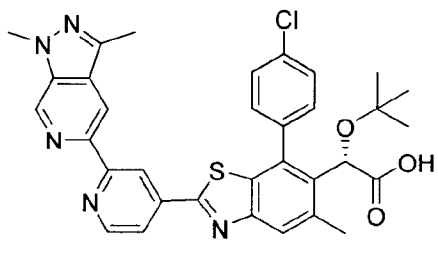
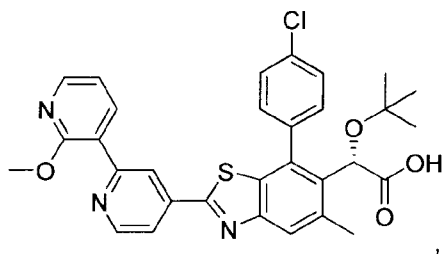
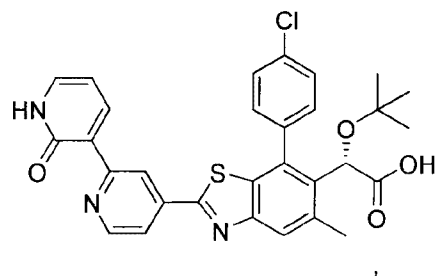
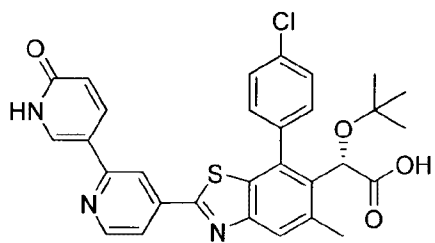
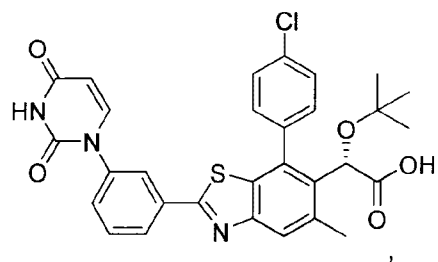
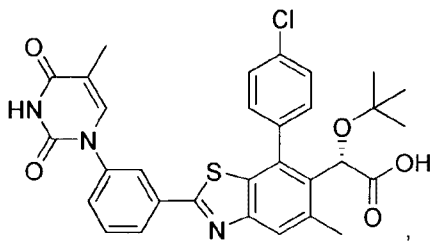
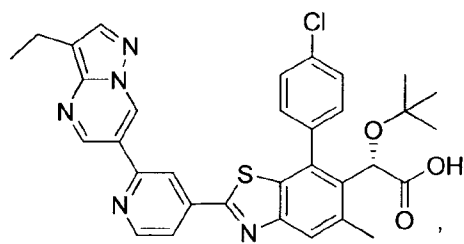
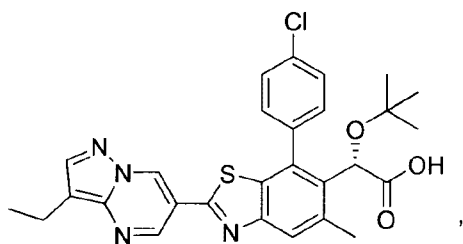
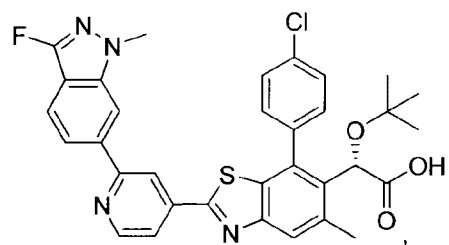
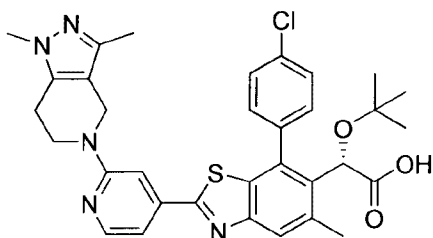


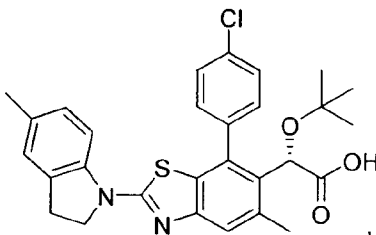
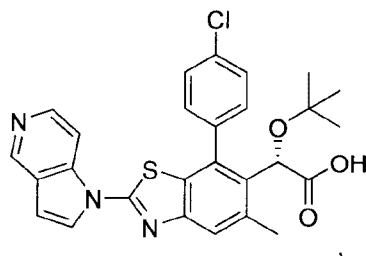
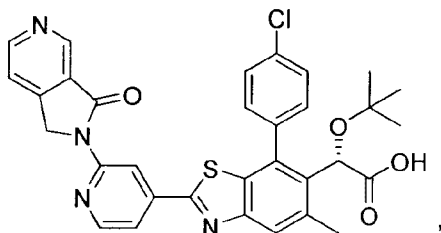
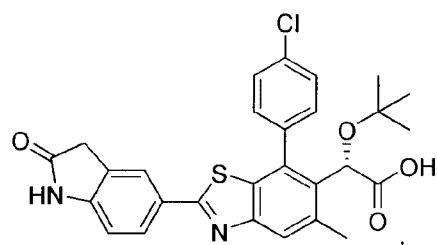
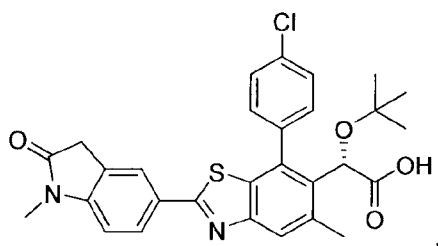
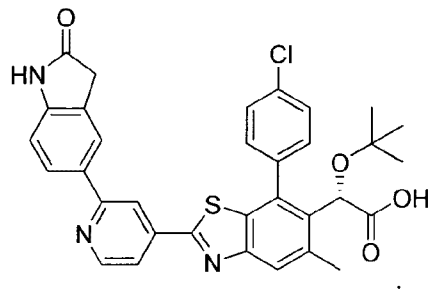
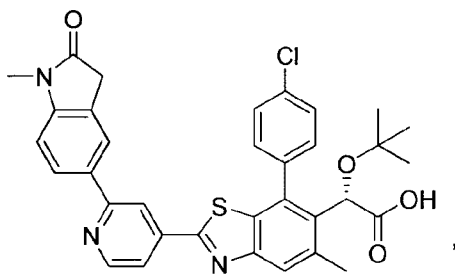
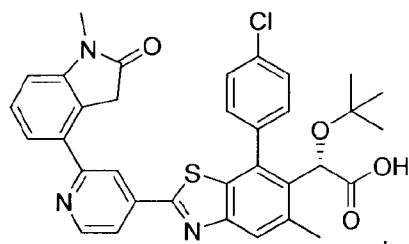
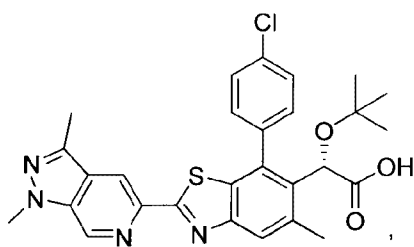
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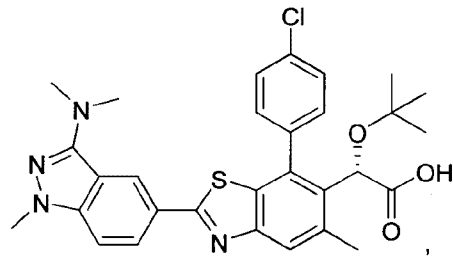
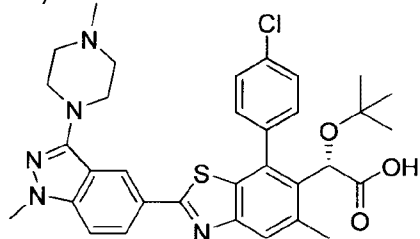
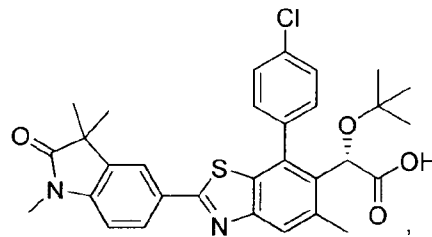
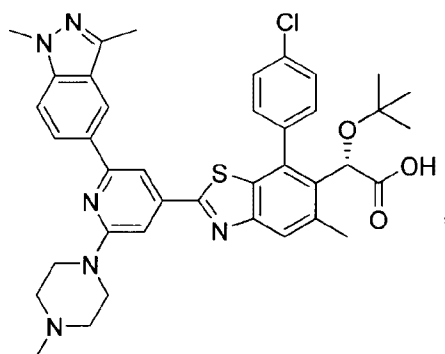
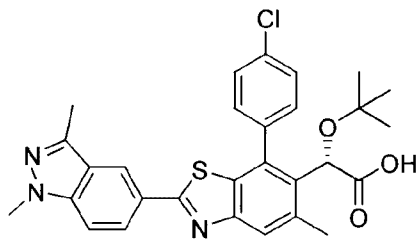
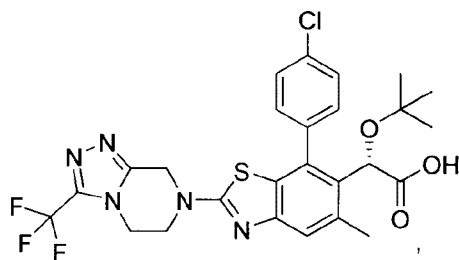
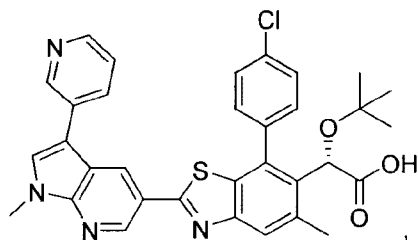
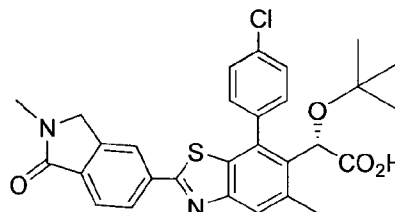
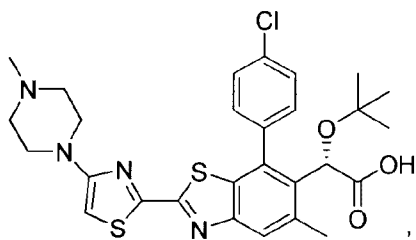
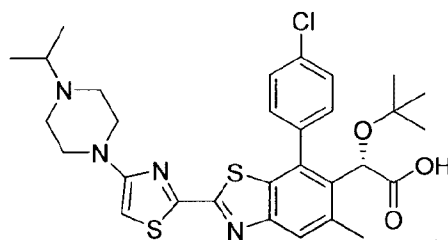
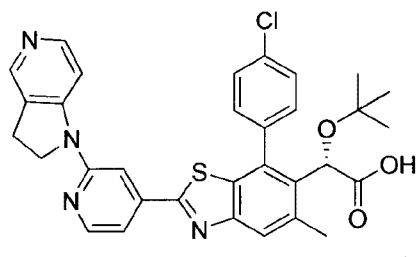
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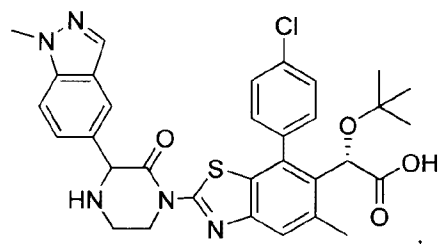
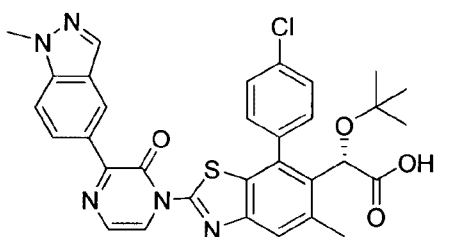
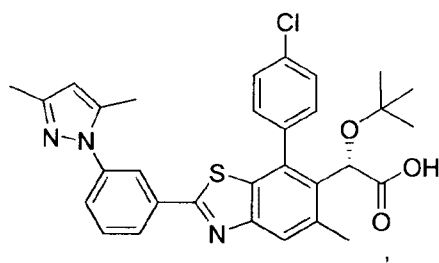
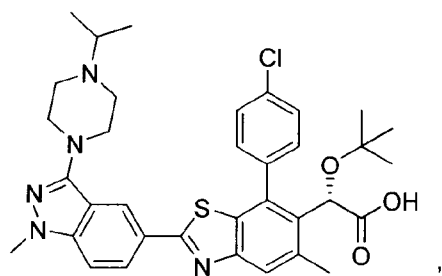
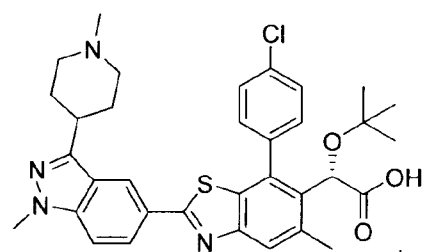
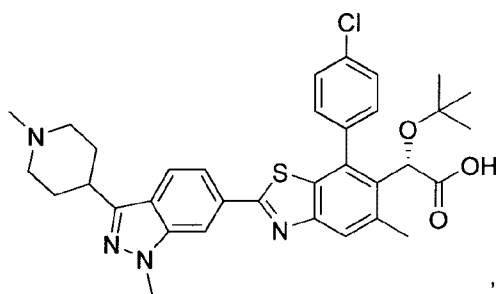
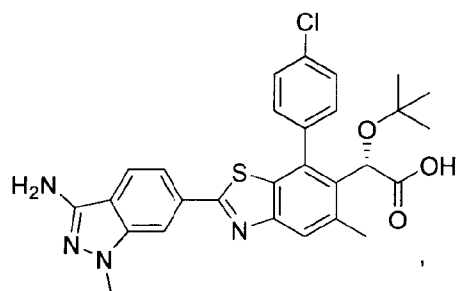
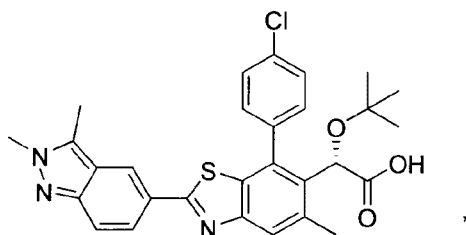
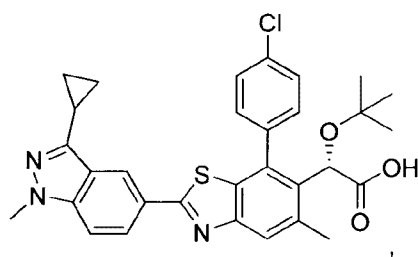
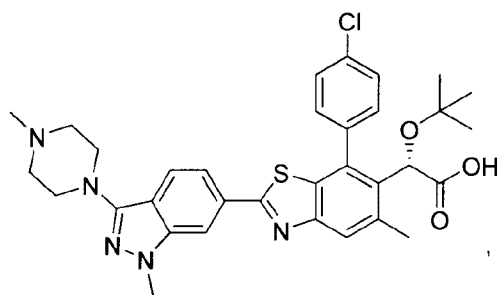


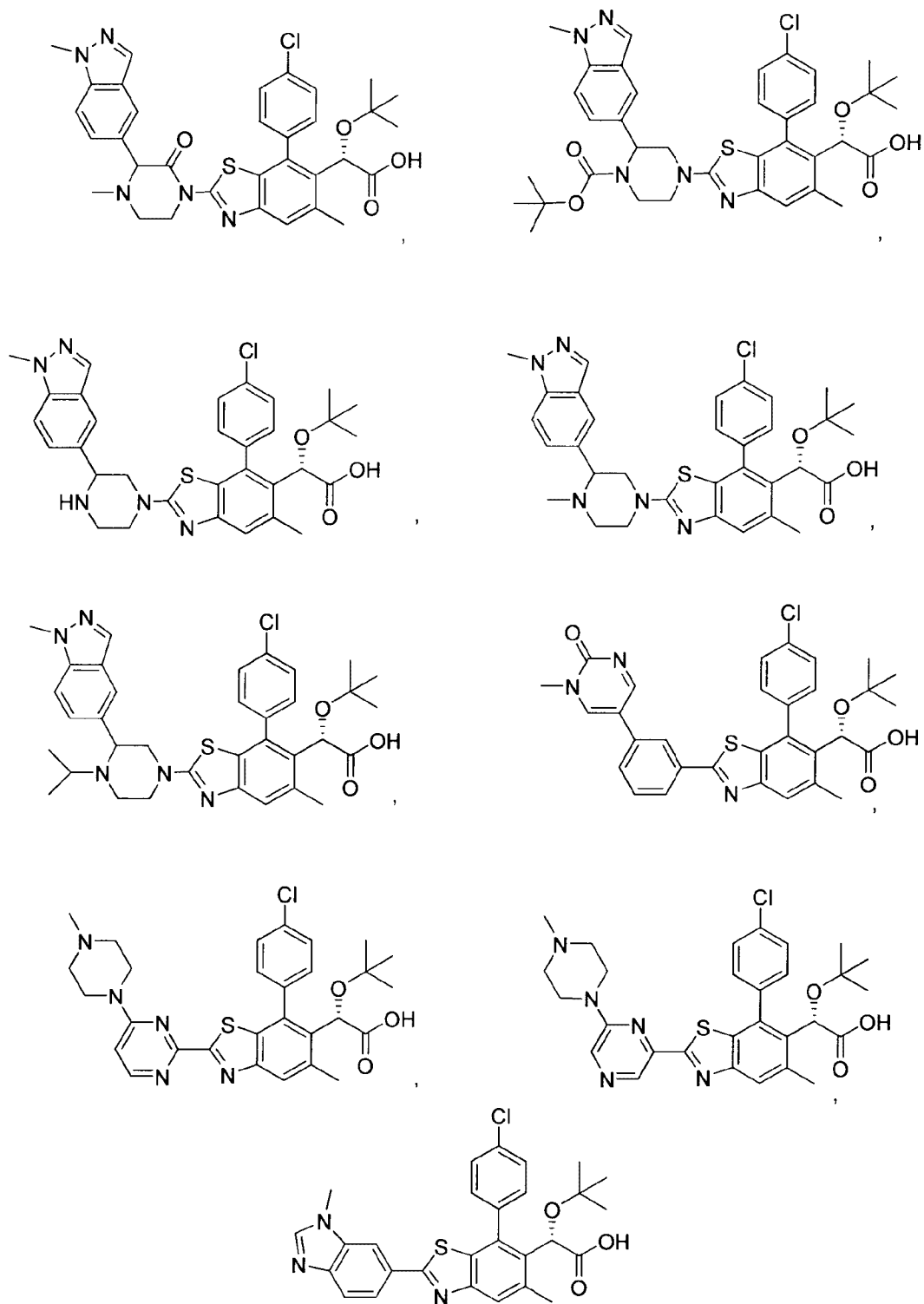






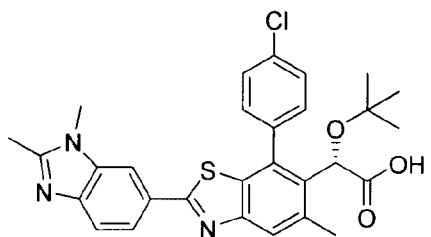
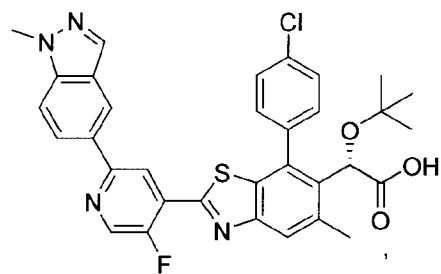
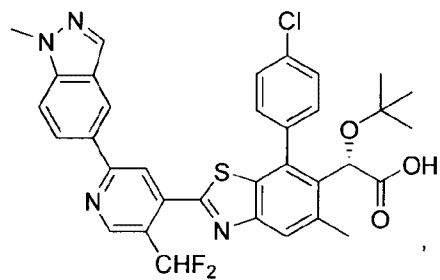
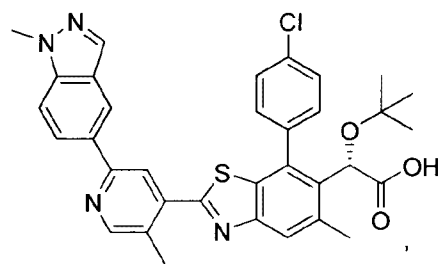
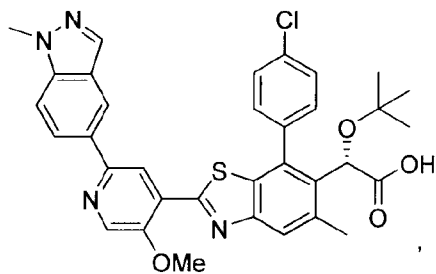
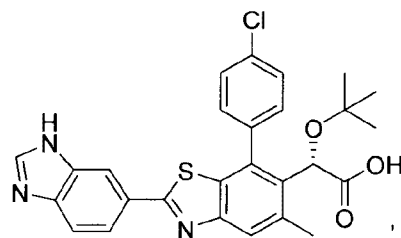
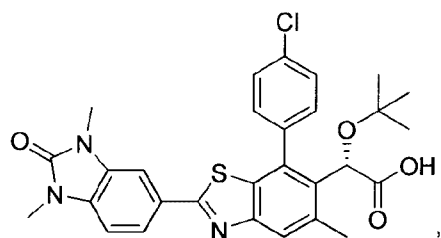
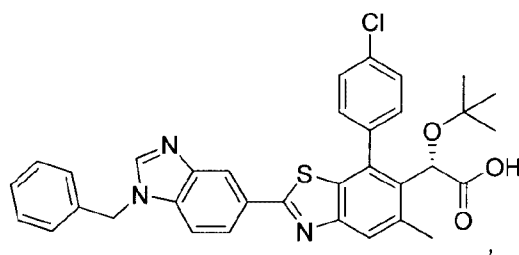
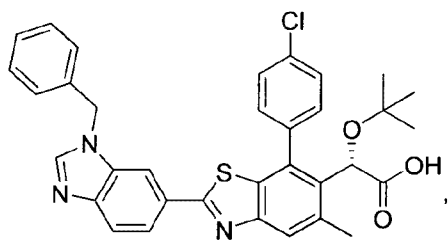


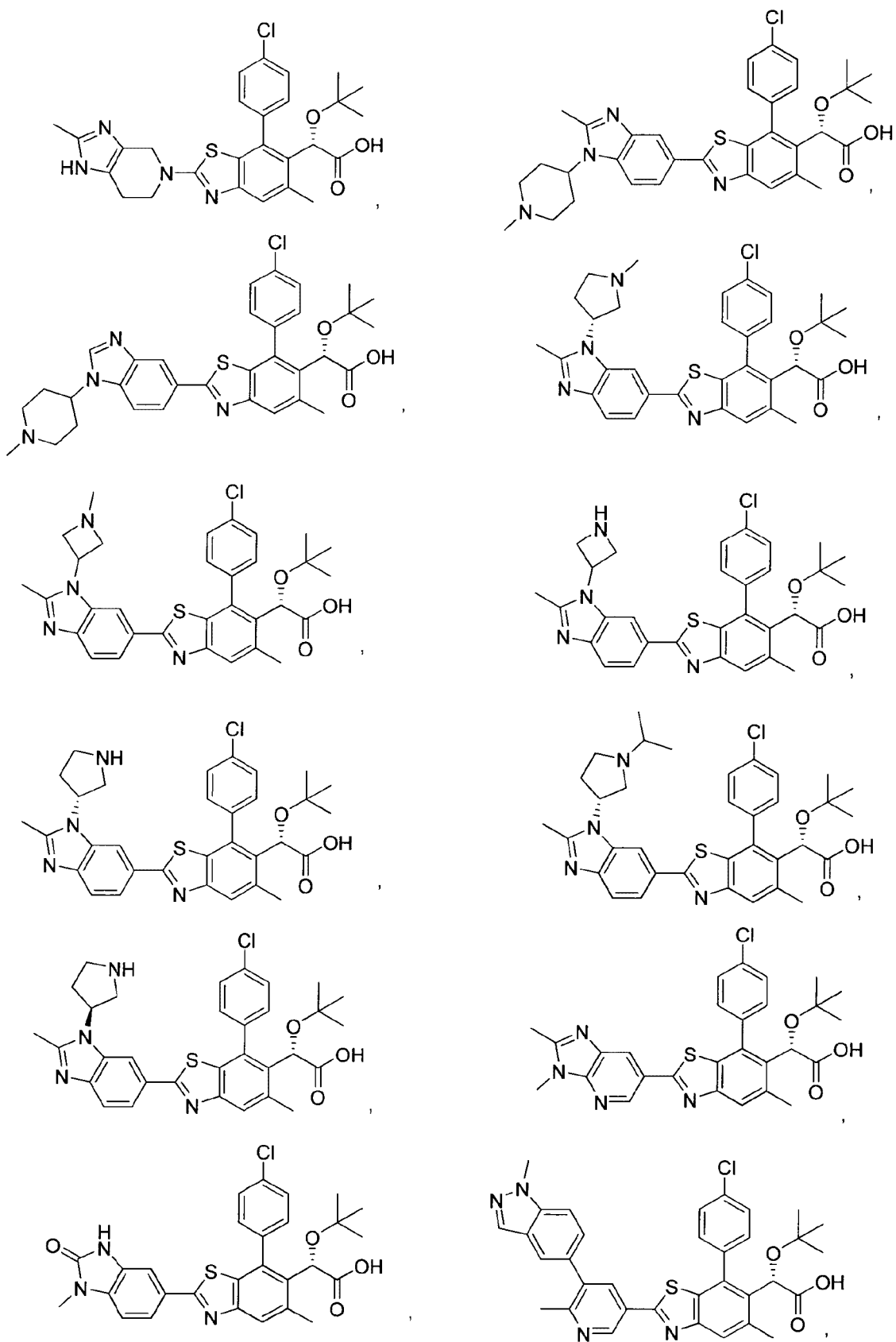


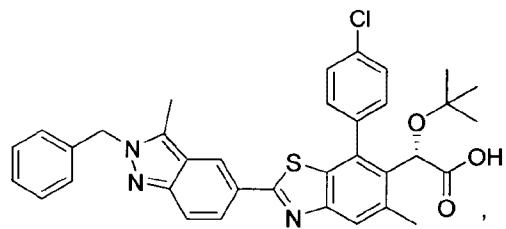
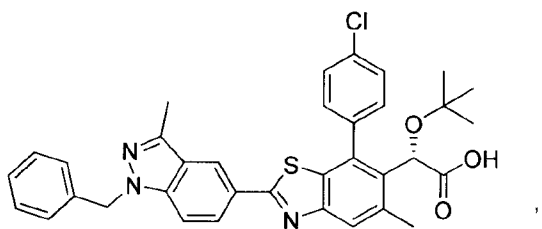
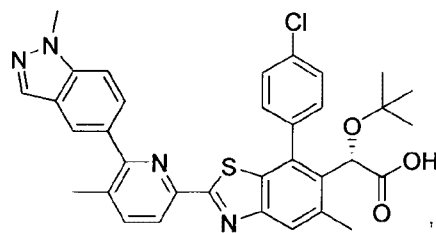
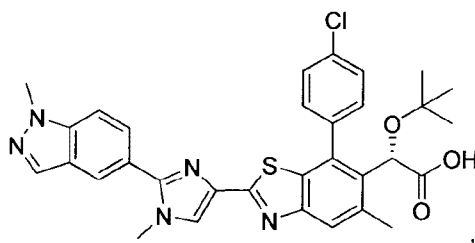
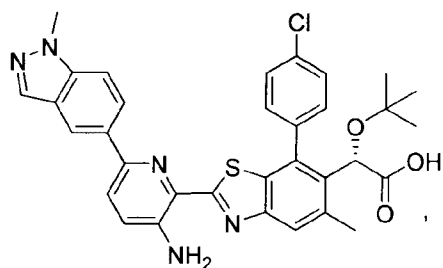
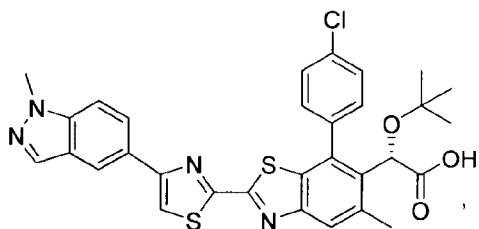
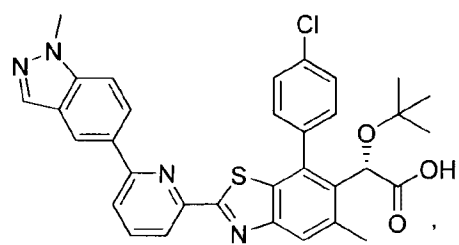
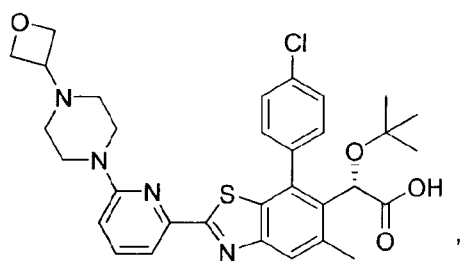
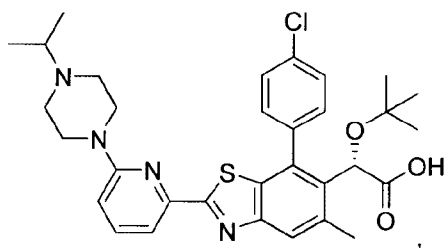
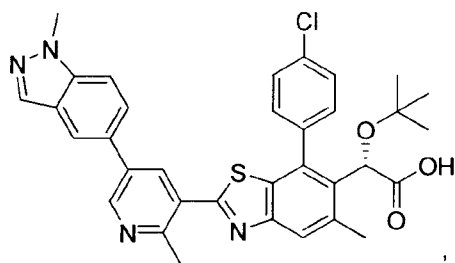


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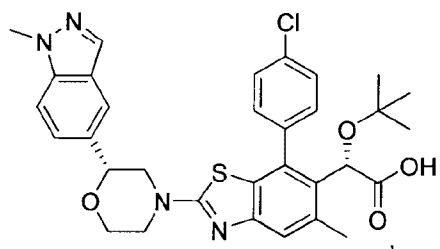
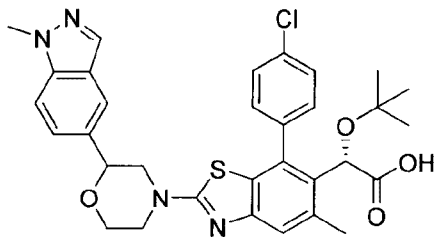
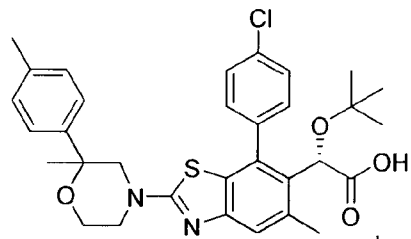
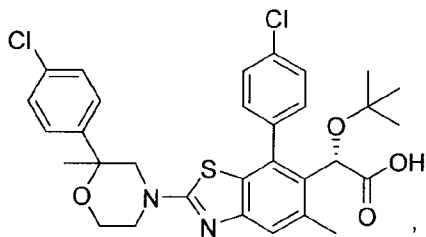
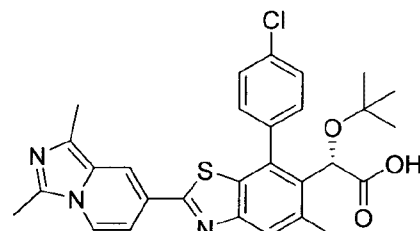
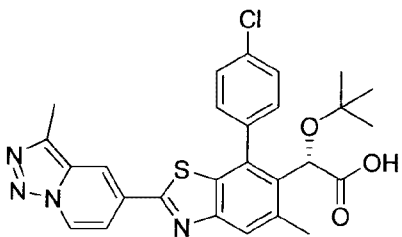
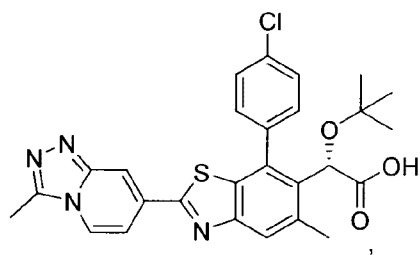
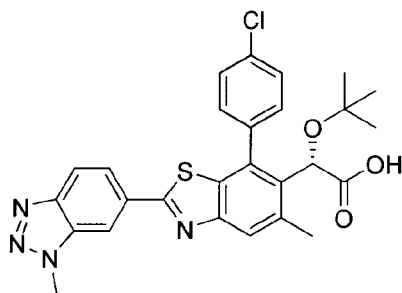






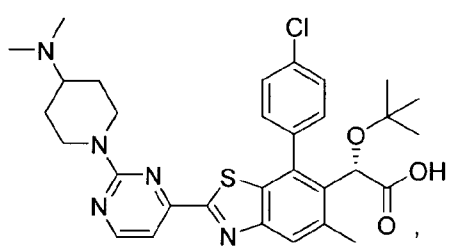
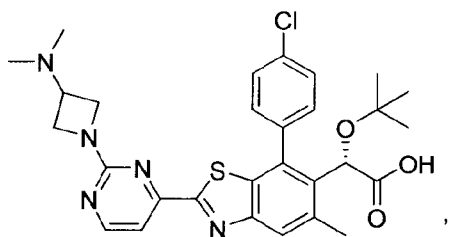
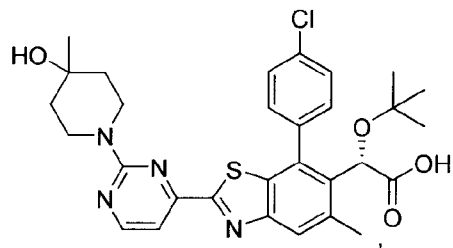
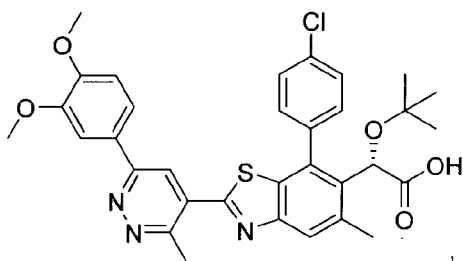
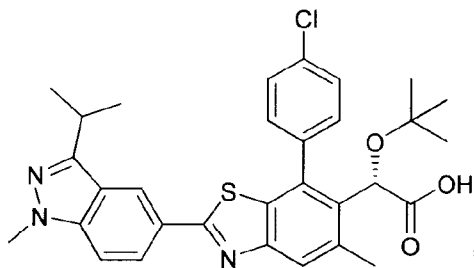
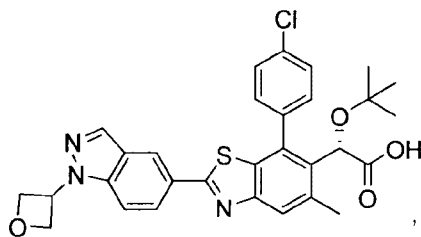
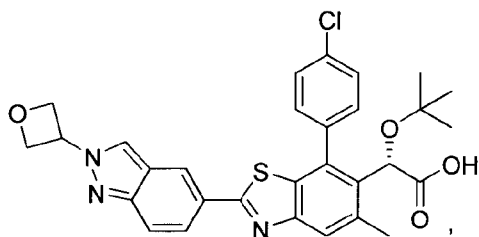
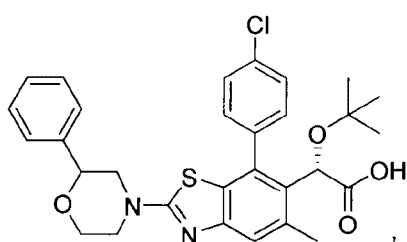
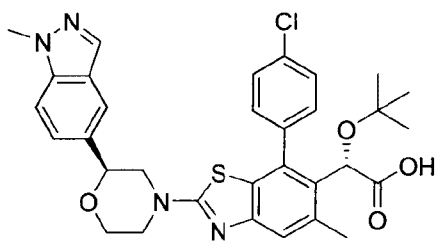
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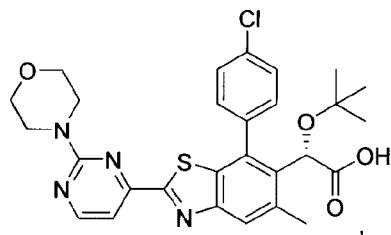
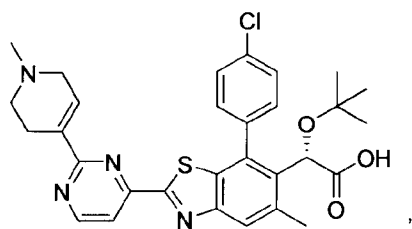
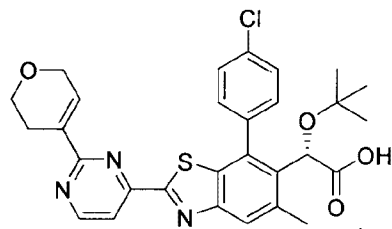
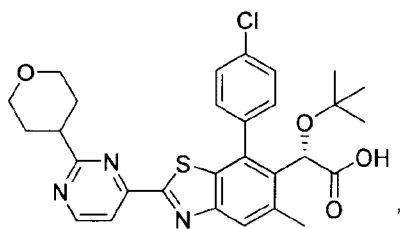
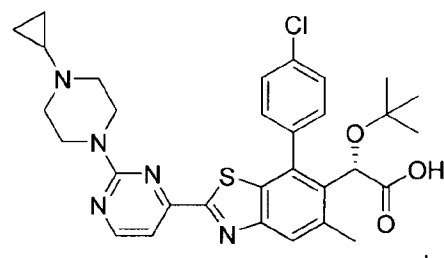
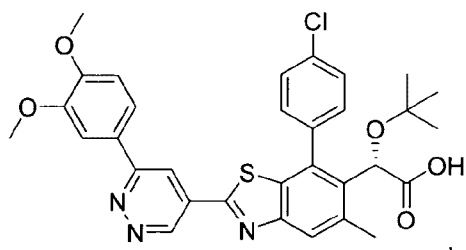
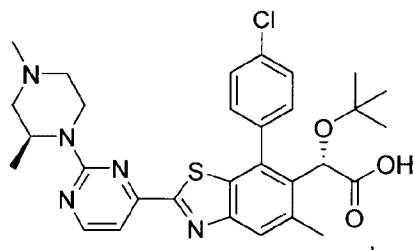
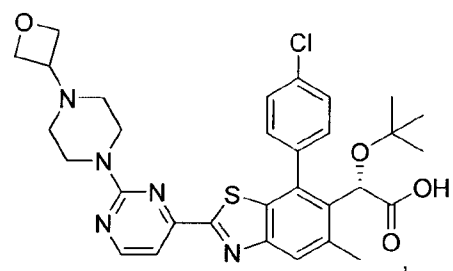
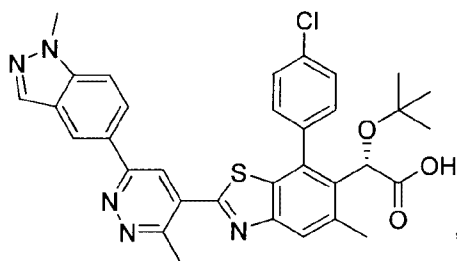
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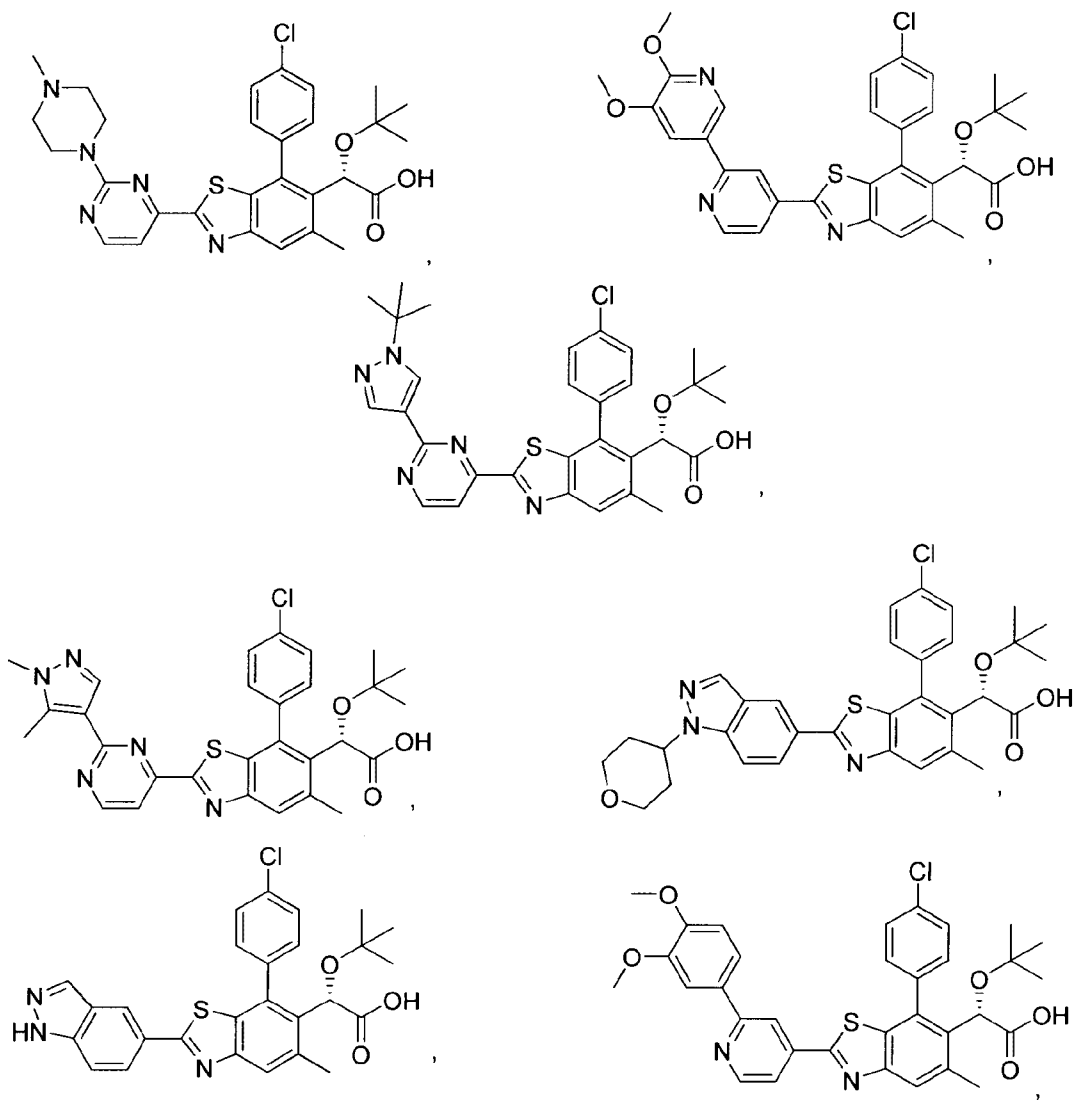
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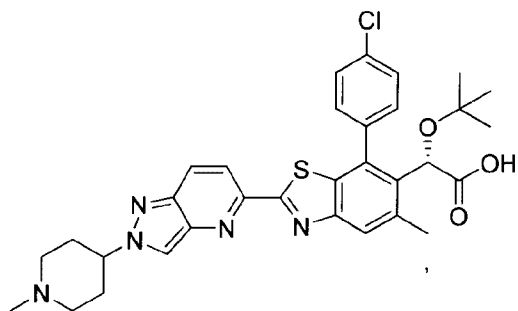
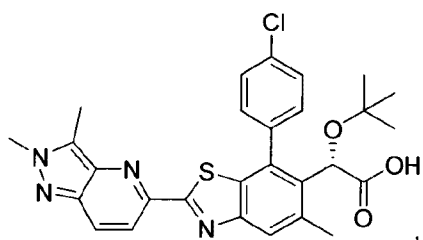
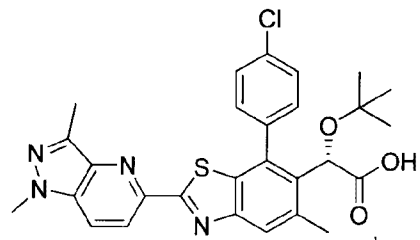
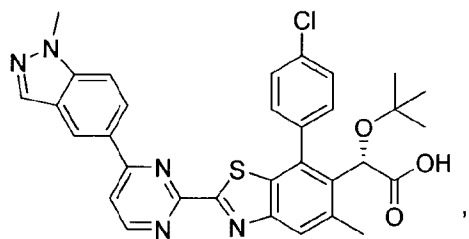
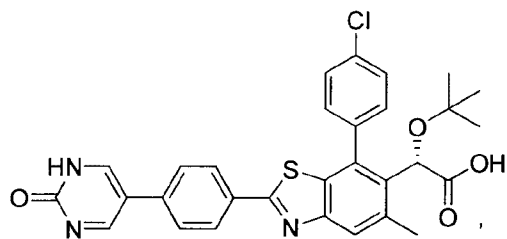
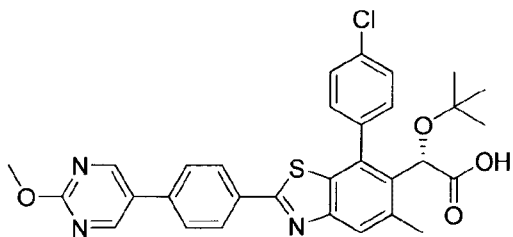
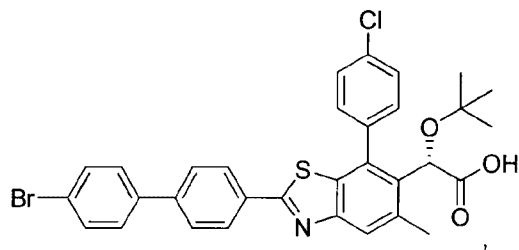
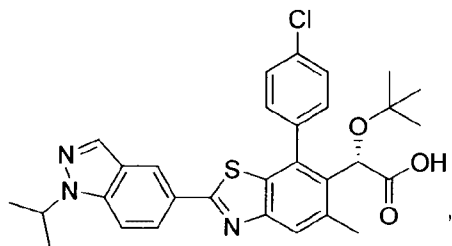
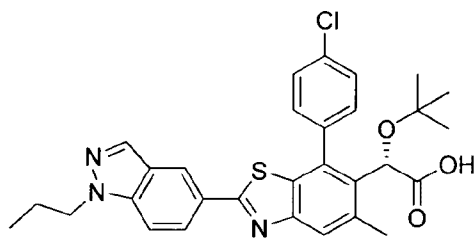
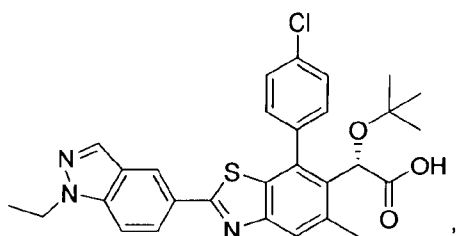


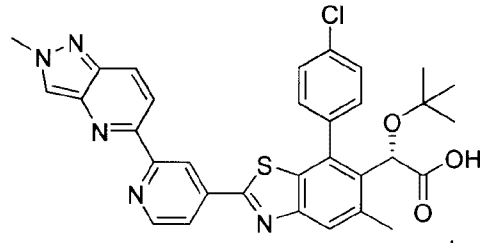
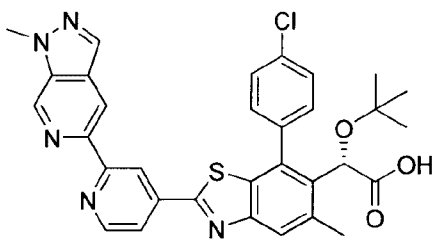
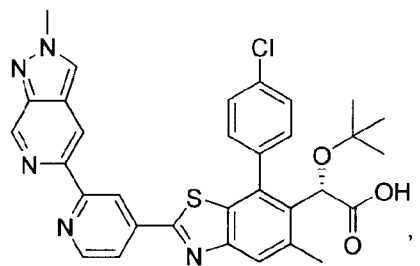
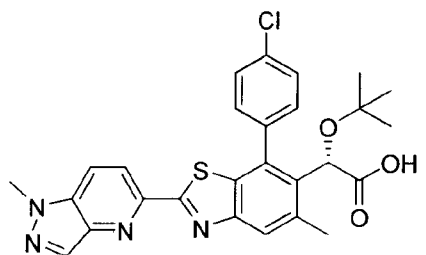
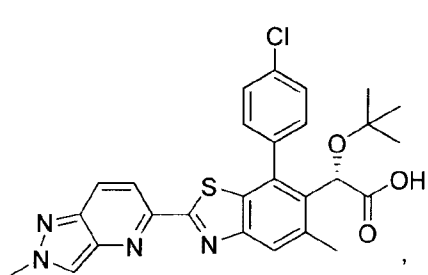
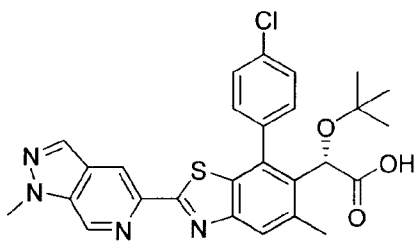
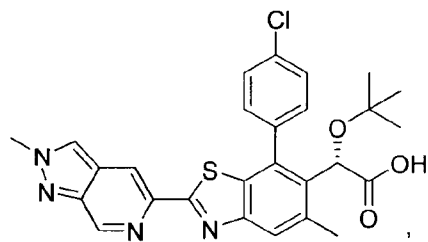
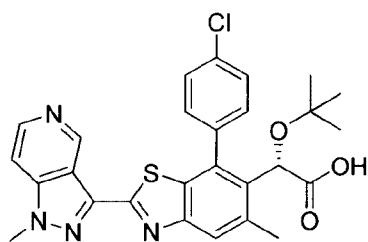
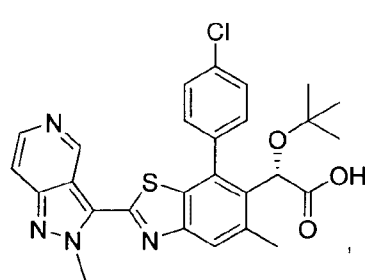
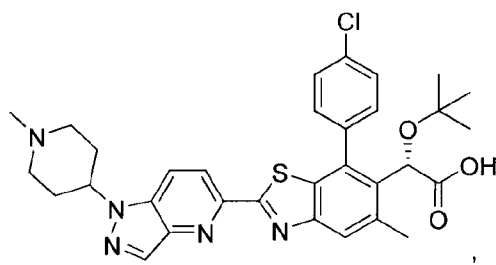
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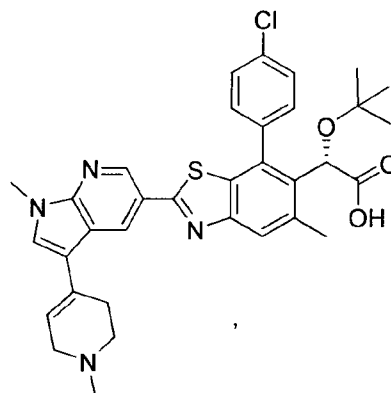
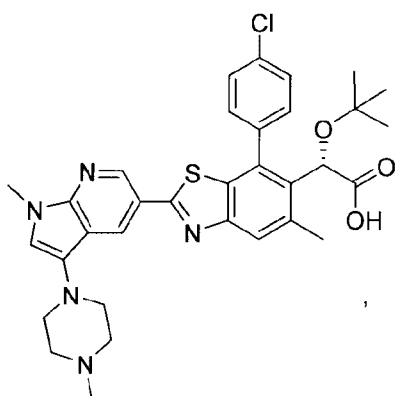
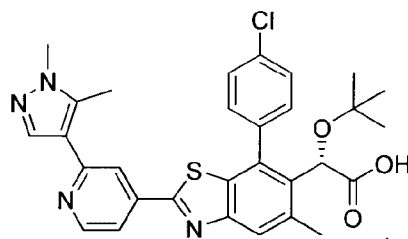
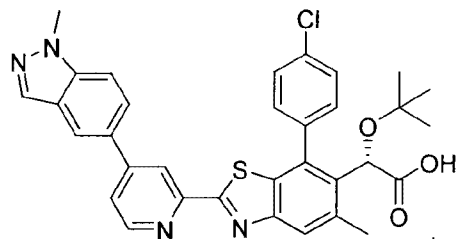
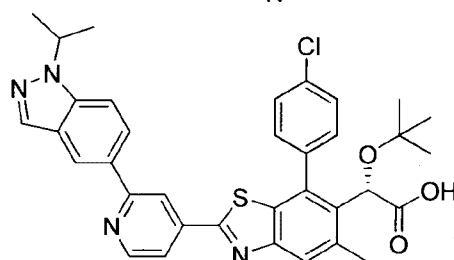
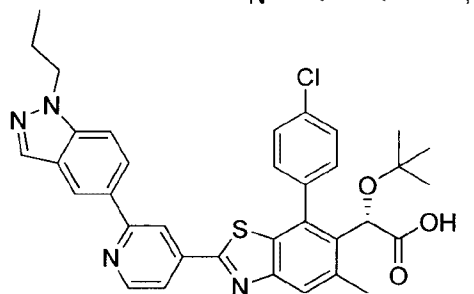
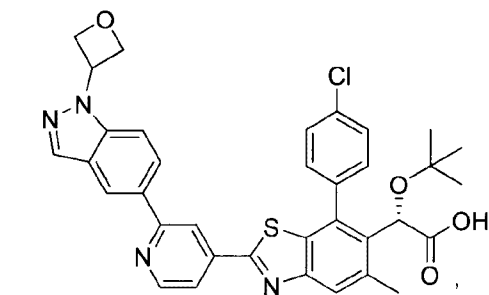
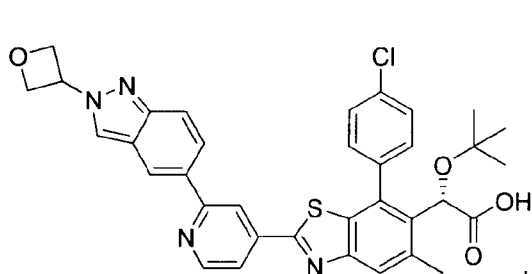
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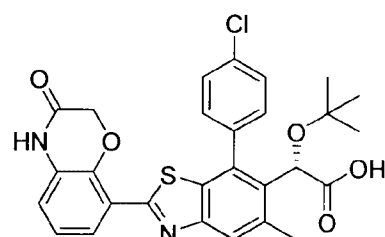
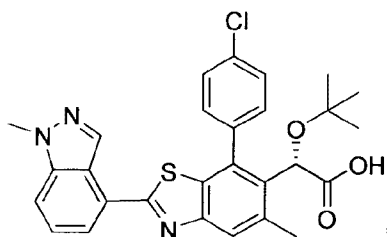
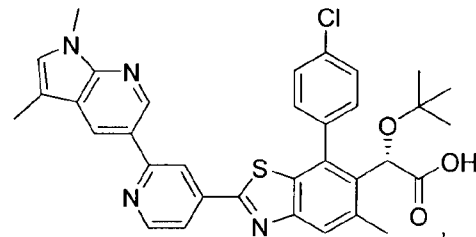
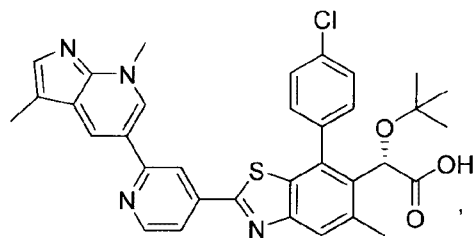
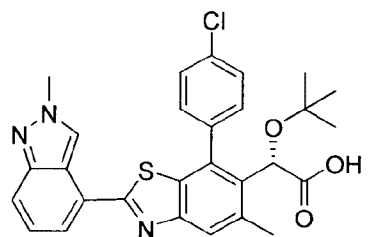
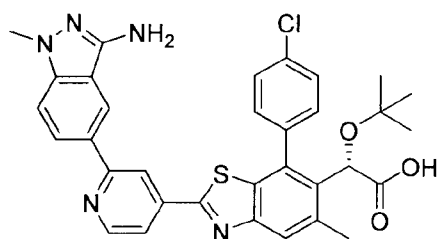
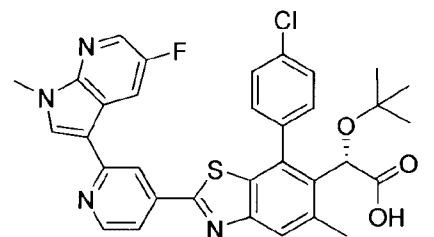
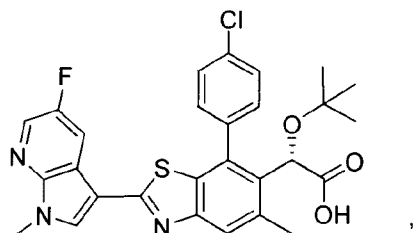
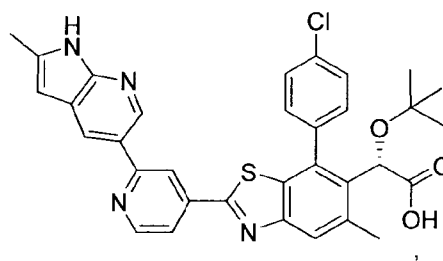
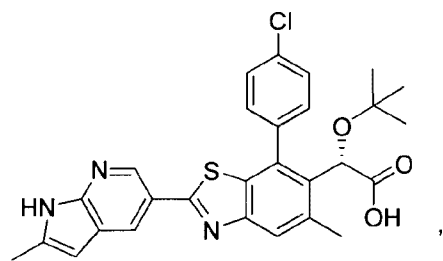






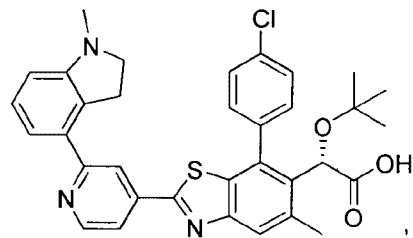
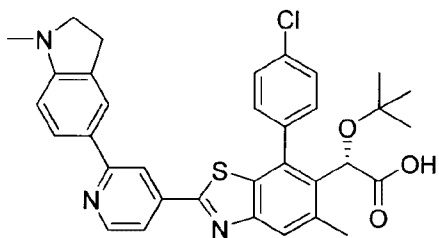
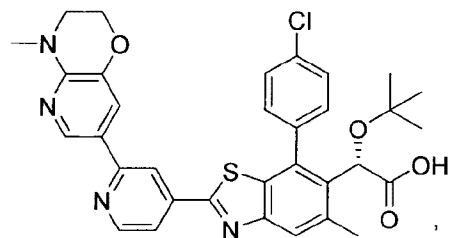
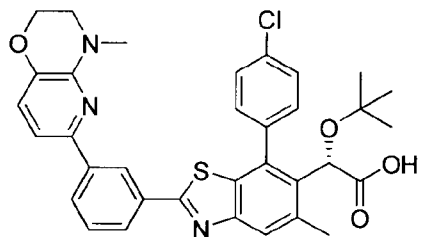
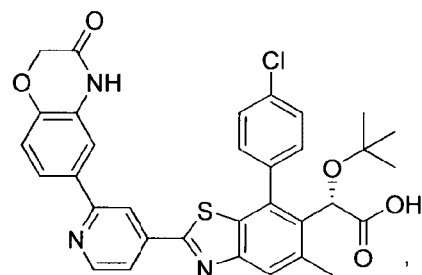
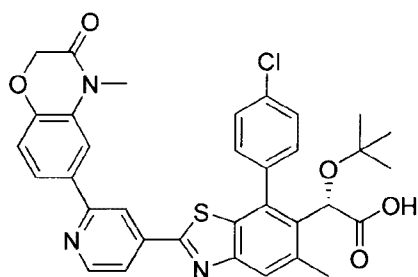
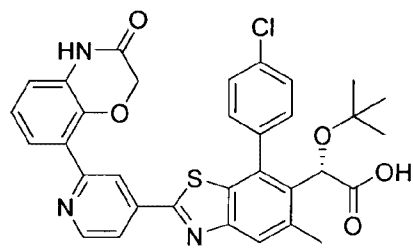
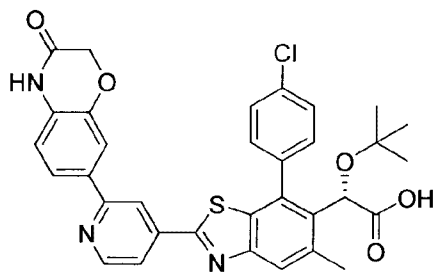
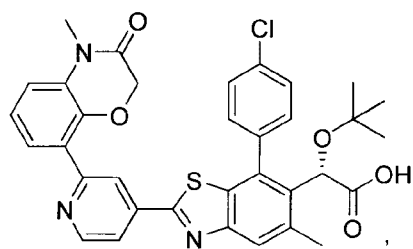
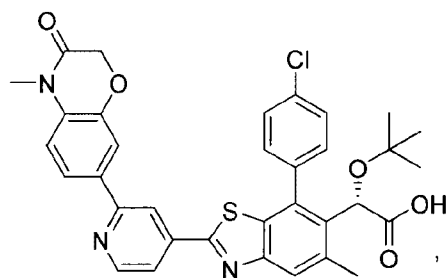






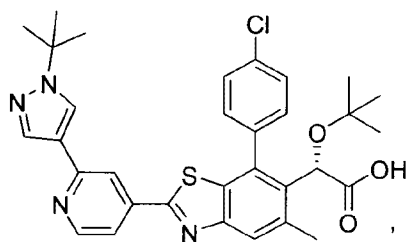
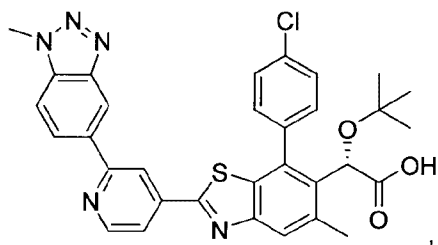
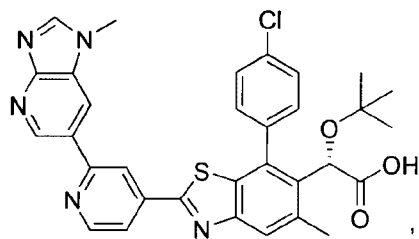
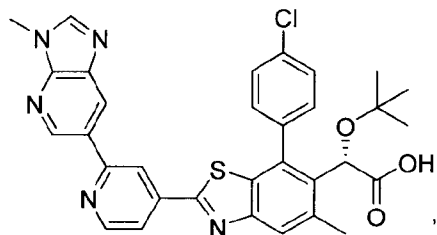
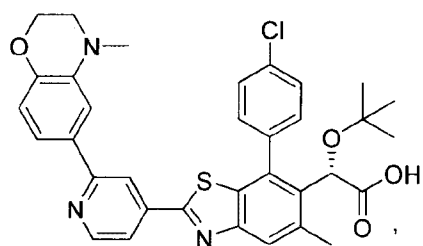
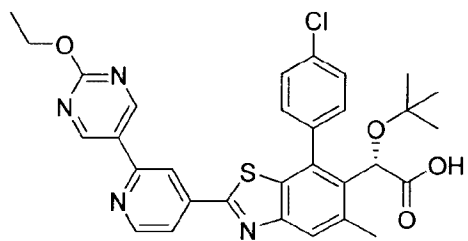
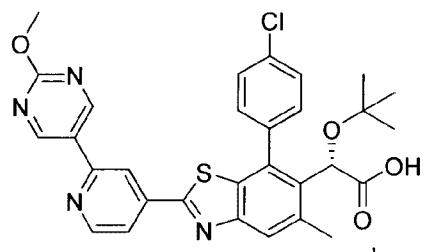
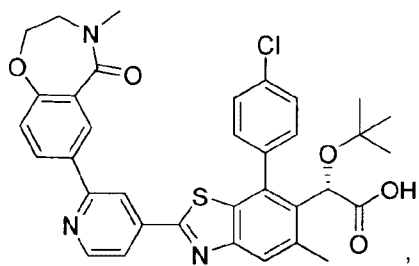
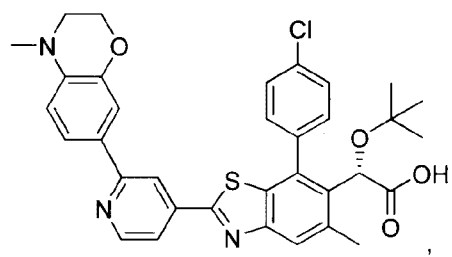
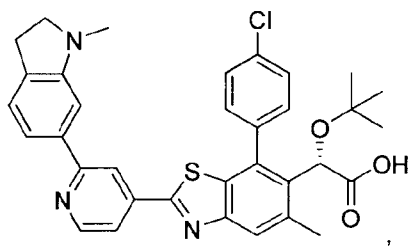
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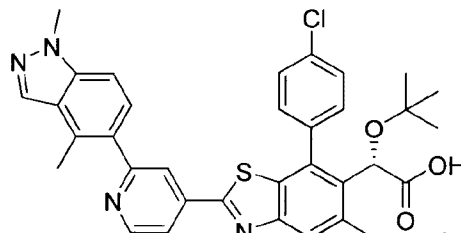
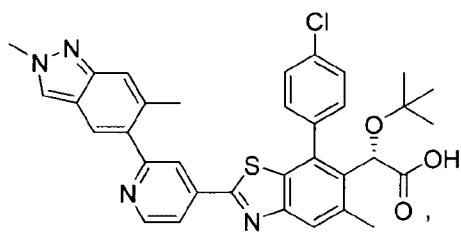
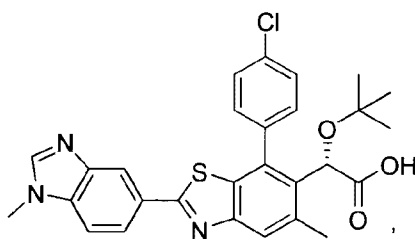
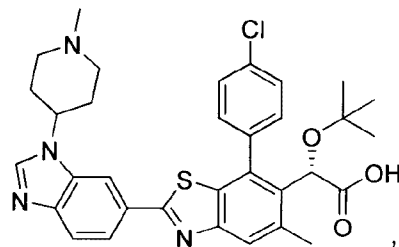
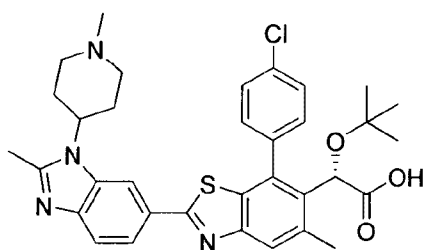
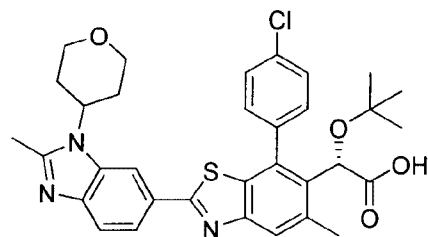
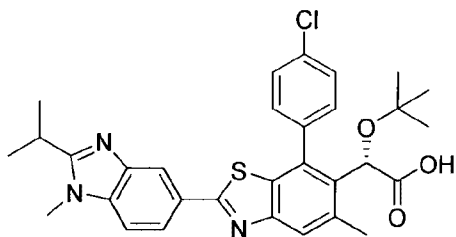
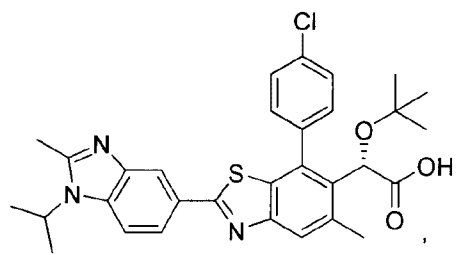
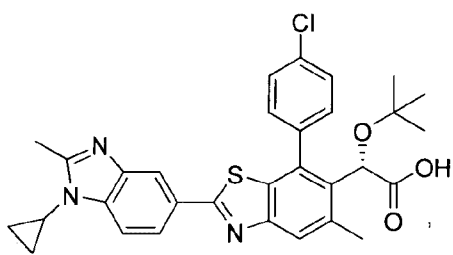
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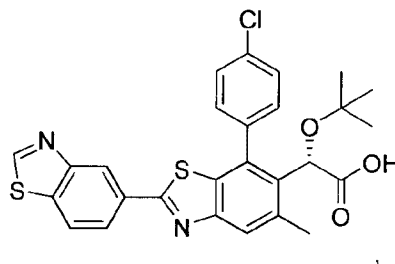
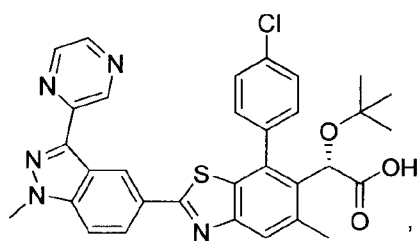
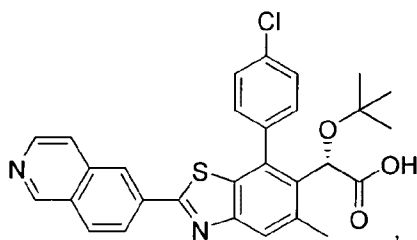
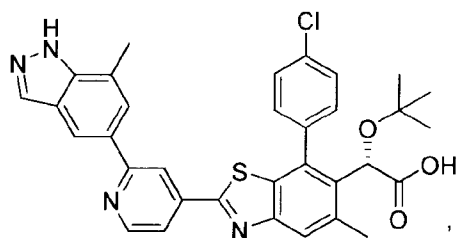
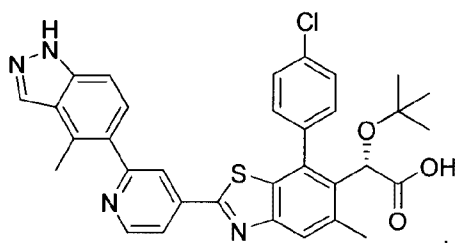
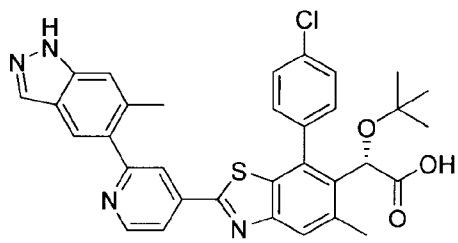
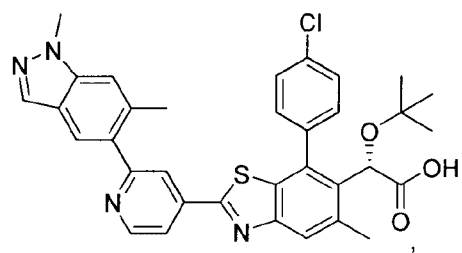
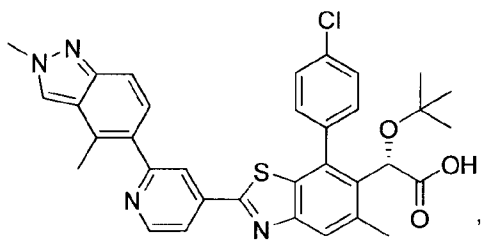
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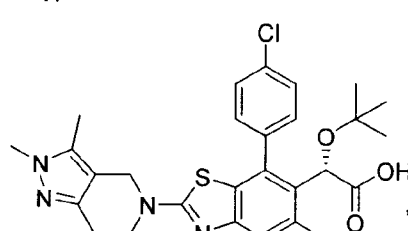
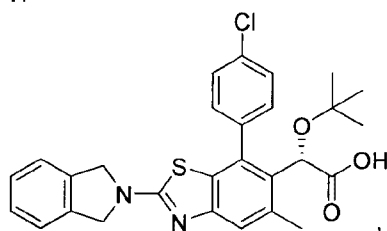
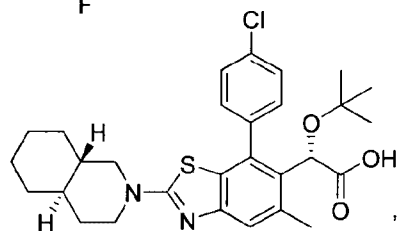
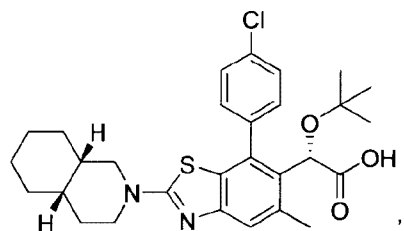
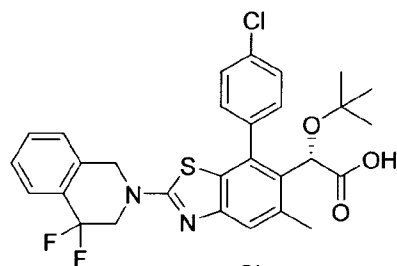
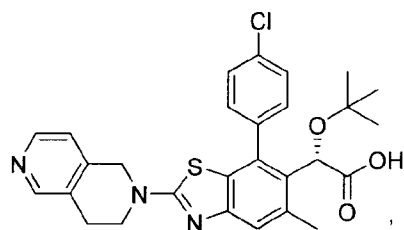
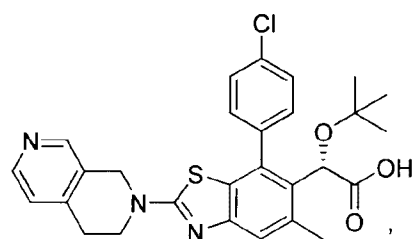
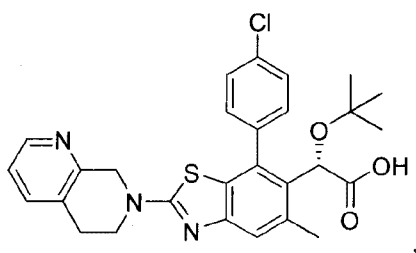
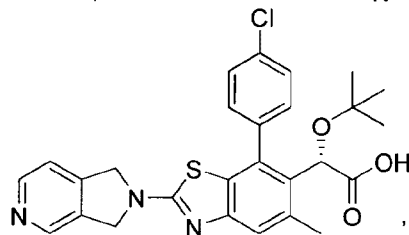
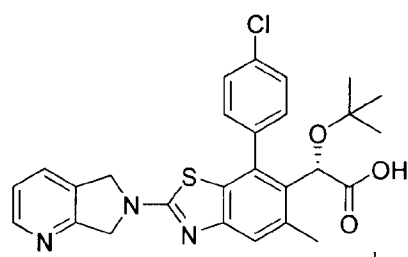
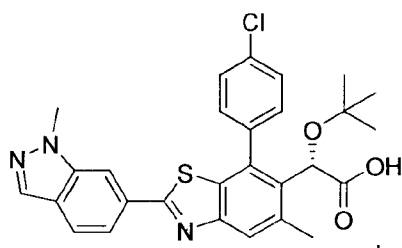


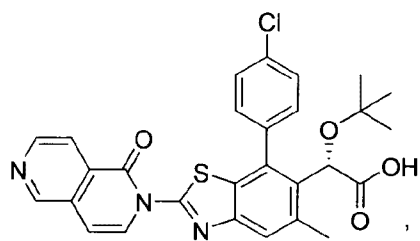
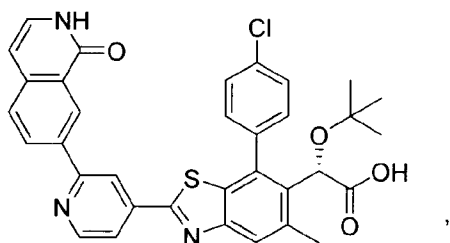
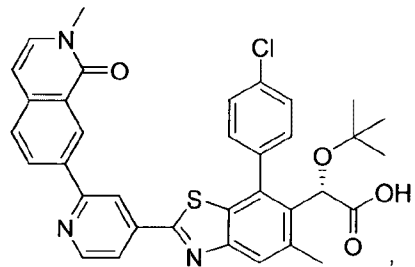
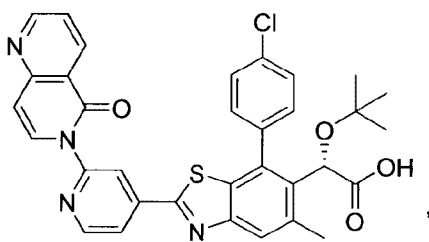
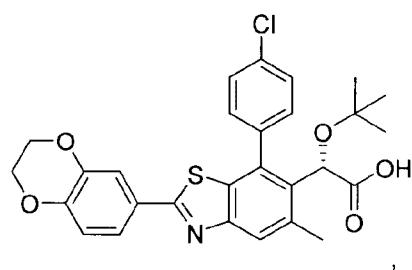
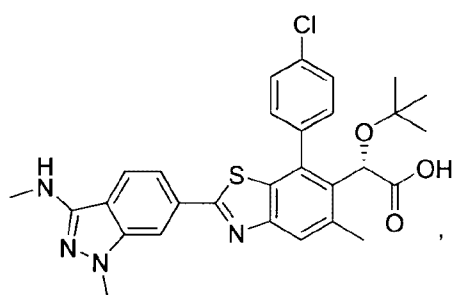
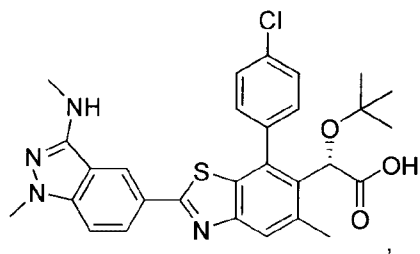
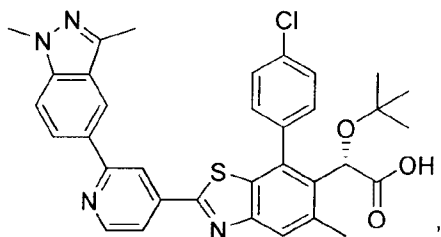
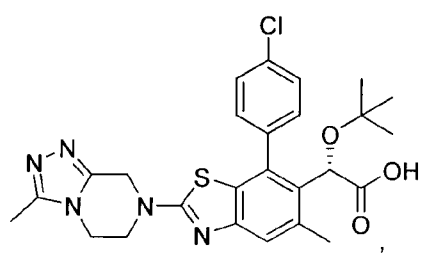
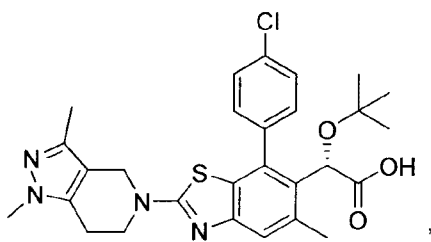


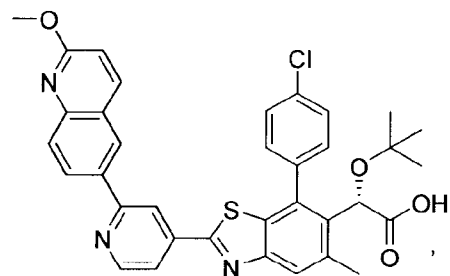
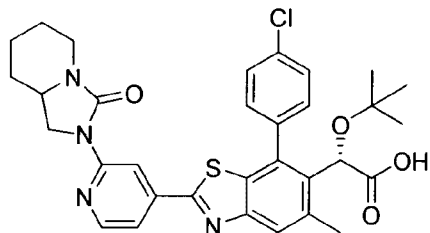
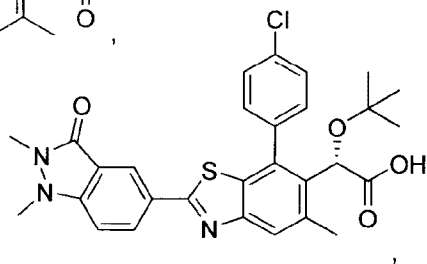
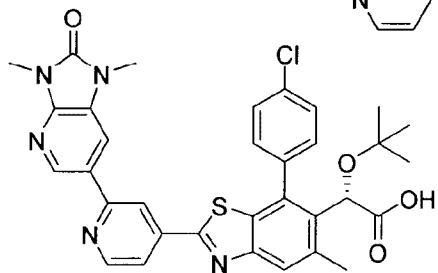
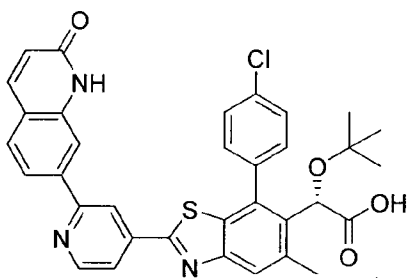
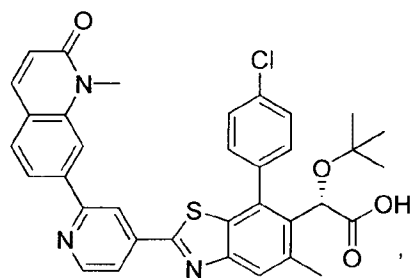
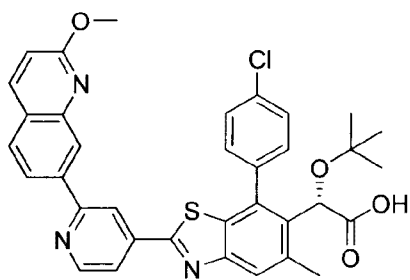
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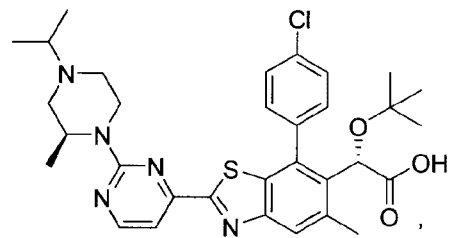
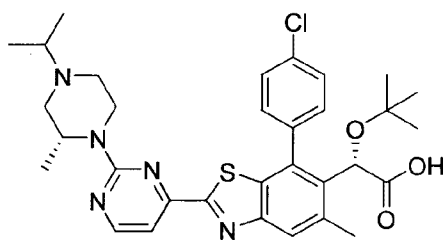
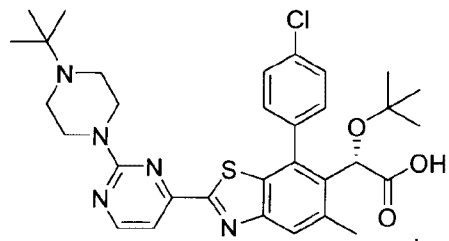
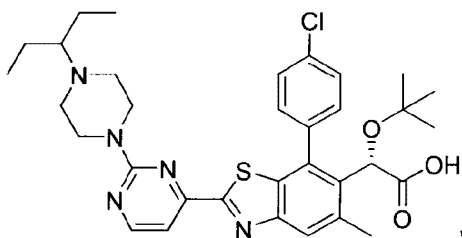
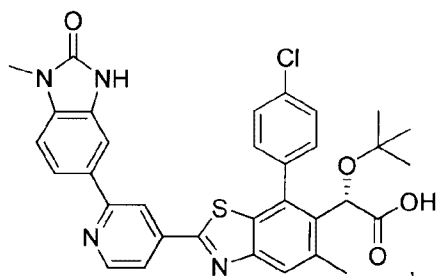
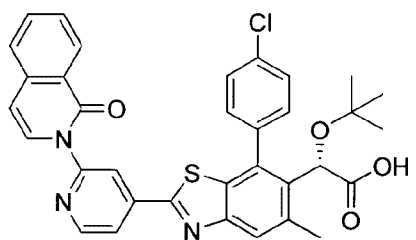
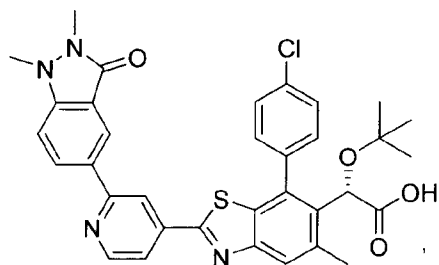
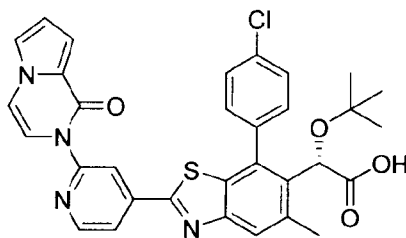
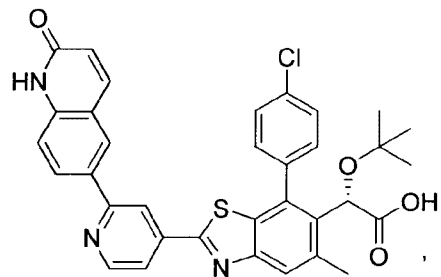
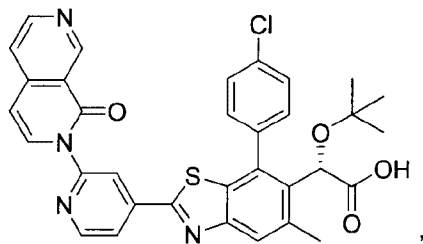
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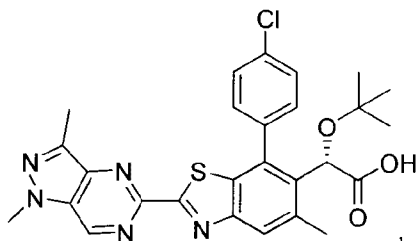
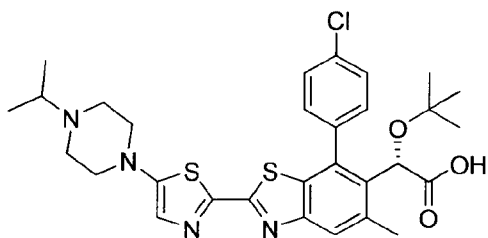
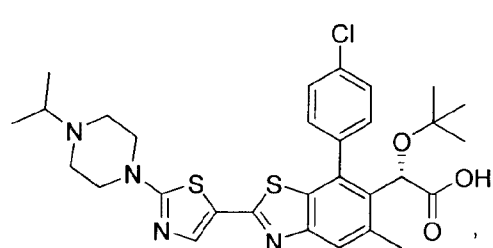
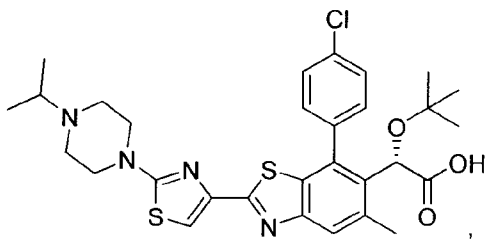
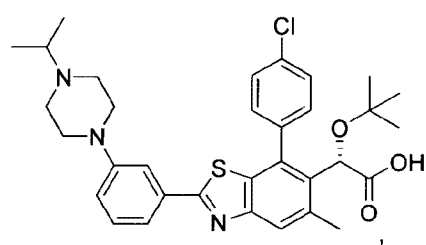
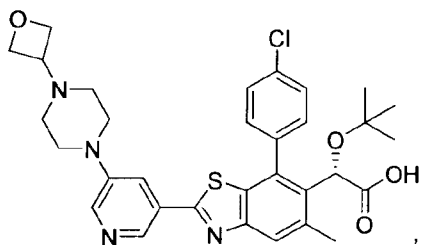
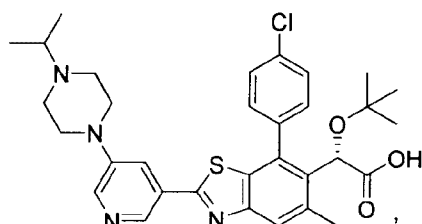
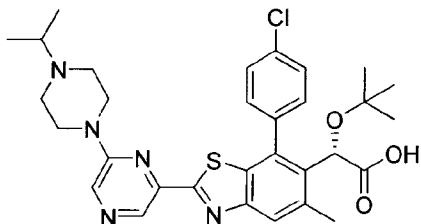
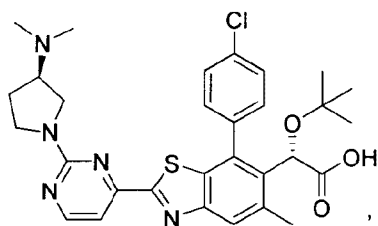
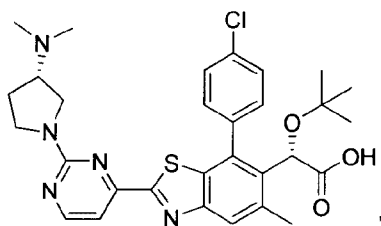


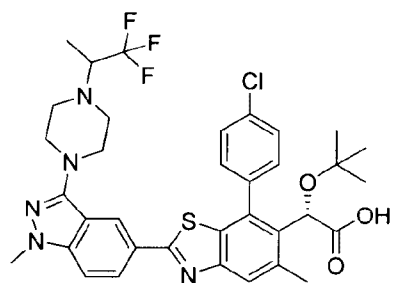
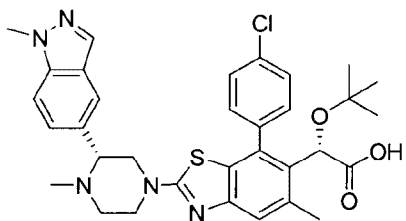
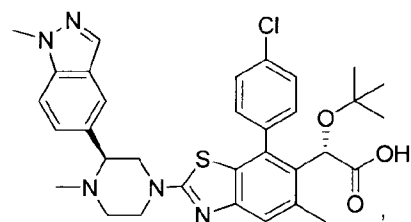
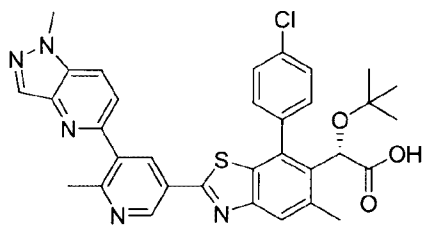
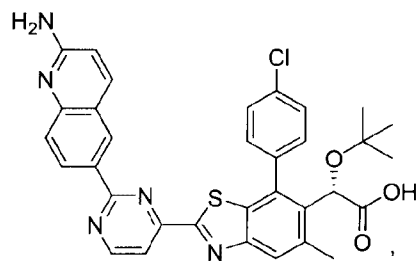
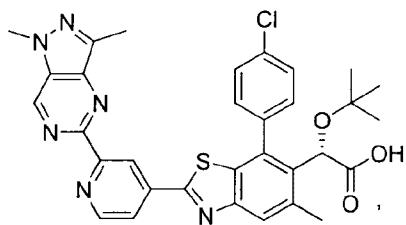




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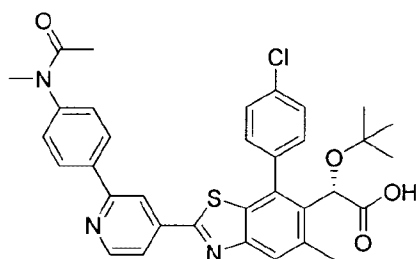
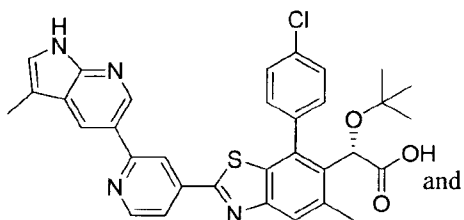
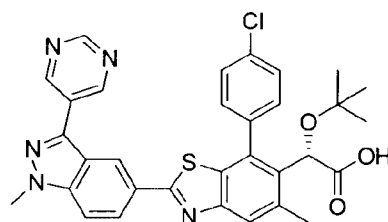
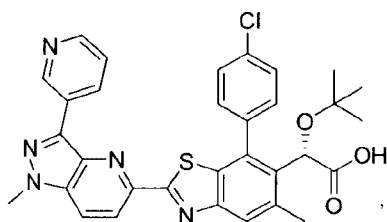
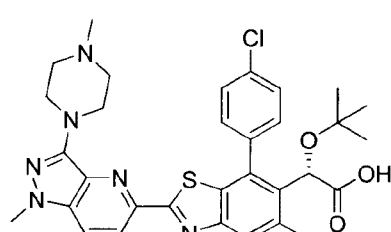
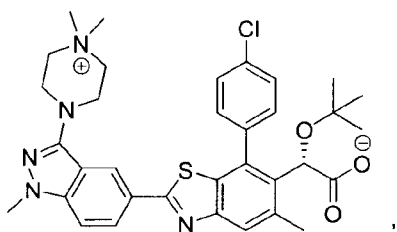
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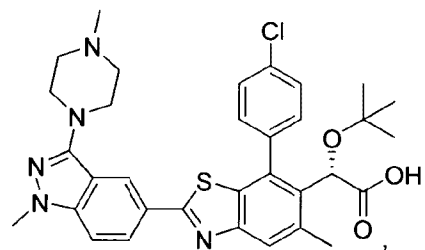
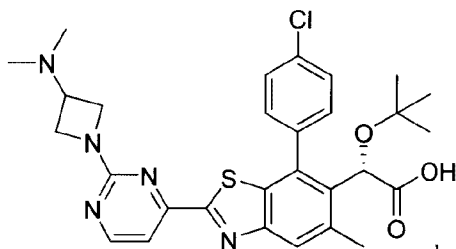
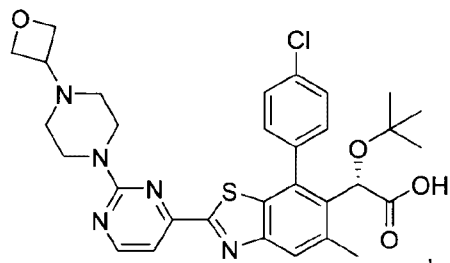
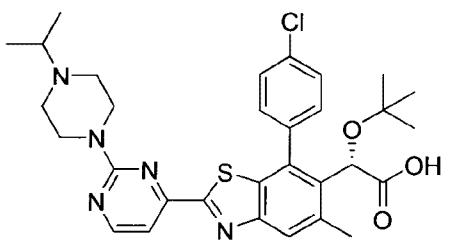
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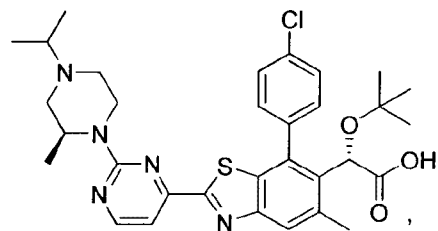
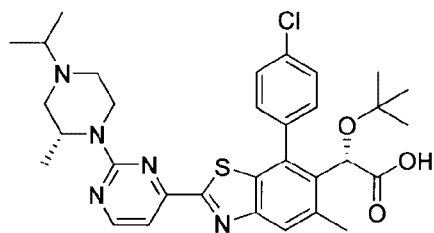
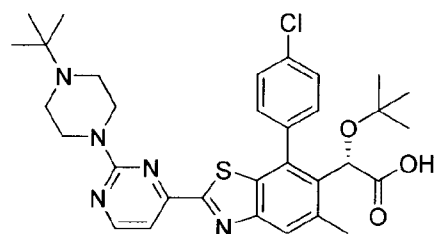
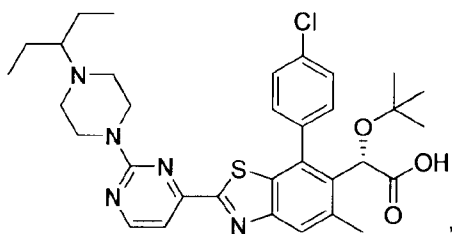
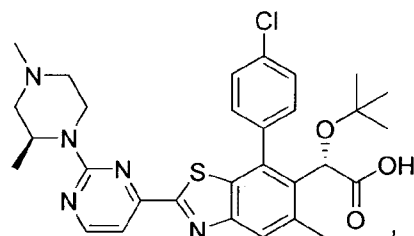
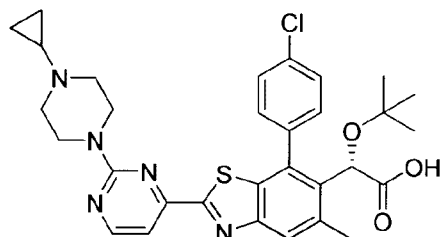
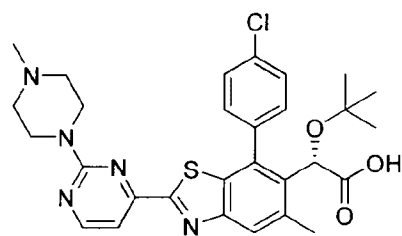
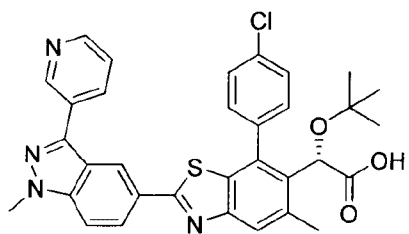


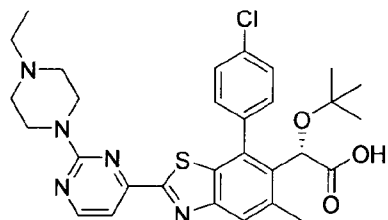
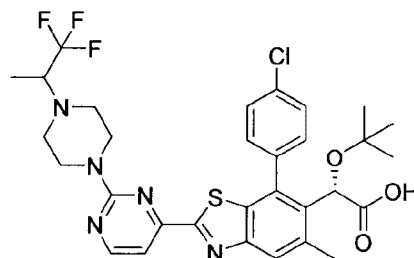
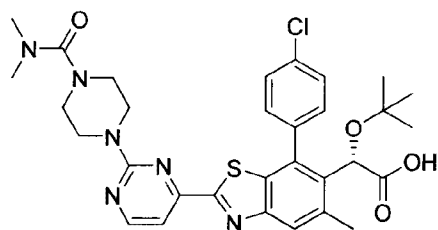
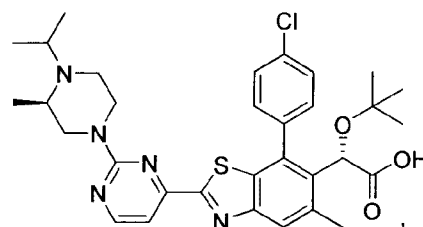
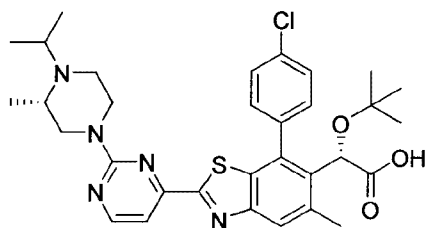
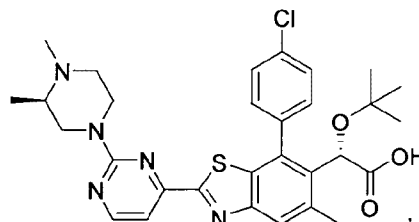
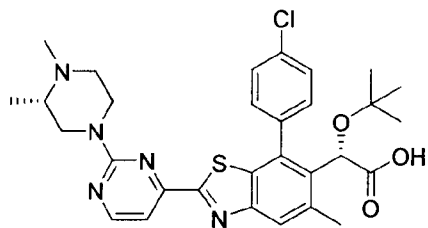
and pharmaceutically acceptable salts thereof.

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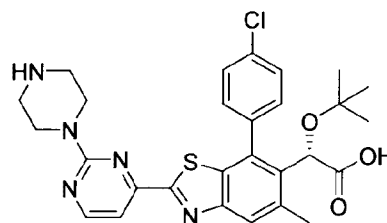
In one embodiment a compound is selected from:







and

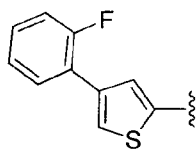


and pharmaceutically acceptable salts thereof.

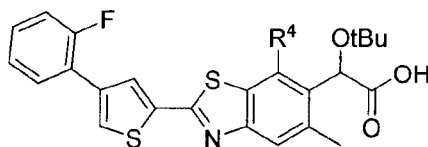
- 5 In one embodiment the compounds of the invention do not include compounds wherein A is thiophene.

In another embodiment the compounds of the invention do not include compounds wherein A is thiophenyl and B is phenyl, wherein phenyl is optionally substituted with one or Z^{1b} groups.

- 10 In another embodiment the compounds of the invention do not include compounds wherein A-B is:

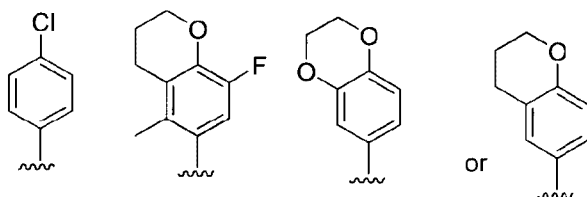


In another embodiment the compounds of the invention do not include the compounds of the following formula:



5

wherein R^4 is:



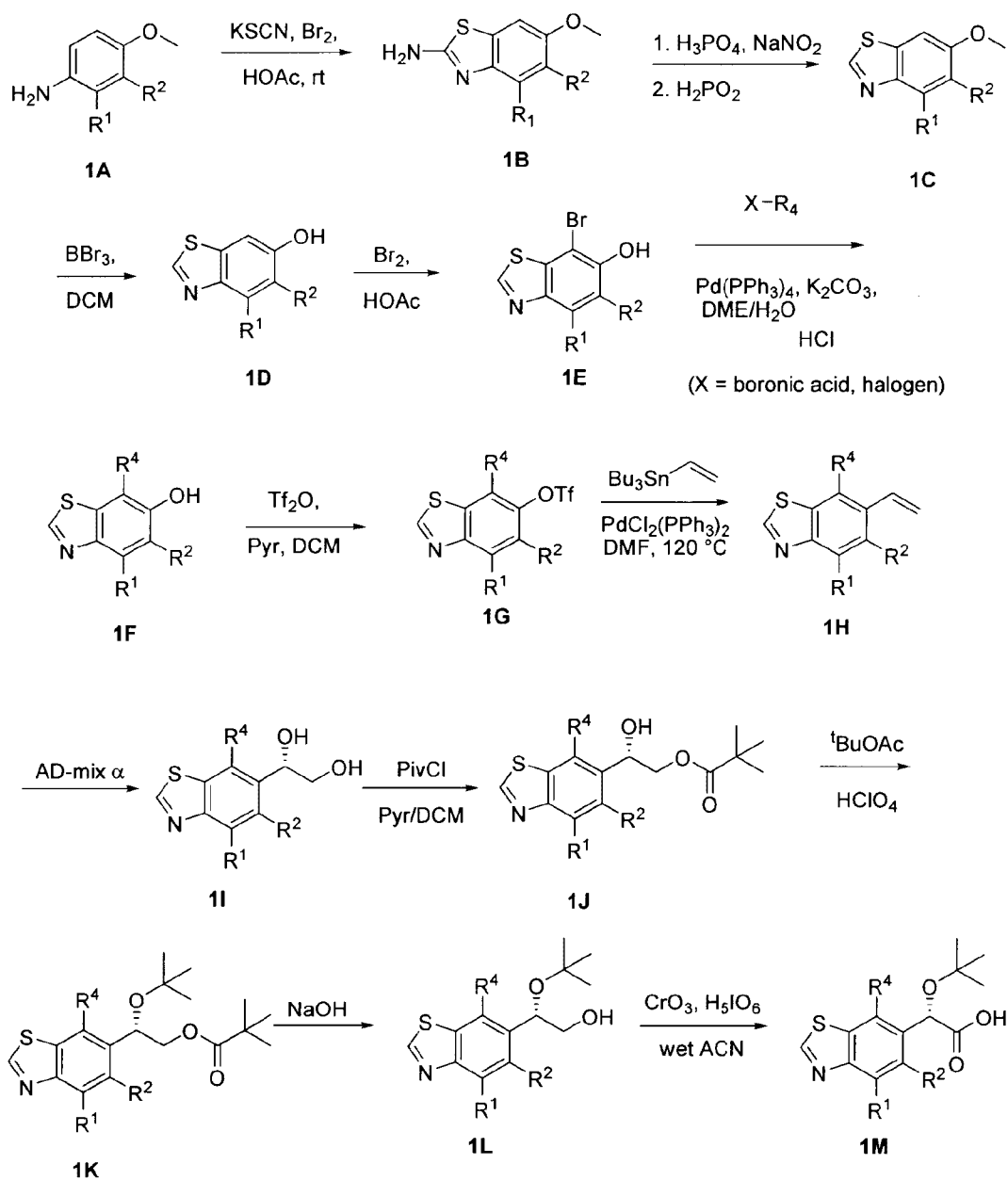
or salts thereof.

General Synthetic Procedures

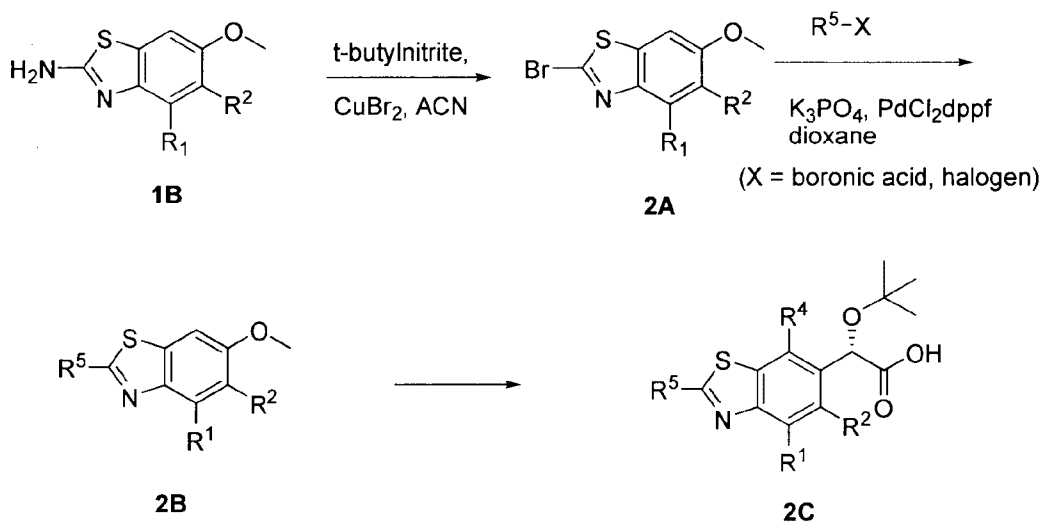
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Schemes 1-17 are provided as further embodiments of the invention and illustrate general methods which were used to prepare compounds of the invention and which can be used to prepare additional compounds of the invention.

Scheme 1



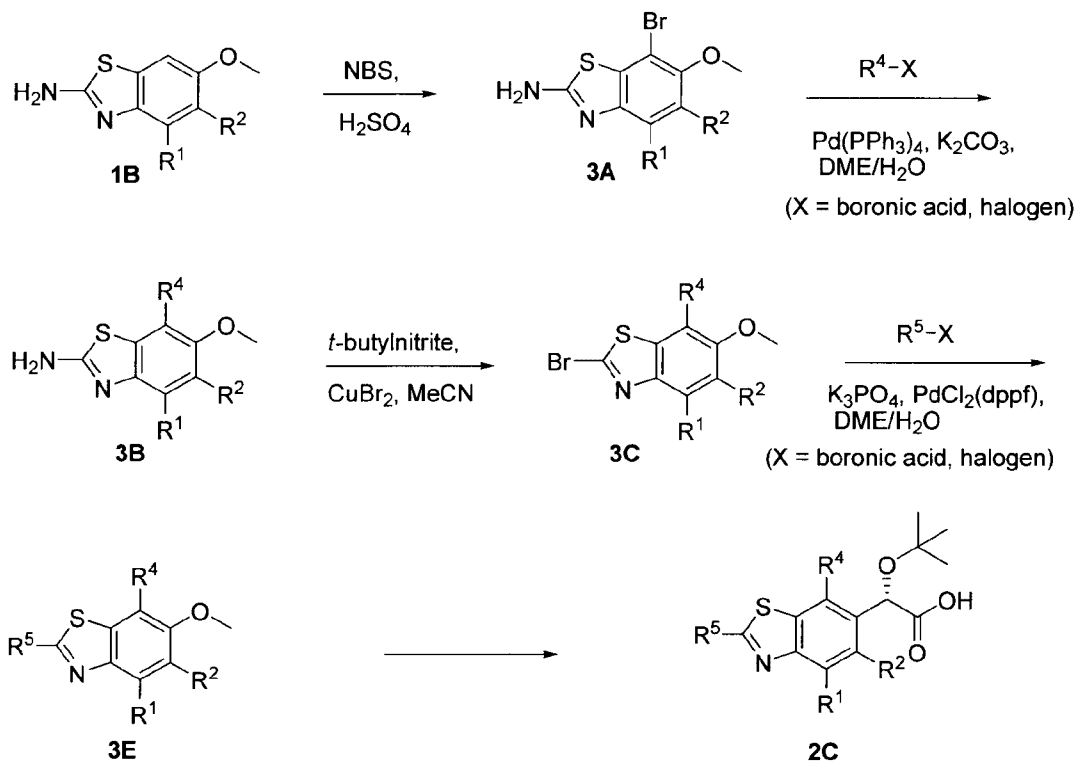
Scheme 2



In certain embodiments, the benzothiazole intermediate **2B** is converted to the final compound **2C** by the methods used to convert **1C** to **1M** as outlined in Scheme 1.

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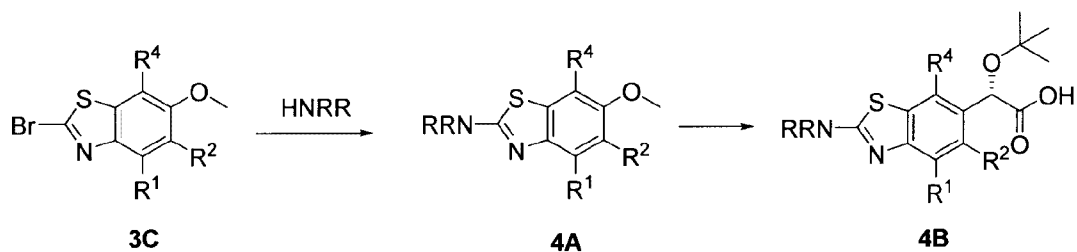
Scheme 3



In certain embodiments, the benzothiazole intermediate **3E** is converted to the final compound **2C** by the methods used to convert **1C** to **1D** and **1F** to **1M** as outlined in Scheme 1.

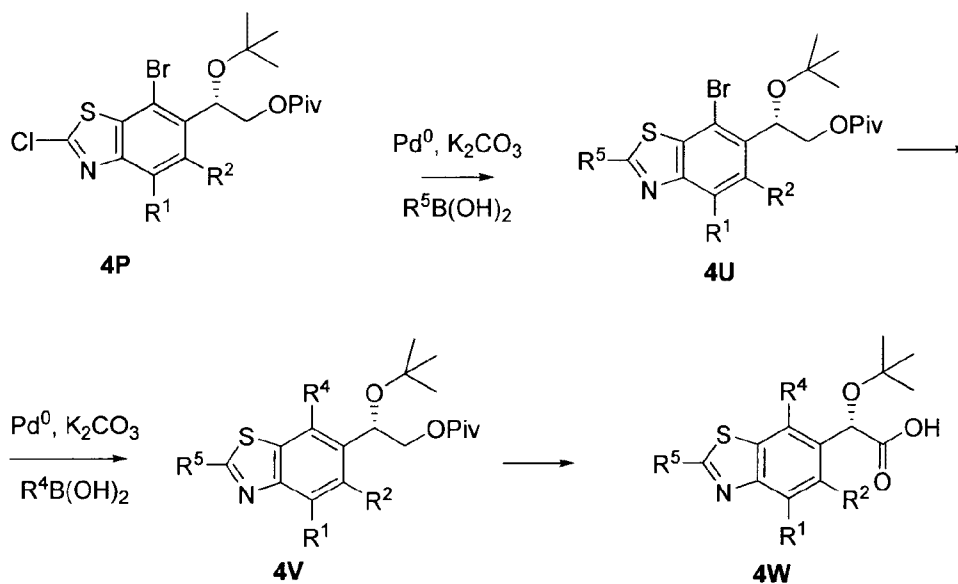
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Scheme 4



- 5 In certain embodiments the benzothiazole intermediate **4A** is converted to the final compound **4B** by the methods used to convert **1C** to **1D** and **1F** to **1M** as outlined in Scheme 1 wherein HNRR a heterocycle (*i.e.*, when R and R taken together with the nitrogen to which they are attached form a ring).

Scheme 5

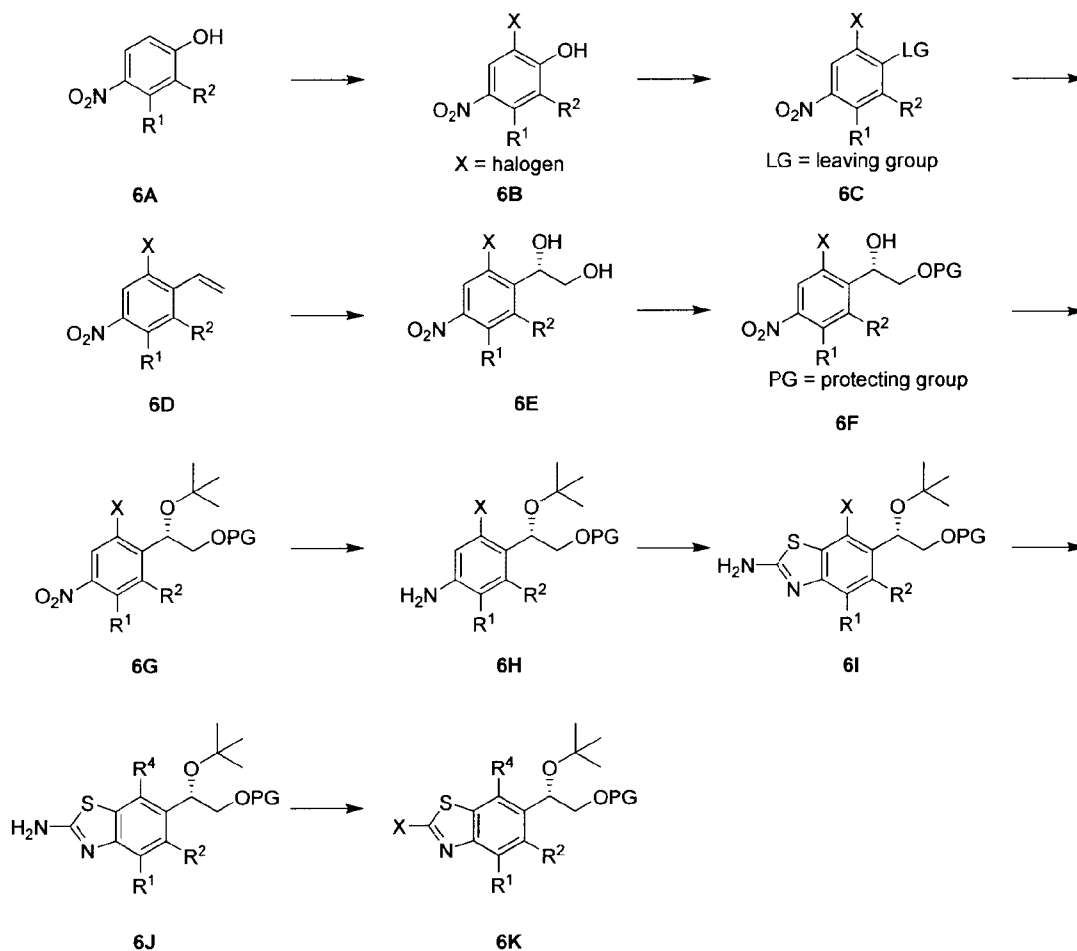


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- In certain embodiments the benzothiazoline intermediate **4V** is converted to the final compound **4W** by the methods used to convert **1C** to **1M** as outlined in Scheme 1.

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Scheme 6

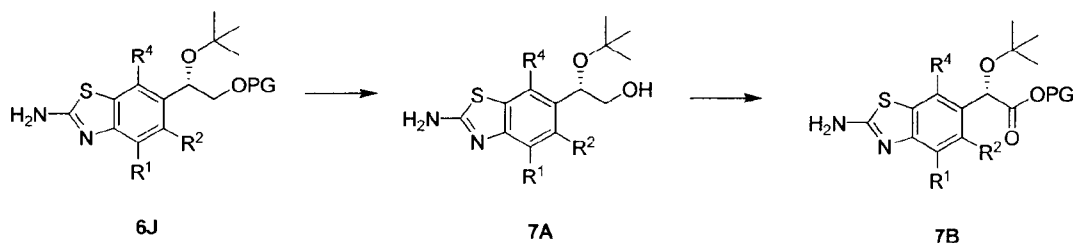


In certain embodiments, an appropriately substituted phenol **6A** is halogenated by the treatment of dihalide, for example bromine, in a suitable solvent such as, for example acetic acid. The phenol **6B** is converted to a leaving group (e.g., triflate) known to undergo cross-coupling reactions. The corresponding activated phenol **6C** undergoes a selective cross-coupling reaction such as, for example Stille cross-coupling using a tin reagent such as tributyl(vinyl)tin and a palladium catalyst such as bis(triphenylphosphine) palladium(II) dichloride to give the corresponding cross-coupled naphthalene such as styrene **6D**. The styrene is dihydroxylated to provide **6E** by methods known to those skilled in the art such as, Sharpless asymmetric dihydroxylation using, for example, commercially available AD mix- α . The resulting diol **6E** is protected at the primary hydroxyl by suitable protecting groups such as pivalate ester using pivaloyl chloride and pyridine to provide **6F**. The secondary hydroxyl is converted to the corresponding ether such as tert-butyl ether using methods known to those skilled in the art such as, tert-butyl acetate and perchloric acid to provide **6G**.

The nitro group of **6G** is reduced to the corresponding aniline **6H** by catalytic hydrogenation using platinum on carbon, for example, under a hydrogen atmosphere.

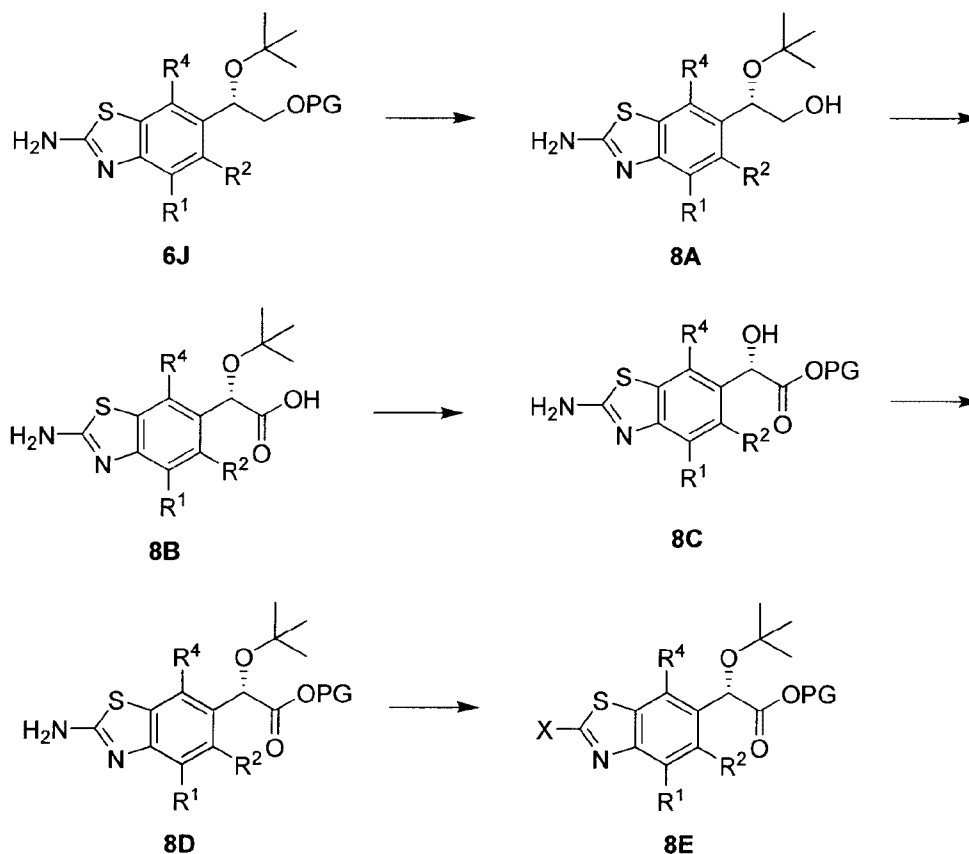
Benzothiazole **6I** is formed by methods known to those skilled in the art such as potassium thiocyanate and pyridinium perbromide, for example. The resulting benzothiazole undergoes cross-coupling reaction such as Suzuki cross-coupling using a boronic acid or ester and a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) to give the corresponding cross-coupled benzothiazole **6J**. The corresponding halobenzothiazole **6K** is formed by methods known to those skilled in the art such as *tert*-butyl nitrite and a copper(II) halide such as copper(II) bromide, for example.

Scheme 7



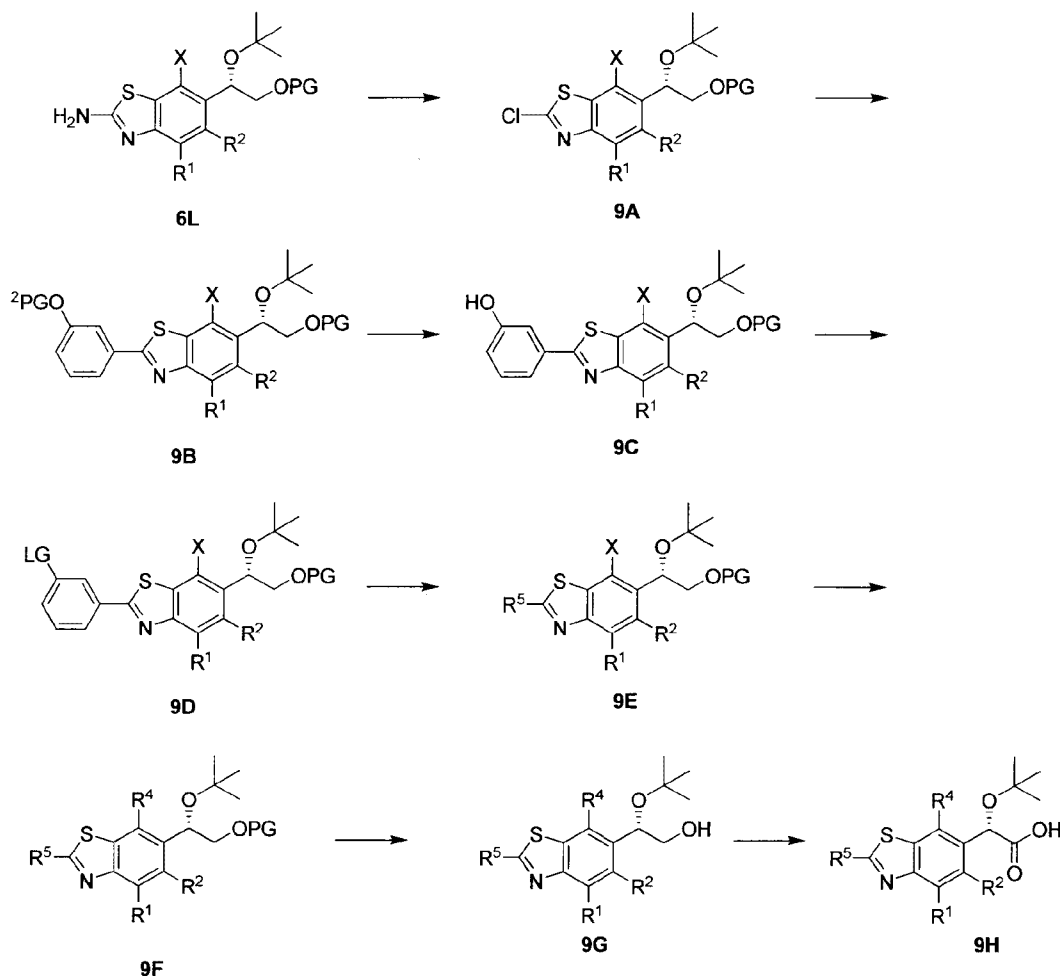
In certain embodiments the protected primary hydroxyl **6J** is deprotected by methods known to those skilled in the art such as the deprotection of a pivalate protecting group under basic conditions for example, using sodium hydroxide, to give the corresponding primary hydroxyl compound **7A**. The primary hydroxyl is oxidized to the corresponding carboxylic acid **7B** by methods known to those skilled in the art such as, for example, periodic acid and chromium trioxide. The resulting carboxylic acid is protected by formation of corresponding carboxylic ester **7B** with treatment of, for example, trimethylsilyldiazomethane, to form the corresponding methyl ester.

Scheme 8



In certain embodiments the protected primary hydroxyl **6J** is deprotected by methods known to those skilled in the art such as the deprotection of a pivalate protecting group under basic conditions for example, using sodium hydroxide, to give the corresponding primary hydroxyl compound **8A**. The primary hydroxyl is oxidized to the corresponding carboxylic acid **8B** by periodic acid and chromium trioxide, for example. The carboxylic acid is protected as, for example, a methyl ester by treatment with sulfuric acid in methanol. The tert-butyl ether is re-installed by treating **8C** with tert-butyl acetate and perchloric acid, for example, to provide **8D**. The corresponding halobenzothiazole **8E** is formed by methods known to those skilled in the art such as *tert*-butyl nitrite and a copper(II)halide such as copper(II)bromide, for example.

Scheme 9



In certain embodiments chlorobenzothiazole **9A** is formed from **6J** by methods known to those skilled in the art such as *tert*-butyl nitrite and a copper(II)halide such as

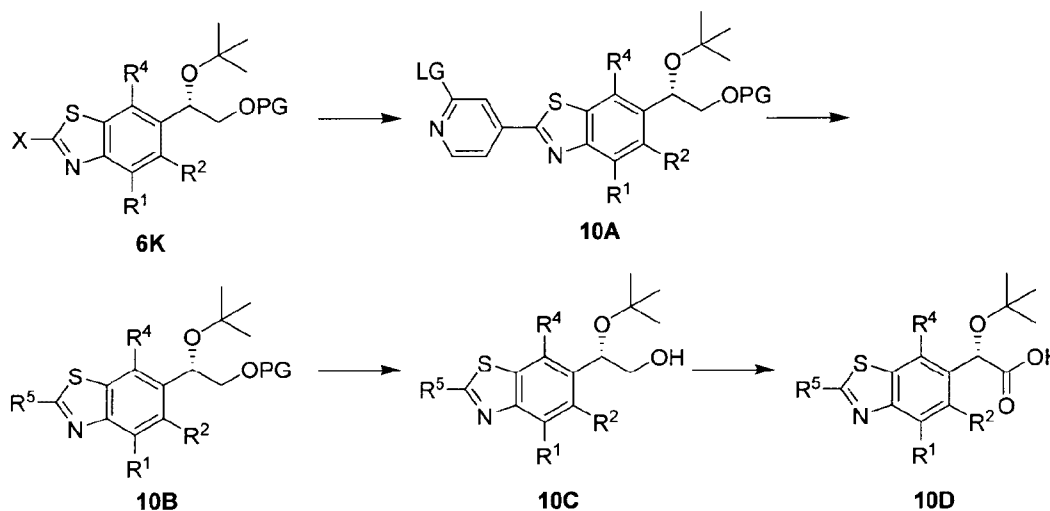
- 5 copper(II)bromide, for example. Selective palladium-catalyzed cross-coupling such as Suzuki or Stille with protected phenol boronic acid/ester or stannane, respectively, provides **9B**. Selective deprotection of PG² such as catalytic hydrogenation of a benzyl ether gives phenol **9C**, which is converted to a leaving group (e.g., triflate) known to undergo cross-coupling reactions. The corresponding activated phenol **9D** undergoes a selective cross-coupling reaction such as,
- 10 for example Suzuki cross-coupling using a boronic acid or ester and a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) to give the corresponding cross-coupled benzothiazole **9E**.

- In certain embodiments the R⁴ moiety is introduced by cross-coupling reaction such as, for example Suzuki cross-coupling using a boronic acid or ester and a palladium catalyst such as
- 15 tetrakis(triphenylphosphine)palladium(0) to give the corresponding cross-coupled benzothiazole **9F**. The protected primary hydroxyl **9F** is deprotected by methods known to those skilled in the

art such as the deprotection of a pivalate protecting group under basic conditions for example, using sodium hydroxide, to give the corresponding primary hydroxyl compound **9G**. The primary hydroxyl is oxidized to the corresponding carboxylic acid **9H** by periodic acid and chromium trioxide, for example.

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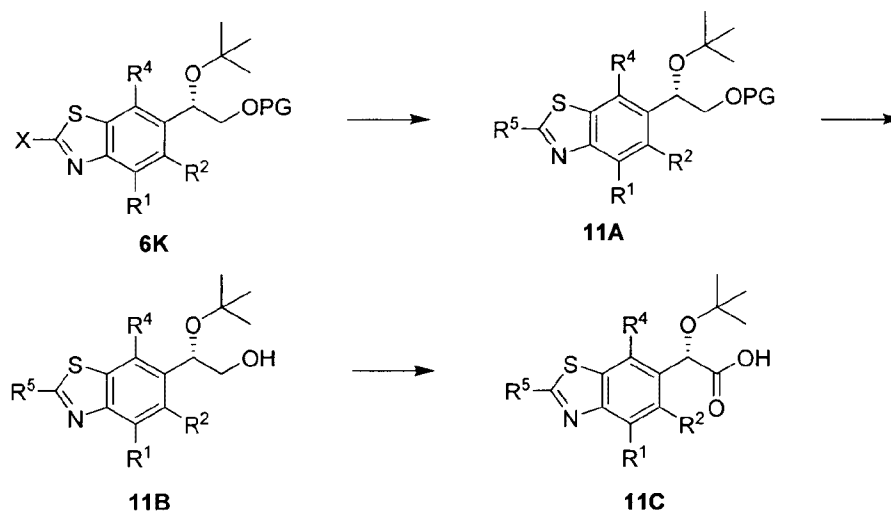
Scheme 10



In certain embodiments halobenzothiazole **6K** undergoes selective palladium-catalyzed cross-coupling such as Suzuki or Stille with a boronic acid/ester or stannane that also contains a leaving group such as for example, a chloropyridylboronic acid, known to undergo cross-coupling reactions to give **10A**. The activated moiety **10A** undergoes a cross-coupling reaction such as, for example Suzuki or Stille cross-coupling using a boronic acid/ester or stannane, respectively and a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) to give the corresponding cross-coupled benzothiazole **10B**. The protected primary hydroxyl **10B** is deprotected by methods known to those skilled in the art such as the deprotection of a pivalate protecting group under basic conditions for example, using sodium hydroxide, to give the corresponding primary hydroxyl compound **10C**. The primary hydroxyl is oxidized to the corresponding carboxylic acid **10D** by periodic acid and chromium trioxide, for example.

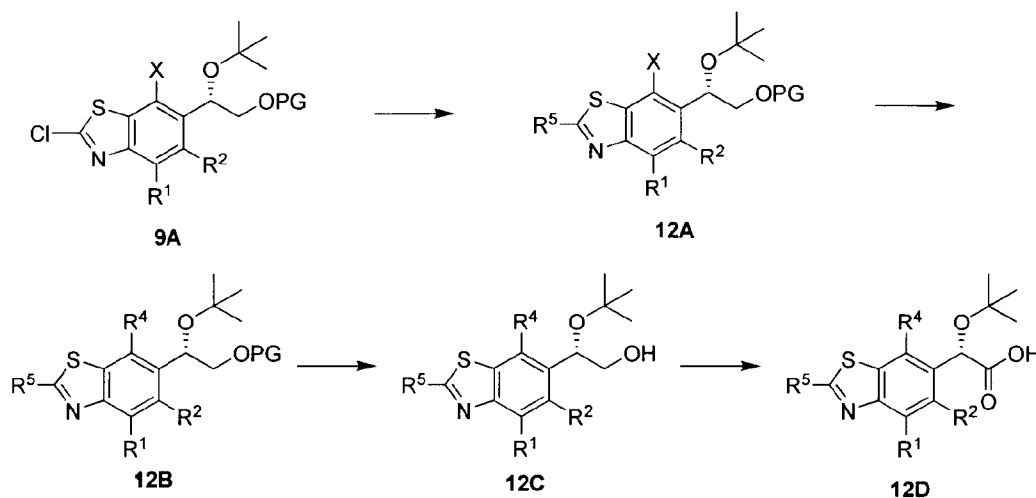
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Scheme 11



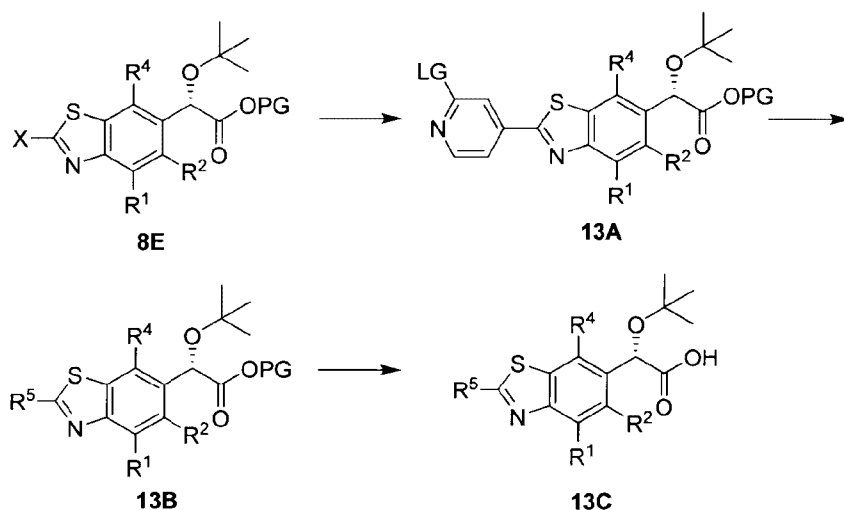
In certain embodiments halobenzothiazole **6K** undergoes palladium-catalyzed cross-coupling such as Suzuki with a boronic acid or ester; Stille with a stannane; palladium-catalyzed carbonylation using carbon monoxide, for example in the presence of an amine; copper(I)halide catalyzed or Buchwald-Hartwig amination; palladium-catalyzed amidation; S_NAr with an amine; to introduce the R⁵ moiety in **11A**. The protected primary hydroxyl of **11A** is deprotected by methods known to those skilled in the art such as the deprotection of a pivalate protecting group under basic conditions for example, using sodium hydroxide, to give the corresponding primary hydroxyl compound **11B**. The primary hydroxyl is oxidized to the corresponding carboxylic acid **11C** by periodic acid and chromium trioxide, for example.

Scheme 12



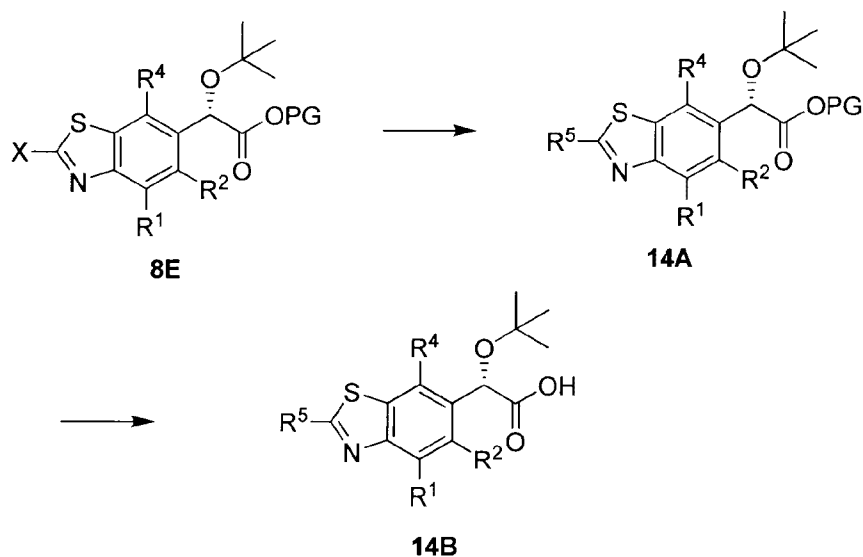
In certain embodiments chlorobenzothiazole **9A** undergoes selective palladium-catalyzed cross-coupling such as Suzuki or Stille with protected phenol boronic acid/ester or stannane, respectively, to provide **12A**. The R⁴ moiety is introduced by cross-coupling reaction such as, for example Suzuki cross-coupling using a boronic acid or ester and a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) to give the corresponding cross-coupled benzothiazole **12B**. The protected primary hydroxyl in **12B** is deprotected by methods known to those skilled in the art such as the deprotection of a pivalate protecting group under basic conditions for example, using sodium hydroxide, to give the corresponding primary hydroxyl compound **12C**. The primary hydroxyl is oxidized to the corresponding carboxylic acid **12D** by periodic acid and chromium trioxide, for example.

Scheme 13



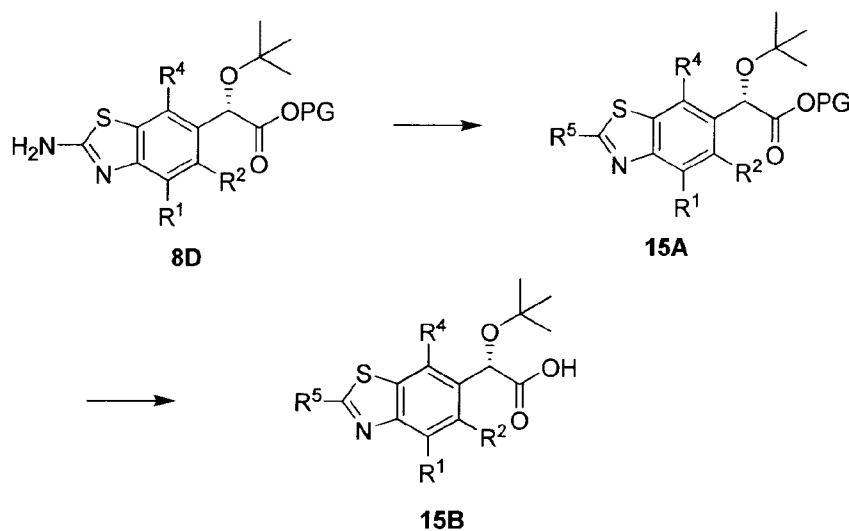
In certain embodiments halobenzothiazole **8E** undergoes selective palladium-catalyzed cross-coupling such as Suzuki or Stille with a boronic acid/ester or stannane that also contains a leaving group such as for example, a chloropyridylboronic acid, known to undergo cross-coupling reactions to give **13A**. The activated moiety **13A** undergoes an S_NAr reaction with for example a secondary amine, or a cross-coupling reaction such as, for example Suzuki or Stille cross-coupling using a boronic acid/ester or stannane, respectively and a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) to give the corresponding cross-coupled benzothiazole **13B**. The protected carboxylic acid **13B** is deprotected by methods known to those skilled in the art such as the deprotection of a carboxylic ester under basic conditions for example, using sodium hydroxide, or treatment with lithium iodide in pyridine, to give the corresponding carboxylic acid **13C**.

Scheme 14



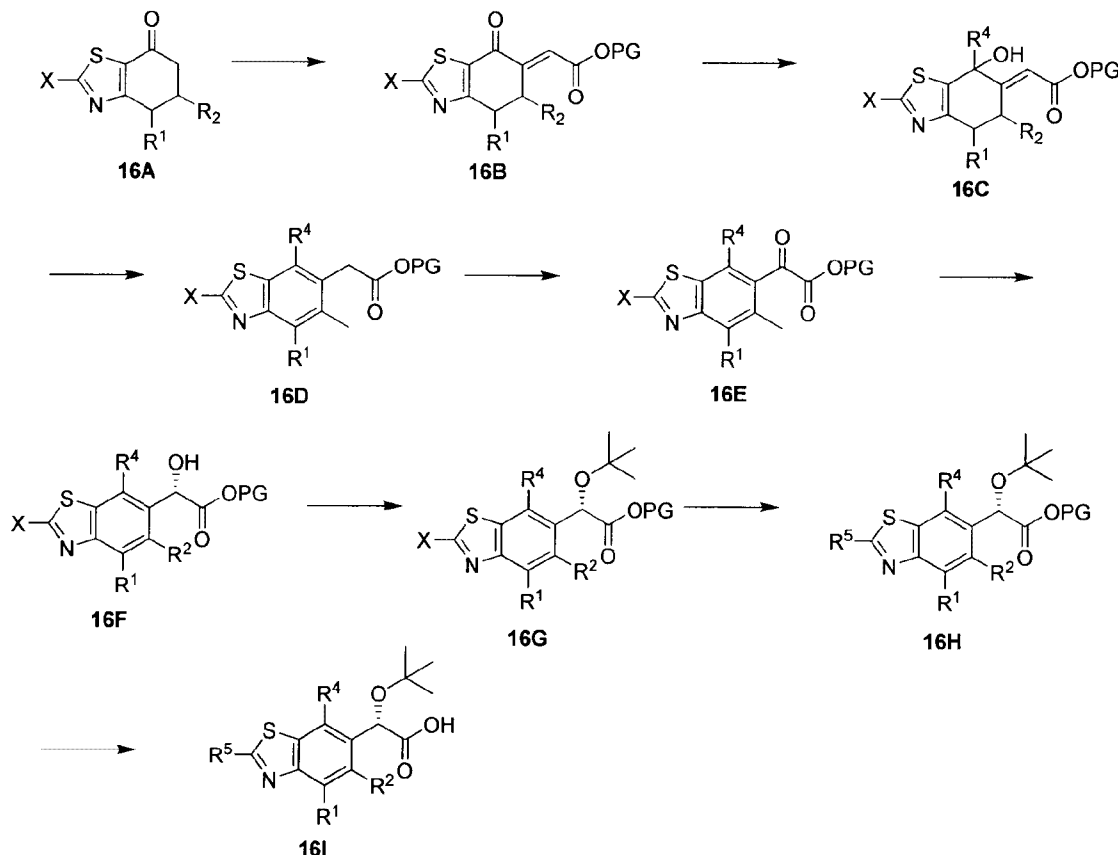
In certain embodiments halobenzothiazole **8E** undergoes palladium-catalyzed cross-coupling such as Suzuki with a boronic acid or ester; Stille with a stannane; palladium-catalyzed carbonylation using carbon monoxide, for example in the presence of an amine; copper(I)halide catalyzed or Buchwald-Hartwig amination; palladium-catalyzed amidation; S_NAr with an amine or alcohol; to introduce the R^5 moiety in **14A**. The protected carboxylic acid **14A** is deprotected by methods known to those skilled in the art such as the deprotection of a carboxylic ester under basic conditions for example, using sodium hydroxide, or treatment with lithium iodide in pyridine to give the corresponding carboxylic acid **14B**.

Scheme 15



In certain embodiments aminobenzothiazole **8D** undergoes reactions known to those skilled in the art such as amide formation using carboxylic acid EDCI, for example; sulfonamide formation using a sulfonyl chloride; urea formation using CDI in the presence of an amine; to introduce the R^5 moiety in **15A**. The protected carboxylic acid **15A** is deprotected by methods known to those skilled in the art such as the deprotection of a carboxylic ester under basic conditions for example, using sodium hydroxide, to give the corresponding carboxylic acid **15B**.

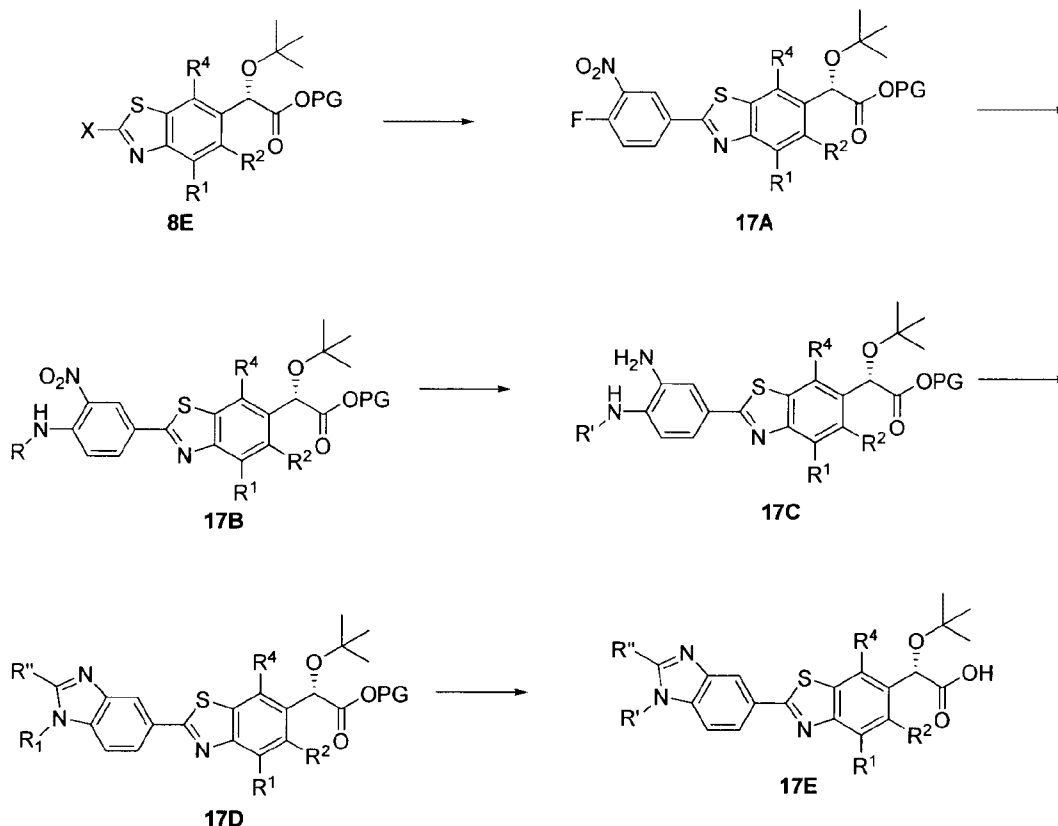
Scheme 16



In certain embodiments, ketone **16A** undergoes reactions known to those skilled in the art such as aldol condensation to give enone **16B**. Enone **16B** can undergo 1,2 organometallic additions such as Grignard additions to give tertiary alcohol **16C**. Under the action of an acid such as polyphosphoric acid, **16C** is converted to benzthiazole **16D**. Reaction of **16D** under basic conditions such as lithium hexamethyldisilazane in the presence of oxaziridine such as Davis reagent, followed oxidation with an oxidant such as Dess-Martin periodinane can give ketoester **16E**. Chiral reductions of **16E** such as CBS or Noyori can give chiral alcohol **16F**. The secondary hydroxyl is converted to the corresponding ether such as tert-butyl ether using methods known to those skilled in the art such as, tert-butyl acetate and perchloric acid to provide **16G**. The activated benzthiazole **16G** undergoes a cross-coupling reaction such as, for

example Buchwald, Heck, Negishi, Suzuki or Stille cross-coupling using a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0); S_NAr reactions with for example, a secondary amine; to give the corresponding benzothiazole **16H**. The protected carboxylic acid **16H** is deprotected by methods known to those skilled in the art such as the deprotection of a carboxylic ester under basic conditions for example, using sodium hydroxide, or treatment with lithium iodide in pyridine to give the corresponding carboxylic acid **16I**.

Scheme 17



- 10 In certain embodiments, halobenzthiazole **8E** undergoes palladium-catalyzed cross-coupling such as Suzuki with a boronic acid or ester, for example 2-(4-fluoro-3-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to give **17A**, known to those skilled in the art to undergo S_NAr reaction with nucleophiles, such as, for example methylamine, to give **17B**. Hydrogenation under platinum on carbon, for example provides the bis-aniline **17C**.
- 15 Cyclization with an orthoformate, such as triethylorthoformate in acetic acid, for example gives benzimidazole **17D**. The protected carboxylic acid **17D** is deprotected by methods known to those skilled in the art such as the deprotection of a carboxylic ester under basic conditions for example, using sodium hydroxide, or treatment with lithium iodide in pyridine to give the corresponding carboxylic acid **17E**.

Prodrugs

In one embodiment, a prodrug of a compound described herein is provided. The term “prodrug” as used herein refers to any compound that when administered to a biological system generates a compound of the invention that inhibits the replication of HIV (“the active inhibitory compound”). The compound may be formed from the prodrug as a result of: (i) spontaneous chemical reaction(s), (ii) enzyme catalyzed chemical reaction(s), (iii) photolysis, and/or (iv) metabolic chemical reaction(s).

“Prodrug moiety” refers to a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, “Design and Application of Prodrugs” in A Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-\text{CH}_2\text{OC}(=\text{O})\text{R}^{99}$ and acyloxymethyl carbonates $-\text{CH}_2\text{OC}(=\text{O})\text{OR}^{99}$ where R^{99} is C_1 – C_6 alkyl, C_1 – C_6 substituted alkyl, C_6 – C_{20} aryl or C_6 – C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al. (1983) *J. Pharm. Sci.* 72: 24; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-\text{CH}_2\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (De Lombaert et al. (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to a phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate parent phosphonic acids.

In some cases, substituents at the *ortho*- or *para*- position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, *e.g.*, esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate phosphoric acid and a quinone methide intermediate.

- 5 Examples of this class of prodrugs are described by Mitchell et al. (1992) *J. Chem. Soc. Perkin Trans. II* 2345; Glazier WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either
- 10 esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al. (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al. (1996) *J. Med. Chem.* 39: 4958).

15 Combination Therapy

- In one embodiment, a method for treating an HIV infection is provided, comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable
- 20 for treating an HIV infection.

- In one embodiment, pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier are provided. For example, the therapeutic agent used in combination with the compound disclosed herein can be any anti-HIV
- 25 agent.

- One embodiment provides pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase
- 30 inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof, and a pharmaceutically acceptable carrier.

One embodiment provides pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent selected from the group consisting of:

- (1) HIV protease inhibiting compounds selected from the group consisting of
 5 amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;
- (2) HIV non-nucleoside inhibitors of reverse transcriptase selected from the group
 10 consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, rilpivirene, BILR 355 BS, VRX 840773, UK-453061, RDEA806, KM023 and MK-1439;
- (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir,
 15 amdoxovir, elvucitabine, alovudine, MIV-210, \pm -FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosaltudine tidoxil (formerly HDP 99.0003) ;
- (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate (Gilead Sciences),
 20 adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix);
- (5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of
 25 tyrphostin, quercetin, derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810, raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, GS-5696, elvitegravir and dolutegravir;
- (6) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, FB006M, and TRI-1144;
- (7) the CXCR4 inhibitor AMD-070;
- (8) the entry inhibitor SP01A;
- (9) the gp120 inhibitor BMS-488043;
- (10) the G6PD and NADH-oxidase inhibitor immunitin;

(11) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(12) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevrimat),
 5 HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040).

Another embodiment provides pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent selected from the group consisting of:

10 (1) HIV protease inhibiting compounds selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

15 (2) HIV non-nucleoside inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, rilpivirene, BILR 355 BS, VRX 840773, UK-453061, and RDEA806;

(3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting
 20 of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, \pm -FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003) ;

(4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting
 25 of tenofovir, tenofovir disoproxil fumarate, GS-7340 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix)

(5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic
 30 acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810, raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011 and dolutegravir;

(6) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, FB006M, and TRI-1144;

- (7) the CXCR4 inhibitor AMD-070;
 (8) the entry inhibitor SP01A;
 (9) the gp120 inhibitor BMS-488043;
 (10) the G6PD and NADH-oxidase inhibitor immunitin;
 5 (11) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;
 (12) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevrimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798,
 10 MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040).

In another embodiment, the invention provides pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with two, three, four or more additional therapeutic agents. For example, a compound disclosed herein, or a pharmaceutically acceptable salt, thereof, is combined with two, three, four or more
 15 additional therapeutic agents selected from the classes of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors and other drugs for treating HIV. The two, three four or more additional therapeutic
 20 agents can be different therapeutic agents selected from the same class of therapeutic agents, or they can be selected from different classes of therapeutic agents.

One embodiment provides for a combination pharmaceutical agent comprising:

- a) a compound disclosed herein, or a pharmaceutically acceptable salt, thereof; and
- b) at least one additional active agent which is suitable for treating an HIV infection.

25 Another embodiment provides a combination pharmaceutical agent comprising:

- a) a compound disclosed herein, or a pharmaceutically acceptable salt thereof; and
- b) at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse
 30 transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors and other drugs for treating HIV.

It is also possible to combine any compound disclosed herein with one or more other active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential

regimen. When administered sequentially, the combination may be administered in two or more administrations.

It is also possible to co-administer a compound disclosed herein with one or more other active therapeutic agents. Co-administration of a compound disclosed herein with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein and one or more other active therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound disclosed herein can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active therapeutic agents.

Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound disclosed herein within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound disclosed herein first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein.

The combination therapy may provide "synergy" and "synergistic effect", *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

Another embodiment provides a method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound

disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV.

Another embodiment provides a method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of:

(1) HIV protease inhibiting compounds selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) HIV non-nucleoside inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, rilpivirene, BILR 355 BS, VRX 840773, UK-453061, RDEA806, KM023 and MK-1439 ;

(3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, \pm -FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003) ;

(4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix);

(5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810,

raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, GS-5696, elvitegravir and dolutegravir;

(6) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, FB006M, and TRI-1144;

5 (7) the CXCR4 inhibitor AMD-070;

(8) the entry inhibitor SP01A;

(9) the gp120 inhibitor BMS-488043;

(10) the G6PD and NADH-oxidase inhibitor immunitin;

10 (11) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(12) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040).

15 Another embodiment provides a method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of:

20 (1) HIV protease inhibiting compounds selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

25 (2) HIV non-nucleoside inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, rilpivirene, BILR 355 BS, VRX 840773, UK-453061, and RDEA806;

30 (3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, \pm -FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosaltvudine tidoxil (formerly HDP 99.0003), ;

(4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, GS-7340 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix)

(5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810, raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011 and dolutegravir;

(6) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, FB006M, and TRI-1144;

(7) the CXCR4 inhibitor AMD-070;

(8) the entry inhibitor SP01A;

(9) the gp120 inhibitor BMS-488043;

(10) the G6PD and NADH-oxidase inhibitor immunitin;

(11) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(12) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040).

Pharmaceutical Formulations

The compounds disclosed herein are formulated with conventional carriers (e.g., inactive ingredient or excipient material), which will be selected in accord with ordinary practice.

Tablets will contain excipients, including glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. One embodiment provides the formulation as a solid dosage form including a solid oral dosage form. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations (compositions). The formulations,

both for veterinary and for human use, of the invention comprise at least one active ingredient, together with one or more acceptable carriers and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

5 The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the inactive
10 ingredients (e.g., a carrier, pharmaceutical excipients, etc.) which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations described herein that are suitable for oral administration may be presented
15 as discrete units including but not limited to capsules, cachets or tablets each containing a predetermined amount of the active ingredient.

Pharmaceutical formulations disclosed herein comprise one or more compounds disclosed herein together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active
20 ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or
25 more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium,
30 povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a

sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

The amount of active ingredient that is combined with the inactive ingredients to produce a dosage form will vary depending upon the host treated and the particular mode of administration. For example, in some embodiments, a dosage form for oral administration to humans contains approximately 1 to 1000 mg of active material formulated with an appropriate amount of carrier material (e.g., inactive ingredient or excipient material). In certain embodiments, the carrier material varies from about 5 to about 95% of the total composition (weight:weight).

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Certain embodiments provide veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

Routes of Administration

One or more compounds disclosed herein (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

The antiviral properties of a compound of the invention may be determined using Test A described below.

Test A: Antiviral Assay in MT4 Cells

For the antiviral assay utilizing MT-4 cells, 0.4 μ L of 189X test concentration of 3-fold serially diluted compound in DMSO was added to 40 μ L of cell growth medium (RPMI 1640, 10%FBS, 1% penicilline/Streptomycine, 1% L-Glutamine, 1% HEPES) in each well of 384-well assay plates (10 concentrations) in quadruplicate.

One mL aliquots of 2×10^6 MT-4 cells were pre-infected for 1 and 3 hours respectively, @ 37°C with 25 μ L (MT4) or of either cell growth medium (mock-infected) or a fresh 1:250 dilution of an HIV-IIIb concentrated ABI stock (0.004m.o.i. for MT4 cells). Infected and uninfected cells were diluted in cell growth medium and 35 μ L of 2000 (for MT4) cells was added to each well of the assay plates.

Assay plates were then incubated in a 37°C incubator. After 5 days of incubation, 25 μ L of 2X concentrated CellTiter-Glo™ Reagent (catalog # G7573, Promega Biosciences, Inc., Madison, WI) was added to each well of the assay plate. Cell lysis was carried out by incubating at room temperature for 2-3 min and then chemiluminescence was read using the Envision reader (PerkinElmer).

Compounds disclosed herein demonstrate antiviral activity in this assay (Test A) as depicted in Table 1 and Table 2 below. Accordingly, the compounds may be useful for treating an HIV infection, the proliferation of the HIV virus, treating AIDS or delaying the onset of AIDS or ARC symptoms.

Table 1

Compound Number	EC50 (nM)
50	52.8
51	5250
52	53.4
53	37500
54	274
55	53000
56	62.4
57	147
58	3520
76	26
78	726

Compound Number	EC50 (nM)
89	36.6
104	42
105	16
106	103
107	46
108	33
109	82
110	14
111	8
112	28
113a	16
113b	18
114	13
115	13
116	19
117	14
118	101
119	237
120	23
121	27
122	5518
123	18
124	21
125	205
126	722
129	48
130	100
131	8
132	12
133	18
134	3226
135	17

Compound Number	EC50 (nM)
136	12
137	21
138	65
139	61
140	5
141	77
142	48
143	24
144	2608
145	34
146	92
147	59
148	2698
149	153
150	91
151	32
152	46
153	15
154	16
155	66
156	26
157	29
158	17
159	46
160	136
161	116
162	350
163	18
164	483
167	39
168	42
169	33

Compound Number	EC50 (nM)
170	35

Table 2

Compound Number	EC50 (nM)
173	11
174	26
175	33
176	18
177	39
178	89
179	73
180	5
181	27
182	80
183	18
184	19
186	4
187	25
188	12
189	249
190	112
191	10
192	12
193	9
194	21
195	11
196	33
197	12
198	39
199	95
200	14

Compound Number	EC50 (nM)
201	7
202	2
203	12
204	155
205	18
206	24
207	19
208	62
209	16
210	6
212	6
213	4
214	17
215	27
216	15
217	7
218	116
219	39
220	43
221	24
222	49
223	312
224	12
225	96
226	36
227	85
228	910
229	1737
230	131
232	86
233	33
234	13

Compound Number	EC50 (nM)
235	14
236	31
237	10
238	25
239	26
240	76
241	3
242	494
243	424
245	9
246	9
247	10
248	13
249	7
250	235
254	8
255	12
256	9
257	5
258	13
259	12
264	17
265	15
266	10
267	11
268	12
269	12
272	78
273	53
274	31
275	21
276	37

Compound Number	EC50 (nM)
277	26
278	4
279	16
280	248
281	31
282	3
283	51
284/285	23
286	10
287	113
288	65
289	25
290	87
291	76
292	23
293	215
294	36
295	34
296	13
297	17
298	181
299	130
300	12
301	109
302	8
303	19
305	10
306	14
307	4
308	6
309	37
310	26

Compound Number	EC50 (nM)
311	45
312	37
313	14
314	42
315	34
316	18
317	13
318	10
319	5
322	640
323	384
324	13
325	10
326	66
327	162
328	44
329	14
330	19
331	44
332	5
333	3
334	5
335	14
336	2
337	4
338	11
339	11
340	9
341	14
342	5
343	26
344	6

Compound Number	EC50 (nM)
345	28
346	11
347	42
348	30
349	42
350	14
351	21
352	29
353	31
354	1372
355	182
356	3332
357	12
358	241
359	21
360	13
361	20
362	21
363	15
364	9
365	29
366	6
367	6
368	5
369	8
370	4
371	7
372	7 ---
373	37
374	45
375	228
376	19

Compound Number	EC50 (nM)
377	32
378	51
379	15
380	25
381	47
382	91
383	18
384	332
385	143
386	56
387	530
388	28
389	7
390	9
391	11
392	27
393	33
394	25
395	61
396	10
397	32
398	36
399	43
400	16
401	23
402	35
403	42
404	41
405	37
406	149
407	14
408	27

Compound Number	EC50 (nM)
409	10
410	9
411	8
412	16
413	33
414	32
415	10
416	25
417	18
418	11
419	13
420	14
421	20
422	32
427	14
428	7
429	43
430	29
431	18
432	18
433	38
434	42
435	39
436	67
437	309
438	258
439	20
440	11
441	4
442	1159
443	24
444	10

Compound Number	EC50 (nM)
445	5
446	173
447	5
448	9
449	30
450	25
451	86
452	16
453	36
454	18
455	17
456	20
457	96
458	5
459	28
460	31
461	14
462	42
463	52
464	12
465	2
466	5
467	5
468	8
469	8
470	3
471	3
472	4
473	8
474	40
475	6
476	128

Compound Number	EC50 (nM)
477	14
478	4
479	4
480	2
481	17
482	14
483	37
484	9
485	15
486	31
487	12
488	11
489	20
490	3
491	51
492	3
493	51
494	2878
495	4
496	5
497	4
498	34
499	12

In certain embodiments, the compounds demonstrate an EC50 of < 50 μ M. In certain embodiments, the compounds demonstrate an EC50 of < 30 μ M. In certain embodiments, the compounds demonstrate an EC50 of < 10 μ M. In certain embodiments, the compounds demonstrate an EC50 of < 1 μ M. In certain embodiments, the compounds demonstrate an EC50 of < 0.5 μ M. In certain embodiments, the compounds demonstrate an EC50 of < 0.1 μ M. In certain embodiments, the compounds demonstrate an EC50 of < 0.05 μ M. In certain embodiments, the compounds demonstrate an EC50 of < 0.01 μ M. It is to be understood that the compounds disclosed herein can be grouped according to their % inhibition as described above.

Test B: Metabolic Stability Assay with Human Liver Microsomes

Effective viral suppression in the HIV infected patient requires that the antiviral drug persists in the patient's body at concentrations exceeding the minimum concentration required to inhibit viral proliferation. One of the factors controlling the drug levels after dosing is metabolic conversion. The liver is one site of drug metabolism. Approximately 60% of marketed drugs are cleared by hepatic metabolism (McGinnity DF et al. (2004) Drug Metab Dispos 32; 1247-1253). Liver microsomes are subcellular fractions which contain membrane bound drug metabolising enzymes. Human liver microsomes provide a convenient and concentrated source of the key liver metabolic enzymes (e.g., cytochromes P450, UDP-glucuronosyltransferases, and many others) and can be used to predict the metabolic stability of drug candidates (e.g., agents).

Cluster tubes containing 500 μ L of 1 μ M compound with 1 mg/mL human liver microsomal proteins (BD Biosciences, BD452117)/50 mM K-phosphate buffer pH7.4/NADPH regenerating system/and UDP-glucuronosyltransferase cofactors, were incubated on the Precision-2000 workstation at 37 $^{\circ}$ C for 0, 10, 25, 60 minutes. The reactions were quenched with 100 μ L of 0.2% formic acid in 90%ACN; containing 50 nM of an internal standard. The samples were analyzed on LC/MS/MS instrument (Q-Trap). Metabolic stabilities in microsomal fractions and hepatocytes were determined by measuring the rate of disappearance of the compound. Data (% of parent remaining) were plotted on a semi logarithmic scale and fitted using an exponential fit. The predicted hepatic half-life was calculated from these data (Obach RS, Baxter JG, Liston TE, Silber BM, Jones BC, MacIntyre F, et al. J Pharmacol Exp Ther 1997; 283 (1):46-58). These results are shown in Table 3. Human microsomal stability equal to A refers to a compound having a human microsomal stability half-life of greater than or equal to 300 minutes. Human microsomal stability equal to B refers to a compound having a human microsomal stability half-life of less than 300 minutes but greater than or equal to 150 minutes. Human microsomal stability equal to C refers to a compound having a human microsomal stability half-life of less than 150 minutes.

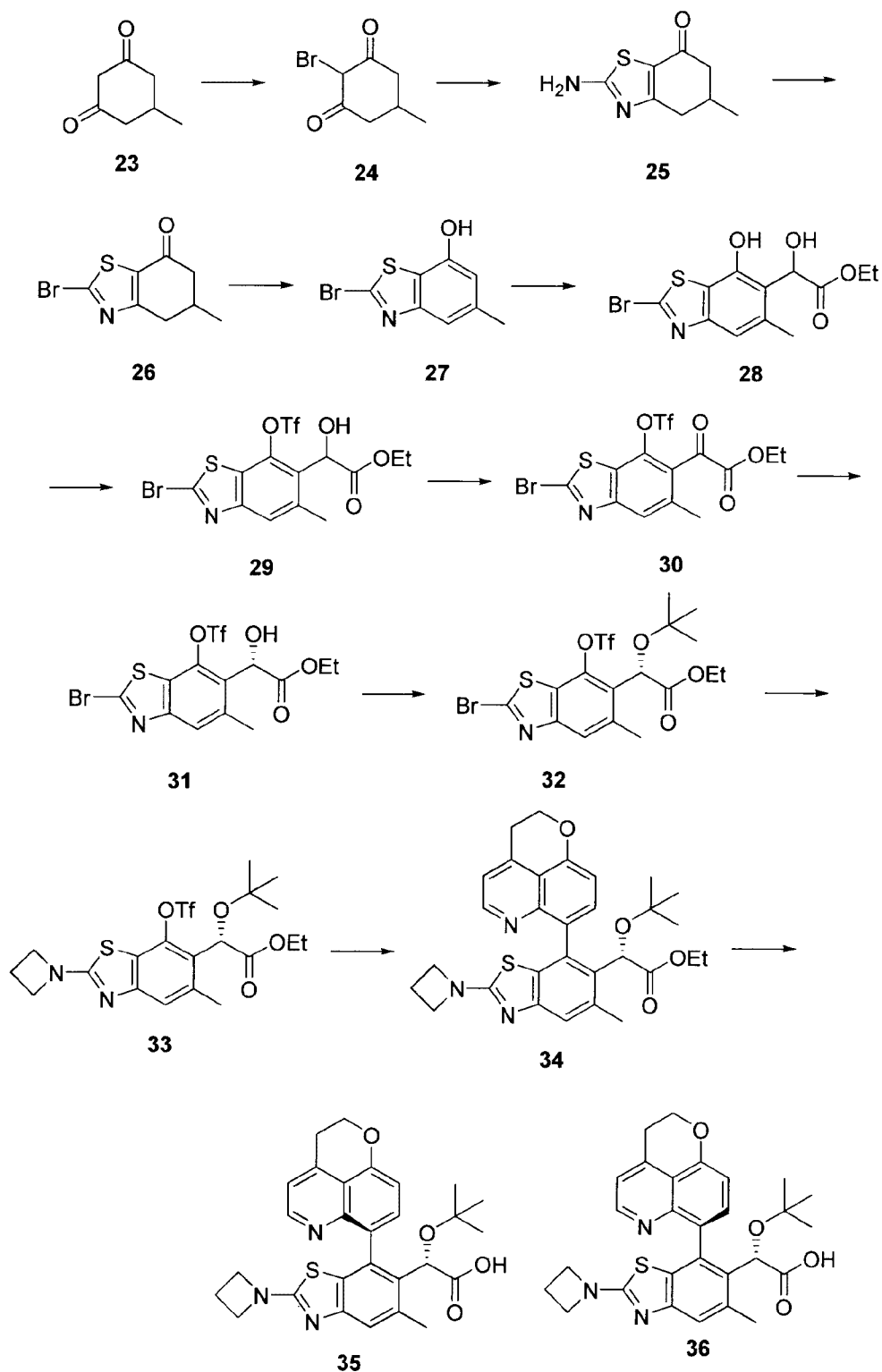
Table 3

Compound Number	Human Microsomal stability
104	C
107	C
109	B
141	B
152	C
158	C
163	C
186	C
202	A
206	C
212	A
257	A
278	B
285	A
333	A
336	A
113a	A

The specific pharmacological responses observed may vary according to and depending
5 on the particular active compound selected or whether there are present pharmaceutical carriers,
as well as the type of formulation and mode of administration employed, and such expected
variations or differences in the results are contemplated in accordance with practice of the
present invention.

The invention has been described with reference to various specific and preferred
10 embodiments and techniques. However, it should be understood that many variations and
modifications may be made while remaining within the spirit and scope of the invention.

The invention will now be illustrated by the following non-limiting examples of
compounds (including compounds of the invention) and intermediates useful for preparing
15 compounds of the invention.

Example 1. Preparation of intermediates 24-32.

To a solution of **34** (23 mg, 0.043 mmol) in THF (1 mL) and MeOH (1 mL) was added a
 5 solution of NaOH (2 M, ~400 μ L). The reaction mixture was heated at 70 $^{\circ}$ C for 4 h. The

reaction was brought to ~pH 5 with TFA and was then purified by reverse phase HPLC (ACN/H₂O containing 0.1% TFA) to give 6 mg of compound **35** and 10 mg of compound **36**.

Compound **35**: ¹H-NMR: 400 MHz, (CD₃OD) δ: 8.75 (d, J = 2.6 Hz, 1H), 7.80 (d, J = 4.0 Hz, 1H), 7.72 (d, J = 2.6 Hz, 1H), 7.47 (s, 1H), 7.34 (d, J = 4.0 Hz, 1H), 5.13 (s, 1H), 4.67-4.65 (m, 2H), 4.17 (t, J = 7.6 Hz, 4H), 3.59-3.58 (m, 2H), 2.66 (s, 3H), 2.52-2.50 (m, 2H), 0.88 (s, 9H). LCMS-ESI⁺: calc'd for C₂₈H₂₉N₃O₄S: 504.2 (M+H⁺); Found: 504.0 (M+H⁺).

Compound **36**: ¹H-NMR: 400 MHz, (CD₃OD) δ: 8.67 (d, J = 2.2 Hz, 1H), 8.01 (d, J = 4.0 Hz, 1H), 7.49 (d, J = 2.6 Hz, 1H), 7.40 (s, 1H), 7.27 (d, J = 4.2 Hz, 1H), 5.18 (s, 1H), 4.60-4.57 (m, 2H), 4.27 (t, J = 7.8 Hz, 4H), 3.48-3.45 (m, 2H), 2.61 (s, 3H), 2.58-2.54 (m, 2H), 0.80 (s, 9H). LCMS-ESI⁺: calc'd for C₂₈H₂₉N₃O₄S: 504.2 (M+H⁺); Found: 504.1 (M+H⁺).

Preparation of (2S)-ethyl 2-(2-(azetidin-1-yl)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**34**).

Step 1.

Preparation of 2-bromo-5-methylcyclohexane-1,3-dione (**24**). To a solution of 5-methyl-1,3-cyclohexanedione (**23**) (45.4 g, 360 mmol) in acetic acid (540 mL) was added bromine (19.4 mL, 378 mmol) over 5 min. After 30 min of stirring (with mechanical stirrer), the reaction mixture was filtered. The solid was left under high vacuum overnight and used in the subsequent step without further purification.

Step 2.

Preparation of 2-amino-5-methyl-5,6-dihydrobenzo[d]thiazol-7(4H)-one (**25**). To a solution of **24** in acetic acid (540 mL) was added sodium acetate (44.3 g, 540 mmol) and thiourea (28.8 g, 378 mmol). The reaction mixture was stirred with a mechanical stirrer at 100 °C for 3 h. The reaction mixture was partially concentrated *in vacuo*. EtOAc was added (500 mL). The mixture was made basic with 1 M NaOH, and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo* to give 49.3 g of **25**, which was taken on without further purification. LCMS-ESI⁺: calc'd for C₈H₁₁N₂OS: 183.1 (M+H⁺); Found: 183.1 (M+H⁺).

Step 3.

Preparation of 2-bromo-5-methyl-5,6-dihydrobenzo[d]thiazol-7(4H)-one (**26**). To a solution of **25** (53.9 g, 296 mmol) in ACN (600 mL) at 0 °C, while mechanically stirred), was added copper (II) bromide (79.2 g, 355 mmol) then *t*-butyl nitrite (46.8 mL, 355 mmol). The reaction mixture was stirred from 0 °C to room temperature over 2 h and was then partially concentrated. EtOAc (400 mL) and a 0.5 M HCl solution were added. The layers were

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separated, and the organic layer was washed with a brine solution. The combined organic layers were dried, filtered, and concentrated *in vacuo*. The crude product was adsorbed on ~150 g of silica then run through a plug of silica with 40% EtOAc/hexanes to give 58.3 g of **26**. ¹H-NMR: 400 MHz, (CDCl₃) δ: 3.16 (dd, 1H, *J* = 18, 4 Hz), 2.66 (m, 2H), 2.47 (m, 1H), 2.34 (dd, 1H, *J* = 16, 12 Hz), 1.19 (d, 3H, *J* = 7 Hz). LCMS-ESI⁺: calc'd for C₈H₉BrNOS: 245.9 (M+H⁺); Found: 246.1 (M+H⁺).

Step 4.

Preparation of 2-bromo-5-methylbenzo[d]thiazol-7-ol (**27**). To a solution of **26** (7.38 g, 30.0 mmol) in CCl₄ (90 mL) was added NBS (5.61 g, 31.5 mmol) and dibenzoyl peroxide (727 mg, 3.0 mmol). The reaction was heated at 90 °C in a sealed reaction vessel for about 4 h. Then DBU (6.73 mL, 45.0 mmol) in CH₂Cl₂ (15 mL) was added. The mixture was heated a reflux for 30 min, then a 1 M HCl solution was added. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with a brine solution. The organic layer was then dried, filtered, and concentrated *in vacuo*. The crude product was adsorbed on ~30 g of silica then run through a plug of silica with 40% EtOAc/hexanes to give 5.2 g of **27**. ¹H-NMR: 400 MHz, (CD₃OH) δ: 7.25 (s, 1H), 6.69 (s, 1H), 2.40 (s, 3H). LCMS-ESI⁺: calc'd for C₈H₇BrNOS: 243.9 (M+H⁺); Found: 244.1 (M+H⁺).

Step 5.

Preparation of ethyl 2-(2-bromo-7-hydroxy-5-methylbenzo[d]thiazol-6-yl)-2-hydroxyacetate (**28**). To a solution of **27** (3.90 g, 16.0 mmol) in CH₂Cl₂ (80 mL) at 0 °C was added triethylamine (2.45 mL, 16.8 mmol) then a solution of titanium tetrachloride in CH₂Cl₂ (1.0 M, 16.8 mL, 16.8 mmol). After 15 min, ethyl glyoxalate (50% in toluene, 3.49 mL, 17.6 mmol) was added. The reaction mixture was stirred for 2 h while warming to room temperature. Water (50 mL) and a saturated solution of potassium sodium tartrate (50 mL) were added. The mixture was stirred vigorously for 2 h. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography to give 2.48 g of **28** and recovered ~500 mg of **27**. ¹H-NMR: 400 MHz, (CD₃OH) δ: 7.33 (s, 1H), 5.69 (s, 1H), 4.17 (m, 2H), 2.50 (s, 3H), 1.18 (t, 3H, *J* = 7 Hz). LCMS-ESI⁺: calc'd for C₁₂H₁₃BrNO₄S: 346.0 (M+H⁺); Found: 346.1 (M+H⁺).

Step 6.

Preparation of ethyl 2-(2-bromo-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-hydroxyacetate (**29**). To a solution of **28**

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(2.42 g, 7.00 mmol) in CH₂Cl₂ (30 mL) at -78 °C was added triethylamine (1.02 mL, 7.70 mmol) followed by trifluoromethanesulfonic anhydride (1.24 mL, 7.35 mmol). After 15 min, saturated NH₄Cl was added. The layers were separated. The organic layer was dried, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography to give 2.17 g of **29**. ¹H-NMR: 400 MHz, (CDCl₃) δ: 7.84 (s, 1H), 5.67 (s, 1H), 4.27 (m, 2H), 2.50 (s, 3H), 1.23 (t, 3H, *J* = 7 Hz). LCMS-ESI⁺: calc'd for C₁₃H₁₂BrF₃NO₆S₂: 477.9 (M+H⁺); Found: 478.2 (M+H⁺).

Step 7.

Preparation of ethyl 2-(2-bromo-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-oxoacetate (**30**). To a solution of **29** (9.85 g, 20.6 mmol) in CH₂Cl₂ (100 mL) was added Dess-Martin periodinane (9.61 g, 22.6 mmol). After 30 min, water (75 mL) and saturated Na₂S₂O₄ solution (75 mL) was added. The mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography to give 8.32 g of **30**. ¹H-NMR: 400 MHz, (CDCl₃) δ: 7.91 (s, 1H), 4.40 (q, 2H, *J* = 7 Hz), 2.49 (s, 3H), 1.39 (t, 3H, *J* = 7 Hz). LCMS-ESI⁺: calc'd for C₁₃H₁₀BrF₃NO₆S₂: 475.9 (M+H⁺); Found: 476.1 (M+H⁺).

Step 8.

Preparation of (S)-ethyl 2-(2-bromo-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-hydroxyacetate (**31**). To a solution of **30** (8.30 g, 17.4 mmol) in toluene (70 mL) was added ((R)-2-methyl-CBS-oxazaborolidine (725 mg, 2.61 mmol). The reaction mixture was then cooled to -35 °C and a solution of catecholborane (freshly distilled) (1 M in toluene, 20.9 mL, 20.9 mmol) was added via addition funnel over 30 min. The reaction was stirred for 20 min while warming to -20 °C. A 2 M solution of Na₂CO₃ was added (50 mL). The layers were separated, and the organic layer was washed with additional Na₂CO₃ solution (3 x 25 mL). The organic layer was dried, filtered, and concentrated *in vacuo* to give **31**, which had analytical data to match **29**. The compound was taken on to the next step without further purification.

Step 9.

Preparation of (S)-ethyl 2-(2-bromo-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**32**). To a solution of **31** (~17 mmol) in *t*-butylacetate (70 mL) was added perchloric acid (1.23 mL, 20.4 mmol). After 3 h, water was added (50 mL). The layers were separated. The organic layer

was washed with a saturated solution of NaHCO_3 . The organic layer was dried, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (EtOAc/hexanes) to give 7.22 g of **32** and 1.58 g of **31**. $^1\text{H-NMR}$: 400 MHz, (CD_3OH) δ : 7.82 (s, 1H), 5.59 (s, 1H), 4.08-4.25 (m, 2H), 2.55 (s, 3H), 1.20 (s, 9H), 1.16 (t, 3H, $J = 7$ Hz).

5 LCMS-ESI $^+$: calc'd for $\text{C}_{17}\text{H}_{20}\text{BrF}_3\text{NO}_6\text{S}_2$: 534.0 ($\text{M}+\text{H}^+$); Found: 534.1 ($\text{M}+\text{H}^+$).

Step 10.

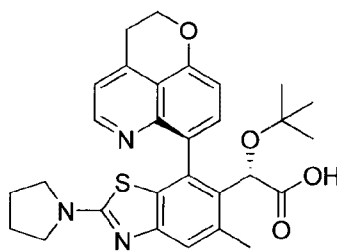
Preparation of (S)-ethyl 2-(2-(azetidin-1-yl)-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**33**). To a solution of **32** (50 mg, 0.094 mmol) in THF (1 mL) was added azetidine (20 μL). The reaction mixture was
 10 heated at 70 $^\circ\text{C}$ for 30 min. A saturated solution of NH_4Cl (3 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer were dried, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (EtOAc/hexanes) to give 38 mg of **33**. LCMS-ESI $^+$: calc'd for $\text{C}_{20}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_6\text{S}_2$: 511.1 ($\text{M}+\text{H}^+$); Found: 511.0 ($\text{M}+\text{H}^+$).

15 Step 11.

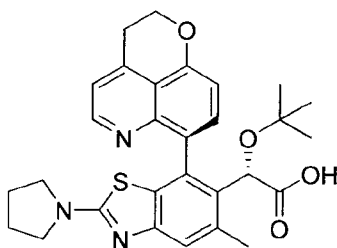
Preparation of (2S)-ethyl 2-(2-(azetidin-1-yl)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**34**). To a solution of **33** (38 mg, 0.075 mmol) in freshly distilled DME (1 mL) was added 2,3-dihydropyrano[4,3,2-de]quinolin-7-ylboronic acid hydrochloride (24 mg, 0.097 mmol), chloro(2-dicyclohexylphosphino-2',6'-
 20 dimethoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(II) methyl-t-butylether adduct, [SPhos Palladacycle] (5 mg, 0.0075 mmol), and cesium fluoride (46 mg, 0.3 mmol). The reaction mixture was heated in the microwave at 110 $^\circ\text{C}$ for 45 min. A saturated solution of NaHCO_3 (3 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer were dried, filtered, and concentrated *in vacuo*. The
 25 crude material was purified by column chromatography (EtOAc/hexanes) to give 21 mg of **34**. LCMS-ESI $^+$: calc'd for $\text{C}_{30}\text{H}_{33}\text{N}_3\text{O}_4\text{S}$: 532.2 ($\text{M}+\text{H}^+$); Found: 532.0 ($\text{M}+\text{H}^+$).

Example 2. Preparation of (S)-2-tert-butoxy-2-((S)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methyl-2-(pyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (**50**) and (S)-2-tert-butoxy-2-
 30 ((R)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methyl-2-(pyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (**51**).

Compounds **50** and **51** were prepared from compound **32** according to the procedure used to prepare compound **35** (except that pyrrolidine was used instead of azetidine) in Example 1.

**50**

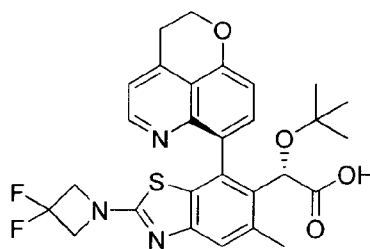
Compound **50**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ 8.76 (d, $J = 5.3$ Hz, 1H), 7.80 (d, $J = 8.1$ Hz, 1H), 7.69 (d, $J = 5.1$ Hz, 1H), 7.50 (s, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 5.15 (s, 1H), 9.03 – 0.64 (m, 79H), 4.70 – 4.60 (m, 2H), 3.56 (dd, $J = 13.8, 7.7$ Hz, 6H), 2.68 (s, 3H), 2.10 (t, $J = 6.7$ Hz, 4H), 0.89 (s, 10H). LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{32}\text{N}_3\text{O}_4\text{S}$: 518.21 ($\text{M}+\text{H}^+$); Found: 517.99, 518.97 ($\text{M}+\text{H}^+$).

**51**

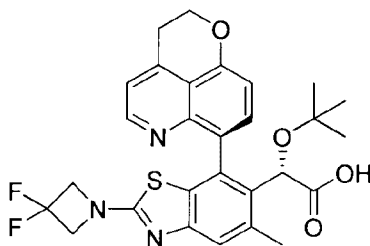
Compound **51**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ 8.67 (d, $J = 4.7$ Hz, 1H), 8.01 (d, $J = 8.1$ Hz, 1H), 7.46 (d, $J = 4.8$ Hz, 1H), 7.44 (s, 1H), 7.27 (d, $J = 8.1$ Hz, 1H), 5.20 (s, 1H), 4.68 – 4.50 (m, 2H), 3.57 (s, 3H), 3.45 (t, $J = 5.8$ Hz, 2H), 2.63 (s, 4H), 2.14 (t, $J = 6.3$ Hz, 4H), 0.79 (s, 9H). LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{32}\text{N}_3\text{O}_4\text{S}$: 518.21 ($\text{M}+\text{H}^+$); Found: 518.07, 519.07 ($\text{M}+\text{H}^+$).

Example 3. Preparation of (S)-2-tert-butoxy-2-((S)-2-(3,3-difluoroazetidin-1-yl)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (**52**) and (S)-2-tert-butoxy-2-((R)-2-(3,3-difluoroazetidin-1-yl)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (**53**).

Compounds **52** and **53** were prepared from compound **32** according to the procedure used to prepare compound **35** (except that 2,2-difluoroazetidine was used instead of azetidine) in Example 1.

**52**

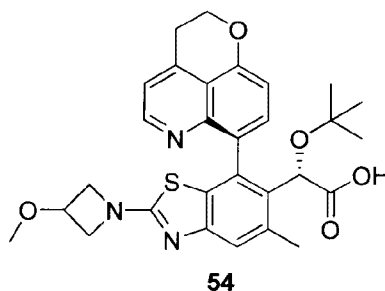
Compound **52**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ 8.80 (d, $J = 5.6$ Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.83 (d, $J = 5.6$ Hz, 1H), 7.61 (s, 1H), 7.41 (d, $J = 8.2$ Hz, 1H), 5.17 (s, 1H), 4.76 – 4.64 (m, 2H), 4.56 – 4.43 (m, 4H), 3.65 (t, $J = 5.9$ Hz, 2H), 2.69 (s, 3H), 0.91 (s, 9H). ^{19}F NMR (377 MHz, CD_3OD) δ -77.88 (s). LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{28}\text{F}_2\text{N}_3\text{O}_4\text{S}$: 540.18 (M+H $^+$); Found: 539.96, 540.96 (M+H $^+$).

**53**

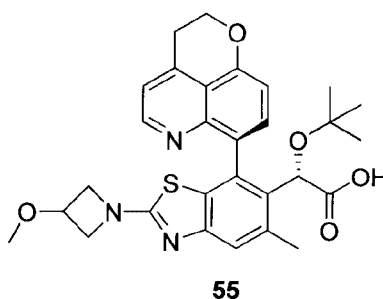
Compound **53**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ 8.71 (d, $J = 5.4$ Hz, 1H), 8.14 (d, $J = 8.2$ Hz, 1H), 7.69 (d, $J = 5.4$ Hz, 1H), 7.57 (s, 1H), 7.40 (d, $J = 8.2$ Hz, 1H), 5.21 (s, 1H), 4.72 – 4.60 (m, 2H), 4.56 – 4.42 (m, 4H), 3.58 (t, $J = 6.0$ Hz, 2H), 2.65 (s, 3H), 0.91 (s, 9H). LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{28}\text{F}_2\text{N}_3\text{O}_4\text{S}$: 540.18 (M+H $^+$); Found: 539.98, 541.02 (M+H $^+$).

Example 4. Preparation of (S)-2-tert-butoxy-2-((S)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-2-(3-methoxyazetidin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (**54**) and (S)-2-tert-butoxy-2-((R)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-2-(3-methoxyazetidin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (**55**).

Compounds **54** and **55** were prepared from compound **32** according to the procedure used to prepare compound **35** (except that 2-methoxyazetidine was used instead of azetidine) in Example 1.



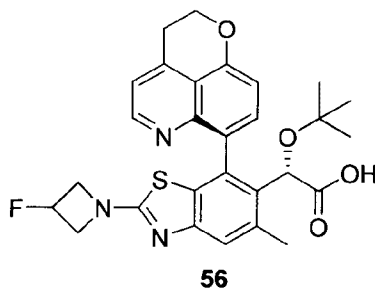
Compound **54**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ : 8.78 (d, $J = 5.5$ Hz, 1H), 7.84 (d, $J = 8.5$ Hz, 1H), 7.77 (d, $J = 6.1$ Hz, 1H), 7.52 (s, 1H), 7.37 (d, $J = 7.8$ Hz, 1H), 5.16 (s, 1H), 4.73 – 4.64 (m, 2H), 4.41 (ddd, $J = 9.9, 6.2, 3.4$ Hz, 1H), 4.31 (td, $J = 7.7, 1.0$ Hz, 2H), 4.02 – 3.90 (m, 2H), 3.62 (t, $J = 5.7$ Hz, 2H), 2.68 (s, 4H), 0.91 (s, 11H). LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{32}\text{N}_3\text{O}_5\text{S}$: 534.21 ($\text{M}+\text{H}^+$); Found: 533.95, 534.97 ($\text{M}+\text{H}^+$).



Compound **55**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ : 8.67 (d, $J = 5.1$ Hz, 1H), 8.04 (d, $J = 8.2$ Hz, 1H), 7.52 (d, $J = 4.7$ Hz, 1H), 7.43 (s, 1H), 7.30 (d, $J = 8.1$ Hz, 1H), 5.19 (s, 1H), 4.66 – 4.56 (m, 2H), 4.42 (m, 1H), 4.38 – 4.32 (m, 2H), 4.08 – 4.01 (m, 2H), 3.49 (t, $J = 6.0$ Hz, 3H), 2.61 (s, 3H), 0.82 (s, 10H). LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{32}\text{N}_3\text{O}_5\text{S}$: 534.21 ($\text{M}+\text{H}^+$); Found: 534.03, 535.08 ($\text{M}+\text{H}^+$).

Example 5. Preparation of (S)-2-tert-butoxy-2-((S)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-2-(3-fluoroazetidin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (**56**).

Compound **56** was prepared from compound **32** according to the procedure used to prepare compound **35** (except that 2-fluoroazetidine was used instead of azetidine) in Example 1.



WO 2013/159064

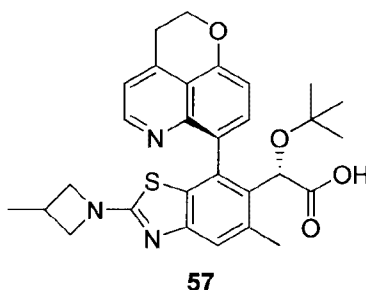
PCT/US2013/037483

Compound **56**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ 8.79 (d, $J = 5.5$ Hz, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 7.79 (d, $J = 5.1$ Hz, 1H), 7.55 (s, 1H), 7.39 (d, $J = 7.9$ Hz, 1H), 5.58 – 5.38 (m, 1H), 5.16 (s, 1H), 4.70 (td, $J = 5.9, 3.1$ Hz, 2H), 4.49 – 4.35 (m, 2H), 4.28 – 4.12 (m, 2H), 3.63 (t, $J = 6.0$ Hz, 2H), 2.68 (s, 3H), 0.91 (s, 9H).

5 LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{29}\text{FN}_3\text{O}_4\text{S}$: 522.19 ($\text{M}+\text{H}^+$); Found: 521.97, 523.02 ($\text{M}+\text{H}^+$).

Example 6. Preparation of (S)-2-tert-butoxy-2-((S)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methyl-2-(3-methylazetidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (**57**).

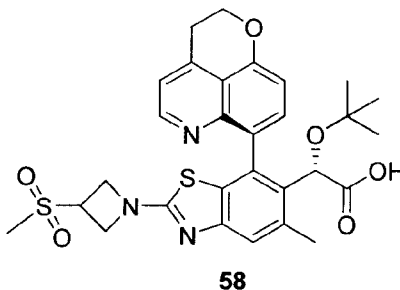
10 Compound **57** was prepared from compound **32** according to the procedure used to prepare compound **35** (except that 2-methylazetidine was used instead of azetidine) in Example 1.



15 Compound **57**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ : δ 8.92 (s, 1H), 7.90 (d, $J = 7.6$ Hz, 2H), 7.56 (s, 1H), 7.44 (d, $J = 7.3$ Hz, 1H), 5.18 (s, 1H), 4.73 (s, 2H), 4.48 (s, 2H), 3.99 (s, 2H), 3.68 (s, 2H), 3.12 (m, 1H), 2.73 (s, 3H), 1.35 (d, $J = 5.6$ Hz, 3H), 0.91 (s, 9H). LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{32}\text{N}_3\text{O}_4\text{S}$: 518.21 ($\text{M}+\text{H}^+$); Found: 518.09, 519.12 ($\text{M}+\text{H}^+$).

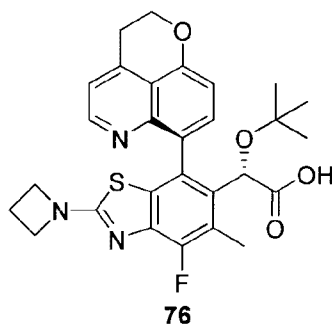
20 Example 7. Preparation of (S)-2-tert-butoxy-2-((S)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methyl-2-(3-(methylsulfonyl)azetidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (**58**).

Compound **58** was prepared from compound **32** according to the procedure used to prepare compound **35** (except that 2-methylsulfonylazetidine was used instead of azetidine) in Example 1.

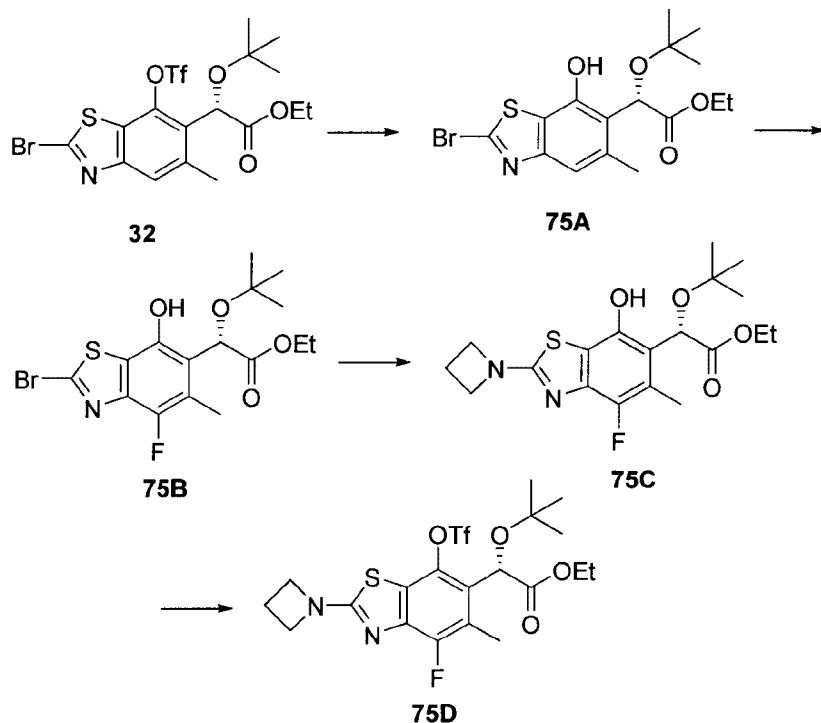


Compound **58**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ : $^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.85 (d, $J = 5.3$ Hz, 1H), 7.89 (t, $J = 6.7$ Hz, 2H), 7.61 (s, 1H), 7.44 (d, $J = 8.1$ Hz, 1H), 5.18 (s, 1H), 4.72 (dd, $J = 9.0, 6.2$ Hz, 2H), 4.59 – 4.35 (m, 5H), 3.01 (s, 3H), 2.72 (s, 3H), 0.92 (s, 9H). LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{32}\text{N}_3\text{O}_6\text{S}$: 582.17 ($\text{M}+\text{H}^+$); Found: 581.95, 583.02($\text{M}+\text{H}^+$).

Example 8. Preparation of (S)-2-((S)-2-(azetidin-1-yl)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-4-fluoro-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetic acid (**76**).



Compound **76**: $^1\text{H-NMR}$: 400 MHz, (CD_3OD) δ : 8.65 (d, $J = 4.4$ Hz, 1H); 7.70 (d, $J = 7.6$ Hz, 1H); 7.39 (d, $J = 4.4$ Hz, 1H); 7.16 (d, $J = 7.6$ Hz, 1H); 5.04 (s, 1H); 4.57 (t, $J = 6.0$ Hz, 2H); 4.15-4.10 (m, 4H); 3.41 (t, $J = 6.0$ Hz, 2H); 2.50-2.46 (m, 6H); 0.90 (s, 9H). LCMS-ESI $^+$ (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{29}\text{FN}_3\text{O}_4\text{S}$: 522.19 ($\text{M}+\text{H}^+$); Found: 521.99, 523.00($\text{M}+\text{H}^+$).



Step 1.

Preparation of (S)-ethyl 2-(2-bromo-7-hydroxy-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**75A**): To a solution of (S)-ethyl 2-(2-bromo-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**32**): (500 mg, 0.938 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 4 mL) slowly. The reaction mixture was stirred at room temperature for 1h. The reaction mixture was washed by a mixture of H₂O (20 mL) and HOAc(200 ul), extracted by EtOAc, the organic phase was washed by sat. NaHCO₃, dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-40% EtOAc in hexanes to give **75A** (380 mg). LCMS-ESI⁺: calc'd for C₁₆H₂₀BrNO₄S: 402.0 (M+H⁺); Found: 401.9 (M+H⁺).

10 Step 2.

Preparation of (S)-ethyl 2-(2-bromo-4-fluoro-7-hydroxy-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**75B**): The reaction mixture of (S)-ethyl 2-(2-bromo-7-hydroxy-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**75A**) (380 mg, 0.948 mmol), Selectfluor (1.9 g, 4.74 mmol) in acetonitrile (7 mL) was reacted at 0 °C for 5 days. The reaction mixture was washed by 1.5 M KH₂PO₄, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-40% EtOAc in hexanes to give **75B** (137 mg, 35%). LCMS-ESI⁺: calc'd for C₁₆H₁₉FNO₄S: 420.0 (M+H⁺); Found: 420.1 (M+H⁺).

Step 3.

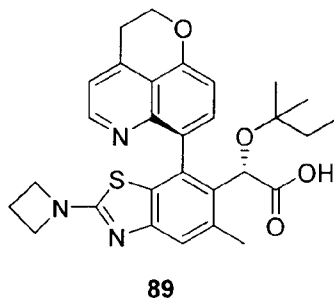
20 Preparation of (S)-ethyl 2-(2-(azetidin-1-yl)-4-fluoro-7-hydroxy-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**75C**): Prepared by the similar method to make (S)-ethyl 2-(2-(azetidin-1-yl)-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**33**) in Example 10. LCMS-ESI⁺: calc'd for C₁₉H₂₅FN₂O₄S: 397.2 (M+H⁺); Found: 397.0 (M+H⁺).

25 Step 4.

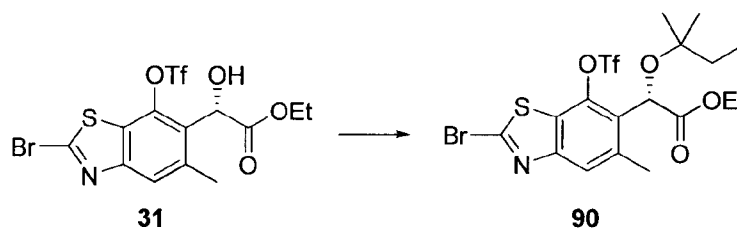
Preparation of (S)-ethyl 2-(2-(azetidin-1-yl)-4-fluoro-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**75D**): The reaction mixture of (S)-ethyl 2-(2-(azetidin-1-yl)-4-fluoro-7-hydroxy-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**75C**) (50 mg, 0.126 mmol), N-phenyl triflate (90 mg, 0.252 mmol), Cs₂CO₃ (82 mg, 0.126 mmol) in THF (2 mL) was stirred at rt. After the reaction finished, the reaction was washed by sat NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-40% EtOAc in hexanes to give **75D** (50 mg, 75%). LCMS-ESI⁺: calc'd for C₂₀H₂₄F₄N₂O₆S₂: 529.1 (M+H⁺); Found: 529.0 (M+H⁺).

The remainder of the synthesis of compound **76** is analogous to the preparation of compound **35** from compound **33** in example 1.

- 5 **Example 9.** Preparation of (S)-2-((S)-2-(azetidin-1-yl)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methylbenzo[d]thiazol-6-yl)-2-(tert-pentyloxy)acetic acid (**89**).



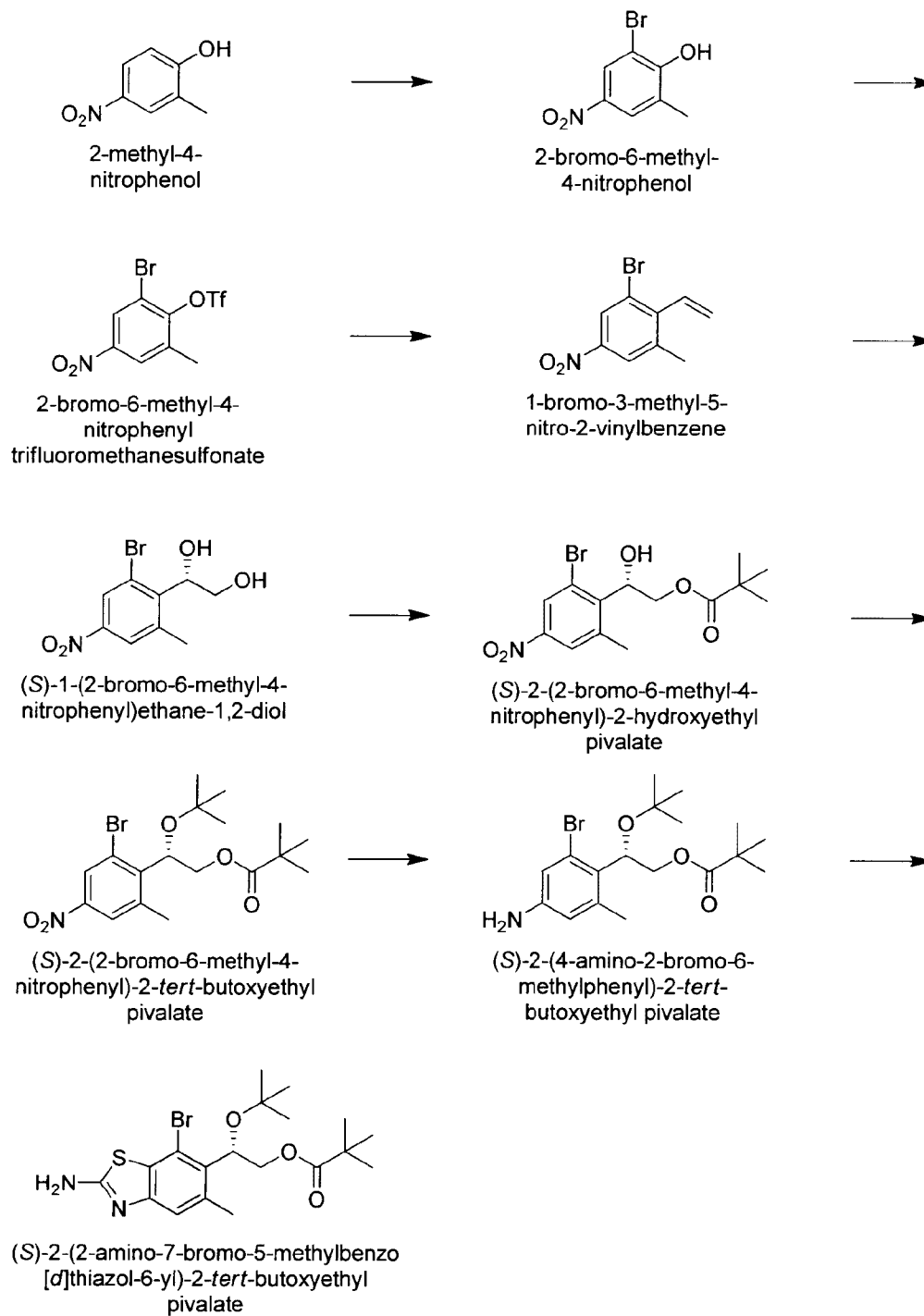
Compound **89**: ^1H NMR (400 MHz, CD_3OD) δ 8.75 (d, $J = 5.1$ Hz, 1H), 7.82 (d, $J = 8.3$ Hz, 1H), 7.71 (d, $J = 5.6$ Hz, 1H), 7.47 (s, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 5.09 (d, $J = 0.6$ Hz, 1H), 4.69 – 4.62 (m, 2H), 4.17 (t, $J = 7.7$ Hz, 4H), 3.61 – 3.55 (m, 2H), 2.66 (s, 3H), 2.58 – 2.42 (m, 2H), 0.87 (d, $J = 2.9$ Hz, 6H), 0.59 (t, $J = 7.0$ Hz, 3H). ^{19}F NMR (377 MHz, CD_3OD) δ -77.77. LCMS: calc'd = 518.64, observed: 518.08



Preparation of **90**: A slurry of **31** (740 mg, 1.55 mmol) in tert-amyl acetate (7.0 mL) was treated with 70% aq. HClO_4 (5 μL) was added at 23 $^\circ\text{C}$. Reaction became cloudy, but LCMS analysis indicated minimal conversion. More 70% aq. HClO_4 (50 μL) was introduced. After 2 h, the reaction was added dropwise over 5 min to sat. aq. NaHCO_3 (20 mL). H_2O (10 mL) was added, and the system was extracted with DCM (3 x 20 mL). Combined organic layers were dried (Na_2SO_4), filtered, concentrated, and treated with hexane (10 mL). The system was concentrated again to remove some residual t-amyl alcohol. The residue was treated with Benzene and loaded onto a 12 gram “gold” ISCO silica gel column. Chromatography (eluent: Hexanes / Ethyl Acetate) gave **90** (134 mg, 16% yield) along with some recovered **31**. ^1H -NMR: 400 MHz, (CDCl_3) δ : 7.80 (s, 1H), 5.49 (s, 1H), 4.24-4.06 (m, 2H), 2.57 (s, 3H), 1.60-1.40 (m, 2H), 1.17 (s, 3H), 1.16 (t, $J = 7.0$ Hz, 3H), 1.05 (s, 3H), 0.80 (t, $J = 7.0$ Hz, 3H). ^{19}F -NMR: 376 MHz, (CDCl_3) δ : -73.8

The remainder of the synthesis of **89** follows the same route as Example 10 from compound **32**.

Example 10. Preparation of (*S*)-2-(2-amino-7-bromo-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (100).



Preparation of 2-bromo-6-methyl-4-nitrophenol: Br₂ (122.2 g, 0.765 mol) was added into a solution of 2-methyl-4-nitrophenol (90.0 g, 0.588 mol) in HOAc (1.17 L) at room temperature. The resulting solution was stirred at room temperature for 4 h. TLC showed the reaction was complete. The solution was added into ice - water (3 L) slowly and filtered. The filter cake was dissolved into EA (2.5 L) and washed with saturated NaHSO₃ (3 x 500 mL). The EtOAc layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford 2-bromo-6-methyl-4-nitrophenol (110 g, 80%) as yellow solid. ¹H-NMR: 400 MHz, (CDCl₃) δ: 8.30 (d, *J* = 2.0 Hz, 1H), 8.05 (s, 1H), 6.22 (s, broad, 1H), 2.41 (s, 3H).

Preparation of 2-Bromo-6-methyl-4-nitrophenyl trifluoromethanesulfonate: To a solution of 2-bromo-6-methyl-4-nitrophenol (110.0 g, 0.474 mol) in DCM (950 mL) at -70 °C was added Et₃N (62.3 g, 0.616 mol) and Tf₂O (147.1 g, 0.521 mol). The resulting solution was stirred at -70 °C for 20 min. TLC showed the reaction was complete. Aqueous HCl (0.5 M, 1 L) was added to quench the reaction. The DCM layers were separated, dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo and purified by silica gel column (Petroleum Ether → Petroleum Ether:EtOAc (20:1)) to afford desired 2-Bromo-6-methyl-4-nitrophenyl trifluoromethanesulfonate (146.7 g, 85%) as yellow solid. ¹H-NMR: 400 MHz, (CDCl₃) δ: 8.41 (d, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 2.8 Hz, 1H), 2.59 (s, 3H).

Preparation of 1-Bromo-3-methyl-5-nitro-2-vinylbenzene: The reaction mixture of 2-Bromo-6-methyl-4-nitrophenyl trifluoromethanesulfonate (10.0 g, 27.5 mmol), vinyl-tri-*n*-butyltin (8.7 g, 27.5 mmol), LiCl (1.4 g, 33.0 mmol), Pd(dppf)Cl₂ (673 mg, 0.92 mmol) and DMF (50 mL) was stirred at 70 °C for 3 h under N₂. Then 2 N aq. NaOH (30 mL) was added and stirred at 70 °C for 10 min. The reaction mixture was cooled down, washed with saturated aqueous NaHCO₃ (100 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo, and purified by silica gel column (Petroleum Ether → Petroleum Ether:EtOAc (50: 1)) to afford 1-Bromo-3-methyl-5-nitro-2-vinylbenzene (2.01 g, 30%) as yellow oil. ¹H-NMR: 400 MHz, (CDCl₃) δ: 8.29 (d, *J* = 2.0 Hz, 1H), 8.02 (s, 1H), 6.67 (dd, *J* = 17.6, 11.6 Hz, 1H), δ 5.75 (d, *J* = 11.6 Hz, 1H), δ 5.49 (d, *J* = 18.0 Hz, 1H), δ 2.48 (s, 3H).

Preparation of (*S*)-1-(2-Bromo-6-methyl-4-nitrophenyl)ethane-1,2-diol: The reaction mixture of 1-Bromo-3-methyl-5-nitro-2-vinylbenzene (30.0 g, 0.124 mol), AD-mix α (173.5 g: 0.104 g of K₂OsO₄·2 H₂O; 1.389 g of (DHQ)₂PHAL; 51.038 g of K₂CO₃ and 120.99 g of

K₄Fe(CN)₆, MeSO₂NH₂ (11.8 g, 0.124 mol) in *t*-BuOH (250 mL) and H₂O (250 mL) was stirred at 0 °C for 3 days. Na₂SO₃ (15 g) was added and stirred at room temperature for 40 min to quench the reaction. The reaction mixture was treated with water (1 L) and the resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo, and purified by silica gel column (Petroleum Ether: EtOAc (2:1), isocratic) to afford (*S*)-1-(2-Bromo-6-methyl-4-nitrophenyl)ethane-1,2-diol (17 g, 50%) as yellow solid. ¹H-NMR: 400 MHz, (CDCl₃) δ: 8.26 (s, 1H), 7.99 (s, 1H), 5.56-5.54 (m, 1H), 3.94- 3.92 (m, 1H), 3.81- 3.78 (m, 1H), 2.82 (d, broad, 1H), 2.67 (s, 3H), 2.18-2.15 (m, 1H).

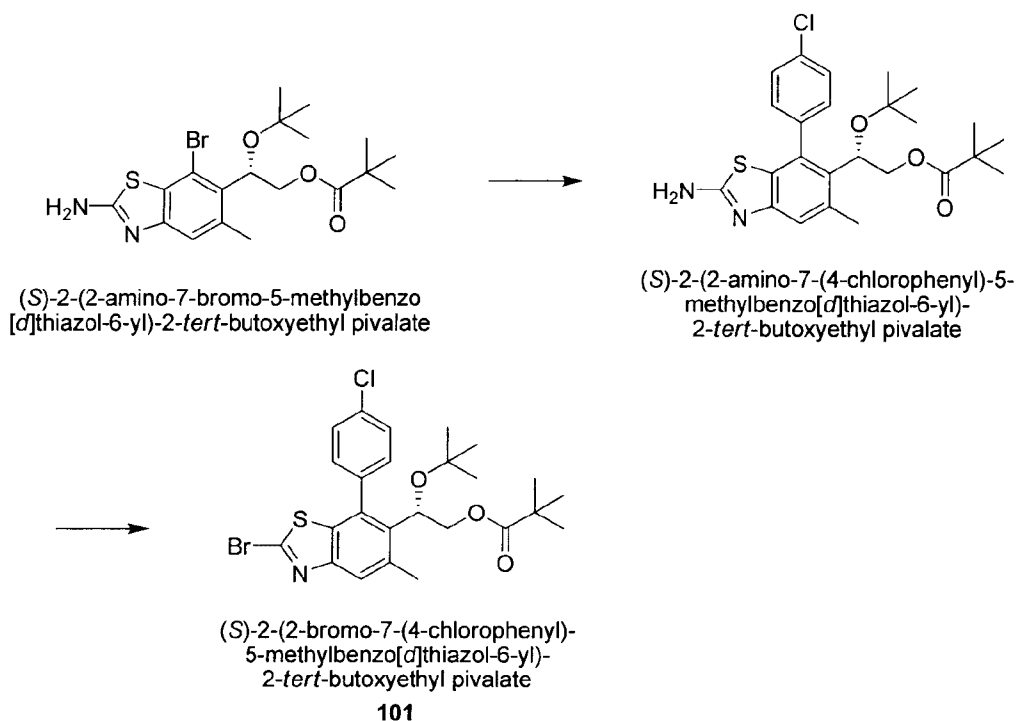
Preparation of (*S*)-2-(2-Bromo-6-methyl-4-nitrophenyl)-2-hydroxyethyl pivalate: To a suspension of (*S*)-1-(2-Bromo-6-methyl-4-nitrophenyl)ethane-1,2-diol (17.0 g, 61.6 mmol) in DCM (435 mL) at 0 °C was added pyridine (18.6 g, 235.4 mmol) and PivCl (13.4 g, 110.8 mmol) slowly. After stirring at 0 °C for 5 min, the system was raised to room temperature and stirred at this temperature for 5 h. TLC showed the reaction was complete. The reaction mixture was treated with saturated aqueous NaHCO₃ (500 mL), and the resulting system was extracted with DCM (2 x 200 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered, concentrated in vacuum, and purified by silica gel column (Petroleum Ether: EtOAc (30:1)) to afford (*S*)-2-(2-Bromo-6-methyl-4-nitrophenyl)-2-hydroxyethyl pivalate (17 g, 77%) as yellow solid. ¹H-NMR: 400 MHz, (CDCl₃) δ: 8.28 (s, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 5.70-5.66 (m, 1H), 4.58-4.53 (m, 1H), 4.31-4.26 (m, 1H), 2.84 (d, *J* = 5.6 Hz), 2.68 (s, 3H), 1.22 (s, 9H).

Preparation of (*S*)-2-(2-Bromo-6-methyl-4-nitrophenyl)-2-*tert*-butoxyethyl pivalate: To a solution of (*S*)-2-(2-Bromo-6-methyl-4-nitrophenyl)-2-hydroxyethyl pivalate (13 g, 0.036 mol) in *t*-BuOAc (300 mL) at 0 °C was added HClO₄ (20.7 g, 0.144 mol) slowly. The solution was stirred at 0 °C for 5 min, then warmed to room temperature and stirred at this temperature for 1.5 h. The solution was alkalized by saturated aqueous NaHCO₃ until the pH of solution > 8. The mixture was extracted with EtOAc (3 x 1 L). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo, and purified by silica gel column (Petroleum Ether:EtOAc (50:1)) to afford (*S*)-2-(2-Bromo-6-methyl-4-nitrophenyl)-2-*tert*-butoxyethyl pivalate (9.3 g, 62%) as yellow solid. ¹H-NMR: 400 MHz, (CDCl₃) δ: 8.26 (s, 1H), 7.98 (s, 1H), 5.60-5.57 (m, 1H), 4.32-4.27 (m, 1H), 4.18-4.14 (m, 1H), 2.73 (s, 3H), 1.17 (s, 9H), 1.14 (s, 9H).

Preparation of (*S*)-2-(4-amino-2-bromo-6-methylphenyl)-2-*tert*-butoxyethyl pivalate: To a solution of (*S*)-2-(2-Bromo-6-methyl-4-nitrophenyl)-2-*tert*-butoxyethyl pivalate (9 g, 0.022 mol) in EtOH (50 mL) and EtOAc (50 mL) was added Pt/C (1.4 g), and the reaction was fitted with a balloon of H₂. The reaction mixture was stirred at room temperature for 3 h. TLC showed the reaction was complete. The reaction mixture was filtered over Celite[™]. The filtrate was concentrated in vacuo to give (*S*)-2-(4-amino-2-bromo-6-methylphenyl)-2-*tert*-butoxyethyl pivalate (7 g, 82%) as brown oil, which was immediately used for next step without further purification. ¹H-NMR: 400 MHz, (CDCl₃) δ: 6.70 (s, 1H), 6.40 (s, 1H), 5.38 (app. s, broad, 1H), 4.22 (app. s, broad, 1H), 4.05 (app. s, broad, 1H), 3.60 (app. s, broad, 2H), 2.47 (s, 3H), 1.17 (s, 9H), 1.13 (s, 9H).

Preparation of (*S*)-2-(2-amino-7-bromo-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate: To a solution of freshly prepared (*S*)-2-(4-amino-2-bromo-6-methylphenyl)-2-*tert*-butoxyethyl pivalate (7 g, 18.1 mmol) in HOAc (90 mL) was added KSCN (1.76 g, 18.1 mmol) at r.t. The reaction mixture was stirred at r.t. for 0.5 h. Pyridinium perbromide (5.79 g, 18.1 mmol) was added slowly over a period of 10 min, and stirred at r.t. for 2 h. The mixture was alkalized to pH = 8 using saturated aqueous NaHCO₃ solution, then extracted with EtOAc (3 x 600 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo, and purified by silica gel column (Petroleum Ether:EtOAc (10:1 → 5:1)) to afford (*S*)-2-(2-amino-7-bromo-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (2.74 g, 34.3%) as yellow solid. LCMS-ESI⁺: calc'd for C₁₉H₂₇BrN₂O₃S: 443.1 and 445.1 (M+H⁺); found: 443.1 and 445.1 (M+H⁺). ¹H-NMR: 400 MHz, (CD₃OD) δ: 7.15 (s, 1H), 5.53-5.49 (m, 1H), 4.31-4.26 (m, 1H), 4.17-4.13 (m, 1H), 2.64 (s, 3H), 1.15 (s, 9H), 1.11 (s, 9H).

Example 11. Preparation of (*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (101).

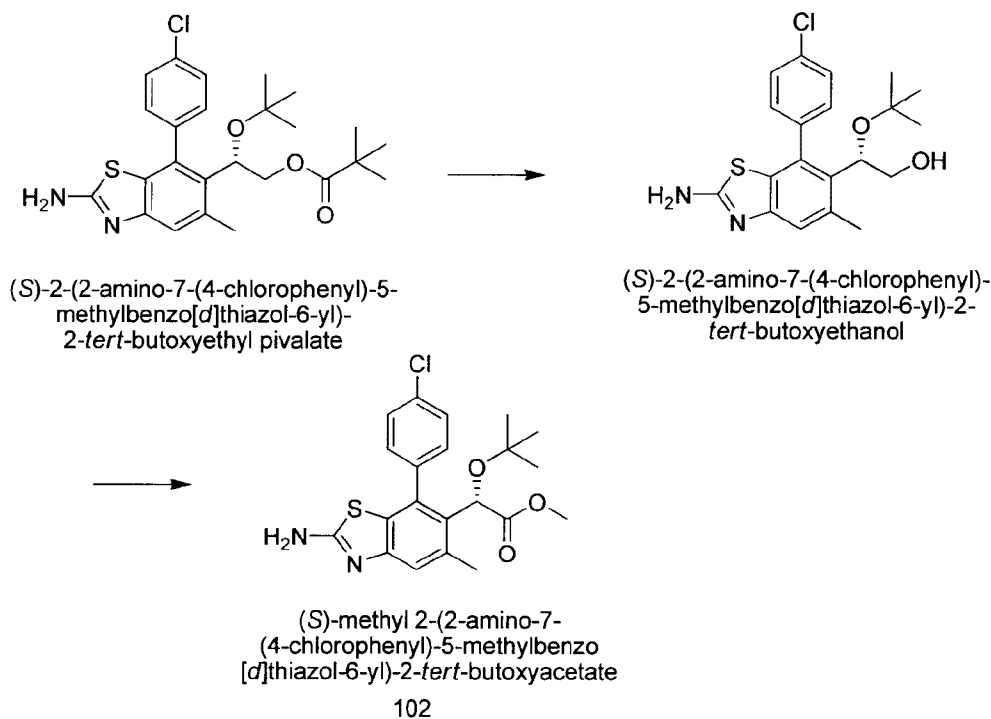


Preparation of (S)-2-(2-Amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate: 2 separate microwave tubes were each charged with (S)-2-(2-Amino-7-bromo-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate (768 mg, 1.74 mmol), K₂CO₃ (960 mg, 6.96 mmol), 4-chlorophenylboronic acid (325 mg, 2.09 mmol), Pd(PPh₃)₄ (200 mg, 0.174 mmol), dioxane (8.0 mL), and H₂O (2.0 mL). The two sealed vessels were separately heated at 110 °C for 3 h. The reactions were cooled to 23 °C and combined. H₂O (50 mL) was added, and the system was extracted with EtOAc (3 x 50 mL). The combined extracts were dried (Na₂SO₄), filtered, and concentrated. The residue was treated with benzene and purified via chromatography on silica gel (80 g “gold” ISCO column; Hex / EtOAc) giving (S)-2-(2-Amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate (1.55 g, 90% yield). LCMS-ESI⁺: calc’d for C₂₅H₃₁ClN₂O₃S: 475.2 and 477.2 (M+H⁺); found: 475.3 and 477.3 (M+H⁺). ¹H-NMR: 400 MHz, (CDCl₃) δ: 7.49-7.41 (m, 2H), 7.36-7.32 (m, 2H), 7.22 (d, J = 7.3 Hz, 1H), 5.19 (s, broad, 2H), 4.67 (dd, J = 9.0, 2.7 Hz, 1H), 4.36 (dd, J = 11.7, 9.0 Hz, 1H), 4.23 (dd, J = 11.7, 2.7 Hz, 1H), 2.68 (s, 3H), 1.14 (s, 9H), 0.94 (s, 9H).

Preparation of (S)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate: At 23 °C, in a water bath, a solution of (S)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate (1.13 g, 2.37 mmol) in CH₃CN (22 mL) was treated with solid anhydrous CuBr₂ (635 mg, 2.84 mmol). Reaction was fitted with a

mineral oil bubbler. A freshly prepared solution of *t*-butyl nitrite (269 mg, 2.61 mmol) in CH₃CN (2.0 mL) was added dropwise over a 5 min period. The water bath was removed. Gas evolution was monitored using the bubbler. At 1 h, gas evolution ceased. The reaction was poured into EtOAc (50 mL) and treated with H₂O (50 mL). A brown solid precipitated. The suspension was filtered over Celite, which was thoroughly washed with EtOAc. The filtrate was transferred to a separatory funnel. The organic phase was collected. The aq. phase was extracted with EtOAc. The total organic layers were combined, dried (Na₂SO₄), filtered, and concentrated. The residue was treated with benzene and purified via chromatography on silica gel (80 g "gold" ISCO column; Hex / EtOAc) giving (*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (675 mg, 53% yield). LCMS-ESI⁺: calc'd for C₂₅H₂₉BrClNO₃S: 538.1, 540.1, and 542.1.1 (M+H⁺); found: 538.2, 540.2, and 542.2 (M+H⁺). ¹H-NMR: 400 MHz, (CDCl₃) δ: 7.76 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 4.76 (dd, *J* = 9.0, 3.5 Hz, 1H), 4.39 (dd, *J* = 11.7, 9.0 Hz, 1H), 4.25 (dd, *J* = 11.7, 3.5 Hz, 1H), 2.76 (s, 3H), 1.14 (s, 9H), 0.94 (s, 9H).

Example 12. Preparation of (*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (102).

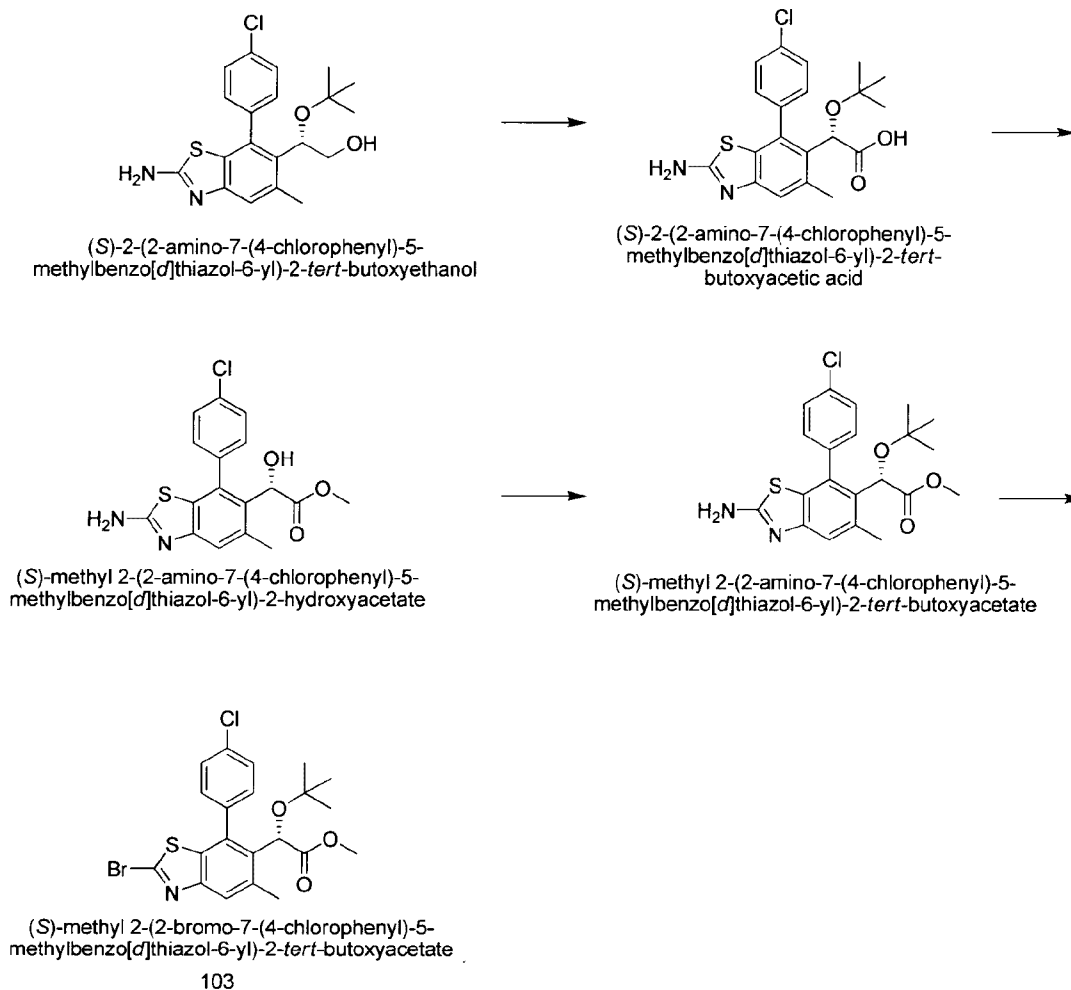


Preparation of (*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethanol: A flask was charged with (*S*)-2-(2-Amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (2.15 g, 4.52 mmol), LiOH monohydrate (2.00 g, 47.4 mmol), H₂O (4 mL), EtOH (absolute, 4.0 mL), and THF (8.0 mL).

- 5 The reaction was placed under N₂ and heated to 100 °C. After 2 h, the reaction was cooled to 23 °C, diluted with H₂O, and extracted with EtOAc several times. The combined organic phases were dried (Na₂SO₄), filtered, and concentrated. The residue was treated with benzene and purified via chromatography on silica gel (80 g “gold” ISCO column; Hex / EtOAc) giving (*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethanol (1.10 g, 62% yield). LCMS-ESI⁺: calc'd for C₂₀H₂₃ClN₂O₂S: 391.1 and 393.1 (M+H⁺); found: 391.2 and 393.2 (M+H⁺). ¹H-NMR: 400 MHz, (CDCl₃) δ: 7.49-7.41 (m, 2H), 7.36-7.32 (m, 2H), 7.20 (d, *J* = 7.3 Hz, 1H), 5.39 (s, broad, 2H), 4.52-4.50 (m, 1H), 3.85-3.70 (m, 2H), 2.63 (s, 3H), 0.99 (s, 9H).

- 15 Preparation of (*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: A solution of (*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethanol (1.10 g, 2.81 mmol) in CH₃CN (40 mL) and H₂O (10 mL) was treated with H₅IO₆ (2.00 g, 8.77 mmol) at 0 °C. Then solid CrO₃ (500 mg, 5.00 mmol) was added in one portion. All solids dissolved initially, then precipitate developed. Reaction was warmed to 23 °C. After 1.5 h, the reaction was treated with 1.0 M aq. Na₂HPO₄ until the pH was ~8. Then 1.0 M aq. NaH₂PO₄ was added to pH = 5. The resulting system was extracted with DCM (50 mL). The organic phase was dried (Na₂SO₄), filtered, and treated with MeOH (20 mL). Trimethylsilyldiazomethane (2.0 M in hexane, 3.0 mL) was added slowly. The reaction was then stirred for 5 min. Glacial AcOH (300 μL) was added carefully. Saturated aq. Na₂HPO₄ (50 mL) was added. The organic phase was collected, and the aq. layer was extracted with DCM. Combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The residue was purified via chromatography on silica gel (80 g “gold” ISCO column; Hex / EtOAc) giving (*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (206 mg, 19% yield). LCMS-ESI⁺: calc'd for C₂₁H₂₃ClN₂O₃S: 419.1 and 421.1 (M+H⁺); found: 419.2 and 421.2 (M+H⁺). ¹H-NMR: 400 MHz, (CDCl₃) δ: 7.50-7.31 (m, 5H), 5.17 (s, broad, 2H), 5.10 (s, 1H), 3.72 (s, 3H), 2.49 (s, 3H), 0.95 (s, 9H).

Example 13. Preparation of (*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (103).



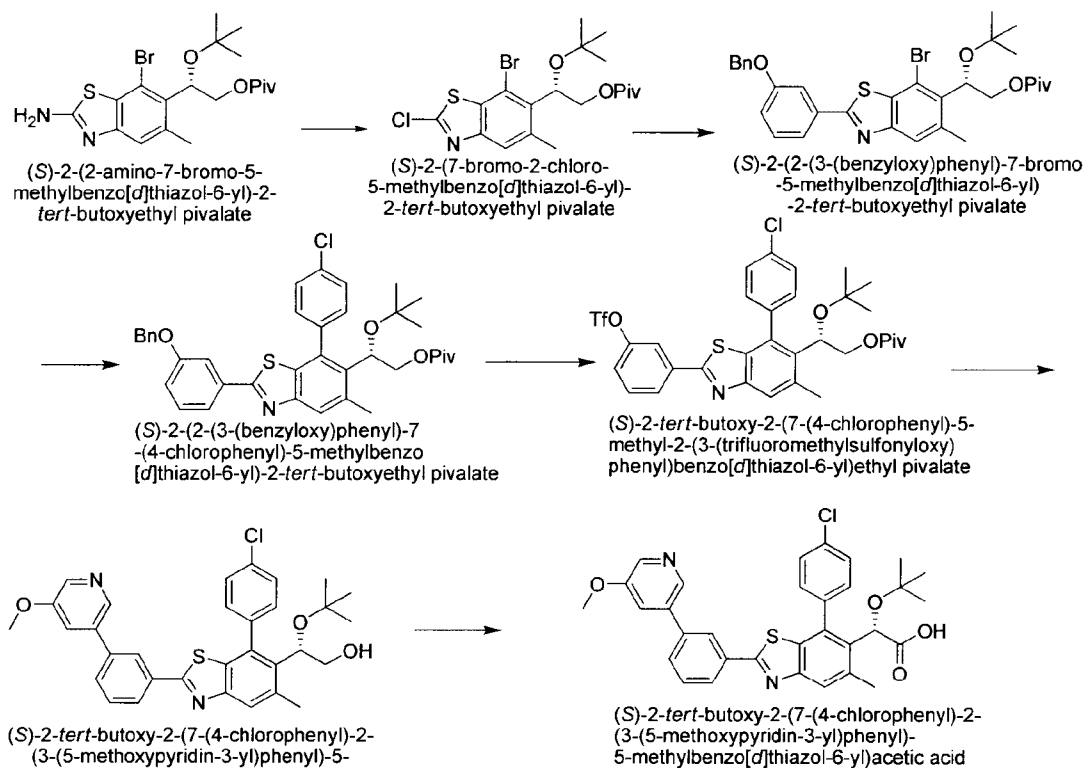
- Preparation of (*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid. To a solution of (*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethanol (1.95 g, 5.00 mmol) in acetonitrile (25 mL) and water (1 mL) was added H₅IO₆ (1.37 g, 6.00 mmol) and CrO₃ (1.00 g, 10.0 mmol). The mixture was stirred at room temperature for 1 h and was diluted with EtOAc (50 mL) and a saturated solution of Na₂SO₃ (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc.
- The crude material was taken on without further purification. ¹H-NMR: 400 MHz, (CDCl₃) δ: 7.42-7.61 (m, 4H), 7.20 (s, 1H), 5.11 (s, 1H), 2.47 (s, 3H), 0.93 (s, 9H).

- Preparation of (*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate. To a solution of Preparation of (*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid from above in MeOH (25 mL) was added H₂SO₄ (200 μL). The reaction mixture was stirred at overnight. EtOAc (20 mL) and saturated

NaHCO₃ solution (50 mL) were added. The layers were separated, dried, filtered, and concentrated *in vacuo*. The crude mixture was a mixture of the desired (*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate and (*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-hydroxyacetate. *t*-Butyl acetate was added (20 mL) and perchloric acid (500 μ L). The mixture was stirred at rt for 3 hr, where all (*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-hydroxyacetate was converted to (*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate. EtOAc (10 mL) and saturated NaHCO₃ solution (50 mL) were added. The layers were separated, dried, filtered, and concentrated *in vacuo*. LCMS-ESI⁺: calc'd for C₂₁H₂₃ClN₂O₃S: 419.1 and 421.1 (M+H⁺); found: 419.2 and 421.2 (M+H⁺).

Preparation of (*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate. To a solution of (*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate from above in acetonitrile (25 mL) was added CuBr₂ (1.1 g, 5.0 mmol) and *t*-butyl nitrite (600 μ L, 5.0 mmol). The reaction was stirred at room temperature for 30 min, and then a saturated solution of Na₂SO₃ (25 mL) was added. The layers were separated, dried, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (EtOAc/hexanes) to give 642 mg of (*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate. LCMS-ESI⁺: calc'd for C₂₁H₂₁BrClNO₃S: 482.0 and 484.0 (M+H⁺); found: 482.1 and 484.1 (M+H⁺). ¹H-NMR: 400 MHz, (CDCl₃) δ : 7.70 (s, 1H), 7.41 (br s, 3H), 7.19 (s, 1H), 5.09 (s, 1H), 3.67 (s, 3H), 2.49 (s, 3H), 0.88 (s, 9H).

Example 14. Method B: Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(5-methoxypyridin-3-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (104).



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Preparation of (S)-2-(7-bromo-2-chloro-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate: To a solution of (S)-2-(2-amino-7-bromo-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate (1g, 2.26mmol) in acetonitrile (15 mL) was added t-butyl nitrite (350 μ L, 2.94 mmol) and CuCl_2 (364 mg, 2.7 mmol). The reaction mixture was stirred at room temperature for 5 hours. After the reaction finished, the reaction mixture was diluted by EtOAc, washed by water, extracted by EtOAc. The organic phase was dried over MgSO_4 , filtered, concentrated down and purified by silica gel column, eluting by 0-50% EtOAc in hexanes to give the product (850 mg, 81%). LCMS-ESI⁺: calc'd for $\text{C}_{19}\text{H}_{25}\text{BrClNO}_3\text{S}$: 462.0 ($\text{M}+\text{H}^+$); Found: 462.14 ($\text{M}+\text{H}^+$).

Preparation of (S)-2-(2-(3-(benzyloxy)phenyl)-7-bromo-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate: To a solution of (S)-2-(7-bromo-2-chloro-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate (130 mg, 0.282 mmol) in dioxane, was added 3-benzyloxyphenylboronic acid pinacol ester (105 mg, 0.338 mmol), $\text{Pd}(\text{PPh}_3)_4$ (16 mg, 0.014 mmol), 2N K_2CO_3 (700 μ L). The reaction mixture in sealed tube was heated at 95 °C for 1.5hs. Then the reaction was cooled down. The reaction mixture was washed by sat. NaHCO_3 , and extracted by EtOAc. The organic phase was filtered, concentrated down, purified by silica gel

column, eluting by 0-50% EtOAc in hexanes to give the product (100mg, 58%). LCMS-ESI⁺: calc'd for C₃₂H₃₆BrNO₄S: 610.2 (M+H⁺); Found: 610.2 (M + H⁺).

Preparation of (*S*)-2-(2-(3-(benzyloxy)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate: The mixture of (*S*)-2-(2-(3-(benzyloxy)phenyl)-7-bromo-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (100mg, 0.164 mmol), 4-chlorophenylboronic acid (38 mg, 0.246 mmol), 2N K₂CO₃ (400μL), Pd(PPh₃)₄ (18 mg, 0.016 mmol) in dioxane in sealed tube was heated at 120 °C. After the reaction is finished, the reaction mixture was washed by sat. NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column (0-50% EtOAc in Hexanes) to give the product (103 mg, 97%). LCMS-ESI⁺: calc'd for C₃₈H₄₀ClNO₄S: 642.2 (M+H⁺); Found: 642.3 (M + H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethylsulfonyloxy)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate: To a solution of (*S*)-2-(2-(3-(benzyloxy)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (410 mg, 0.638 mmol) in EtOH/EtOAc (1:1, 4 mL) was added Pd/C (10%, 600mg). Then hydrogen balloon was attached to the flask, and the reaction was reacted at room temperature for 1h. After the reaction was finished, the catalyst was removed over Celite pad and the solution was concentrated down to dryness. The residue was dissolved in DCM (5 mL), to the solution was added pyridine (2mL), Tf₂O (210 μL, 1.25 mmol) at 0 °C and the reaction was stirred at 0 °C for 1h. Then the reaction was quenched by sat. NaHCO₃, extracted by DCM, dried over MgSO₄, filtered, concentrated down and purified by silica gel column (0-40% EtOAc in hexanes) to give the product (360 mg, 82%). LCMS-ESI⁺: calc'd for C₃₂H₃₃ClF₃NO₆S₂: 684.1 (M+H⁺); Found: 684.1 (M + H⁺).

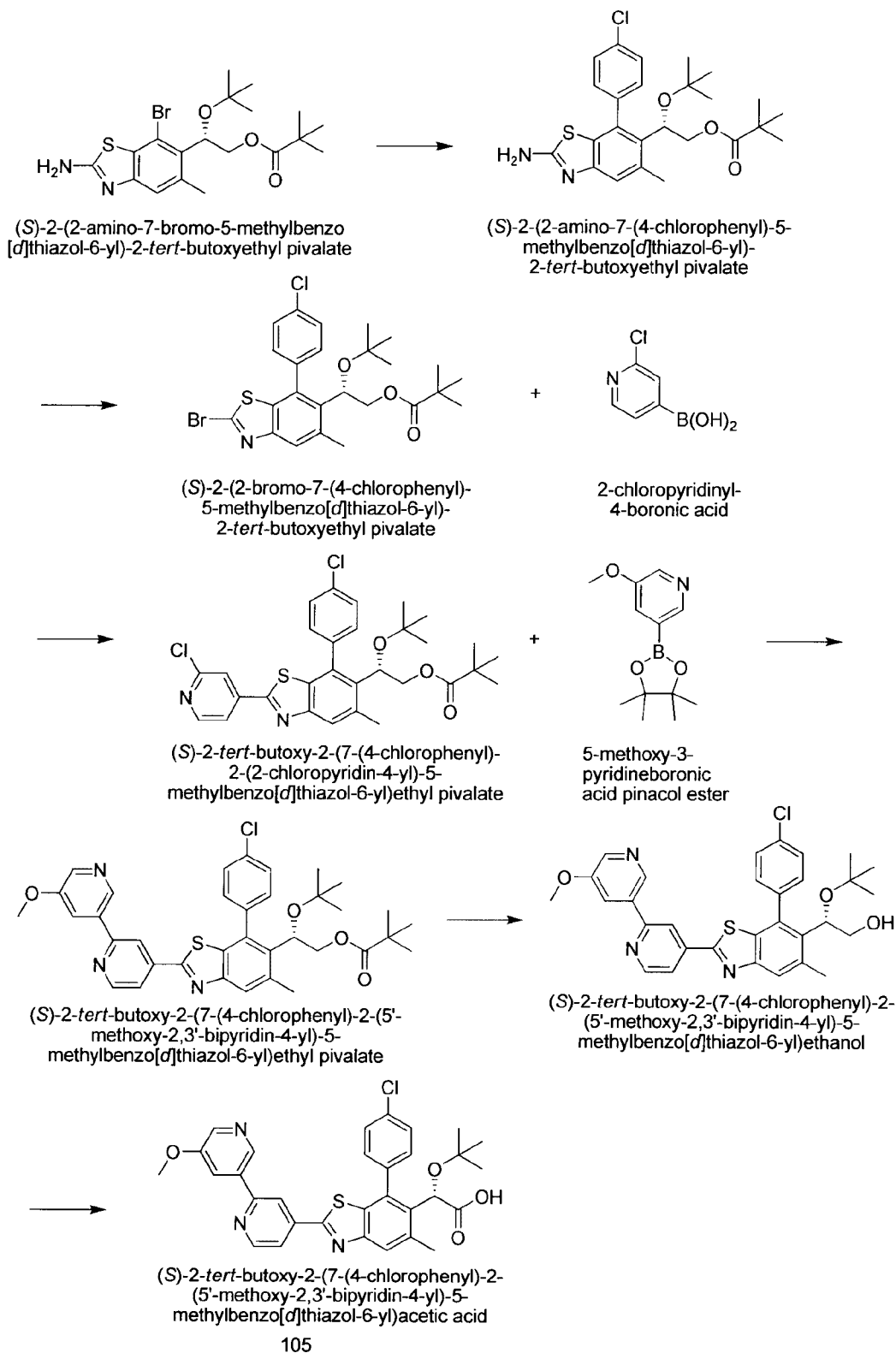
Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(5-methoxypyridin-3-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)ethanol: The reaction mixture of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethylsulfonyloxy)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate (20 mg, 0.029 mmol), 3-methoxypyridine-5-boronic acid pinacol ester (10 mg, 0.043 mmol), 2N K₂CO₃ (70 μL), Pd(PPh₃)₄ (3.3 mg, 0.0029 mmol) in dioxane (1 mL) was heated at 120 °C in sealed tube for 2 hours. After the reaction finished, the reaction was cooled down, to the reaction mixture was added MeOH (1 mL), 2N NaOH (500 μL) and heated at 45 °C for 3 hours. Then reaction mixture was washed by sat. NaHCO₃,

extracted by EtOAc, the organic phase was dried over MgSO_4 , filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product (10 mg, 62 %). LCMS-ESI⁺: calc'd for $\text{C}_{32}\text{H}_{31}\text{ClN}_2\text{O}_3\text{S}$: 559.2 ($\text{M}+\text{H}^+$); Found: 559.2 ($\text{M}+\text{H}^+$).

- 5 Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(5-methoxypyridin-3-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(5-methoxypyridin-3-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)ethanol (10 mg, 0.0179 mmol) in wet acetonitrile (0.75 w% H_2O , 1 mL), was added stock solution of $\text{H}_5\text{IO}_6/\text{CrO}_3$ (0.439 M in 0.75% H_2O in acetonitrile, 400 μL) at 0 °C for ½ hour. The reaction
- 10 mixture was filtered and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA give the product (5 mg, 40%). LCMS-ESI⁺: calc'd for $\text{C}_{32}\text{H}_{29}\text{ClN}_2\text{O}_4\text{S}$: 573.2 ($\text{M}+\text{H}^+$); Found: 573.2 ($\text{M}+\text{H}^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.59 (s, 1H), 8.40-8.38 (m, 2H), 8.09 (d, $J = 4.2$ Hz, 1H), 7.97 (s, 1H), 7.89-7.88 (m, 2H), 7.70-7.60 (m, 5H), 5.26 (s, 1H), 4.03 (s, 3H), 2.62 (s, 3H), 0.97 (s, 9H).

15

Example 15. Method C: Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (105).



105

Preparation of (S)-2-(2-Amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate: 2 separate microwave tubes were each charged with (S)-2-(2-Amino-7-

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bromo-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (768 mg, 1.74 mmol), K₂CO₃ (960 mg, 6.96 mmol), 4-chlorophenylboronic acid (325 mg, 2.09 mmol), Pd(PPh₃)₄ (200 mg, 0.174 mmol), dioxane (8.0 mL), and H₂O (2.0 mL). The two sealed vessels were separately heated at 110 °C for 3 h. The reactions were cooled to 23 °C and combined. H₂O (50 mL) was added, and the system was extracted with EtOAc (3 x 50 mL). The combined extracts were dried (Na₂SO₄), filtered, and concentrated. The residue was treated with benzene and purified via chromatography on silica gel (80 g "gold" ISCO column; Hex / EtOAc) giving (*S*)-2-(2-Amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (1.55 g, 90% yield). LCMS-ESI⁺: calc'd for C₂₅H₃₁ClN₂O₃S: 475.2 and 477.2 (M+H⁺); found: 475.3 and 477.3 (M+H⁺). ¹H-NMR: 400 MHz, (CDCl₃) δ: 7.49-7.41 (m, 2H), 7.36-7.32 (m, 2H), 7.22 (d, *J* = 7.3 Hz, 1H), 5.19 (s, broad, 2H), 4.67 (dd, *J* = 9.0, 2.7 Hz, 1H), 4.36 (dd, *J* = 11.7, 9.0 Hz, 1H), 4.23 (dd, *J* = 11.7, 2.7 Hz, 1H), 2.68 (s, 3H), 1.14 (s, 9H), 0.94 (s, 9H).

Preparation of (*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate: At 23 °C, in a water bath, a solution of (*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (1.13 g, 2.37 mmol) in CH₃CN (22 mL) was treated with solid anhydrous CuBr₂ (635 mg, 2.84 mmol). Reaction was fitted with a mineral oil bubbler. A freshly prepared solution of *t*-butyl nitrite (269 mg, 2.61 mmol) in CH₃CN (2.0 mL) was added dropwise over a 5 min period. The water bath was removed. Gas evolution was monitored using the bubbler. At 1 h, gas evolution ceased. The reaction was poured into EtOAc (50 mL) and treated with H₂O (50 mL). A brown solid precipitated. The suspension was filtered over Celite, which was thoroughly washed with EtOAc. The filtrate was transferred to a separatory funnel. The organic phase was collected. The aq. phase was extracted with EtOAc. The total organic layers were combined, dried (Na₂SO₄), filtered, and concentrated. The residue was treated with benzene and purified via chromatography on silica gel (80 g "gold" ISCO column; Hex / EtOAc) giving (*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate. LCMS-ESI⁺: calc'd for C₂₅H₂₉BrClNO₃S: 538.1, 540.1, and 542.1.1 (M+H⁺); found: 538.2, 540.2, and 542.2 (M+H⁺). ¹H-NMR: 400 MHz, (CDCl₃) δ: 7.76 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 4.76 (dd, *J* = 9.0, 3.5 Hz, 1H), 4.39 (dd, *J* = 11.7, 9.0 Hz, 1H), 4.25 (dd, *J* = 11.7, 3.5 Hz, 1H), 2.76 (s, 3H), 1.14 (s, 9H), 0.94 (s, 9H).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate: (*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-

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methylenbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (400.0 mg, 0.742 mmol), 2-chloro-4-pyridinylboronic acid (140.2 mg, 0.891 mmol), potassium carbonate (307.7 mg, 2.227 mmol), and Pd(PPh₃)₄ (128.7 mg, 0.111 mmol) were placed in a microwave vial and the vial was vacuum pumped and flushed with argon three times. To this mixture was added degassed 1,4-dioxane (3.5 mL) and water (0.7 mL). The reaction mixture was heated at 90 °C for 4.5 h then cooled to rt. The aqueous layer was separated and extracted three times with ethyl acetate. All organic layers were combined, dried over Na₂SO₄, and concentrated. Purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the final compound. LCMS-ESI⁺: calc'd for C₃₀H₃₃Cl₂N₂O₃S: 571.2 (M+H⁺); Found: 571.1 (M + H⁺); ¹H NMR (400 MHz, CDCl₃) δ 8.49 (d, *J* = 4.9 Hz, 1H), 7.93 (s, 2H), 7.77 (d, *J* = 5.0 Hz, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 4.82 (dd, *J* = 8.9, 2.7 Hz, 1H), 4.42 (dd, *J* = 11.2, 9.3 Hz, 1H), 4.29 (dd, *J* = 11.5, 3.2 Hz, 1H), 2.80 (s, 3H), 1.14 (s, 9H), 0.97 (s, 9H).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylenbenzo[d]thiazol-6-yl)ethyl pivalate: (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylenbenzo[d]thiazol-6-yl)ethyl pivalate (40.0 mg, 0.070 mmol), 5-methoxy-3-pyridineboronic acid pinacol ester (19.7 mg, 0.084 mmol), potassium carbonate (29.0 mg, 0.210 mmol), and Pd(PPh₃)₄ (12.1 mg, 0.010 mmol) were placed in a microwave vial and the vial was vacuum pumped and flushed with argon three times. To this mixture was added degassed 1,4-dioxane (0.8 mL) and water (0.2 mL). The reaction mixture was heated at 110 °C for 1 h then cooled to rt. The aqueous layer was separated and extracted three times with ethyl acetate. All organic layers were combined, dried over Na₂SO₄, and concentrated. Purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the product. LCMS-ESI⁺: calc'd for C₃₆H₃₉ClN₃O₄S: 644.2 (M+H⁺); Found: 644.1 (M + H⁺); ¹H NMR (400 MHz, CDCl₃) δ 8.89 (s, 1H), 8.81 (d, *J* = 4.9 Hz, 1H), 8.40 (d, *J* = 2.7 Hz, 1H), 8.35 (s, 1H), 8.02 (s, 1H), 7.95 (s, 1H), 7.83 (d, *J* = 5.2 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 4.83 (dd, *J* = 9.4, 2.7 Hz, 1H), 4.43 (dd, *J* = 11.2, 9.5 Hz, 1H), 4.30 (dd, *J* = 12.1, 2.9 Hz, 1H), 3.99 (s, 3H), 2.81 (s, 3H), 1.15 (s, 9H), 0.97 (s, 9H).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylenbenzo[d]thiazol-6-yl)ethanol: To a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylenbenzo[d]thiazol-6-yl)ethyl pivalate

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(40.5mg, 0.063 mmol) in THF (0.5 mL) and methanol (0.5 mL) was added NaOH (0.5 mL, 2N solution). The reaction mixture was heated at 40 °C for 4 h, cooled, diluted with satd. aqueous NH₄Cl, and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered and concentrated to give the crude product which was used without further purification. LCMS-

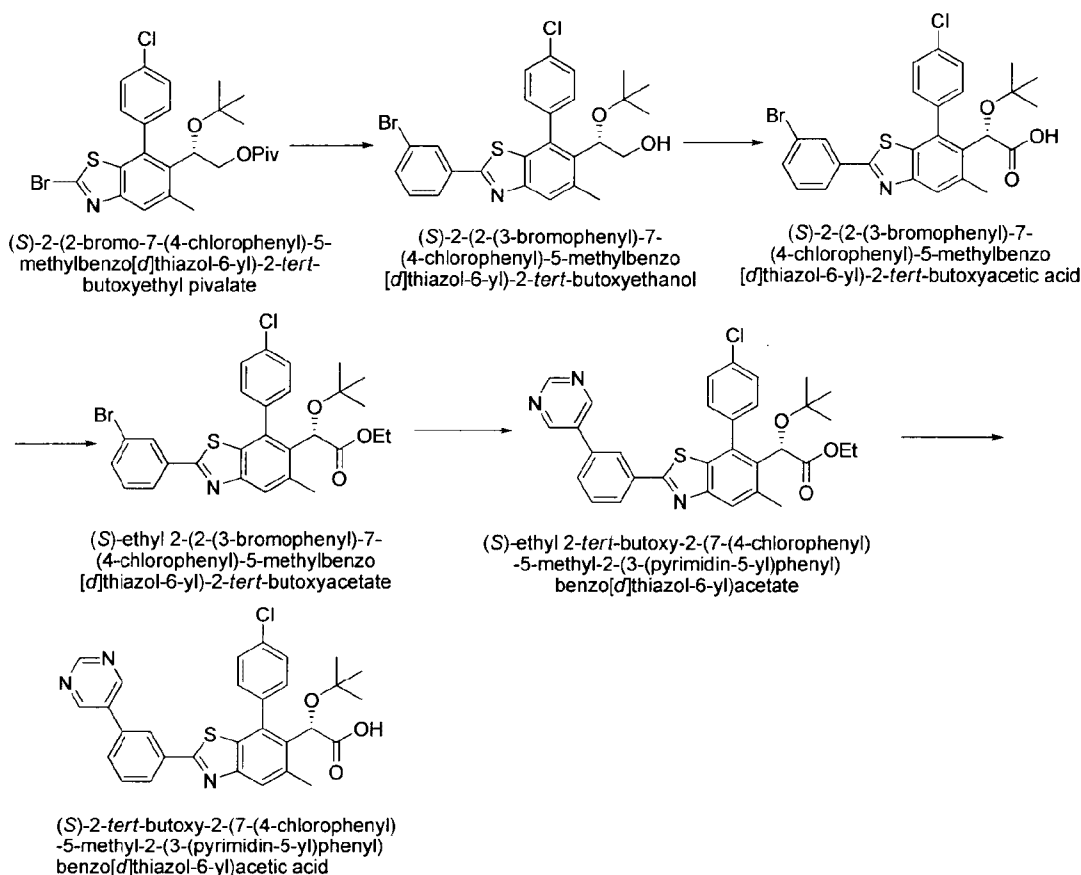
5 ESI⁺: calc'd for C₃₁H₃₁ClN₃O₃S: 560.2 (M+H⁺); Found: 560.0 (M + H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A stock solution of periodic

acid/chromium trioxide was prepared according to WO 99/52850 by dissolving

10 periodic acid (11.4 g, 50.0 mmol) and chromium trioxide (23 mg, 1.2 mol %) in wet acetonitrile (0.75% H₂O) to a volume of 114 mL. To a solution of crude (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethanol from the previous reaction (assume 0.063 mmol) in 25% water/acetonitrile (1.6 mL) was added sequentially, a stock solution of CrO₃/H₅IO₆ (0.72 mL, 0.439 M solution) and CrO₃ (9.4 mg, 15 0.094 mmol) at room temperature. The reaction was stirred for 1 h and quenched with aqueous Na₂SO₃ (10% w/v). When the reaction mixture turned green, it was extracted 3 times with ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated, taken up in THF (0.3 mL), methanol (0.3 mL), and water (0.15 mL), filtered, and purified by reverse phase HPLC. Fractions containing the product were pooled and lyophilized to provide the TFA salt of 20 the product. ¹H NMR (400 MHz, CD₃OD) δ 9.03 (s, 1H), 8.84 (d, *J* = 5.1 Hz, 1H), 8.61 (s, 1H), 8.50 (s, 2H), 8.02 (d, *J* = 5.2 Hz, 1H), 7.94 (s, 1H), 7.70 (d, *J* = 9.6 Hz, 1H), 7.64 – 7.56 (m, 3H), 5.28 (s, 1H), 4.08 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H). LCMS-ESI⁺: calc'd for C₃₁H₂₉ClN₃O₄S: 574.1 (M+H⁺); Found: 574.0 (M + H⁺).

25 Example 16. Method D: Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid (106).



106

Preparation of (S)-2-(2-(3-bromophenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethanol: To a solution of (S)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate (310 mg, 0.577 mmol) in dioxane (5 mL), was added 3-bromophenylboronic acid (173 mg, 0.865 mmol), Ph(PPh₃)₄ (33 mg, 0.029 mmol) 2N K₂CO₃ (850 µL) in sealed tube. The reaction mixture was heated at 90 °C for 3hs. Then the reaction was cooled down and to the mixture was added MeOH (5 mL), 2N NaOH (1.5 mL) and heated at 45 °C. After the reaction was finished, the reaction was washed by water, extracted by EtOAc. The organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-50% EtOAc in hexanes to give the product (110 mg, 36%). LCMS-ESI⁺: calc'd for C₂₆H₂₅BrClNO₂S: 530.0 (M+H⁺); Found: 530.2 (M + H⁺).

Preparation of (S)-2-(2-(3-bromophenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetic acid: To a solution of (S)-2-(2-(3-bromophenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethanol (110 mg, 0.208 mmol) in wet acetonitrile (0.75% H₂O, 2.5 mL), was added H₅IO₆/CrO₃ stock solution (0.439 M in wet acetonitrile, 2.4 mL) at 0 °C. The reaction was stirred at 0 °C for ½ h. The reaction mixture was washed by sat.

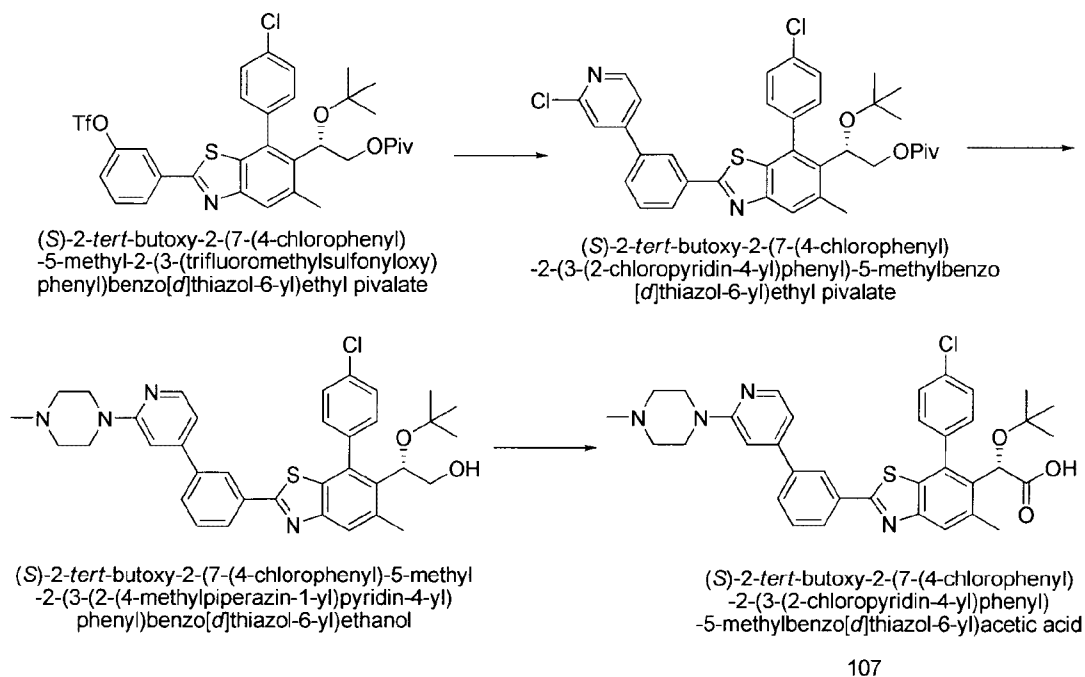
NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI⁺: calc'd for C₂₆H₂₃BrClNO₃S: 544.0 (M+H⁺); Found: 544.1 (M + H⁺).

- 5 Preparation of (*S*)-ethyl 2-(2-(3-bromophenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: To a solution of (*S*)-2-(2-(3-bromophenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (104 mg, 0.191 mmol) in DMF, was added Cs₂CO₃ (152 mg, 0.467 mmol), ethyl iodide (30 μ L, 0.343 mmol). The reaction was stirred at room temperature for 2hs. The reaction mixture was washed by sat. NaHCO₃, extracted by EtOAc, dry over MgSO₄, filtered, purified by silica gel column, eluting by 0-50% EtOAc in hexanes to give the product. LCMS-ESI⁺: calc'd for C₂₈H₂₇BrClNO₃S: 572.1 (M+H⁺); Found: 572.2 (M + H⁺).

- 15 Preparation of (*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetate: The reaction mixture of (*S*)-ethyl 2-(2-(3-bromophenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (12 mg, 0.025 mmol), 5-pyrimidineboronic acid (5 mg, 0.0375 mmol), 2N K₂CO₃ (60 μ L), Pd(PPh₃)₄ (3 mg, 0.0025 mmol) in dioxane (1 mL) was heated at 120 °C in sealed tube. After the reaction was finished, the reaction was washed by sat. NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI⁺: calc'd for C₃₂H₃₀ClN₃O₃S: 572.2 (M+H⁺); Found: 572.2 (M + H⁺).

- 25 Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid: The reaction mixture of (*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetate (9 mg, 0.0157 mmol), excess NaOH, in MeOH/THF(1:1, 2 mL) was heated at 45 °C overnight. After reaction finished, the solvent was removed and the residue was dissolved in MeOH and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H₂O with 0.1% TFA to give the product. LCMS-ESI⁺: calc'd for C₃₀H₂₆ClN₃O₃S: 544.1 (M+H⁺); Found: 544.2 (M + H⁺). ¹H NMR (400 MHz, CD₃OD): δ 9.18 (s, 1H), 9.16 (s, 2H), 8.40 (s, 1H), 8.12 (d, *J* = 4 Hz, 1H), 7.91-7.88 (m, 2H), 7.71-7.67 (m, 2H), 7.60-7.58 (m, 3H), 5.26 (s, 1H), 2.62 (s, 3H), 0.97 (s, 9H).

Example 17. Method E: Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2-chloropyridin-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (107).



5 Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2-chloropyridin-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate: The reaction mixture of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethylsulfonyloxy)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate (30 mg, 0.0438 mmol), 2-chloropyridine-4-boronic acid (10 mg, 0.0657 mmol), 2N K₂CO₃ (100 μ L), Pd(PPh₃)₄ (5.0 mg, 0.0044mmol) in dioxane (2 mL) was heated at 120°C in sealed tube for 2hs. The reaction was washed by sat. NaHCO₃, extracted by EtOAc, dried by MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI⁺: calc'd for C₃₆H₃₆Cl₂N₂O₃S: 647.2 (M+H⁺); Found: 647.3 (M + H⁺).

15 Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)phenyl)benzo[d]thiazol-6-yl)ethanol: The reaction mixture of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2-chloropyridin-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate (16 mg, 0.025 mmol), 1-methylpiperazine (1 mL) was heated at 120 °C overnight. Then the reaction mixture was washed by sat. NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated. To the residue was added THF, MeOH, 2N NaOH, the mixture was heated at 45 °C. After the reaction finished, the reaction was washed by sat NaHCO₃, extracted by EtOAc, the organic phase was

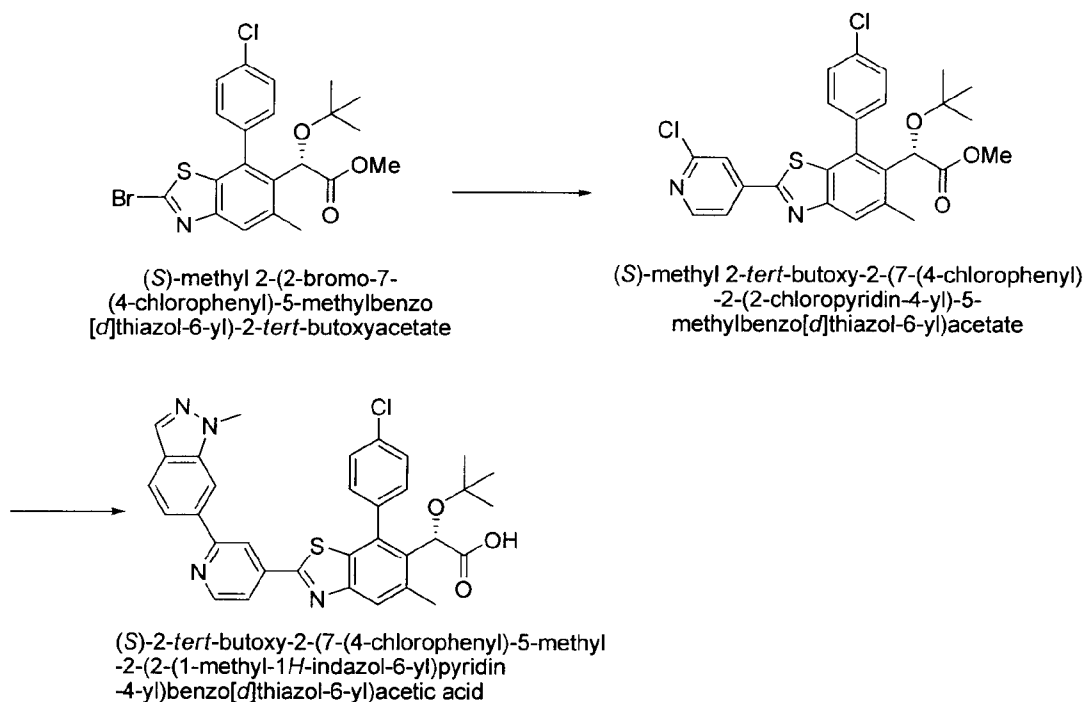
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dried over MgSO_4 , filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI⁺: calc'd for $\text{C}_{36}\text{H}_{39}\text{ClN}_4\text{O}_2\text{S}$: 627.2 ($\text{M}+\text{H}^+$); Found: 627.3 ($\text{M}+\text{H}^+$).

- 5 Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2-chloropyridin-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)phenyl)benzo[d]thiazol-6-yl)ethanol in DCM (1 mL) was added Dess-Martin periodinane (8.8 mg, 0.020 mmol). After 1h, more Dess-Martin periodinane was added (10 mg) and the reaction mixture was reacted at room
- 10 temperature overnight. The mixture was washed by sat. NaHCO_3 , 1M $\text{Na}_2\text{S}_2\text{O}_3$, extracted by DCM, dried over MgSO_4 , filtered, concentrated down. To the residue was added *t*-BuOH (600 μL), 1M NaH_2PO_4 (300 μL), 2-methylbut-2-ene (500 μL) and NaClO_2 (14 mg). The reaction mixture was reacted at room temperature. After the reaction finished, the mixture was treated with MeOH, filtered, purified by reverse phase HPLC to give the product. LCMS-ESI⁺: calc'd
- 15 for $\text{C}_{36}\text{H}_{37}\text{ClN}_4\text{O}_3\text{S}$: 641.2 ($\text{M}+\text{H}^+$); Found: 641.2 ($\text{M}+\text{H}^+$).

Example 18. Method F: Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-6-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (108).



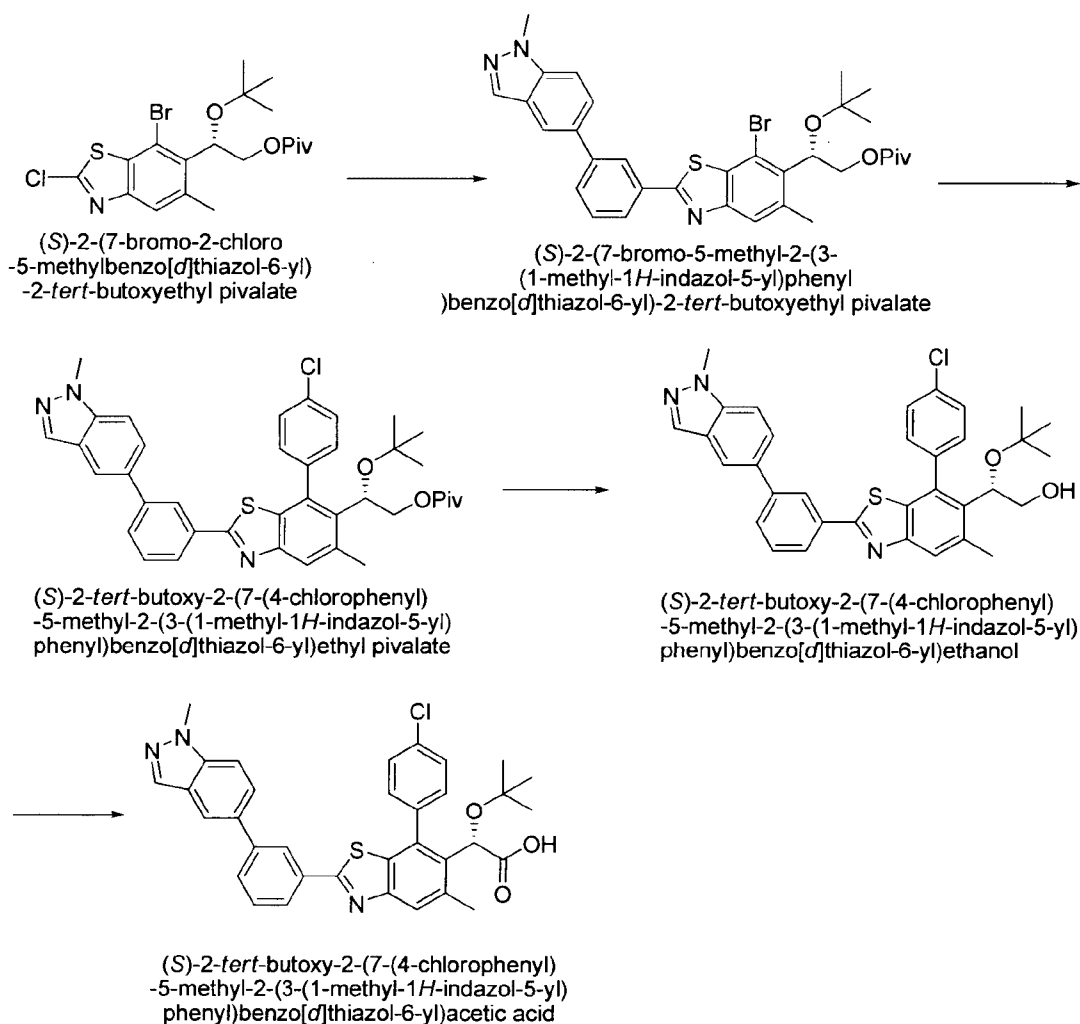
108

Preparation of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: The reaction mixture of (*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (370 mg, 0.769 mmol), 2-chloropyridine-4-boronic acid (157 mg, 0.99 mmol), 2N K₂CO₃ (1.9 mL), Pd(PPh₃)₄ (80 mg, 0.077 mmol) in dioxane (10 mL) was heated at 95 °C for 2 h. The reaction mixture was diluted by EtOAc, washed by sat. NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI⁺: calc'd for C₂₆H₂₄Cl₂N₂O₃S: 515.1 (M+H⁺); Found: 515.1 (M + H⁺).

10

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-6-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: The reaction mixture of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (20 mg, 0.039 mmol), 1-methyl-1H-indazole-6-boronic acid (10.3 mg, 0.058 mmol), 2N K₂CO₃ (100 μL, 0.19 mmol), Pd(PPh₃)₄ (4.3 mg, 0.004 mmol) in dioxane (1.5 mL) in sealed tube was heated at 110 °C for 2h. After the starting material consumed, the reaction was cooled down, to the mixture was added MeOH, excess NaOH, the reaction mixture was heated at 45°C overnight. Then the reaction mixture was neutralized by acetic acid, concentrated down, then treated by MeOH, and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H₂O with 0.1% TFA to give the product. LCMS-ESI⁺: calc'd for C₃₃H₂₉ClN₄O₃S: 597.2 (M+H⁺); Found: 597.2 (M + H⁺). ¹H NMR (400 MHz, CD₃OD): δ 8.78 (d, *J* = 2.6 Hz, 1H), 8.60 (s, 1H), 8.26 (s, 1H), 8.06 (s, 1H), 8.03-7.82 (m, 4H), 7.71-7.69 (m, 1H), 7.61-7.60 (m, 3H), 5.28 (s, 1H), 4.16 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H).

25 Example 19. Method G: Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid (109).



109

Preparation of (S)-2-(7-bromo-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate: The reaction mixture of (S)-2-(7-bromo-2-chloro-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate (300 mg, 0.65 mmol), 1-methyl-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-indazole (260 mg, 0.78 mmol), Pd(PPh₃)₄ (75 mg, 0.065 mmol), 2N K₂CO₃ (1.6 mL) in dioxane (5 mL) was heated at 95 °C for hours. After the reaction finished, the reaction mixture was diluted by EtOAc, washed by sat. NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI⁺: calc'd for C₃₃H₃₆BrN₃O₃S: 634.2 (M+H⁺); Found: 634.1 (M+H⁺).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate: The mixture of (S)-2-(7-bromo-5-

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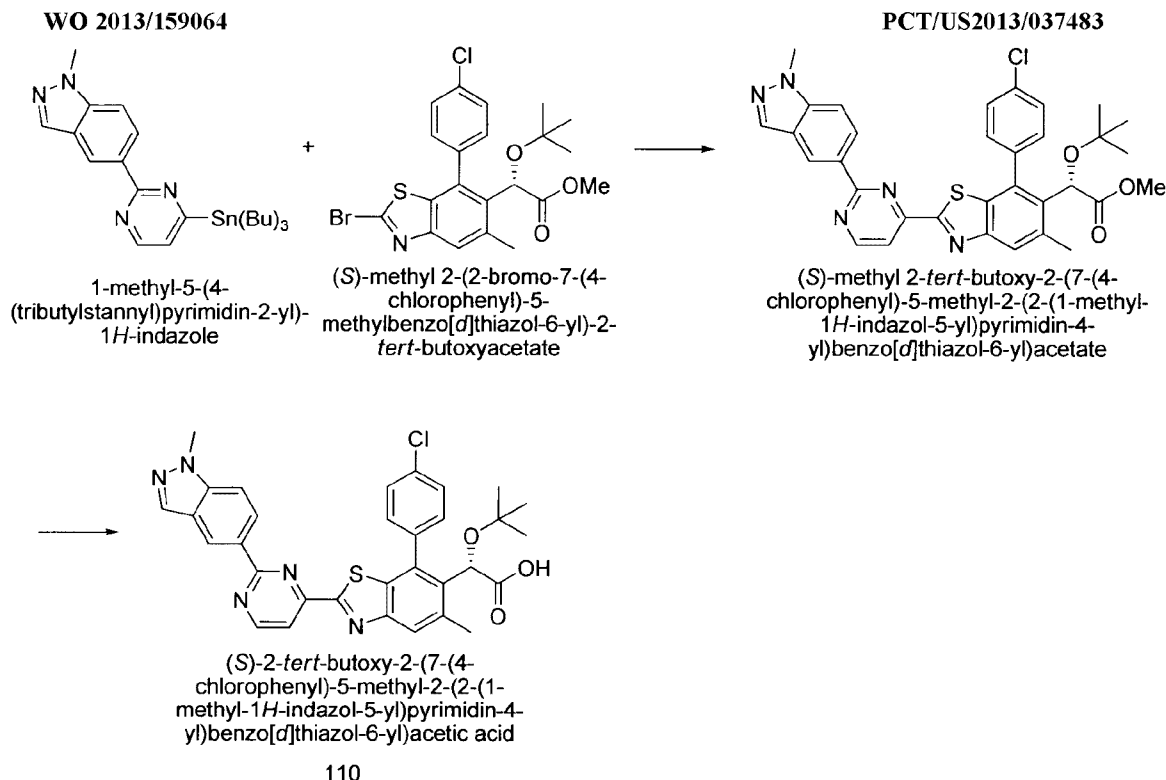
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methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (24 mg, 0.0379 mmol), 4-chlorophenylboronic acid (9 mg, 0.0568 mmol), 2N NaHCO₃ (100 μ L), Pd(PPh₃)₄ (4 mg, 0.0038 mmol) in dioxane (2 mL) was heated at 120 °C for 3 h. The reaction mixture was diluted by EtOAc, washed by sat. NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI⁺: calc'd for C₃₉H₄₀ClN₃O₃S: 666.2 (M+H⁺); Found: 666.1 (M + H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)ethanol: The reaction mixture of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate (10 mg, 0.015 mmol), 2N NaOH (150 μ L) in THF/MeOH (1:1, 1 mL) was heated at 40 °C. After reaction finished, the reaction mixture was diluted by EtOAc, washed by sat. NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI⁺: calc'd for C₃₄H₃₂ClN₃O₂S: 582.2 (M+H⁺); Found: 582.2 (M + H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid: To the solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)ethanol (6 mg, 0.010 mmol) in wet acetonitrile (0.75 w% H₂O, 1 mL), was added stock solution of H₅IO₆/CrO₃ (0.439 M in wet acetonitrile, 150 μ L) at 0 °C for ½ hour. The reaction mixture was filtered and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H₂O with 0.1% TFA give the product. LCMS-ESI⁺: calc'd for C₃₄H₃₀ClN₃O₃S: 596.2 (M+H⁺); Found: 596.2 (M + H⁺). ¹H NMR (300 MHz, CD₃OD): δ 8.24 (s, 1H), 7.95-7.98 (m, 2H), 7.88-7.50 (m, 10H), 5.17 (s, 1H), 4.01 (s, 3H), 2.52 (s, 3H), 0.88 (s, 9H).

Example 20. Method H: Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid (110).



Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate: (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (17.4 mg, 0.036 mmol), Pd(PPh₃)₄ (2.1 mg, 0.002 mmol), lithium chloride (2.3 mg, 0.054 mmol), and copper(I) iodide (1.0 mg, 0.005 mmol) were taken in a microwave vial and the vial was vacuum pumped and flushed with argon three times. To this mixture was added 1-methyl-5-(4-(tributylstannyl)pyrimidin-2-yl)-1H-indazole (9.0 mg, 0.018 mmol) in degassed 1,4-dioxane (0.5 mL). The reaction mixture was heated at 100 °C for 5 h, cooled, filtered through celite (ethyl acetate eluent), and concentrated. Purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the product. LCMS-ESI⁺: calc'd for C₃₃H₃₁ClN₅O₃S: 612.2 (M+H⁺); Found: 611.9 (M + H⁺).

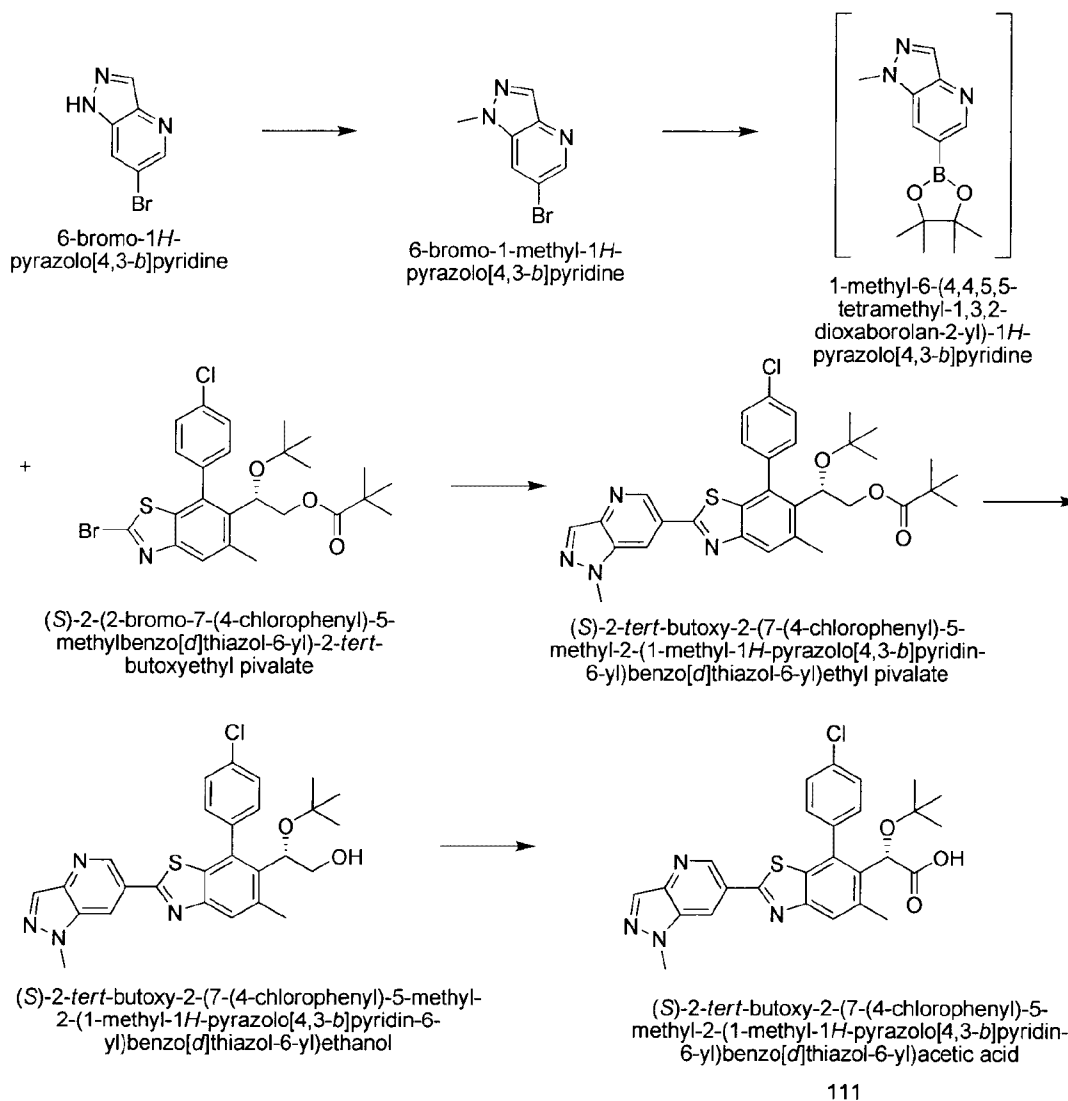
Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate (4.8 mg, 0.008 mmol) in THF (0.3 mL) and methanol (0.3 mL) was added NaOH (0.3 mL of a 2N solution). The reaction mixture was heated at 45 °C for 6 h, cooled, filtered, and purified by reverse phase HPLC. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ¹H NMR (400 MHz, CD₃OD) δ 8.94 (d, *J* = 5.1 Hz, 1H), 8.83 (s, 1H), 8.49 (dd, *J* = 9.0, 1.4 Hz, 1H), 8.12 (s, 1H), 8.05 (d, *J* =

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5.1 Hz, 1H), 7.87 (s, 1H), 7.76 – 7.71 (m, 1H), 7.68 – 7.59 (m, 3H), 7.57 (d, $J = 8.9$ Hz, 1H), 5.29 (s, 1H), 4.07 (s, 3H), 2.63 (s, 3H), 0.99 (s, 9H). LCMS-ESI⁺: calc'd for C₃₂H₂₉ClN₅O₃S: 598.2 (M+H⁺); Found: 598.3 (M + H⁺).

- 5 **Example 21.** Method I: Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-6-yl)benzo[*d*]thiazol-6-yl)acetic acid (111).



Preparation of 6-bromo-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine: To a solution of 6-bromo-1*H*-pyrazolo[4,3-*b*]pyridine (200 mg, 1.01 mmol) in DMF (5mL) was added cesium carbonate (494 mg, 1.515 mmol). The reaction solution was stirred at room temperature for 5 minutes, iodomethane (215 mg, 1.515 mmol) was added. The reaction solution was stirred for 2 h and quenched with water. Volatiles were removed and the residue partitioned between ethyl acetate and water. The organic phase was washed with brine, dried (MgSO₄), filtered and concentrated

to give crude product which was purified by chromatographic column to afford the desired product 6-bromo-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine. LCMS-ESI⁺: calc'd for C₇H₆BrN₃: 211.98 (M+H⁺); Found: 212.1 (M + H⁺).

5 Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine-6-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate: To a solution of 6-bromo-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (20 mg, 0.094 mmol) in dioxane (2 mL) was added bis(pinacolato)diboron (29 mg, 0.113 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (8 mg, 0.0094 mmol), potassium acetate (19 mg, 0.189 mmol). The mixture was degassed and heated
10 at 100 °C for 2 h. The mixture was cooled, and then added (*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (25 mg, 0.046 mmol), tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol), K₂CO₃ (33 mg, 0.23 mmol) and water (0.3 mL, degassed). The reaction mixture was heated at 90 °C for 1 h, cooled and
15 partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated to give crude product which was purified by chromatographic column to afford the desired product. LCMS-ESI⁺: calc'd for C₃₂H₃₅ClN₄O₃S: 591.22 (M+H⁺); Found: 591.2 (M + H⁺).

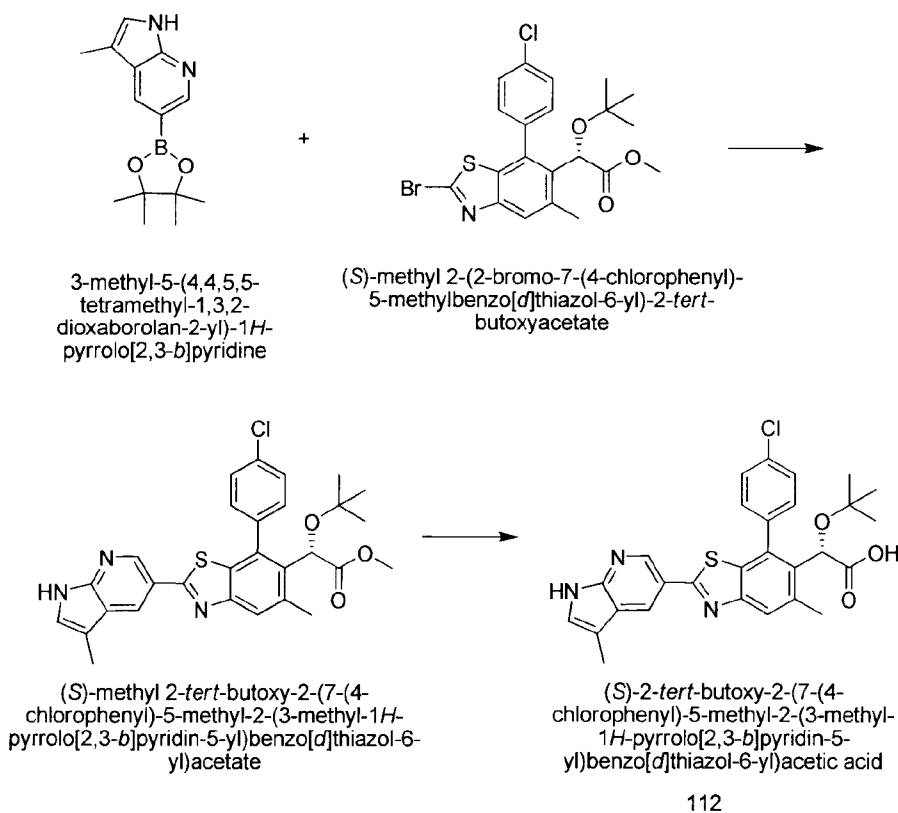
20 Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-6-yl)benzo[*d*]thiazol-6-yl)ethanol: To a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine-6-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate: (68 mg, 0.115 mmol) in THF/CH₃OH (1.5 mL/1.5 mL) was added 2N NaOH (0.57mL, 1.15mmol). The reaction mixture was heated at 45 °C for 2 h and cooled to rt. The
25 reaction solution is quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic solution is washed with water, brine, dried and concentrated to give crude product which was carried to next reaction without further purification. LCMS-ESI⁺: calc'd for C₂₇H₂₇ClN₄O₂S: 507.16 (M+H⁺); Found: 507.2 (M + H⁺).

30 Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-6-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-6-yl)benzo[*d*]thiazol-6-yl)ethanol (50 mg, 0.099 mmol) in acetonitrile/ water (2 mL/0.5 mL) was added CrO₃/H₅IO₆ (0.439M, 1.1 mL, 0.483mmol) and CrO₃ (20 mg, 0.198 mmol). The reaction solution was stirred

at room temperature for 1 h and quenched with 5% Na₂S₂O₃ solution. The mixture was extracted with ethyl acetate, washed with water and brine. The organic solution was dried and concentrated to give crude which was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H₂O with 0.1% TFA to give the desired product. LCMS-ESI⁺: calc'd for

- 5 C₂₇H₂₅ClN₄O₃S: 521.14 (M+H⁺); Found: 521.2 (M + H⁺), ¹H NMR (400 MHz, CD₃OD) δ 9.20 (d, *J* = 8 Hz, 1H), 8.67 (s, 1H), 8.24 (s, 1H), 7.88 (s, 1H), 7.71 – 7.59 (m, 4H), 5.27 (s, 1H), 4.16 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).

- 10 Example 22. Method J: Preparation of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetic acid (112).



- Preparation of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetate: To a solution of (*S*)-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (22 mg, 0.085 mmol) and (*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate (20 mg, 0.041 mmol) in dioxane (1.2 mL, degassed) was added tetrakis(triphenylphosphine)palladium(0) (2.4 mg, 0.00207 mmol), K₂CO₃ (29 mg, 0.207mmol) and water (0.4 mL, degassed). The reaction mixture was heated at 90 °C for 1 h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated to give crude which was purified by chromatographic column to afford
- 15
- 20

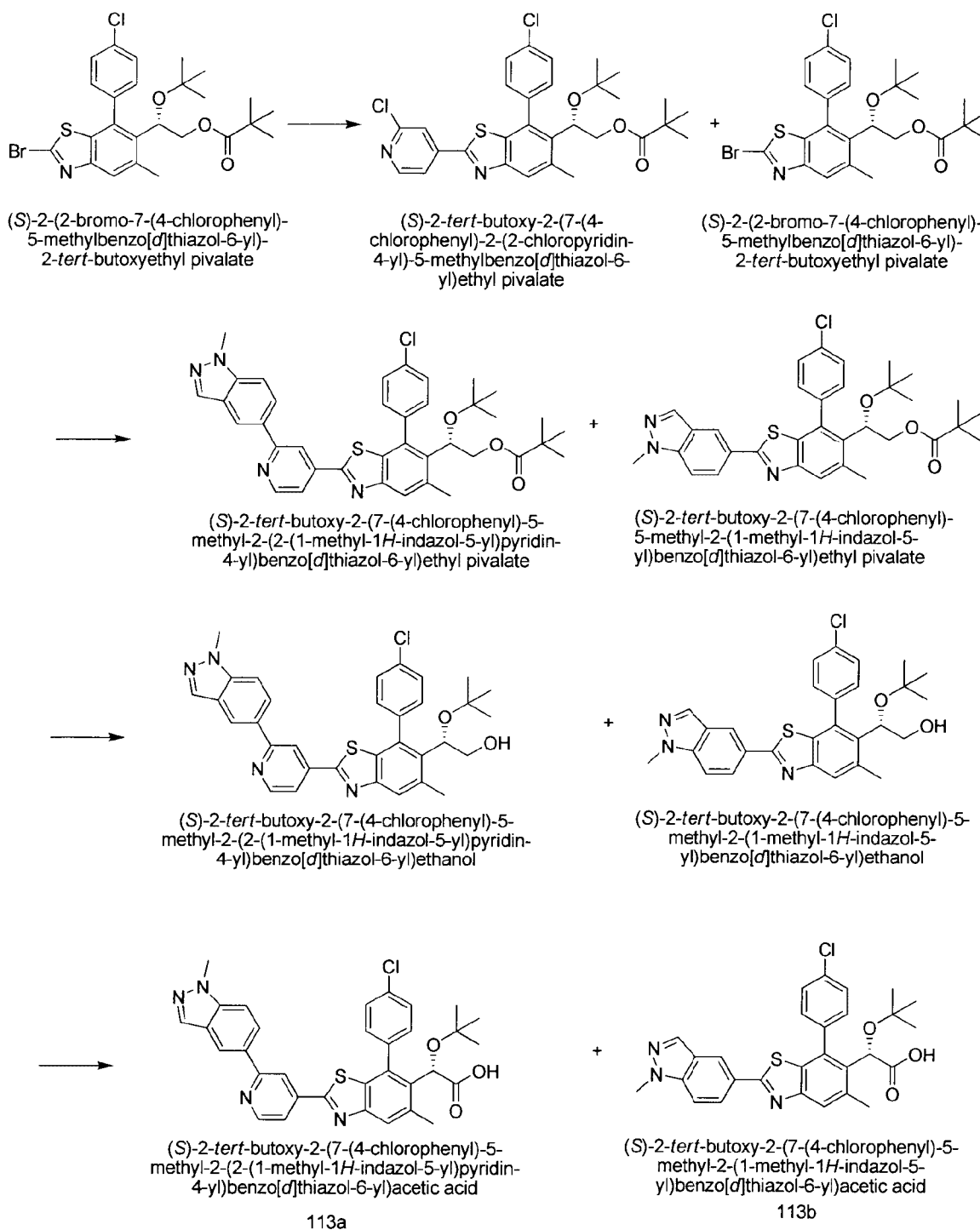
the desired product. LCMS-ESI⁺: calc'd for C₂₉H₂₈ClN₃O₃S: 534.16 (M+H⁺); Found: 534.4 (M + H⁺).

Preparation of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a solution of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetate: (8 mg, 0.015 mmol) in THF/CH₃OH (0.5 mL/0.5 mL) was added 2N NaOH (75 μL, 0.15 mmol). The reaction mixture was heated at 50 °C for 2 h and the crude was purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H₂O with 0.1% TFA to give the product. LCMS-ESI⁺: calc'd for C₂₈H₂₆ClN₃O₃S: 520.14 (M+H⁺); Found: 520.2 (M + H⁺). ¹H NMR (400 MHz, CD₃OD): δ 8.86 (d, *J* = 1 Hz, 1H), 8.57 (d, *J* = 1 Hz, 1H), 7.84 (s, 1H), 7.71-7.26 (m, 5H), 5.26 (s, 1H), 2.62 (s, 3H), 2.36 (s, 3H), 0.94 (s, 9H).

Example 23. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid (113a) and (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid (113b) .

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Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-6-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)ethanol: A mixture of (S)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate (0.190 g, 0.35 mmol),

5 2-chloropyridin-4-ylboronic acid (0.66 g, 0.42 mmol), Pd(PPh₃)₄ (0.020g, 0.0175, aq. 2M potassium carbonate solution (0.7 mL, 1.4 mmol) in degassed dioxane (2.0 mL) was heated at 90 °C for 3 hr. LC/MS indicated a 1.5:1 ratio of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-

chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate to (*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate. Reaction mixture was used in next step without further purification.

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate: LCMS-ESI⁺: calc'd for C₃₀H₃₃Cl₂N₂O₃S: 571.2 (M+H⁺); found: 571.2 (M+H⁺).

(*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate: LCMS-ESI⁺: calc'd for C₂₅H₂₉BrClNO₃S: 538.1, 540.1, and 542.1.1 (M+H⁺); found: 538.2, 540.2, and 542.2 (M+H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)ethyl pivalate and (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate: One-half of above reaction mixture containing (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate to (*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (1.5:1 ratio) was telescoped into the subsequent reaction. 1-Methyl-1H-indazol-5-ylboronic acid was added to the previous reaction mixture and reaction continued was heated at 120 °C for 30 minutes to give (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)ethyl pivalate and (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate.

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)ethyl pivalate: LCMS-ESI⁺: calc'd for C₃₈H₄₀ClN₄O₃S: 667.2 (M+H⁺); found: 667.4 (M+H⁺).

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate: LCMS-ESI⁺: calc'd for C₃₃H₃₆ClN₃O₃S: 590.2 (M+H⁺); found: 590.2 (M+H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)ethanol and (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)ethanol: (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-6-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)ethyl pivalate and (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate was telescoped into the

subsequent reaction. To the previous reaction mixture, methanol and 2M NaOH were added and reaction mixture was heated at 55 °C overnight. Reaction mixture was cooled to rt, diluted with ethyl acetate and washed with brine. The organic layer was dried (MgSO₄), filtered, concentrated and purified by CombiFlash (Hex/EtOAc) to give (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)ethanol.

LCMS-ESI⁺: calc'd for C₃₃H₃₂ClN₄O₂S: 583.2 (M+H⁺); found: 583.2 (M+H⁺).

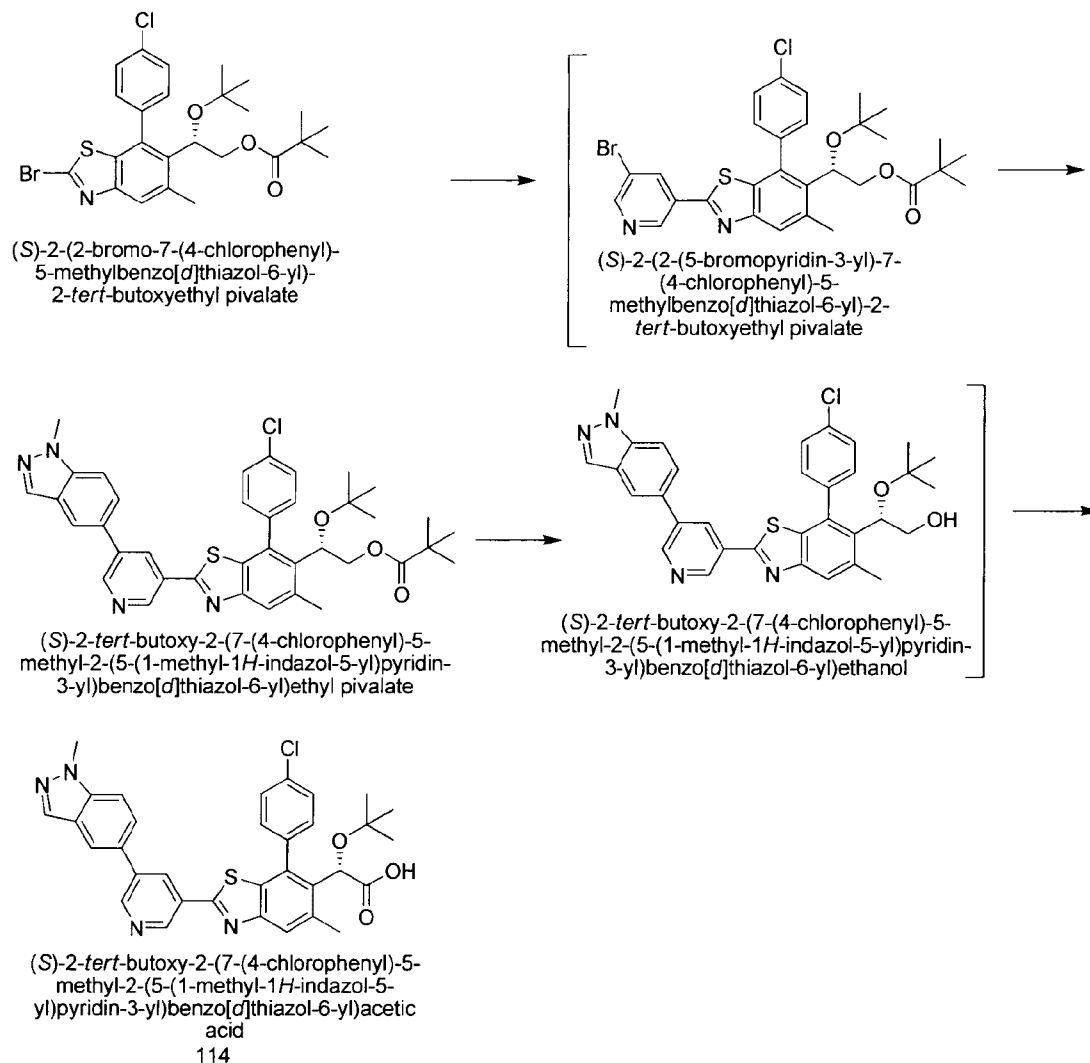
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)ethanol was also isolated.

LCMS-ESI⁺: calc'd for C₂₈H₂₉ClN₃O₂S: 506.2 (M+H⁺); found: 506.2 (M+H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: A stock solution of periodic acid/chromium trioxide was prepared according to WO 99/52850 by dissolving periodic acid (11.4 g, 50.0 mmol) and chromium trioxide (23 mg, 1.2 mol %) in wet acetonitrile (0.75% H₂O) to a volume of 114 mL. This stock solution (0.6 mL) was added to a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-6-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)ethanol (25 mg, 0.049 mmol) in ACN (3 mL) at room temperature and stirred for one hour. The reaction mixture was quenched with saturated Na₂SO₃ solution and extracted with EtOAc. The organic layer was dried (MgSO₄), filtered, concentrated and purified by reverse phase HPLC (H₂O/ACN + 0.1% TFA) to give the desired product after lyophilization. LCMS-ESI⁺: calc'd for C₃₃H₃₀ClN₄O₃S: 597.2 (M+H⁺); found: 597.2, 599.2. ¹H NMR (400 MHz, CD₃OD) δ 8.72 (d, *J* = 5.3 Hz, 1H), 8.46 (s, 1H), 8.43 (s, 1H), 8.14 – 8.08 (m, 2H), 7.94 – 7.87 (m, 2H), 7.73 – 7.63 (m, 2H), 7.61 – 7.54 (m, 3H), 5.26 (s, 1H), 4.10 (s, 3H), 2.63 (s, 3H), 0.97 (s, 9H).

The preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (114b) followed the procedure described above for (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid. LCMS-ESI⁺: calc'd for C₃₃H₃₀ClN₄O₃S: 520.05 (M+H⁺); found: 520.2, 522.1. ¹H NMR (400 MHz, CD₃OD) δ 8.38 (s, 1H), 8.09 (d, *J* = 11.2 Hz, 2H), 7.78 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 8.9 Hz, 1H), 7.60 – 7.53 (m, 3H), 5.24 (s, 1H), 4.08 (s, 3H), 2.59 (s, 3H), 0.97 (s, 9H).

Example 24. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid (114).



Preparation of (*S*)-2-(2-(5-bromopyridin-3-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate: A mixture of (*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (0.134 g, 0.25 mmol), 3-bromo-pyridin-5-ylboronic acid (0.55 g, 0.27 mmol), Pd(PPh₃)₄ (0.014 g, 0.013 mmol), aq. 2M potassium carbonate solution (0.5 mL, 1.0 mmol) in degassed dioxane (2.0 mL) was heated in microwave at 80 °C for 30 minutes to give (*S*)-2-(2-(5-bromopyridin-3-yl)-7-(4-

chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate. LCMS-ESI⁺: calc'd for C₃₀H₃₂BrClN₂O₃S: 617.1 (M+H⁺); found: 617.2 (M+H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)ethyl pivalate: (*S*)-2-(2-(5-bromopyridin-3-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate was telescoped into the subsequent reaction. 1-Methyl-1*H*-indazol-5-ylboronic acid (0.024 g, 0.14 mmol) was added to the one-half of the previous reaction mixture and reaction heated in microwave at 115 °C for 30 minutes. Reaction mixture was portioned between ethyl acetate and H₂O, the organic layer removed and concentrated to give (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)ethyl pivalate. LCMS-ESI⁺: calc'd for C₃₈H₄₀ClN₄O₃S: 667.2 (M+H⁺); found: 667.3 (M+H⁺).

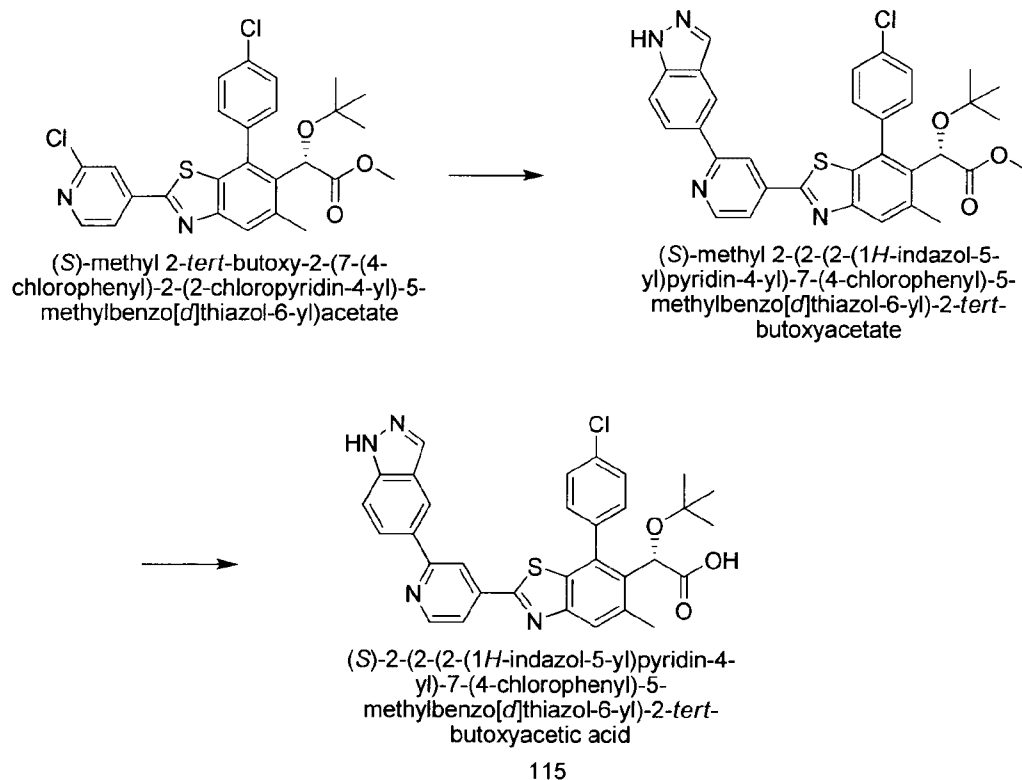
Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)ethanol: To a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)ethyl pivalate from above reaction was added THF:MeOH (1:1, 2 mL) and 2M NaOH (0.5 mL) were added and reaction mixture was heated at 55 °C for 3 h. Reaction mixture was cooled to rt, diluted with ethyl acetate and washed with saturated ammonium chloride solution. The organic layer was dried (MgSO₄), filtered, concentrated and purified by CombiFlash (EtOAc/Hex) to give (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)ethanol (15 mg). LCMS-ESI⁺: calc'd for C₃₃H₃₂ClN₄O₂S: 583.2 (M+H⁺); found: 583.3 (M+H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid: A stock solution of periodic acid/chromium trioxide was prepared according to WO 99/52850 by dissolving periodic acid (11.4 g, 50.0 mmol) and chromium trioxide (23 mg, 1.2 mol %) in wet acetonitrile (0.75% H₂O) to a volume of 114 mL. This stock solution (0.3 mL) was added to a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-6-yl)pyridin-5-yl)benzo[d]thiazol-6-yl)ethanol (15 mg, 0.027 mmol) in 0.75% H₂O in ACN (3 mL). The reaction mixture was stirred at room temperature for 45 minutes, quenched with saturated Na₂SO₃ solution and extracted with EtOAc. The organic layer was dried (MgSO₄), filtered, concentrated and purified by reverse phase HPLC (H₂O/ACN + 0.1% TFA) to give the desired

product after lyophilization. LCMS-ESI⁺: calc'd for C₃₃H₃₀ClN₄O₃S: 597.2 (M+H⁺); found: 597.2, 599.2. ¹H NMR (400 MHz, CD₃OD) δ 9.13 (s, 1H), 8.98 (s, 1H), 8.67 (s, 1H), 8.16 (s, 1H), 8.12 (s, 1H), 7.92 (s, 1H), 7.83 (dd, J = 8.8, 1.6 Hz, 1H), 7.73 (dd, J = 13.4, 5.2 Hz, 2H), 7.60 (d, J = 8.0 Hz, 3H), 5.27 (s, 1H), 4.11 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H) (115).

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Example 25. Preparation of (*S*)-2-(2-(2-(1*H*-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (115).



10 Preparation of (*S*)-methyl 2-(2-(2-(1*H*-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: A microwave tube was charged with (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (25.0 mg, 48.5 μmol), 5-(4',4',5',5'-tetramethyl-1',3',2'-dioxaborolan-2'-yl)-1*H*-indazole (14.2 mg, 58.2 μmol), Pd(PPh₃)₄ (5.6 mg, 4.86 μmol), K₂CO₃ (27 mg, 0.19 mmol), H₂O

15 (400 μL), and dioxane (1.6 mL). The reaction was sealed and heated to 110 °C. The reaction failed to reach completion during the next 2 h (boronate ester was fully consumed (LCMS analysis), yet (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate remained.). The reaction was cooled to 23 °C and charged with more 5-(4',4',5',5'-tetramethyl-1',3',2'-dioxaborolan-2'-yl)-1*H*-indazole (10 mg, 41

20 μmol). Heating to 110 °C was continued. Reaction progressed further, but was still incomplete

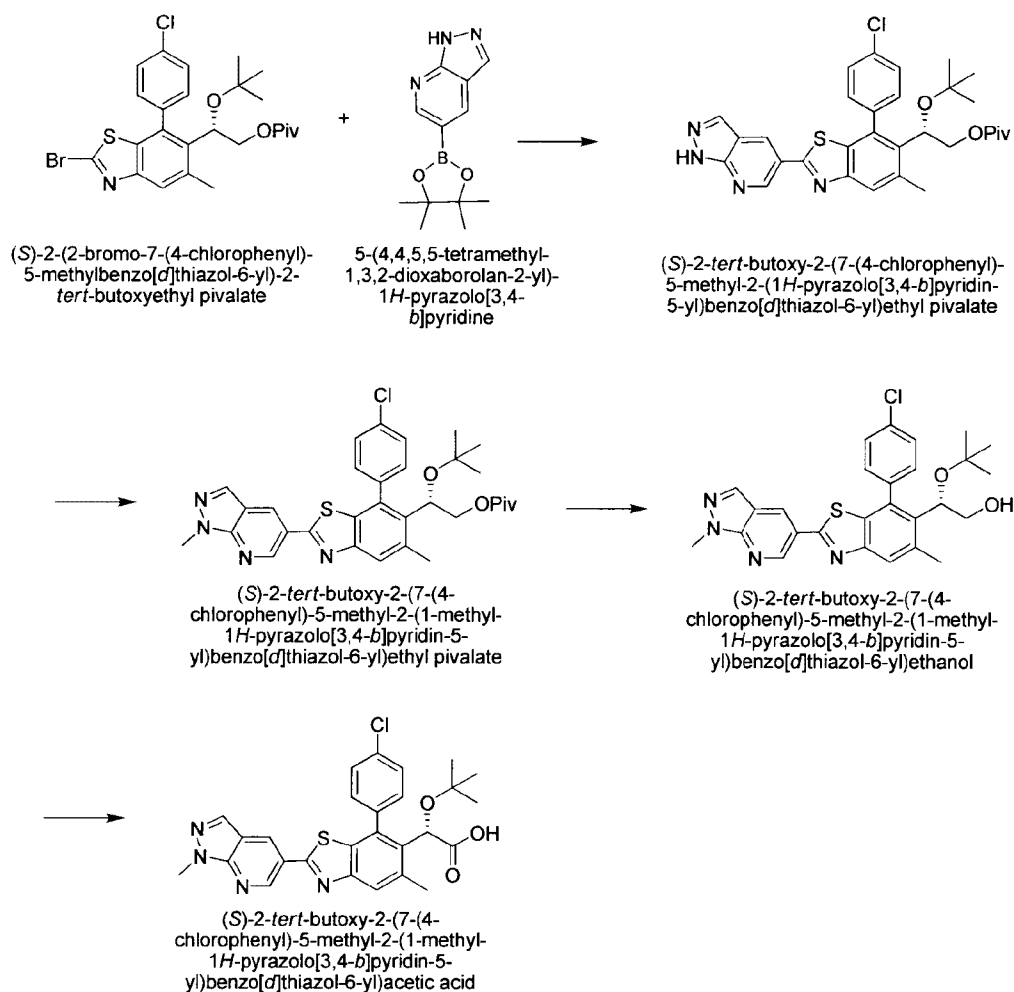
after 1 h. Again, the reaction was cooled to 23 °C and this time charged with 1H-indazole-5-boronic acid (20 mg, 120 µmol) and K₂CO₃ (15 mg, 0.11 mmol); heating to 110 °C was resumed. Reaction reached completion in 1 h. The crude product (*S*)-methyl 2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate was detected in solution. The solution was used crude in the next reaction. LCMS-ESI⁺: calc'd for C₃₃H₂₉ClN₄O₃S: 597.2 and 599.2 (M+H⁺); found: 597.3 and 599.3 (M+H⁺).

Preparation of (*S*)-2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid: The solution of crude (*S*)-methyl 2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate from the previous reaction was treated directly with LiOH monohydrate (60 mg, 1.42 mmol), H₂O (500 µL), and MeOH (500 µL). The reaction was heated to 50 °C for 15 h. The reaction failed to reach completion (LCMS analysis). The reaction was then heated to 100 °C for 30 min and reached completion. The system was cooled to 23 °C and filtered (0.45 micron Teflon® filter). The filtrate was purified directly on a C-18 Gemini column using a Gilson liquid handler (Eluent H₂O / CH₃CN gradient with both mobile phase components spiked 0.1% v/v with TFA). The title compound was obtained as a mono-trifluoroacetic acid salt. LCMS-ESI⁺: calc'd for C₃₂H₂₇ClN₄O₃S: 583.2 and 585.2 (M+H⁺); Found: 583.3 and 585.3 (M+H⁺). ¹H NMR (400 MHz, CD₃OD) δ: 8.78 (d, *J* = 5.5 Hz, 1H), 8.58 (s, 1H), 8.51 (s, 1H), 8.22 (s, 1H), 8.11 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.04 (dd, *J* = 5.4, 1.2 Hz, 1H), 7.99 (s, 1H), 7.74-7.70 (m, 2H), 7.65-7.60 (m, 3H), 5.23 (s, 1H), 2.65 (s, 3H), 0.99 (s, 9H).

Example 26. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-pyrazolo[3,4-*b*]pyridin-5-yl)benzo[d]thiazol-6-yl)acetic acid (116).

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Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1H-pyrazolo[3,4-b]pyridin-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate: To a solution of (S)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl pivalate (51 mg, 0.095 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazolo[3,4-b]pyridine (28 mg, 0.123 mmol) in degassed 1,4-dioxane (250 μ L) and water (25 μ L) was added aqueous K_2CO_3 (95 μ L of a 2.0 M solution) and tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol). The reaction mixture was heated at 100 $^{\circ}C$ for 6 h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4 and concentrated. The crude material was used without any further purification. LCMS-ESI $^{+}$: calc'd for $C_{31}H_{34}ClN_4O_3S$: 577.2 (M+H $^{+}$); Found: 577.3 (M + H $^{+}$).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate: To a solution of the crude

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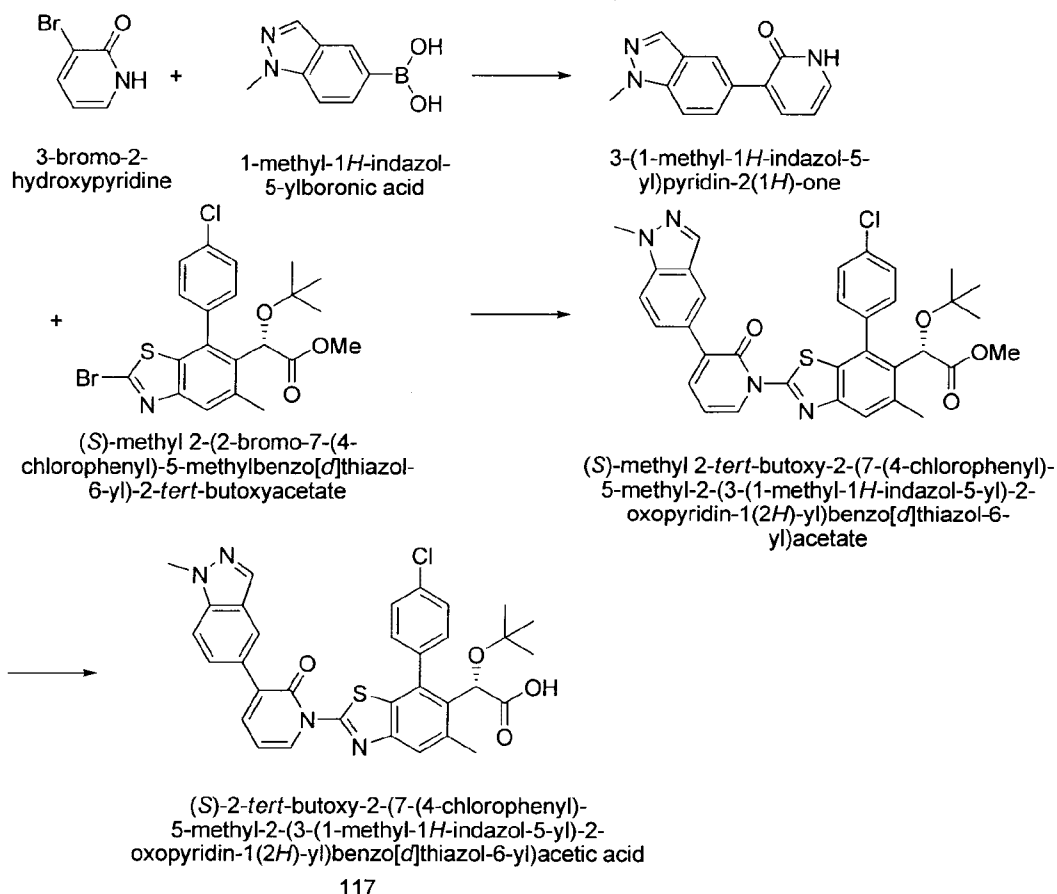
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material from the previous reaction (assume 0.095 mmol) in dry DMF (1.0 mL) was added Cs₂CO₃ (60 mg, 0.185 mmol) at room temperature. After 15 min, neat methyl iodide (12 μ L, 0.19 mmol) was added and the reaction was allowed to stir for 6 h. The reaction was then partitioned between ethyl acetate and water and extracted. The organic layer was washed sequentially with aqueous 5% LiCl, brine, dried over Na₂SO₄ and concentrated to give the desired product. Purification by flash column chromatography on silica gel using 30% ethyl acetate in hexanes provided a pale foam (14 mg, 25% for two steps). LCMS-ESI⁺: calc'd for C₃₂H₃₆ClN₄O₃S: 591.2 (M+H⁺); Found: 591.3 (M + H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)benzo[d]thiazol-6-yl)ethanol: To a solution of compound (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate (14 mg, 0.024 mmol) in THF (0.50 mL) and MeOH (0.50 mL) was added aqueous NaOH (0.10 mL of a 2 N solution). The reaction mixture was heated at 50 °C for 17 h, cooled, diluted with satd. aqueous NH₄Cl and extracted with ethyl acetate. The organic layer was dried and concentrated to give the desired product which was used without any further purification. LCMS-ESI⁺: calc'd for C₂₇H₂₈ClN₄O₂S: 507.2 (M+H⁺); 507.2 (M + H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)benzo[d]thiazol-6-yl)ethanol from previous reaction (assume 0.024 mmol) in 25% water/acetonitrile (0.70 mL) was added sequentially, a stock solution of CrO₃/H₅IO₆ (296 μ L, 0.439 M solution) and CrO₃ (3 mg, 0.030 mmol) at room temperature. The reaction was stirred for 1 h, diluted with acetonitrile, filtered and purified by reverse phase HPLC. Fractions containing product were pooled and evaporated to the desired product. LCMS-ESI⁺: calc'd for C₂₇H₂₆ClN₄O₃S: 521.1 (M+H⁺); 521.2 (M + H⁺); 1H NMR (400 MHz, CD₃OD): δ 9.26 (d, *J* = 1.9 Hz, 1H), 8.79 (d, *J* = 1.9 Hz, 1H), 8.20 (s, 1H), 7.87 (s, 1H), 7.69 (d, *J* = 9.4 Hz, 1H), 7.61 – 7.59 (m, 3H), 5.26 (s, 1H), 4.15 (s, 3H), 2.61 (s, 3H), 0.97 (s, 9H).

Example 27. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid (117).



Preparation of 3-(1-methyl-1H-indazol-5-yl)pyridin-2(1H)-one: The suspension of 3-bromo-2-hydroxypyridine (80 mg, 0.46 mmol), 1-methyl-1H-indazol-5-ylboronic acid (121 mg, 0.69 mmol) and sodium carbonate (146 mg, 1.38 mmol) in DMF (2.0 mL) and H₂O (0.4 mL) was degassed with N₂ for 5 minutes. To the mixture was added bis(triphenylphosphine)palladium (II) dichloride (67 mg, 0.09 mmol), and the resulting mixture was heated at 90 °C for 2 h. The reaction mixture was filtered and purified by reverse phase HPLC (Gemini, 5 to 100% ACN/H₂O + 0.1% TFA) to give the product. LCMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₁₃H₁₂N₃O: 226.25; Found: 226.2.

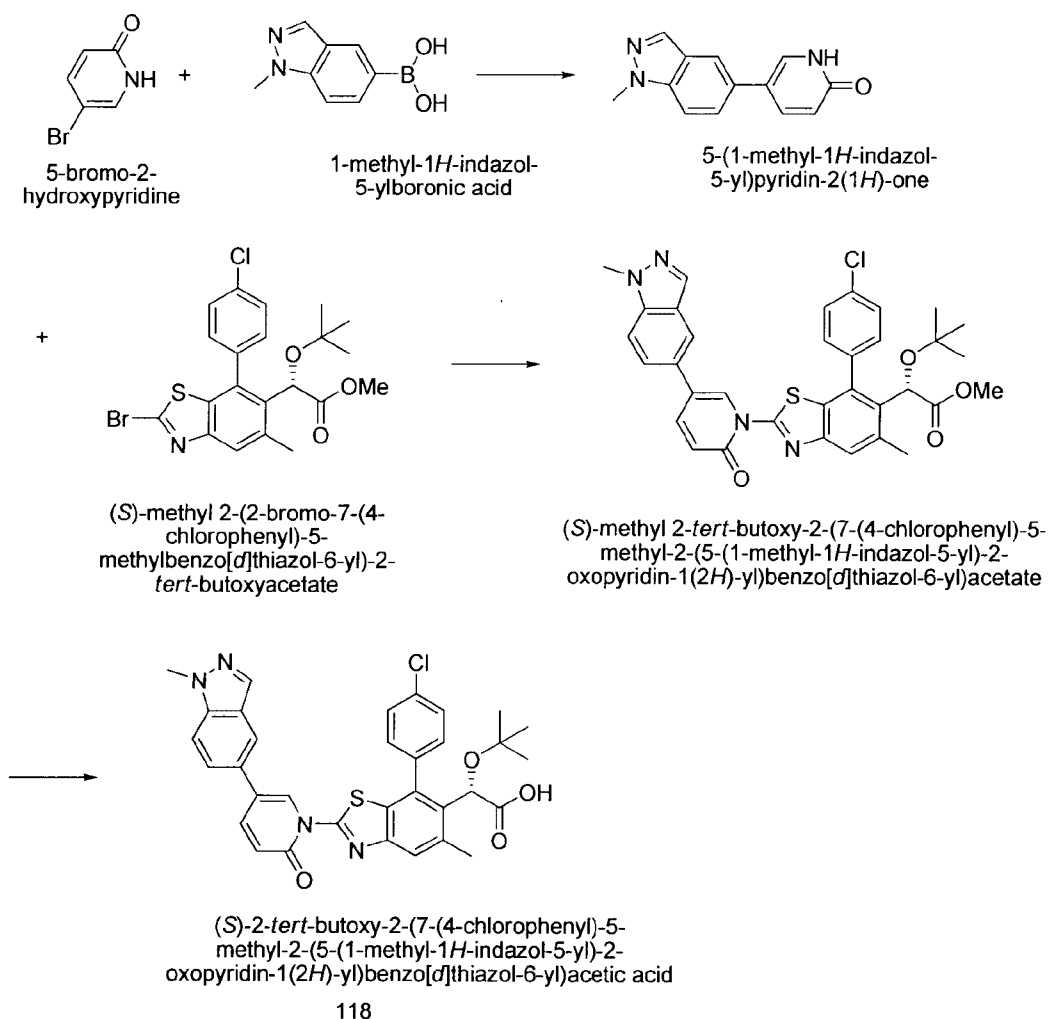
Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate: To a solution of 3-(1-methyl-1H-indazol-5-yl)pyridin-2(1H)-one (13.0 mg, 0.055 mmol), (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (22 mg, 0.046 mmol), trans-N1,N2-dimethylcyclohexane-1,2-diamine (9 µL, 0.055 mmol) and potassium carbonate (13 mg, 0.091 mmol) in DMF (0.5 mL) was added copper(I) iodide (5.0 mg, 0.026 mmol). The mixture was degassed with N₂ for 5 minutes and then heated at 110 °C for 3 h. The mixture was then

diluted with EtOAc, extracted with H₂O, brine, dried over Na₂SO₄, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the product. LCMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₃₄H₃₂ClN₄O₄S: 627.18; Found: 627.2.

5 Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid: To a stirred solution of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate (12.6 mg, 0.020 mmol) in THF (1.2 mL) and methanol (0.5 mL) was added 1 M NaOH solution (0.3 mL, excess). The reaction mixture was
10 stirred at 37 °C for 6 h. The reaction mixture was purified by reverse phase HPLC (Gemini, 5 to 100% ACN/H₂O + 0.1% TFA) to give the product. LCMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₃₃H₃₀ClN₄O₄S: 613.17; Found: 613.2; ¹H-NMR: 400 MHz, (CD₃OD) δ 8.89 (dd, *J* = 7.6, 2 Hz, 1H), 8.02 (s, 2H), 7.75 (s, 1H), 7.70 - 7.63 (m, 3H), 7.53 - 7.49 (m, 4H), 6.61 (t, *J* = 7.2 Hz, 1H), 5.27 (s, 1H), 4.06 (s, 3H), 2.60 (s, 3H), 0.95 (s, 9H).

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Example 28. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid (118).



Preparation of 5-(1-methyl-1H-indazol-5-yl)pyridin-2(1H)-one: The suspension of 5-bromo-2-hydroxypyridine (80 mg, 0.46 mmol), 1-methyl-1H-indazol-5-ylboronic acid (121 mg, 0.69 mmol) and 2N sodium carbonate solution (1.0 mL, 2 mmol) in DMF (2.1 mL) was degassed with N₂ for 5 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium(0) (53 mg, 0.04 mmol), and the resulting mixture was heated at 80 °C overnight. The mixture was then diluted with CH₂Cl₂, extracted with H₂O, brine, dried over Na₂SO₄, filtered and concentrated and purified by reverse phase HPLC (Gemini, 5 to 100% ACN/H₂O + 0.1% TFA) to give the product. LCMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₁₃H₁₂N₃O: 226.25; Found: 226.3.

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate:
Compound (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate was prepared following the

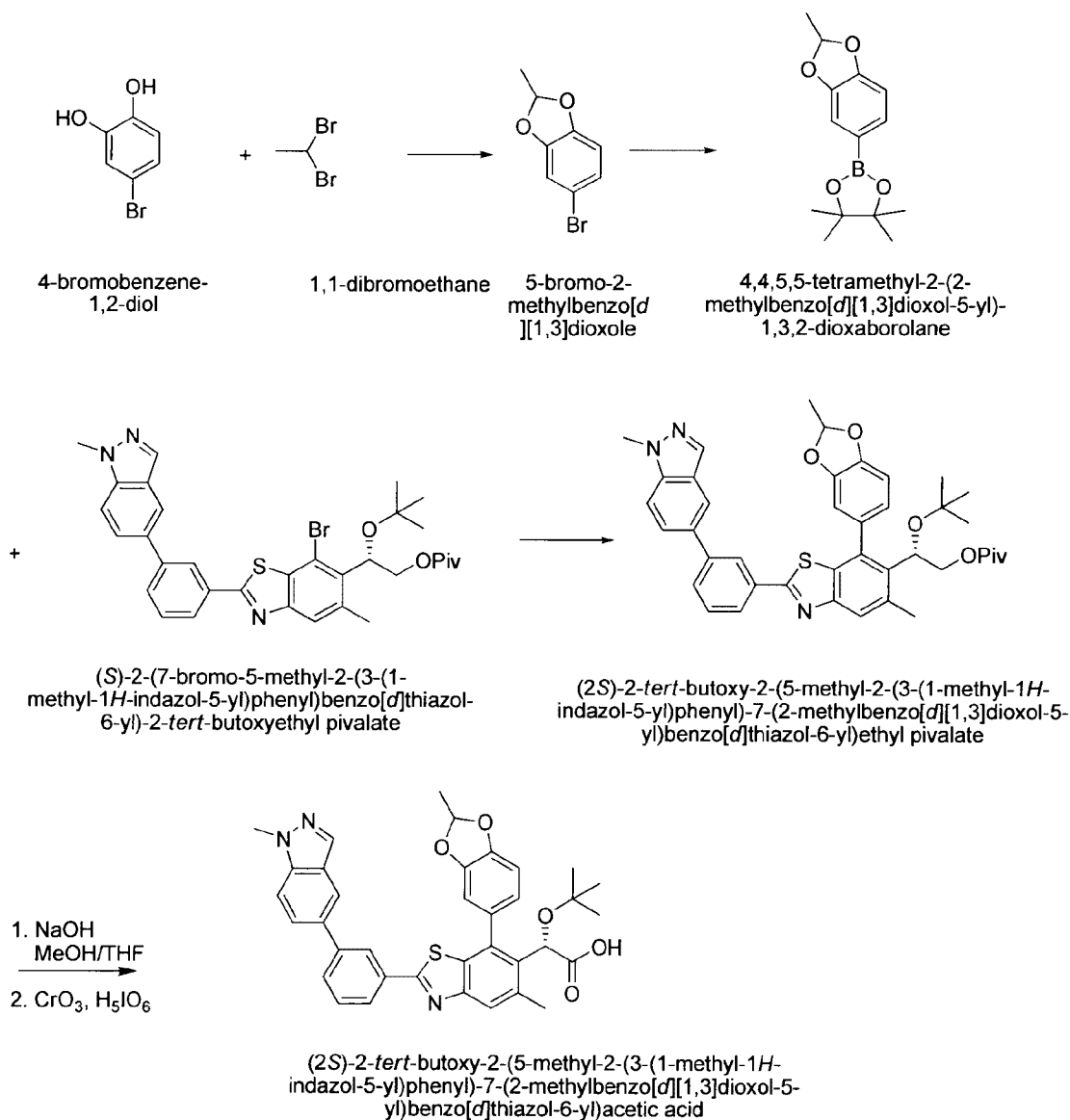
procedure used to prepare (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate of Example 27, except that 5-(1-methyl-1H-indazol-5-yl)pyridin-2(1H)-one was used instead of 3-(1-methyl-1H-indazol-5-yl)pyridin-2(1H)-one. LCMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₃₄H₃₂ClN₄O₄S:

5 627.18; Found: 627.2.

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid: Compound (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid was prepared following the procedure used to (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid of Example 27, except that (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate was used instead of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate. ¹H-NMR: 400 MHz, (CD₃OD) δ 9.07 (d, *J* = 2.8 Hz, 1H), 8.04 (s, 1H), 7.97 (s, 1H), 7.93 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.69 - 7.62 (m, 4H), 7.55 - 7.51 (m, 3H), 6.72 (d, *J* = 9.6 Hz, 1H), 5.25 (s, 1H), 4.09 (s, 3H), 2.56 (s, 3H), 0.96 (s, 9H); LCMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₃₃H₃₀ClN₄O₄S: 613.17; Found: 613.2.

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Example 29. Preparation of (2*S*)-2-*tert*-butoxy-2-(5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)-7-(2-methylbenzo[d][1,3]dioxol-5-yl)benzo[d]thiazol-6-yl)acetic acid (119).



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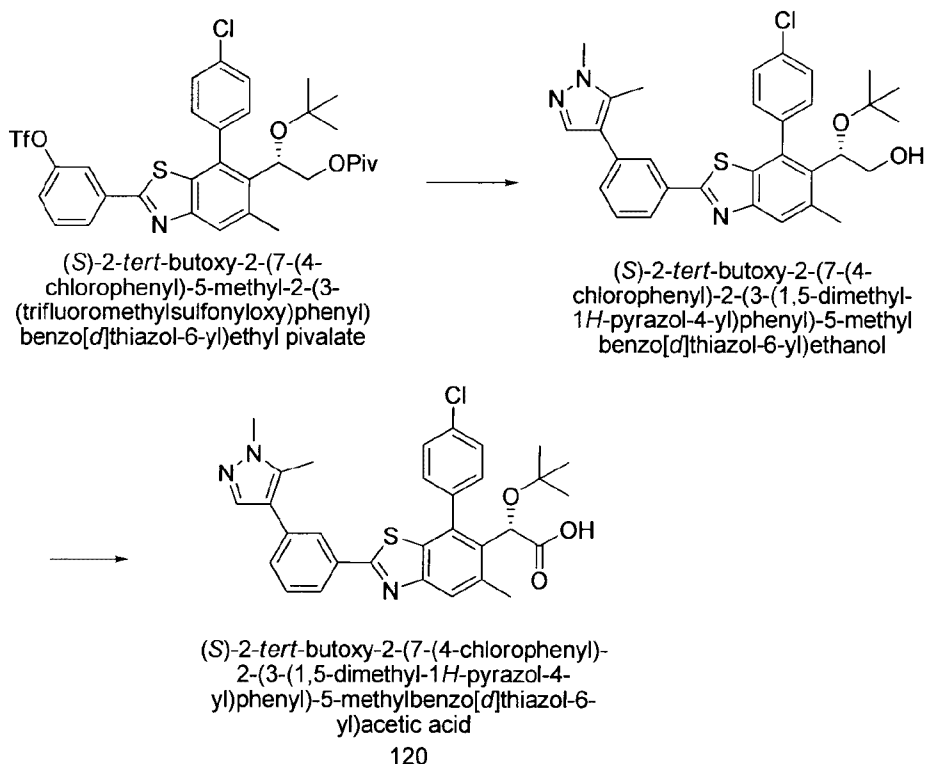
Preparation of 5-bromo-2-methylbenzo[d][1,3]dioxole: To a solution of 4-bromobenzene-1,2-diol (500 mg, 2.65 mmol) in acetone (4 mL) was added cesium carbonate (1.90 g, 5.82 mmol) and 1,1-dibromoethane (1.09 g, 5.82 mmol). The mixture was microwaved to 120 °C for 3 h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H₂O, brine, dried over Na₂SO₄, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 10% ethyl acetate/hexanes) to give the product. ¹H-NMR: 400 MHz, (CDCl₃) δ 6.93 - 6.89 (m, 2H), 6.63 (d, *J* = 8 Hz, 1H), 6.27 (q, *J* = 9.6 Hz, 1H), 1.67 (d, *J* = 4.4 Hz, 3H).

Preparation of 4,4,5,5-tetramethyl-2-(2-methylbenzo[d][1,3]dioxol-5-yl)-1,3,2-dioxaborolane: The suspension of 5-bromo-2-methylbenzo[d][1,3]dioxole (36 mg, 0.17 mmol), bis(pinacolato)diboron (56 mg, 0.22 mmol) and potassium carbonate (50 mg, 0.51 mmol) in DME (0.4 mL) was degassed with N₂ for 5 minutes. To the mixture was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (12 mg, 0.02 mmol), and the resulting mixture was heated at 90 °C for 2 h. Concentrated in vacuo and then purified by flash column chromatography (silica gel, 0 to 50% ethyl acetate/hexanes) to give the product. ¹H-NMR: 400 MHz, (CDCl₃) δ 7.34 - 7.32 (m, 1H), 7.19 (d, *J* = 0.8 Hz, 1H), 6.78 - 6.75 (m, 1H), 6.29 - 6.23 (m, 1H), 1.68 - 1.64 (m, 3H), 1.32 (s, 12 H).

Preparation of (2S)-2-*tert*-butoxy-2-(5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)-7-(2-methylbenzo[d][1,3]dioxol-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate: To a solution of (*S*)-2-(7-bromo-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (16 mg, 0.025 mmol) and 4,4,5,5-tetramethyl-2-(2-methylbenzo[d][1,3]dioxol-5-yl)-1,3,2-dioxaborolane (13 mg, 0.050 mmol) in 1,4-dioxane was added Pd(PPh₃)₄ (4 mg, 3.1 x 10⁻³ mmol) and 2M K₂CO₃ (66 μL, 0.133 mmol). The reaction was degassed for 5 minutes with N₂ and then heated to 110°C for 1 h. After cooling, the reaction mixture was diluted with EtOAc, extracted with saturated NaHCO₃, brine, dried over Na₂SO₄, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 10% ethyl acetate/hexanes) to give the product. LCMS-ESI+ (*m/z*): [M+H]⁺ calcd for C₄₁H₄₄N₃O₅S: 690.30; found: 690.4.

Preparation of (2S)-2-*tert*-butoxy-2-(5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)-7-(2-methylbenzo[d][1,3]dioxol-5-yl)benzo[d]thiazol-6-yl)acetic acid: prepared in a similar manner as (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in Method G, except using (2S)-2-*tert*-butoxy-2-(5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)-7-(2-methylbenzo[d][1,3]dioxol-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate instead of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate. LCMS-ESI⁺ (*m/z*): [M+H]⁺ calcd for C₃₆H₃₄N₃O₅S: 620.2; Found: 620.3; ¹H-NMR: 400 MHz, (CD₃OD) δ 8.34 - 8.32 (m, 1H), 8.08 (s, 2H), 8.00 - 7.94 (m, 1H), 7.85 - 7.84 (m, 3H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.17 - 7.11 (m, 1H), 7.06 - 7.00 (m, 1H), 6.97 - 6.94 (m, 1H), 6.43 - 6.37 (m, 1H), 5.46 - 5.36 (m, 1H), 4.10 (s, 3H), 2.60 (s, 3H), 1.74 - 1.68 (m, 3H), 0.99 (s, 9H).

Example 30. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (120).



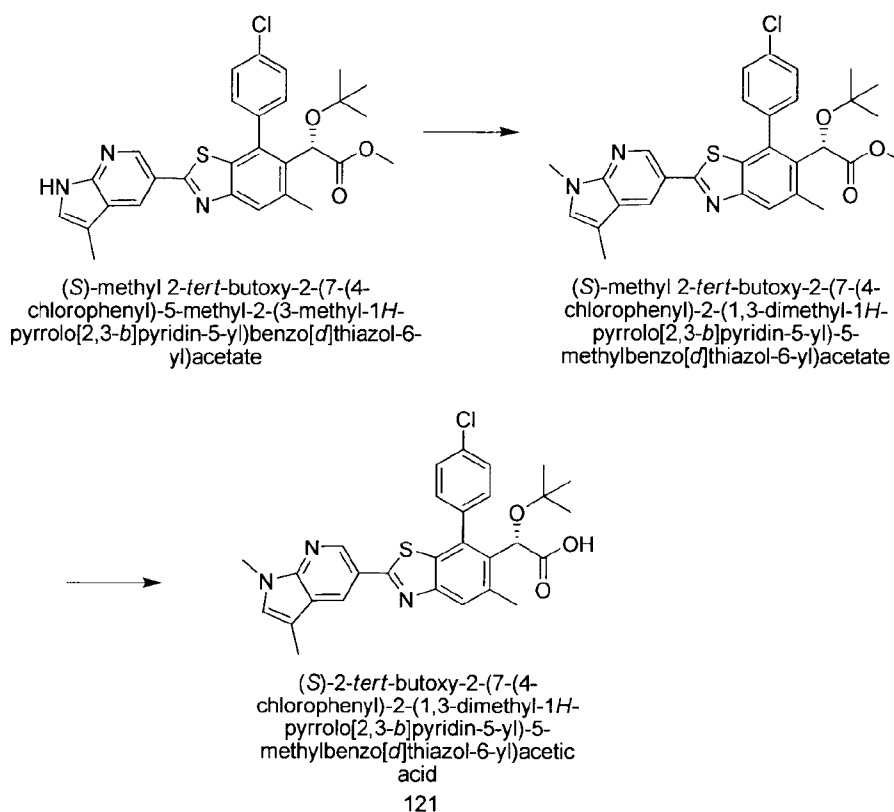
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Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethylsulfonyloxy)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate: The reaction mixture of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethylsulfonyloxy)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate (20 mg, 0.029 mmol), 1,5-dimethyl-1H-pyrazole-5-boronic acid pinacolate ester (13 mg, 0.058 mmol), 2N K₂CO₃ (80 μ L), Pd(PPh₃)₄ (3.3 mg, 0.0029 mmol) in dioxane (1 mL) was heated at 120 °C in sealed tube for 2 hours. After the reaction finished, the reaction was cooled down, to the reaction mixture was added MeOH (1 mL), 2N NaOH (500 μ L) and heated at 45 °C overnight. Then reaction mixture was washed by sat. NaHCO₃, extracted by EtOAc, the organic phase was dried over MgSO₄, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the desired product. LCMS-ESI⁺: calc'd for C₃₁H₃₂ClN₃O₂S: 546.2 (M+H⁺); Found: 546.3 (M + H⁺).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-

chlorophenyl)-2-(3-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)ethanol (11 mg, 0.020 mmol) in wet acetonitrile (0.75 w% H₂O, 1 mL), was added stock solution of H₅IO₆/CrO₃ (0.439 M in wet acetonitrile, 400 μ L) at 0 °C for ½ hour. The reaction mixture was filtered and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H₂O with 0.1% TFA give the product. LCMS-ESI⁺: calc'd for C₃₁H₃₀ClN₃O₃S: 560.2 (M+H⁺); Found: 560.2 (M + H⁺). ¹H NMR (400 MHz, CD₃OD): δ 8.05 (s, 1H), 7.88 (d, *J* = 3.4 Hz, 1H), 7.84 (s, 1H), 7.69-7.66 (m, 2H), 7.59-7.51 (m, 5H), 5.25 (s, 1H), 3.86 (s, 3H), 2.61 (s, 3H), 2.45 (s, 3H), 0.97 (s, 9H).

- 10 **Example 31.** Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (121).



- Preparation (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[d]thiazol-6-yl)acetate (12 mg, 0.022 mmol) in DMF (5mL) was added cesium carbonate (11 mg, 0.033 mmol). The reaction solution was stirred at room temperature for 5 minutes, iodomethane (4.7 mg, 0.033 mmol) was added. The reaction solution was stirred for 30

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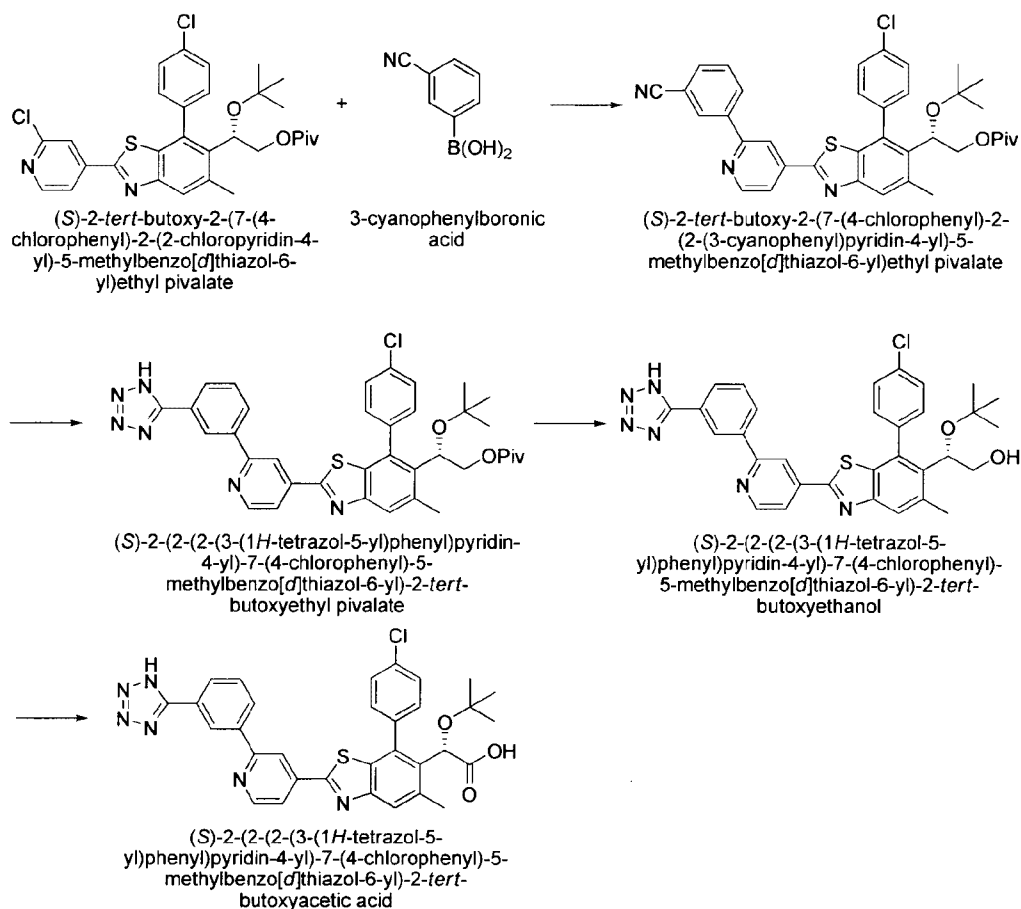
minutes and quenched with water. Volatiles were removed and the residue partitioned between ethyl acetate and water. The organic phase was washed with brine, dried (MgSO₄), filtered and concentrated to give crude product which was purified by chromatographic column to afford the desired product. LCMS-ESI⁺: calc'd for C₃₀H₃₀ClN₃O₃S: 548.17 (M+H⁺); Found: 548.4 (M +

5 H⁺).

Preparation (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: (4 mg, 0.0073 mmol) in THF/CH₃OH (0.5 mL/0.5 mL) was added 2N NaOH (37 μ L, 0.073 mmol). The reaction mixture was heated at 50 °C for 2 h and the crude was purified by reverse phase HPLC, eluting with 5-100% acetonitrile in H₂O with 0.1% TFA to give desired product. LCMS-ESI⁺: calc'd for C₂₉H₂₈ClN₃O₃S: 534.16 (M+H⁺); Found: 534.2 (M + H⁺). ¹H NMR (400 MHz, CD₃OD): δ 8.88 (d, *J* = 1 Hz, 1H), 8.51 (d, *J* = 1 Hz, 1H), 7.82 (s, 1H), 7.71-7.58 (m, 4H), 7.21 (s, 1H), 5.26 (s, 1H), 3.83 (s, 3H), 2.61 (s, 3H), 2.34 (s, 3H), 0.97 (s, 9H).

Example 32. Preparation of (*S*)-2-(2-(2-(3-(1*H*-tetrazol-5-yl)phenyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid (122).

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Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-cyanophenyl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate: (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate (19.7 mg, 0.034 mmol), 3-cyanophenylboronic acid (6.1 mg, 0.041 mmol), Pd(PPh₃)₄, and K₂CO₃ (14.3 mg, 0.103 mmol) were placed in a microwave vial and the vial was vacuum pumped and flushed with argon three times. To this mixture was added degassed 1,4-dioxane (0.4 mL) and degassed water (0.1 mL). The reaction mixture was heated at 110 °C for 1.5 h, cooled, diluted with ethyl acetate, filtered through Celite (ethyl acetate eluent), and concentrated. Purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the product. LCMS-ESI⁺: calc'd for C₃₇H₃₇ClN₃O₃S: 638.2 (M+H⁺); Found: 637.9 (M + H⁺).

Preparation of (*S*)-2-(2-(2-(3-(1*H*-tetrazol-5-yl)phenyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate: To a solution of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-cyanophenyl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethyl

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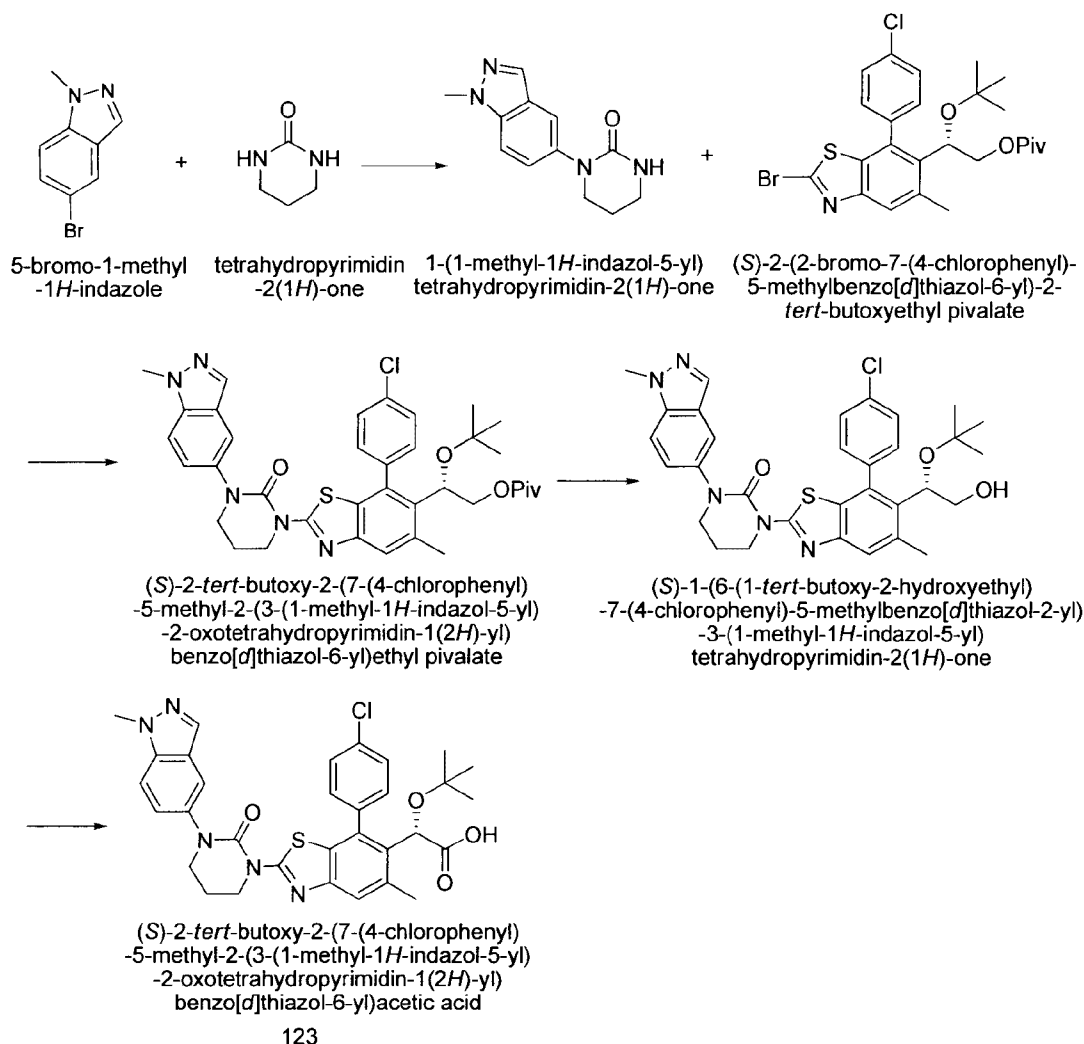
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pivalate (17.2 mg, 0.027 mmol) in DMF (0.5 mL) was added ammonium chloride (7.2 mg, 0.135 mmol) and sodium azide (9.4 mg, 0.144 mmol). The reaction mixture was heated at 120 °C for 6 h then cooled. The crude reaction mixture was passed through a silica gel plug (hexanes/ethyl acetate eluent) to remove the DMF and salts, concentrated, and used without further purification. LCMS-ESI⁺: calc'd for C₃₇H₃₈ClN₆O₃S: 681.2 (M+H⁺); Found: 680.9 (M + H⁺).

Preparation of (*S*)-2-(2-(2-(3-(1H-tetrazol-5-yl)phenyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethanol: To a solution of crude (*S*)-2-(2-(2-(3-(1H-tetrazol-5-yl)phenyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate from the previous reaction (assume 0.027 mmol) in THF (0.4 mL) and methanol (0.4 mL) was added NaOH (0.4 mL of a 2N solution). The reaction mixture was heated at 40 °C for 2 h, cooled, quenched with NH₄Cl (sat. aq.), and extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated to give the crude product which was used without further purification. LCMS-ESI⁺: calc'd for C₃₂H₃₀ClN₆O₂S: 597.2 (M+H⁺); Found: 597.0 (M + H⁺).

Preparation of (*S*)-2-(2-(2-(3-(1H-tetrazol-5-yl)phenyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid: To a solution of crude (*S*)-2-(2-(2-(3-(1H-tetrazol-5-yl)phenyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethanol from the previous reaction (assume 0.023 mmol) in 25% water/acetonitrile (0.75 mL) was added sequentially, a stock solution of CrO₃/H₅IO₆ (0.27 mL, 0.439 M solution) and CrO₃ (3.5 mg, 0.035 mmol) at room temperature. The reaction was stirred for 2 h, filtered, and purified by reverse phase HPLC. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ¹H NMR (400 MHz, CD₃OD) δ 8.84 (dd, *J* = 5.2, 0.6 Hz, 1H), 8.80 – 8.77 (m, 1H), 8.58 (s, 1H), 8.37 – 8.31 (m, 1H), 8.19 – 8.14 (m, 1H), 8.01 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.98 (s, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.65 – 7.59 (m, 3H), 5.29 (s, 1H), 2.65 (s, 3H), 0.99 (s, 9H). LCMS-ESI⁺: calc'd for C₃₂H₂₈ClN₆O₃S: 611.2 (M+H⁺); Found: 610.9 (M + H⁺).

Example 33. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxotetrahydropyrimidin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid (123).



Preparation of 1-(1-methyl-1H-indazol-5-yl)tetrahydropyrimidin-2(1H)-one: To a solution of 5-bromo-1-methyl-1H-indazole (76 mg, 0.36 mmol) in 1,4-dioxane (5 mL) was added tetrahydropyrimidin-2(1H)-one (Aldrich, 216 mg, 2.16 mmol), followed by $\text{Pd}_2(\text{dba})_3$ (16 mg, 0.02 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (31 mg, 0.06 mmol) and cesium carbonate (176 mg, 0.54 mmol). The reaction mixture was degassed with nitrogen and heated at 100 °C for 16 hours. The mixture was diluted with ethyl acetate, washed with water and brine, and dried over Na_2SO_4 and filtered. Concentration and purification by flash column chromatography (hexanes/EtOAc) yielded 1-(1-methyl-1H-indazol-5-yl)tetrahydropyrimidin-2(1H)-one. LCMS-ESI⁺: calc'd for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}$: 231.2 ($\text{M}+\text{H}^+$); Found: 231.2 ($\text{M}+\text{H}^+$).

Preparation of ((S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxotetrahydropyrimidin-1(2H)-yl)benzo[d]thiazol-6-yl)ethyl pivalate: To a solution of (S)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyethyl

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pivalate (27 mg, 0.05 mmol) in 1,4-dioxane (1.5 mL) was added 1-(1-methyl-1H-indazol-5-yl)tetrahydropyrimidin-2(1H)-one (23 mg, 0.1 mmol), followed by Pd₂(dba)₃ (5 mg, 0.006 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (10 mg, 0.02 mmol) and cesium carbonate (60 mg, 0.18 mmol). The reaction mixture was degassed with nitrogen and heated at 100 °C for 16 hours. The mixture was diluted with ethyl acetate, washed with water and brine, and dried over Na₂SO₄ and filtered. Concentration and purification by flash column chromatography (hexanes/EtOAc) yielded ((*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxotetrahydropyrimidin-1(2H)-yl)benzo[d]thiazol-6-yl)ethyl pivalate. LCMS-ESI⁺: calc'd for C₃₇H₄₂ClN₅O₄S: 688.3 (M+H⁺); Found: 688.4 (M+H⁺).

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Preparation of (*S*)-1-(6-(1-*tert*-butoxy-2-hydroxyethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-3-(1-methyl-1H-indazol-5-yl)tetrahydropyrimidin-2(1H)-one: To the solution of ((*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxotetrahydropyrimidin-1(2H)-yl)benzo[d]thiazol-6-yl)ethyl pivalate (20 mg) in THF/MeOH (1 mL/1 mL) was added sodium hydroxide solution (1 mL, 1 N, 1 mmol). The mixture was heated at 50 °C for 12 hours. The mixture was diluted with water, and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over sodium sulfate and filtered. Concentration gave (*S*)-1-(6-(1-*tert*-butoxy-2-hydroxyethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-3-(1-methyl-1H-indazol-5-yl)tetrahydropyrimidin-2(1H)-one. LCMS-ESI⁺: calc'd for C₃₂H₃₄ClN₅O₃S: 604.2 (M+H⁺); Found: 604.3 (M+H⁺).

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Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxotetrahydropyrimidin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid: . A stock solution of periodic acid/chromium trioxide was prepared according to WO 99/52850 by dissolving periodic acid (11.4g, 50.0 mmol) and chromium trioxide (23 mg, 1.2 mol %) in wet acetonitrile (0.75% H₂O, 114 mL). To a solution of (*S*)-1-(6-(1-*tert*-butoxy-2-hydroxyethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-3-(1-methyl-1H-indazol-5-yl)tetrahydropyrimidin-2(1H)-one (16 mg) in wet acetonitrile (1.0 mL, 0.75% H₂O) at 0 °C was added the above stock solution (0.6 mL) at 0 °C. Filtration and purification by reverse phase HPLC gave (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxotetrahydropyrimidin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid. LCMS-ESI⁺: calc'd for C₃₂H₃₂ClN₅O₄S: 618.2 (M+H⁺); Found: 618.3 (M+H⁺), 615.8 (M+H⁺); ¹H-NMR 400 MHz, (CD₃OD) δ 7.99 (s, 1 H), 7.70 (s, 1 H), 7.62-7.50 (m, 3 H), 7.50-7.47 (m, 3 H), 7.37 (m, 1 H),

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DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

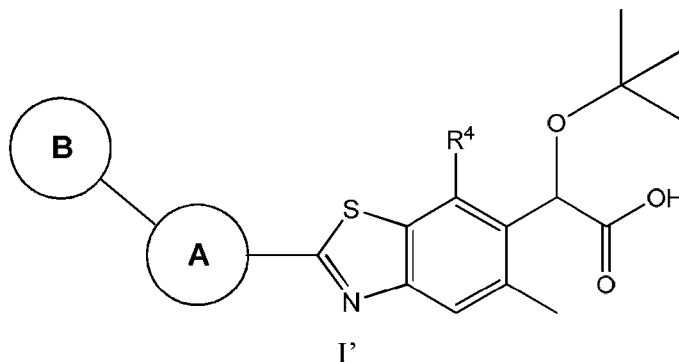
THIS IS VOLUME __1__ OF __3__

NOTE: For additional volumes please contact the Canadian Patent Office.

CLAIMS

What is claimed is:

1. A compound of formula I':



wherein:

R⁴ is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R⁴ is optionally substituted with one or more groups each independently selected from halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₁-C₆)haloalkyl, (C₃-C₇)cycloalkyl, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl, -OH, -O(C₁-C₆)alkyl, -SH, -S(C₁-C₆)alkyl, NH₂, -NH(C₁-C₆)alkyl and -N((C₁-C₆)alkyl)₂, wherein (C₁-C₆)alkyl is optionally substituted with hydroxy, -O(C₁-C₆)alkyl, cyano or oxo;

A is phenyl, monocyclic heteroaryl or monocyclic heterocycle, wherein any phenyl, monocyclic heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups; or A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle, wherein bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more Z^{1b} groups;

each Z^{1a} is independently selected from halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, (C₁-C₃)haloalkyl, (C₃-C₇)carbocycle, heterocycle, -O(C₁-C₃)alkyl, -O(C₂-C₃)alkenyl, -O(C₂-C₃)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle and heterocycle of Z^{1a} is optionally substituted with one or more halogen or (C₁-C₆)alkyl;

each Z^{1b} is independently selected from halo, CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, heteroaryl, heterocycle, aryl(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle and heterocycle of Z^{1b} is optionally substituted with one or more halogen or (C₁-C₆)alkyl; and

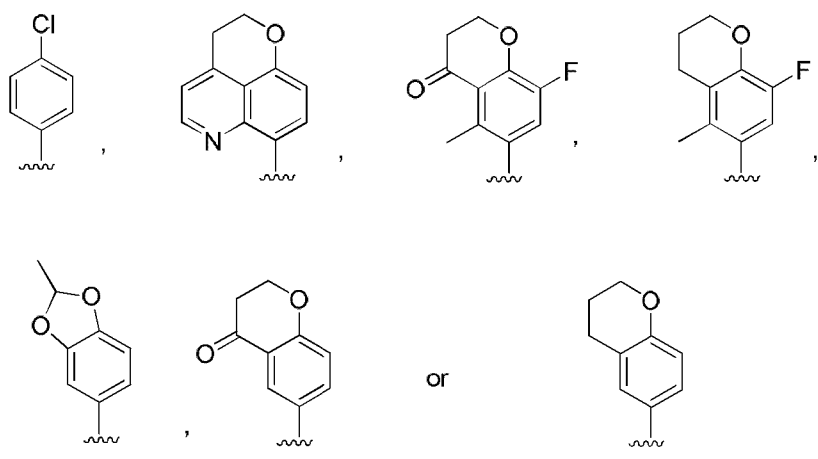
R_a, R_b, R_c and R_d are each independently H or (C₁-C₆)alkyl;
or a salt thereof.

2. The compound of claim 1, or salt thereof, wherein the configuration of the -OC(CH₃)₃ group as shown in formula I' is the (*S*) stereochemistry.

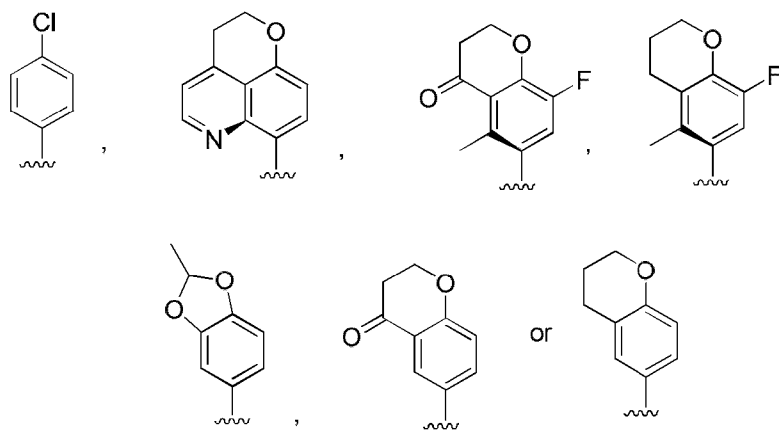
3. The compound of claim 1 or claim 2, or salt thereof, wherein R⁴ is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R⁴ is optionally substituted with one or more halo or (C₁-C₆)alkyl.

4. The compound claim 1 or claim 2, or salt thereof, wherein R⁴ is selected from aryl and heterocycle, wherein any aryl and heterocycle of R⁴ is optionally substituted with one or more chloro, fluoro or methyl.

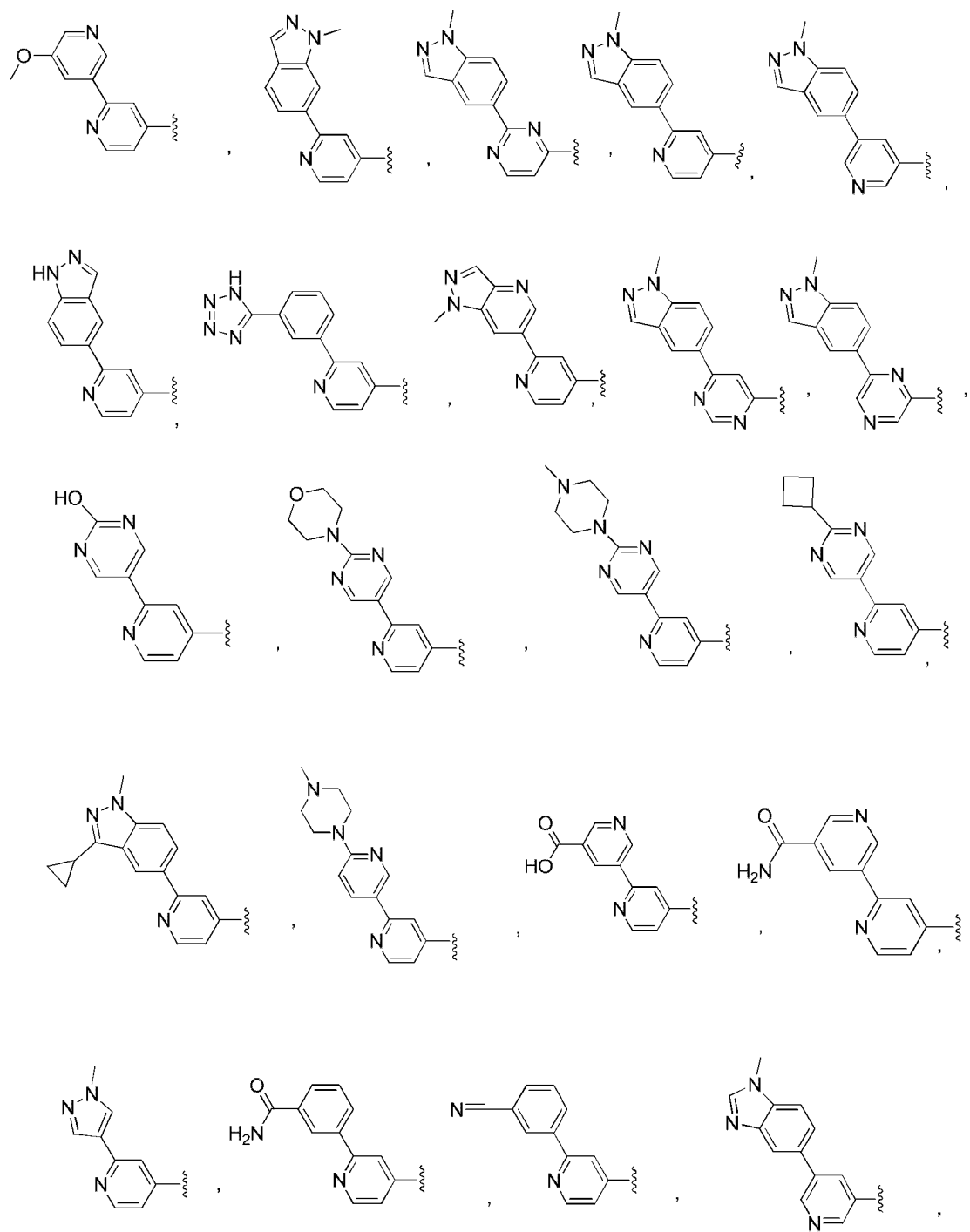
5. The compound of claim 1 or claim 2, or salt thereof, wherein R⁴ is:

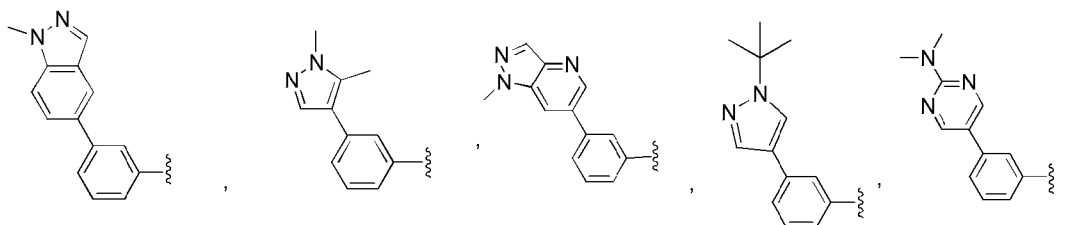
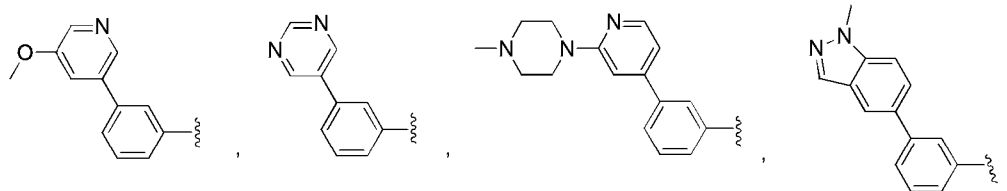
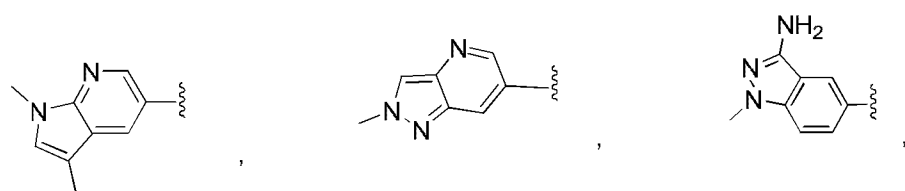
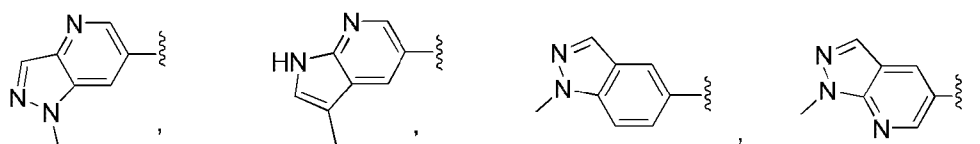
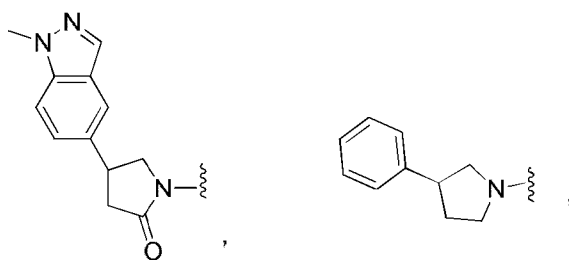
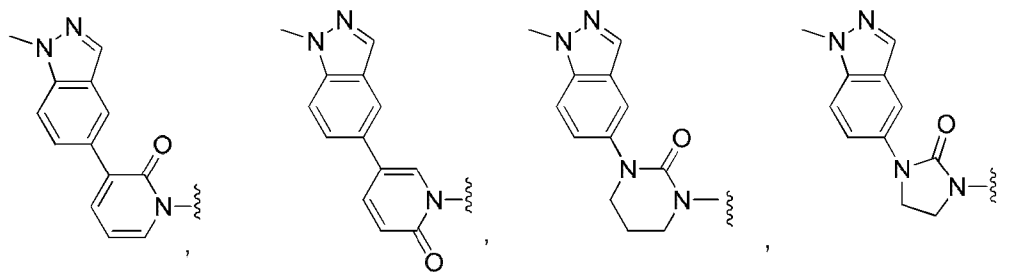


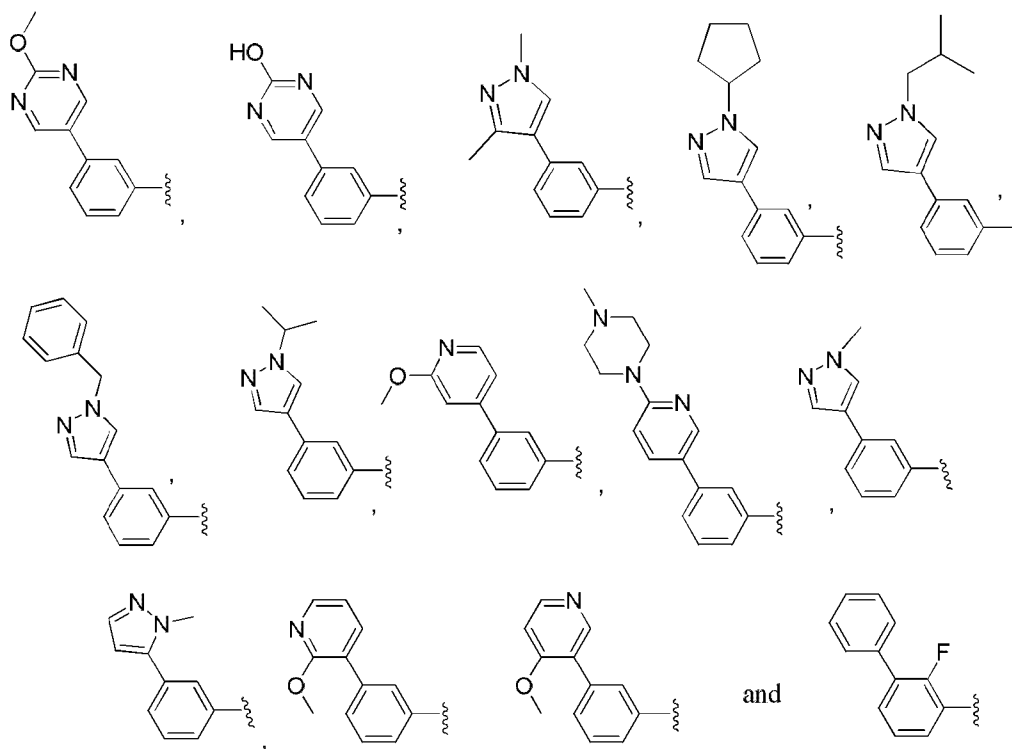
6. The compound of claim 1 or claim 2, or salt thereof, wherein R⁴ is:



7. The compound of any one of claims 1-6, or salt thereof, wherein A is phenyl, monocyclic N-heteroaryl or monocyclic heterocycle, wherein any phenyl, monocyclic N-heteroaryl or monocyclic heterocycle of A is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.
8. The compound of any one of claims 1-6, or salt thereof, wherein A is monocyclic N-heteroaryl, wherein monocyclic N-heteroaryl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.
9. The compound of any one of claims 1-6, or salt thereof, wherein A is pyridinyl, pyrimidinyl or pyrazinyl, wherein pyridinyl, pyrimidinyl or pyrazinyl is optionally substituted with one or more Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.
10. The compound of any one of claims 1-6, or salt thereof, wherein A is pyridinyl, pyrimidinyl or pyrazinyl and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.
11. The compound of any one of claims 1-6, or salt thereof, wherein A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle, wherein bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more Z^{1b} groups.
12. The compound of any one of claims 1-6, or salt thereof, wherein A and B together form a bicyclic heteroaryl, wherein bicyclic heteroaryl is optionally substituted with one or more Z^{1b} groups.
13. The compound of any one of claims 1-6, or salt thereof, wherein A and B together form a pyrrolopyridinyl, pyrazolopyridinyl or indazolyl, wherein pyrrolopyridinyl, pyrazolopyridinyl or indazolyl is optionally substituted with one or more Z^{1b} groups.
14. The compound of any one of claims 1-6, or salt thereof, wherein A-B is selected from:

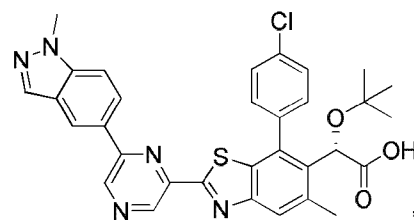
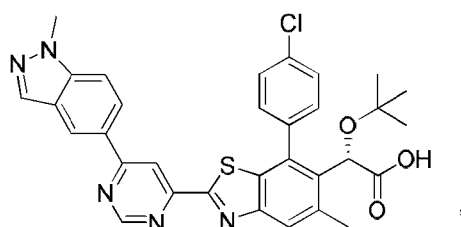
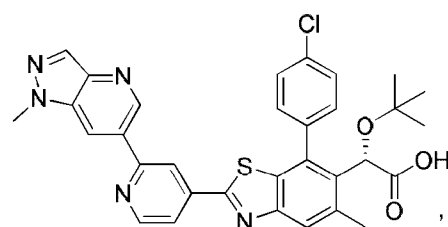
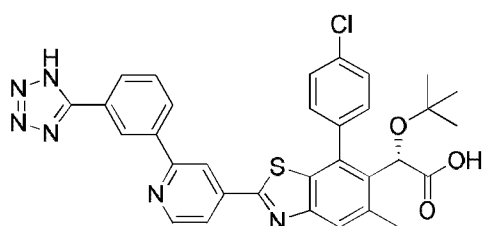
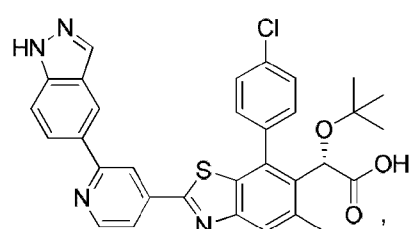
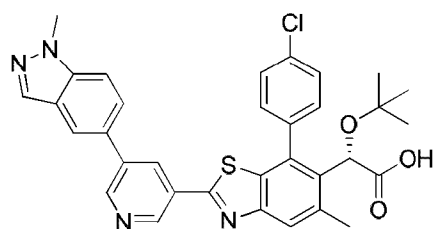
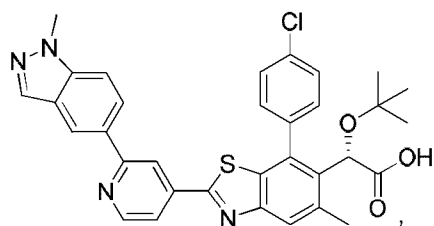
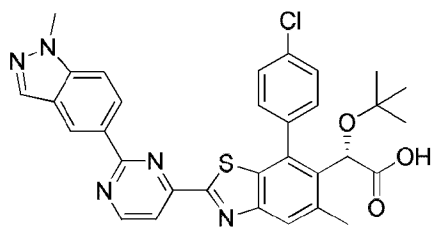
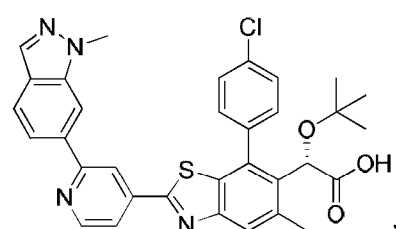
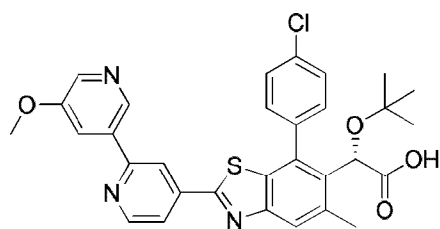


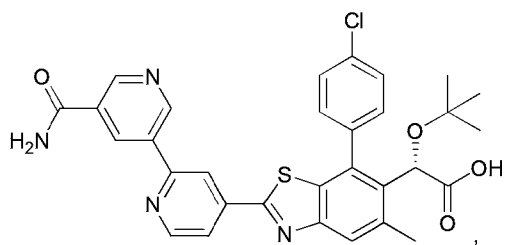
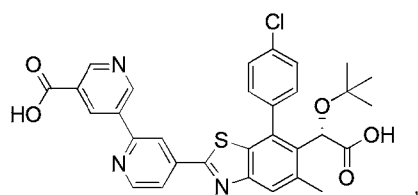
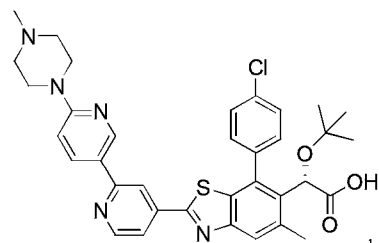
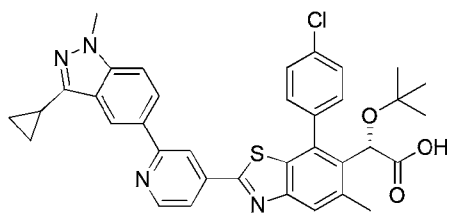
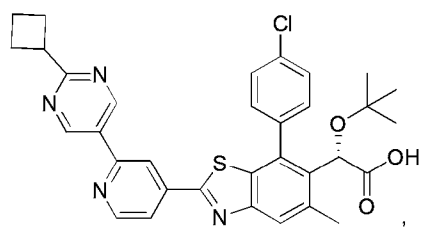
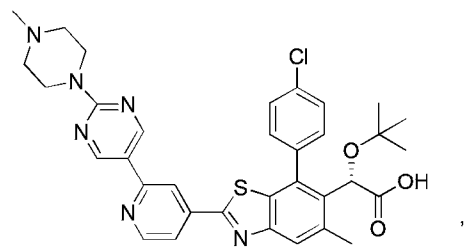
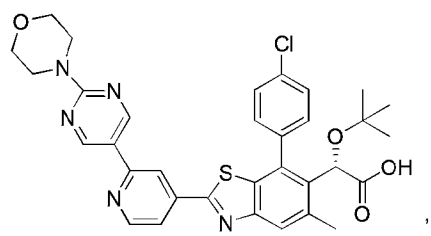
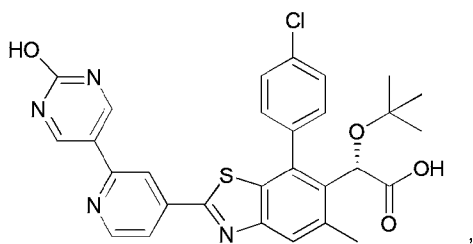


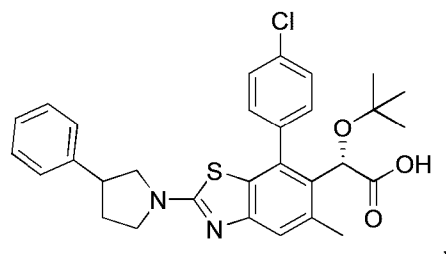
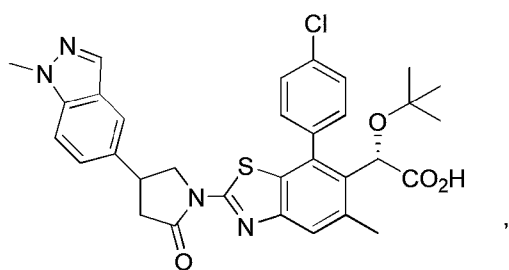
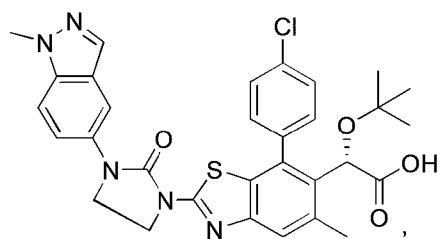
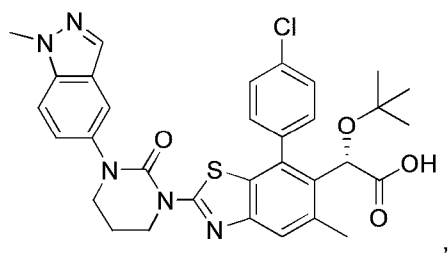
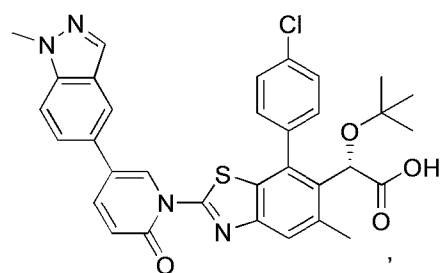
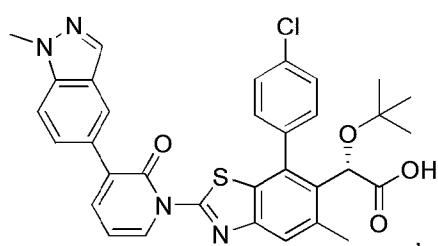
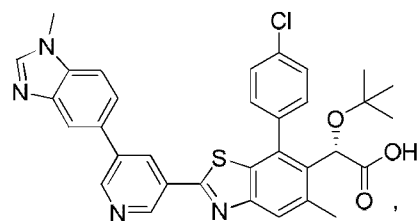
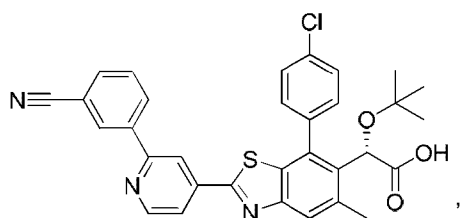
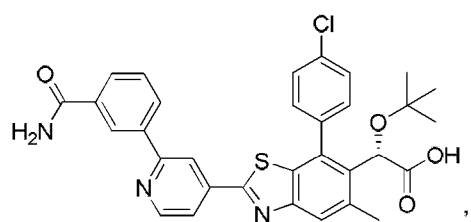
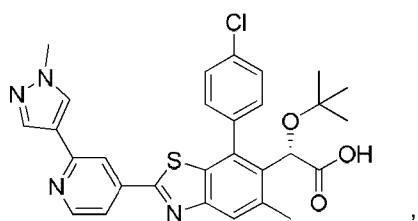


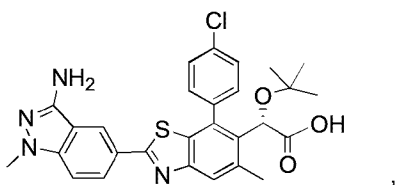
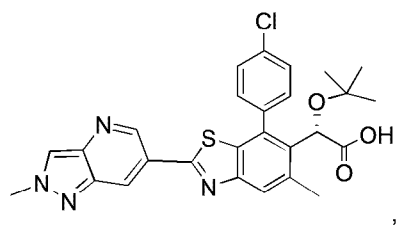
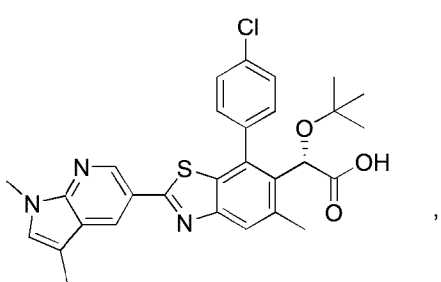
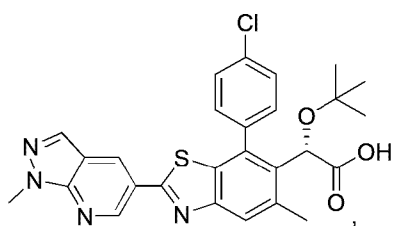
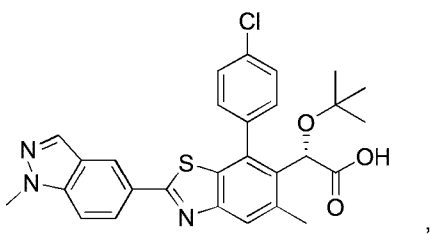
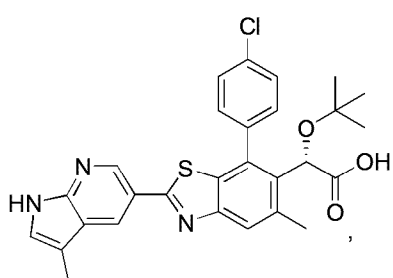
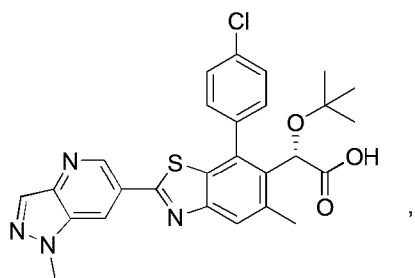
15. The compound of any one of claims 1 to 14 wherein the salt is a pharmaceutically acceptable salt.

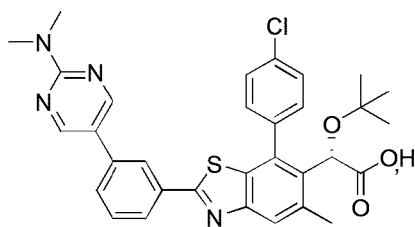
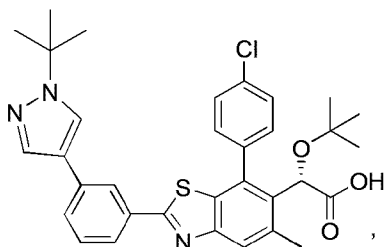
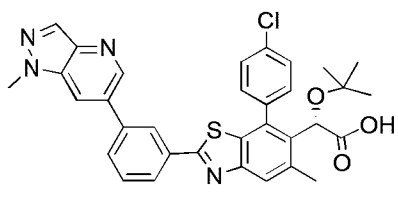
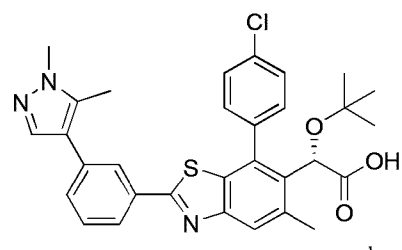
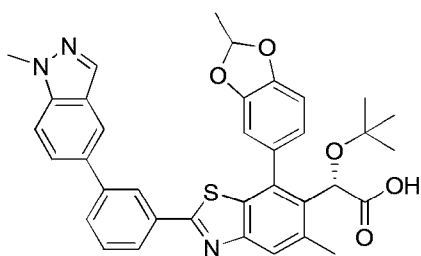
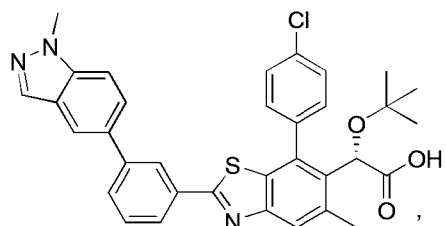
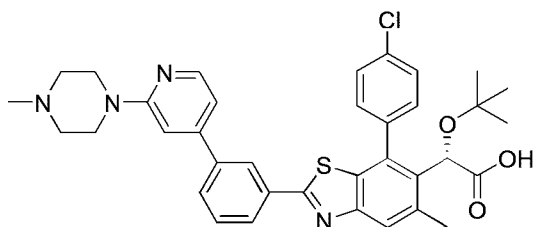
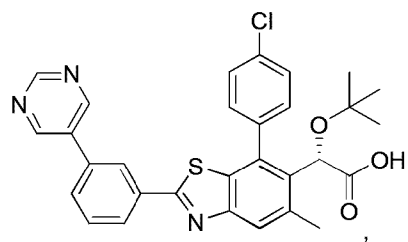
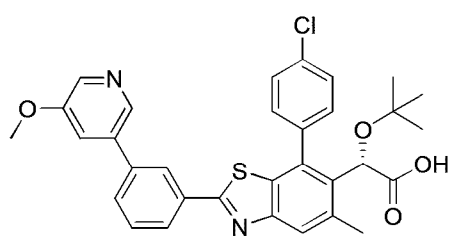
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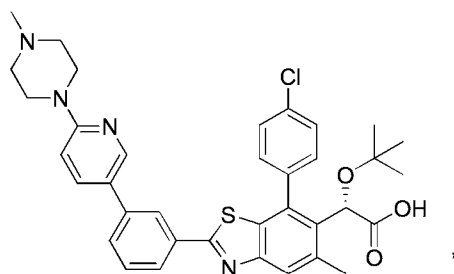
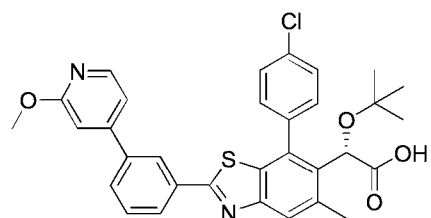
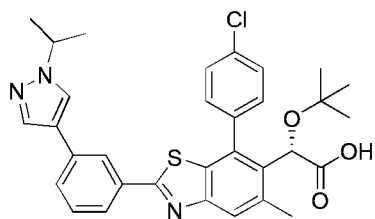
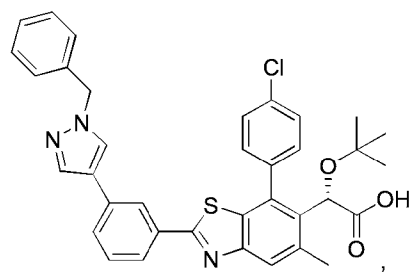
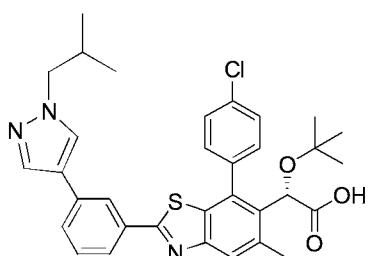
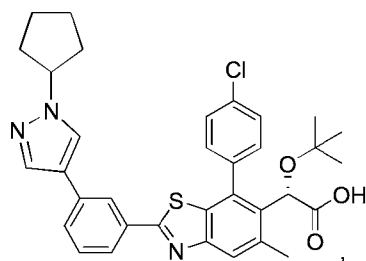
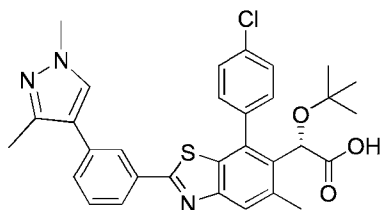
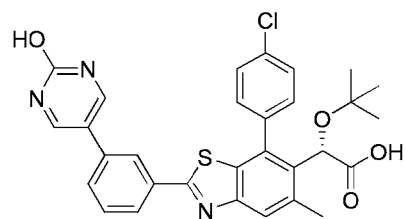
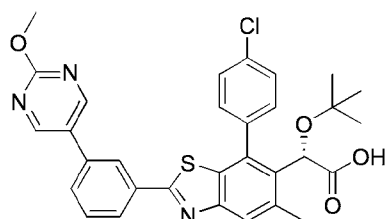


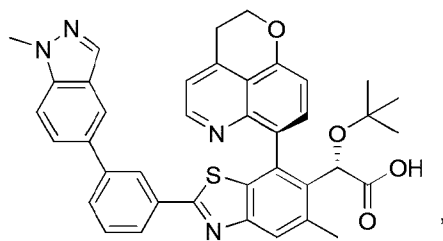
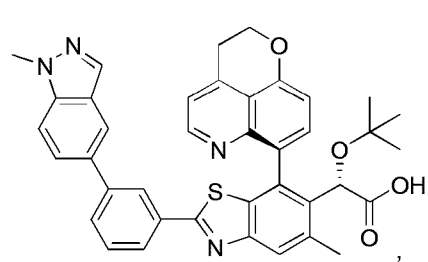
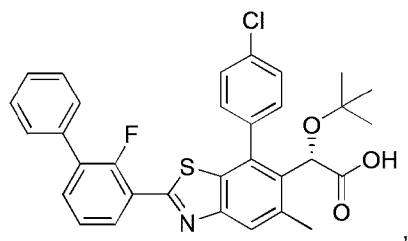
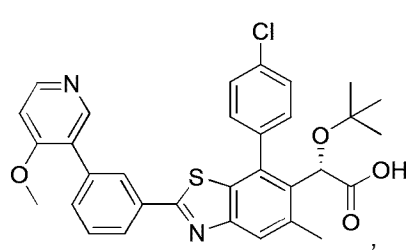
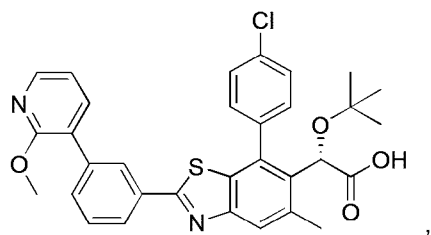
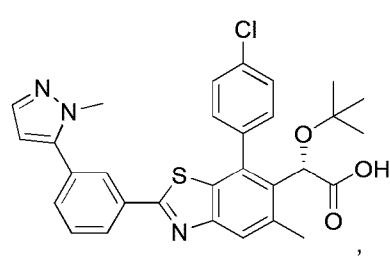
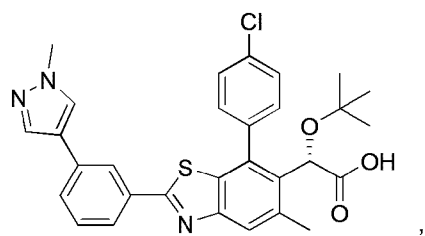


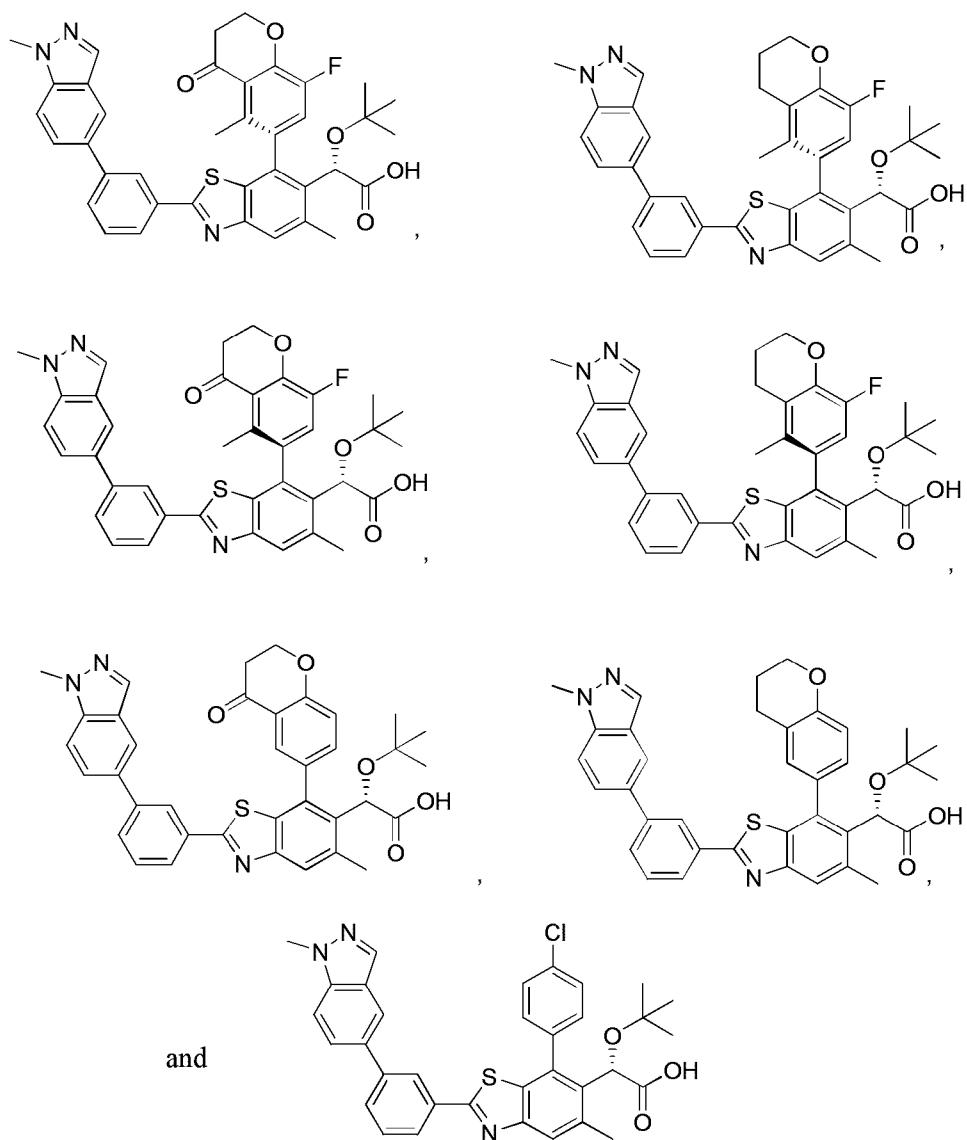






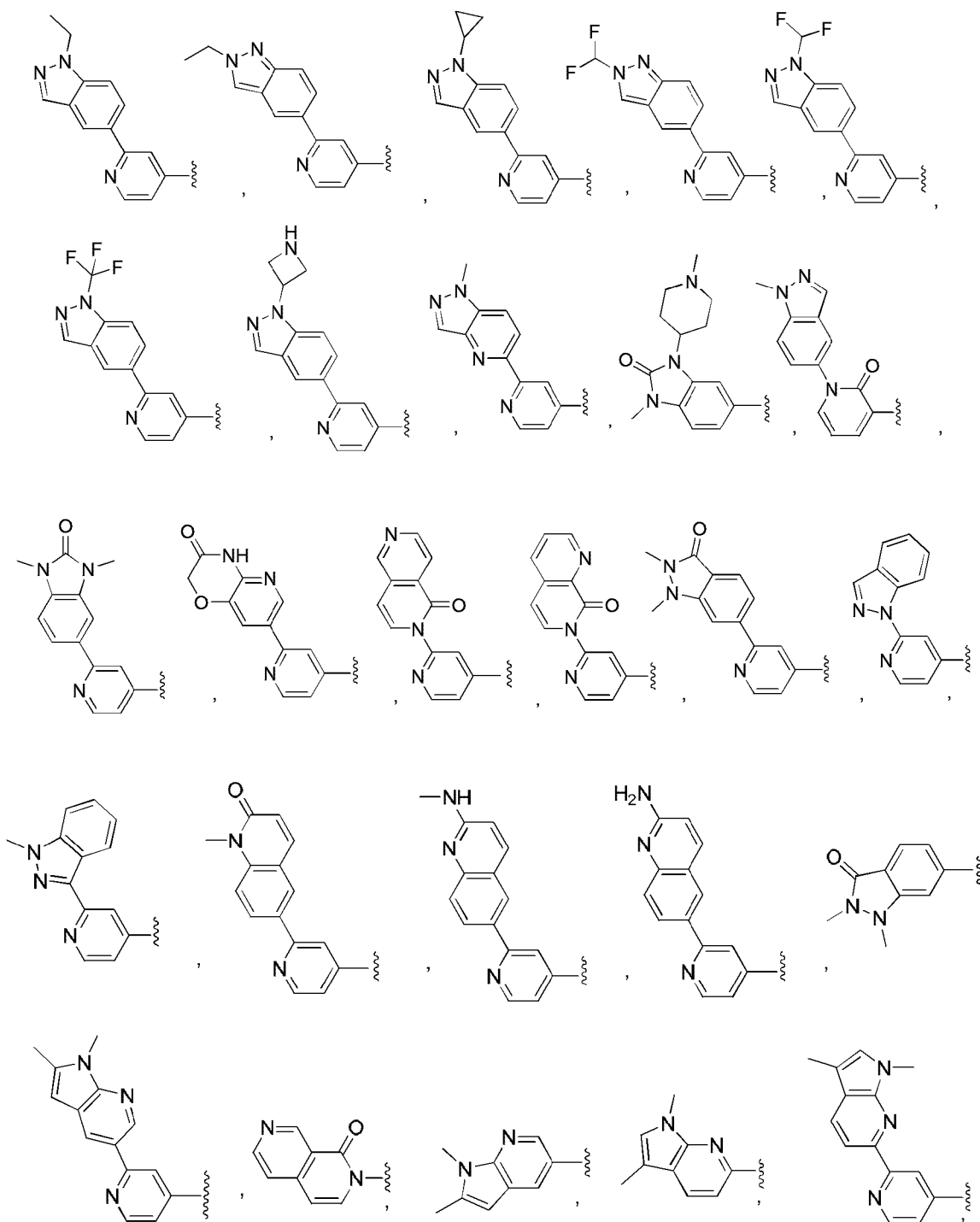


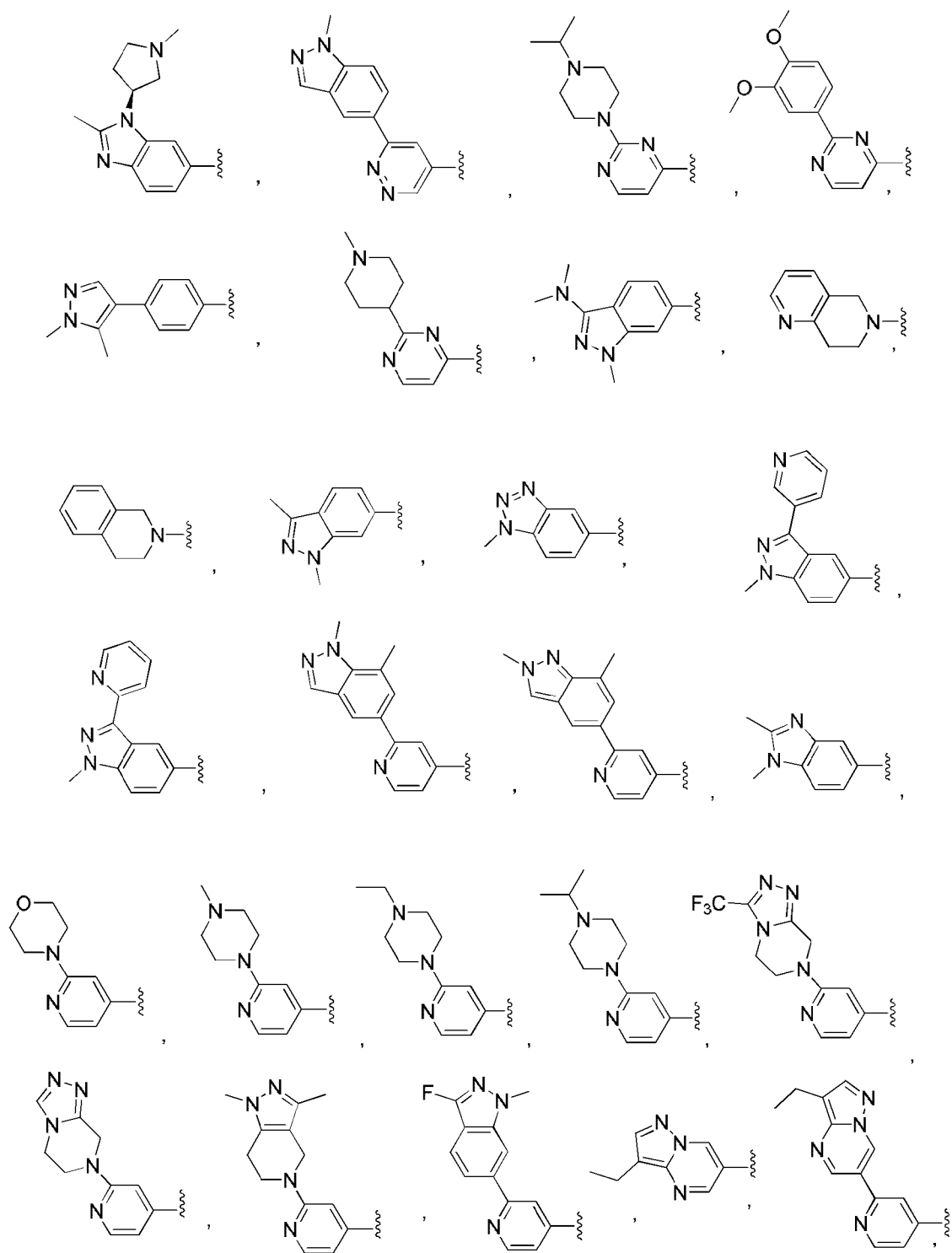


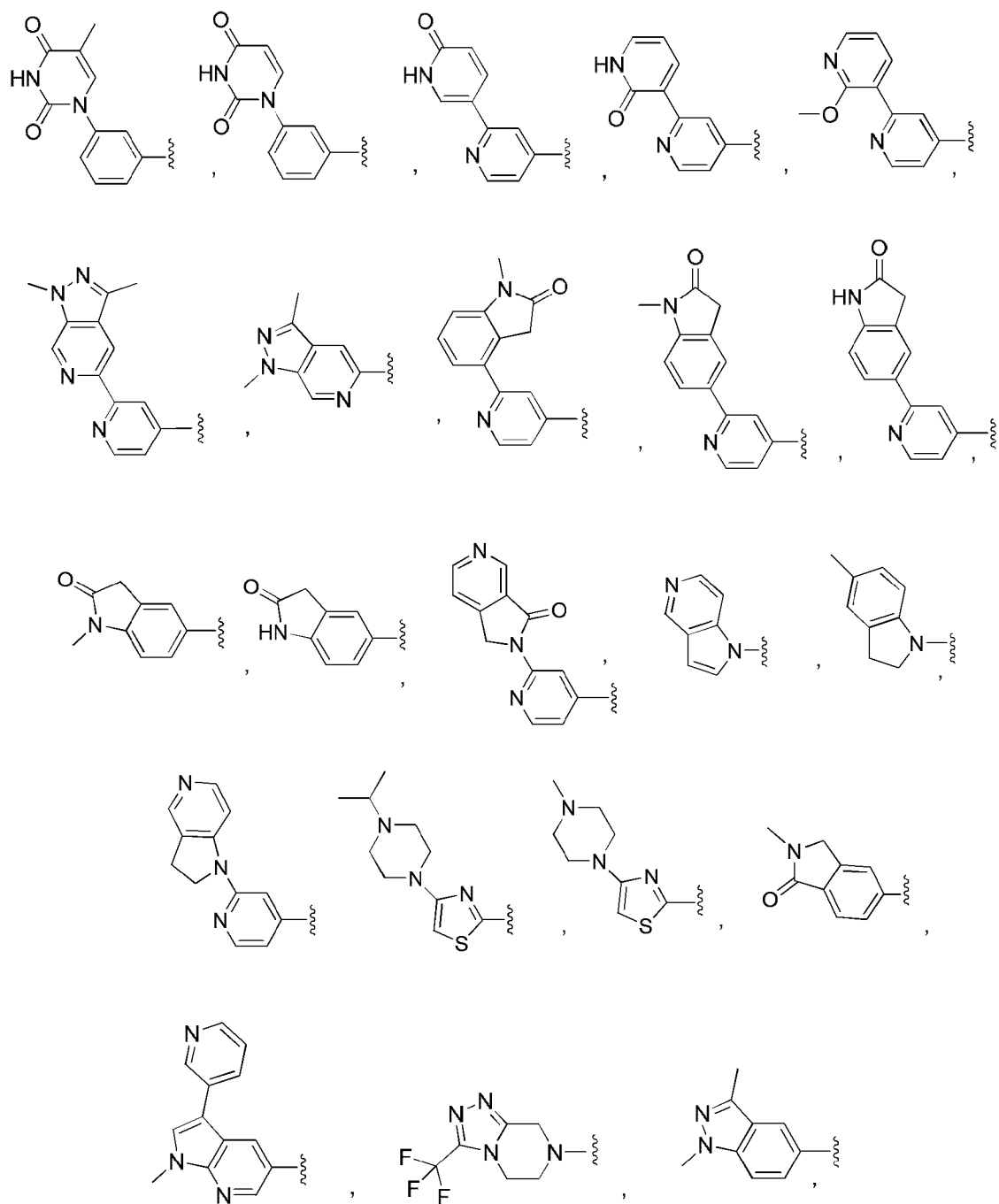


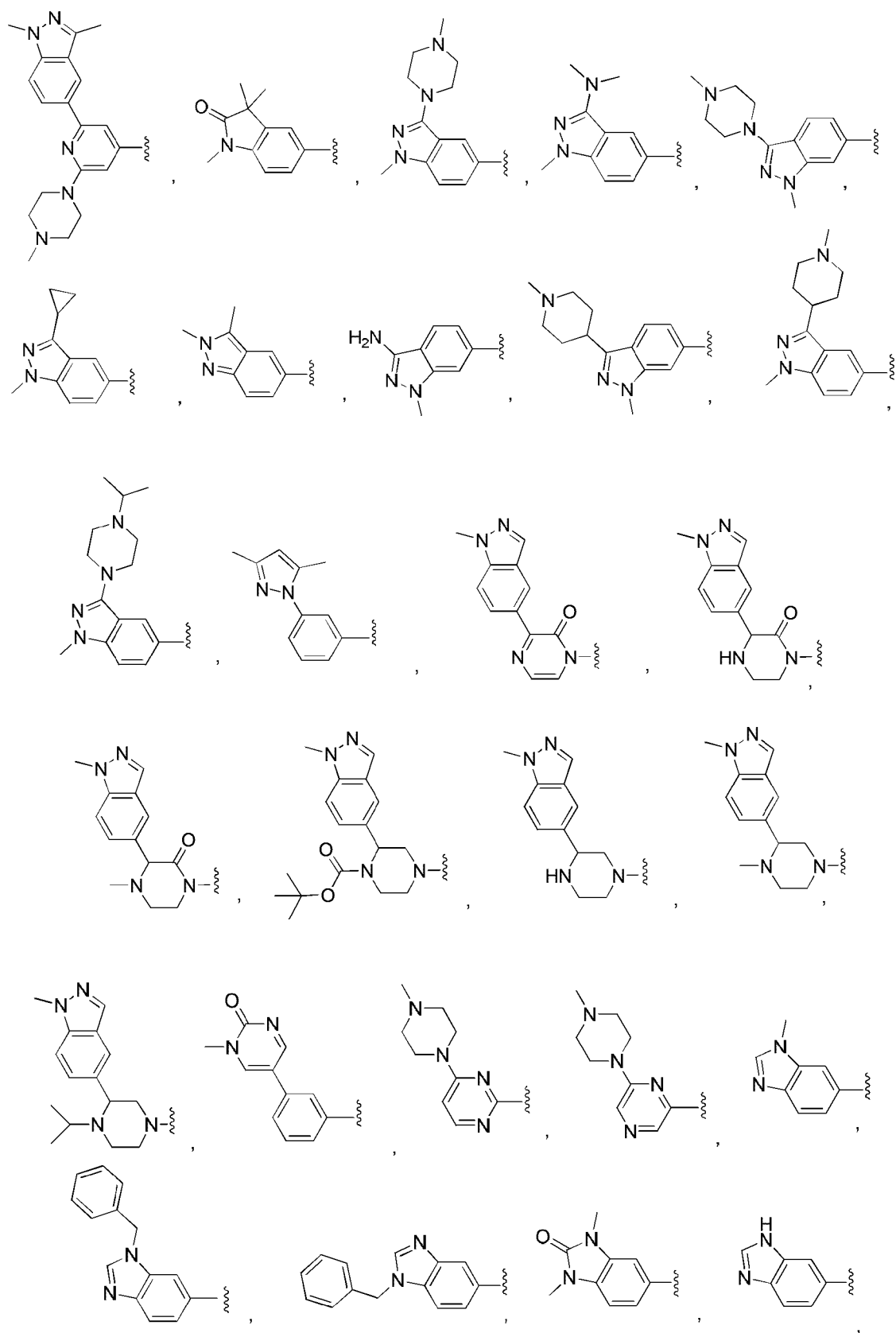
and pharmaceutically acceptable salts thereof.

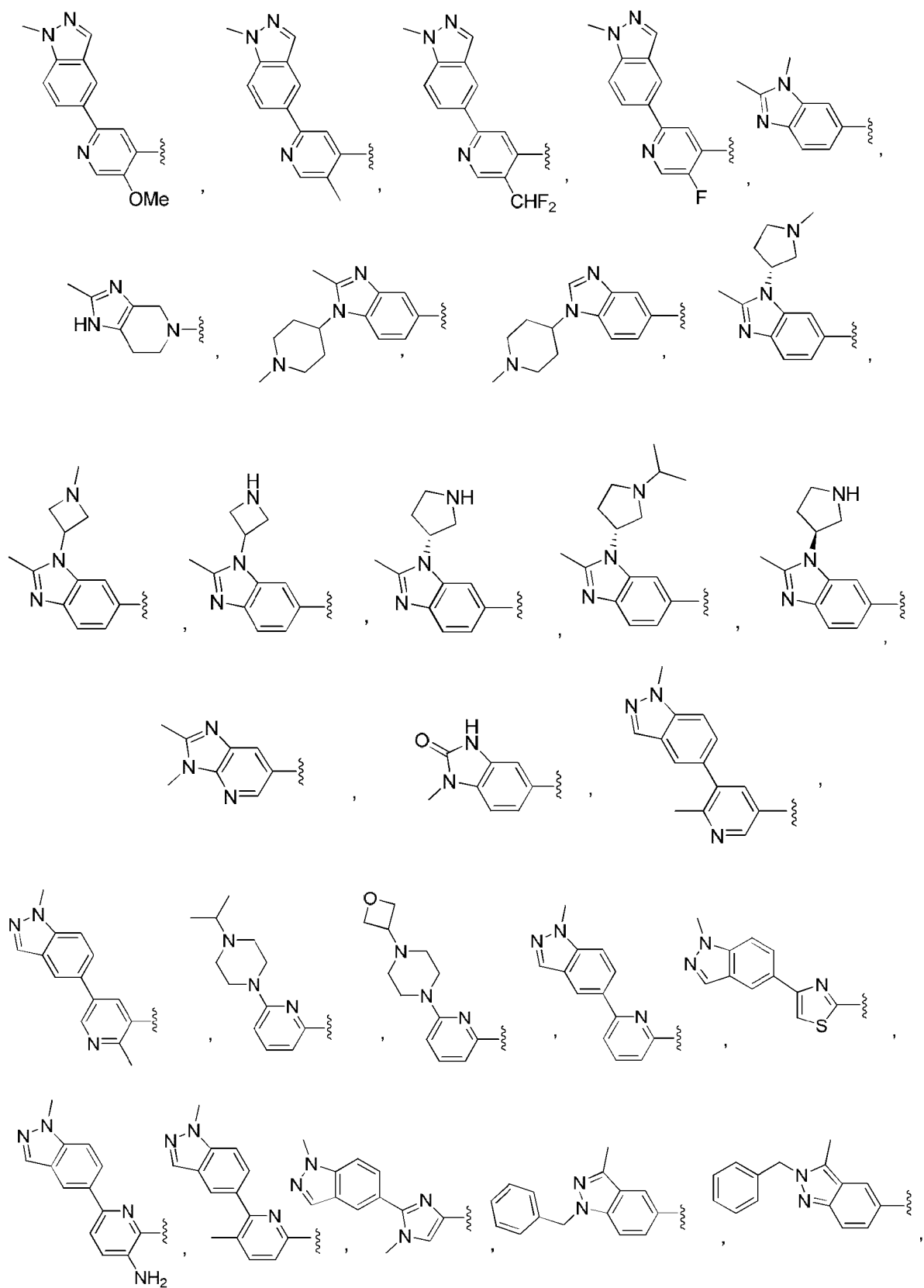
17. The compound of any one of claims 1-6 wherein A-B is selected from:

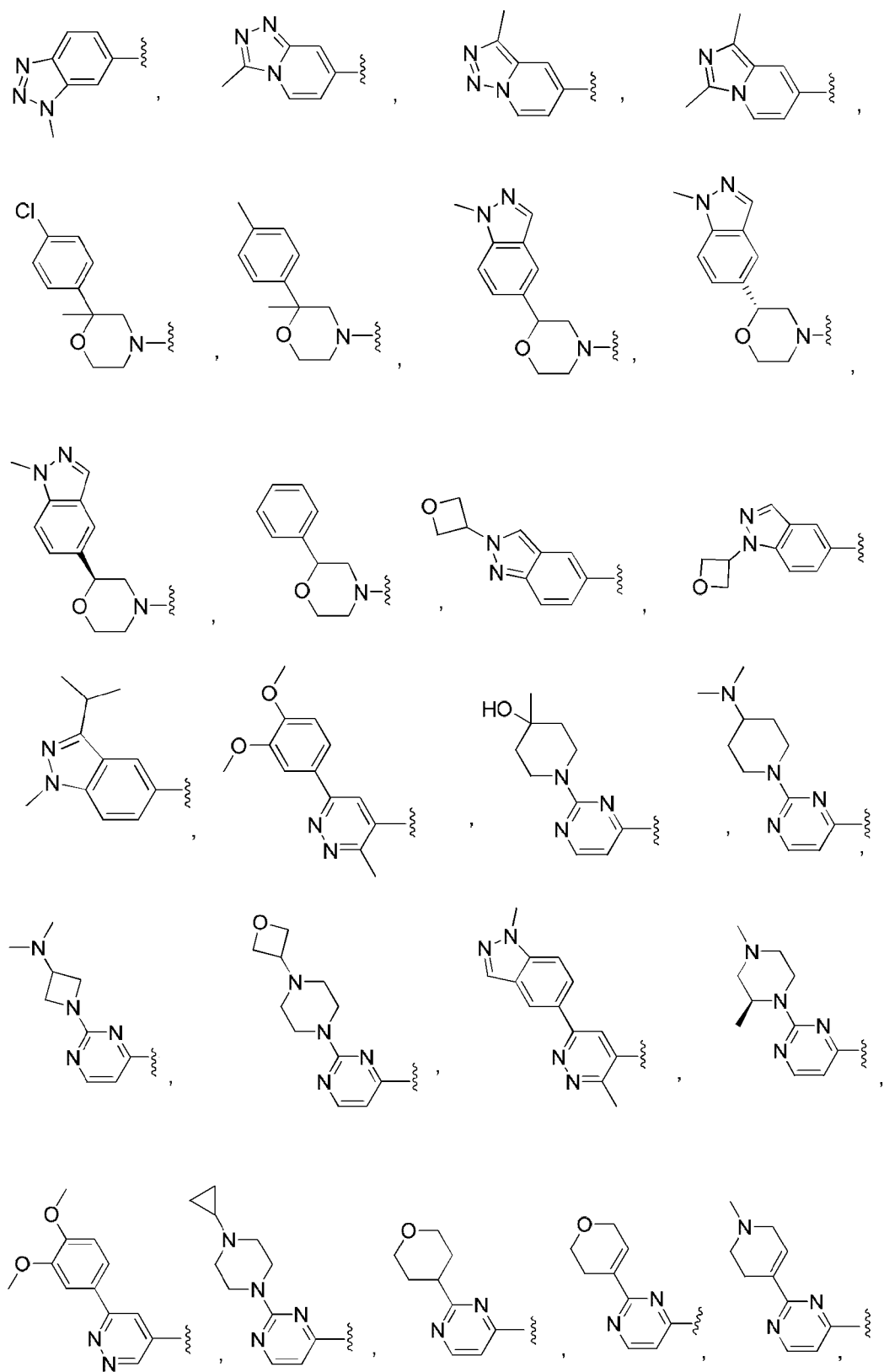


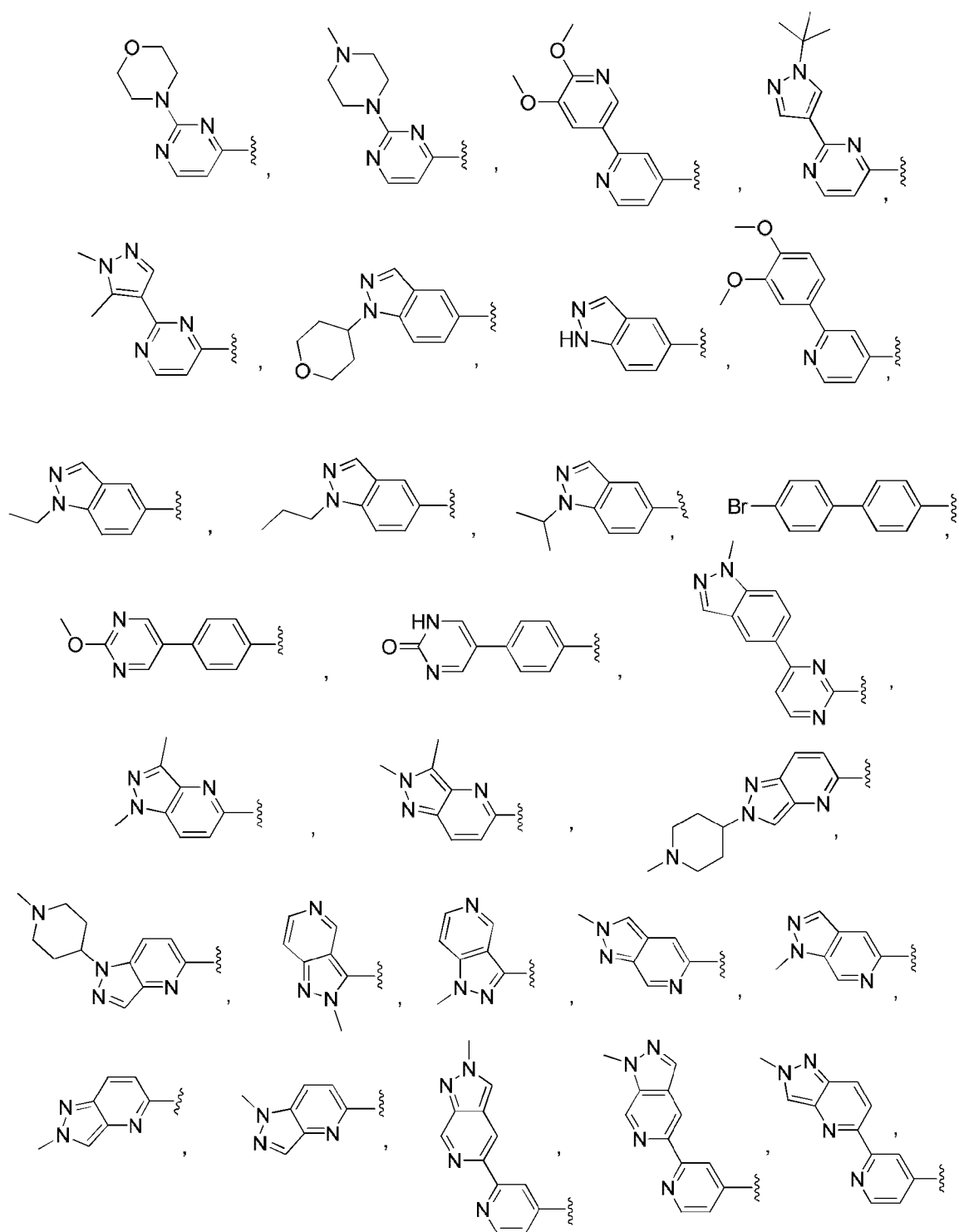


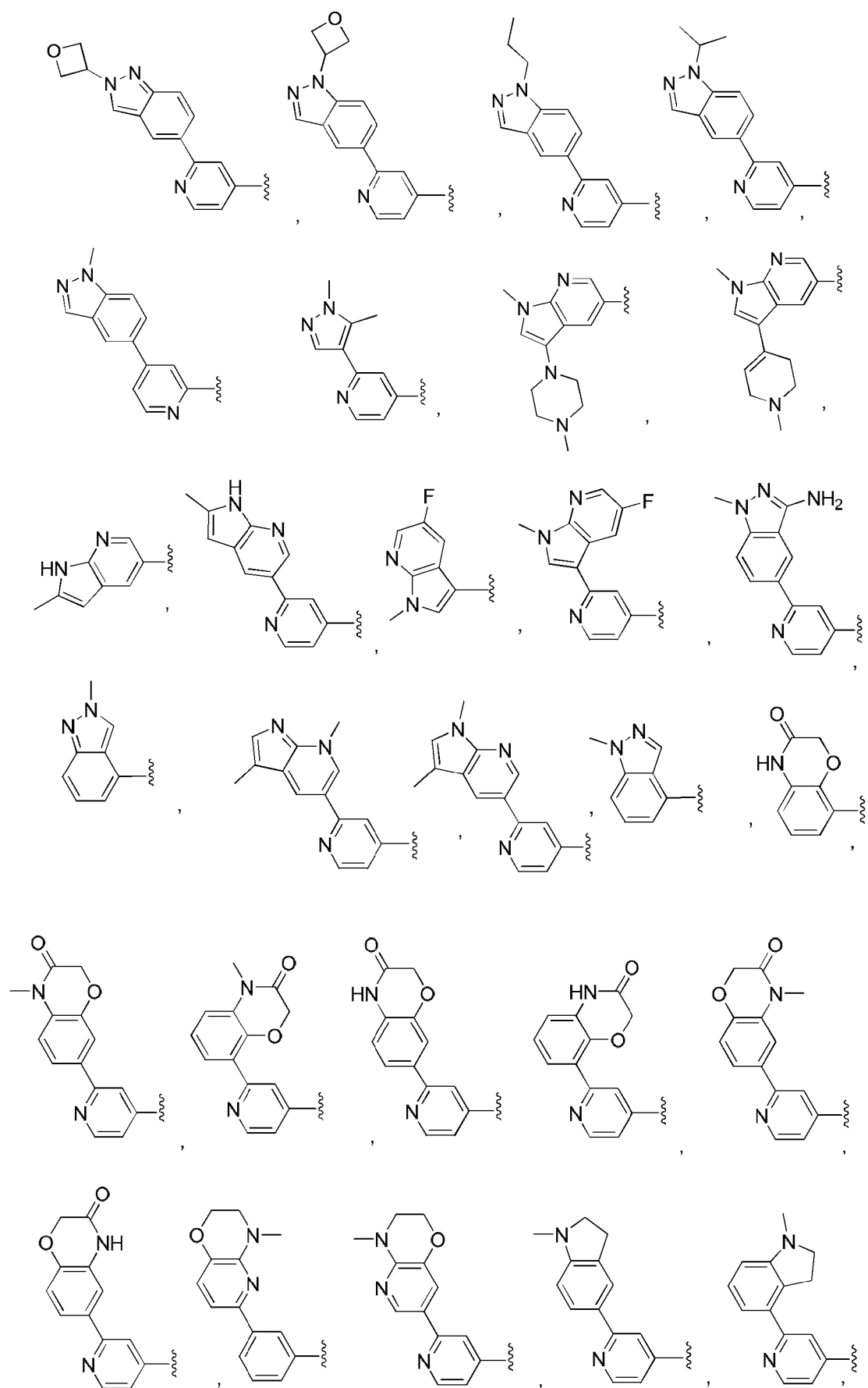


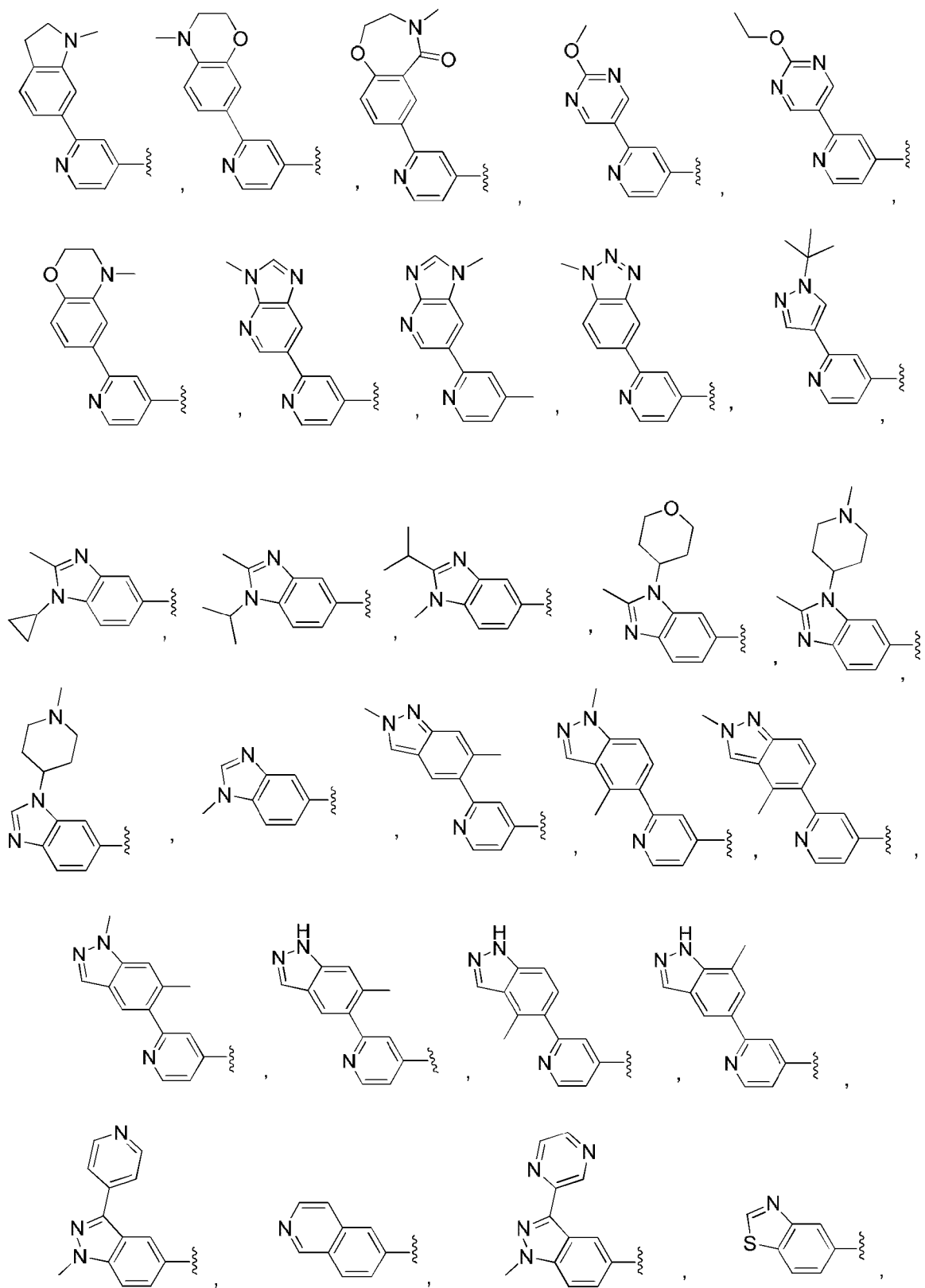


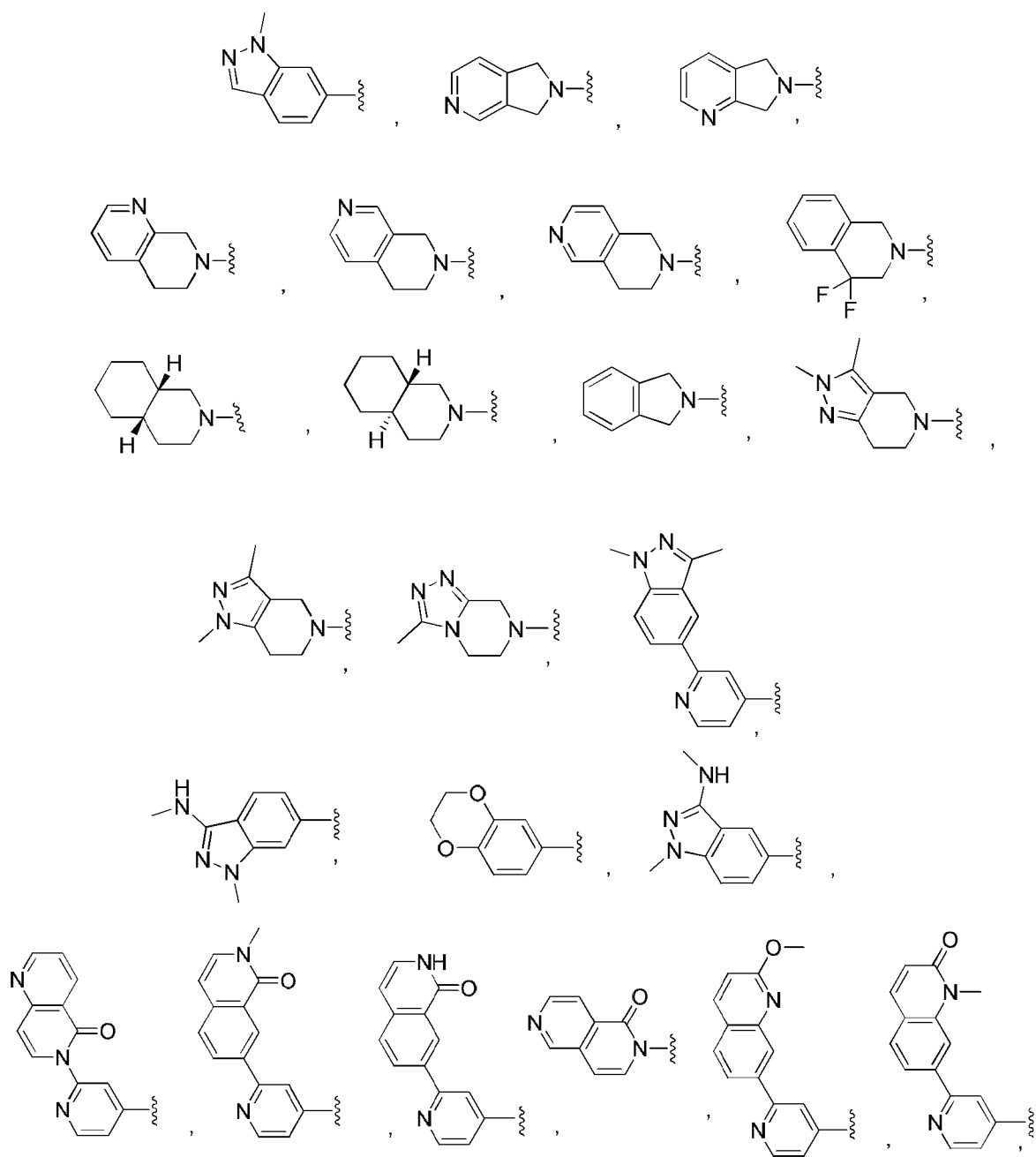


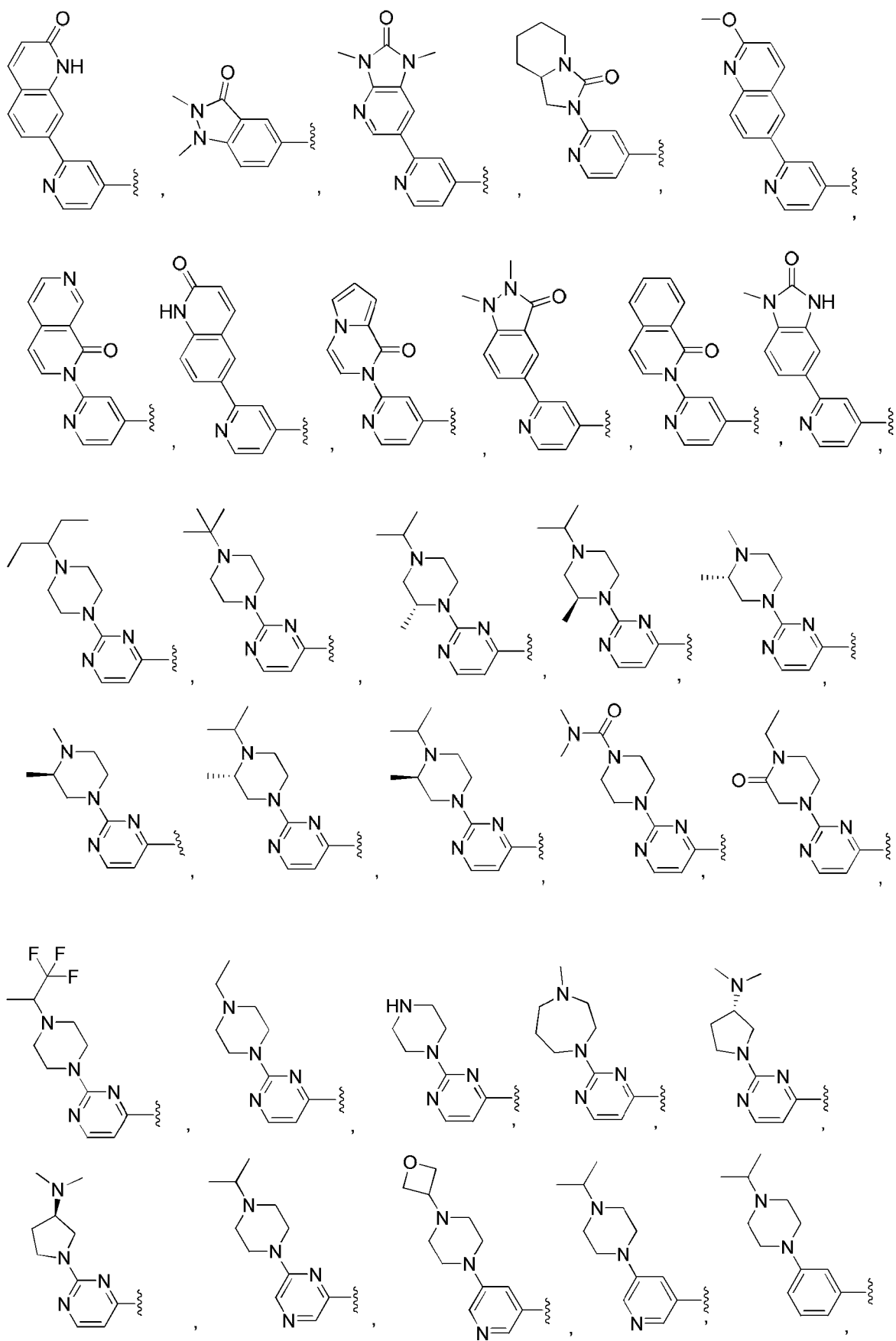


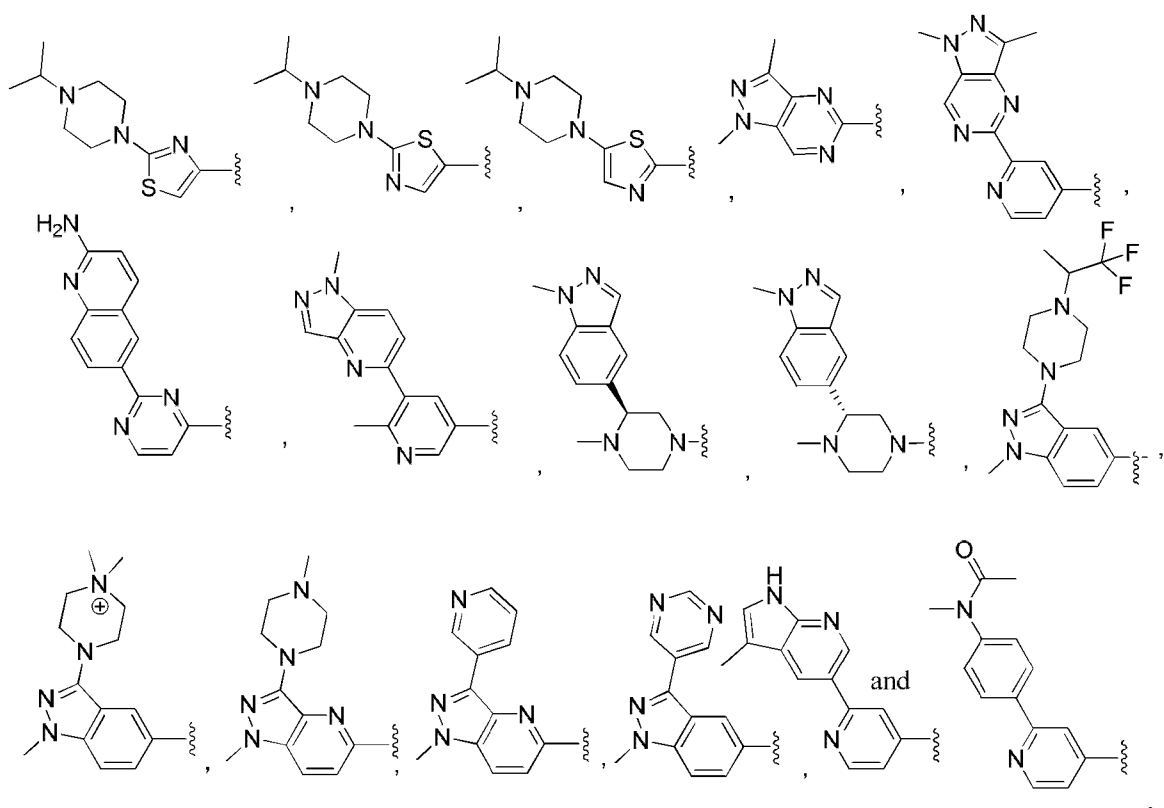




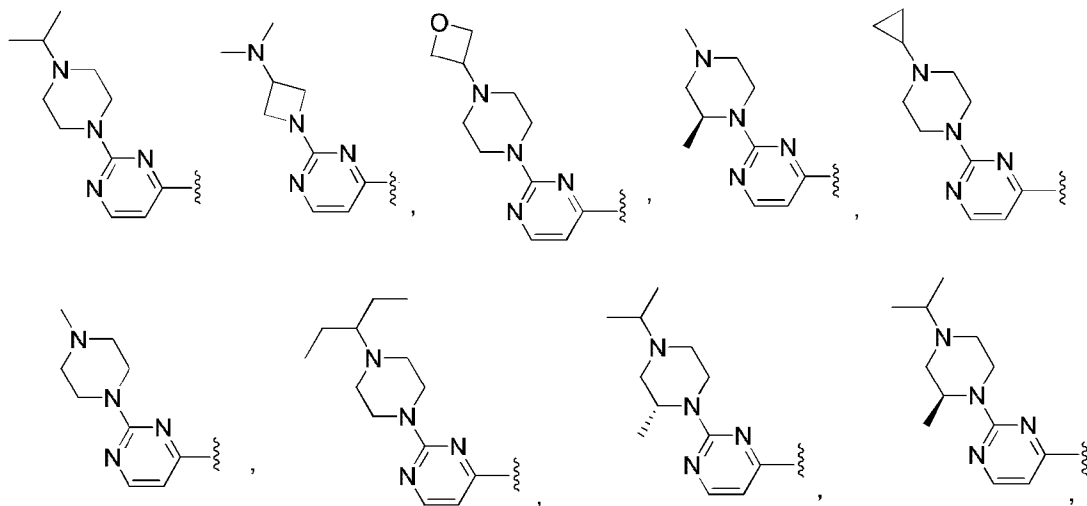


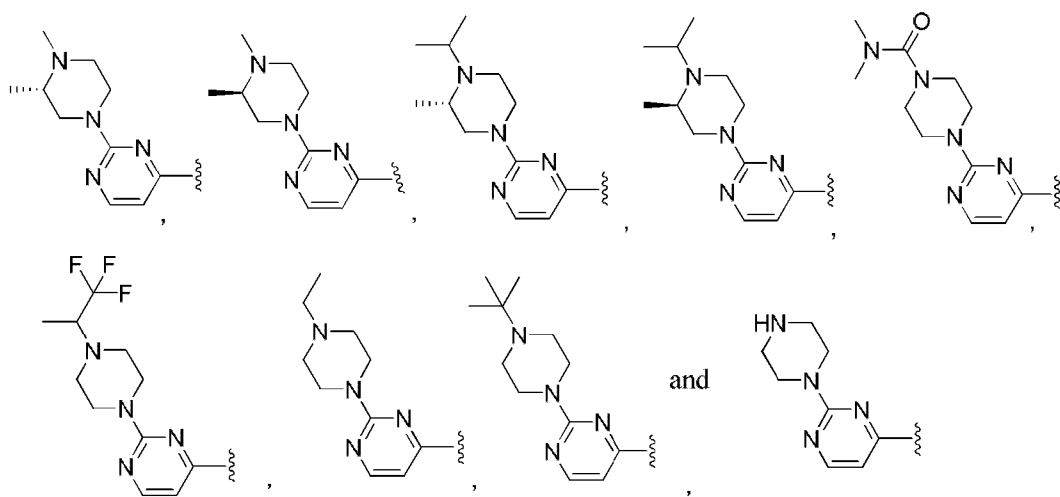




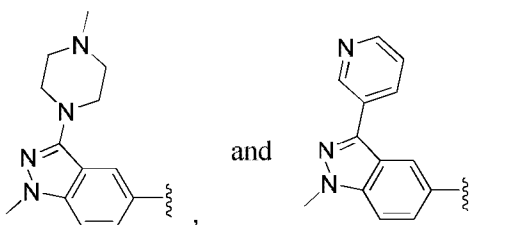


18. The compound of any one of claims 1-6, or salt thereof, wherein A-B is selected from:

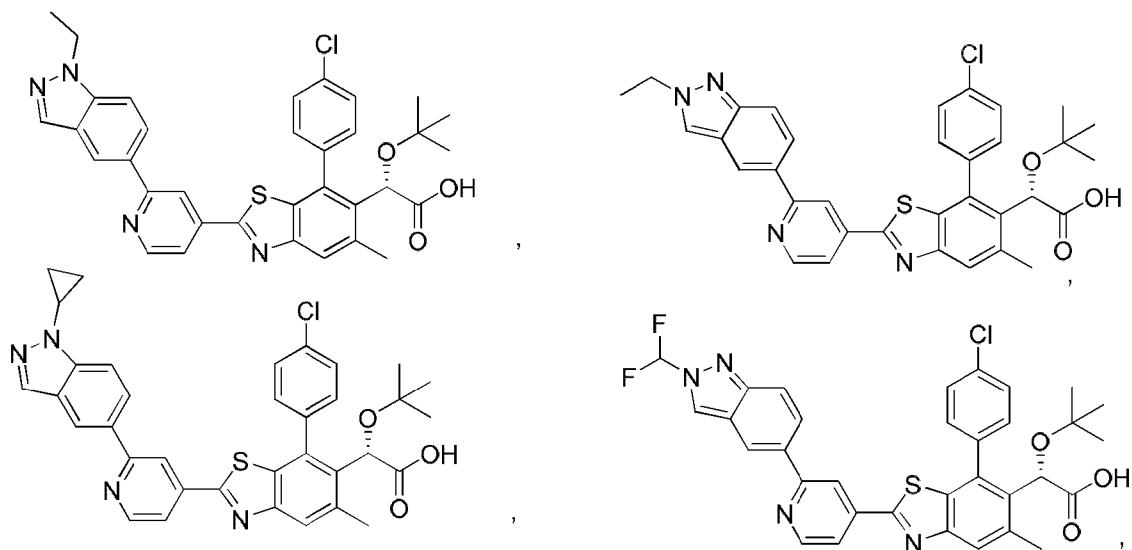


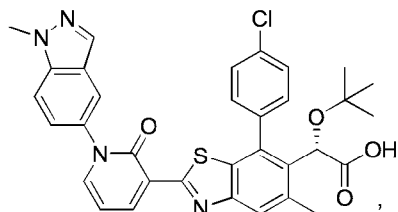
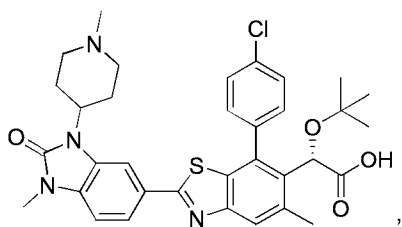
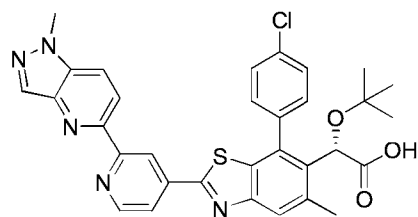
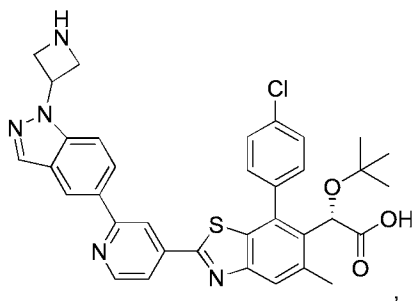
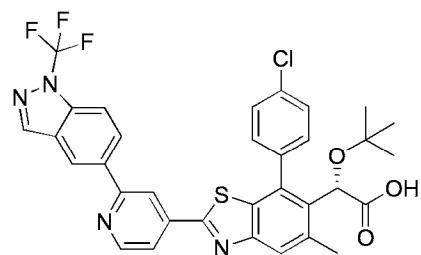
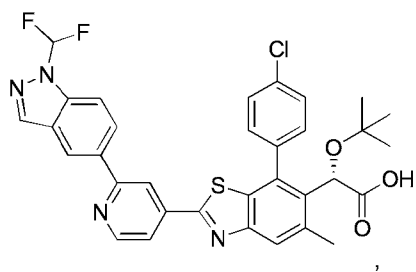


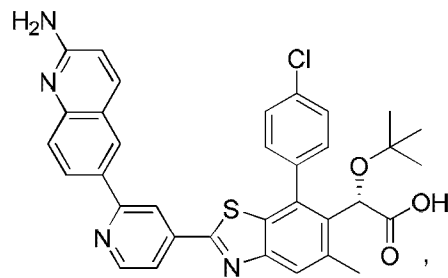
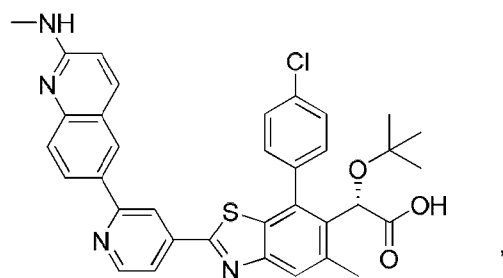
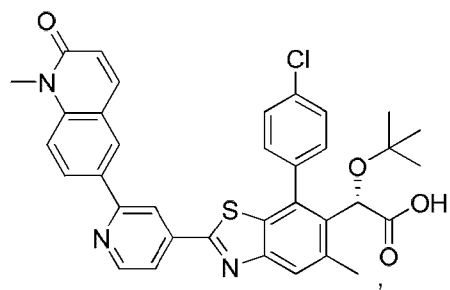
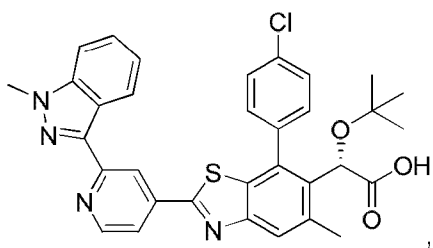
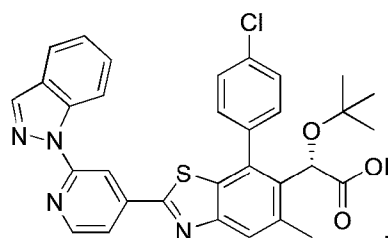
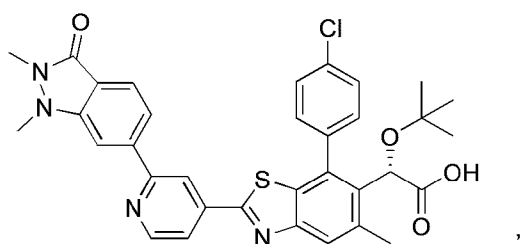
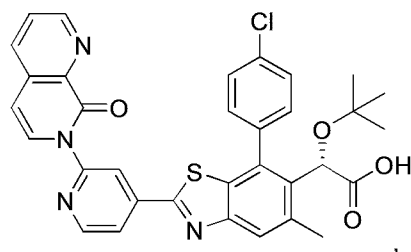
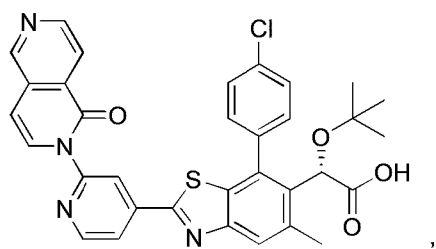
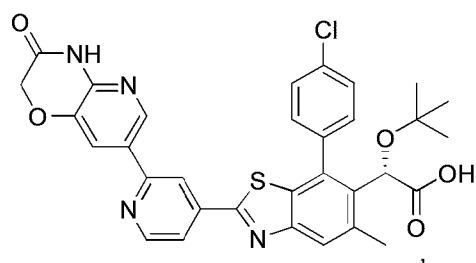
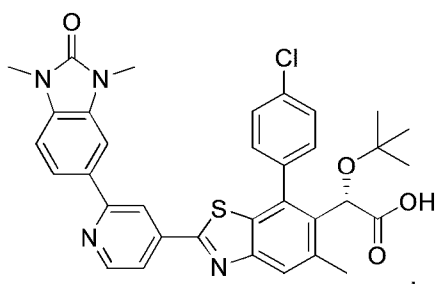
19. The compound of any one of claims 1-6, or salt thereof, wherein A-B is selected from:

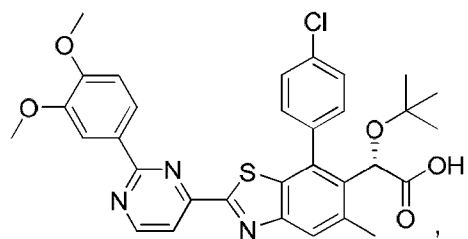
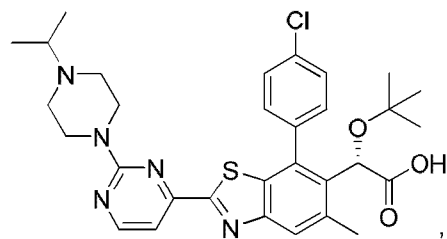
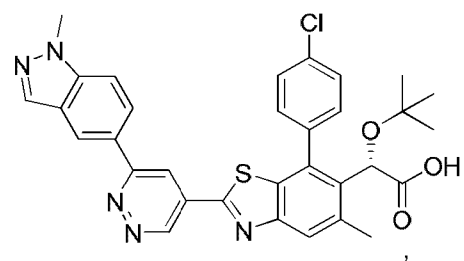
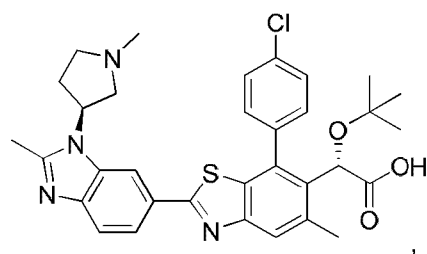
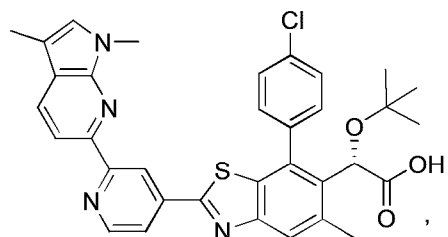
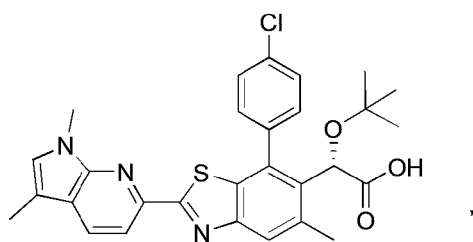
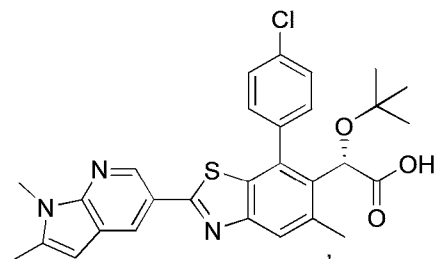
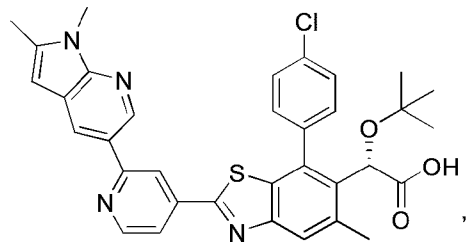
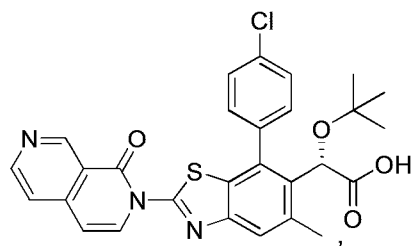
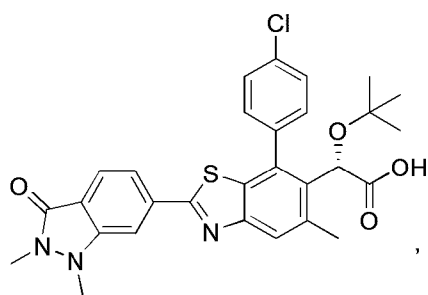


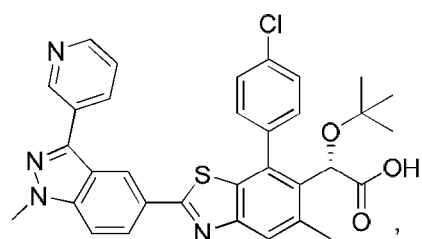
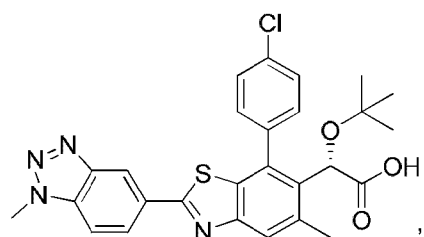
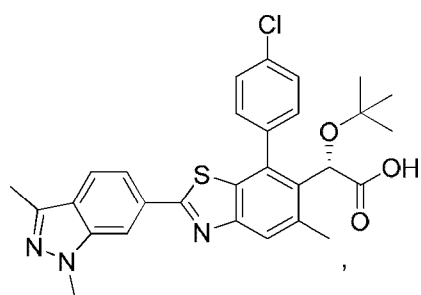
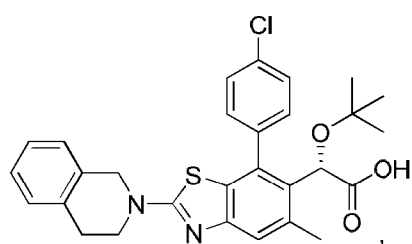
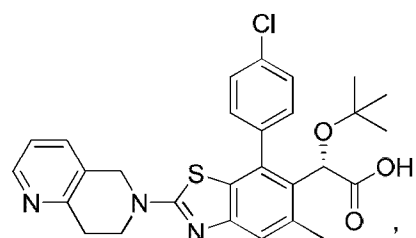
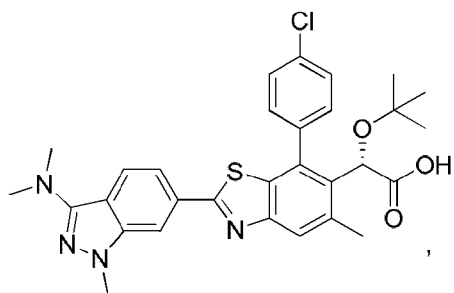
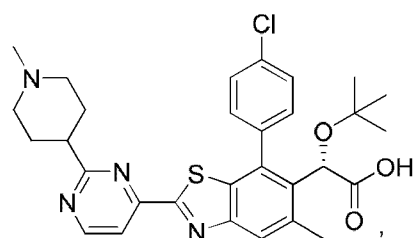
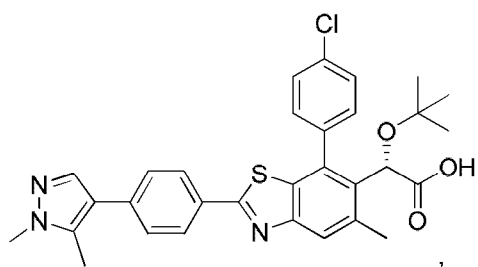
20. The compound of claim 1 which is selected from:

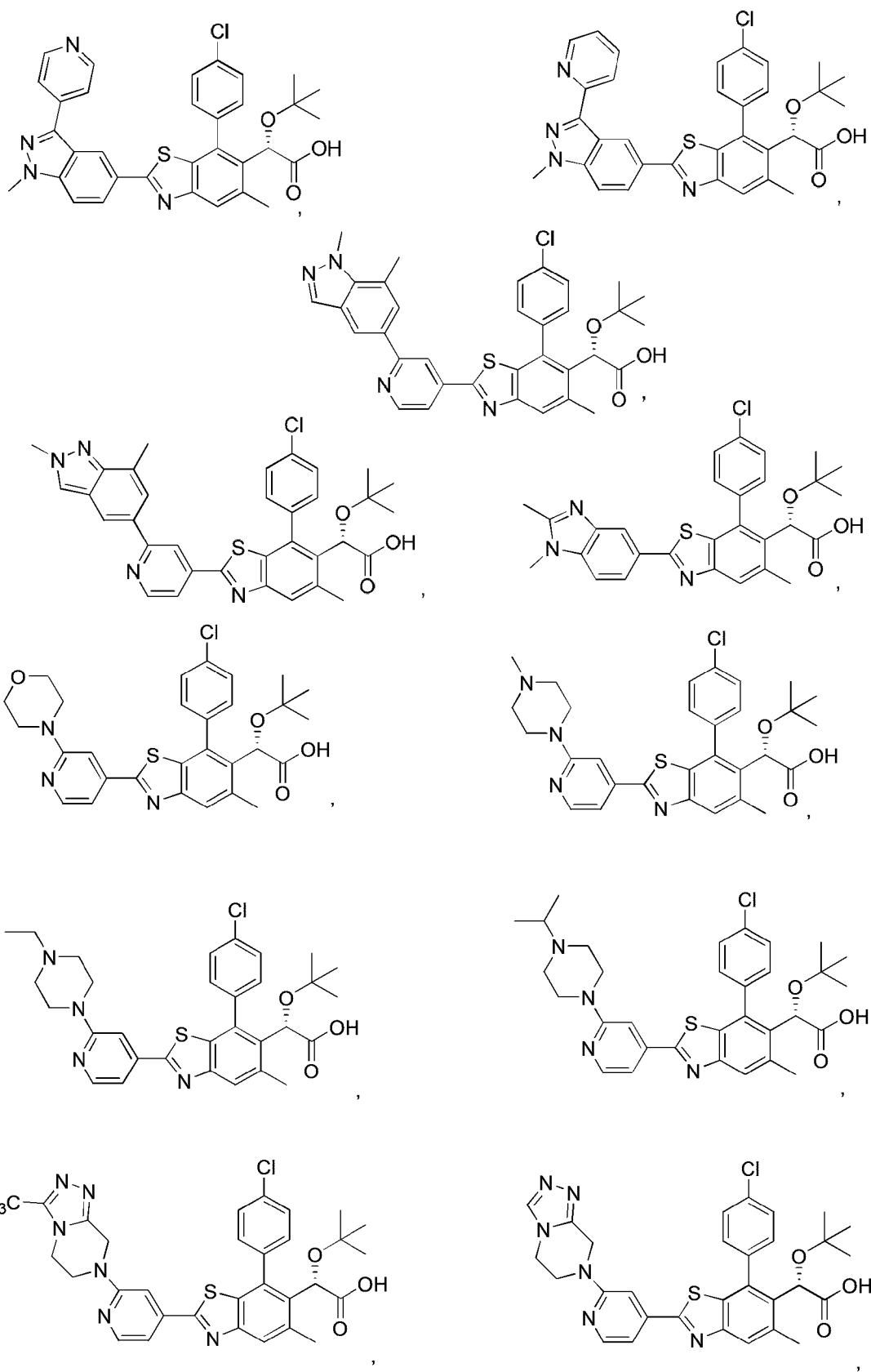


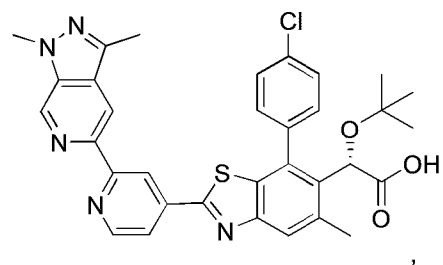
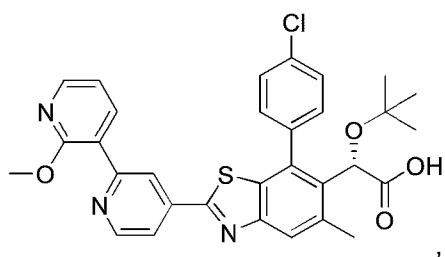
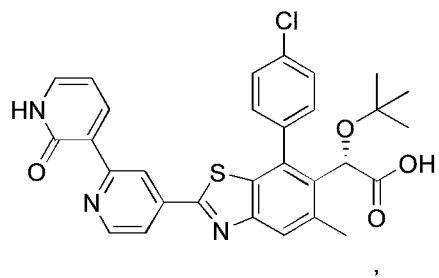
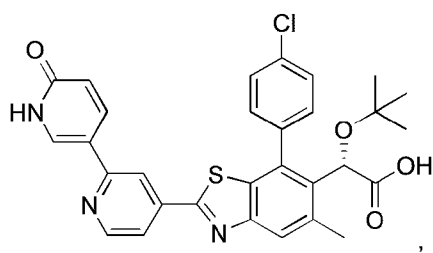
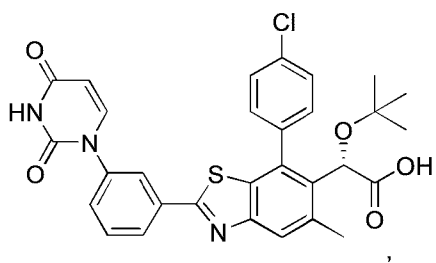
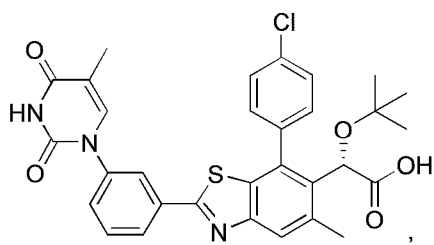
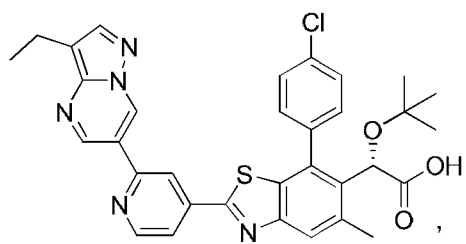
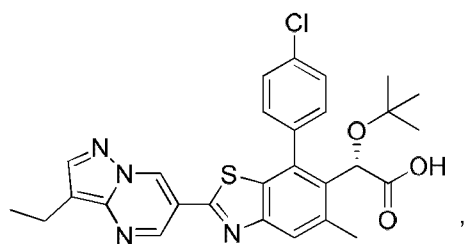
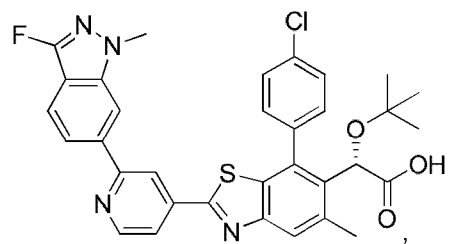
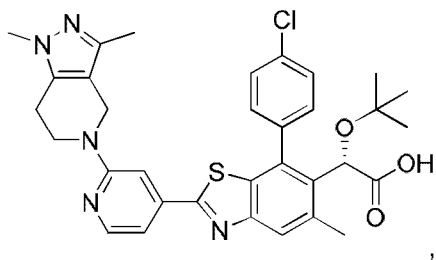


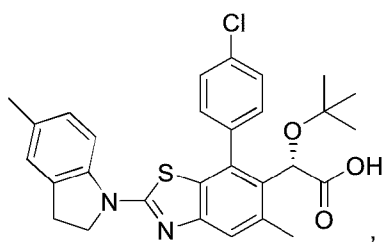
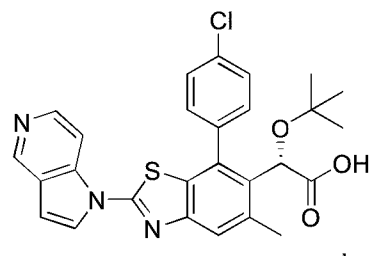
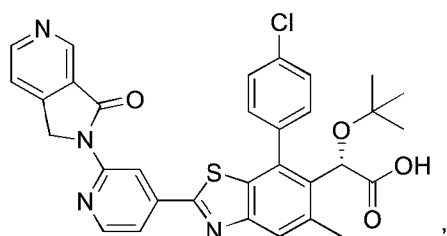
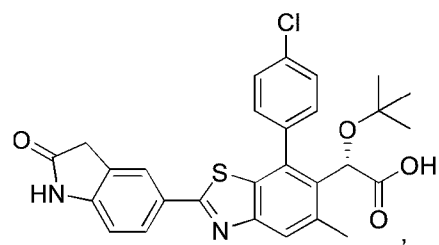
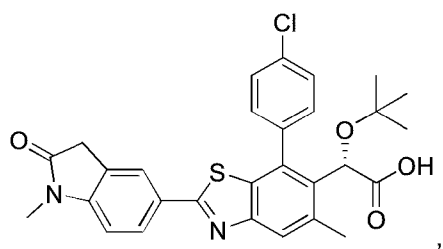
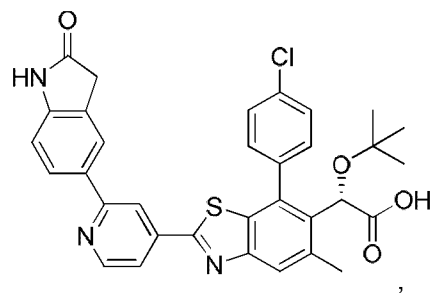
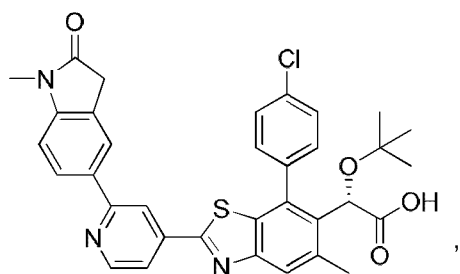
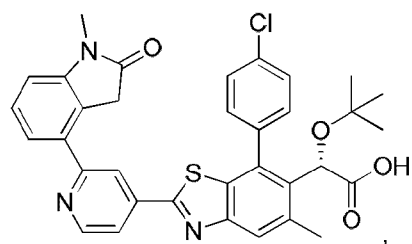
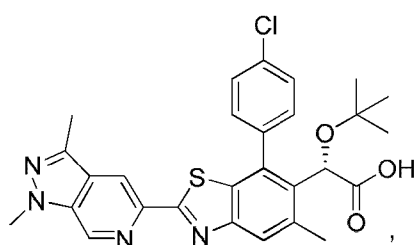


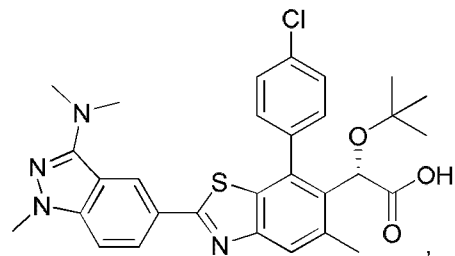
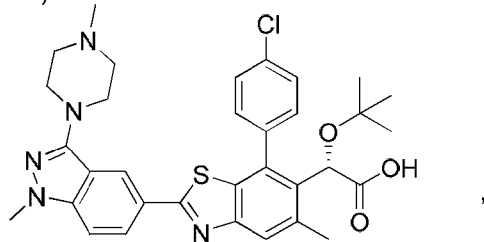
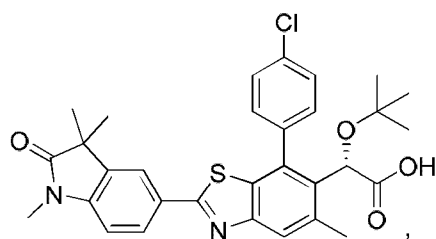
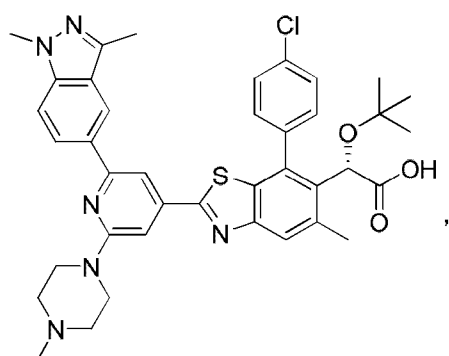
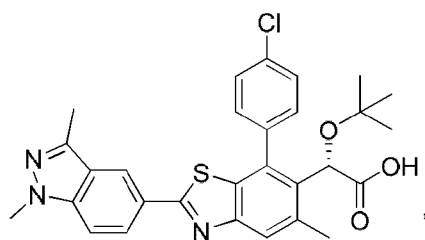
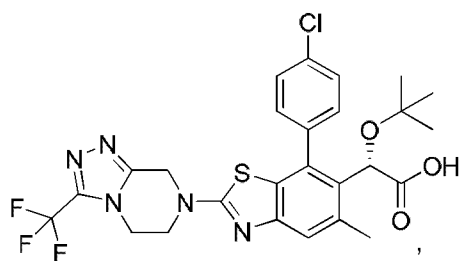
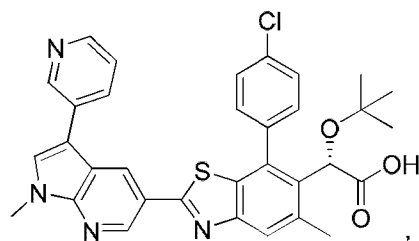
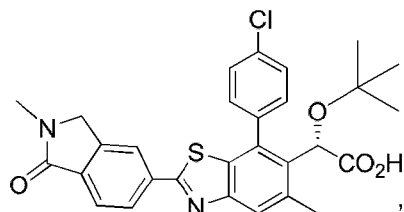
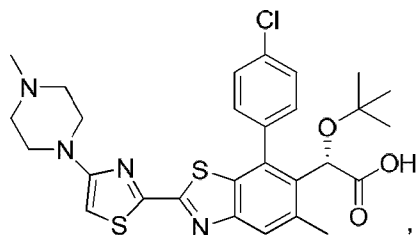
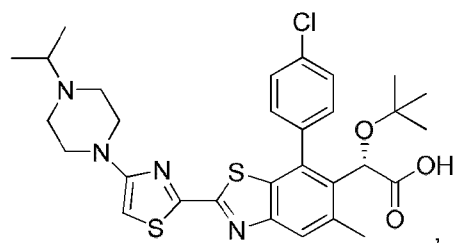
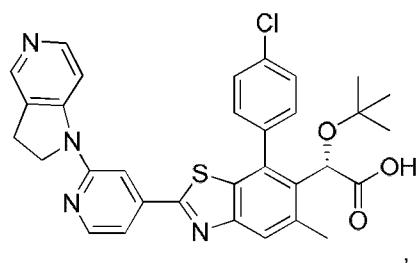


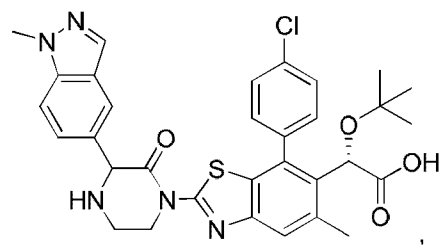
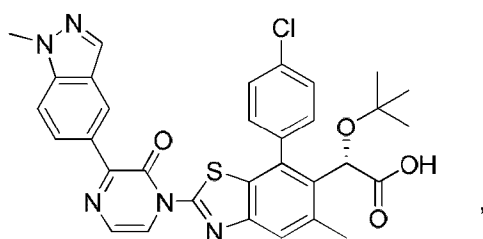
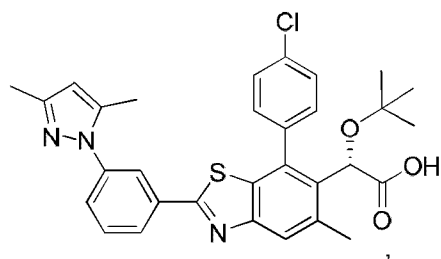
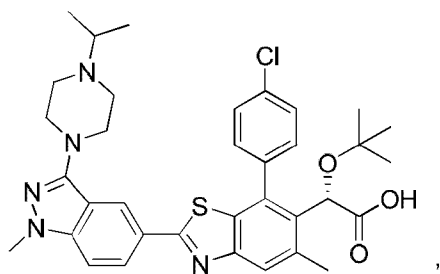
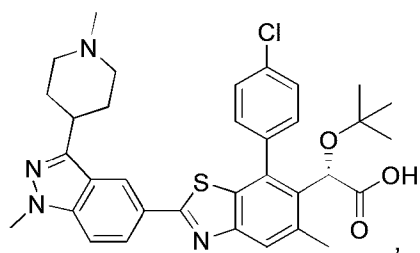
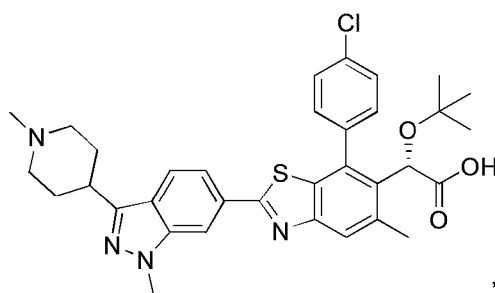
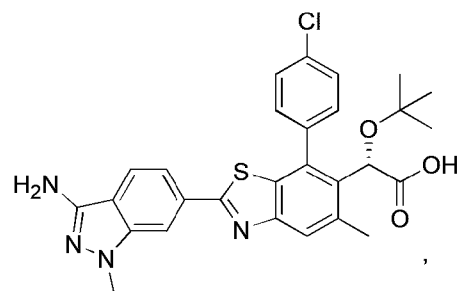
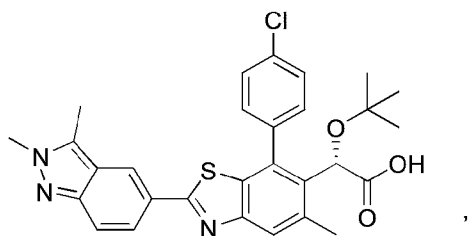
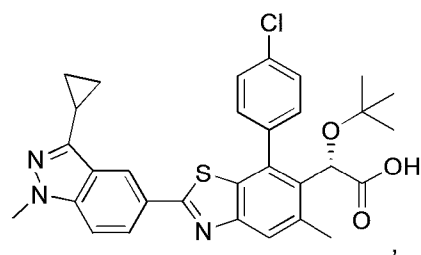
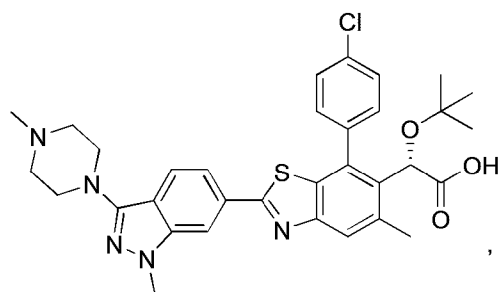


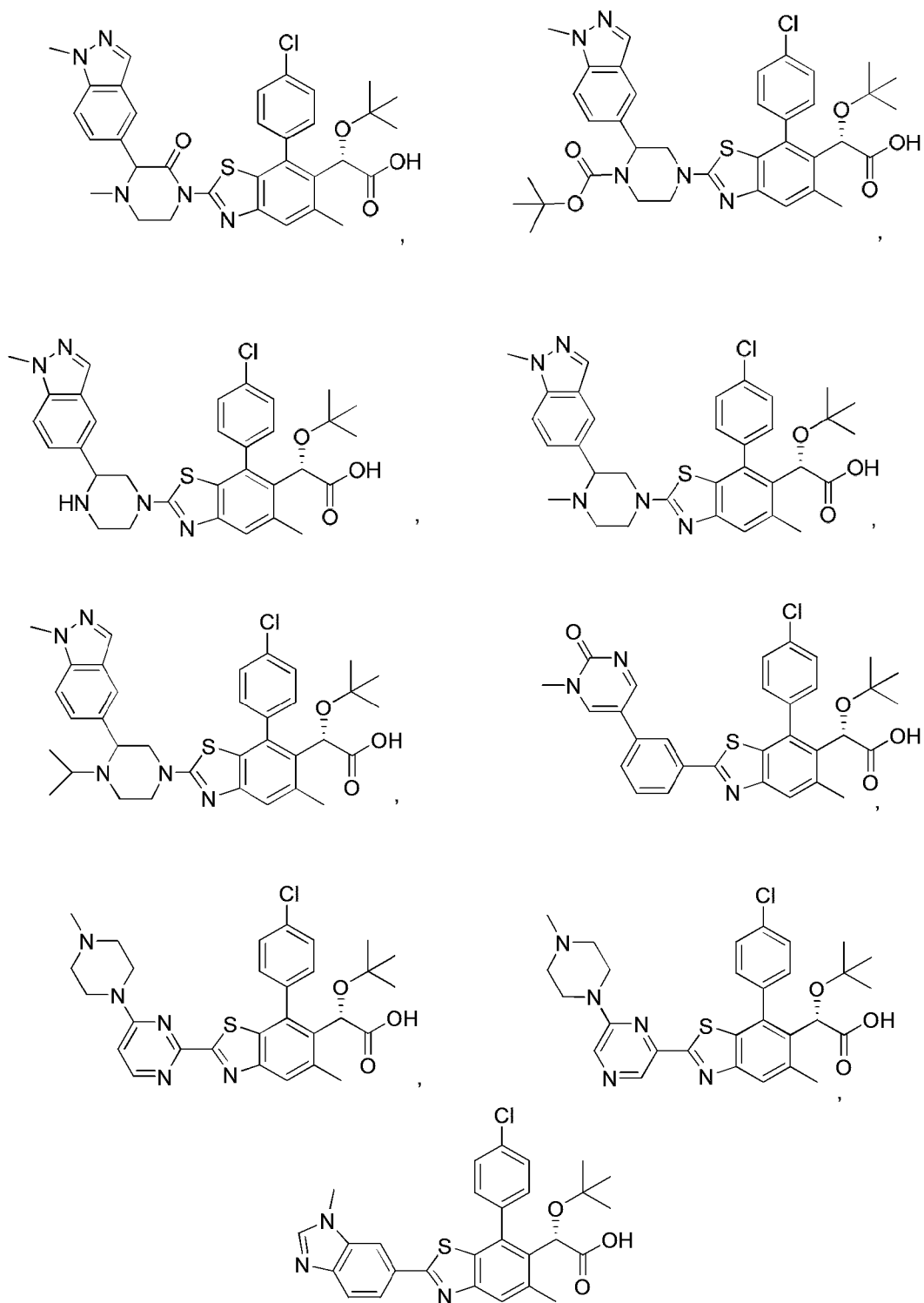


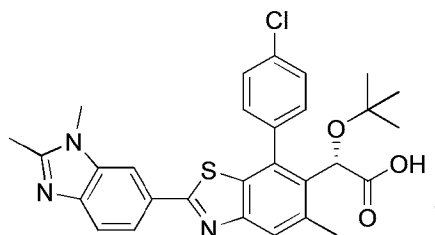
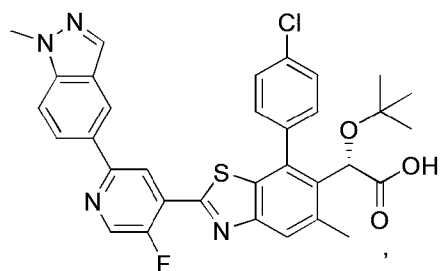
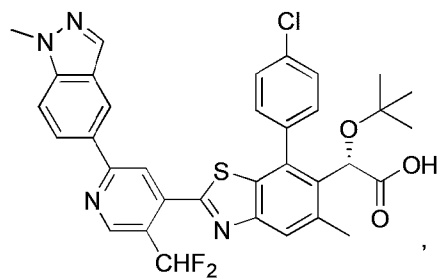
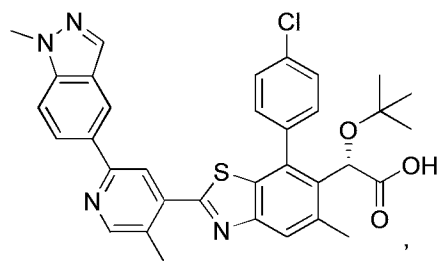
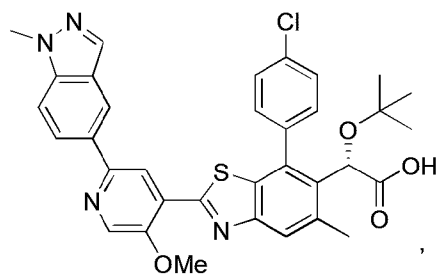
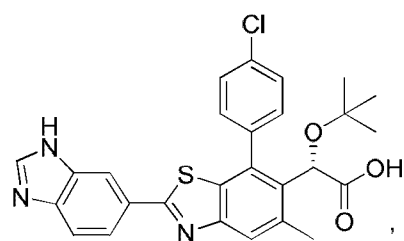
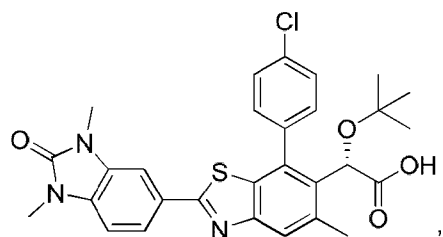
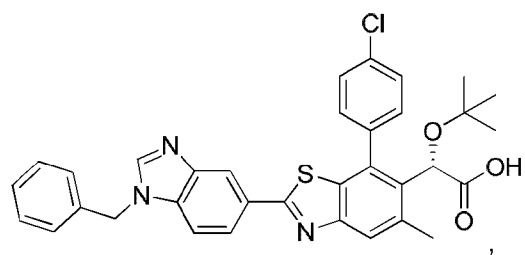
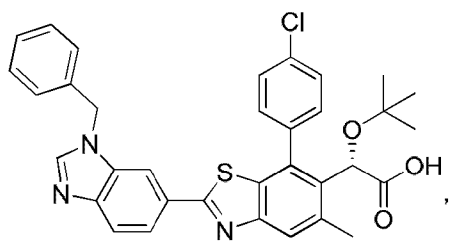


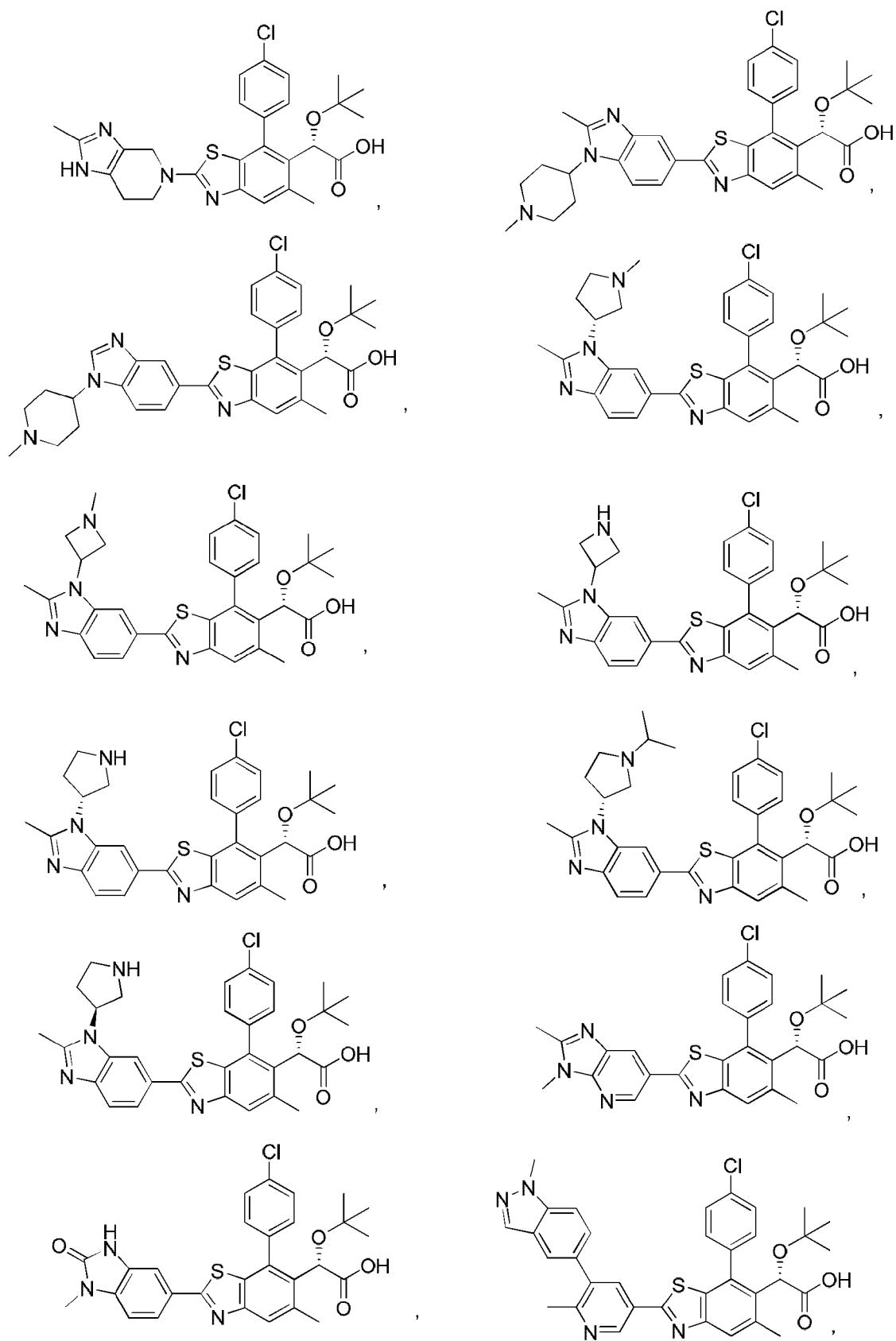


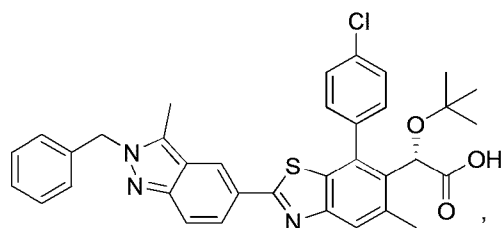
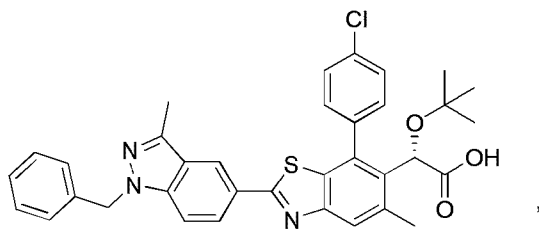
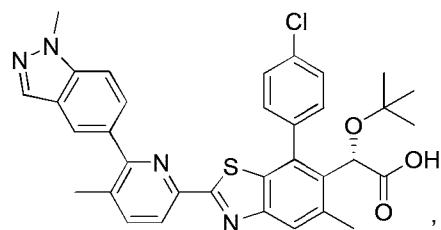
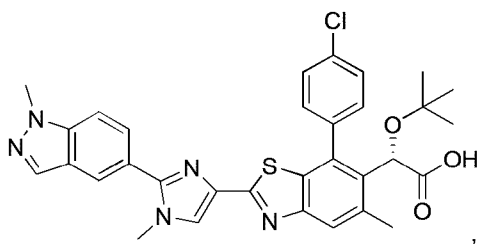
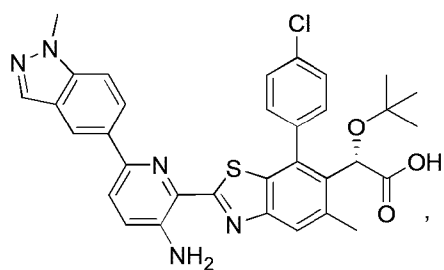
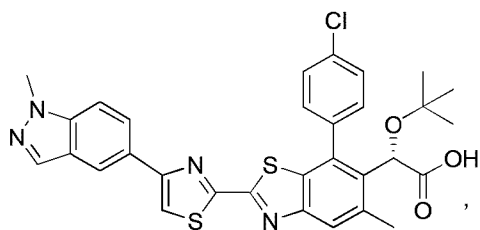
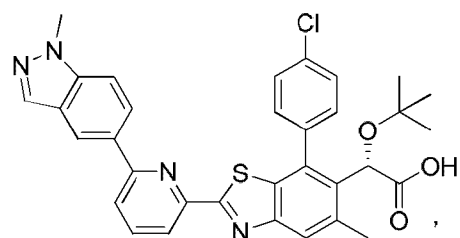
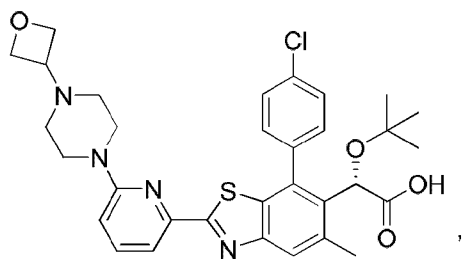
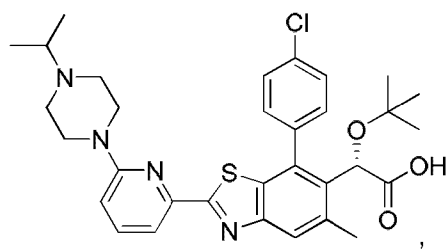
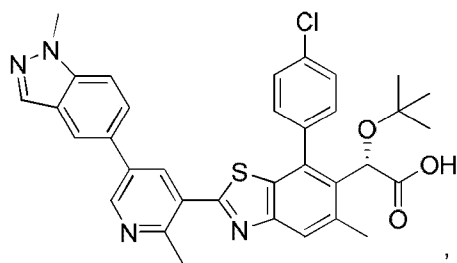


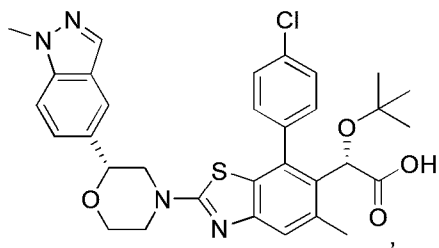
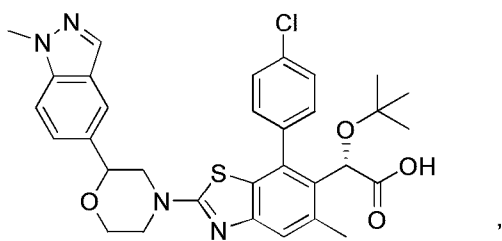
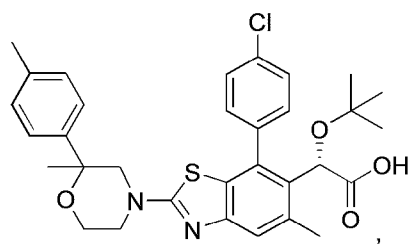
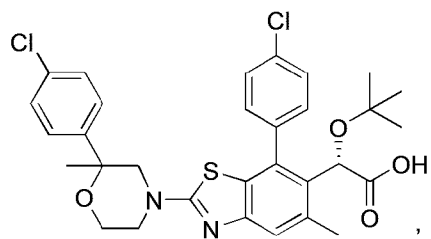
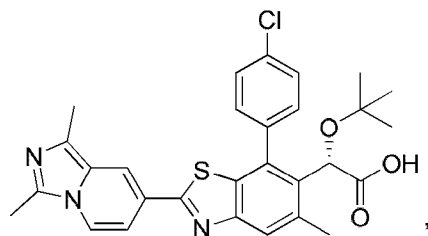
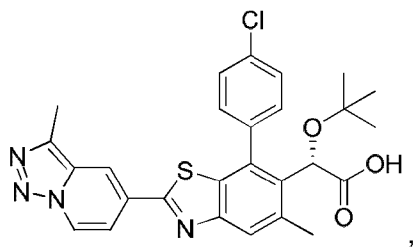
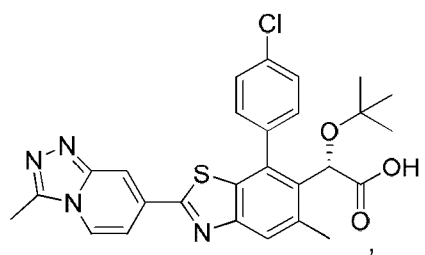
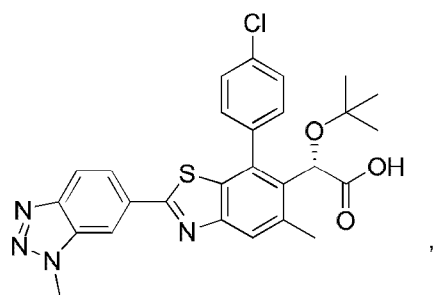


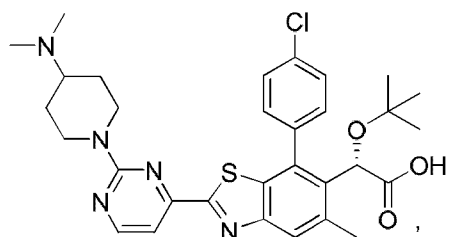
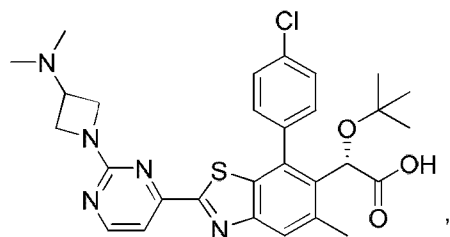
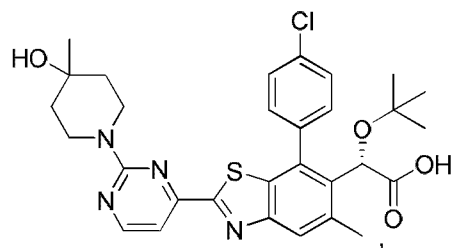
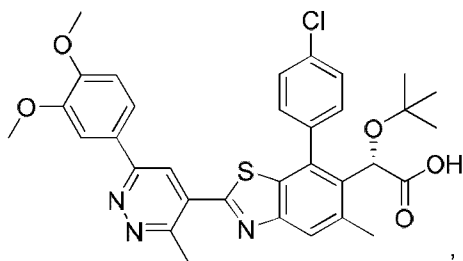
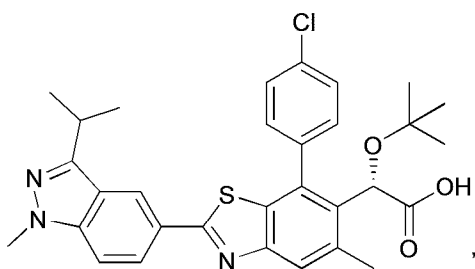
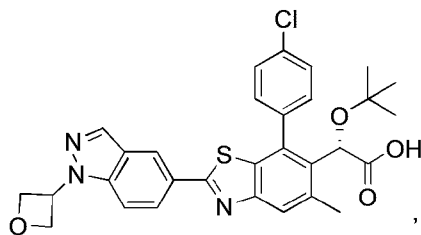
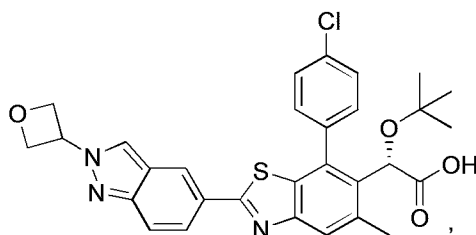
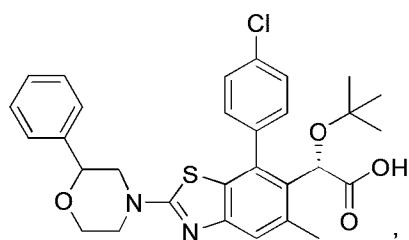
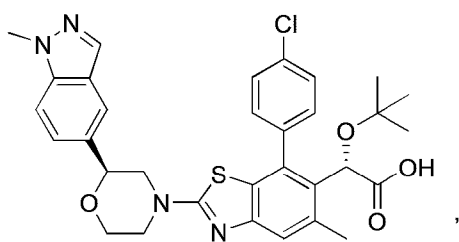


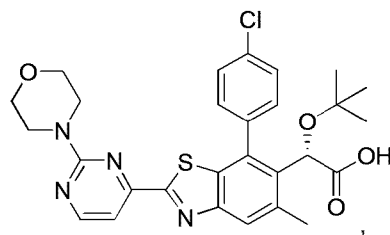
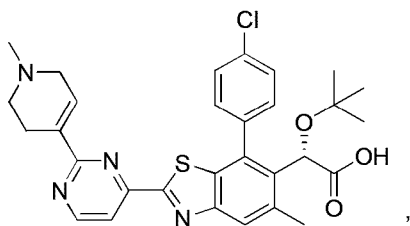
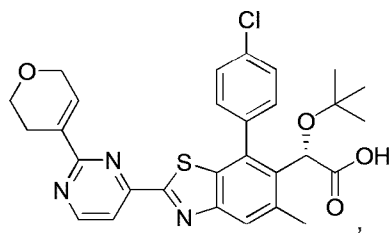
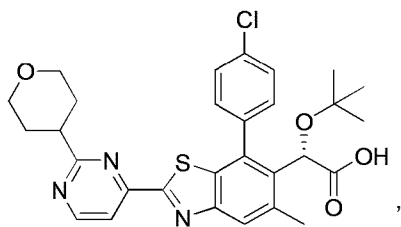
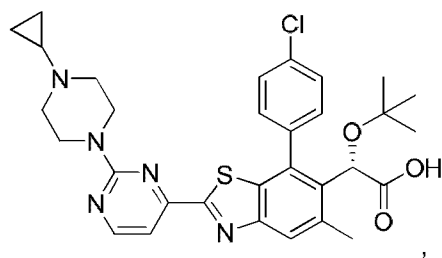
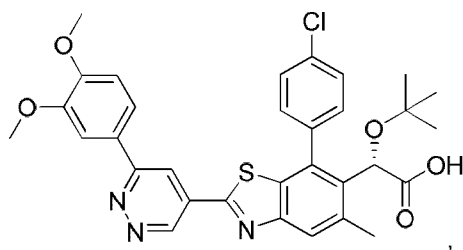
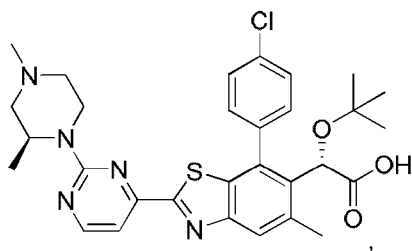
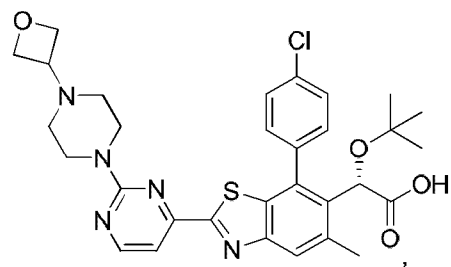
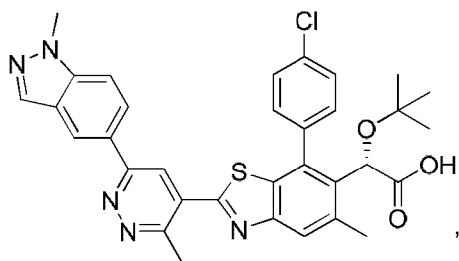


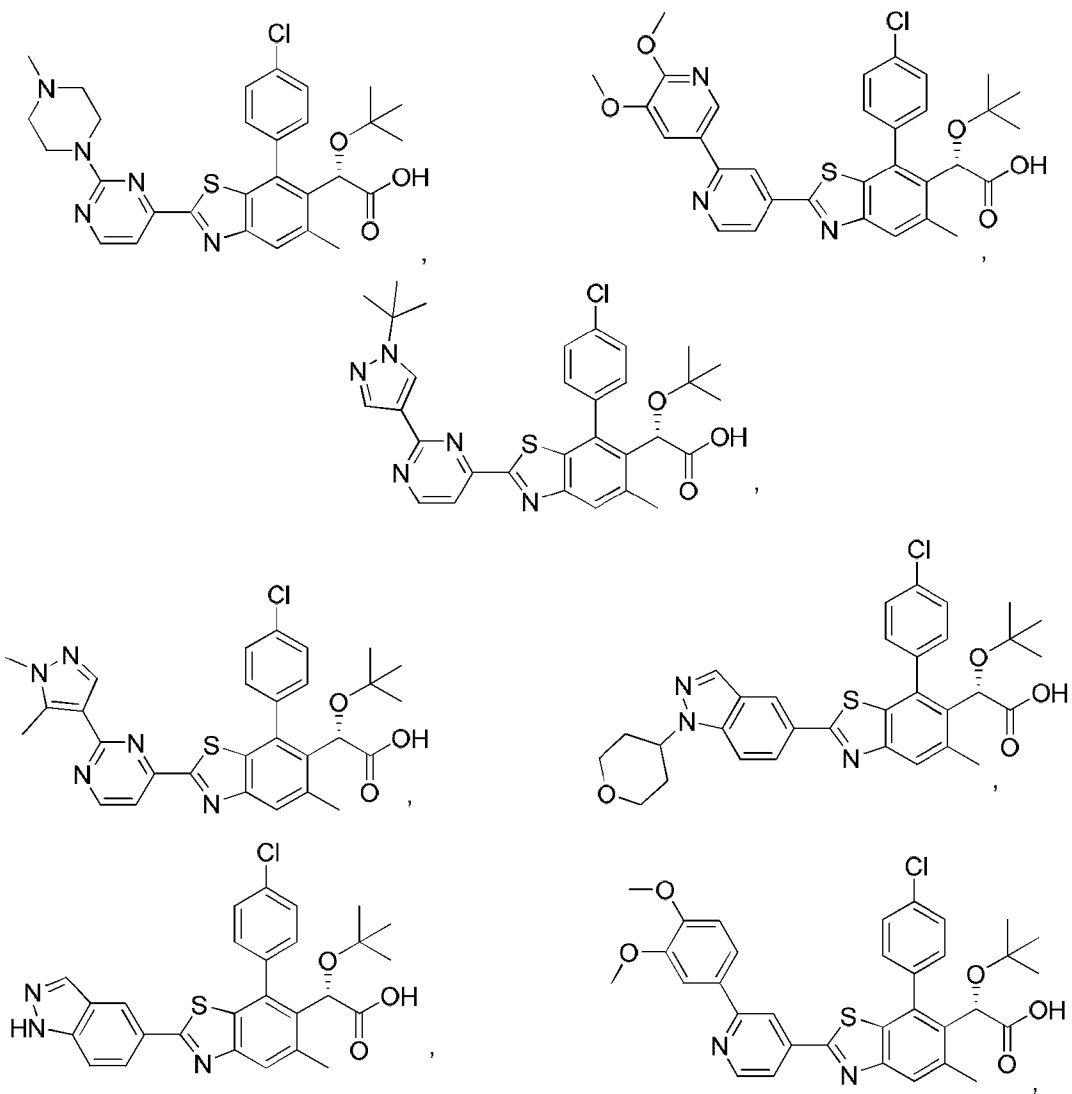


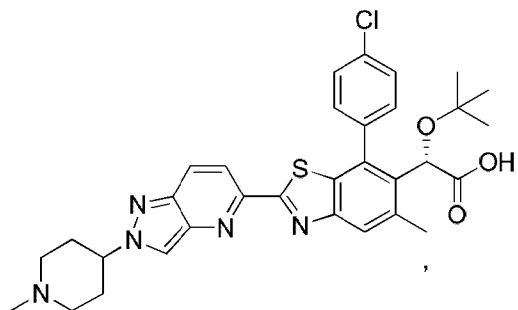
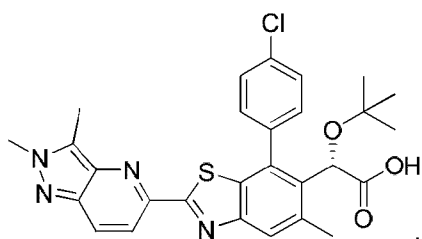
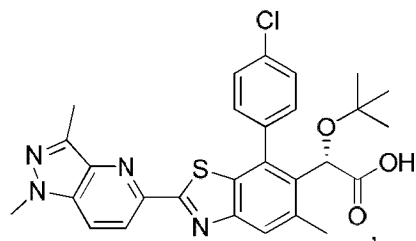
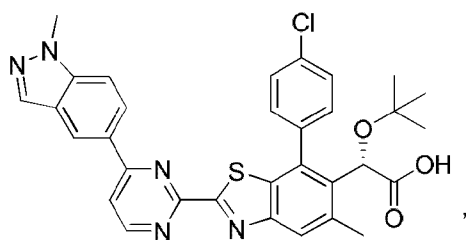
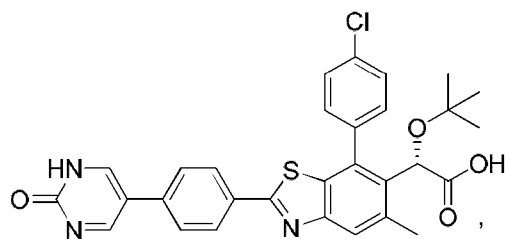
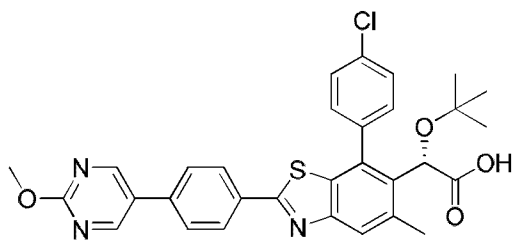
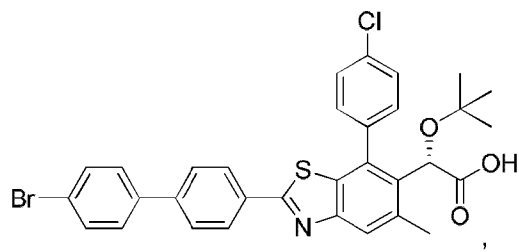
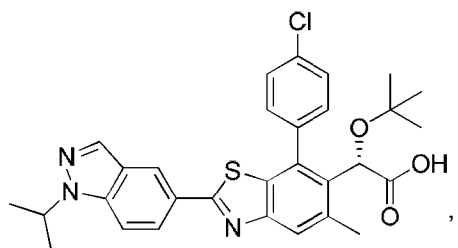
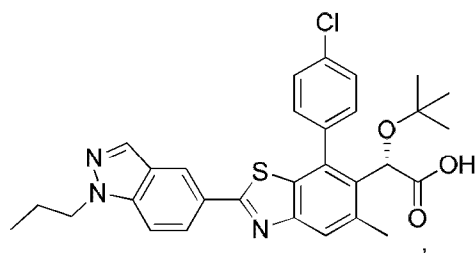
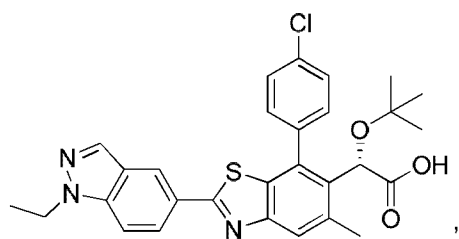


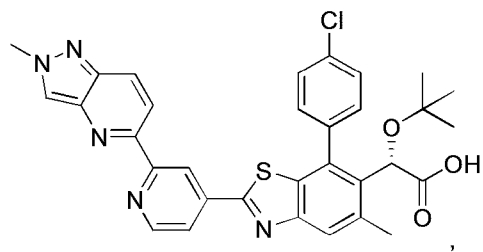
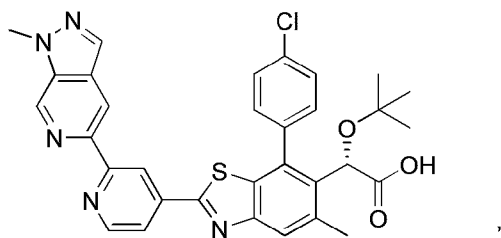
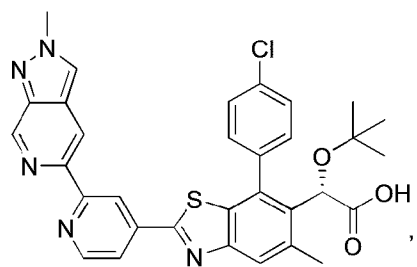
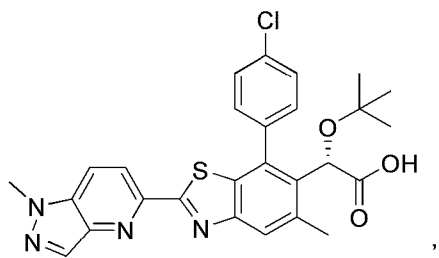
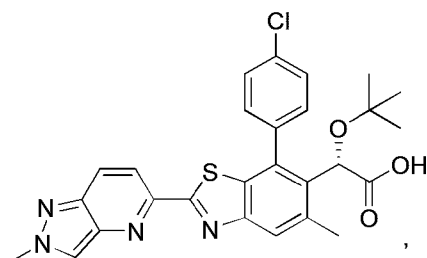
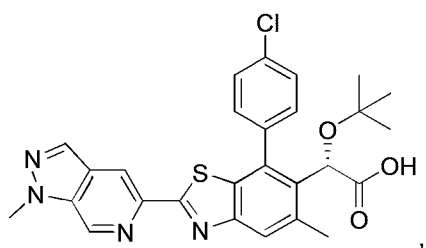
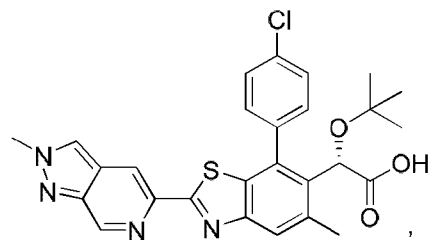
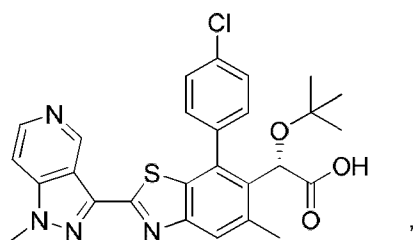
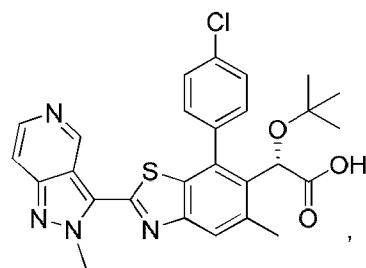
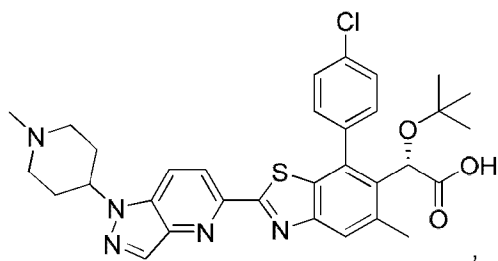


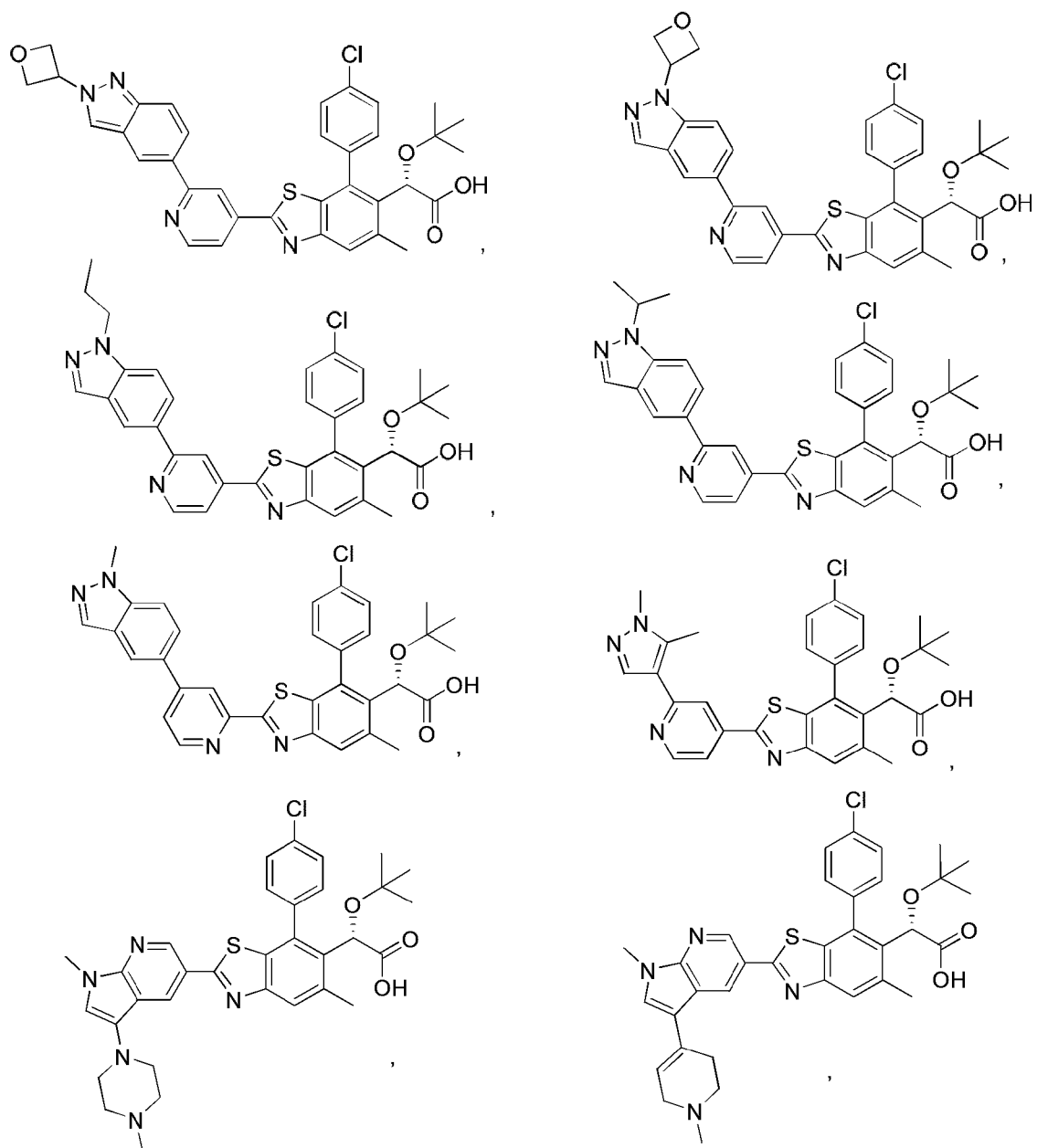


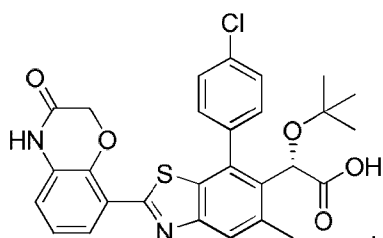
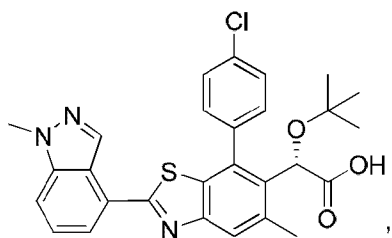
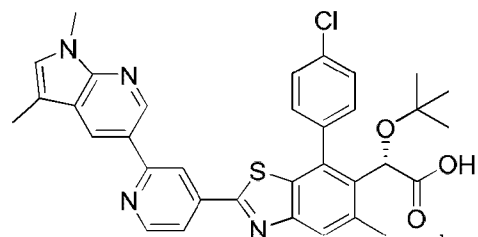
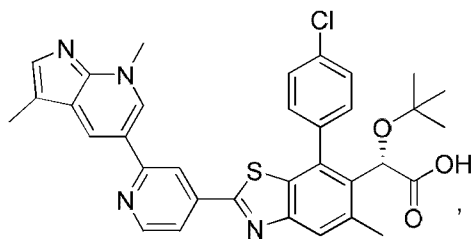
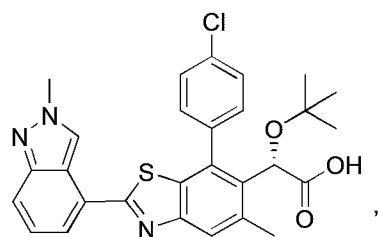
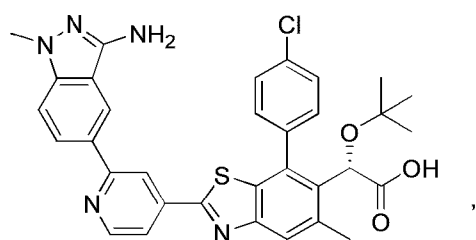
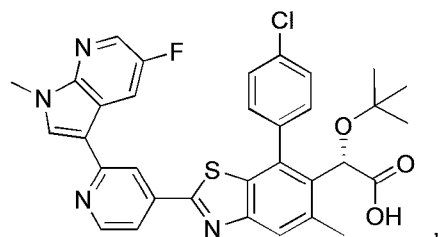
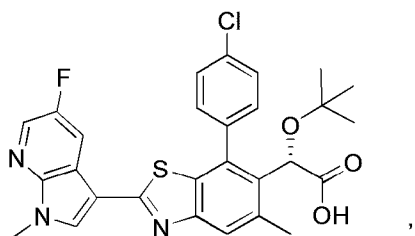
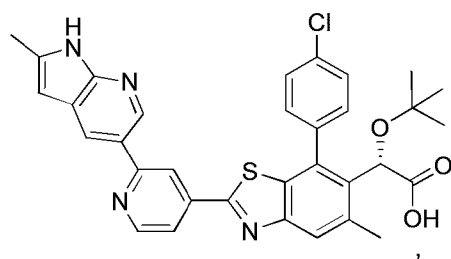
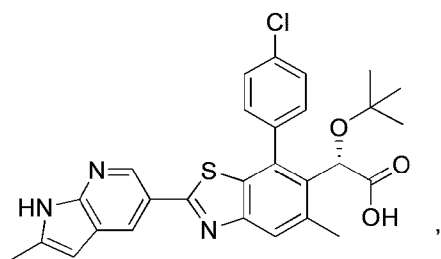


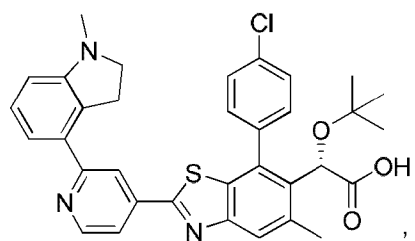
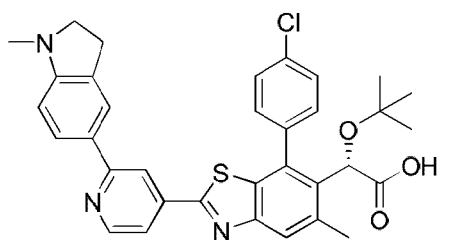
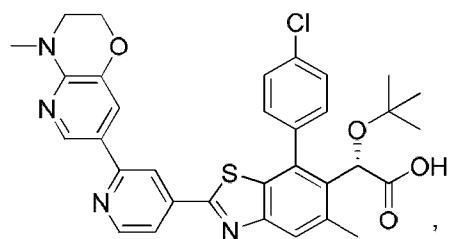
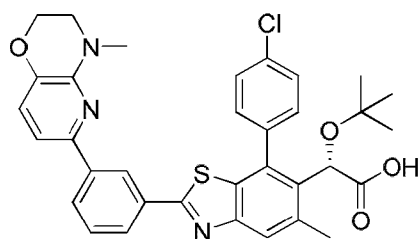
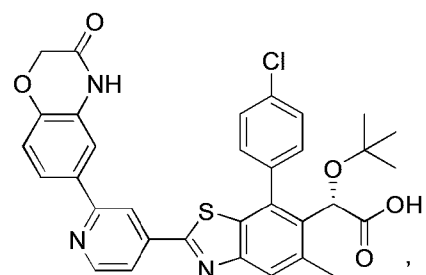
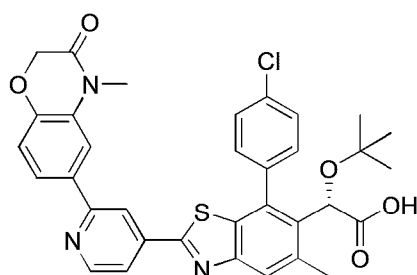
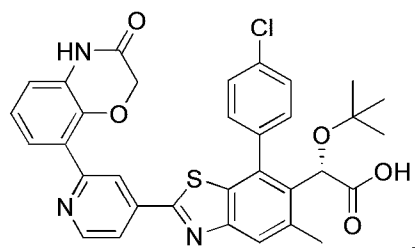
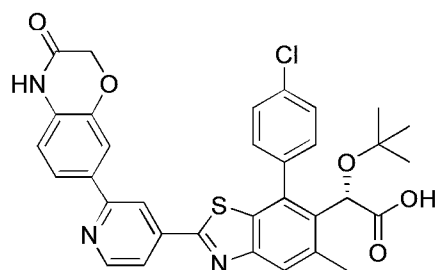
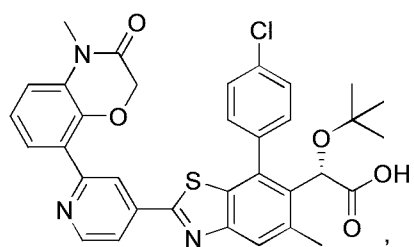
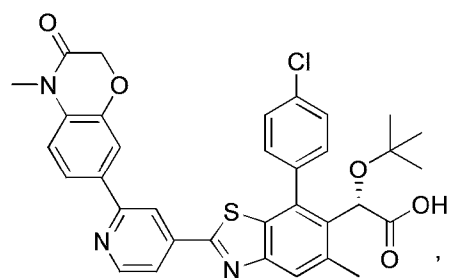


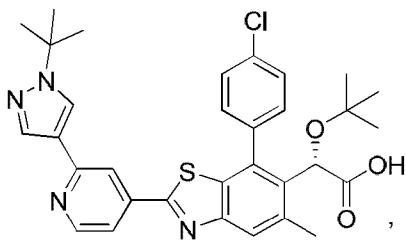
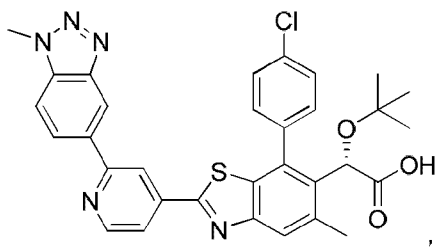
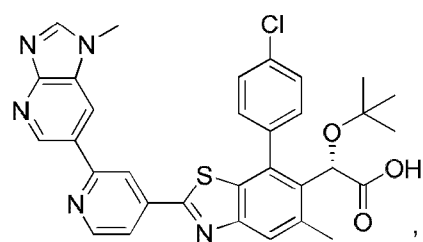
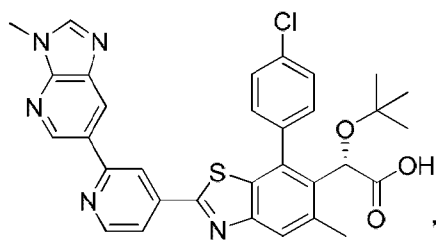
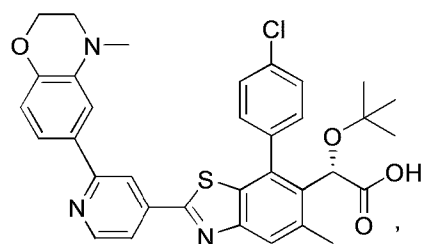
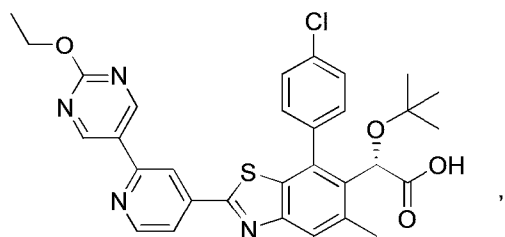
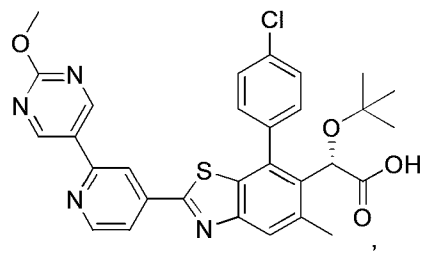
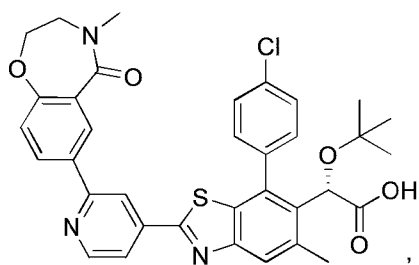
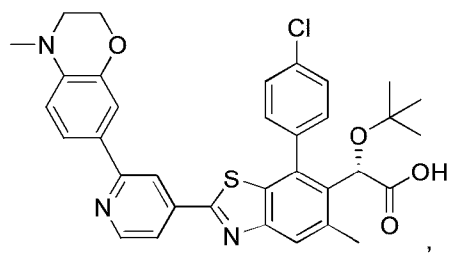
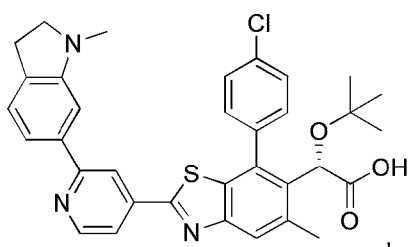


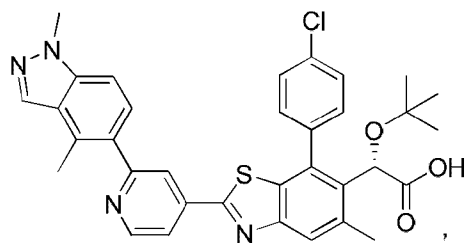
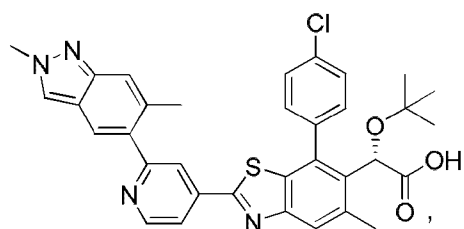
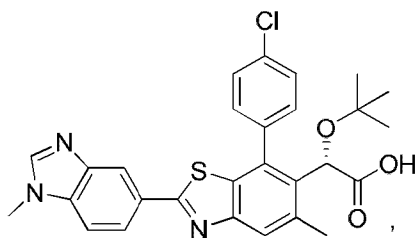
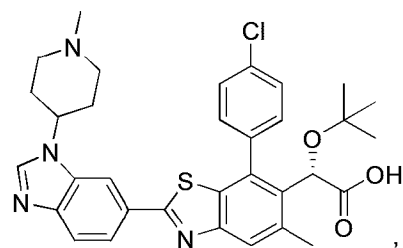
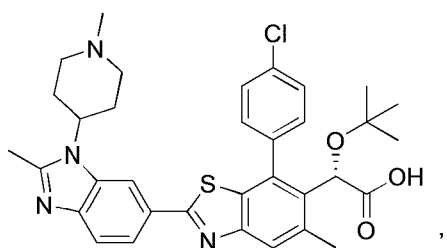
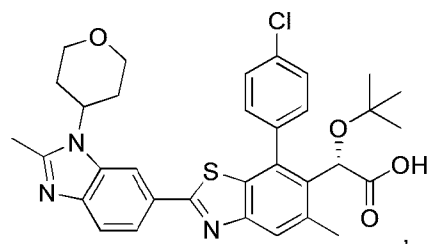
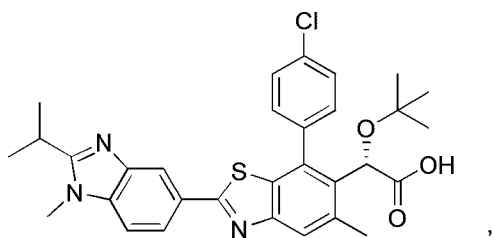
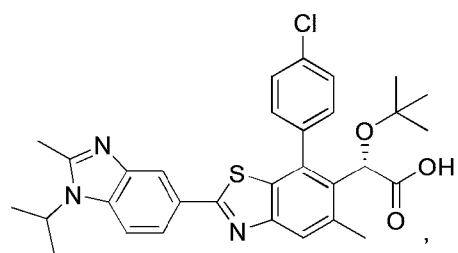
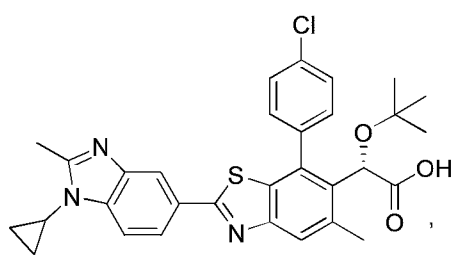


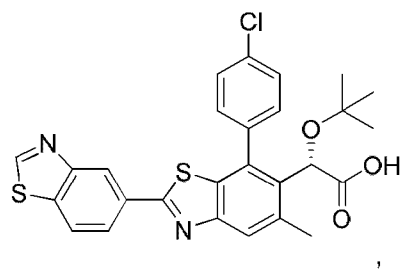
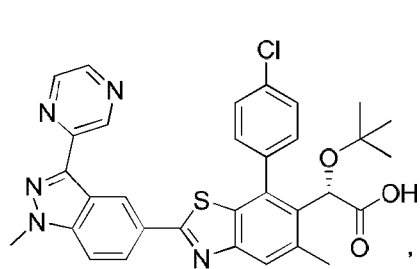
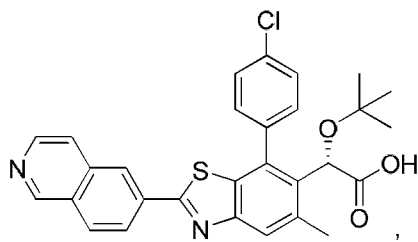
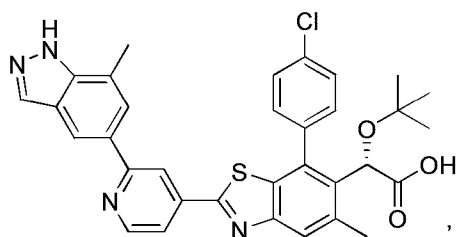
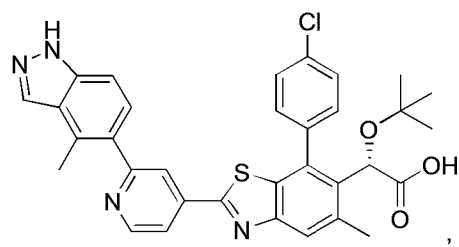
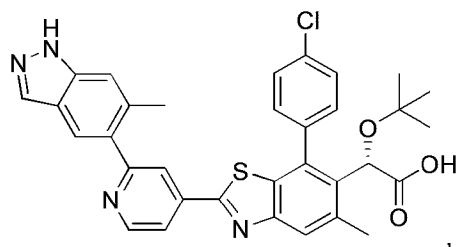
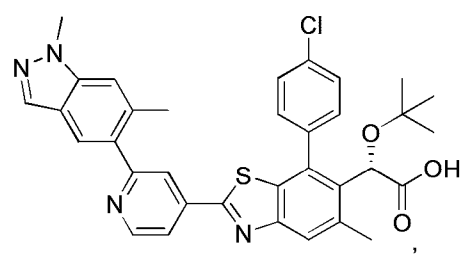
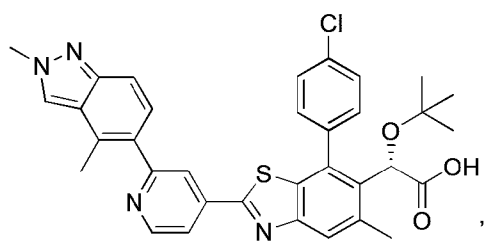


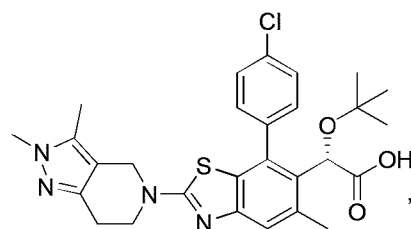
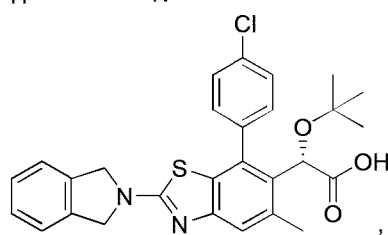
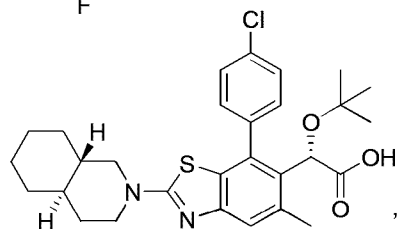
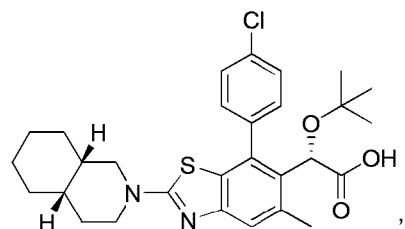
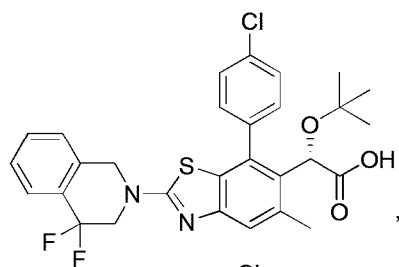
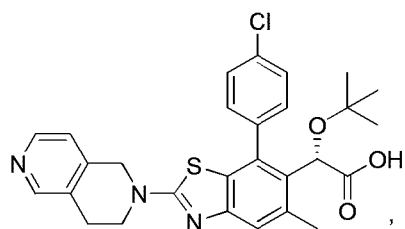
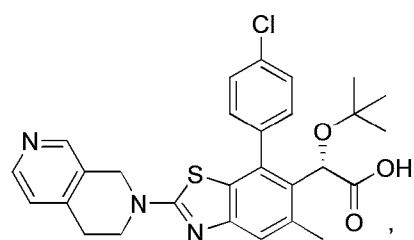
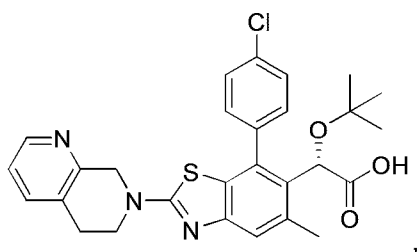
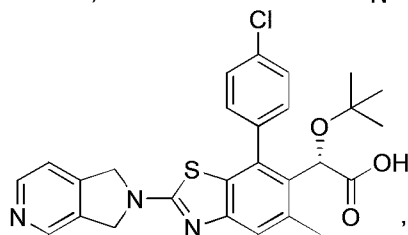
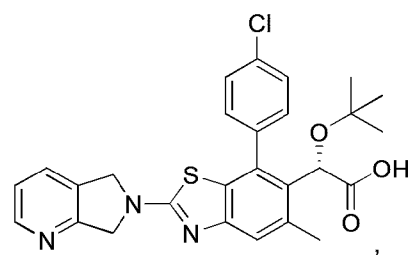
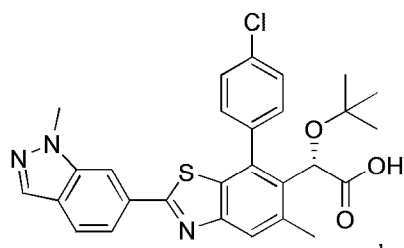


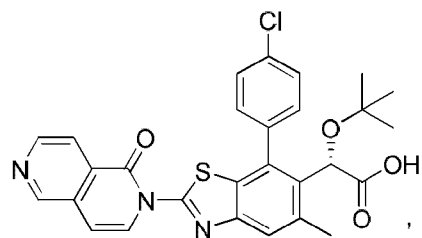
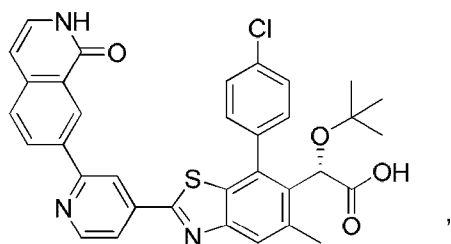
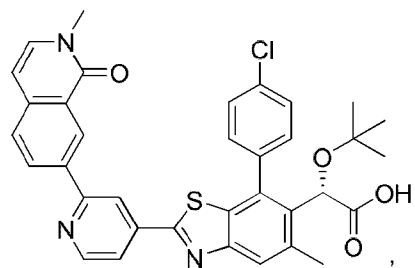
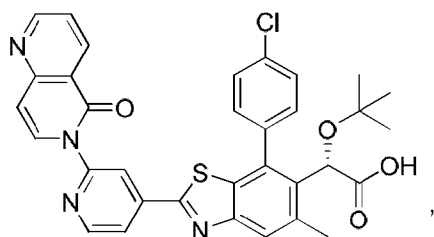
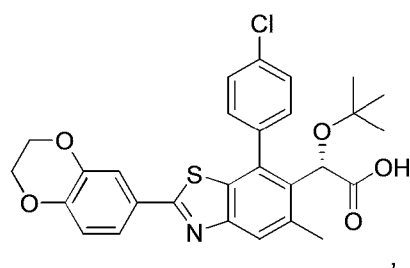
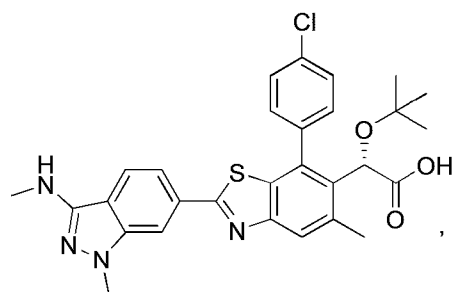
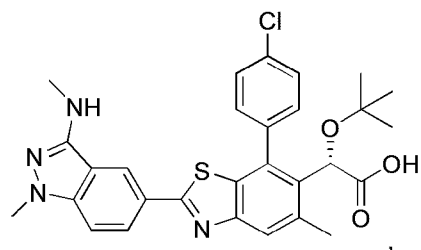
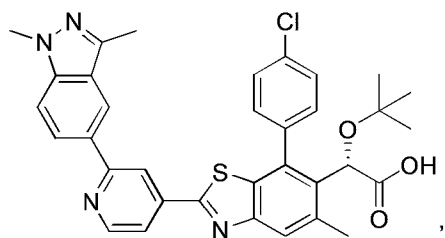
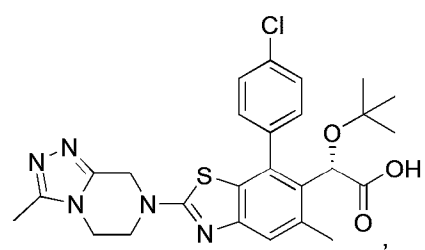
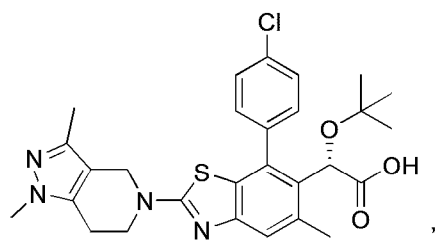


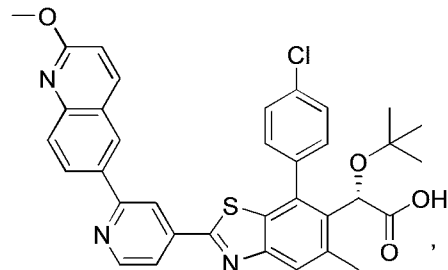
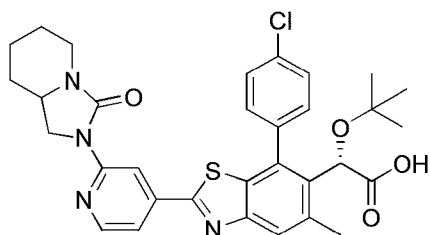
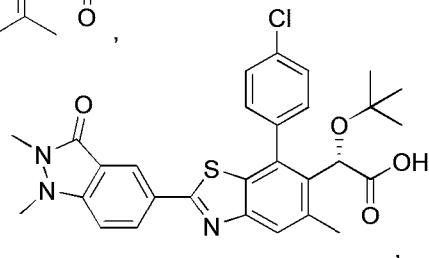
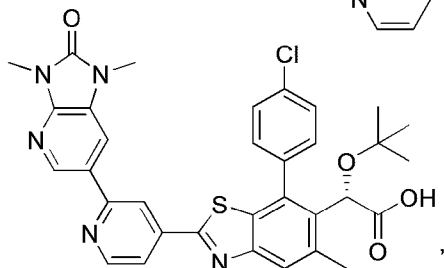
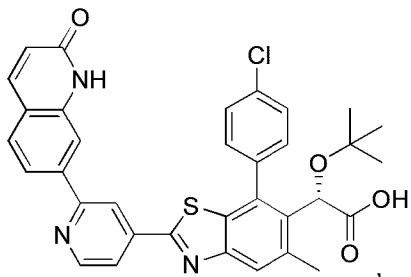
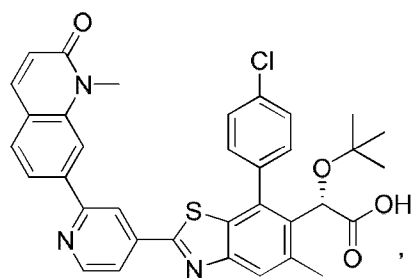
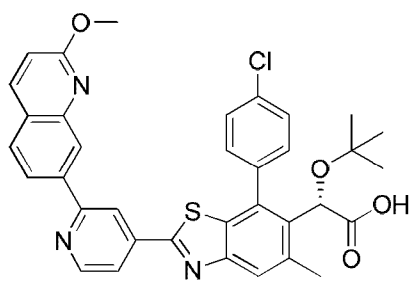


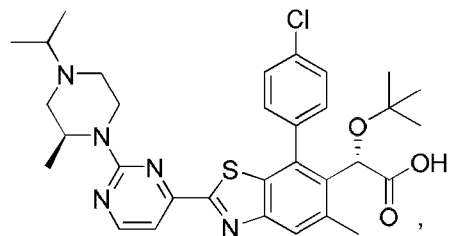
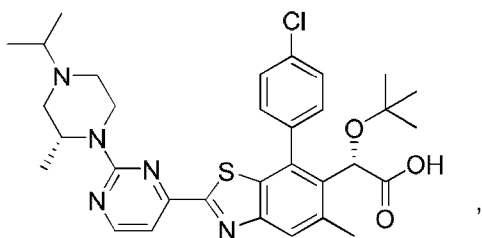
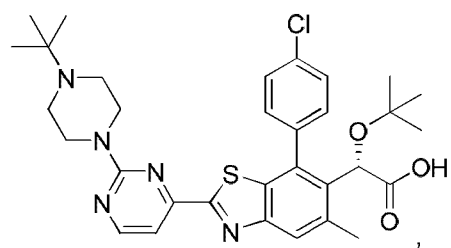
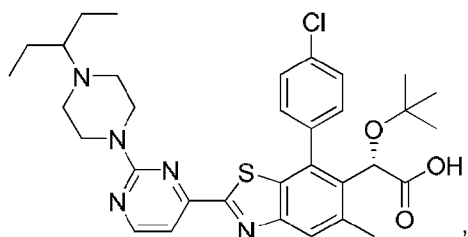
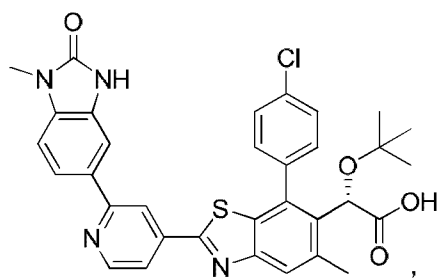
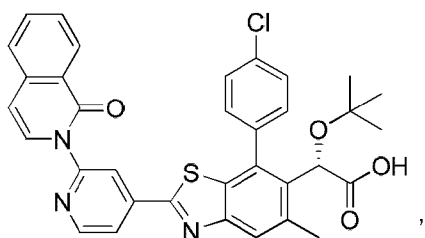
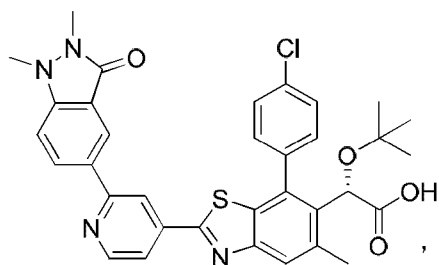
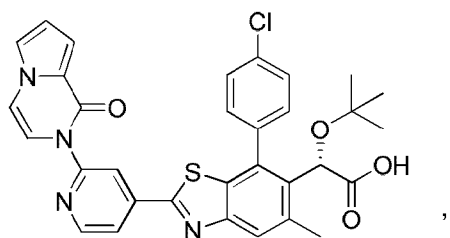
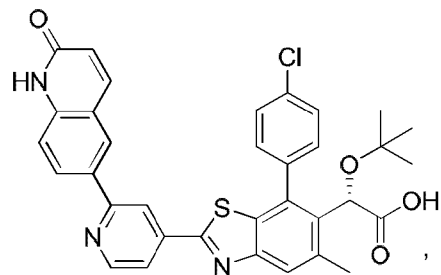
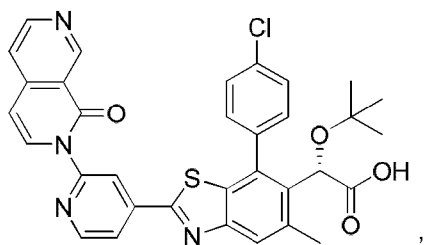


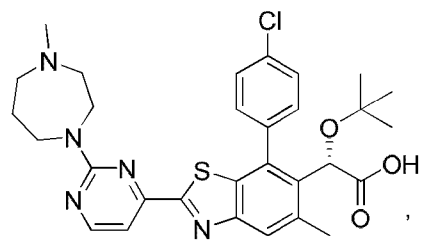
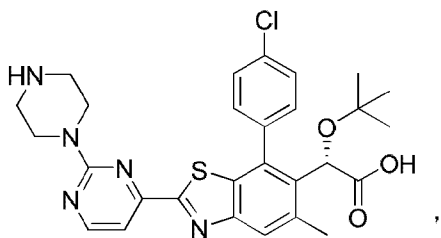
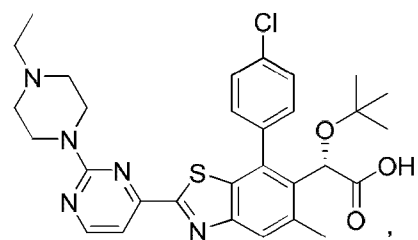
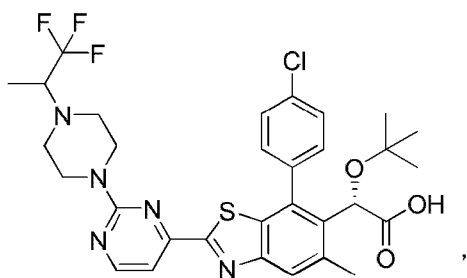
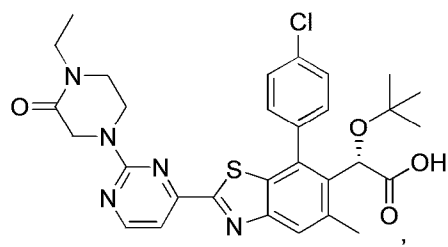
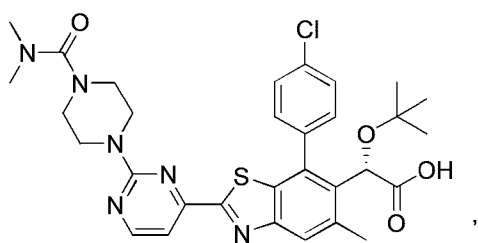
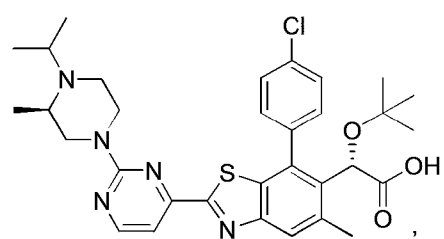
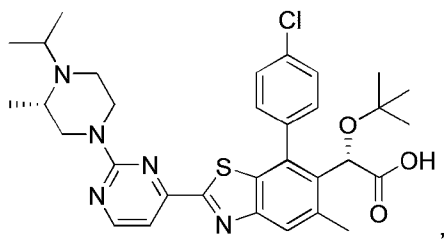
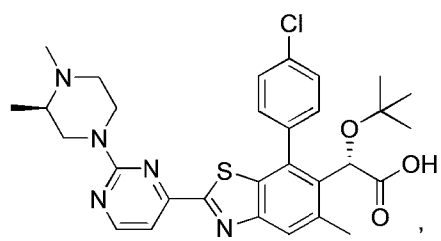
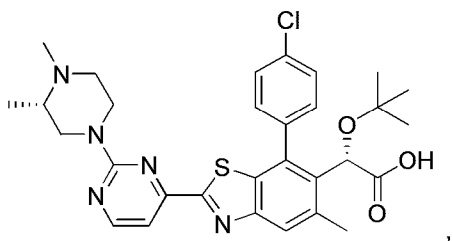


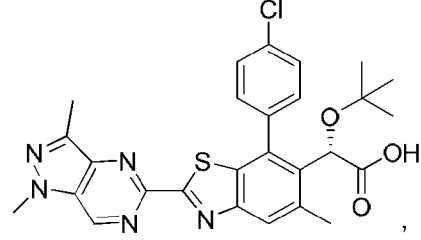
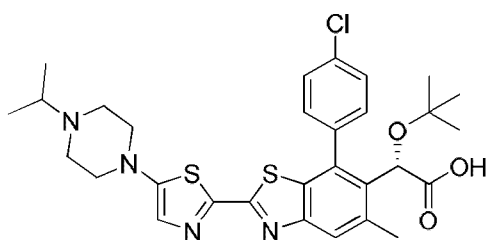
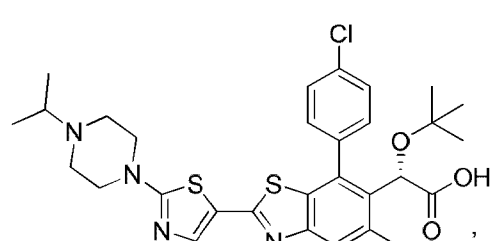
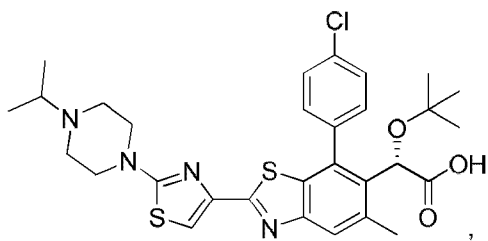
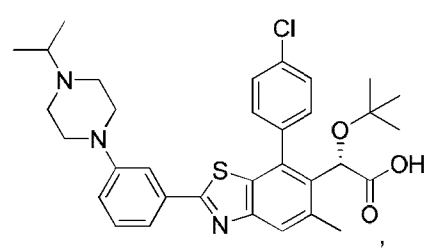
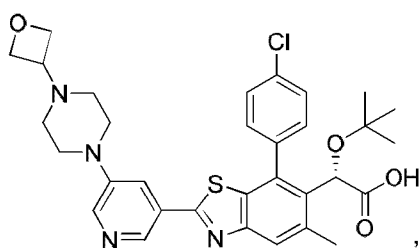
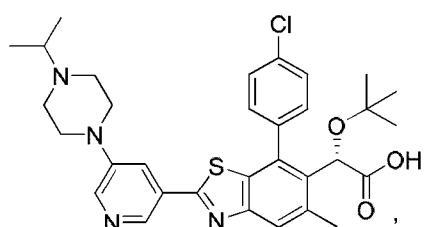
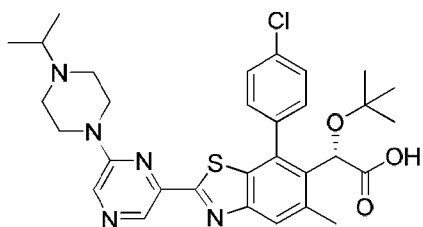
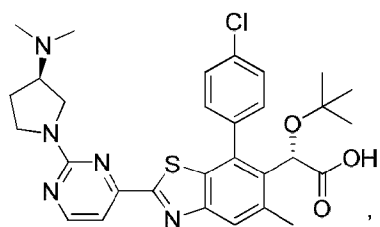
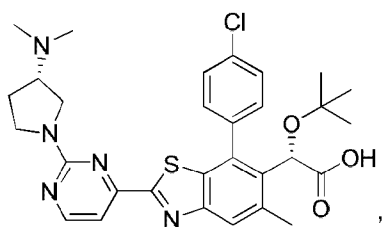


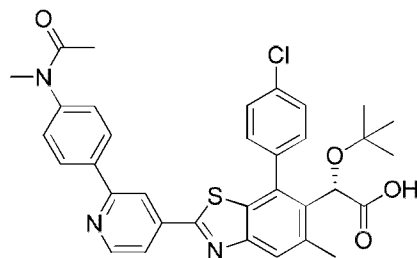
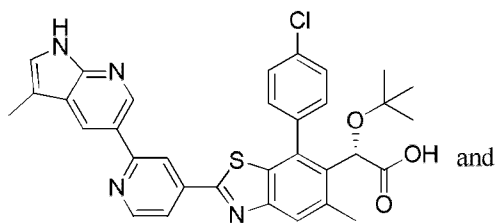
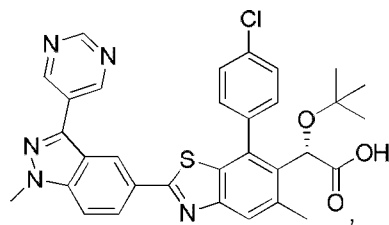
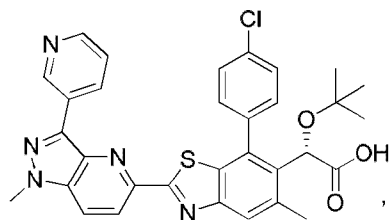
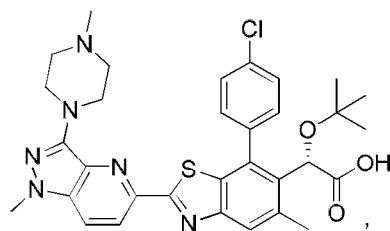
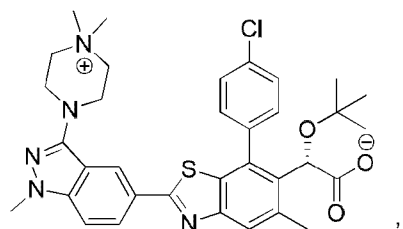
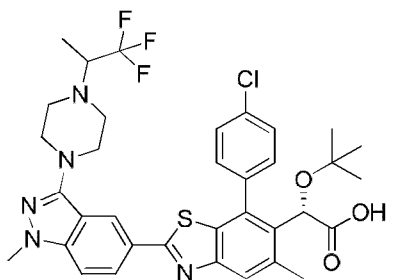
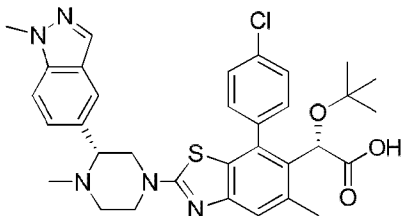
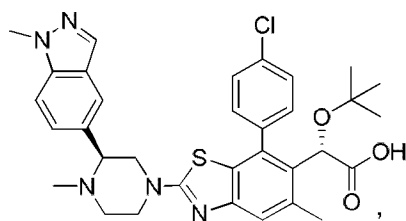
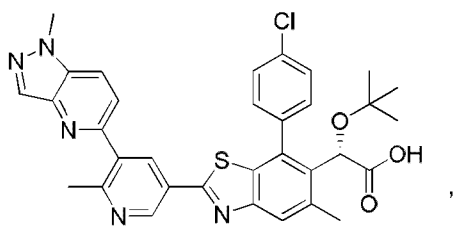
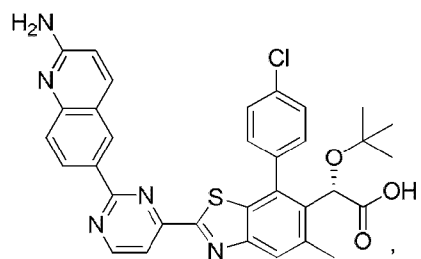
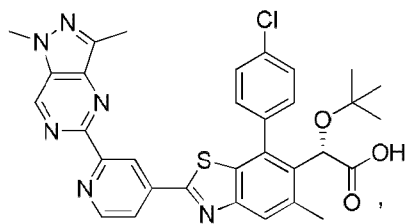




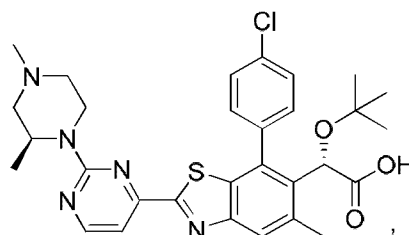
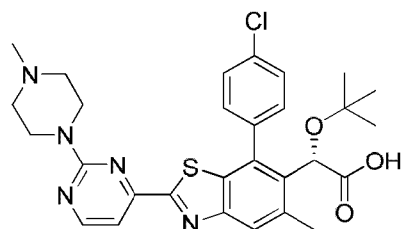
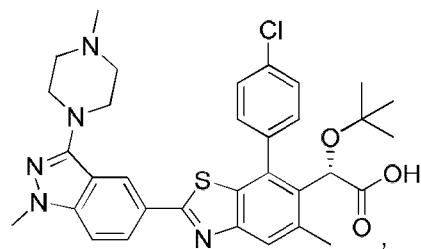
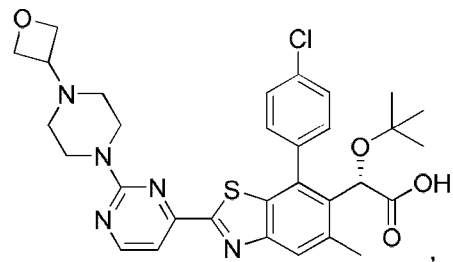


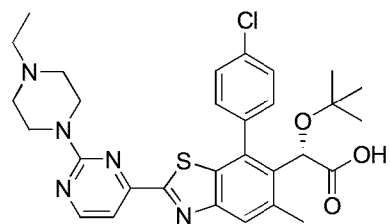
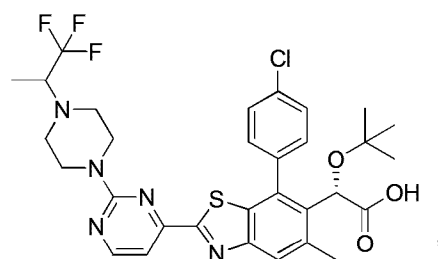
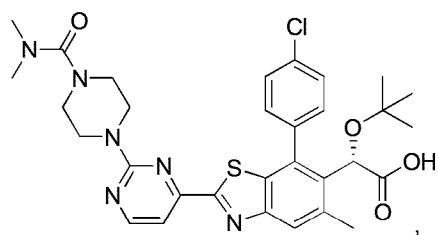
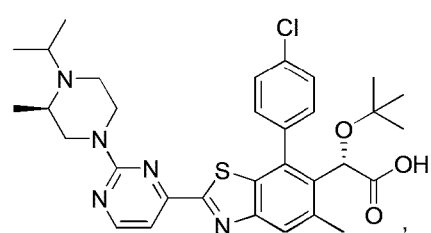
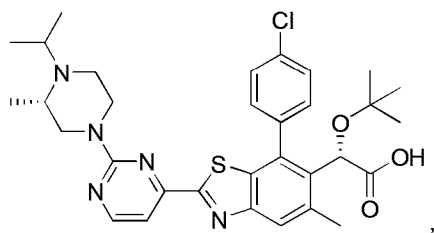
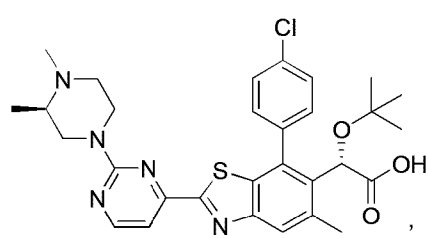
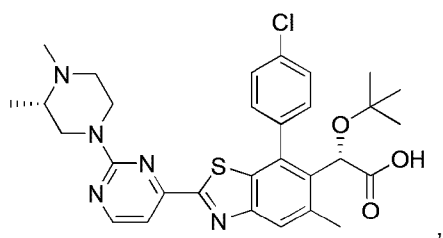
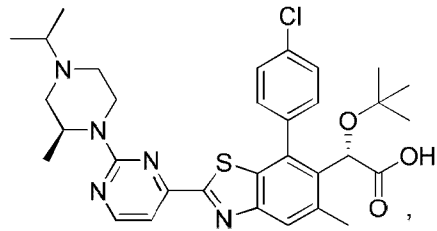
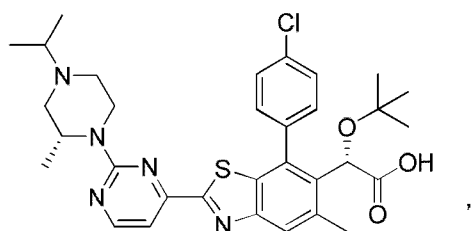
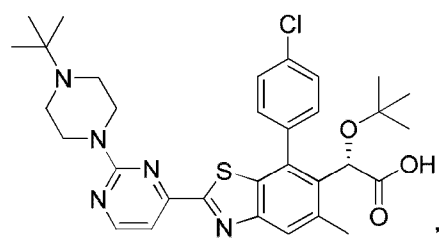
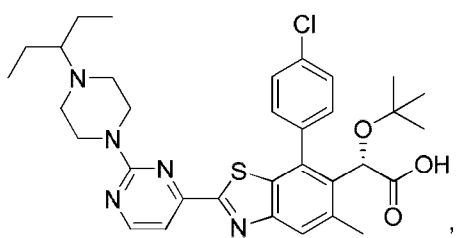




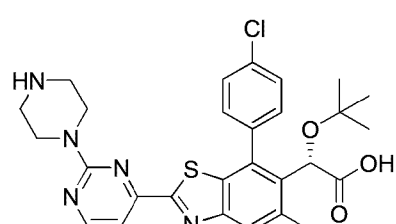


21. The compound of claim 1 which is selected from:



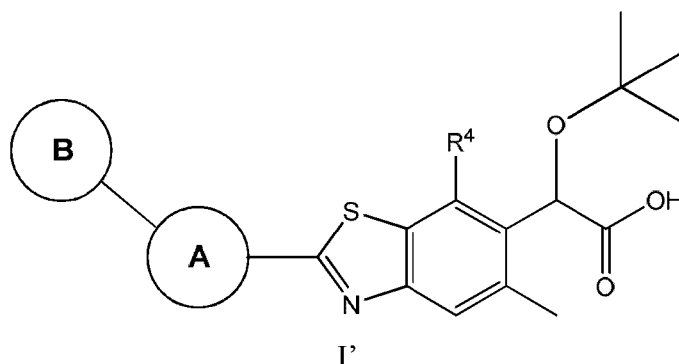


and



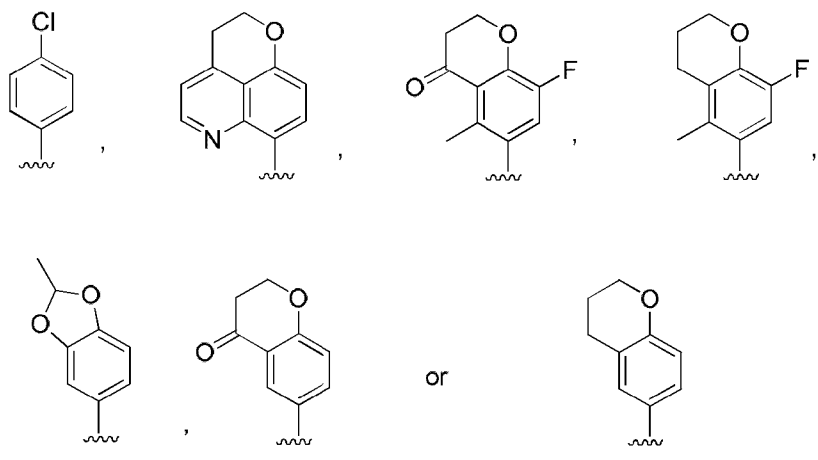
and pharmaceutically acceptable salts thereof.

22. A compound of formula I':



wherein:

R⁴ is:



A is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridinyl-2(1H)-one, tetrahydropyrimidin-2(1H)-one, imidazolidinyl-2-one, pyrrolidinyl-2-one, pyrrolidinyl, pyridazinyl, thiazolyl, pyrazin-2(1H)-one, piperazinyl-2-one, piperazinyl, imidazolyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl or piperidinyl, wherein any phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridinyl-2(1H)-one, tetrahydropyrimidin-2(1H)-one, imidazolidinyl-2-one, pyrrolidinyl-2-one, pyrrolidinyl, pyridazinyl, thiazolyl, pyrazin-2(1H)-one, piperazinyl-2-one, piperazinyl, imidazolyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl or piperidinyl of A is optionally substituted with one to five Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one to five Z^{1b} groups; or A and B together form a (C₉-C₁₄)bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle, wherein (C₉-C₁₄)bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one to five Z^{1b} groups;

each Z^{1a} is independently selected from halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₂-C₃)alkynyl, (C₁-C₃)haloalkyl, (C₃-C₇)carbocycle, heterocycle, -O(C₁-C₃)alkyl, -O(C₂-C₃)alkenyl,

-O(C₂-C₃)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle and heterocycle of Z^{1a} is optionally substituted with one to five halogen or (C₁-C₆)alkyl;

each Z^{1b} is independently selected from halo, CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, heteroaryl, heterocycle, aryl(C₁-C₆)alkyl-, -OH, -O(C₁-C₆)alkyl, -O(C₂-C₆)alkenyl, -O(C₂-C₆)alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d, wherein any (C₃-C₇)carbocycle and heterocycle of Z^{1b} is optionally substituted with one to five halogen or (C₁-C₆)alkyl; and

R_a, R_b, R_c and R_d are each independently H or (C₁-C₆)alkyl;

wherein each heteroaryl is a single aromatic ring of from 1 to 6 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur or is a portion of a multiple condensed ring system comprising 2 or 3 rings; and wherein each heterocycle is a single saturated or partially unsaturated ring of from 1 to 6 carbon atoms and 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur or is a portion of a multiple condensed ring system comprising 2 or 3 rings;

or a pharmaceutically acceptable salt thereof.

23. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A is pyridinyl, pyrimidinyl or pyrazinyl, wherein pyridinyl, pyrimidinyl or pyrazinyl is optionally substituted with one to five Z^{1a} groups, and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one to five Z^{1b} groups.

24. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A is pyridinyl, pyrimidinyl or pyrazinyl and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one to five Z^{1b} groups.

25. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A is pyridinyl, pyrimidinyl or pyrazinyl and B is heteroaryl or heterocycle, wherein any heteroaryl or heterocycle of B is optionally substituted with one to five Z^{1b} groups.

26. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A and B together form a (C₉-C₁₄)bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle, wherein (C₉-C₁₄)bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one to five Z^{1b} groups.

27. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A and B together form a bicyclic heteroaryl, wherein bicyclic heteroaryl is optionally substituted with one to five Z^{1b} groups.

28. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A and B together form a pyrrolopyridinyl, pyrazolopyridinyl or indazolyl, wherein pyrrolopyridinyl, pyrazolopyridinyl or indazolyl is optionally substituted with one to five Z^{1b} groups.

29. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A is pyridinyl, pyrimidinyl or pyrazinyl and B is a 4-6 membered monocyclic heterocycle, wherein any 4-6 membered monocyclic heterocycle of B is optionally substituted with one to five Z^{1b} groups.

30. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A is pyridinyl, pyrimidinyl or pyrazinyl and B is selected from phenyl, pyridinyl, indazolyl, pyrazolo[4,3-b]pyridinyl, pyrimidinyl, pyrazolyl, benzo[d]imidazolyl, indazolyl, 1H-benzo[d]imidazolyl-2(3H)-one, 2H-pyrido[3,2-b][1,4]oxazinyl-3(4H)-one, 2,6-naphthyridin-1(2H)-one, 1,7-naphthyridinyl-8(7H)-one, 1H-indazolyl-3(2H)-one, quinolinyl-2(1H)-one, quinolinyl, pyrrolo[2,3-b]pyridinyl, pyrrolidinyl, piperazinyl, phenyl, imidazolyl, piperidinyl, morpholinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrimidinyl-2,4(1H,3H)-dionyl, pyridinyl-2(1H)-one, 1H-pyrazolo[3,4-c]pyridinyl, indolinyl-2-one, 1H-pyrrolo[3,4-c]pyridinyl-3(2H)-one, 2,3-dihydro-1H-pyrrolo[3,2-c]pyridinyl, pyrazolyl, pyrimidinyl-2(1H)-one, azetidiny, tetrahydro-2H-pyranly, 3,6-dihydro-2H-pyranly, 1,2,3,6-tetrahydropyridine, 1H-pyrazolo[3,4-b]pyridinyl, 2H-benzo[b][1,4]oxaziyl-3(4H)-one, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazinyl, indolinyl, 3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one, 3H-imidazo[4,5-b]pyridinyl and 1H-benzo[d][1,2,3]triazolyl, wherein any phenyl, pyridinyl, indazolyl, pyrazolo[4,3-b]pyridinyl, pyrimidinyl, pyrazolyl, benzo[d]imidazolyl, indazolyl, 1H-benzo[d]imidazolyl-2(3H)-one, 2H-pyrido[3,2-b][1,4]oxazinyl-3(4H)-one, 2,6-naphthyridin-1(2H)-one, 1,7-naphthyridinyl-8(7H)-one, 1H-indazolyl-3(2H)-one, quinolinyl-2(1H)-one, quinolinyl, pyrrolo[2,3-b]pyridinyl, pyrrolidinyl, piperazinyl, phenyl, imidazolyl, piperidinyl, morpholinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrimidinyl-2,4(1H,3H)-dionyl, pyridinyl-2(1H)-one, 1H-pyrazolo[3,4-c]pyridinyl, indolinyl-2-one, 1H-pyrrolo[3,4-c]pyridinyl-3(2H)-one, 2,3-dihydro-1H-pyrrolo[3,2-c]pyridinyl, pyrazolyl, pyrimidinyl-2(1H)-one, azetidiny, tetrahydro-2H-pyranly,

3,6-dihydro-2H-pyranyl, 1,2,3,6-tetrahydropyridine, 1H-pyrazolo[3,4-b]pyridinyl, 2H-benzo[b][1,4]oxazolyl-3(4H)-one, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazinyl, indolinyl, 3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one, 3H-imidazo[4,5-b]pyridinyl, and 1H-benzo[d][1,2,3]triazolyl of B is optionally substituted with one to five Z^{1b} groups.

31. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A is pyridinyl, pyrimidinyl or pyrazinyl and B is piperazinyl or azetidiny, wherein any piperazinyl or azetidiny of B is optionally substituted with one to five Z^{1b} groups.

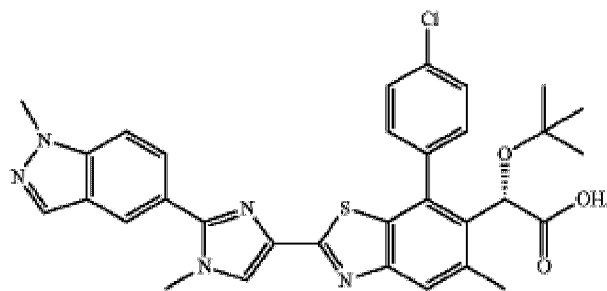
32. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein A is not substituted with Z^{1a} groups.

33. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein Z^{1b} is (C_1-C_6) alkyl.

34. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein Z^{1b} is independently selected from halo, CN, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) haloalkyl, (C_3-C_7) carbocycle, heteroaryl, heterocycle, aryl (C_1-C_6) alkyl-, -OH, -O (C_1-C_6) alkyl-, -O (C_2-C_6) alkenyl, -O (C_2-C_6) alkynyl, -NR_cR_d, -NR_aC(O)R_a, -C(O)OR_b and -C(O)NR_cR_d.

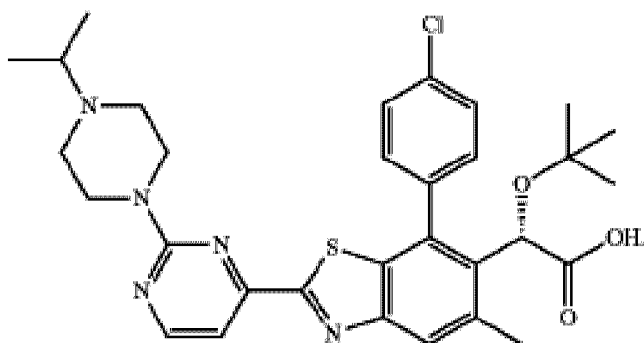
35. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein B is aryl having 6 to 20 carbon atoms.

36. The compound of claim 1 which is:



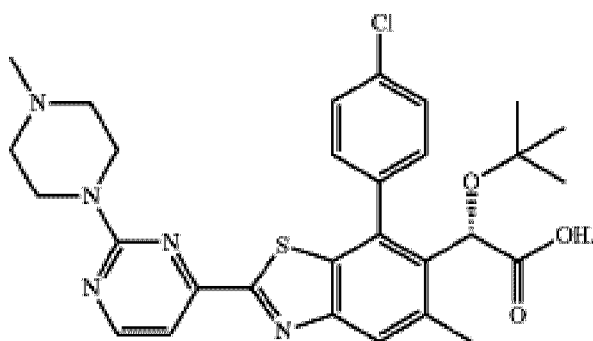
or a pharmaceutically acceptable salt thereof.

37. The compound of claim 1 which is:



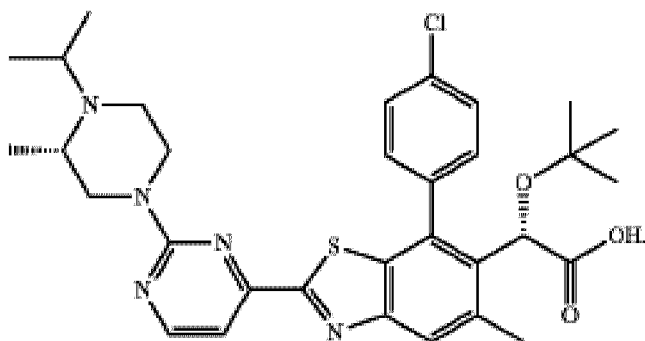
or a pharmaceutically acceptable salt thereof.

38. The compound of claim 1 which is:



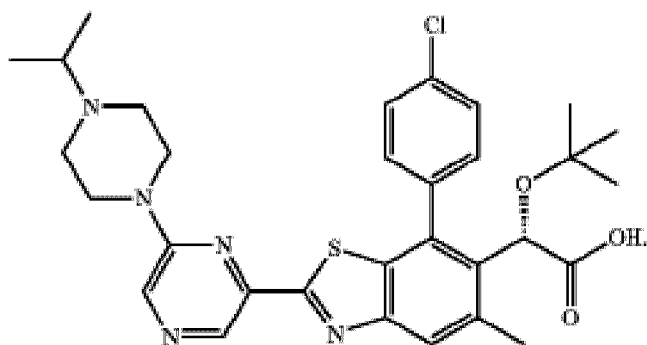
or a pharmaceutically acceptable salt thereof.

39. The compound of claim 1 which is:



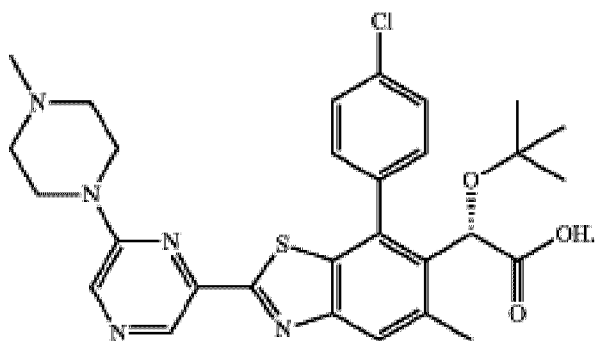
or a pharmaceutically acceptable salt thereof.

40. The compound of claim 1 which is:



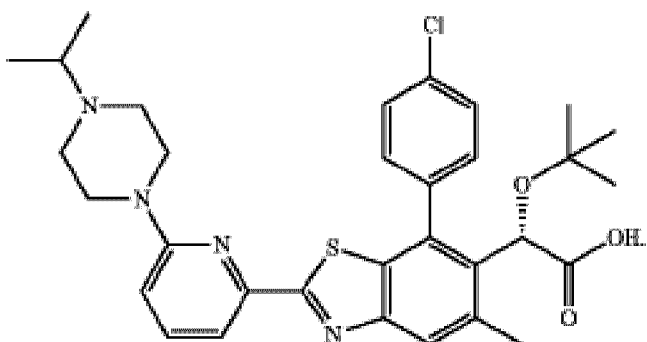
or a pharmaceutically acceptable salt thereof.

41. The compound of claim 1 which is:



or a pharmaceutically acceptable salt thereof.

42. The compound of claim 1 which is:



or a pharmaceutically acceptable salt thereof.

43. A pharmaceutical composition comprising a compound of formula I' as described in any one of claims 1-42, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

44. The pharmaceutical composition of claim 43, further comprising one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof.

45. The use of the pharmaceutical composition of claim 43 or 44 for treating an HIV infection in a mammal.

46. The pharmaceutical composition of claim 43 or 44 for use in treating an HIV infection in a mammal.

47. A compound of formula I' as described in any of claims 1-42, or a pharmaceutically acceptable salt thereof for use in medical therapy.

48. The use of a compound of formula I' as described in any one of claims 1-42, or a pharmaceutically acceptable salt thereof, for treating an HIV infection in a mammal.

49. The use of claim 47 wherein said compound of formula I' is used in combination with one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof.

50. The use of a compound of formula I' as described in any one of claims 1-42, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating an HIV infection in a mammal.

51. A compound of formula I' as described in any one of claims 1-42, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection in a mammal.

52. A compound of formula I' as described in any one of claims 1-42, or a pharmaceutically acceptable salt thereof, for use in combination with one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof for the prophylactic or therapeutic treatment of an HIV infection in a mammal.

53. A compound of formula I' as described in any one of claims 1-42, or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment of an HIV infection in a mammal.

54. A compound of formula I' as described in any one of claims 1-42, or a pharmaceutically acceptable salt thereof, for use in combination with one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and other drugs for treating HIV, and combinations thereof for the therapeutic treatment of an HIV infection in a mammal.

