BENZOTHIAZOL-6-YL ACETIC ACID DERIVATIVES AND THEIR USE FOR TREATING AN HIV INFECTION

Cross Reference to Related Applications

This patent application claims the benefit of priority of U.S. Application Serial No. 61/636602, filed April 20, 2012 and of U.S. application serial No. 61/718165, filed October 24, 2012. The content of each of these provisional applications is hereby incorporated herein in its entirety.

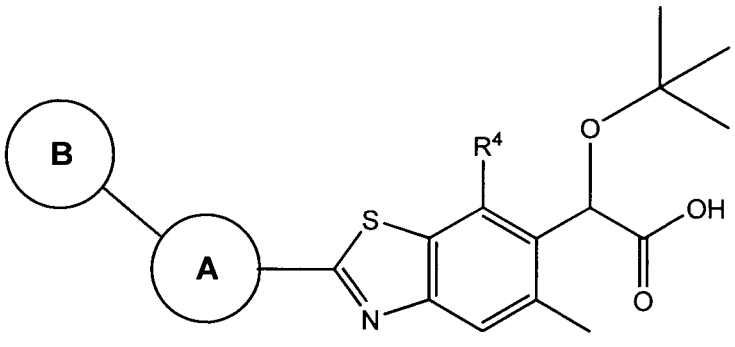
Background of the Invention

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 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 metabolic stability.

Summary

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



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 (e.g., 1, 2, 3, 4 or 5) groups each independently selected from halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$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;

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, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$alkenyl, $(C_2$-$C_3)$alkynyl, $(C_1$-$C_3)$haloalkyl, $(C_3$-$C_7)$carbocycle, 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 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;

each Z^{1b} is independently selected from halo, CN, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$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 -$C(O)NR_cR_d$, 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;

or a 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.

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

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 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.

"Alkyl" is hydrocarbon containing normal, secondary or tertiary atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e.*, (C_1-C_{20})alkyl), 1 to 10 carbon atoms (*i.e.*, (C_1-C_{10})alkyl), 1 to 8 carbon atoms (*i.e.*, (C_1-C_8)alkyl)or 1 to 6 carbon atoms (*i.e.*, (C_1-C_6 alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, and octyl ($-(CH_2)_7CH_3$). "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.*, (C_1-C_{10})alkyl), or 1 to 6 carbon atoms (*i.e.*, (C_1-C_6)alkyl) or 1-3 carbon atoms (*i.e.*, (C_1-C_3)alkyl). Typical alkyl radicals include, but are not limited to, methylene ($-CH_2-$), 1,1-ethyl ($-CH(CH_3)-$), 1,2-ethyl ($-CH_2CH_2-$), 1,1-propyl ($-CH(CH_2CH_3)-$), 1,2-propyl ($-CH_2CH(CH_3)-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), 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 more hydrogen atoms are each replaced by a halo substituent. For example, a (C_1-C_6)haloalkyl is a (C_1-C_6)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(C_1-C_6)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 azetidinyl, tetrahydrofuranyl or piperidinyl. 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., decahydronapthyridinyl), heteroaryls (e.g., 1,2,3,4-tetrahydronaphthyridinyl), carbocycles (e.g., decahydroquinolyl) 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 heterocyle, heteroaryl, aryl or a carbocycle portion of the ring. Exemplary heterocycles include, but are not limited to aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrofuranyl, dihydrooxazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,2,3,4-tetrahydroquinolyl, benzoxazinyl, dihydrooxazolyl, chromanyl, 1,2-dihydropyridinyl, 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 (C_3-C_7)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 (C_3-C_7)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 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(C_1-C_6)alkyl). Heteroarylalkyl groups include, but are not limited to heteroaryl-CH_2-, heteroaryl-$CH(CH_3)$-, heteroaryl-CH_2CH_2-, 2-(heteroaryl)ethan-1-yl, and the like, wherein the "heteroaryl" portion includes any of the heteroaryl groups described 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, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heteroaryls such pyridinylmethyl, pyridizylmethyl, pyrimidylmethyl, pyrazinylmethyl, etc.

"Heterocyclylalkyl" refers to an alkyl radical as defined herein in which one of the hydrogen atoms bonded to a carbon atom is replaced with a heterocyclyl radical as described herein (*i.e.*, a heterocyclyl-alkyl- moiety). The alkyl group of the "heterocyclylalkyl" is typically 1 to 6 carbon atoms (*i.e.* heterocyclyl(C_1-C_6)alkyl). Typical heterocyclylalkyl groups include, but are not limited to heterocyclyl-CH_2-, heterocyclyl-$CH(CH_3)$-, heterocyclyl-CH_2CH_2-, 2-(heterocyclyl)ethan-1-yl, and the like, wherein the "heterocyclyl" portion includes any of the heterocyclyl groups described above. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl portion of the heterocyclyl 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 heterocyclylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such tetrahydrofuranylmethyl and pyrroldinylmethyl, etc., and 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, etc.

The term "carbocycle" or "carbocyclyl" 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. (C_3-C_6)carbocycle). Carbocycle includes multicyclic carbocyles 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 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, 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-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, (C_3-C_7)halocarbocycle is a (C_3-C_7)carbocycle wherein one or more of the hydrogen atoms have been 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, 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 1 to 6 carbon atoms (*i.e.* carbocyclyl(C_1-C_6)alkyl). Typical carbocyclyl alkyl groups include, but are not limited to carbocyclyl-CH_2-, carbocyclyl-$CH(CH_3)$-, carbocyclyl-CH_2CH_2-, 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 "(C_1-C_6)alkyl, either alone or as part of a group, is optionally substituted ", the phrase means that the variable (C_1-C_6)alkyl can be substituted when it is alone and that it can also be substituted when the variable "(C_1-C_6)alkyl" is part of a larger group such as for example an aryl(C_1-C_6)alkyl or a -(C_1-C_6)alkyl-SO_2-(C_1-C_6)alkyl-(C_3-C_7)carbocycle group. Similarly, when stated, other variables (e.g., (C_1-C_6)alkenyl, (C_1-C_6)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)-, -SO_2-, -(C_1-C_6)alkylO-, -(C_1-C_6)alkylC(O)-, -(C_1-C_6)alkylC(O)O-, -(C_1-C_6)alkylS-, -(C_1-C_6)alkylS(O)- and -(C_1-C_6)alkylSO_2-) 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 G^1 or G^2 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.

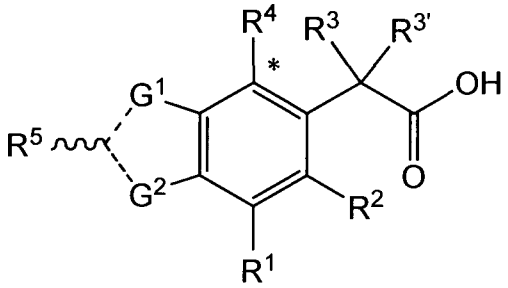
The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"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.

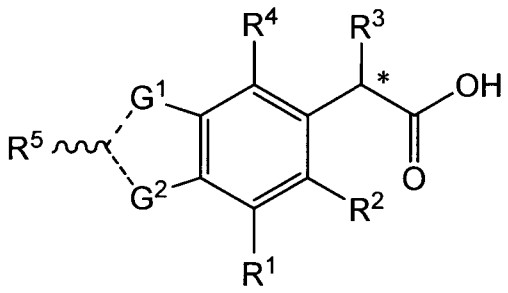
Certain compounds of the invention can exist as atropisomers. For example, it has been discovered that atropisomers exist for certain substituents at the R^4 position of compounds of the invention (e.g., compounds of formula I, I' and related formulas described herein) as marked by an asterisk in the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



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.

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 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 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 R^3 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 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 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 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

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 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, 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 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), which is incorporated by reference in its entirety herein. 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 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 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 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 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 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. 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.

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.

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.

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.

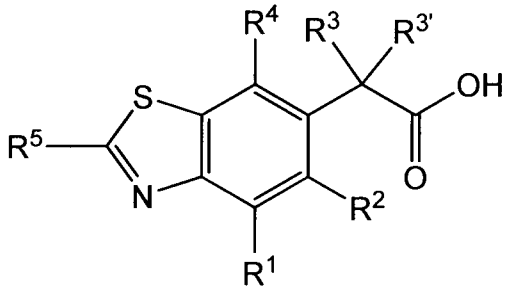
Isotopes

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 example, a $-CH_3$ group may be substituted with $-CD_3$.

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.

Compounds of formula I.

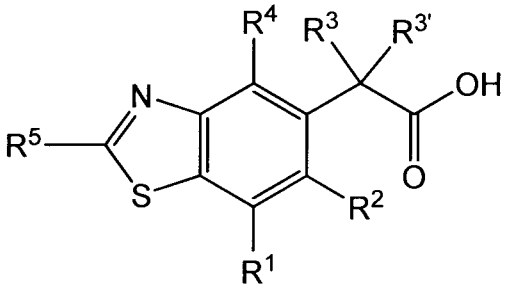
A specific group of compounds of formula I are compounds of formula Ia:



Ia

or a salt thereof.

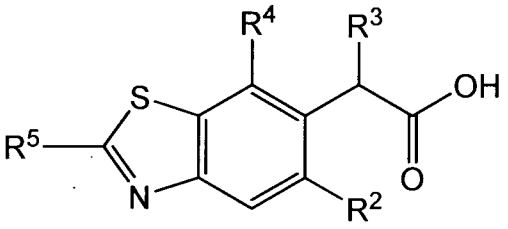
Another specific group of compounds of formula I are compounds of formula Ib:



Ib

or a salt thereof.

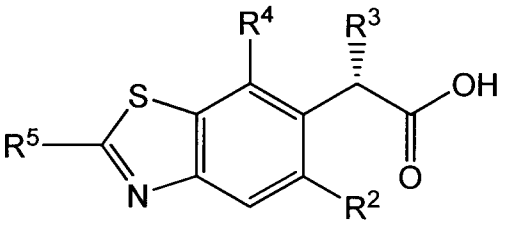
Another specific group of compounds of formula I are compounds of formula Ic:



Ic

wherein R^3 is-O(C_1-C_6)alkyl or a salt thereof.

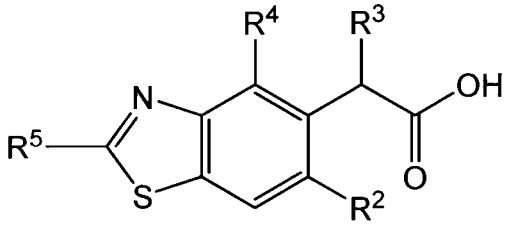
Another specific group of compounds of formula I are compounds of formula Ic':



Ic'

wherein R^3 is-O(C_1-C_6)alkyl or a salt thereof.

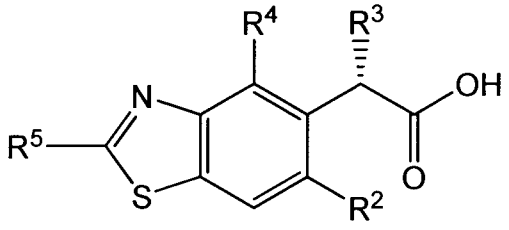
Another specific group of compounds of formula I are compounds of formula Id:



Id

wherein R^3 is-O(C_1-C_6)alkyl, or a salt thereof.

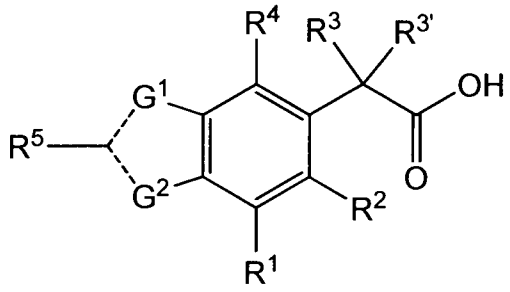
Another specific group of compounds of formula I are compounds of formula Id':



Id'

wherein R^3 is-O(C_1-C_6)alkyl, or a salt thereof.

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



Ie

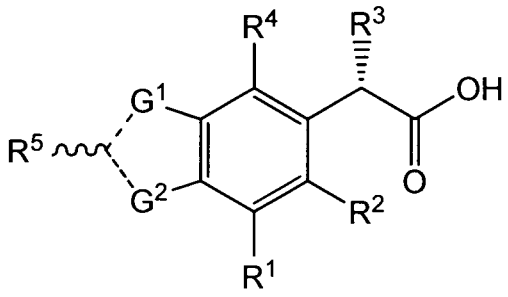
wherein:

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

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

or a salt thereof.

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



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-Ia145, etc.) and for compounds of formulas I' and subformulas or 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}, $R^{3b'}$of 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 $-OC(CH_3)_2CH_2OH$, $-OC(CH_3)_2CH_2OH$, $-O(C_1\text{-}C_6)$alkyl-O-C(O)-NH_2, $-O(C_1\text{-}C_6)$alkyl-O-C(O)-$N(CH_3)_2$or $-O(C_1\text{-}C_6)$alkyl-O-C(O)-NH(phenyl).

Another specific value for R^{3b} is $-(C_1\text{-}C_6)$alkylOH or $-O(C_1\text{-}C_6)$alkyl-O-C(O)-NR_cR_d.

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

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

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 $(C_1\text{-}C_6)$alkyl or $-O(C_1\text{-}C_6)$alkyl.

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

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

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

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

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 $(C_3\text{-}C_7)$carbocycle or heterocycle; wherein the $(C_3\text{-}C_7)$carbocycle or heterocycle is optionally substituted with one or more Z^1 groups.

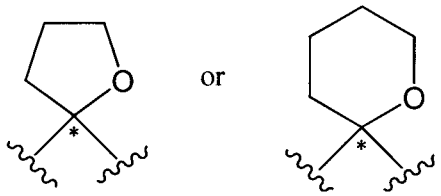
Another specific group of compounds of formula I are compounds wherein R^{3b} and $R^{3b'}$ together with the carbon to which they are attached form a $(C_3\text{-}C_7)$carbocycle or a 4, 5 or 6-membered heterocycle; wherein the $(C_3\text{-}C_6)$carbocycle or the 4, 5 or 6-membered heterocycle is optionally 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 a $(C_4\text{-}C_6)$carbocycle or a 5 or 6-membered heterocycle; wherein the $(C_4\text{-}C_6)$carbocycle or the 5 or 6-membered heterocycle is 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 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:

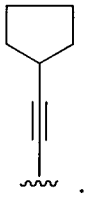


each of which is optionally substituted with one or more Z^1 groups; and wherein "*" denotes the point of attachment to the carbon of the compound of formula I.

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

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

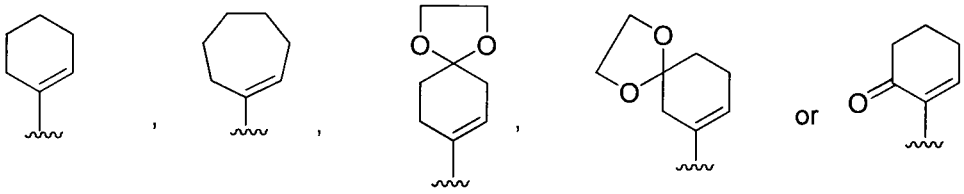
Another specific value for R^{4b} is:



optionally substituted with one or more Z^1 groups.

Another specific value for R^{4b} is $(C_3\text{-}C_7)$carbocycle; wherein $(C_3\text{-}C_7)$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 $(C_3\text{-}C_6)$carbocycle or 5-6-membered heterocycle.

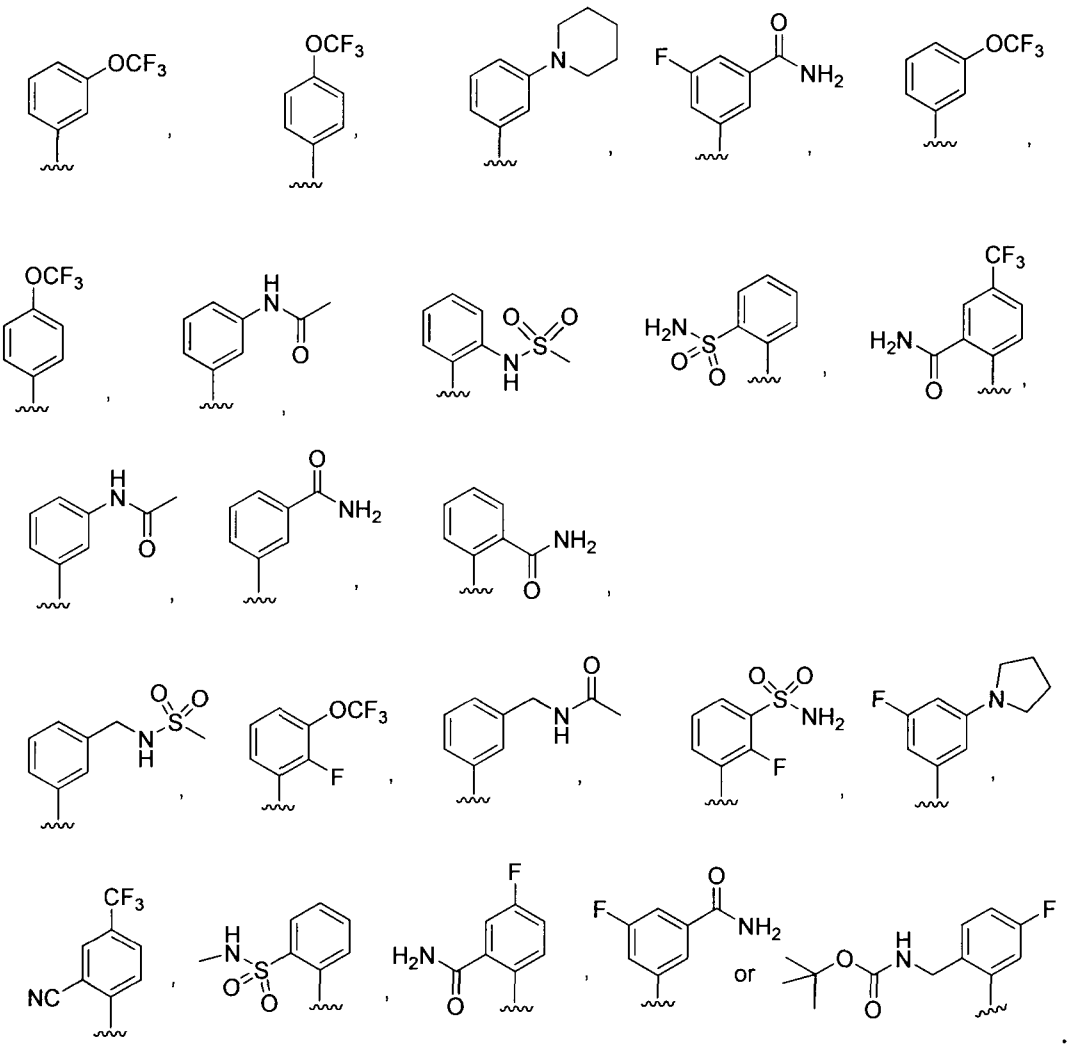
Another specific value for R^{4b} is:



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

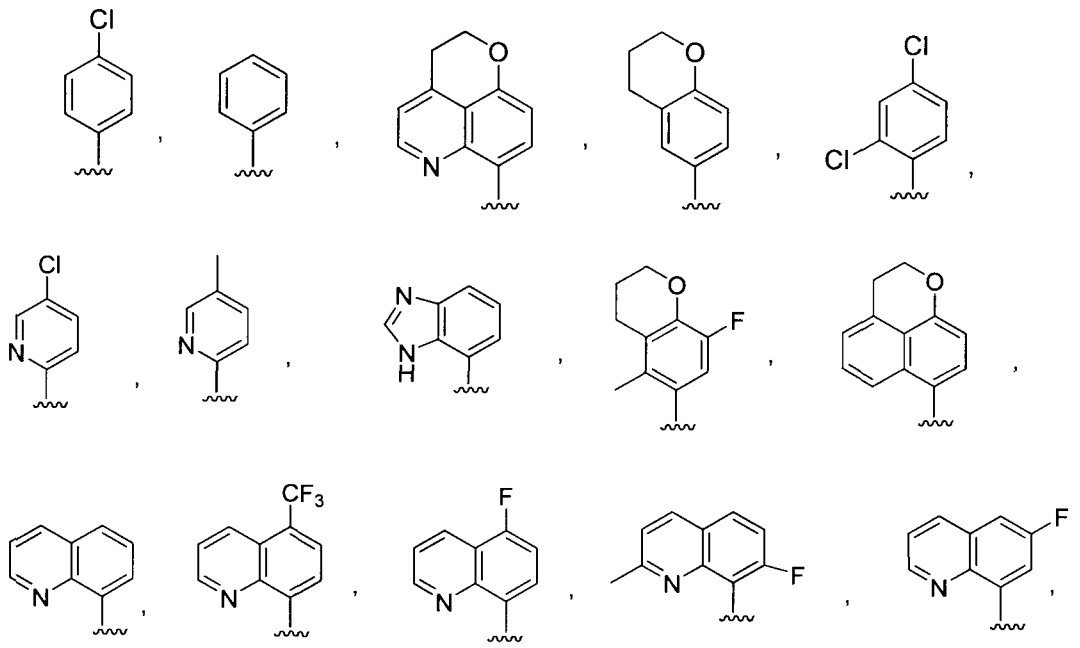
Another specific value for R^{4b} is aryl, heterocycle or heteroaryl; wherein aryl, heterocycle and heteroaryl are each independently substituted with one or more Z^7 groups and optionally substituted with one or more Z^1 groups.

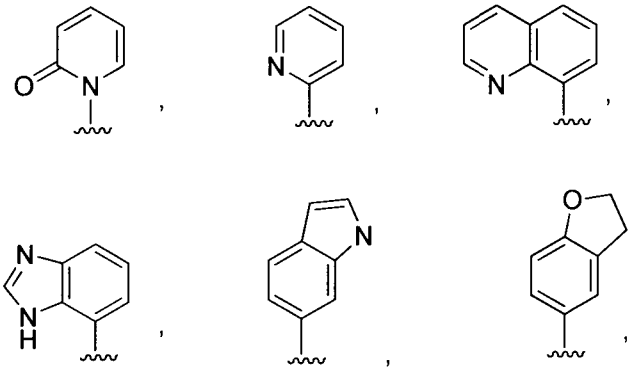
Another specific value for R^{4b} is:



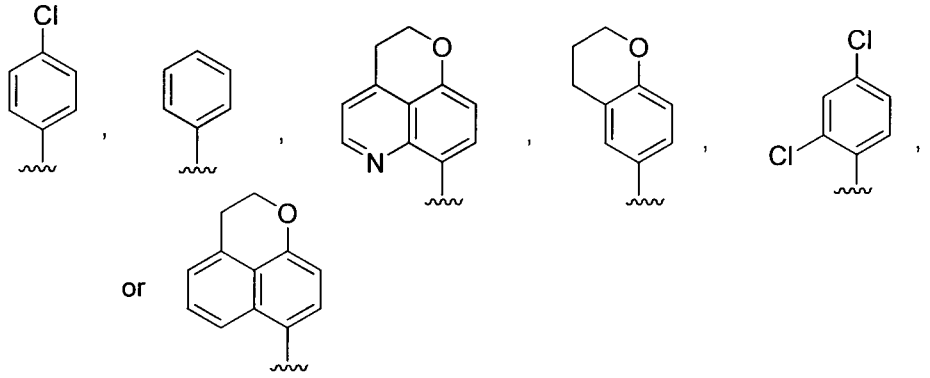
Another specific value for R^4 is R^{4a}.

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

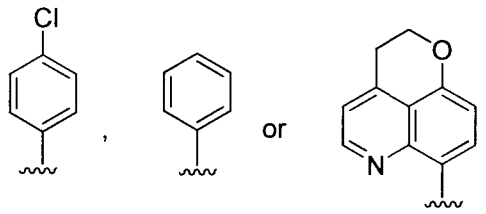




Another specific value for R^{4a} is:



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



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, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$haloalkyl, $(C_3\text{-}C_7)$cycloalkyl, $-(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, -OH, $-O(C_1\text{-}C_6)$alkyl, -SH, $-S(C_1\text{-}C_6)$alkyl, $-NH_2$, $-NH(C_1\text{-}C_6)$alkyl and $-N((C_1\text{-}C_6)\text{alkyl})_2$, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with hydroxy, $-O(C_1\text{-}C_6)$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.

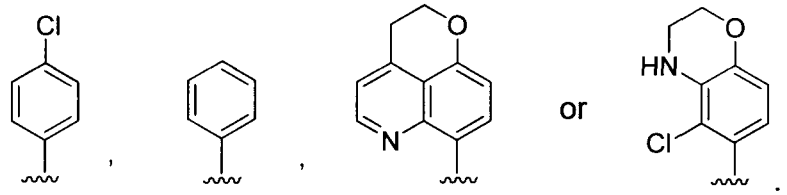
Another specific value for R^4 is selected from:

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, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$haloalkyl, $(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, -OH, -O$(C_1\text{-}C_6)$alkyl, -SH, -S$(C_1\text{-}C_6)$alkyl, $-NH_2$, -NH$(C_1\text{-}C_6)$alkyl and -N$((C_1\text{-}C_6)\text{alkyl})_2$, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with hydroxy, -O$(C_1\text{-}C_6)$alkyl, cyano or oxo; and

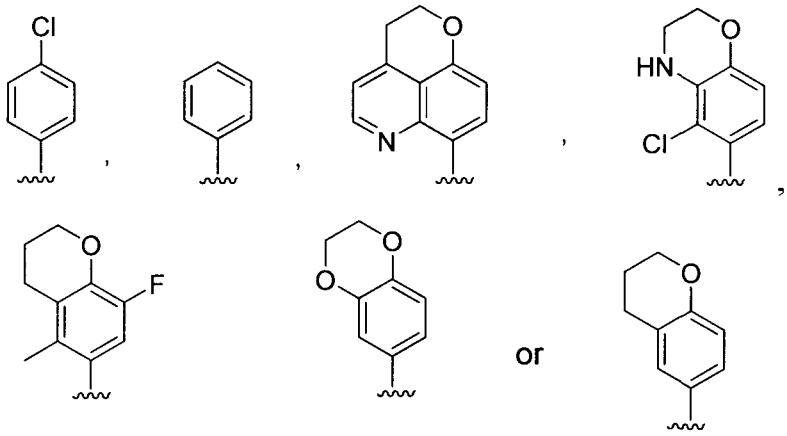
b) aryl and heteroaryl, wherein aryl and heteroaryl are each independently substituted with one or more Z^7 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups.

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, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$haloalkyl, $(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, -OH, -O$(C_1\text{-}C_6)$alkyl, -SH, -S$(C_1\text{-}C_6)$alkyl, $-NH_2$, -NH$(C_1\text{-}C_6)$alkyl and -N$((C_1\text{-}C_6)\text{alkyl})_2$, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with hydroxy, -O$(C_1\text{-}C_6)$alkyl, cyano or oxo.

Another specific value for R^4 is:



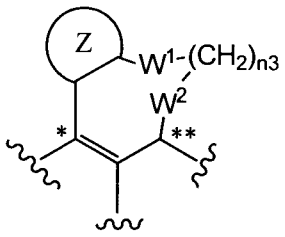
Another specific value for R^4 is:



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, $(C_1\text{-}C_6)$alkyl or -O$(C_1\text{-}C_6)$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:

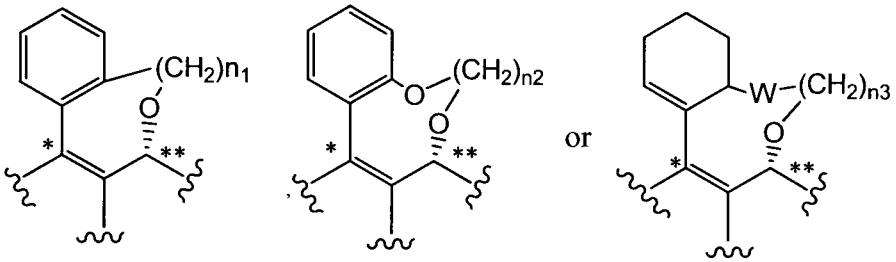
Z is aryl, heteroaryl or (C_3-C_6)carbocycle;

n3 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:

n1 is 3 or 4; n2 is 2, 3 or 4; n3 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}.

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 $(C_1\text{-}C_6)$alkyl.

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

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

Another specific value for R^2 is H or $(C_1\text{-}C_6)$alkyl.

Another specific value for R^2 is $(C_1\text{-}C_6)$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.

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 $(C_1\text{-}C_6)$alkyl.

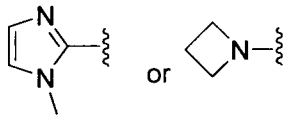
A specific value for R^{10} is H or $(C_1\text{-}C_6)$alkyl.

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

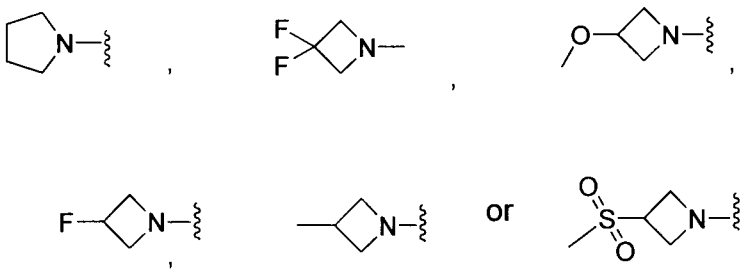
Another specific value for R^{10} is H, $(C_1\text{-}C_6)$alkyl or $-C(=O)\text{-}R^{11}$.

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

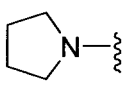
In one embodiment of R^5 does not include:

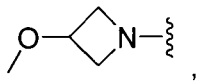
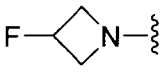
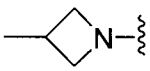
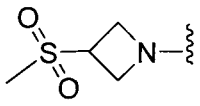


A specific value for R^5 is:



In one embodiment R^5 does not include:






or


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) $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl and $(C_2\text{-}C_6)$alkynyl, wherein any $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

b) $(C_3\text{-}C_{14})$carbocycle, wherein $(C_3\text{-}C_{14})$carbocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 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) Z^1 groups; and

d) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle 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 group of compounds of formula I are compounds wherein R^{4b} is selected from;

a) $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl and $(C_2\text{-}C_6)$alkynyl, wherein any $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

b) $(C_3\text{-}C_{14})$carbocycle, wherein $(C_3\text{-}C_{14})$carbocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; wherein two Z^1 groups together with the atom or atoms to which they are attached optionally form a $(C_3\text{-}C_7)$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) Z^7 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups.

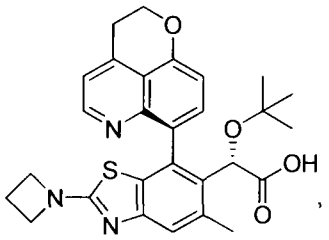
Another specific group of compounds of formula I are compounds wherein R^{4b} is selected from;

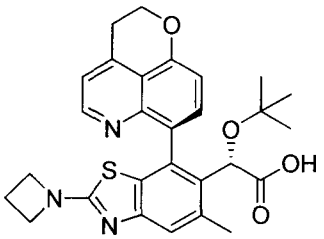
a) $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl and $(C_2\text{-}C_6)$alkynyl, wherein any $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

b) $(C_3\text{-}C_{14})$carbocycle, wherein $(C_3\text{-}C_{14})$carbocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups; and

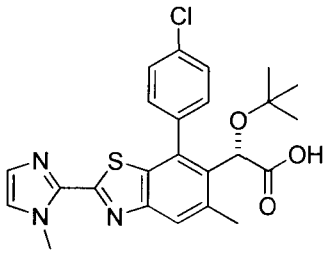
c) aryl, heterocycle and heteroaryl, wherein aryl, heterocycle and heteroaryl are each independently substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^7 groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups.

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





and



and salts thereof.

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.

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

$R^{3'}$ 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;

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^1groups; 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^1groups;

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

R^2 is H or $(C_1\text{-}C_6)$alkyl.

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;

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;

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

R^2 is H or $(C_1\text{-}C_6)$alkyl; and

R^3 is -O(C_1-C_6)alkyl.

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; 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) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups.

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; 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) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1 groups;

and

$R^{3'}$ 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; 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) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1groups;

$R^{3'}$ 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:

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; 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) 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

R^3 is -O(C_1-C_6)alkyl.

Another specific value for R^5 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) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1groups;

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

R^5 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) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1groups; and

$R^{3'}$ is H.

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

R^5 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) Z^{15} groups and optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^1groups;

$R^{3'}$ 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 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

R^3 is -O(C_1-C_6)alkyl.

Another specific value for 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;

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.

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;

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^1groups; 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^1groups;

and

$R^{3'}$ 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;

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^1groups; 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^1groups;

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

R^2 is H or $(C_1\text{-}C_6)$alkyl.

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;

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^1groups; 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^1groups;

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

R^2 is H or $(C_1\text{-}C_6)$alkyl; and

R^3 is -O(C_1-C_6)alkyl.

Another 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 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^1groups; 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^1groups;

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;

wherein 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)$_2$;

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.

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;

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^1groups; 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^1groups;

$R^{3'}$ is H;

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$)_2$;

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.

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;

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^1groups; 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^1groups;

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

R^2 is H or $(C_1$-$C_6)$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$)_2$;

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.

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;

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^1groups; 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^1groups;

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

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

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

each Z^{10} is independently selected from:

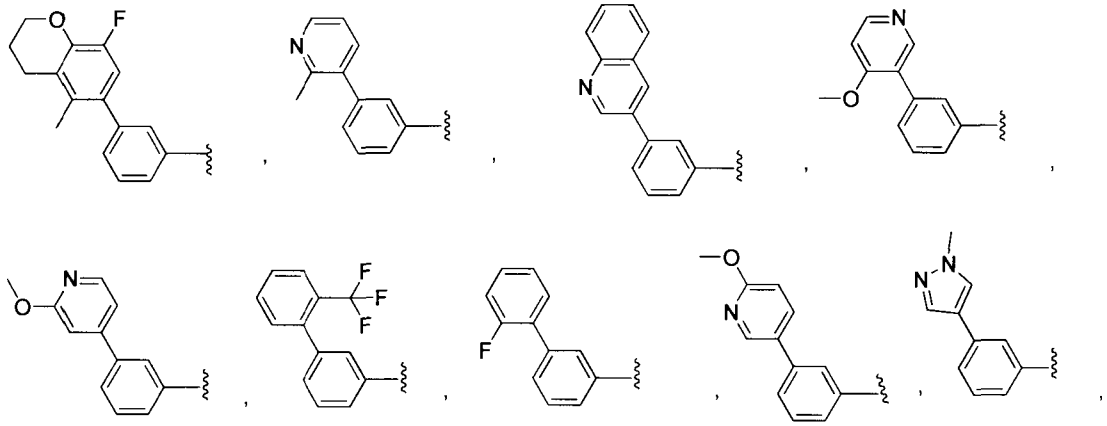
i) halo, oxo, thioxo, (C_2-C_6)alkenyl, (C_1-C_6)haloalkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-(C_1-C_6)alkyl-, -OH, -O(C_1-C_6)alkyl, -O(C_1-C_6)haloalkyl, -SH, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -NH_2, -NH(C_1-C_6)alkyl and -N((C_1-C_6)alkyl)$_2$;

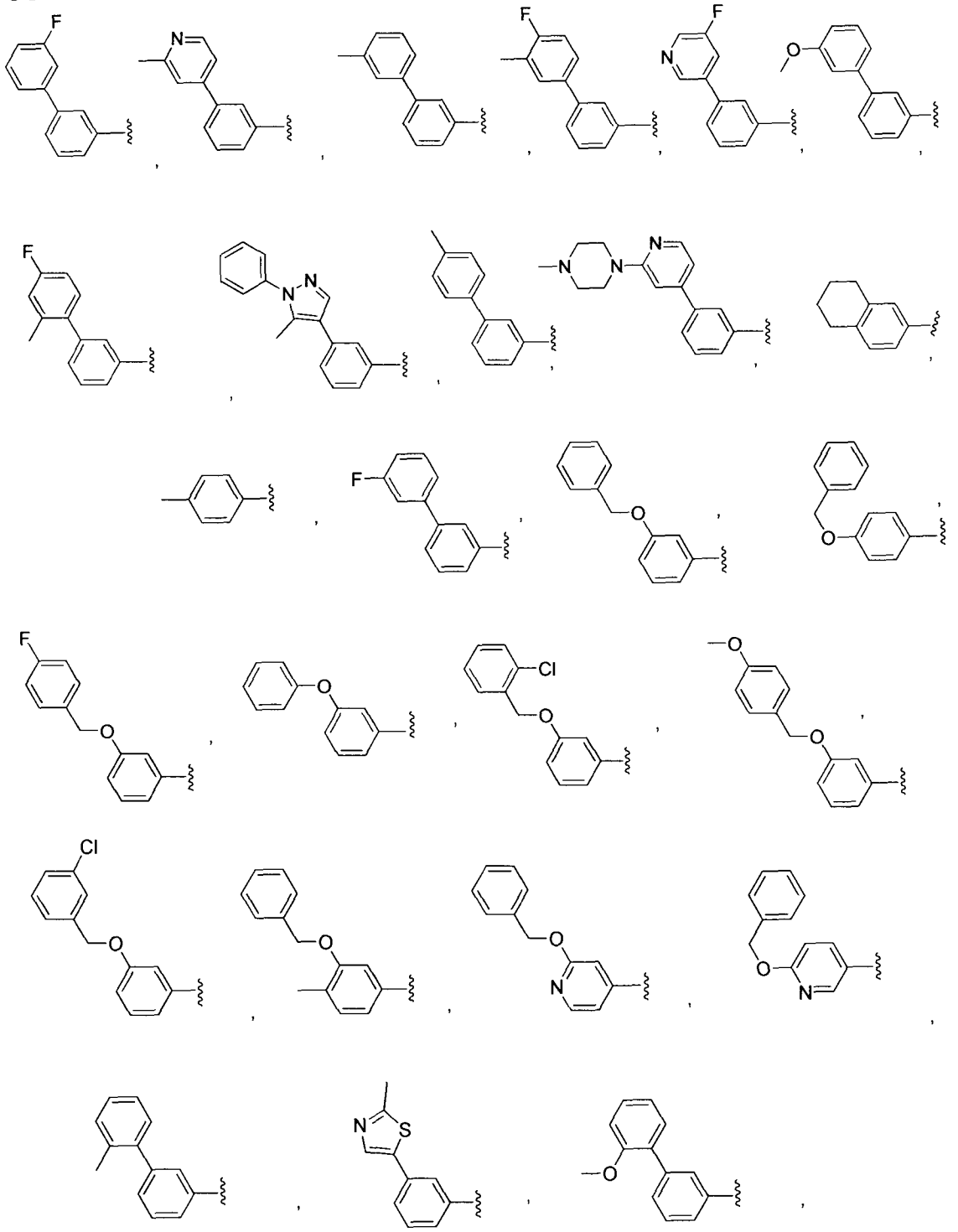
ii) (C_1-C_6)alkyl substituted with -OH, -O-(C_1-C_6)haloalkyl, or -O-(C_1-C_6)alkyl; and

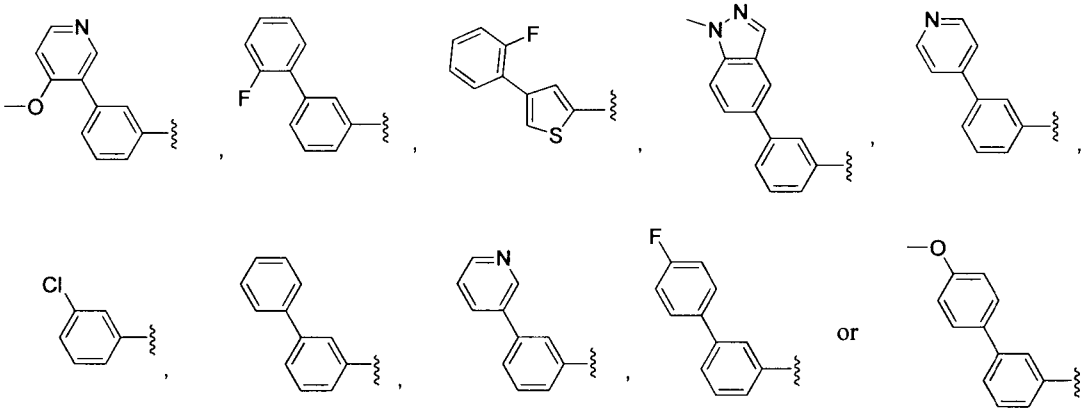
iii) aryl, heterocycle and heteroaryl, which aryl, heterocycle and heteroaryl is optionally substituted with halo, (C_1-C_6)alkyl or COOH; and

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.

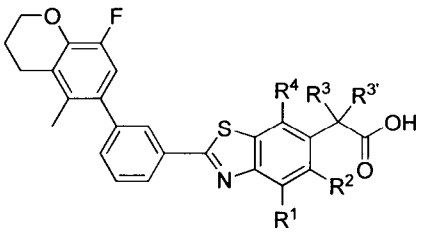
Another specific value for R^5 is:







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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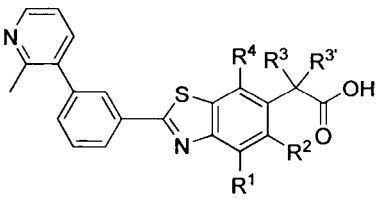

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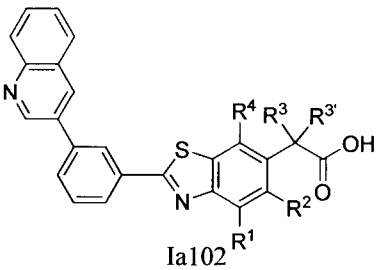

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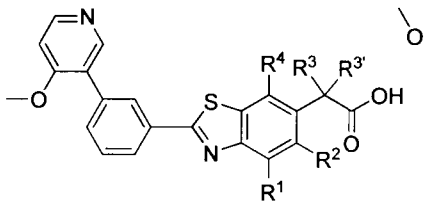

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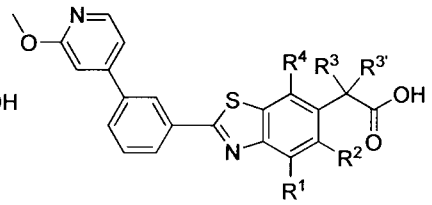

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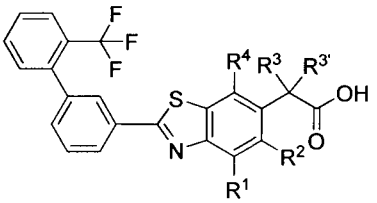

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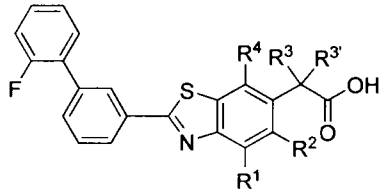

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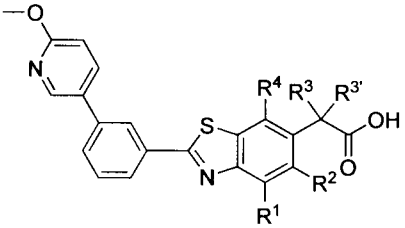

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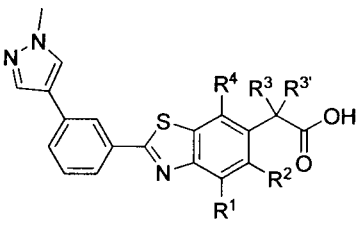

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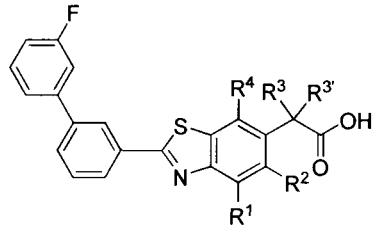

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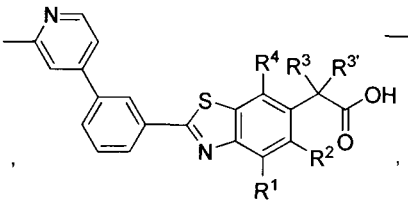

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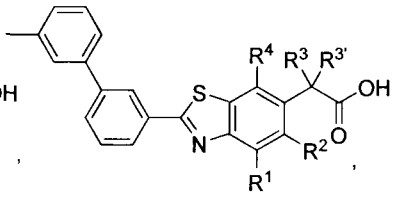

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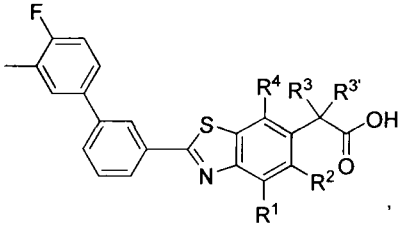

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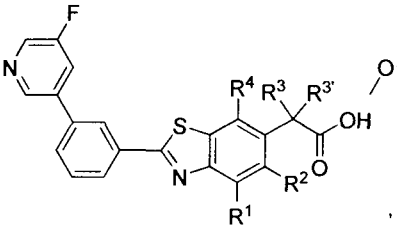

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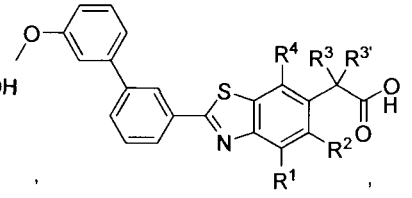

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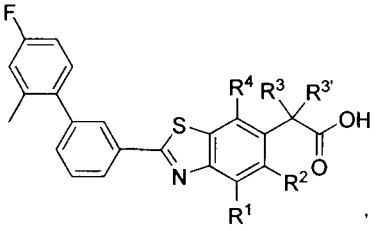

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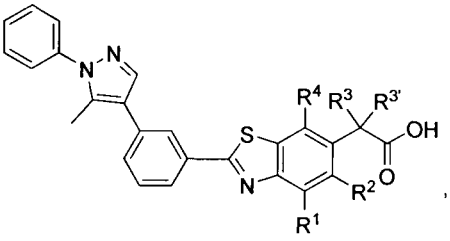

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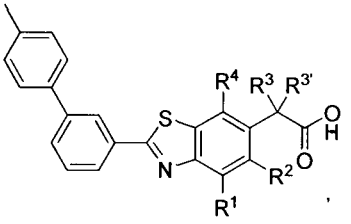

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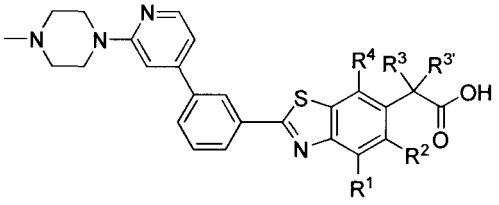

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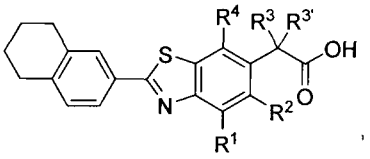

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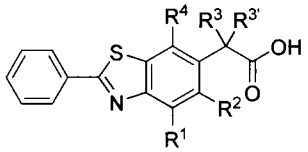

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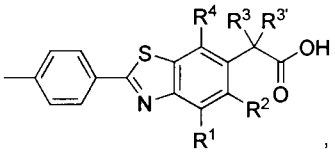

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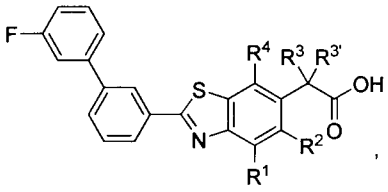

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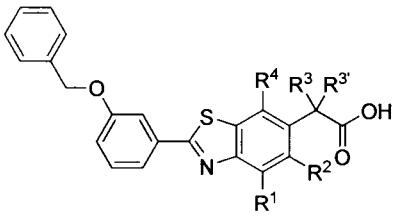

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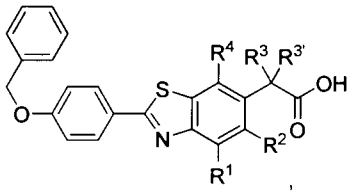

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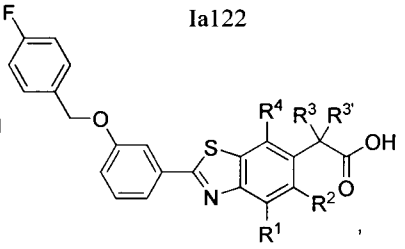

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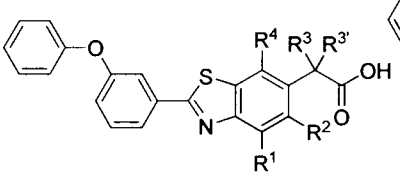

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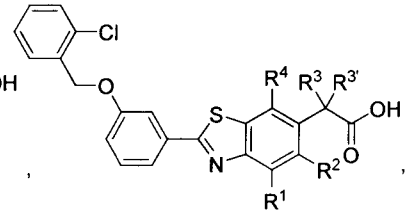

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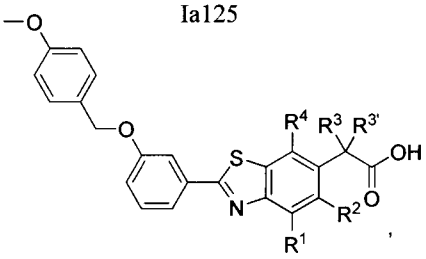

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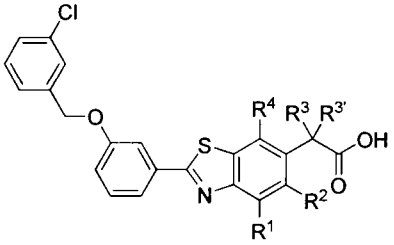

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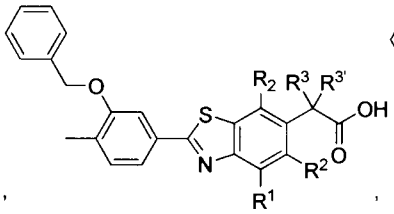

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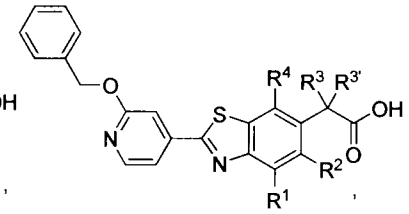

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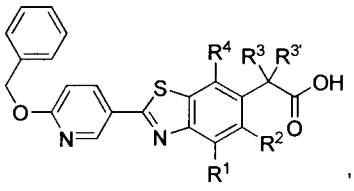

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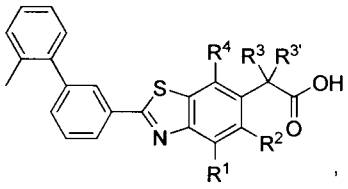

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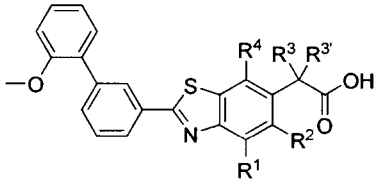

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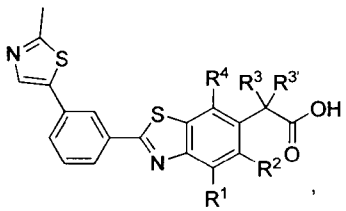
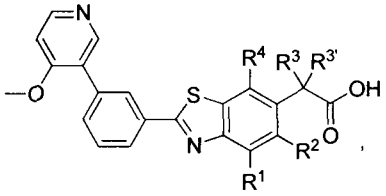


Ia135



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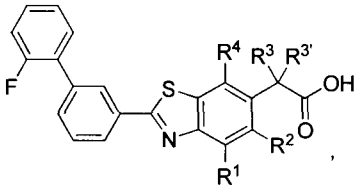

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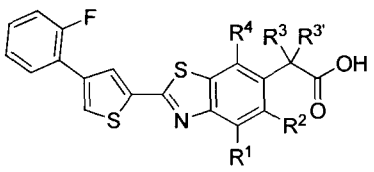

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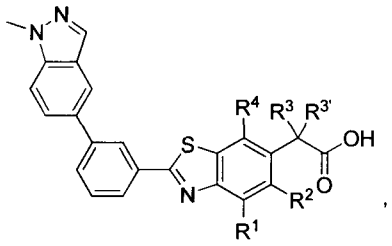
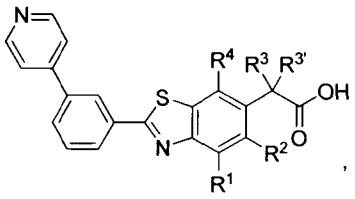
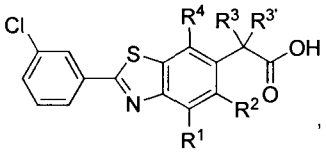


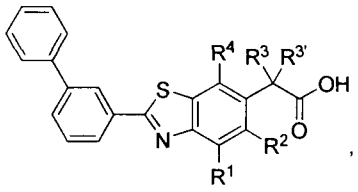
Ia139



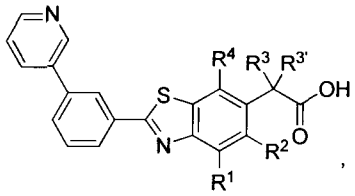
Ia140



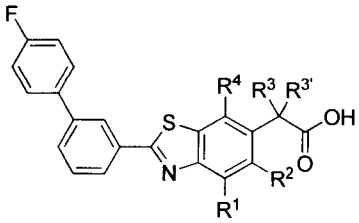
Ia141



Ia142

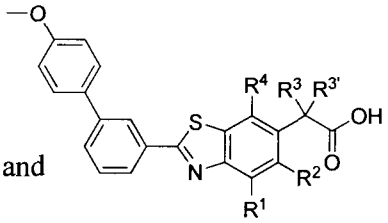


Ia143



Ia144

and



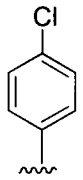
Ia145

and salts thereof.

In one 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

R^4 is:

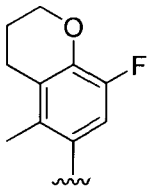


and salts thereof.

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

R^4 is:

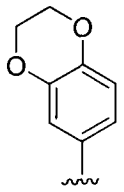


and salts thereof.

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

R^4 is:

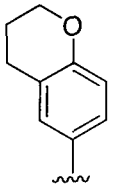


and salts thereof.

In another embodiment of the invention, 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

R^4 is:

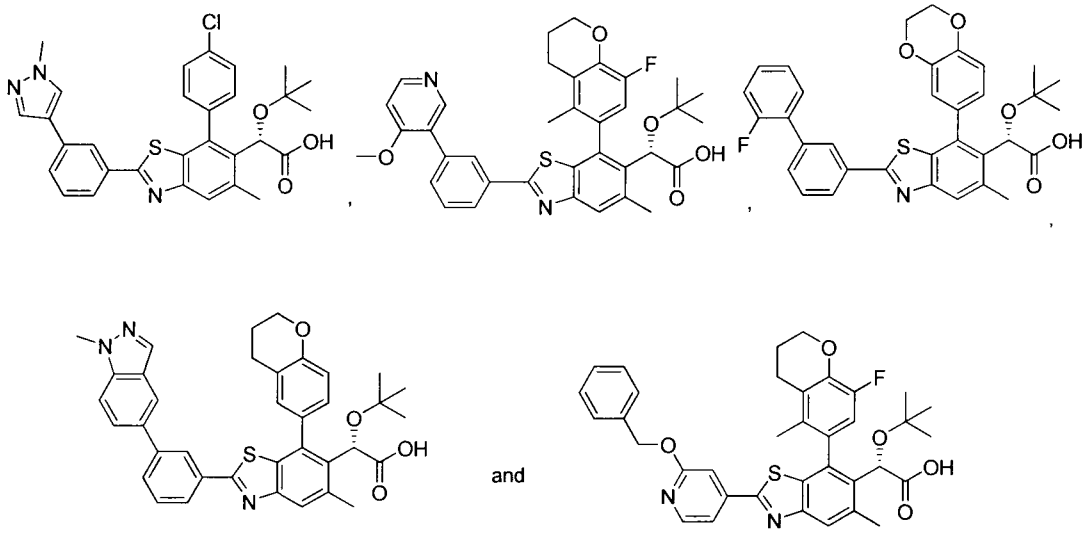


and salts thereof.

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; R^3 is -O(C_1-C_6)alkyl and the stereochemistry of the carbon bearing the R^3 (-O(C_1-C_6)alkyl) group is (S).

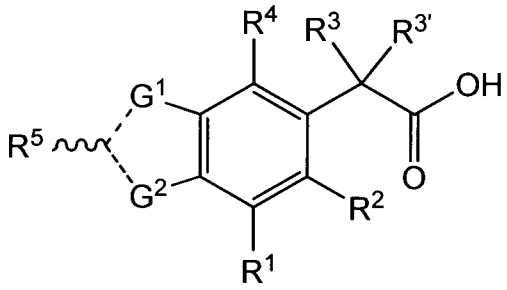
In another embodiment of the invention the compounds of formula I are selected from the compounds of formulas Ia100-Ia145 wherein $R^{3'}$ is H; R^3 is -O(C_1-C_6)alkyl and the stereochemistry of the carbon bearing the R^3 (-O(C_1-C_6)alkyl) group is (R).

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:



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, $(C_1$-$C_6)$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, 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-$SO_2-N(R^9)R^{10}$, wherein each R^9 is independently selected from H, $(C_1$-$C_6)$alkyl and $(C_3$-$C_7)$cycloalkyl, and 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^{1b} is selected from:

a) $-(C_1$-$C_6)$alkyl-$O-(C_1$-$C_6)$alkyl-$(C_3$-$C_7)$carbocycle, $-(C_1$-$C_6)$alkyl-$S-(C_1$-$C_6)$alkyl-$(C_3$-$C_7)$ carbocycle, $-(C_1$-$C_6)$alkyl-$S(O)-(C_1$-$C_6)$alkyl-$(C_3$-$C_6)$ carbocycle, $-(C_1$-$C_6)$alkyl-$SO_2-(C_1$-$C_6)$alkyl-$(C_3$-$C_7)$carbocycle, $-(C_1$-$C_6)$alkyl-$SO_2-(C_1$-$C_6)$alkyl-Z^{13}, $-C(O)-(C_1$-$C_6)$alkyl-Z^{13}, $-O-(C_1$-$C_6)$alkyl-Z^{13}, $-S-(C_1$-$C_6)$alkyl-Z^{13}, $-S(O)-(C_1$-$C_6)$alkyl-Z^{13}, $-SO_2-(C_1$-$C_6)$alkyl-Z^{13}, $-(C_1$-$C_6)$alkyl-Z^{14}, $-(C_1$-$C_6)$alkyl-$C(O)-(C_1$-$C_6)$alkyl-Z^{13}, $-(C_1$-$C_6)$alkyl-$C(O)-O(C_1$-$C_6)$alkyl-Z^{13}, $-(C_1$-$C_6)$alkyl-$O-(C_1$-$C_6)$alkyl-Z^{13}, $-(C_1$-$C_6)$alkyl-$S-(C_1$-$C_6)$alkyl-Z^{13}, $-(C_2$-$C_6)$alkenyl-$(C_1$-$C_6)$haloalkyl, $-(C_2$-$C_6)$alkynyl-$(C_1$-$C_6)$haloalkyl, - $(C_3$-$C_7)$halocarbocycle,-$NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3$-$C_7)$carbocycle, $-NR_aSO_2O$aryl, $-(C_2$-$C_6)$alkenyl-$(C_3$-$C_7)$carbocycle, $-(C_2$-$C_6)$alkenyl-aryl, $-(C_2$-$C_6)$alkenyl-heteroaryl, $-(C_2$-$C_6)$alkenyl-heterocycle, $-(C_2$-$C_6)$alkynyl-$(C_3$-$C_7)$carbocycle, $-(C_2$-$C_6)$alkynyl-aryl, $-(C_2$-$C_6)$alkynyl-heteroaryl $-(C_2$-$C_6)$alkynyl-heterocycle, $-(C_3$-$C_7)$carbocycle-Z^1 or $-(C_1$-$C_6)$haloalkyl-Z^3, wherein any $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_3$-$C_7)$carbocycle, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, aryl or heteroaryl, either alone or as part of a group, is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 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) Z^1 groups, or wherein two Z^1 groups together with the atom or atoms to which they are attached optionally form a carbocycle or heterocycle wherein the carbocycle or heterocycle is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups;

c) $(C_1$-$C_6)$alkyl, wherein $(C_1$-$C_6)$alkyl is substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^2 groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1groups;

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 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^1groups;

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) Z^5 groups and optionally substituted with one or more Z^1groups;

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^1groups;

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)alkylC(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^1groups; and

h) nitro and cyano;

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 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-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) -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-(C_3-C_7)carbocycle, -(C_1-C_6)alkyl-S-(C_1-C_6)alkyl-(C_3-C_7)carbocycle, -(C_1-C_6)alkyl-S(O)-(C_1-C_6)alkyl-(C_3-C_7)carbocycle, -(C_1-C_6)alkyl-SO_2-(C_1-C_6)alkyl-(C_3-C_7)carbocycle, -(C_2-C_6)alkenyl-(C_1-C_6)haloalkyl, -(C_2-C_6)alkynyl-(C_1-C_6)haloalkyl, -(C_1-C_6)alkyl-SO_2-(C_1-C_6)alkyl-Z^{13}, -C(O)-(C_1-C_6)alkyl-Z^{13}, -O-(C_1-C_6)alkyl-Z^{13}, -S-(C_1-C_6)alkyl-Z^{13}, -S(O)-(C_1-C_6)alkyl-Z^{13}, -SO_2-(C_1-C_6)alkyl-Z^{13}, -(C_1-C_6)alkyl-Z^{14}, -(C_1-C_6)alkyl-C(O)-(C_1-C_6)alkyl-Z^{13}, -(C_1-C_6)alkyl-C(O)-O(C_1-C_6)alkyl-Z^{13}, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-Z^{13}, -(C_1-C_6)alkyl-S-(C_1-C_6)alkyl-Z^{13}, -(C_3-C_7)halocarbocycle, -$NR_aSO_2NR_cR_d$, -NR_aSO_2O(C_3-C_7)carbocycle, -NR_aSO_2Oaryl, -(C_2-C_6)alkenyl-(C_3-C_7)carbocycle, -(C_2-C_6)alkenyl-aryl, -(C_2-C_6)alkenyl-heteroaryl, -(C_2-C_6)alkenyl-heterocycle, -(C_2-C_6)alkynyl-(C_3-C_7)carbocycle, -(C_2-C_6)alkynyl-aryl, -(C_2-C_6)alkynyl-heteroaryl, -(C_2-C_6)alkynyl-heterocycle, –(C_3-C_7)carbocycle-Z^1 or –(C_1-C_6)haloalkyl-Z^3, wherein any (C_1-C_6)alkyl, -(C_1-C_6)haloalkyl, (C_3-C_7)carbocycle, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, aryl or heteroaryl, either alone or as part of a group, is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1groups;

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) Z^1 groups, wherein two Z^1 groups together with the atom or atoms to which they are attached optionally form a (C_3-C_7)carbocycle or heterocycle wherein the (C_3-C_6)carbocycle or heterocycle is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups;

c) (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is substituted with one or more Z^2 groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1groups;

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 (e.g. 1, 2, 3, 4 or 5) Z^1groups, and wherein -X(C_2-C_6)alkenyl, -X(C_2-C_6)alkynyl and -X(C_3-C_7)carbocycle are each 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^1groups;

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

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 (e.g. 1, 2, 3, 4 or 5) Z^1groups;

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)alkylC(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 (e.g. 1, 2, 3, 4 or 5) Z^1groups; and

h) nitro and cyano;

or R^1 and R^2 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 Z^1 groups;

or R^1 and R^2 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 each independently substituted with one or more (e.g. 1, 2 or 3) Z^7 or Z^8 groups, or wherein when two Z^7 groups are on same atom the two Z^7 groups together with the atom to which they are attached optionally form a (C_3-C_7)carbocycle or 4, 5 or 6-membered heterocycle;

R^{3a} is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl, -(C_1-C_6)alkyl-aryl, -(C_1-C_6)alkyl-heterocycle, -(C_1-C_6)alkyl-heteroaryl, -O(C_1-C_6)alkyl, -O(C_1-C_6)haloalkyl, -O(C_2-C_6)alkenyl, -O(C_2-C_6)alkynyl, -O(C_3-C_7)cycloalkyl, -Oaryl, -O(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl, -O(C_1-C_6)alkyl-aryl, -O(C_1-C_6)alkyl-heterocycle and -O(C_1-C_6)alkyl-heteroaryl, wherein any (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl, -(C_1-C_6)alkyl-aryl, -(C_1-C_6)alkyl-heterocycle, -(C_1-C_6)alkyl-heteroaryl, -O(C_1-C_6)alkyl, -O(C_1-C_6)haloalkyl, -O(C_2-C_6)alkenyl, -O(C_2-C_6)alkynyl, -O(C_3-C_7)cycloalkyl, -Oaryl, -O(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl, -O(C_1-C_6)alkyl-aryl, -O(C_1-C_6)alkyl-heterocycle or -O(C_1-C_6)alkyl-heteroaryl of R^{3a} is optionally substituted with one or more (e.g. 1, 2 or 3) groups selected from (C_1-C_6)alkyl, -O(C_1-C_6)alkyl, halo, oxo and -CN; and

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

R^{3b} is -(C_3-C_7)carbocycle, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkylOH, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-Z^{12}, -(C_1-C_6)alkyl-O-(C_2-C_6)alkenyl-Z^{12}, -(C_2-C_6)alkyl-O-(C_2-C_6)alkynyl-Z^{12}, -(C_1-C_6)alkyl-S-(C_1-C_6)alkyl-Z^{12}, -(C_1-C_6)alkyl-S-(C_2-C_6)alkenyl-Z^{12}, -(C_2-C_6)alkyl-S-(C_2-C_6)alkynyl-Z^{12}, -(C_1-C_6)alkyl-S(O)-(C_1-C_6)alkyl-Z^{12}, -(C_1-C_6)alkyl-S(O)-(C_2-C_6)alkenyl-Z^{12},

-(C_2-C_6)alkyl-S(O)-(C_2-C_6)alkynyl-Z^{12}, -(C_1-C_6)alkyl-SO_2-(C_1-C_6)alkyl-Z^{12}, -(C_1-C_6)alkyl-SO_2-(C_2-C_6)alkenyl-Z^{12}, -(C_2-C_6)alkyl-SO_2-(C_2-C_6)alkynyl-Z^{12}, -(C_2-C_6)alkyl-NR_aR_b, -(C_2-C_6)alkylOC(O)-NR_cR_d, -(C_2-C_6)alkyl-NR_a-C(O)-OR_b, -(C_2-C_6)alkyl-NR_a-C(O)-NR_aR_b, -(C_1-C_6)alkyl-SO_2(C_1-C_6)alkyl, -(C_1-C_6)alkyl-$SO_2NR_cR_d$, -(C_1-C_6)alkyl-$NR_aSO_2NR_cR_d$, -(C_1-C_6)alkyl-NR_aSO_2O(C_3-C_7)carbocycle, -(C_1-C_6)alkyl-NR_aSO_2Oaryl, -(C_1-C_6)alkyl-NR_a-SO_2-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-NR_a-SO_2-(C_1-C_6)haloalkyl, -(C_1-C_6)alkyl-NR_a-SO_2-(C_2-C_6)alkenyl, -(C_1-C_6)alkyl-NR_a-SO_2-(C_2-C_6)alkynyl, -(C_1-C_6)alkyl-NR_a-SO_2-(C_3-C_7)carbocycle, -(C_1-C_6)alkyl-NR_a-SO_2-(C_3-C_7)halocarbocycle, -(C_1-C_6)alkyl-NR_a-SO_2-aryl, -(C_1-C_6)alkyl-NR_a-SO_2-heteroaryl, -(C_1-C_6)alkyl-NR_a-SO_2-heterocycle, -O(C_1-C_6)alkyl-NR_aR_b, -O(C_1-C_6)alkylOC(O)-NR_cR_d, -O(C_1-C_6)alkyl-NR_a-C(O)-OR_b, -O(C_1-C_6)alkyl-NR_a-C(O)-NR_aR_b, -O(C_1-C_6)alkyl-NR_a-SO_2-(C_1-C_6)alkyl, -O(C_1-C_6)alkyl-NR_a-SO_2-(C_1-C_6)haloalkyl, -O(C_1-C_6)alkyl-NR_a-SO_2-(C_2-C_6)alkenyl, -O(C_1-C_6)alkyl-NR_a-SO_2-(C_2-C_6)alkynyl, -O(C_1-C_6)alkyl-NR_a-SO_2-(C_3-C_7)carbocycle, -O(C_1-C_6)alkyl-NR_a-SO_2-(C_3-C_7)halocarbocycle, -O(C_1-C_6)alkyl-NR_a-SO_2-aryl, -O(C_1-C_6)alkyl-NR_a-SO_2-heteroaryl, -O(C_1-C_6)alkyl-NR_a-SO_2-heterocycle, -O(C_1-C_6)alkyl-NR_a-SO_2-NR_aR_b, -O(C_1-C_6)alkyl-NR_a-SO_2-(C_3-C_7)carbocycle, -O(C_1-C_6)alkyl-NR_a-SO_2-(C_3-C_7)halocarbocycle, -O(C_1-C_6)alkyl-NR_a-SO_2-aryl, -O(C_1-C_6)alkyl-$NR_aSO_2NR_cR_d$, -O(C_1-C_6)alkyl-NR_aSO_2O(C_3-C_7)carbocycle, -O(C_1-C_6)alkyl-NR_aSO_2Oaryl, -Oheteroaryl, -Oheterocycle, -Sheteroaryl, -Sheterocycle, -S(O)heteroaryl, -S(O)heterocycle, -SO_2heteroaryl or -SO_2heterocycle, wherein any (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, aryl, (C_3-C_7)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) Z^1 groups; and

$R^{3b'}$ is H, (C_1-C_6)alkyl or -O(C_1-C_6)alkyl; or

R^{3b} and $R^{3b'}$ together with the carbon to which they are attached form a heterocycle or (C_3-C_7)carbocycle,which heterocycle or (C_3-C_7)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) Z^1 groups;

R^{4a} is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and 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, (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^{4b} is selected from;

a) $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl and $(C_2\text{-}C_6)$alkynyl, wherein $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl are each optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups;

b) $(C_3\text{-}C_{14})$carbocycle, wherein $(C_3\text{-}C_{14})$carbocycle is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups, or wherein two Z^1 groups together with the atom or atoms to which they are attached optionally form a $(C_3\text{-}C_7)$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) Z^1 groups, or wherein two Z^1 groups together with the atom or atoms to which they are attached optionally form a $(C_3\text{-}C_7)$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 Z^7 groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups; or

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 (e.g. 1, 2, 3, 4 or 5) Z^1 groups; and $R^{3b'}$ is H or $(C_1\text{-}C_6)$alkyl, $-O(C_1\text{-}C_6)$alkyl;

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 X is independently selected from O, -C(O)-, -C(O)O-, -S-, -S(O)-, $-SO_2$-, $-(C_1\text{-}C_6)$alkylO-, $-(C_1\text{-}C_6)$alkylC(O)-, $-(C_1\text{-}C_6)$alkylC(O)O-, $-(C_1\text{-}C_6)$alkylS-, $-(C_1\text{-}C_6)$alkylS(O)- and $-(C_1\text{-}C_6)$alkylSO_2-;

each Z^1 is independently selected from halo, $-NO_2$, -OH, $=NOR_a$, -SH, -CN, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$haloalkyl, $(C_3\text{-}C_7)$carbocycle, $(C_3\text{-}C_7)$halocarbocycle, aryl, heteroaryl, heterocycle, $-O(C_1\text{-}C_6)$alkyl, $-O(C_2\text{-}C_6)$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-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, -$SO_2NR_cR_d$, -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^1, 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 Z^2 is independently selected from -NO_2, -CN, spiro-heterocycle, bridge-heterocycle, spiro-bicyclic carbocycle, bridged-bicyclic carbocycle, NR_aSO_2(C_3-C_7)carbocycle, -NR_aSO_2aryl, -NR_aSO_2heteroaryl, -$NR_aSO_2NR_cR_d$, -NR_aSO_2O(C_3-C_7)carbocycle and -NR_aSO_2Oaryl;

each Z^3 is independently selected from -NO_2, -CN, -OH, oxo, =NOR_a, thioxo, aryl, heterocycle, heteroaryl, (C_3-C_7)halocarbocycle, -O(C_1-C_6)alkyl, -O(C_3-C_7)carbocycle, -O(C_3-C_7)halocarbocycle, -Oaryl, -Oheterocycle, -Oheteroaryl, -S(C_1-C_6)alkyl, -S(C_3-C_7)carbocycle, -S(C_3-C_7)halocarbocycle, -Saryl, -Sheterocycle, -Sheteroaryl, -S(O)(C_1-C_6)alkyl, -S(O)(C_3-C_7)carbocycle, -S(O) (C_3-C_7)halocarbocycle, -S(O)aryl, -S(O)heterocycle, -S(O)heteroaryl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_7)carbocycle, -SO_2(C_3-C_7)halocarbocycle, SO_2aryl, -SO_2heterocycle, -SO_2heteroaryl, -NR_aR_b, -$NR_aC(O)R_b$, -$C(O)NR_cR_d$, -$SO_2NR_cR_d$, -$NR_aSO_2NR_cR_d$, -NR_aSO_2O(C_3-C_7)carbocycle and -NR_aSO_2Oaryl;

each Z^4 is independently selected from halogen, -(C_1-C_6)alkyl, (C_3-C_7)carbocycle, -(C_1-C_6)haloalkyl, -NO_2, -CN, -OH, oxo, =NOR_a, thioxo, -aryl, -heterocycle, -heteroaryl, -(C_3-C_7)halocarbocycle, -O(C_1-C_6)alkyl, -O(C_3-C_7)carbocycle, -O(C_3-C_7)halocarbocycle, -Oaryl, -Oheterocycle, -Oheteroaryl, -S(C_1-C_6)alkyl, -S(C_3-C_7)carbocycle, -S(C_3-C_7)halocarbocycle, -Saryl, -Sheterocycle, -Sheteroaryl, -S(O)(C_1-C_6)alkyl, -S(O)(C_3-C_7)carbocycle, -S(O)(C_3-C_7)halocarbocycle, -S(O)aryl, -S(O)heterocycle, -S(O)heteroaryl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_7)carbocycle, -SO_2(C_3-C_7)halocarbocycle, SO_2aryl, -SO_2heterocycle, -SO_2heteroaryl, -NR_aR_b,

$-NR_aC(O)R_a$, $-C(O)NR_cR_d$, $-SO_2NR_cR_d$, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3-C_7)$carbocycle and $-NR_aSO_2O$aryl;

each Z^5 is independently selected from $-NO_2$, -CN, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3-C_7)$carbocycle, $-NR_aSO_2O$aryl, $-NR_aSO_2(C_1-C_6)$alkyl, $-NR_aSO_2(C_2-C_6)$alkenyl, $-NR_aSO_2(C_2-C_6)$alkynyl, $-NR_aSO_2(C_3-C_7)$carbocycle, $-NR_aSO_2(C_3-C_7)$halocarbocycle, $-NR_aSO_2$aryl, $-NR_aSO_2$heteraryl, $-NR_aSO_2$heteroaryl, $-NR_aSO_2$heterocycle, $-NR_aC(O)$alkyl, $-NR_aC(O)$alkenyl, $-NR_aC(O)$alkynyl, $-NR_aC(O)$ (C_3-C_7)carbocycle, $-NR_aC(O)(C_3-C_7)$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 Z^6 is independently selected from $-NO_2$, -CN, $-NR_aR_a$, $NR_aC(O)R_b$,$-C(O)NR_cR_d$, (C_3-C_7)halocarbocycle, aryl, heteroaryl, heterocycle, -Oaryl, -Oheteroaryl, -Oheterocycle, $-O(C_3-C_7)$halocarbocycle, $-O(C_1-C_6)$alkyl, $-O(C_3-C_7)$carbocycle, $-O(C_1-C_6)$haloalkyl, -Saryl, -Sheteroaryl, -Sheterocycle, $-S(C_3-C_7)$halocarbocycle, $-S(C_1-C_6)$alkyl, $-S(C_3-C_7)$carbocycle, $-S(C_1-C_6)$haloalkyl, -S(O)aryl, -S(O)heteroaryl, -S(O)heterocycle, $-S(O)(C_3-C_7)$halocarbocycle, $-S(O)(C_1-C_6)$alkyl, $-S(O)(C_3-C_7)$carbocycle, $-S(O)(C_1-C_6)$haloalkyl, $-SO_2$aryl, $-SO_2$heteroaryl, $-SO_2$heterocycle, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$haloalkyl, $-SO_2(C_3-C_7)$carbocycle, $-SO_2(C_3-C_7)$halocarbocycle, $-SO_2NR_cR_d$, $-NR_aSO_2(C_3-C_7)$halocarbocycle, $-NR_aSO_2$aryl, $-NR_aSO_2$heteraryl, $-NR_aSO_2$heteroaryl, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3-C_7)$carbocycle and $-NR_aSO_2O$aryl, wherein any aryl, of Z^6, either alone or as part of a group, is otionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) halogen, -OH, $-O(C_1-C_6)$alkyl, -CN or $-(C_1-C_6)$alkyl;

each Z^7 is independently selected from $-NO_2$, $=NOR_a$, -CN, $-(C_1-C_6)$alkyl-Z^{12}, $-(C_2-C_6)$alkenyl-Z^{12}, $-(C_2-C_6)$alkenylOH, $-(C_2-C_6)$alkynyl-Z^{12}, $-(C_2-C_6)$alkynyl-OH, $-(C_1-C_6)$haloalkyl-Z^{12}, $-(C_1-C_6)$haloalkylOH, $-(C_3-C_7)$carbocycle-Z^{12}, $-(C_3-C_7)$carbocycleOH, $-(C_3-C_7)$halocarbocycle, $-(C_1-C_6)$alkylNRcRd, $-(C_1-C_6)$alkylNRaC(O)Ra, $-(C_1-C_6)$alkylNRaSO2Ra, aryl, heteroaryl, heterocycle, $-O(C_1-C_6)$alkyl-Z^{12}, $-O(C_2-C_6)$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, $-O(C_1-C_6)$alkylNRcRd, $-O(C_1-C_6)$alkylNRaC(O)Ra, $-O(C_1-C_6)$alkylNRaSO2Ra, -Oheteroaryl, -Oheterocycle, $-S(C_1-C_6)$alkyl-Z^{12}, $-S(C_2-C_6)$alkenyl, $-S(C_2-C_6)$alkynyl, $-S(C_1-C_6)$haloalkyl, $-S(C_3-C_7)$carbocycle, $-S(C_3-C_7)$halocarbocycle, $-S(C_1-C_6)$alkylNRcRd, $-S(C_1-C_6)$alkylNRaC(O)Ra, $-S(C_1-C_6)$alkylNRaSO2Ra, –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, $-S(O)(C_3-C_7)$carbocyle, $-S(O)(C_3-C_7)$halocarbocycle, $-SO_2(C_1-C_6)$alkyl, $-S(O)(C_1-C_6)$alkylNRcRd, $-S(O)(C_1-C_6)$alkylNRaC(O)Ra, $-S(O)(C_1-C_6)$alkylNRaSO2Ra, –S(O)aryl, -S(O)heteroaryl, -S(O)heterocycle, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_2-C_6)$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, $-SO_2$aryl, $-SO_2$heteroaryl, $-SO_2$heterocycle, $-SO_2(C_1-C_6)$alkylNR$_c$R$_d$, $-SO_2(C_1-C_6)$alkylNR$_a$C(O)R$_a$, $-SO_2(C_1-C_6)$alkylNR$_a$SO$_2$R$_a$, $-SO_2$NR$_c$R$_d$, $-NR_aC(O)OR_b$, $-NR_aC(O)NR_cR_d$, $-NR_aSO_2R_b$, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3-C_7)$carbocycle, $-NR_aSO_2O$aryl, $-OS(O)_2R_a$, $-C(O)NR_cR_d$, 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)carbocycle, (C_3-C_7)halocarbocycle, aryl, heteroaryl or heterocycle of Z^7, 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 Z^8 is independently selected from $-NO_2$ or -CN;

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 $-N((C_1-C_6)alkyl)_2$;

ii) (C_1-C_6)alkyl optionally 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;

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^{12} is independently selected from $-NO_2$, $=NOR_a$, thioxo, aryl, heterocycle, heteroaryl, (C_3-C_7)halocarbocycle, (C_3-C_7)carbocycle, $-O(C_3-C_7)$carbocycle, $-O(C_3-C_7)$halocarbocyle, -Oaryl, -Oheterocycle, -Oheteroaryl, $-S(C_1-C_6)$alkyl, $-S(C_3-C_7)$carbocyle, $-S(C_3-C_7)$halocarbocyle, -Saryl, -Sheterocycle, -Sheteroaryl, $-S(O)(C_1-C_6)$alkyl, $-S(O)(C_3-C_7)$carbocyle, $-S(O)(C_3-C_7)$halocarbocycle, -S(O)aryl, -S(O)heterocycle, -S(O)heteroaryl, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_3-C_7)$carbocycle, $-SO_2(C_3-C_7)$halocarbocycle, SO_2aryl, $-SO_2$heterocycle, $-SO_2$heteroaryl, $-NR_aR_a$, $-NR_aC(O)R_b$, $-C(O)NR_cR_d$, $-SO_2NR_cR_d$, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3-C_7)$carbocyle and $-NR_aSO_2O$aryl;

each Z^{13} is independently selected from $-NO_2$, -OH, $=NOR_a$, -SH, -CN, (C_3-C_7)halocarbocycle, $-O(C_1-C_6)$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, $-S(C_3-C_7)$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, -S(O)aryl, -S(O)heteroaryl, -S(O)heterocycle, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_2-$

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, -$SO_2NR_cR_d$, -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^{13}, 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 Z^{14} is independently selected from -NO_2, =NOR_a, -CN, -(C_3-C_7)halocarbocycle, -O(C_3-C_7)halocarbocycle, -S(C_3-C_7)halocarbocycle, -S(O)(C_3-C_7)halocarbocycle, -SO_2(C_3-C_7)halocarbocycle, -$NR_aSO_2NR_cR_d$, -NR_aSO_2O(C_3-C_7)carbocycle, -NR_aSO_2Oaryl, -$OS(O)_2R_a$, wherein any -(C_3-C_7)halocarbocycle of Z^{14}, 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 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-C_6)alkyl-heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{16} groups and optionally subsituted with one or more (e.g. 1, 2, 3, 4 or 5) 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 subsituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups;

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, -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-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, -$SO_2NR_cR_d$, -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, $-NR_aSO_2O$aryl, $-OS(O)_2R_a$, $-C(O)R_a$, $-C(O)OR_b$, $-C(O)NR_cR_d$, 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 (e.g. 1, 2, 3, 4 or 5) 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 (e.g. 1, 2, 3, 4 or 5) 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 (e.g. 1, 2, 3, 4 or 5) halogen, OH and cyano;

R_c and R_d are each independently selected from H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)carbocycle, aryl, aryl(C_1-C_6)alkyl-, heterocycle, 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_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;

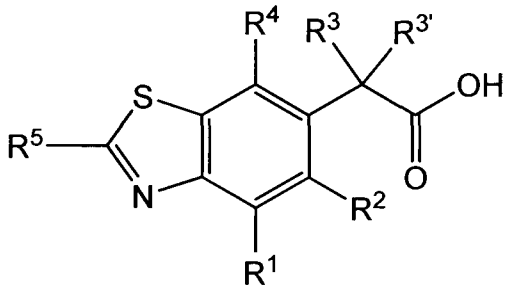
each R_e is independently selected from $-OR_a$, (C_1-C_6)alkyl or (C_3-C_7)carbocycle, wherein (C_1-C_6)alkyl and (C_3-C_7)carbocycle are each independently substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^6 groups and optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^1 groups; (C_2-C_6)haloalkyl, (C_2-C_6)alkenyl and (C_2-C_6)alkynyl, wherein any (C_2-C_6)haloalkyl, (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; 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) Z_5 groups;

each R_f is independently selected from $-R_g$, $-OR_a$, $-(C_1-C_6)$alkyl-Z^6, $-SO_2R_g$, $-C(O)R_g$, $C(O)OR_g$ and $-C(O)NR_eR_g$; and

each R_g is independently selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$carbocycle $(C_1\text{-}C_6)$haloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, aryl, heterocycle and heteroaryl, wherein any $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$carbocycle -$(C_1\text{-}C_6)$haloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$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 $(C_1\text{-}C_6)$alkyl;

R^3 is -$O(C_1\text{-}C_6)$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, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$haloalkyl, $(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, -OH, -$O(C_1\text{-}C_6)$alkyl, -SH, -$S(C_1\text{-}C_6)$alkyl, NH_2, -$NH(C_1\text{-}C_6)$alkyl and -$N((C_1\text{-}C_6)\text{alkyl})_2$, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with hydroxy, -$O(C_1\text{-}C_6)$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, $-NO_2$, -OH, $=NOR_a$, -SH, -CN, (C_1-C_6)alkyl, (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, $-O(C_1$-$C_6)$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, $-S(C_3$-$C_7)$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, $-SO_2$aryl, $-SO_2$heteroaryl, $-SO_2$heterocycle, $-SO_2NR_cR_d$, $-NR_cR_d$, $-NR_aC(O)R_a$, $-NR_aC(O)OR_b$, $-NR_aC(O)NR_cR_d$ $-NR_aSO_2R_b$, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3$-$C_7)$carbocycle, $-NR_aSO_2O$aryl, $-OS(O)_2R_a$, $-C(O)R_a$, $-C(O)OR_b$, $-C(O)NR_cR_d$, 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^1, either alone or as part of a group, is optionally substituted with one or more halogen, -OH, $-OR_b$, -CN, $-NR_aC(O)_2R_b$, heteroaryl, heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or $-S(O)_2NR_cR_d$;

each Z^5 is independently selected from $-NO_2$, -CN, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3$-$C_7)$carbocycle, $-NR_aSO_2O$aryl, $-NR_aSO_2(C_1$-$C_6)$alkyl, $-NR_aSO_2(C_2$-$C_6)$alkenyl, $-NR_aSO_2(C_2$-$C_6)$alkynyl, $-NR_aSO_2(C_3$-$C_7)$carbocycle, $-NR_aSO_2(C_3$-$C_7)$halocarbocycle, $-NR_aSO_2$aryl, $-NR_aSO_2$heteraryl, $-NR_aSO_2$heteroaryl, $-NR_aSO_2$heterocycle, $-NR_aC(O)$alkyl, $-NR_aC(O)$alkenyl, $-NR_aC(O)$alkynyl, $-NR_aC(O)$ (C_3-C_7)carbocycle, $-NR_aC(O)(C_3$-$C_7)$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 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 $-N((C_1$-$C_6)alkyl)_2$;

ii) (C_1-C_6)alkyl optionally substituted with one or more -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 one or more halo, (C_1-C_6)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-C_6)alkyl-heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more Z^{16} groups and optionally subsituted 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 subsituted with one or more Z^1 groups;

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-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, -$SO_2NR_cR_d$, -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 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 halogen, OH or cyano;

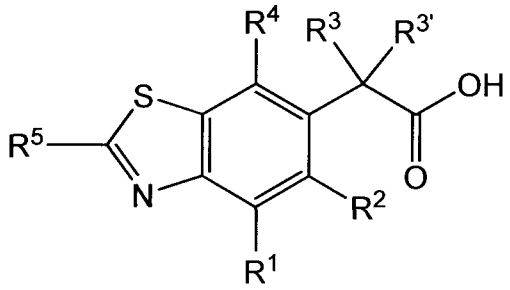
each R_b is independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)carbocycle, heterocycle, aryl, aryl(C_1-C_6)alkyl-, heteroaryl or heteroaryl(C_1-C_6)alkyl-, wherein any (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)carbocycle, heterocycle, aryl, or heteroaryl of 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, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_7)$carbocycle, aryl, aryl$(C_1$-$C_6)$alkyl-, heterocycle, 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_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 azetidinyl 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 $(C_1$-$C_6)$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 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, $-NO_2$, -OH, $=NOR_a$, -SH, -CN, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$haloalkyl, $(C_3$-$C_7)$carbocycle, $(C_3$-$C_7)$halocarbocycle, aryl, heteroaryl, heterocycle, $-O(C_1$-$C_6)$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, $-S(C_3$-$C_7)$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, $-SO_2$aryl, $-SO_2$heteroaryl, $-SO_2$heterocycle, $-SO_2NR_cR_d$, $-NR_cR_d$, $-NR_aC(O)R_a$, $-NR_aC(O)OR_b$, $-NR_aC(O)NR_cR_d$ $-NR_aSO_2R_b$, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3$-$C_7)$carbocycle, $-NR_aSO_2O$aryl, $-OS(O)_2R_a$, $-C(O)R_a$, $-C(O)OR_b$, $-C(O)NR_cR_d$, 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^1, either alone or as part of a group, is optionally substituted with one or more halogen, -OH, $-OR_b$, -CN, $-NR_aC(O)_2R_b$, heteroaryl, heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or $-S(O)_2NR_cR_d$;

each Z^5 is independently selected from $-NO_2$, -CN, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3$-$C_7)$carbocycle, $-NR_aSO_2O$aryl, $-NR_aSO_2(C_1$-$C_6)$alkyl, $-NR_aSO_2(C_2$-$C_6)$alkenyl, $-NR_aSO_2(C_2$-$C_6)$alkynyl, $-NR_aSO_2(C_3$-$C_7)$carbocycle, $-NR_aSO_2(C_3$-$C_7)$halocarbocycle, $-NR_aSO_2$aryl, $-NR_aSO_2$heteraryl, $-NR_aSO_2$heteroaryl, $-NR_aSO_2$heterocycle, $-NR_aC(O)$alkyl, $-NR_aC(O)$alkenyl, $-NR_aC(O)$alkynyl, $-NR_aC(O)$ $(C_3$-$C_7)$carbocycle, $-NR_aC(O)(C_3$-$C_7)$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 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$)_2$;

ii) $(C_1$-$C_6)$alkyl optionally substituted with one or more -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 one or more halo, $(C_1$-$C_6)$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-C_6)alkyl-heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more Z^{16} groups and optionally subsituted 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 subsituted with one or more Z^1 groups;

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-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, -$SO_2N R_c R_d$, -$NR_c R_d$, -$NR_a C(O)R_a$, -$NR_a C(O)OR_b$, -$NR_a C(O)NR_c R_d$, -$NR_a SO_2 R_b$, -$NR_a SO_2 NR_c R_d$, -$NR_a SO_2 O$(C_3-C_7)carbocycle, -$NR_a SO_2$Oaryl, -$OS(O)_2 R_a$, -$C(O)R_a$, -$C(O)OR_b$, -$C(O)NR_c R_d$, and -$OC(O)NR_c R_d$, 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 halogen, (C_1-C_6)alkyl, -OH, -OR_b, -CN, -$NR_a C(O)_2 R_b$, -heteroaryl, -heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or -$S(O)_2 NR_c R_d$;

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 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, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_7)$carbocycle, aryl, aryl$(C_1$-$C_6)$alkyl-, heterocycle, 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_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;

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

In one embodiment, the invention provides a compound of formula 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 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, $-NO_2$, -OH, $=NOR_a$, -SH, -CN, (C_1-C_6)alkyl, (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, $-O(C_1$-$C_6)$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, $-S(C_3$-$C_7)$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, $-SO_2$aryl, $-SO_2$heteroaryl, $-SO_2$heterocycle, $-SO_2NR_cR_d$, $-NR_cR_d$, $-NR_aC(O)R_a$, $-NR_aC(O)OR_b$, $-NR_aC(O)NR_cR_d$ $-NR_aSO_2R_b$, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3$-$C_7)$carbocycle, $-NR_aSO_2$Oaryl, $-OS(O)_2R_a$, $-C(O)R_a$, $-C(O)OR_b$, $-C(O)NR_cR_d$, 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^1, either alone or as part of a group, is optionally substituted with one or more halogen, -OH, $-OR_b$, -CN, $-NR_aC(O)_2R_b$, -heteroaryl, -heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or $-S(O)_2NR_cR_d$;

each Z^5 is independently selected from $-NO_2$, -CN, $-NR_aSO_2NR_cR_d$, $-NR_aSO_2O(C_3$-$C_7)$carbocycle, $-NR_aSO_2$Oaryl, $-NR_aSO_2(C_1$-$C_6)$alkyl, $-NR_aSO_2(C_2$-$C_6)$alkenyl, $-NR_aSO_2(C_2$-$C_6)$alkynyl, $-NR_aSO_2(C_3$-$C_7)$carbocycle, $-NR_aSO_2(C_3$-$C_7)$halocarbocycle, $-NR_aSO_2$aryl, $-NR_aSO_2$heteraryl, $-NR_aSO_2$heteroaryl, $-NR_aSO_2$heterocycle, $-NR_aC(O)$alkyl, $-NR_aC(O)$alkenyl, $-NR_aC(O)$alkynyl, $-NR_aC(O)$ (C_3-C_7)carbocycle, $-NR_aC(O)(C_3$-$C_7)$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 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)$_2$;

ii) (C_1-C_6)alkyl optionally substituted with one or more -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;

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-C_6)alkyl-heterocycle, wherein aryl, heteroaryl and heterocycle are each independently substituted with one or more Z^{16} groups and optionally subsituted 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 subsituted with one or more Z^1 groups;

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, -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-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, -$SO_2NR_cR_d$, -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 halogen, (C_1-C_6)alkyl, -OH, -OR_b, -CN, -$NR_aC(O)_2R_b$, -heteroaryl, -heterocycle, -Oheteroaryl, -Oheterocycle, -NHheteroaryl, -NHheterocycle or -$S(O)_2NR_cR_d$;

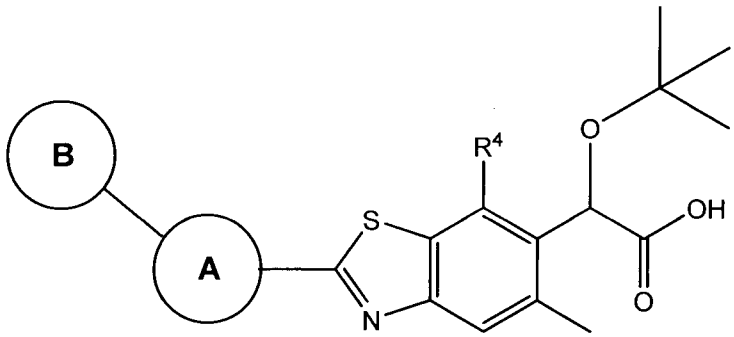
each R_a is independently H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)carbocycle, heterocycle, aryl, aryl(C_1-C_6)alkyl-, heteroaryl or heteroaryl(C_1-C_6)alkyl-, wherein any (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)carbocycle, heterocycle, aryl, or heteroaryl of R_a, either alone or as part of a group, is optionally substituted with one or more 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, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$carbocycle, aryl, aryl$(C_1\text{-}C_6)$alkyl-, heterocycle, heteroaryl or heteroaryl$(C_1\text{-}C_6)$alkyl-, wherein any $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$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':



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, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$haloalkyl, $(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, -OH, -O$(C_1\text{-}C_6)$alkyl, -SH, -S$(C_1\text{-}C_6)$alkyl, NH_2, -NH$(C_1\text{-}C_6)$alkyl and -N$((C_1\text{-}C_6)\text{alkyl})_2$, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with hydroxy, -O$(C_1\text{-}C_6)$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, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_3)$alkenyl, $(C_2\text{-}C_3)$alkynyl, $(C_1\text{-}C_3)$haloalkyl, $(C_3\text{-}C_7)$carbocycle, heterocycle, -O$(C_1\text{-}C_3)$alkyl, -O$(C_2\text{-}C_3)$alkenyl, -O$(C_2\text{-}C_3)$alkynyl, -NR_cR_d, -$NR_aC(O)R_a$, -$C(O)OR_b$, and -$C(O)NR_cR_d$, wherein any $(C_3\text{-}$

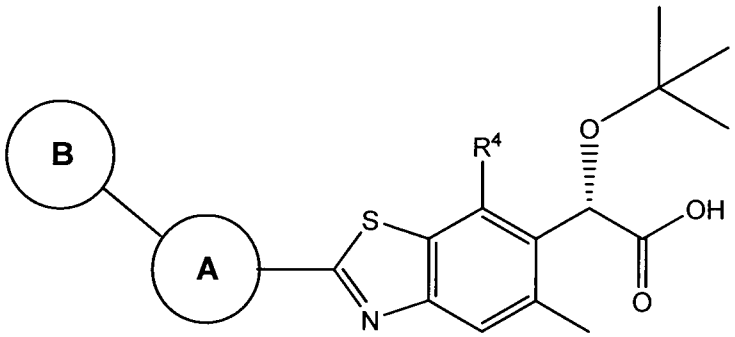
C_7)carbocycle or heterocycle of Z^{1a}, either alone or as part of a group, is optionally substituted with one or more halogen or $(C_1$-$C_6)$alkyl;

each Z^{1b} is independently selected from halo, CN, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$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 -$C(O)NR_cR_d$, wherein any $(C_3$-$C_7)$carbocycle or heterocycle of Z^{1b}, either alone or as part of a group, is optionally substituted with one or more 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;

or a salt thereof.

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



Ia'

or a pharmaceutically acceptable 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 (e.g., 1, 2, 3, 4 or 5) groups each independently selected from halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$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;

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, $(C_1$-$C_3)$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;

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;

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' 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 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.

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.

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.

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 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.

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.

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, $-OCH_3$, t-butyl, $-C(O)OH$, $-NH_2$, $-N(CH_3)_2$, $-OH$, $-C(O)NH_2$, benzyl and CN.

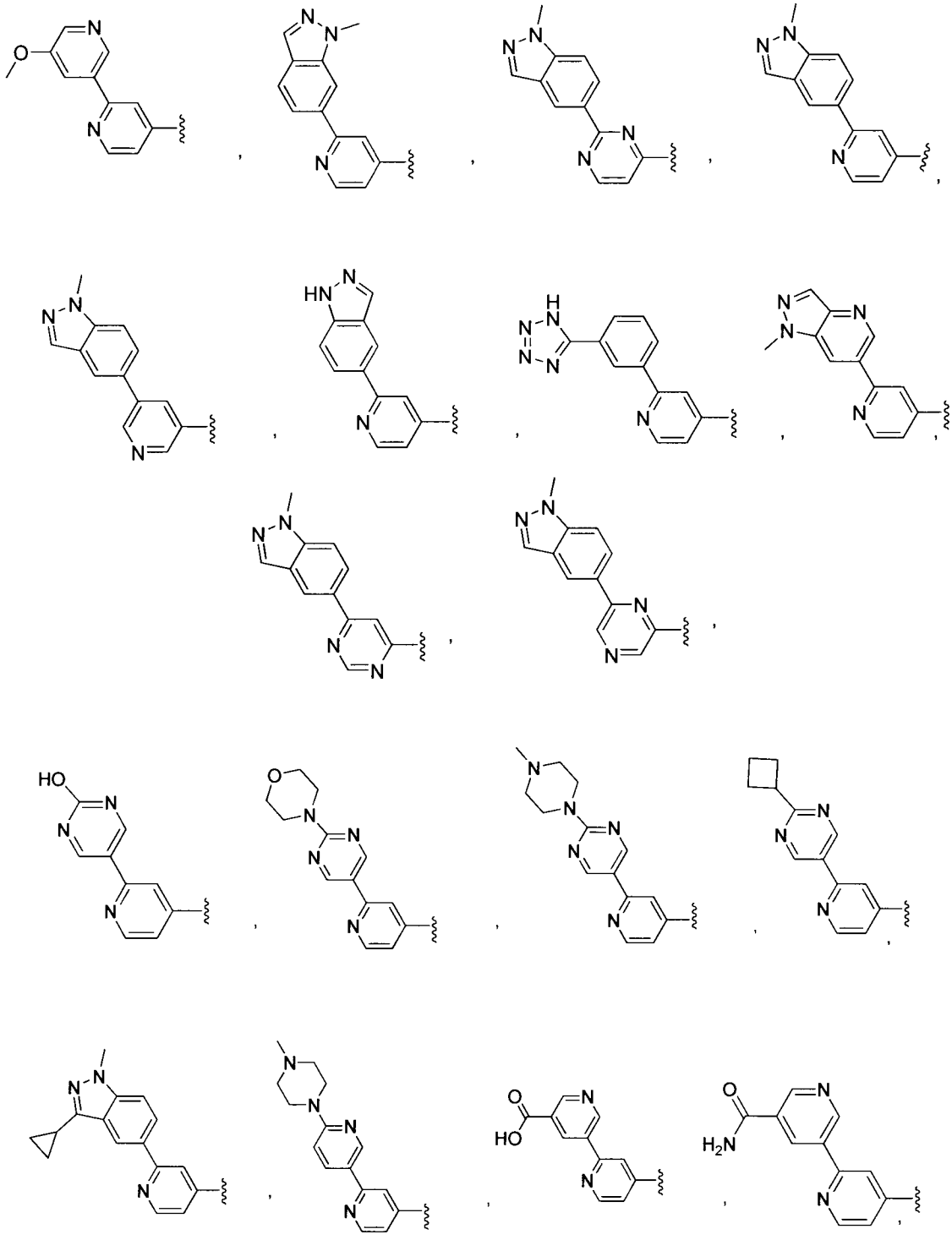
Another specific group of compounds of formula I' are compounds wherein each Z^{1b} is independently selected from methyl, cyclopropyl, cyclobutyl, N-methylpiperazinyl, morpholinyl, tetrazolyl, $-OCH_3$, $-C(O)OH$, $-OH$, $-C(O)NH_2$, NH_2 and CN.

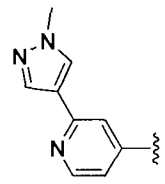
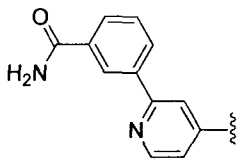
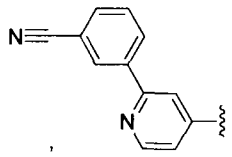
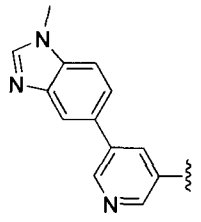
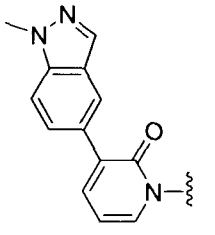
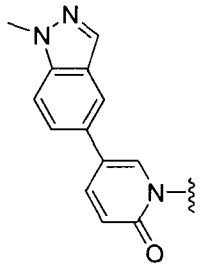
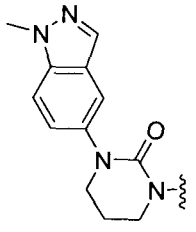
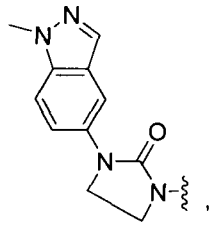
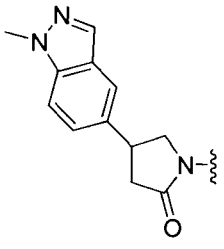
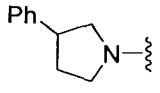
Another specific group of compounds of formula I' are compounds wherein each Z^{1b} is independently selected from methyl, cyclopropyl, cyclobutyl, N-methylpiperazinyl, morpholinyl, tetrazolyl, $-OCH_3$, $-C(O)OH$, $-OH$, $-C(O)NH_2$ and CN.

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, $-OCH_3$, 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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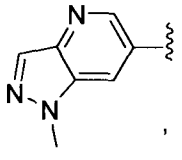
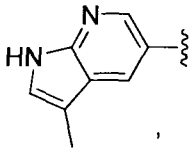
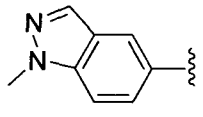
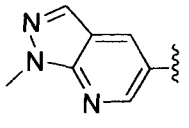
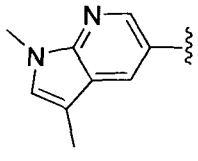
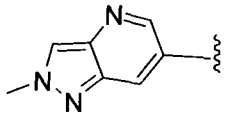
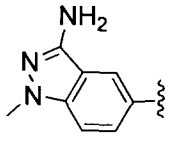

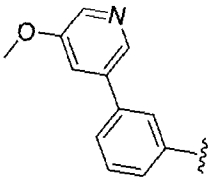
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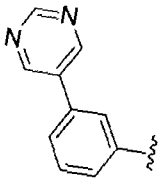
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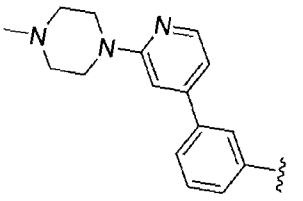
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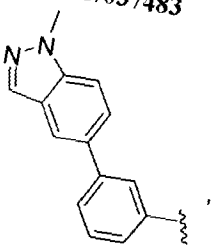
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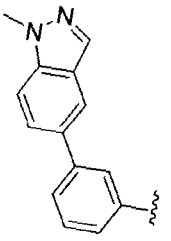
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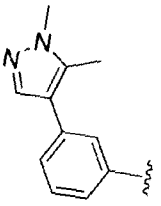
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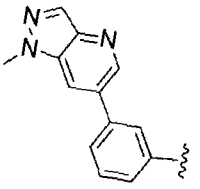
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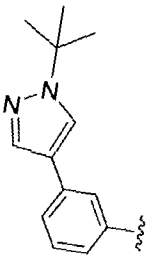
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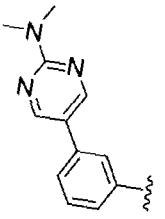
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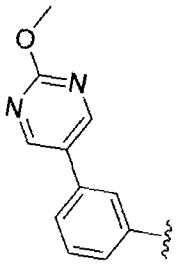
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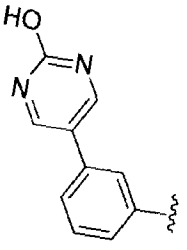
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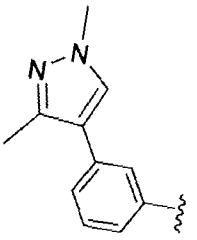
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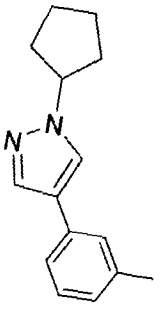
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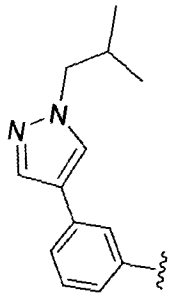
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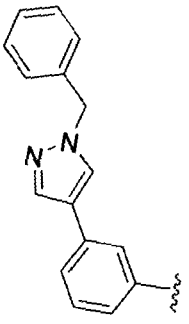
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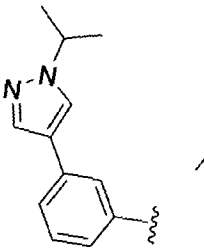
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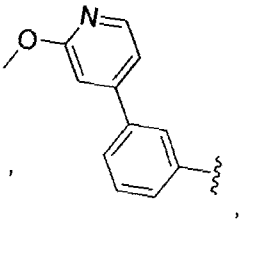
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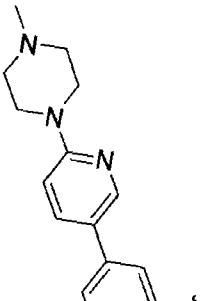
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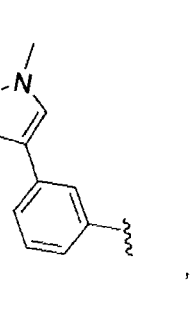
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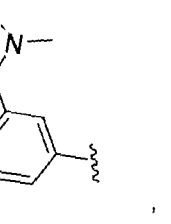
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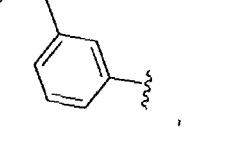
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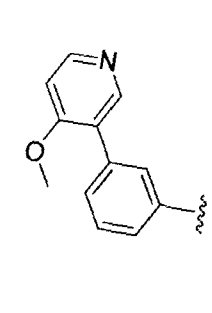
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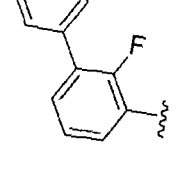
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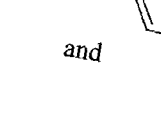
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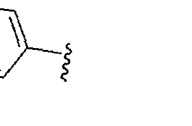
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,

and

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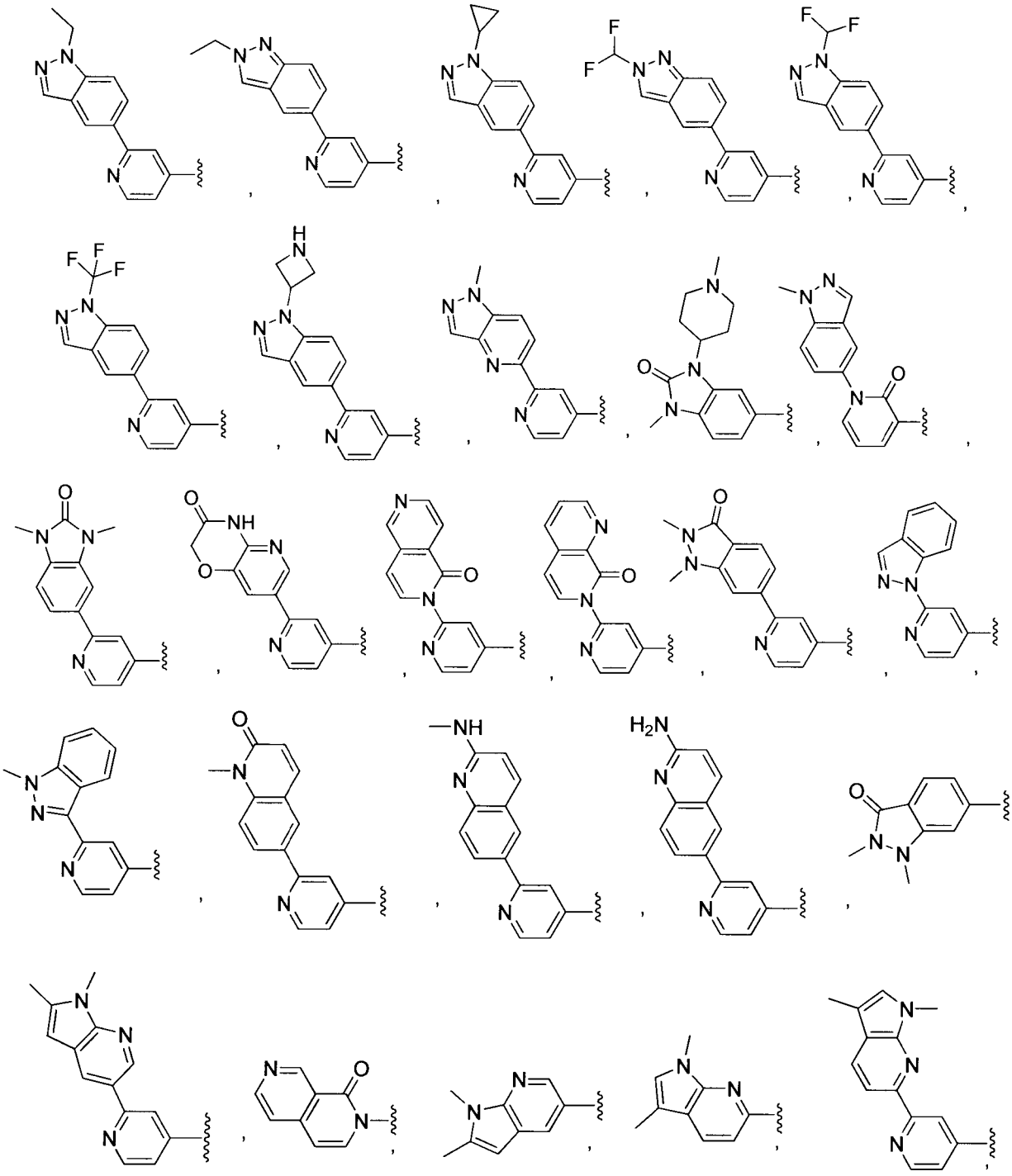
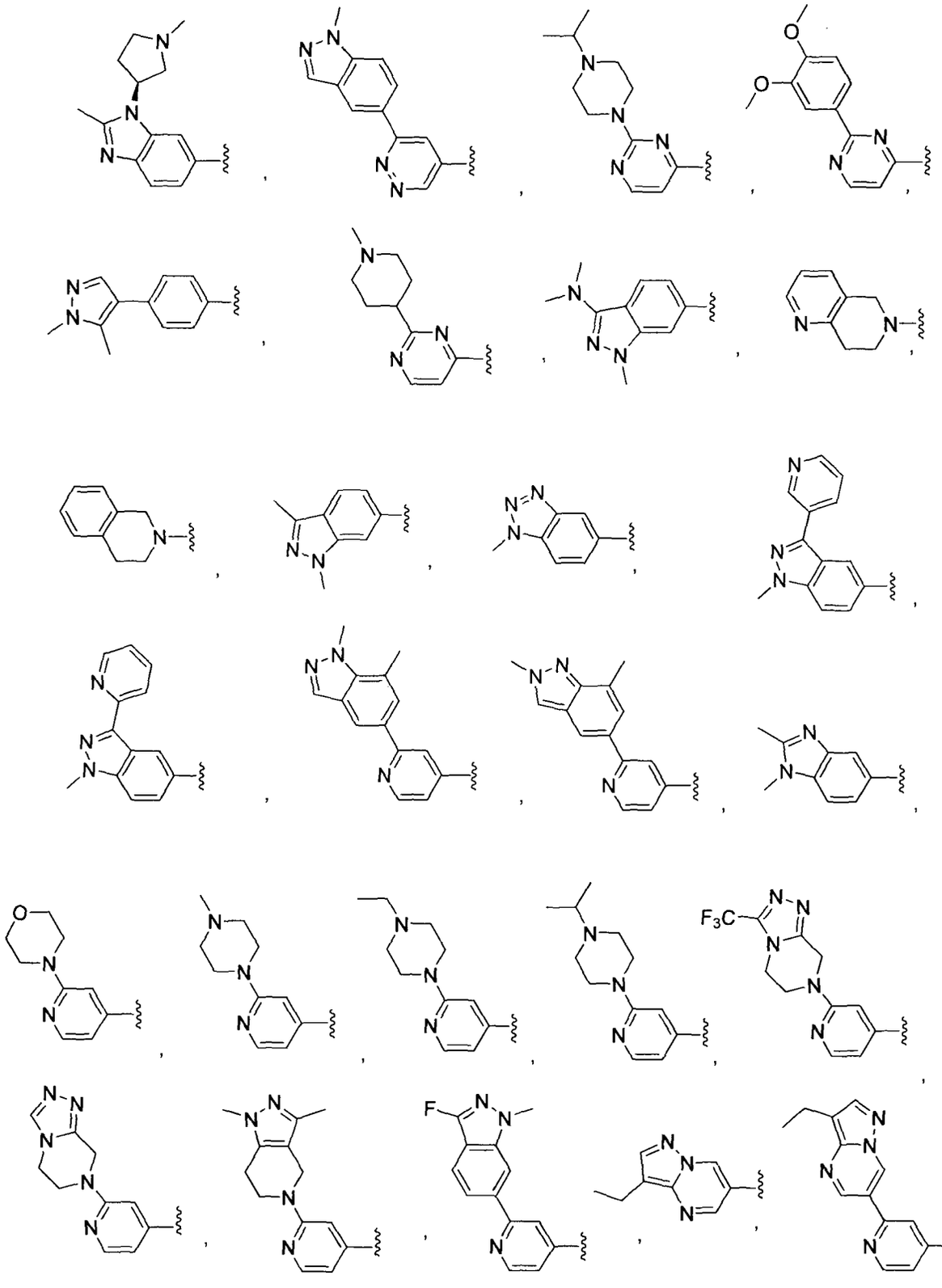
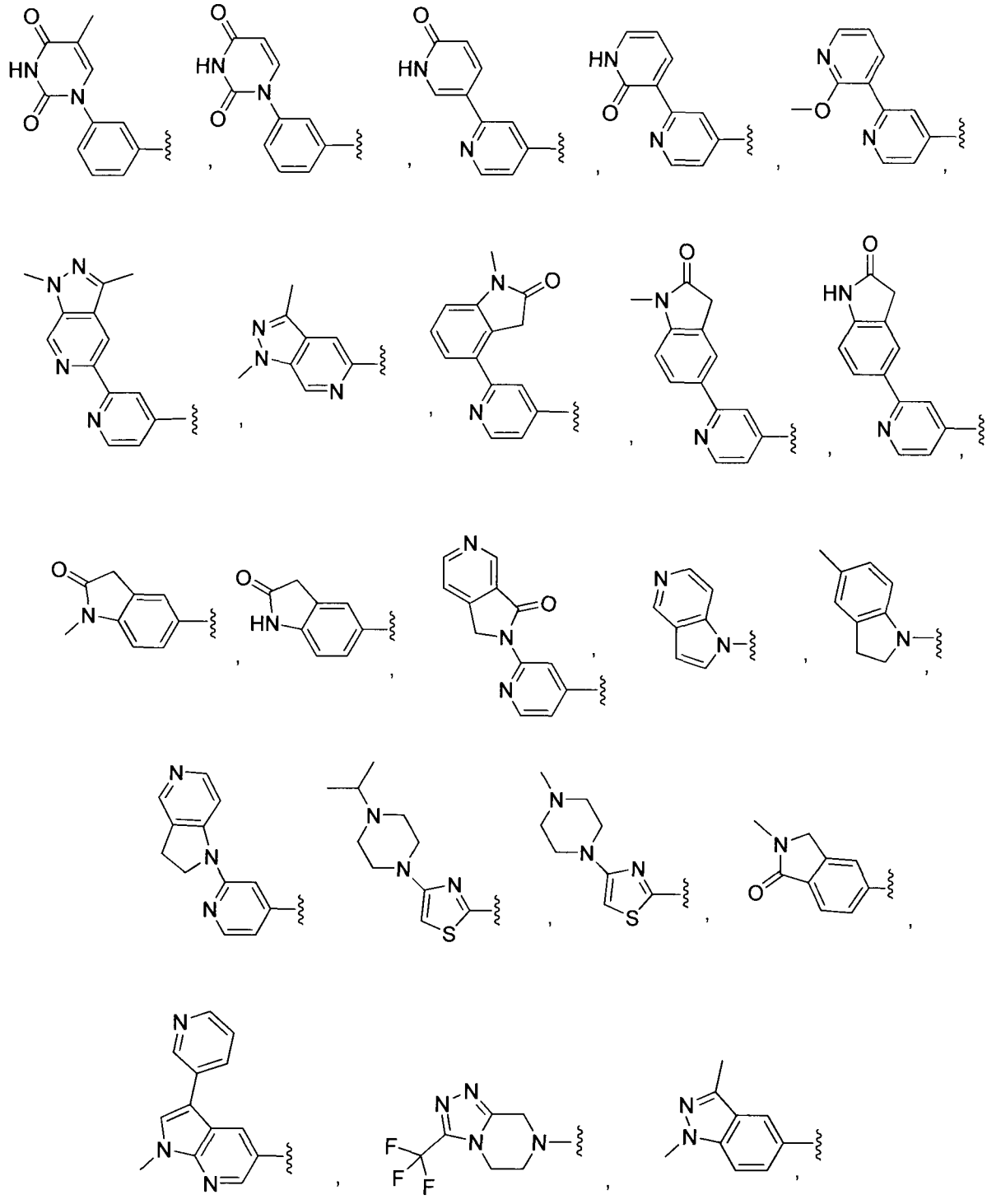
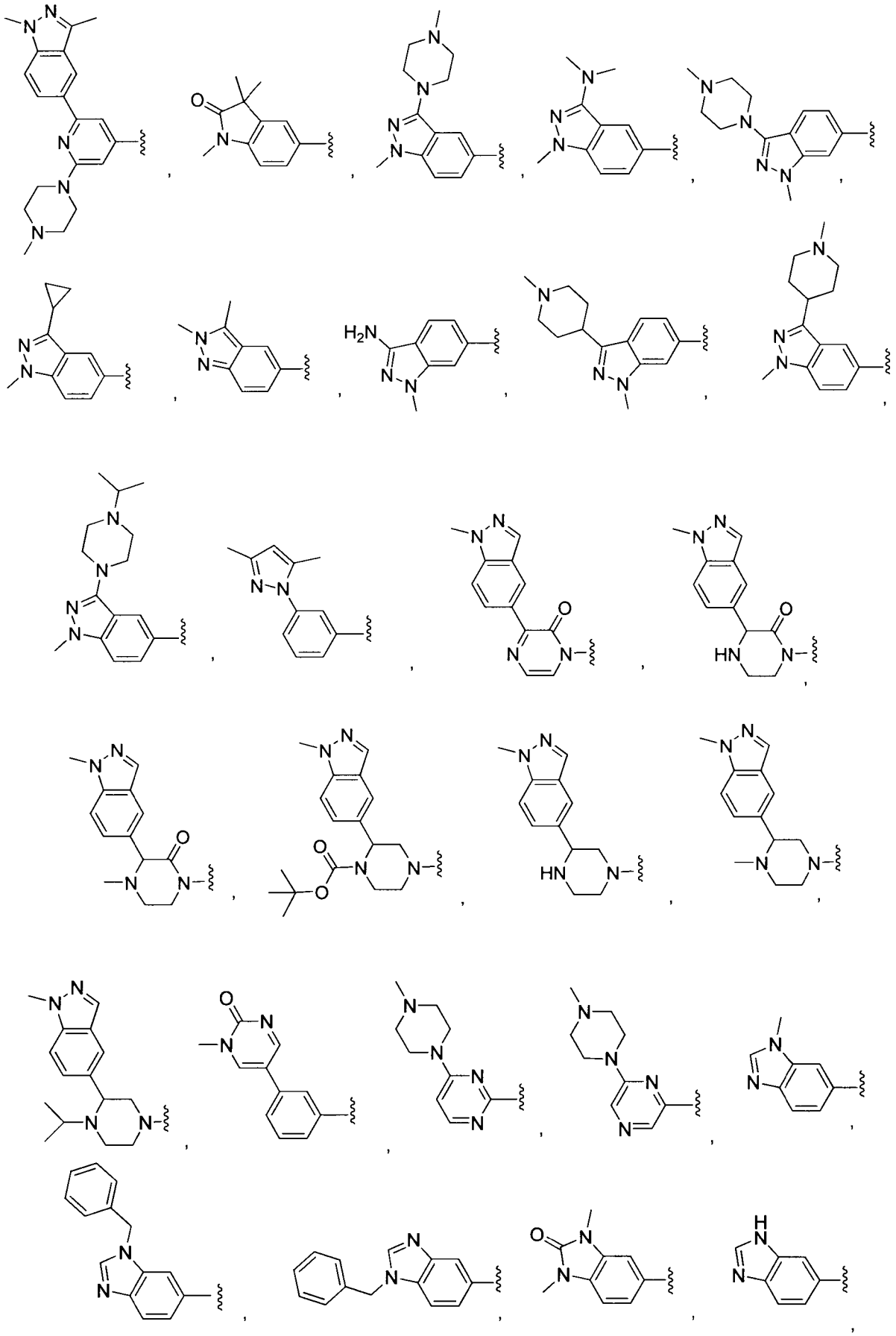
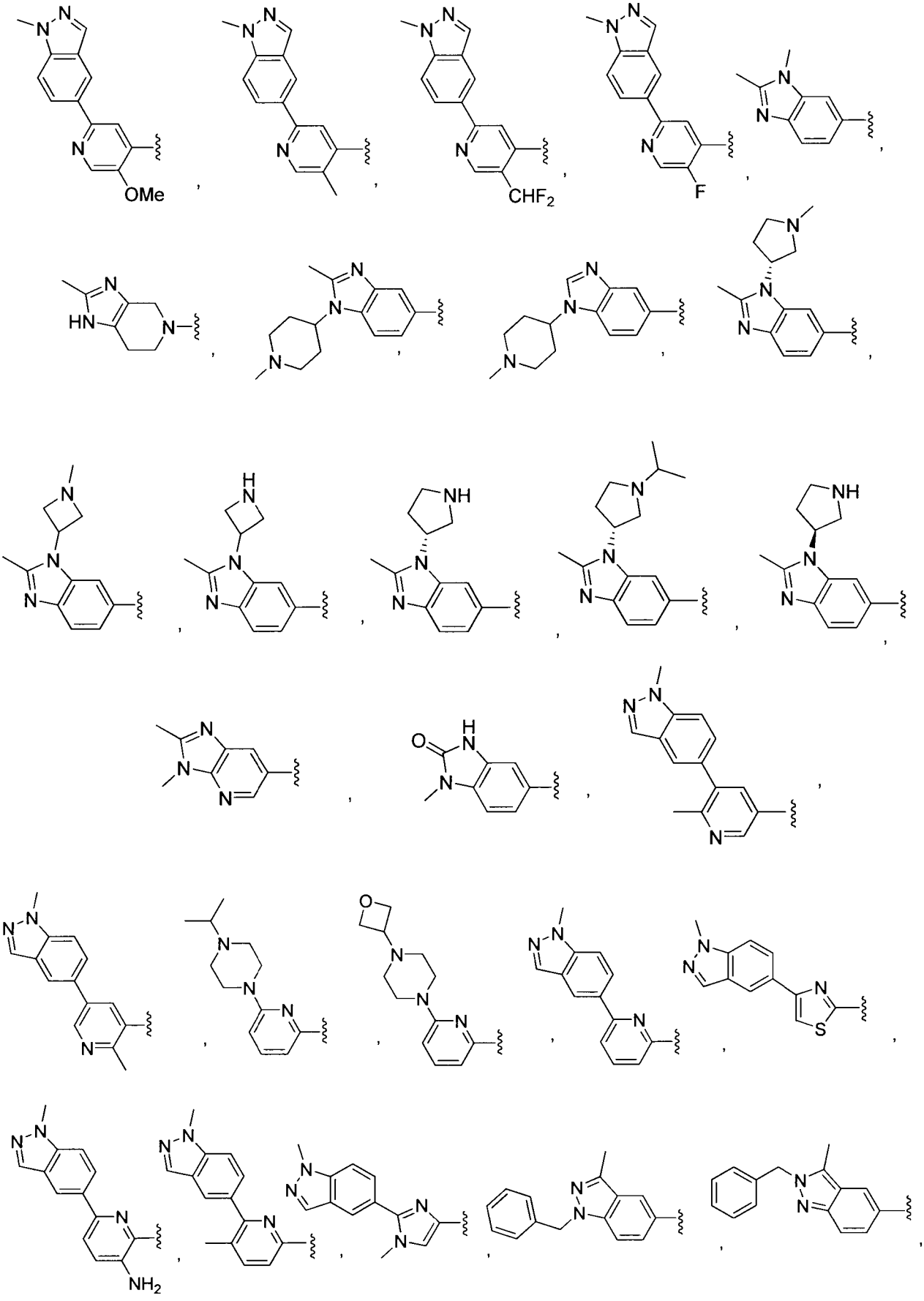
A specific group of compounds of formula I' are compounds wherein A-B is selected from:

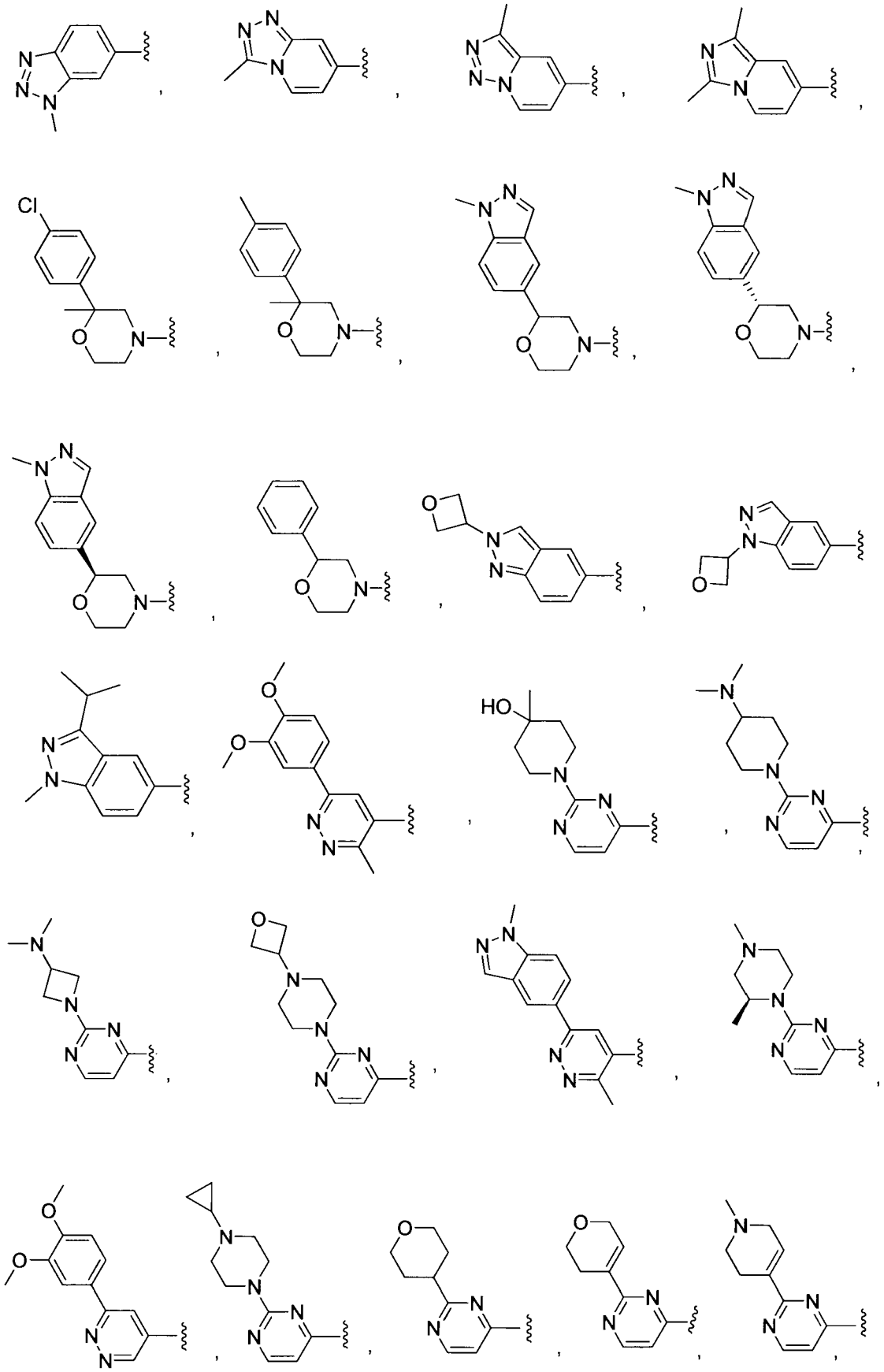












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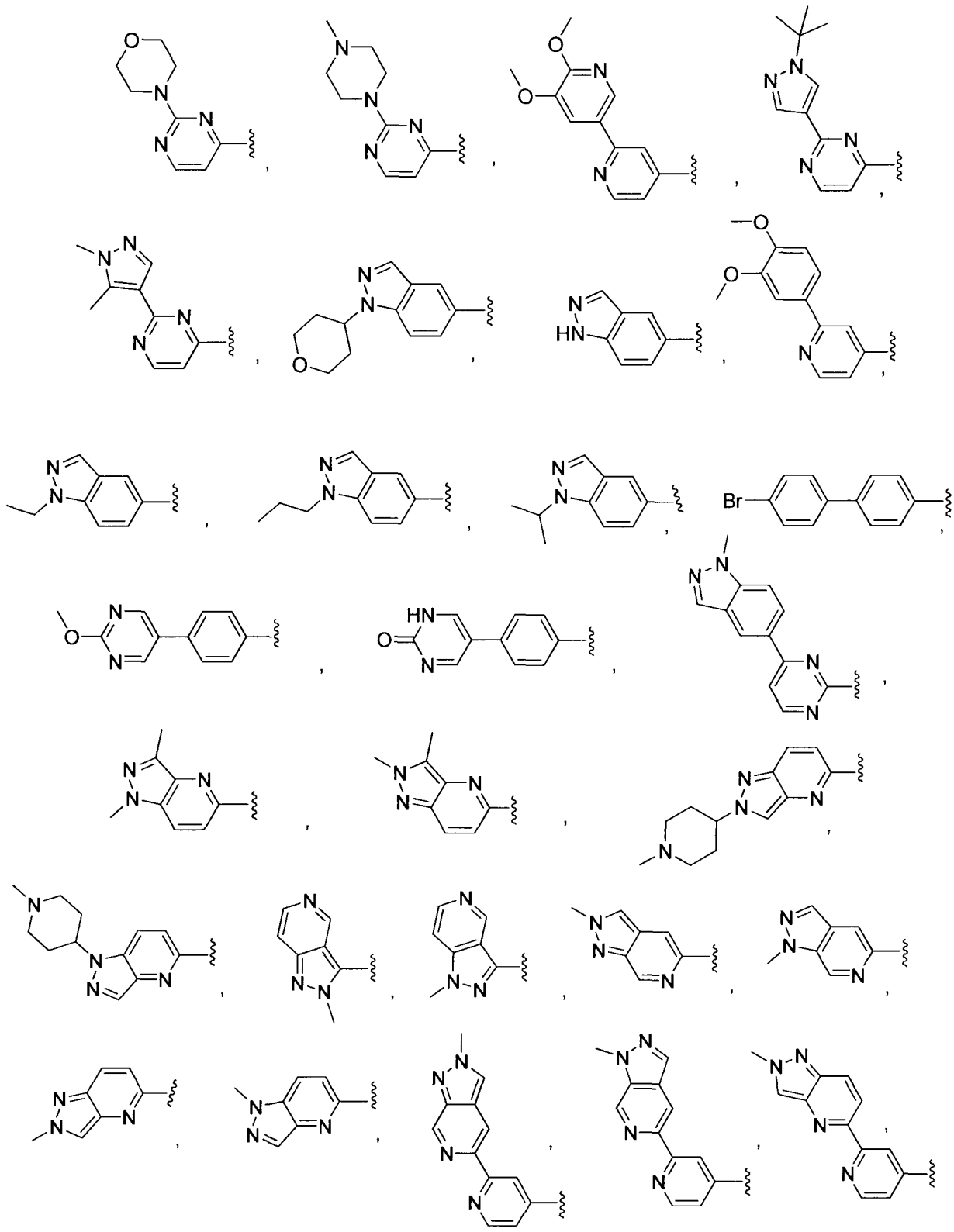
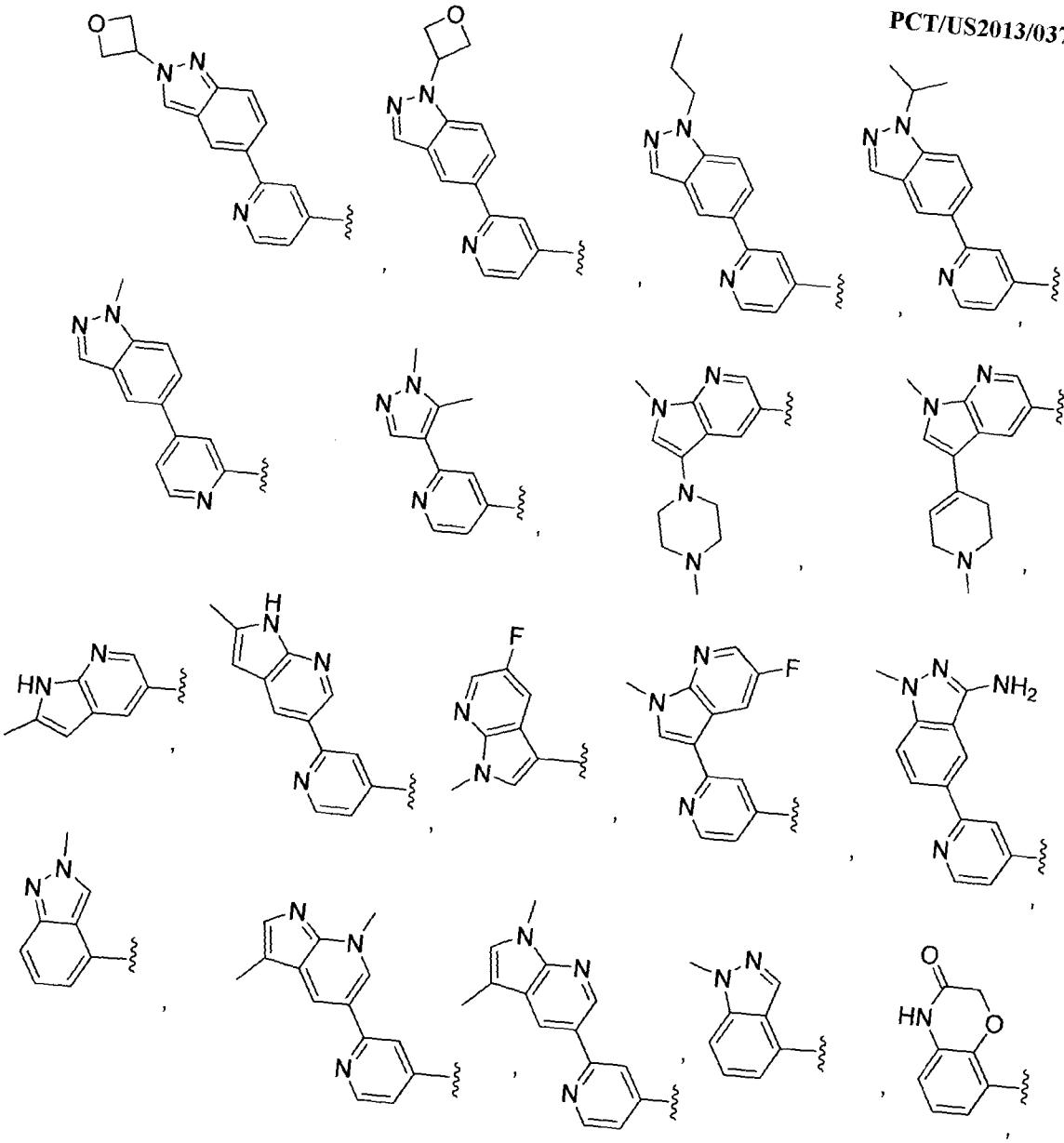
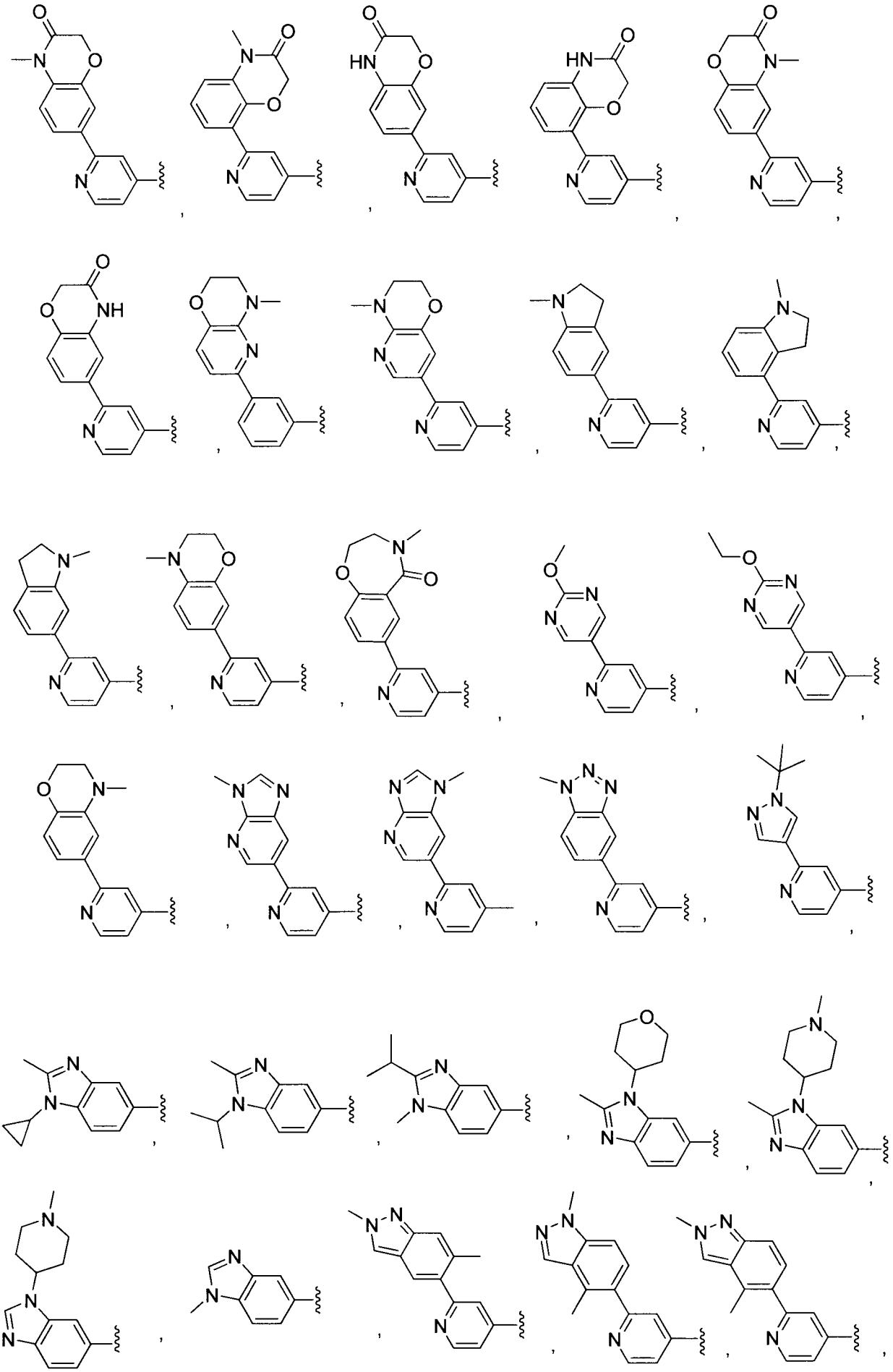
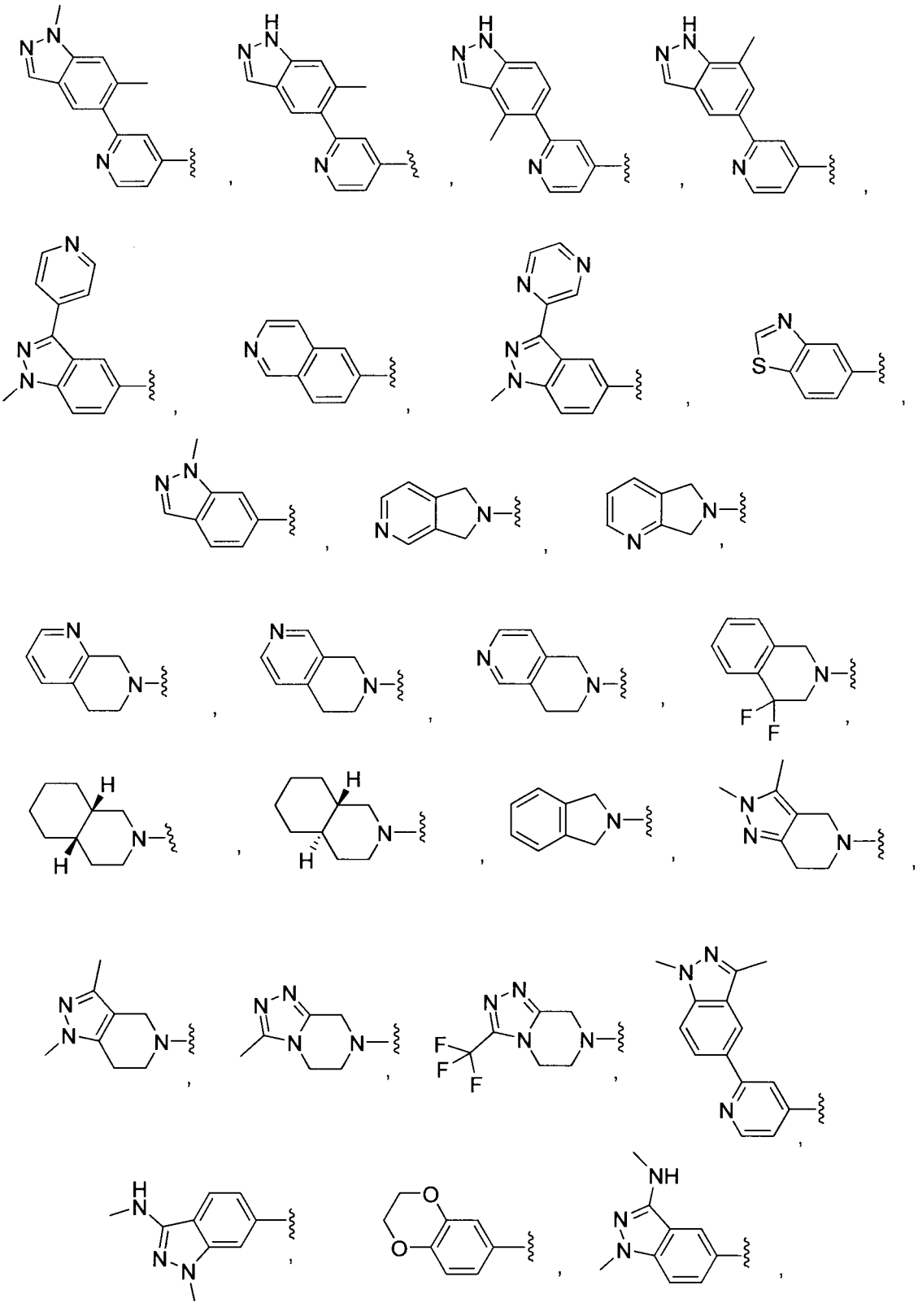
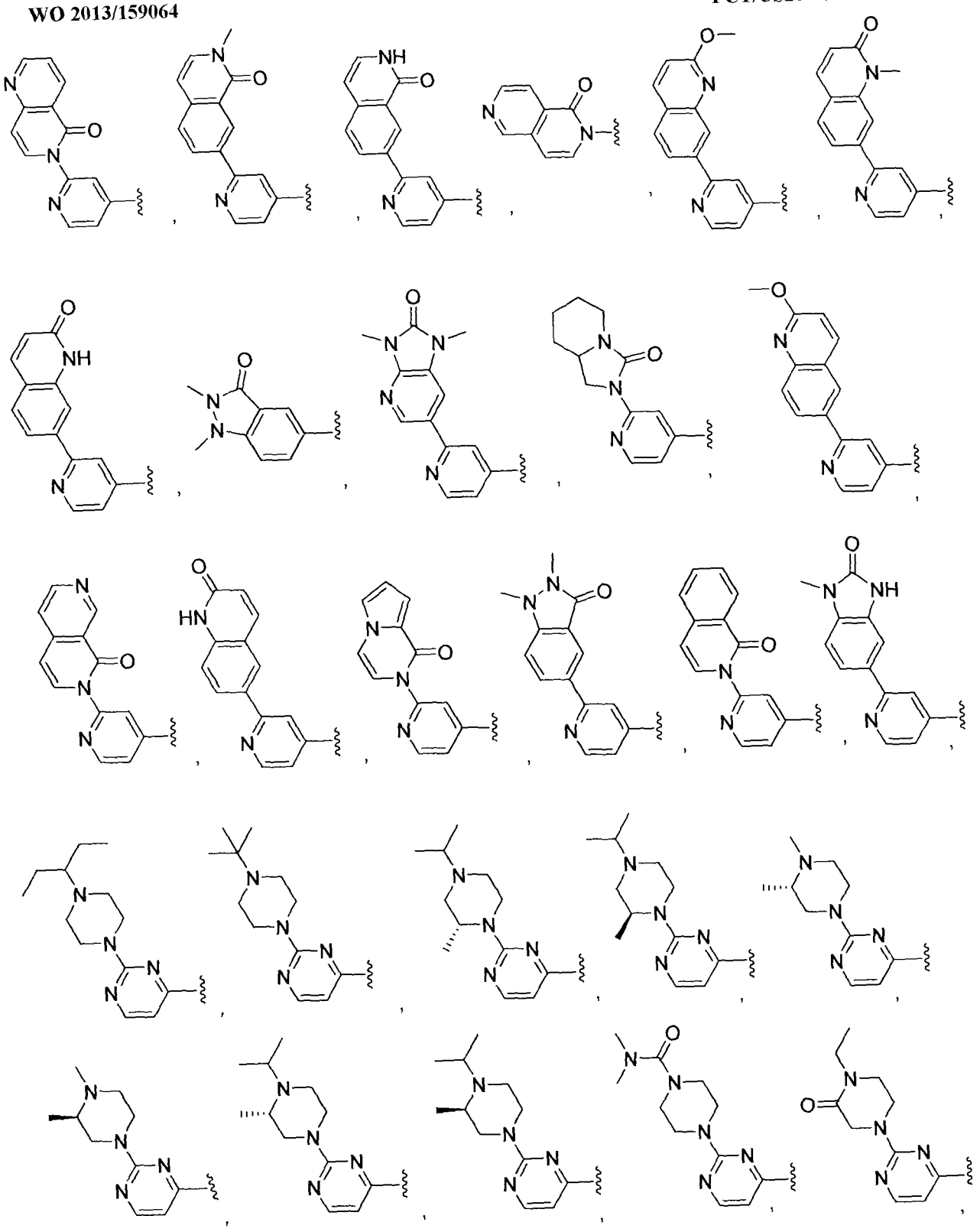
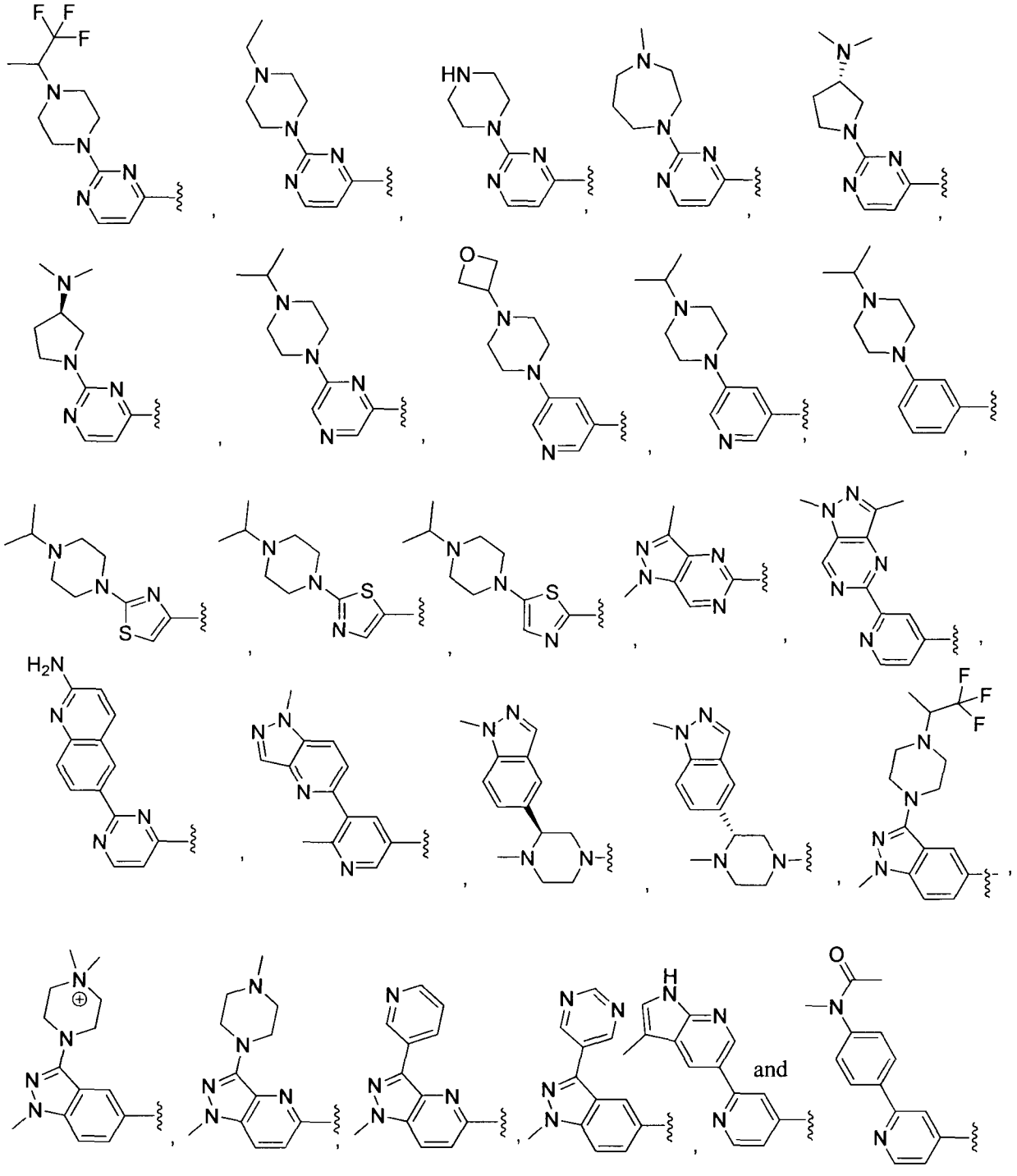




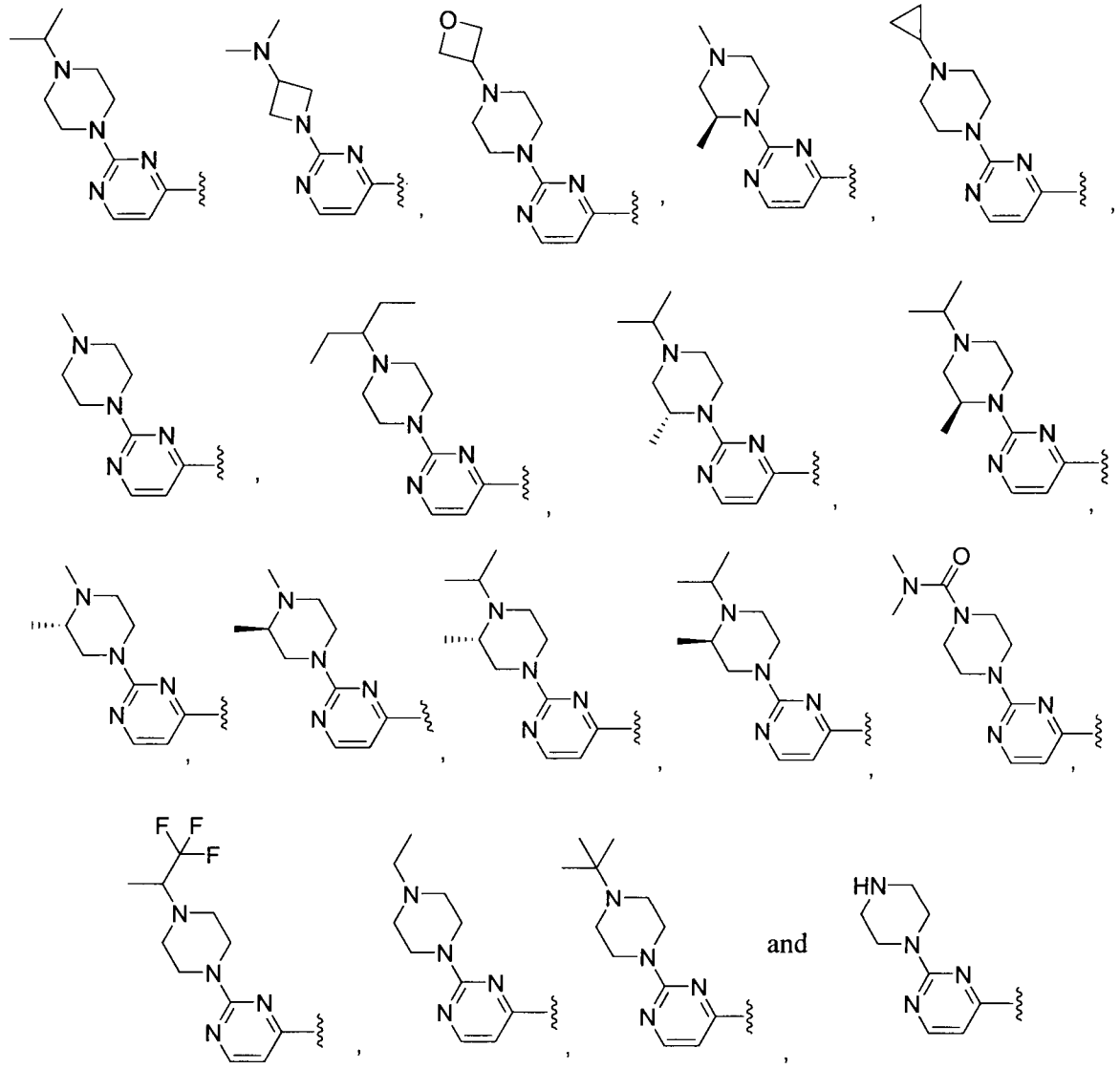




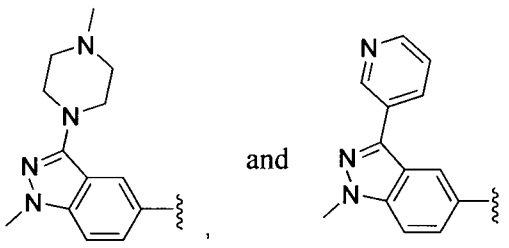




A specific group of compounds of formula I' are compounds wherein A-B is selected from:



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



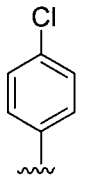
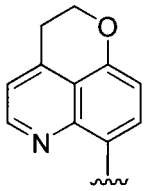
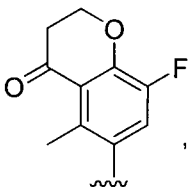
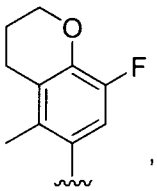
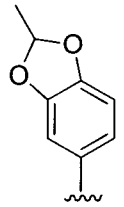
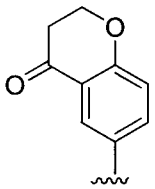
A specific value for R^4 is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R^4 is optionally substituted with one or more halo or $(C_1\text{-}C_6)$alkyl.

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.

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.

A specific value for R^4 is: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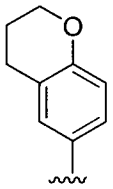
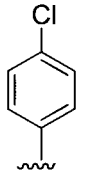
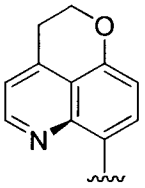
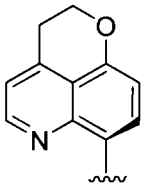
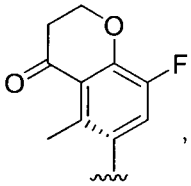
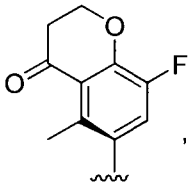
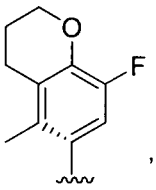
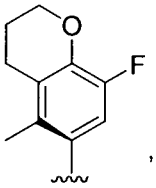
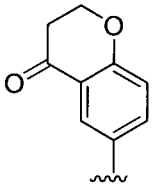


Another specific value for R^4 is: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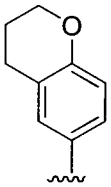
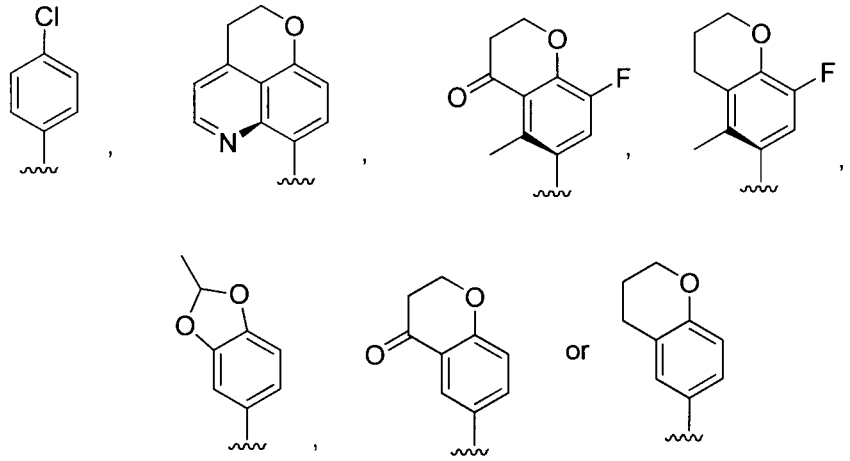
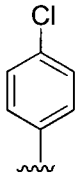


Another specific value for R^4 is:



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 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 $(C_1\text{-}C_6)$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, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$alkenyl, $(C_2$-$C_3)$alkynyl, $(C_1$-$C_3)$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;

each Z^{1b} is independently selected from halo, CN, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$haloalkyl, $(C_3$-$C_7)$carbocycle, 5-6 membered monocyclic heteroaryl, 7-12 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle, 6-11 membered bicyclic heterocycle, phenyl$(C_1$-$C_6)$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 $-C(O)NR_cR_d$, wherein any $(C_3$-$C_7)$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 $(C_1$-$C_6)$alkyl; and

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

or a salt thereof.

A specific value for R^4 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 R^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and $(C_1$-$C_6)$alkyl.

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

A specific value for R^4 is selected from phenyl, bicyclic heterocycle and tricyclic heterocycle, wherein any phenyl, bicyclic heterocycle and tricyclic heterocycle of R^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and (C_1-C_6)alkyl.

A specific value for R^4 is selected from phenyl, bicyclic heterocycle and tricyclic heterocycle, wherein any phenyl, bicyclic heterocycle and tricyclic heterocycle of R^4 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 R^4 is selected from phenyl, bicyclic heterocycle and tricyclic heterocycle, wherein any phenyl, bicyclic heterocycle and tricyclic heterocycle of R^4 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 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 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.

A specific value for 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 specific value for 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 halo and methyl.

A specific value for 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 fluoro, chloro or methyl.

A specific value for R^4 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 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 $(C_1\text{-}C_6)$alkyl.

A specific value for R^4 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 R^4 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 R^4 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 R^4 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 R^4 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-dihydropyrano[4,3,2-de]quinolinyl, chromanyl-4-one, chromanyl and 2-methylbenzo[d][1,3]dioxolyl of R^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo and $(C_1\text{-}C_6)$alkyl.

A specific value for R^4 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-dihydropyrano[4,3,2-de]quinolinyl, chromanyl-4-one, chromanyl and 2-methylbenzo[d][1,3]dioxolyl of R^4 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 R^4 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-dihydropyrano[4,3,2-de]quinolinyl, chromanyl-4-one, chromanyl and 2-methylbenzo[d][1,3]dioxolyl of R^4 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 R^4 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 $(C_1\text{-}C_6)$alkyl.

A specific value for R^4 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 R^4 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 R^4 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 6-11membered 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.

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; 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 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; 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 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.

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 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; 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 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.

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.

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.

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 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 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 inlude one or two nitrogens in the monocyclic ring and which may optionally inlude one oxygen or one sulfur in the monocyclic ring.

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

In one embodiment a N-heteroaryl includes heteroaryls which inlude one or two nitrogens in the heteroary ring and which may optionally inlude 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, 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 pyridizinyl wherein the pyridinyl, pyrimidinyl, pyrazinyl or pyradizinyl 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, azetidinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, 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, azetidinyl, tetrahydro-2H-pyranyl,

3,6-dihydro-2H-pyranyl, 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 of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

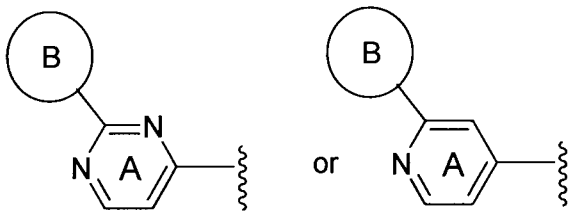
A specific value for B is 3-7 membered monocyclic heterocycle, wherein any 3-7 membered monocyclic heterocycle of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

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.

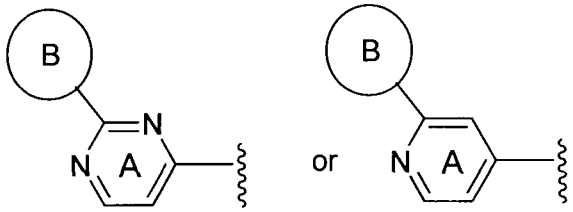
A specific value for B is piperazinyl or azetidinyl, wherein any piperazinyl or azetidinyl of B is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1b} groups.

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



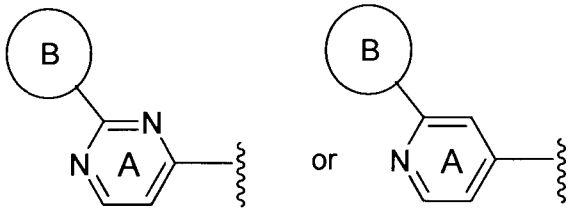
wherein A is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} groups and B is phenyl, 8-11 membered bicyclic aryl, 5-6 membered monocyclic heteroaryl, 7-11 membered bicyclic heteroaryl, 3-7 membered monocyclic heterocycle or 6-11 membered bicyclic heterocycle, wherein any phenyl,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

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



wherein B is azetidinyl or piperazinyl, wherein any azetidinyl or piperazinyl 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' 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., 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 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.

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.

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.

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.

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.

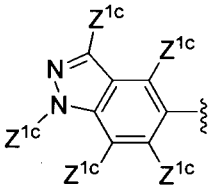
A specific group of compounds of formula I' are compounds wherein wherein A and B together form a pyrazolo[4,3-b]pyridinyl, pyrrolo[2,3-b]pyridinyl, indazolyl, pyrazolo[3,4-b]pyridinyl, 2,7-naphthyridinyl-1(2H)-one, benzoimidazolyl, benzo[1,2,3]triazolyl, pyrazolo[3,4-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, [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.

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,

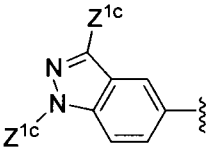
1H-indazolyl-3(2H)-one, 5,6,7,8-tetrahydro-1,6-naphthyridinyl, 1,2,3,4-tetrahydroisoquinolinyl, indolinyl-2-one, isoindolinyl-1-one, indolinyl, 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 2H-benzo[b][1,4]oxazinyl-3(4H)-one, 5,6,7,8-tetrahydro-1,7-naphthyridinyl, 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:



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}.

A specific value for each Z^{1a} is halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$haloalkyl, $(C_3\text{-}C_7)$carbocycle, 3-7 membered monocyclic heterocycle, $-O(C_1\text{-}C_3)$alkyl, $-O(C_2\text{-}C_3)$alkenyl, $-O(C_2\text{-}C_3)$alkynyl, $-NR_cR_d$, $-NR_aC(O)R_a$, $-C(O)OR_b$, and $-C(O)NR_cR_d$, wherein any $(C_3\text{-}C_7)$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 $(C_1\text{-}C_6)$alkyl.

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

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

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

A specific value for Z^{1b} is halo, CN, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_3\text{-}C_7)$carbocycle, 5-6 membered monocyclic heteroaryl, 3-7 membered monocyclic heterocycle, aryl$(C_1\text{-}C_6)$alkyl-, -OH, -O$(C_1\text{-}C_6)$alkyl, $-NR_cR_d$, $-C(O)OR_b$ or $-C(O)NR_cR_d$, wherein any $(C_3\text{-}C_7)$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 $(C_1\text{-}C_6)$alkyl.

A specific value for each Z^{1b} is $(C_1\text{-}C_6)$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 $(C_1\text{-}C_6)$alkyl.

A specific value for Z^{1b} is $(C_1\text{-}C_6)$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 $(C_1\text{-}C_6)$alkyl.

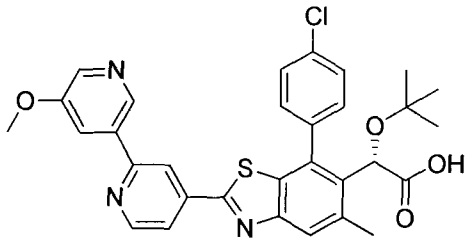
A specific value for Z^{1b} is $(C_1\text{-}C_6)$alkyl, 5-6 membered monocyclic heteroaryl, 3-7 membered monocyclic heterocycle or $-NR_cR_d$, wherein any 5-6 membered monocyclic heterocycle of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen or $(C_1\text{-}C_6)$alkyl.

A specific value for Z^{1b} is methyl, isopropyl, $-N(CH_3)_2$, oxetanyl, pyridinyl, N-methylpiperazinyl.

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

A specific value for Z^{1b} isopropyl, $-N(CH_3)_2$ or oxetanyl.

In one embodiment a compound is selected from:



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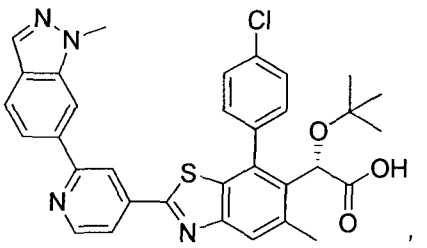

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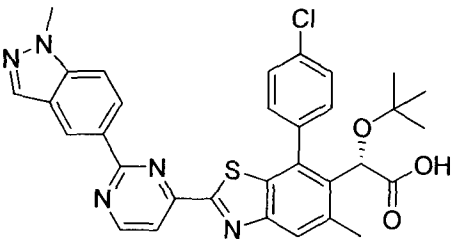

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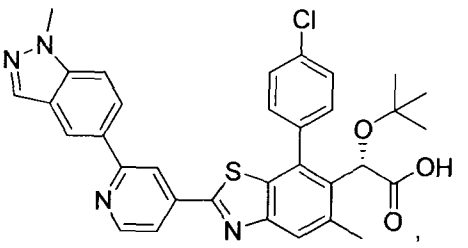

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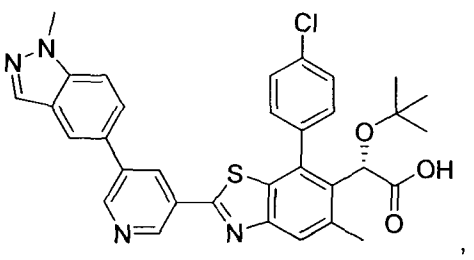

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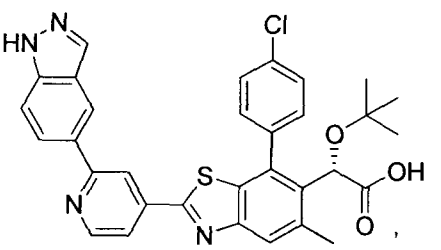

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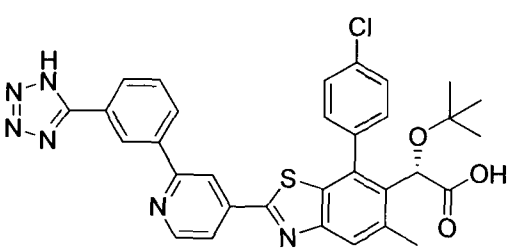

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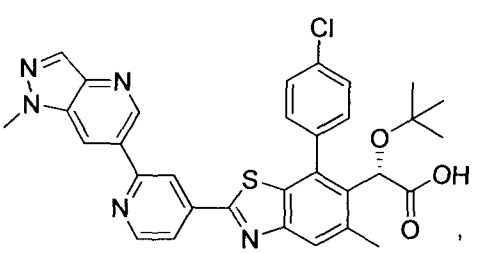

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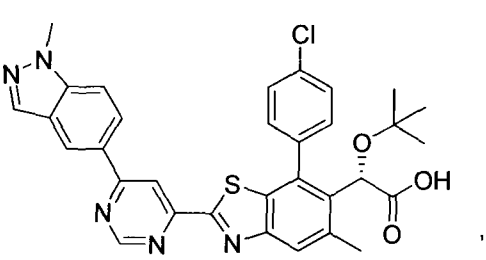

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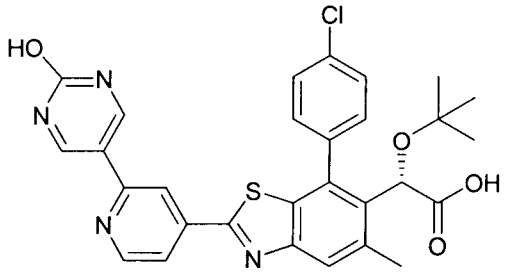

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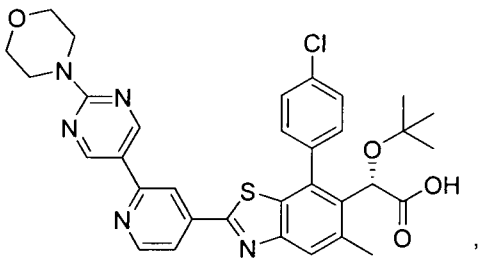

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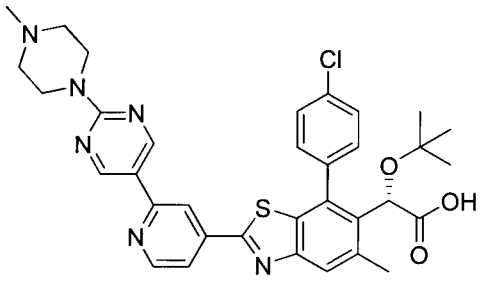

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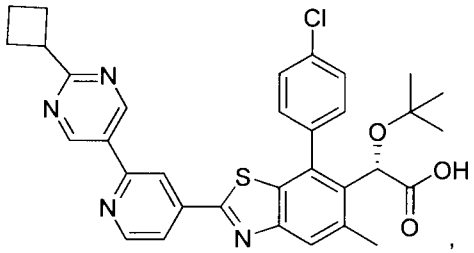

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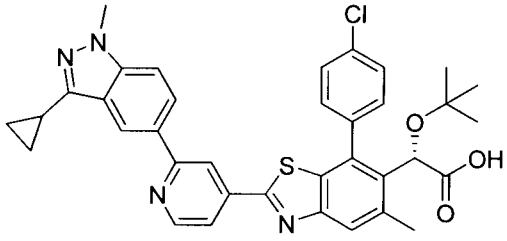

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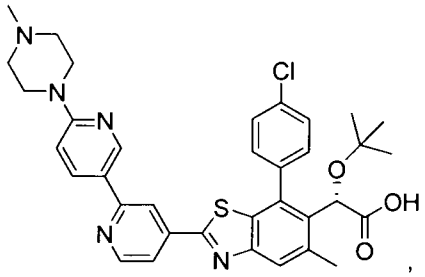

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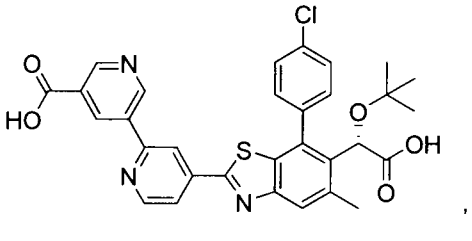

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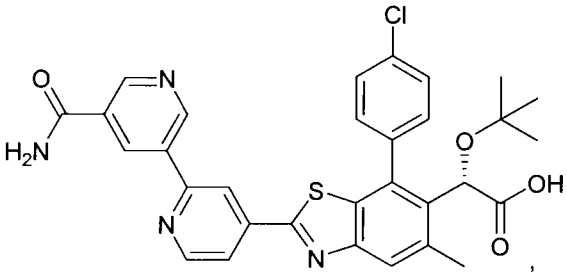

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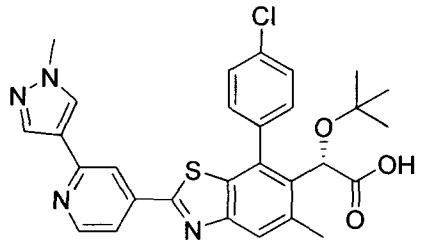

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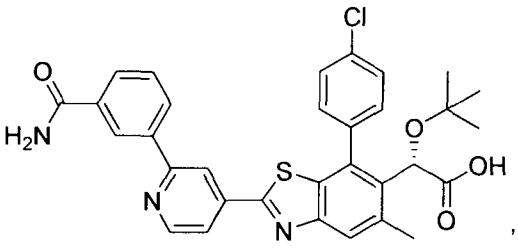

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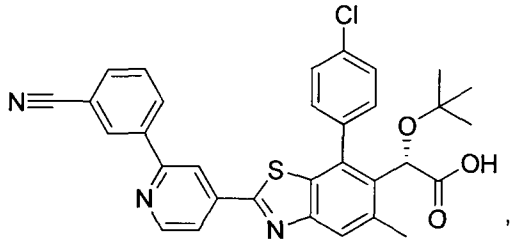

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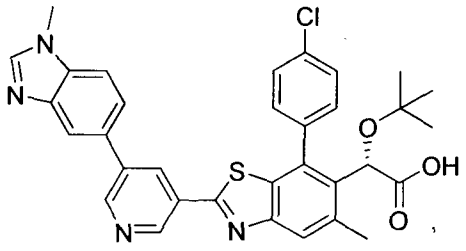

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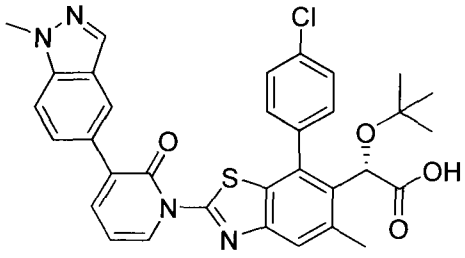

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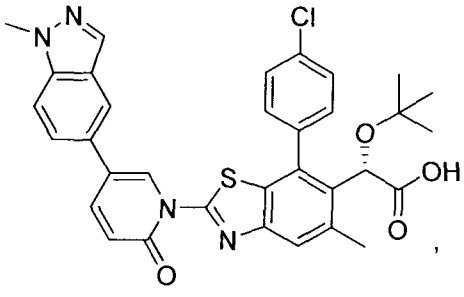

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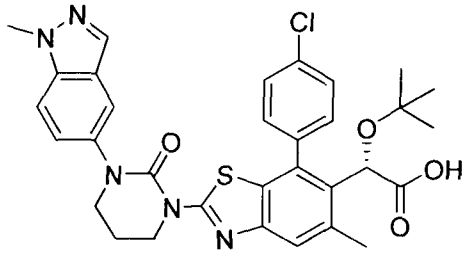

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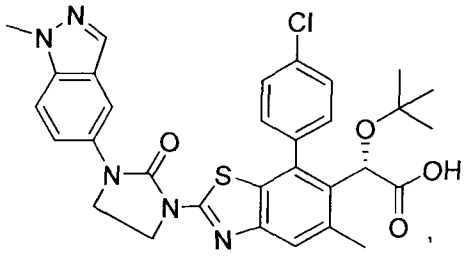

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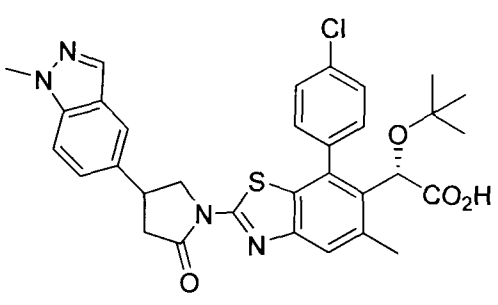

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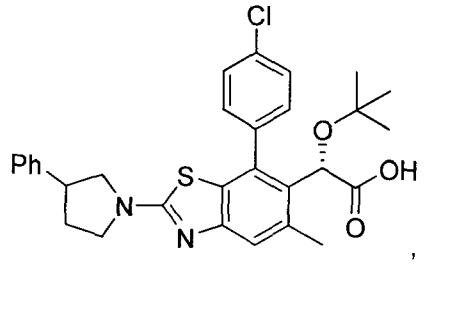

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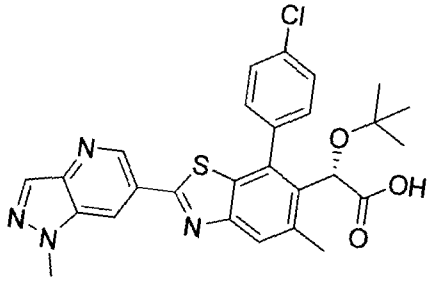

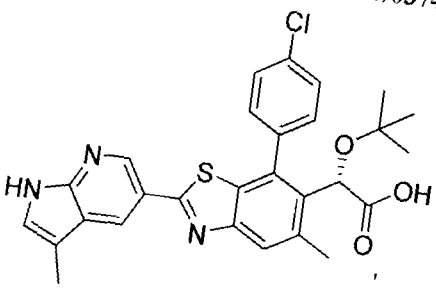

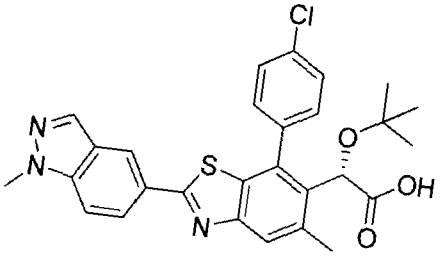

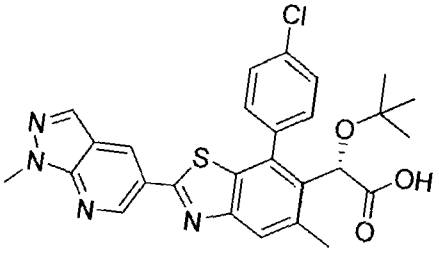

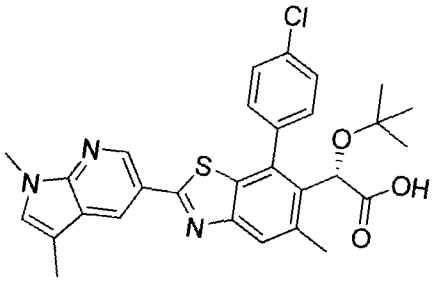

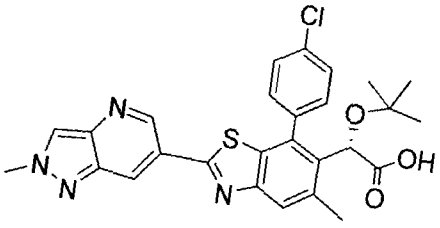

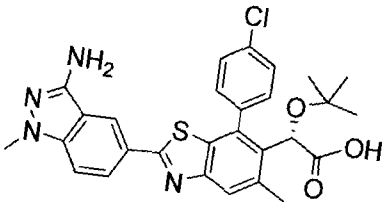

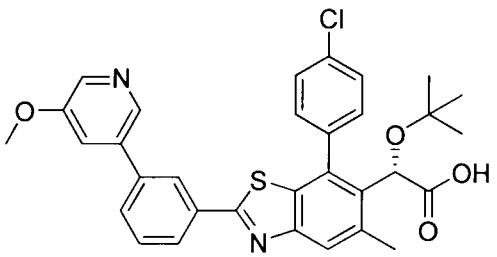

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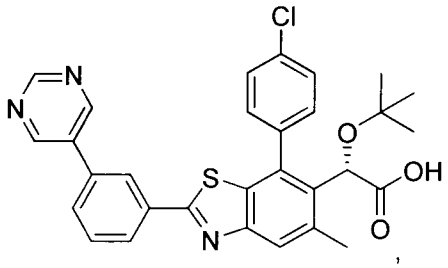

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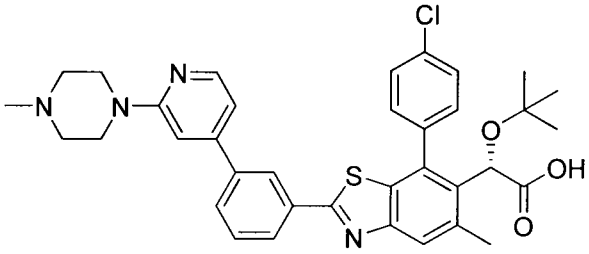

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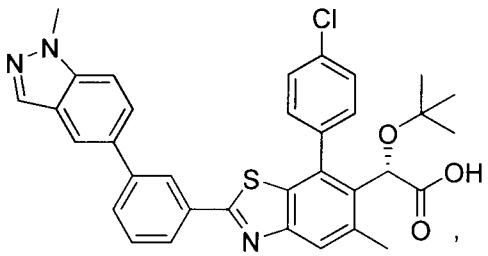

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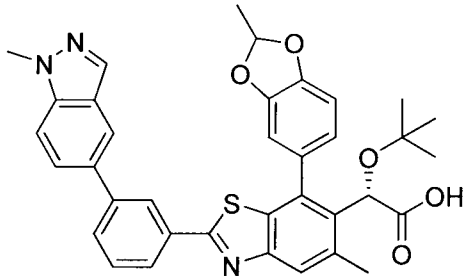

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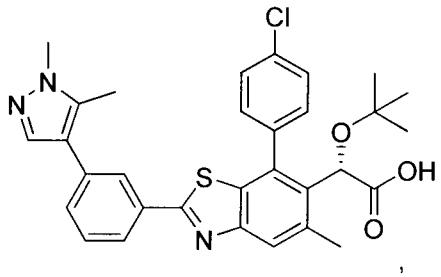

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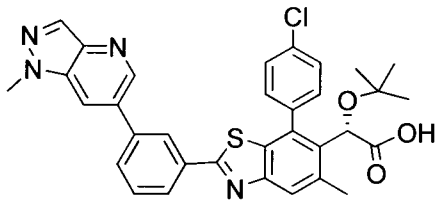

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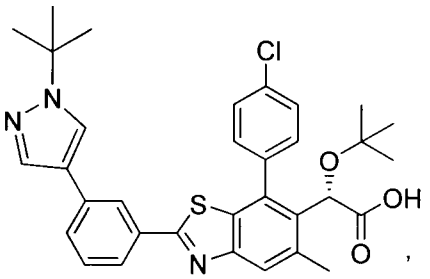

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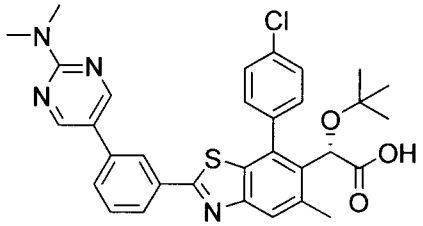

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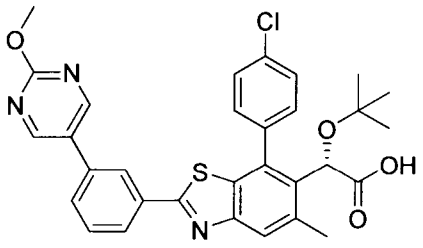

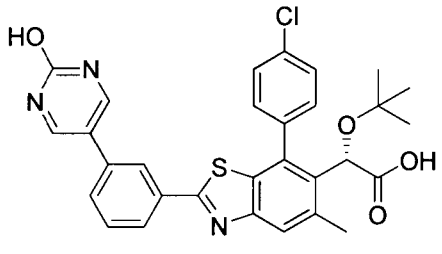

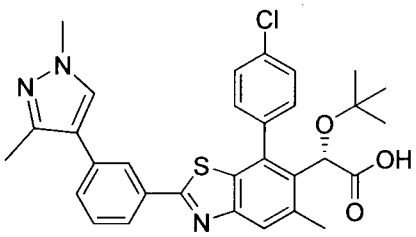

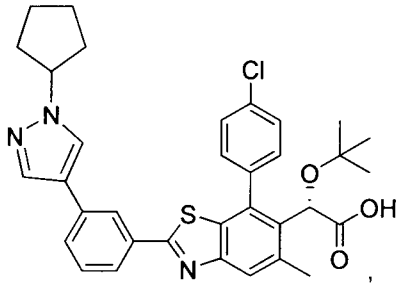

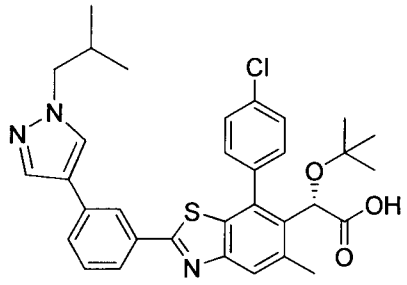

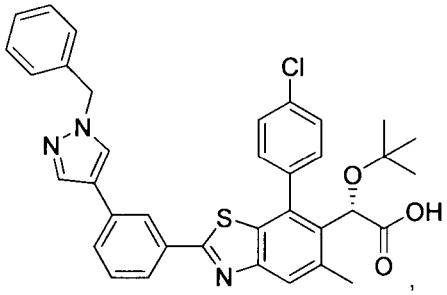

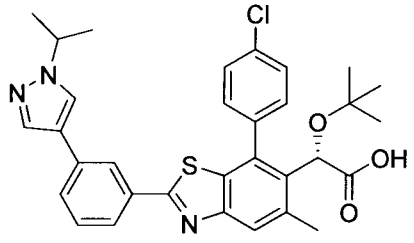

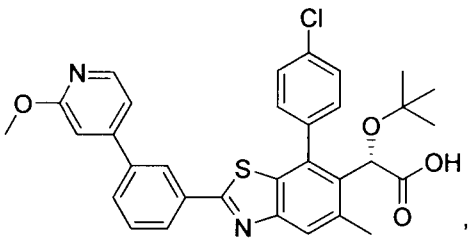

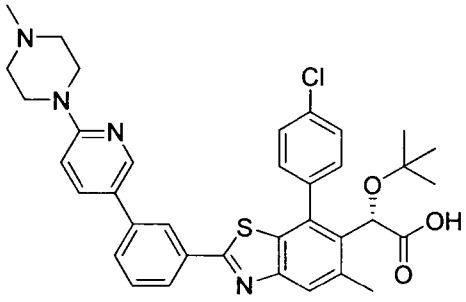

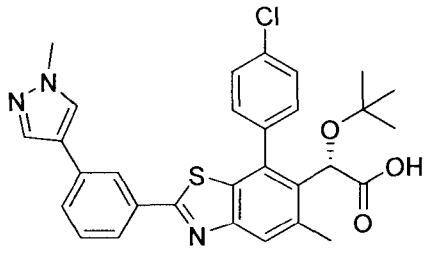

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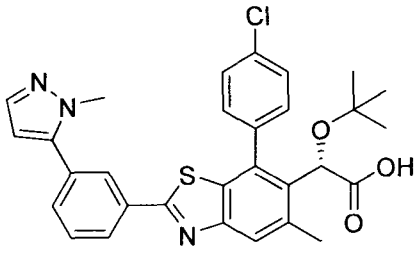

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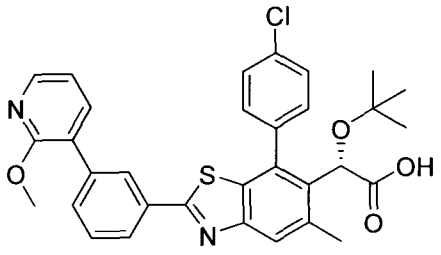

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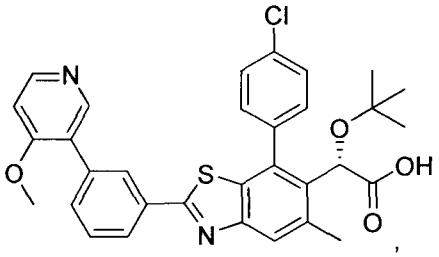

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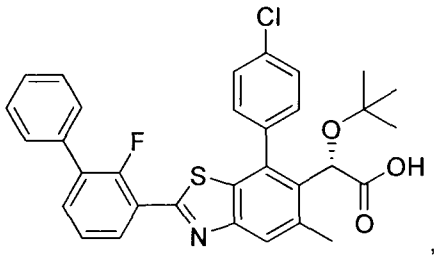

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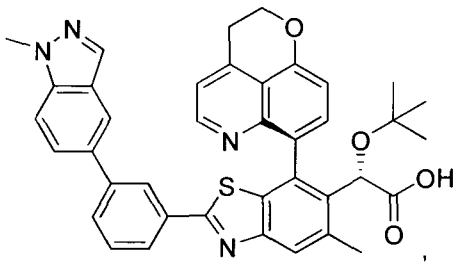

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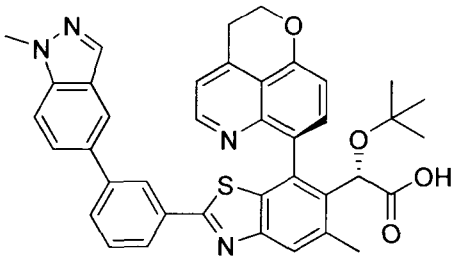

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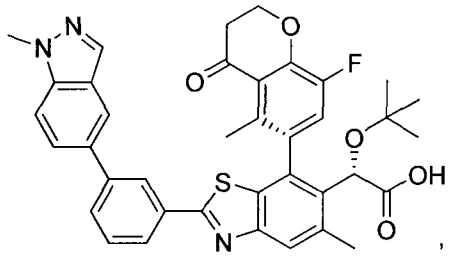

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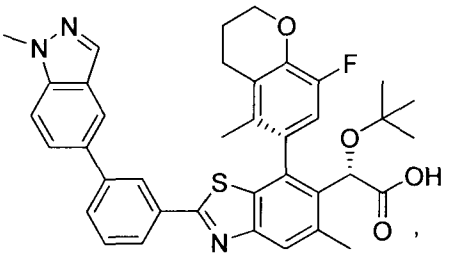

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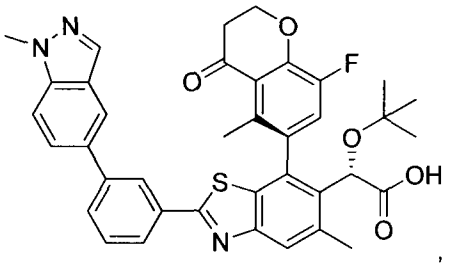

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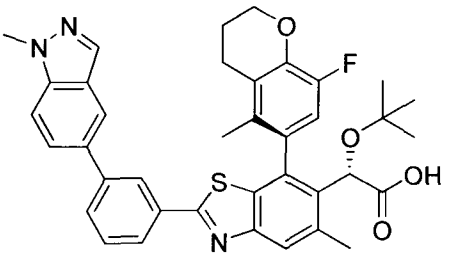

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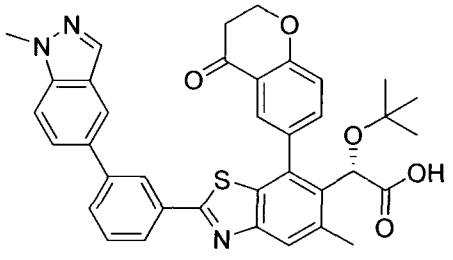

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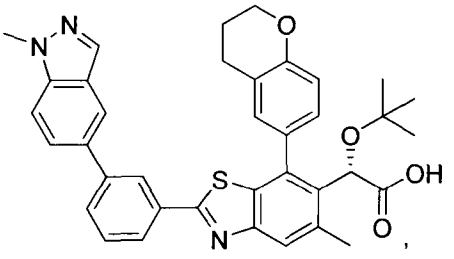

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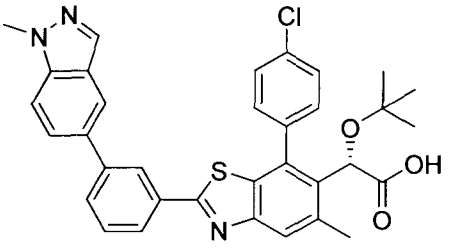
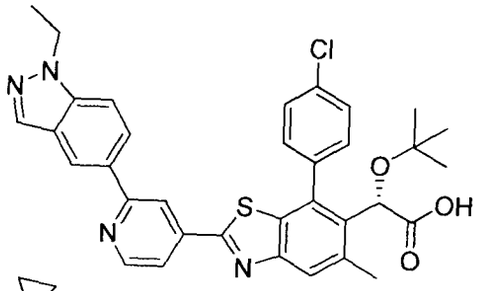


and salts thereof.

In one embodiment a compound is selected from:



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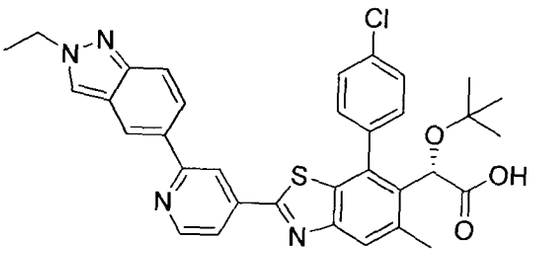

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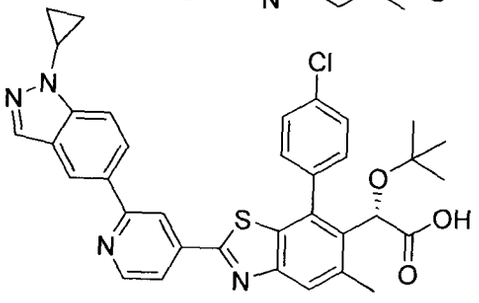

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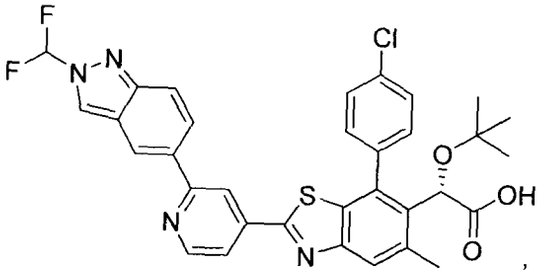

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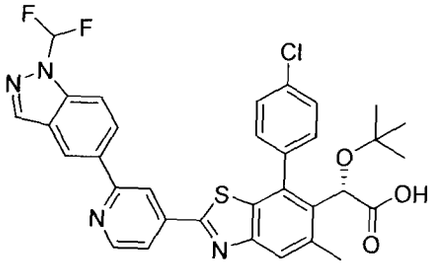

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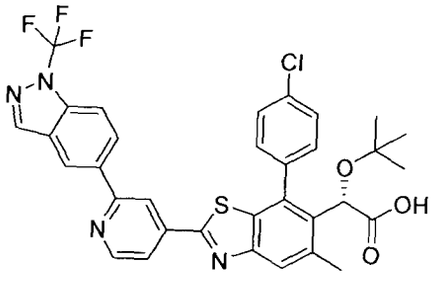

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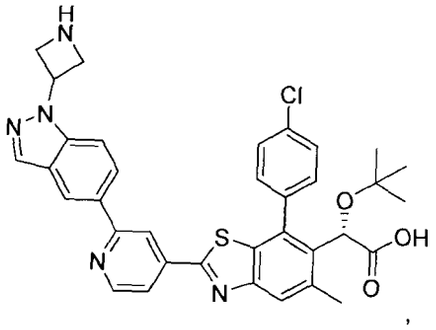

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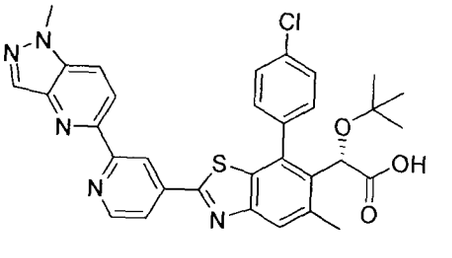

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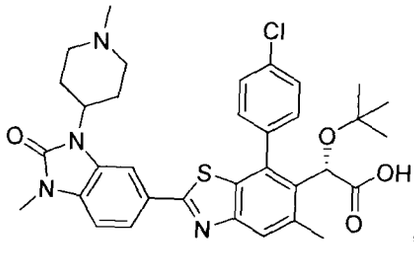

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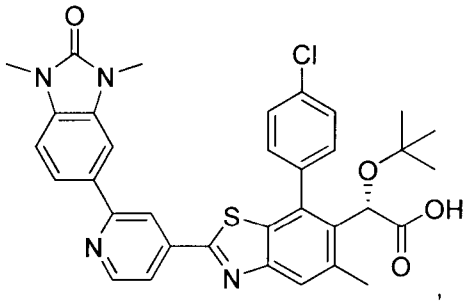

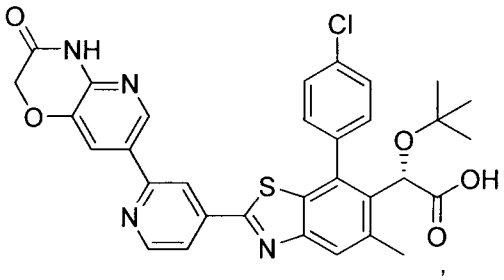

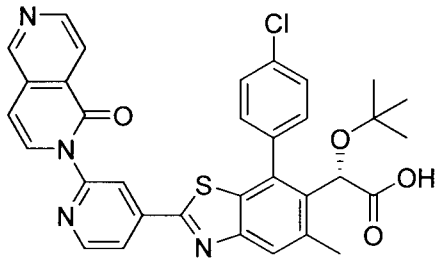

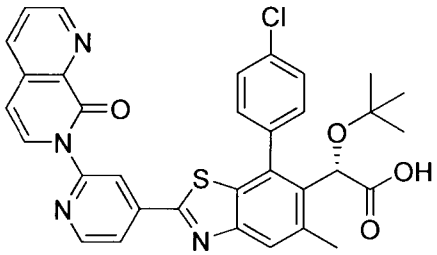

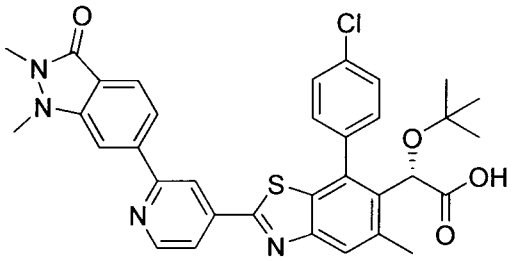

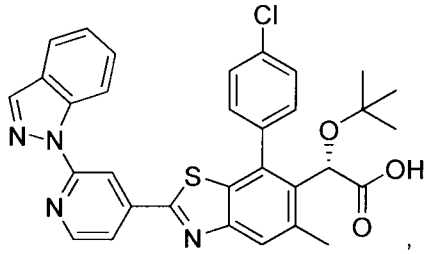

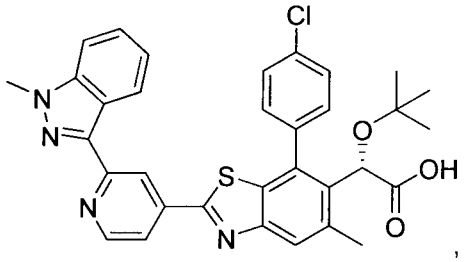

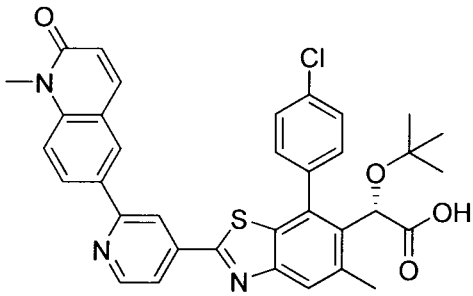

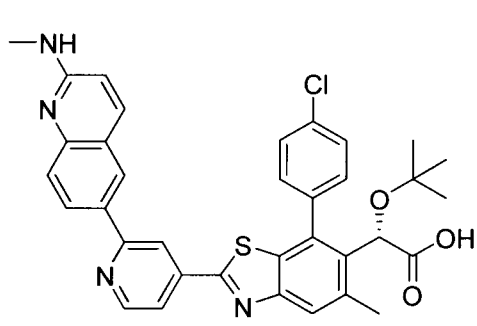

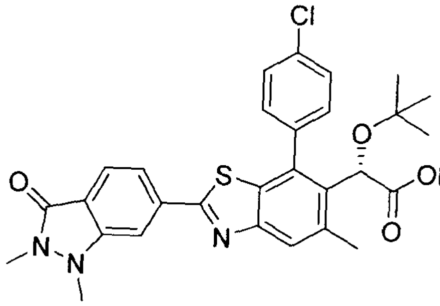
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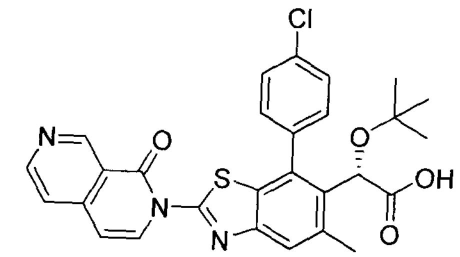
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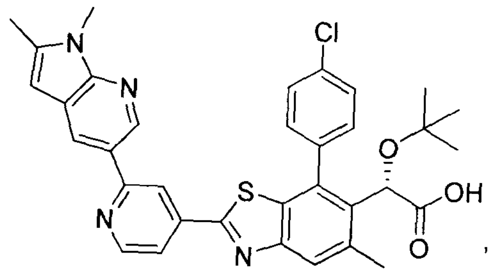
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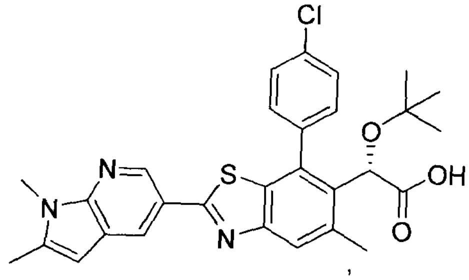
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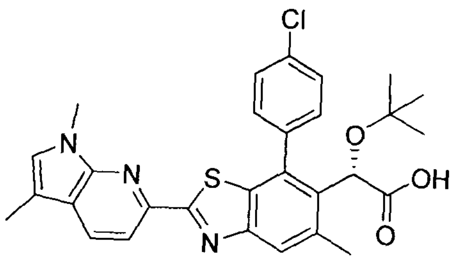
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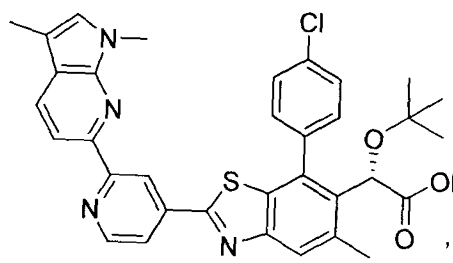
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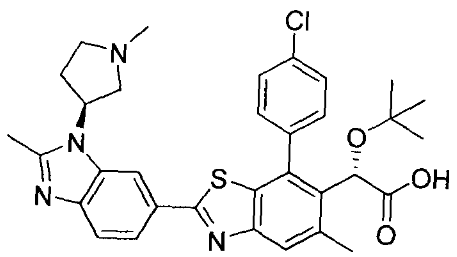
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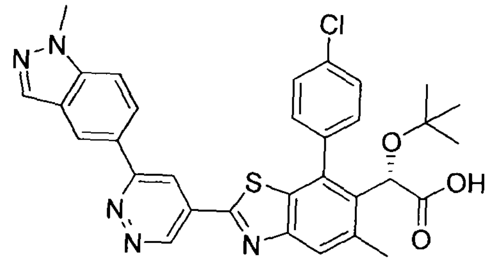
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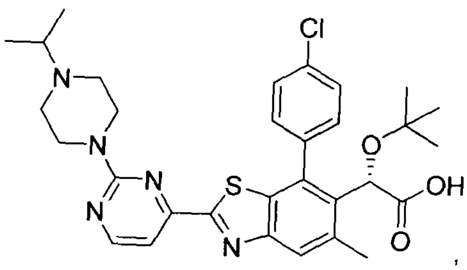
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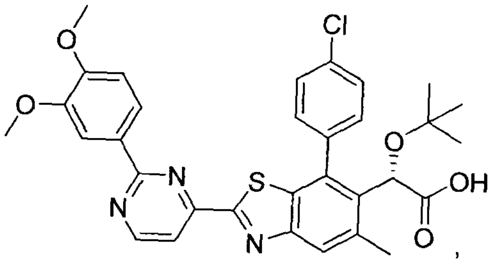
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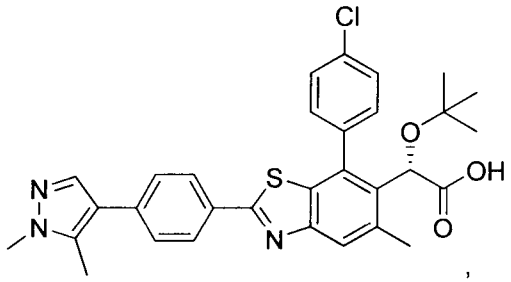

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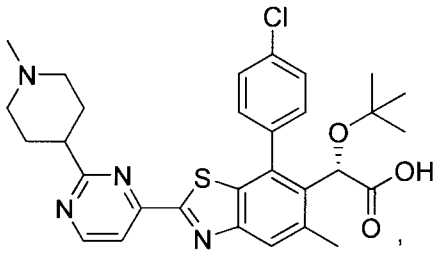

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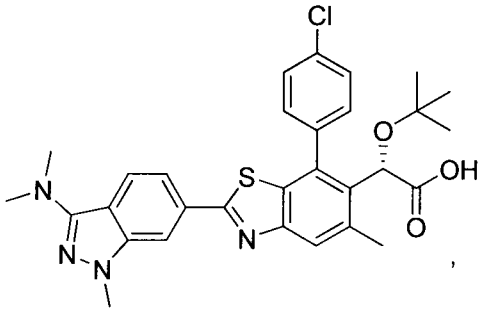

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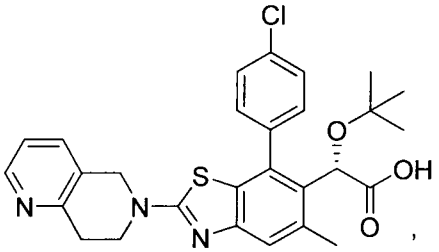

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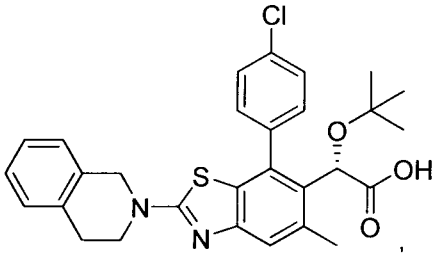

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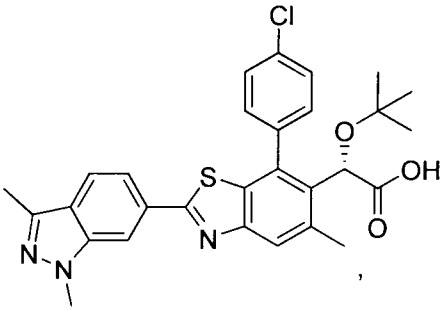

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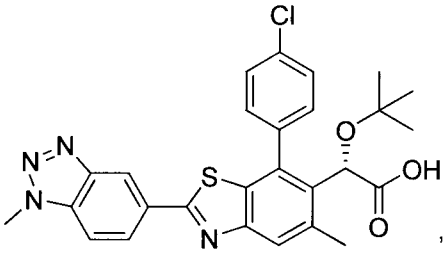

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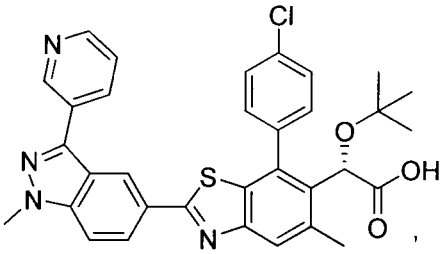

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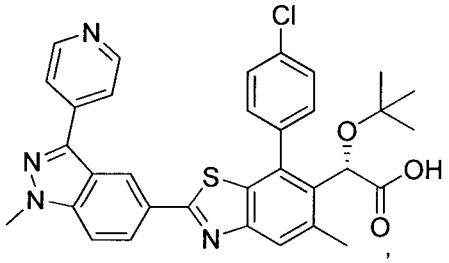

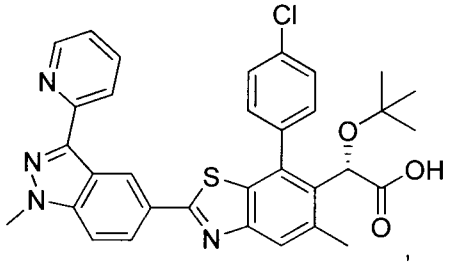

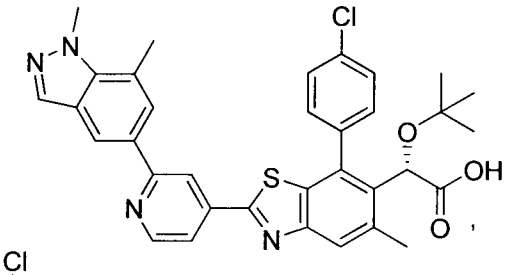

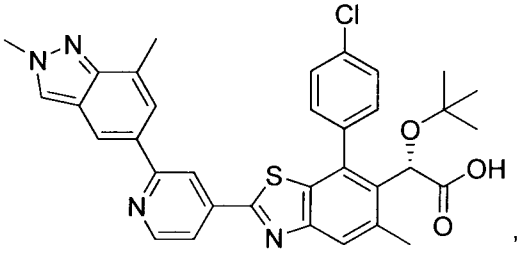

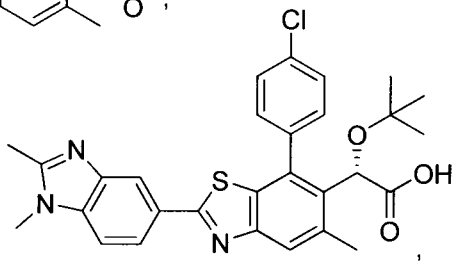

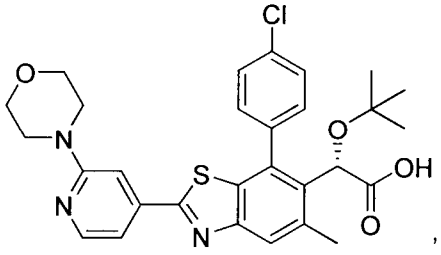

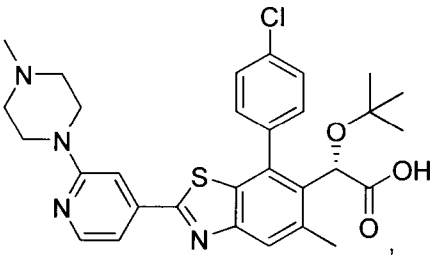

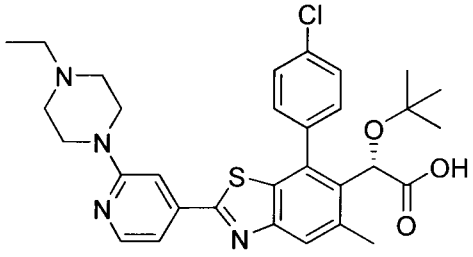

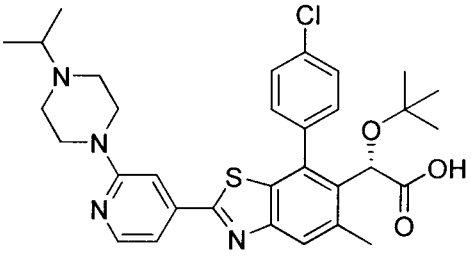

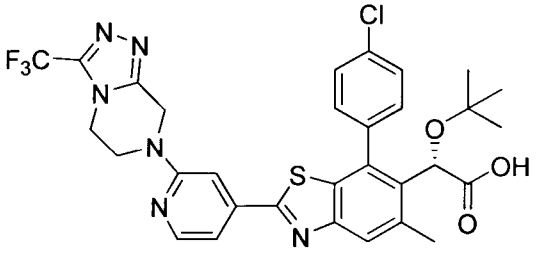

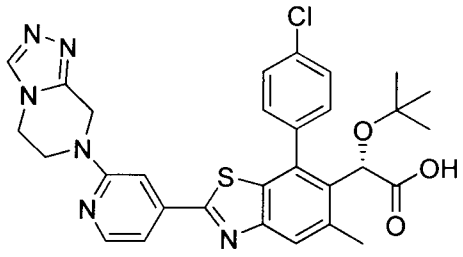

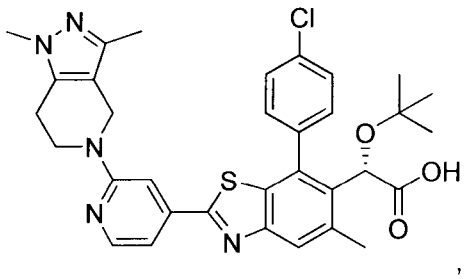

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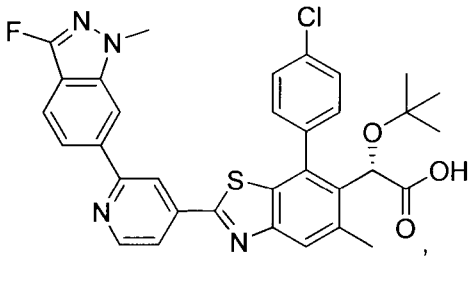

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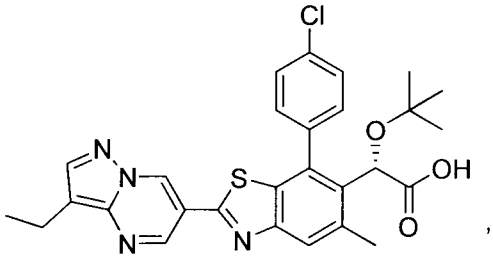

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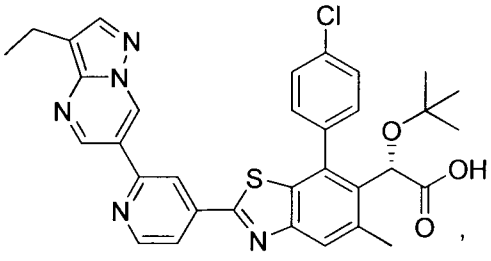

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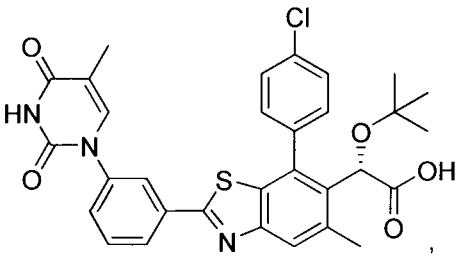

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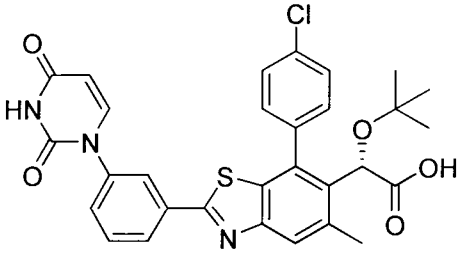

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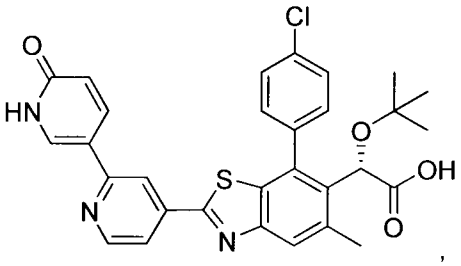

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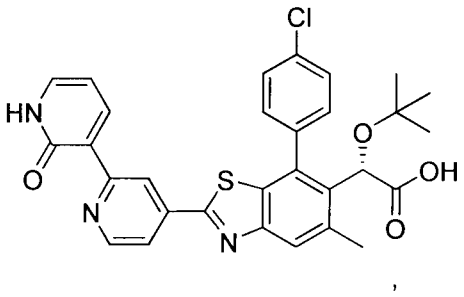

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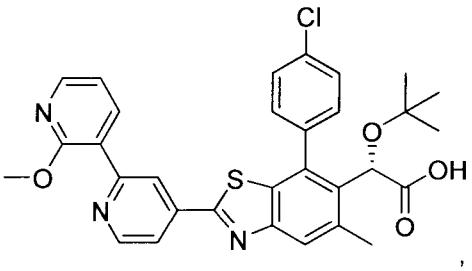

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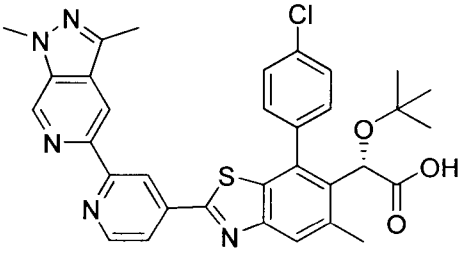

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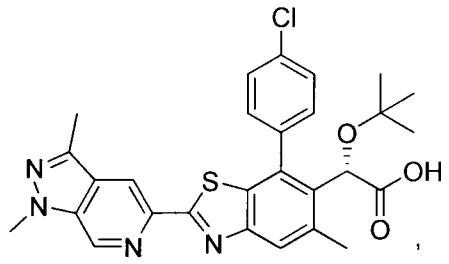

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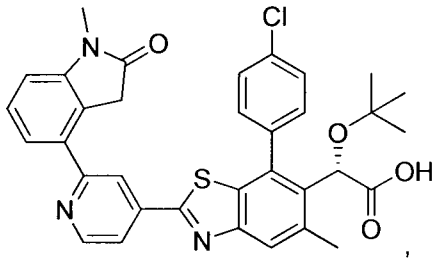

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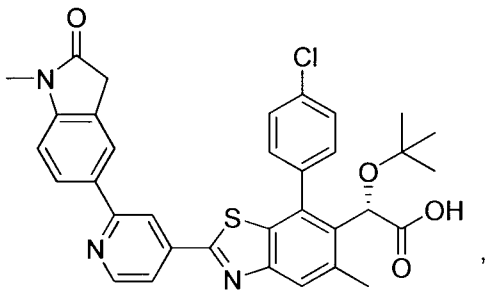

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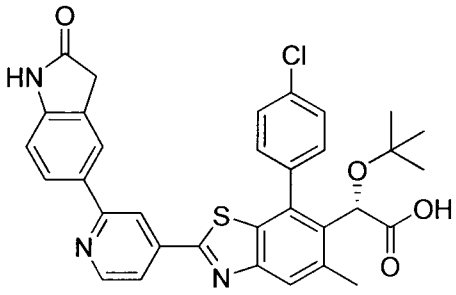

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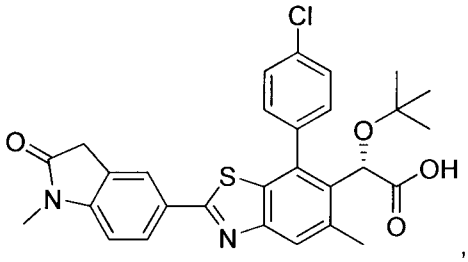

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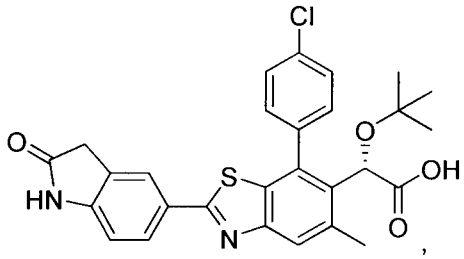

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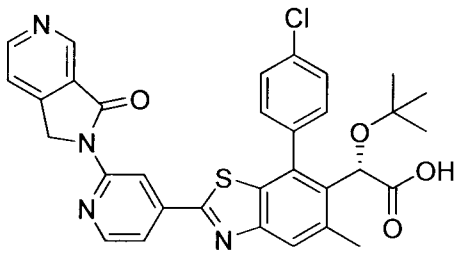

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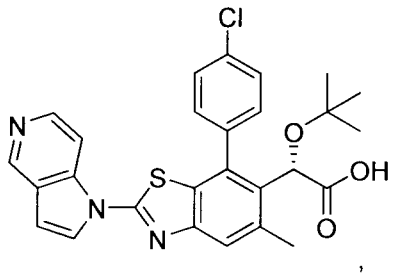

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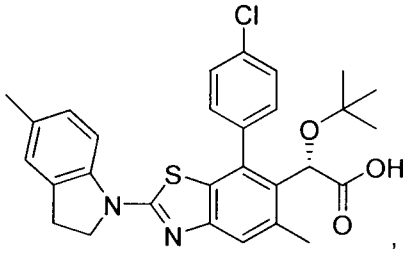

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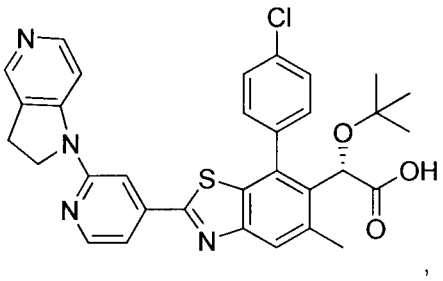

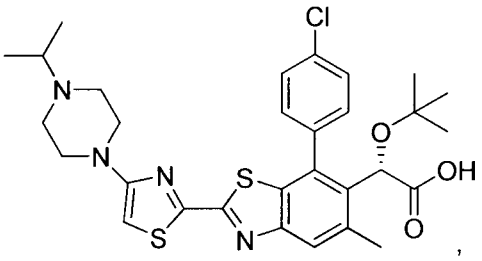

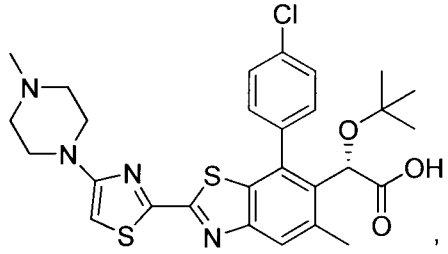

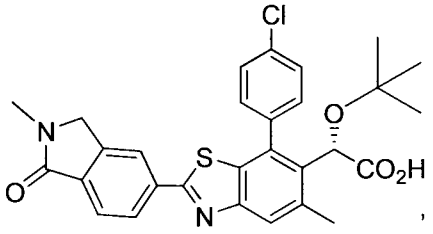

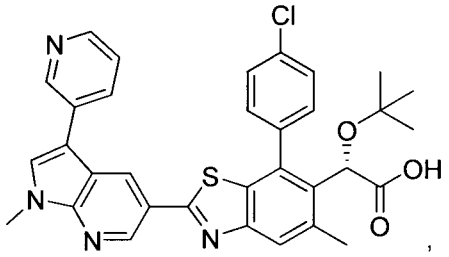

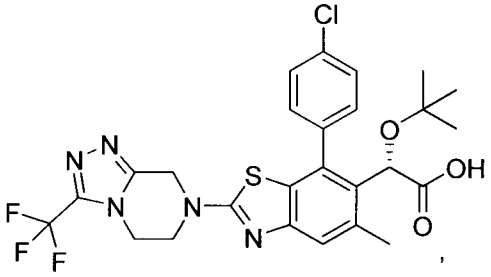

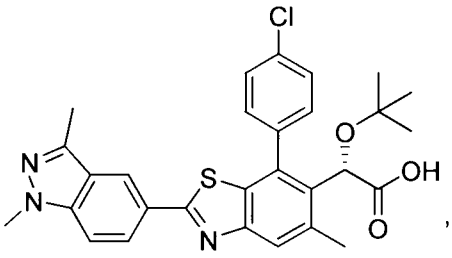

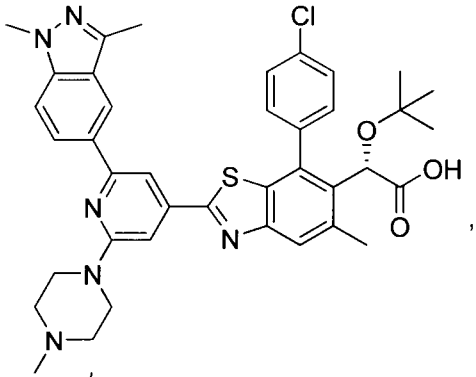

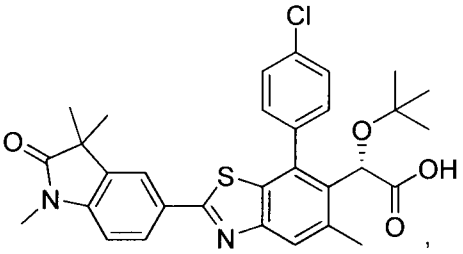

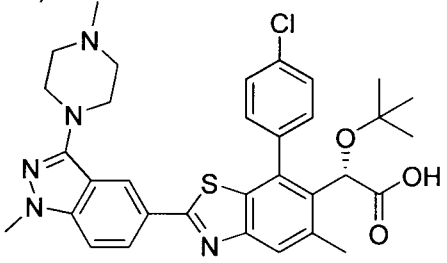

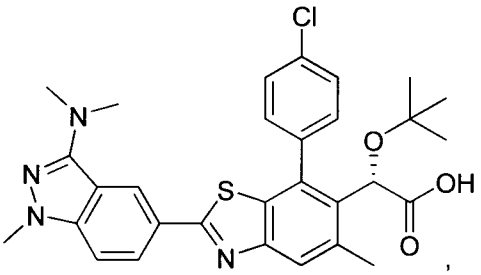

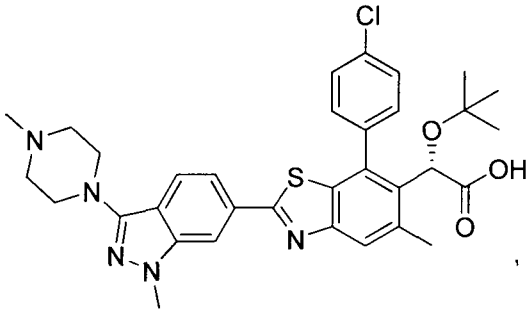

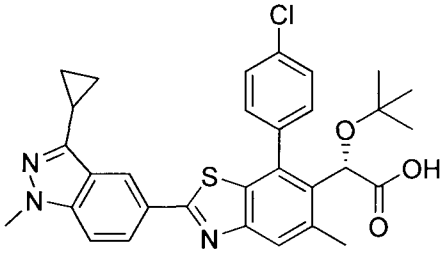

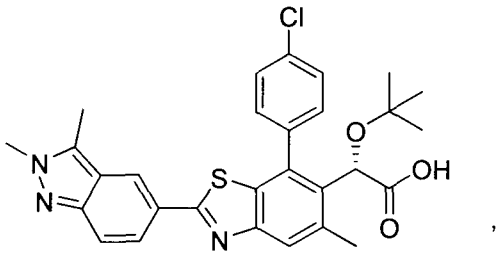

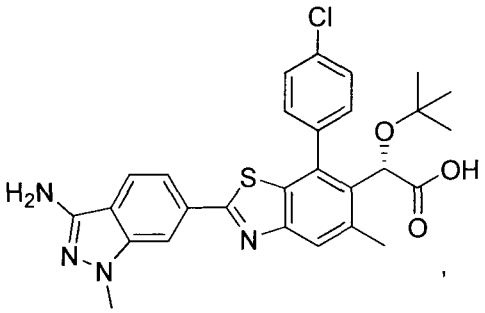

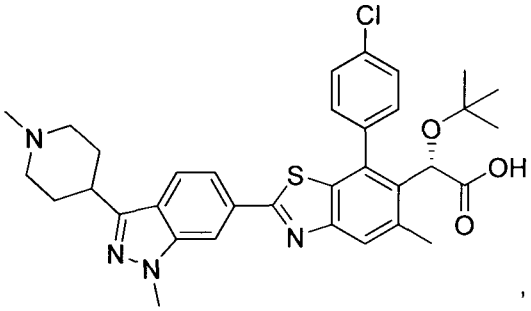

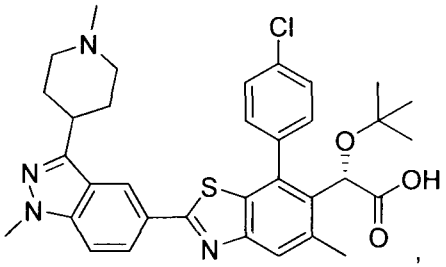

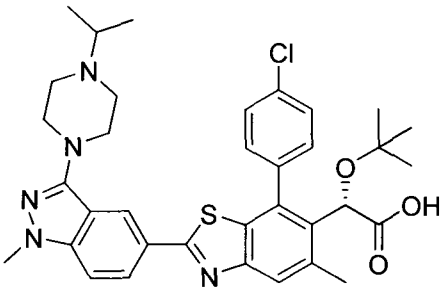

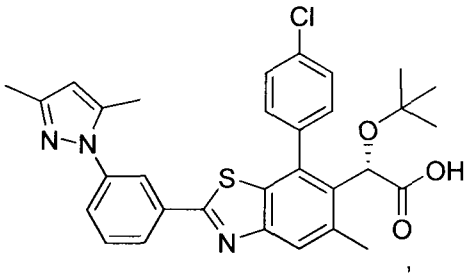

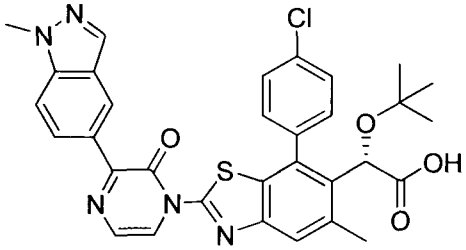

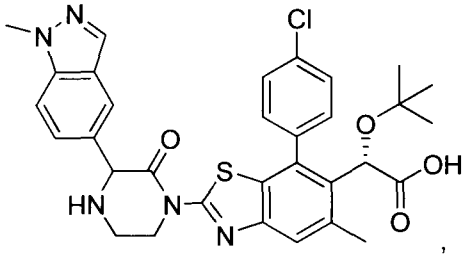

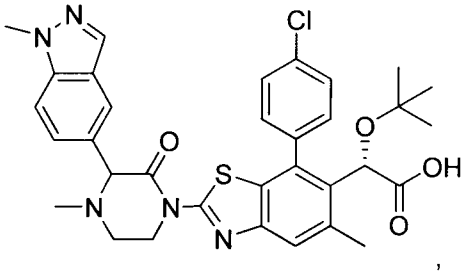

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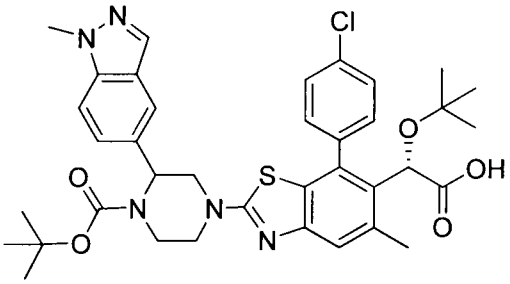

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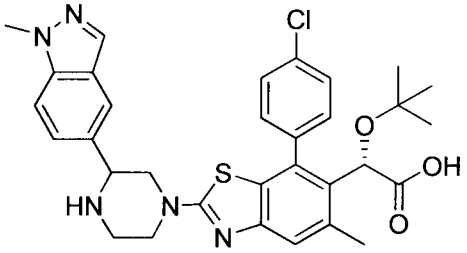

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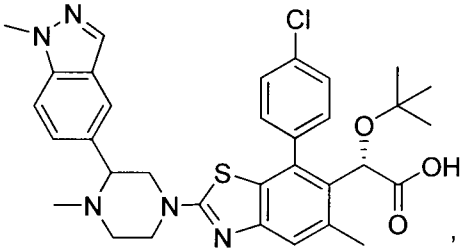

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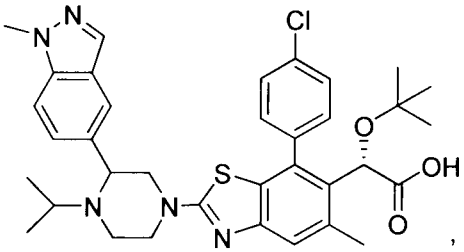

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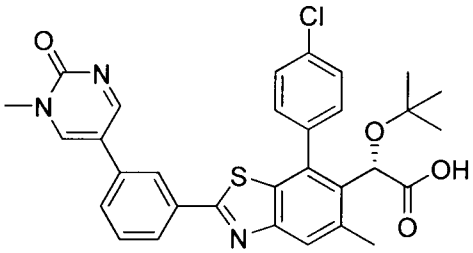

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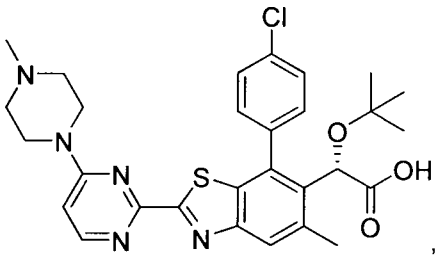

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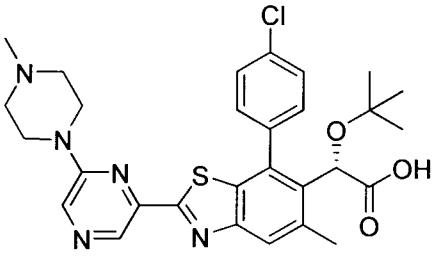

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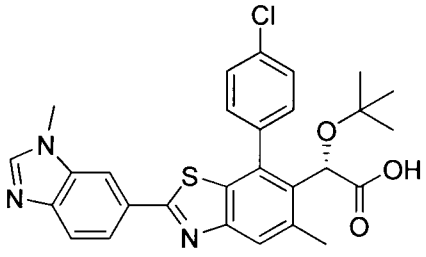

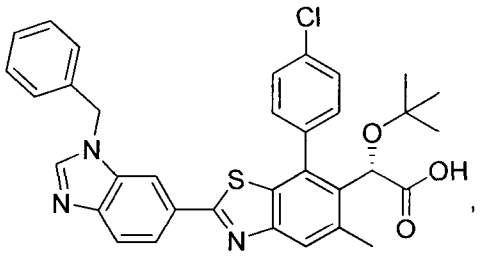

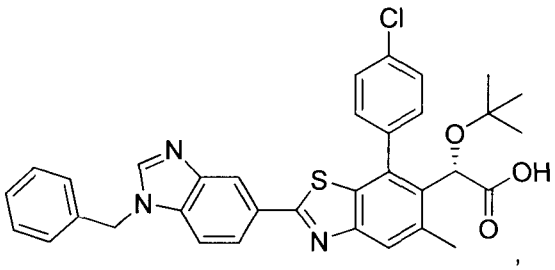

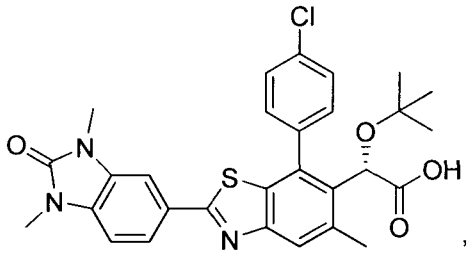

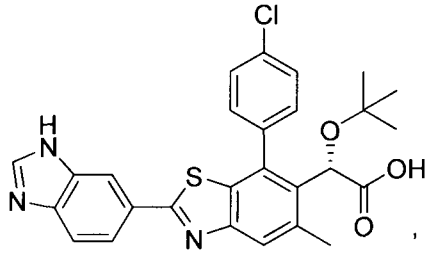

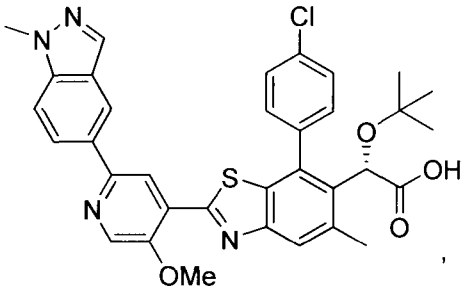
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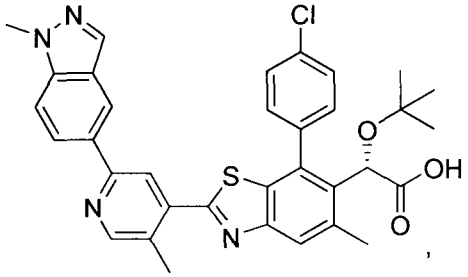

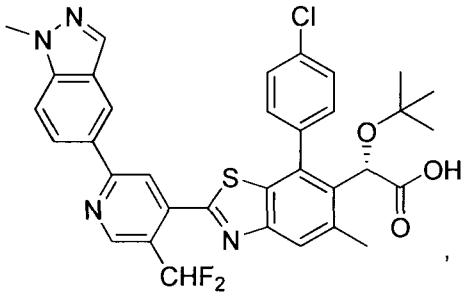
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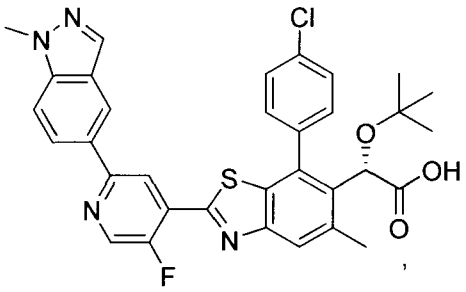
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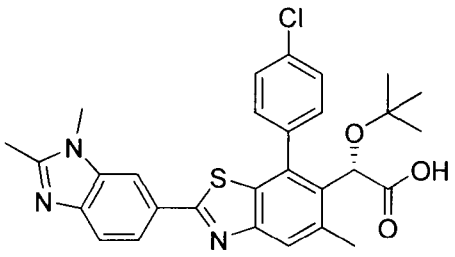

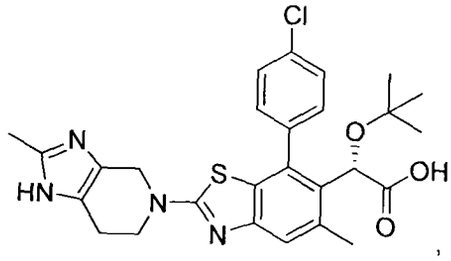

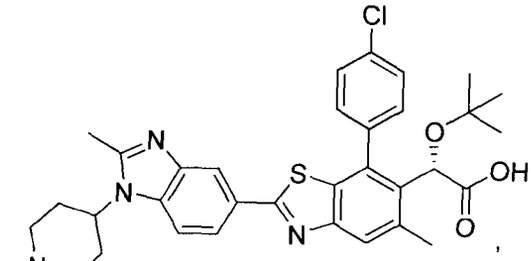

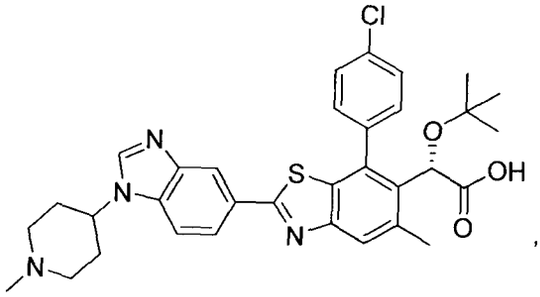

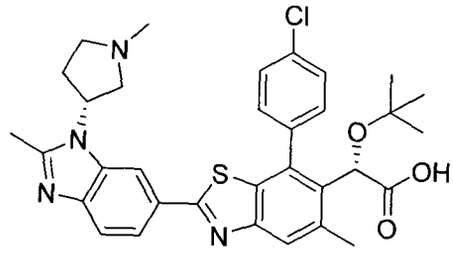

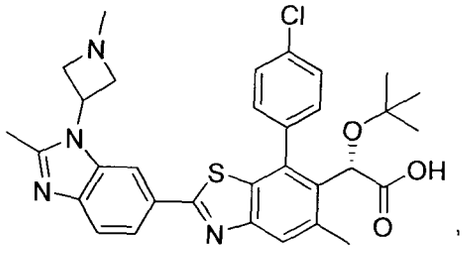

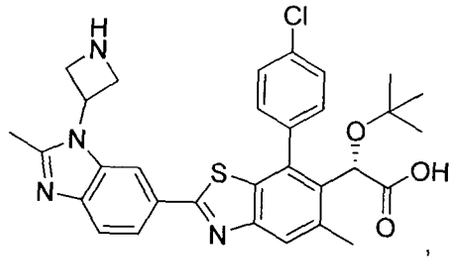

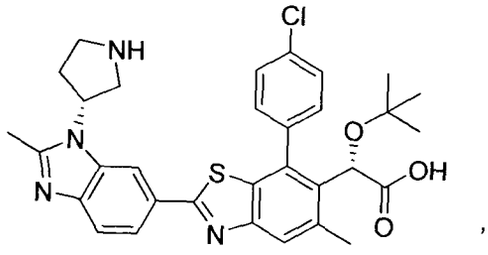

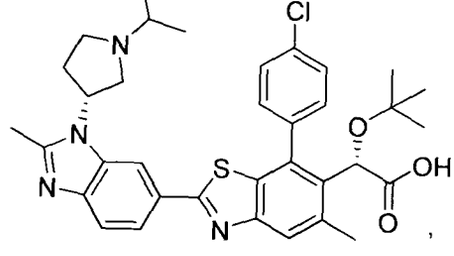

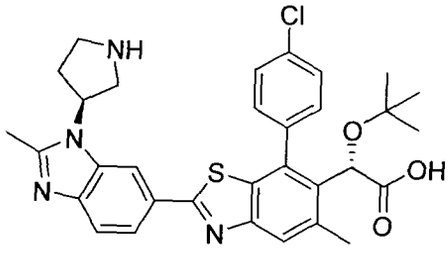

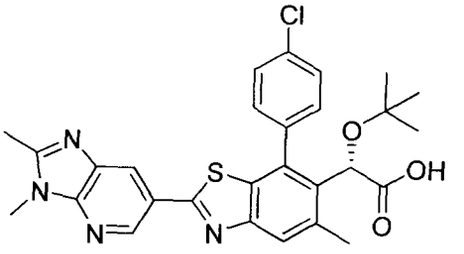

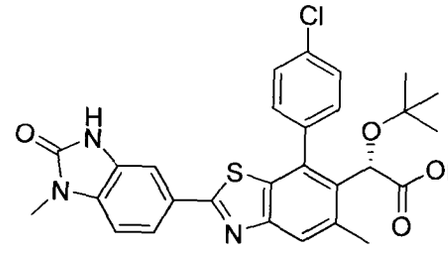

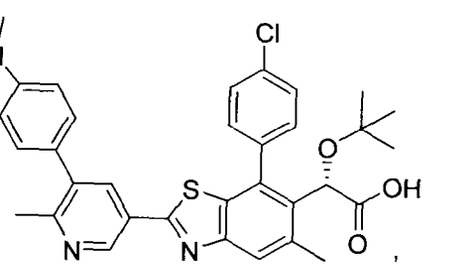

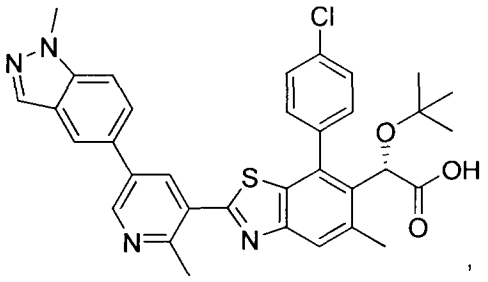

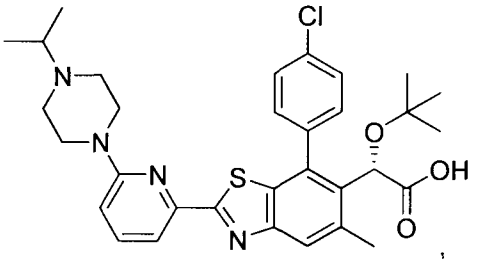

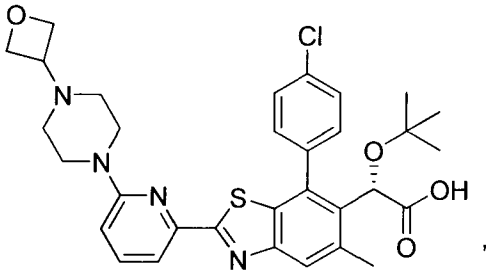

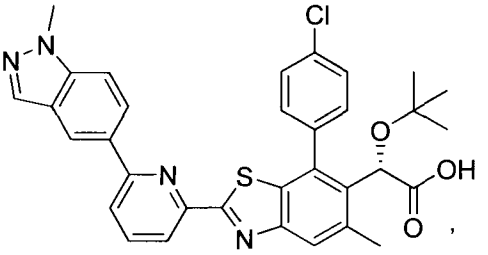

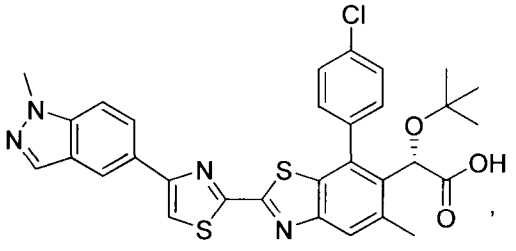

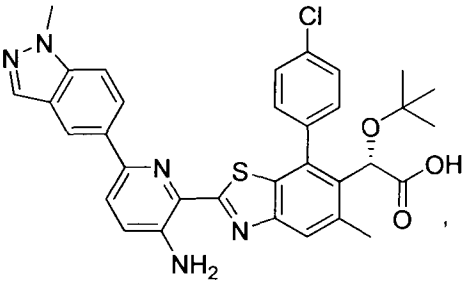

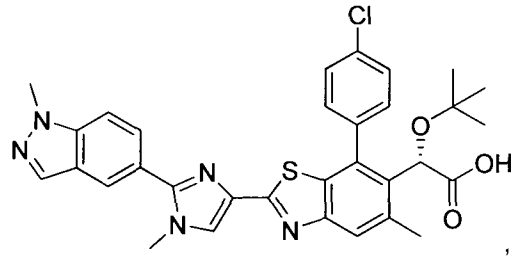

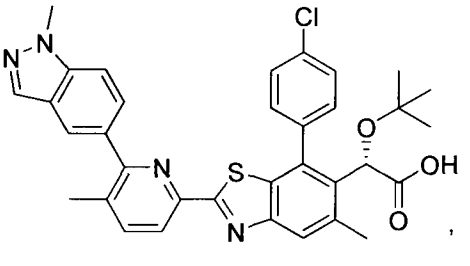

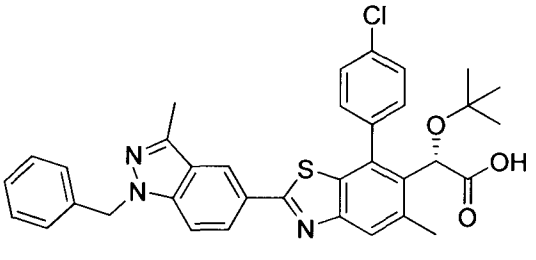

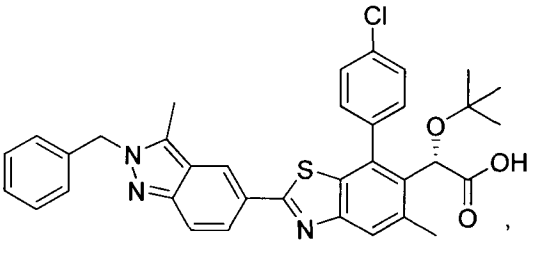

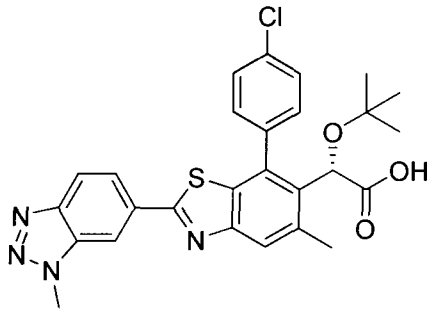

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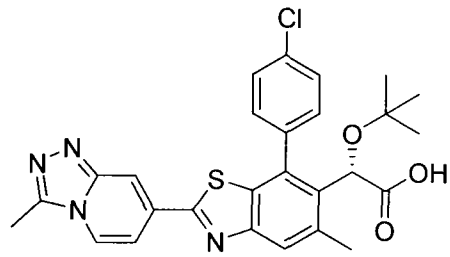

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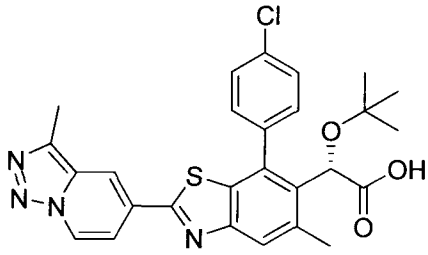

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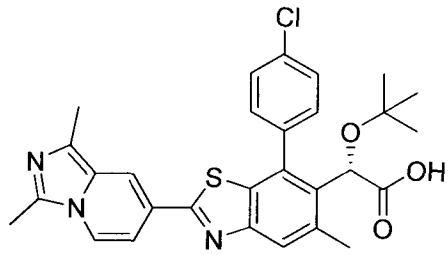

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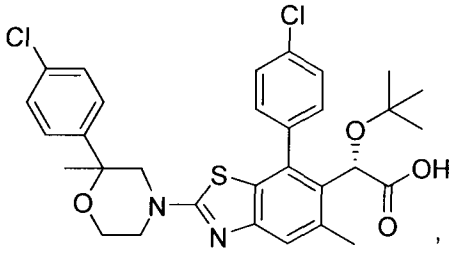

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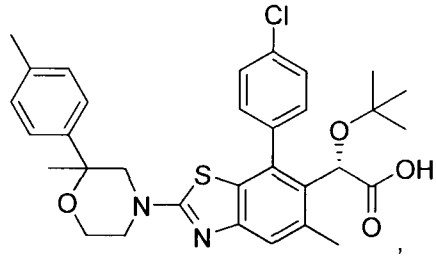

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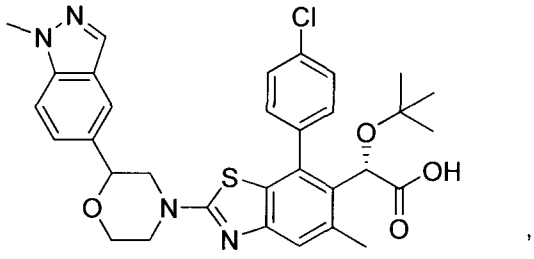

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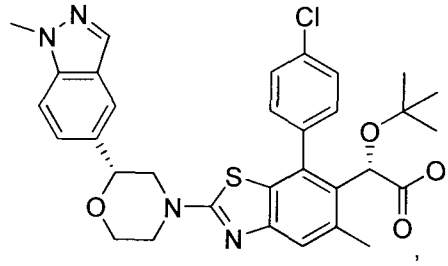

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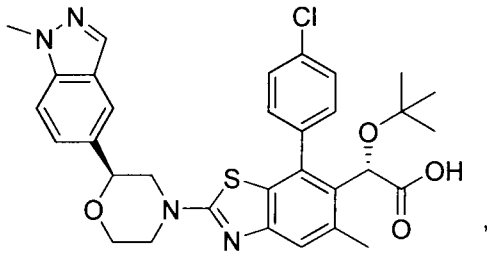

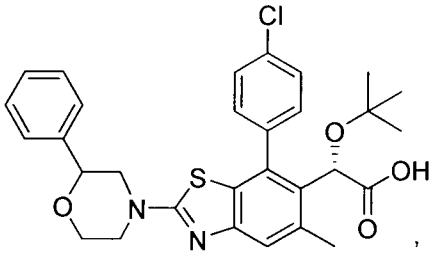

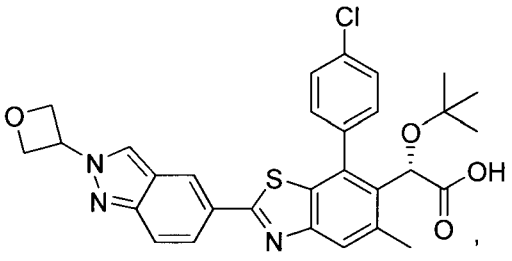

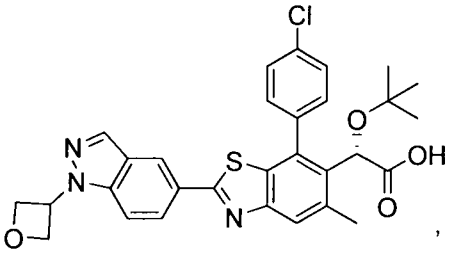

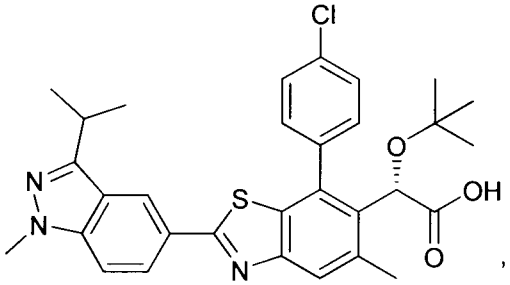

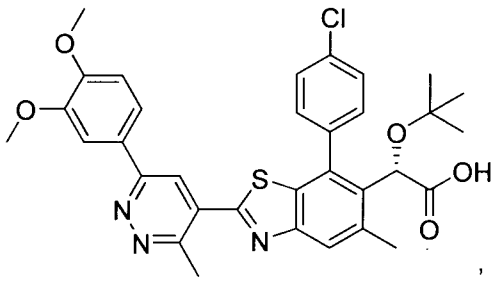

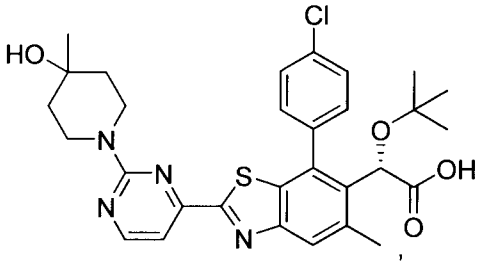

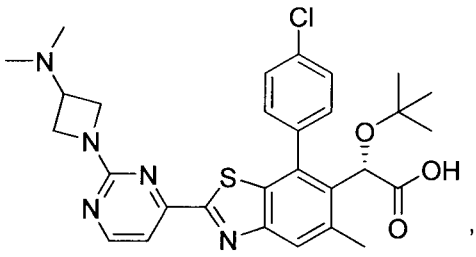

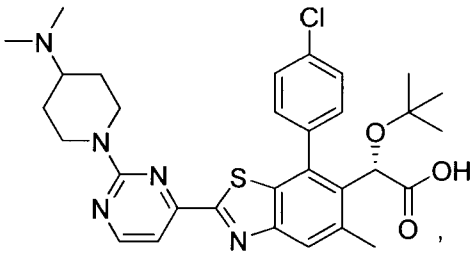

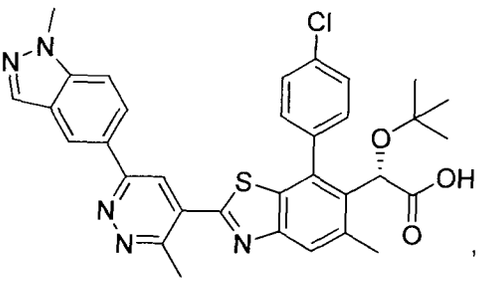

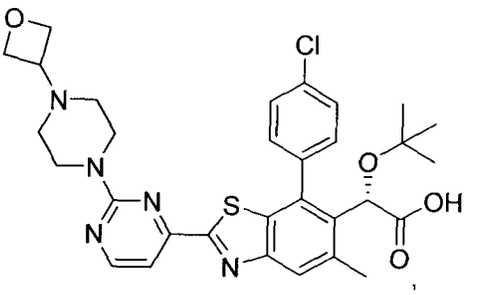

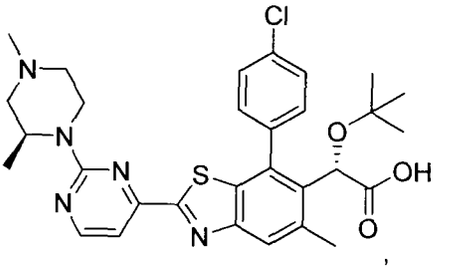

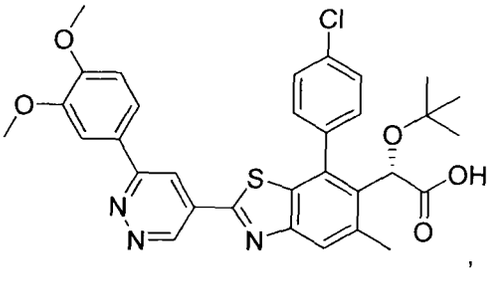

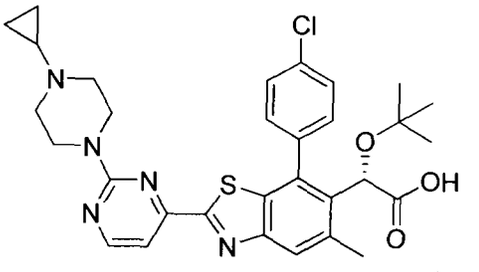

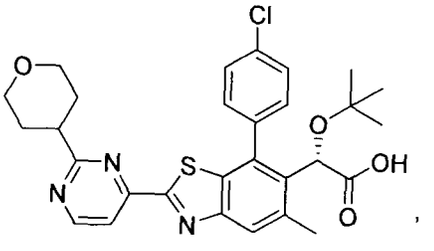

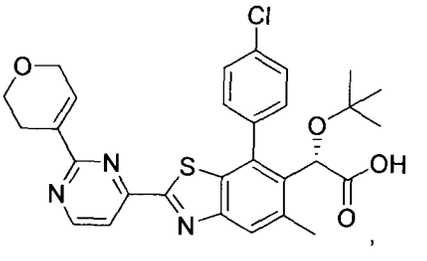

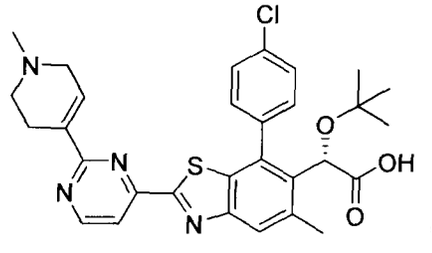

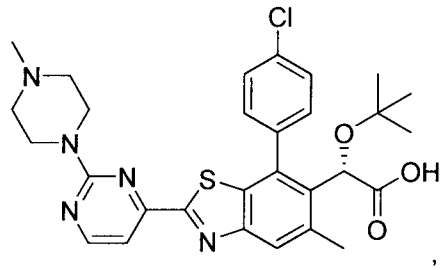

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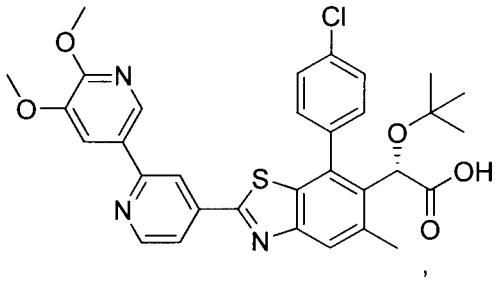

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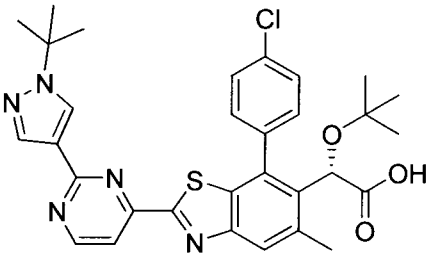

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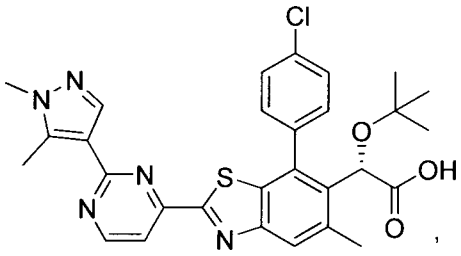

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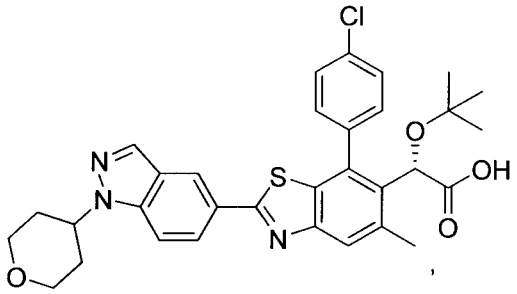

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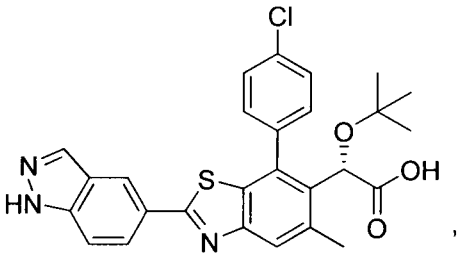

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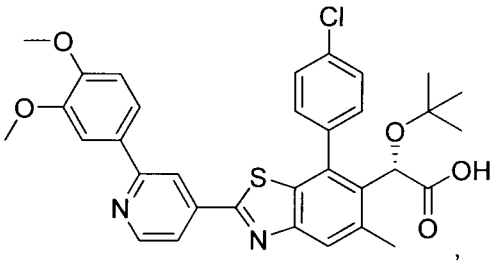

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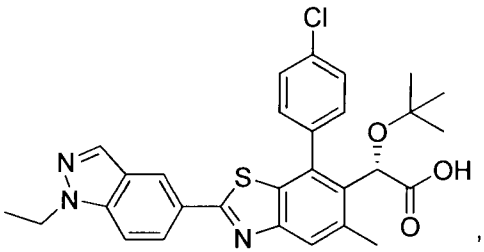

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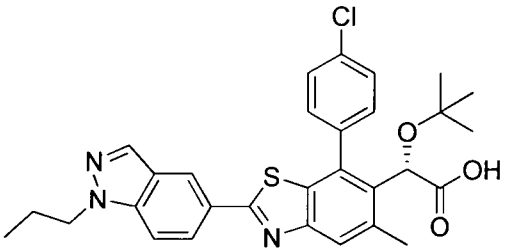

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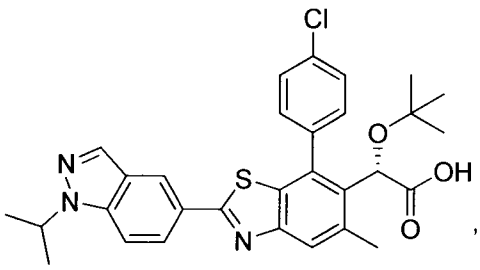

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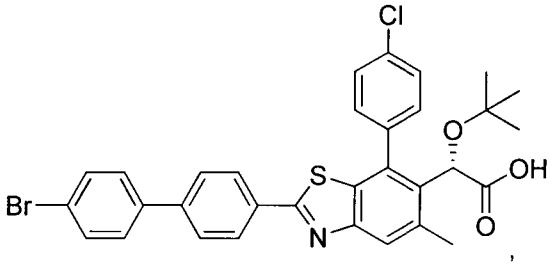

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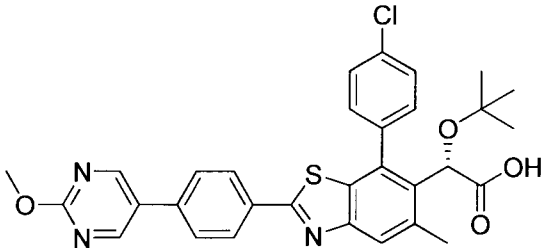

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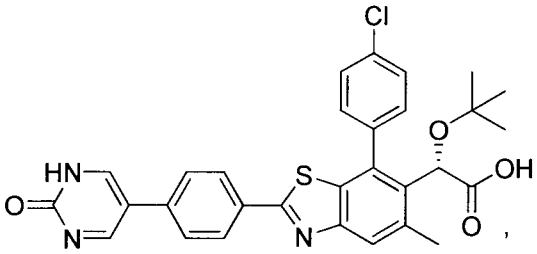

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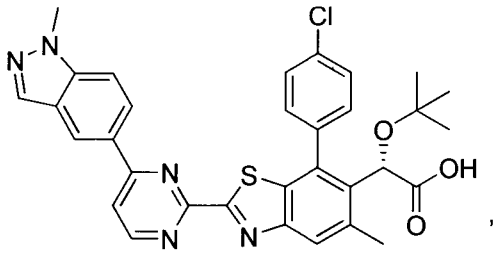

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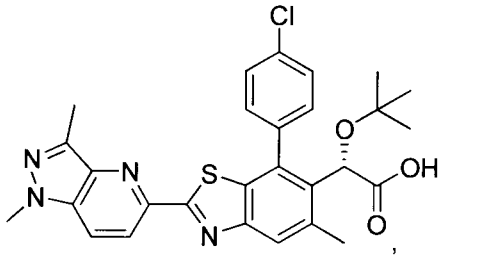

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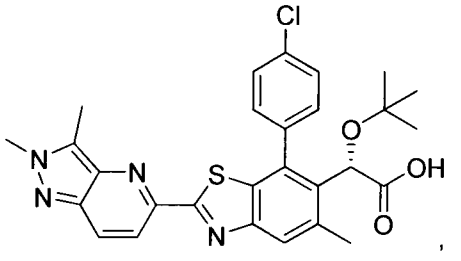

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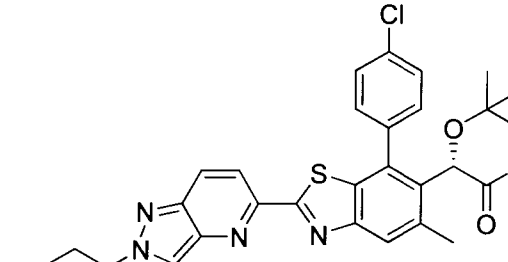

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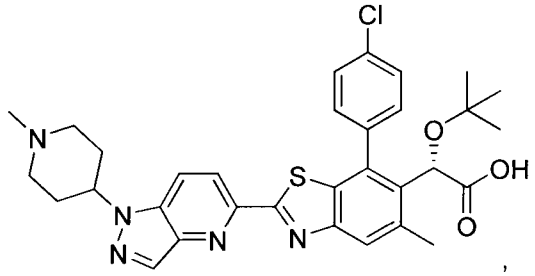

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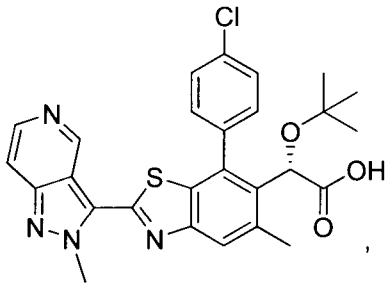

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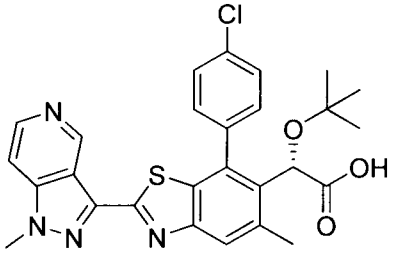

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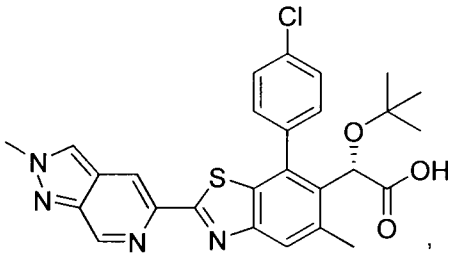

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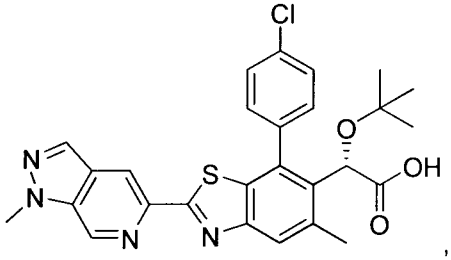

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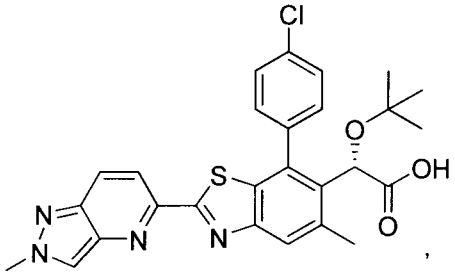

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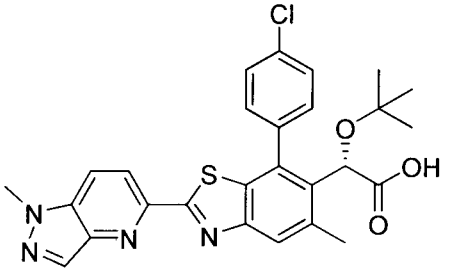

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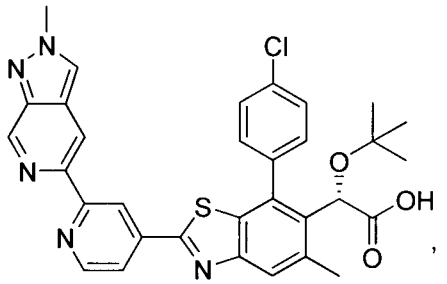

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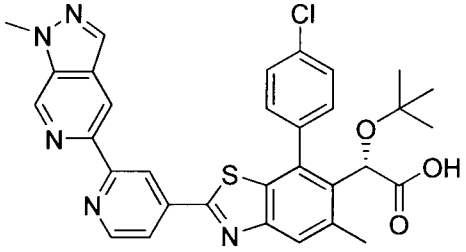

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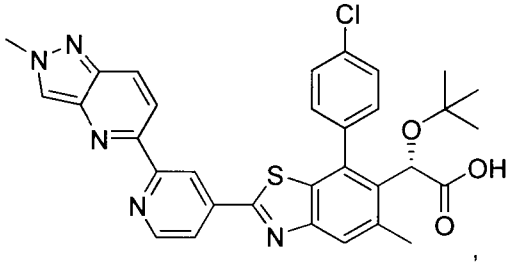

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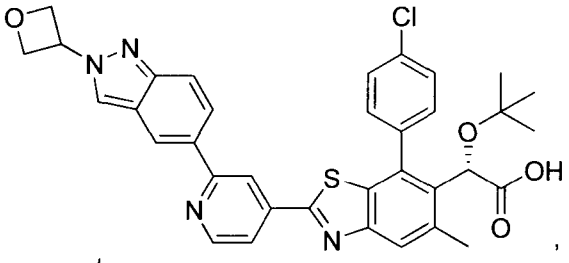

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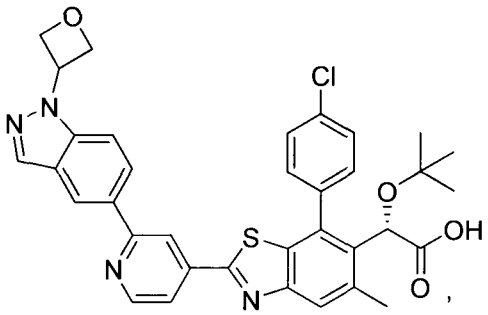

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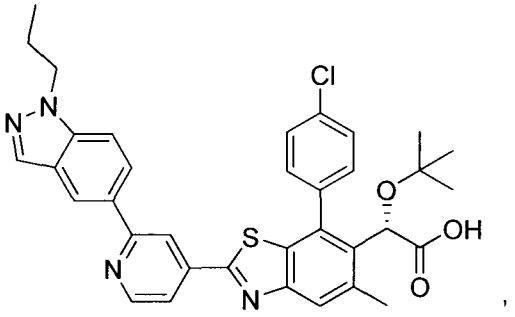

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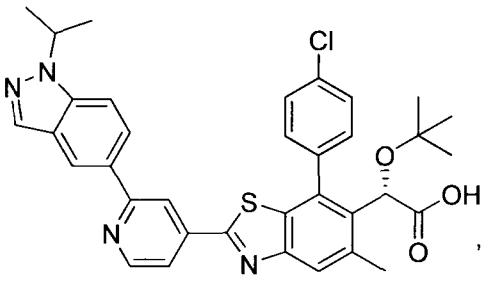

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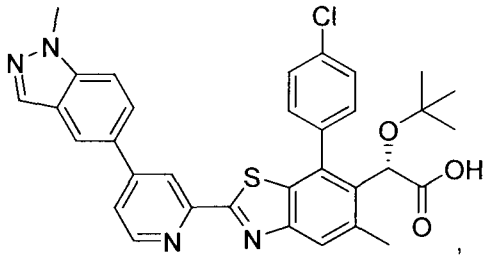

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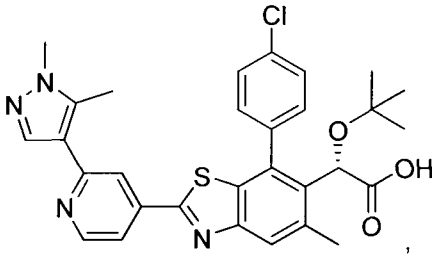

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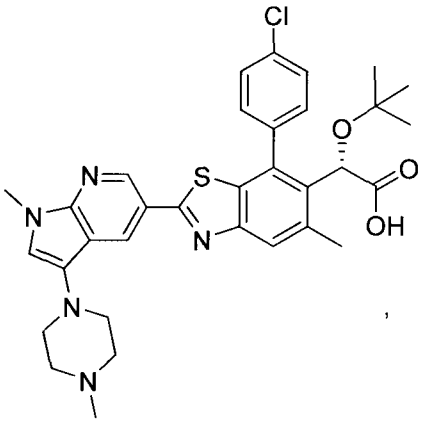

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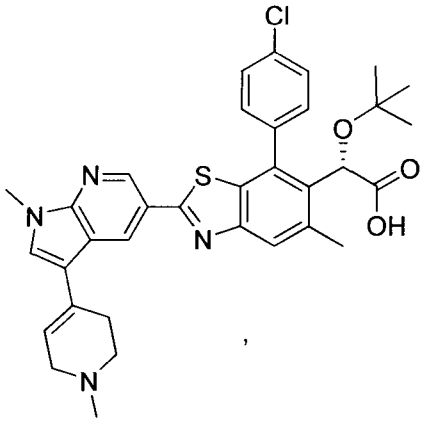

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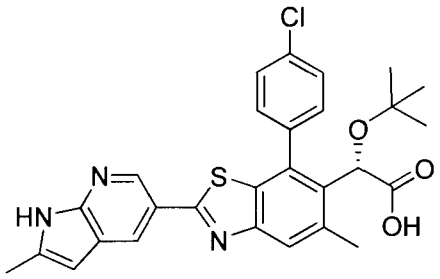

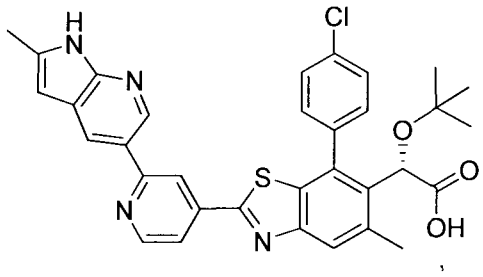

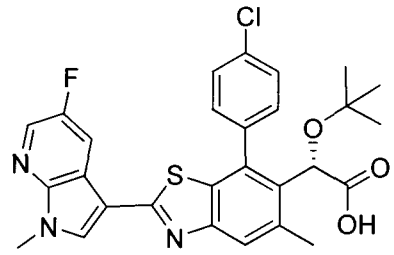

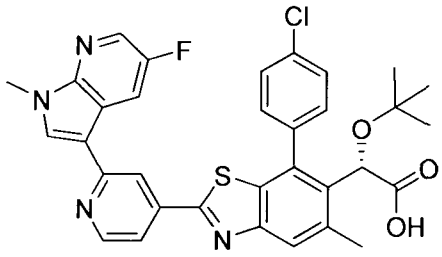

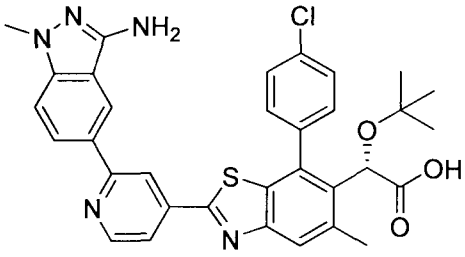

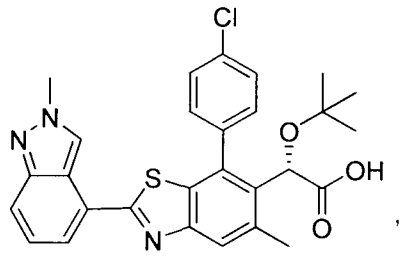

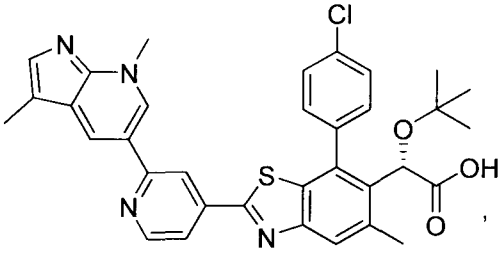

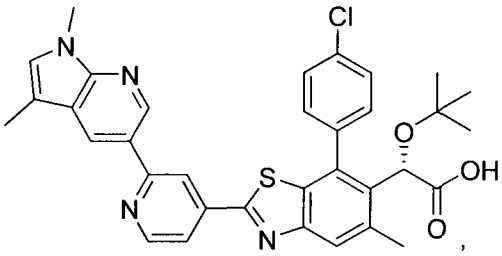

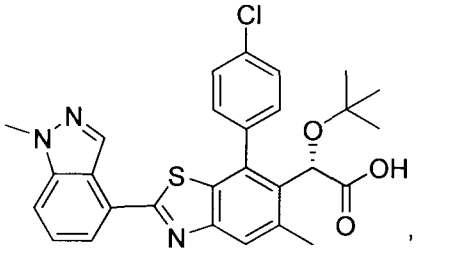

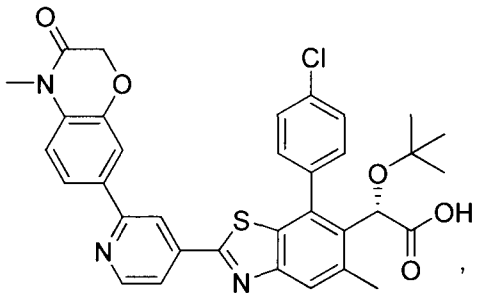

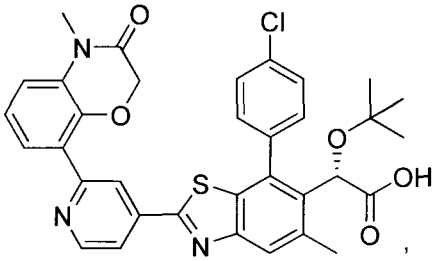

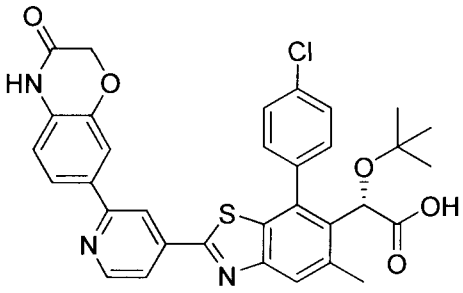

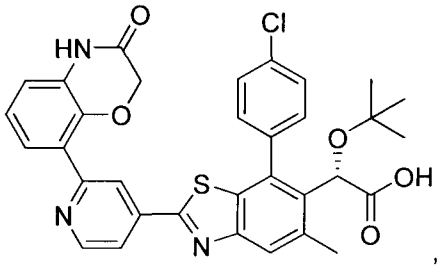

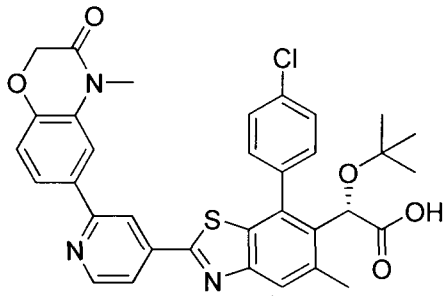

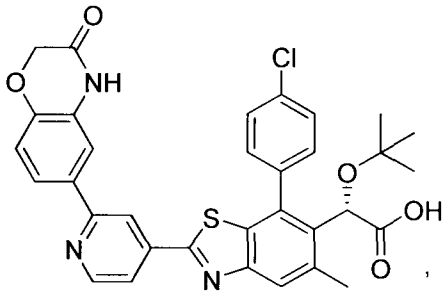

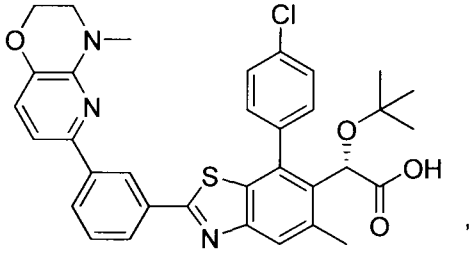

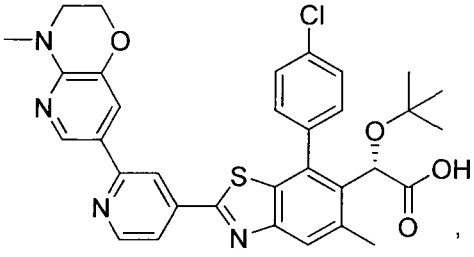

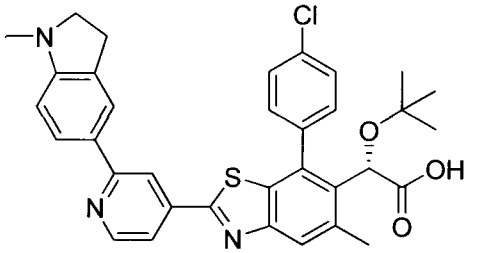

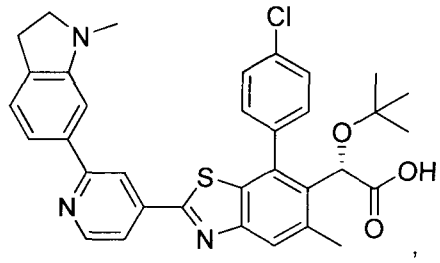

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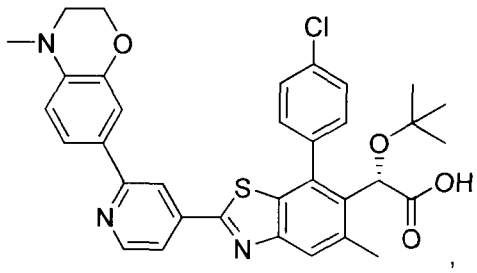

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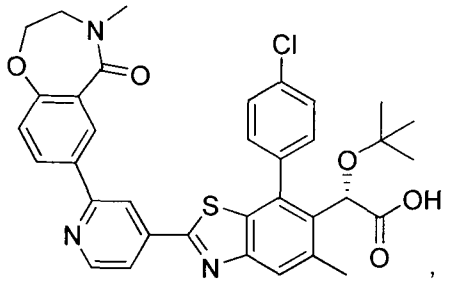

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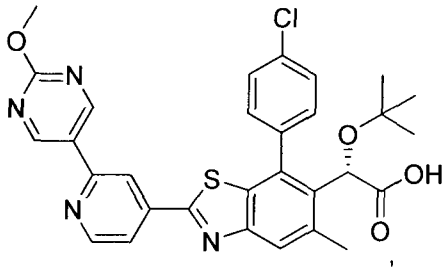

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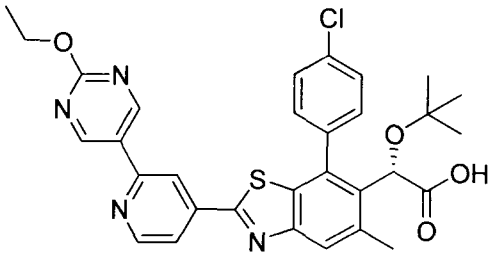

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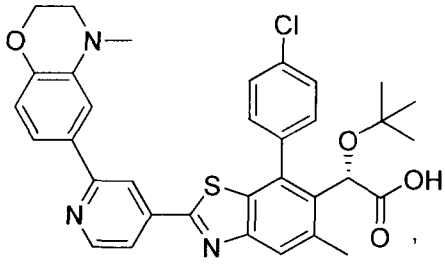

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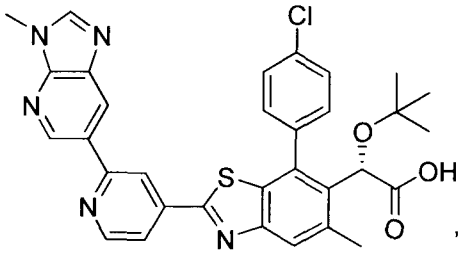

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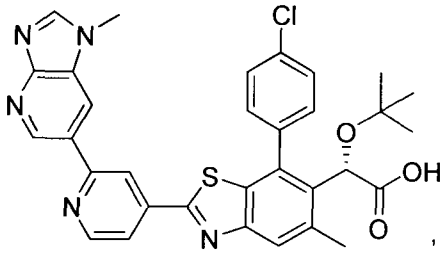

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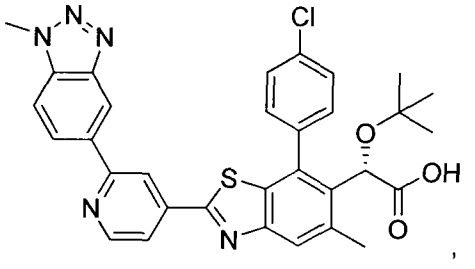

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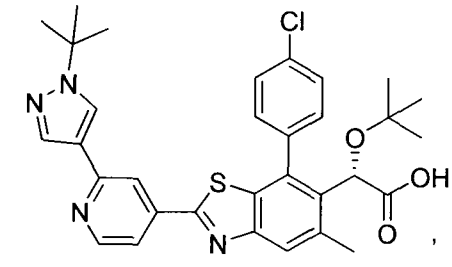

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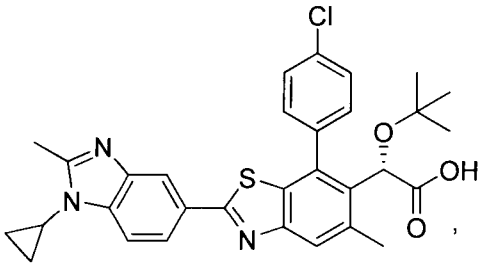

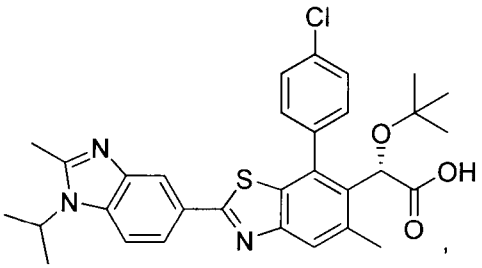

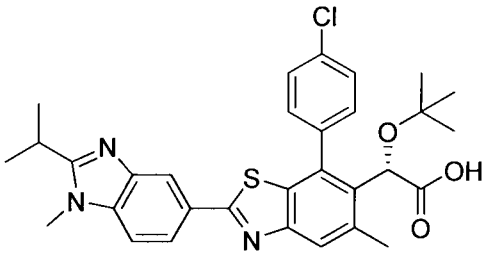

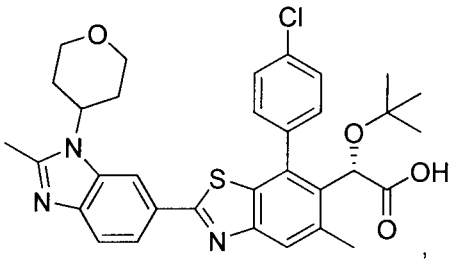

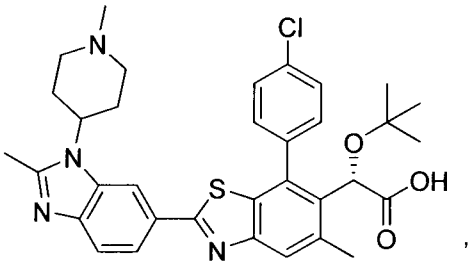

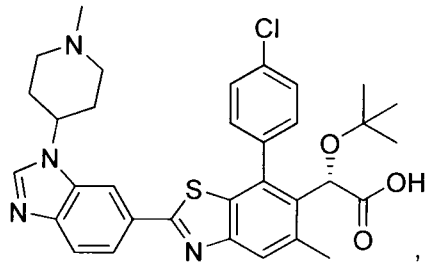

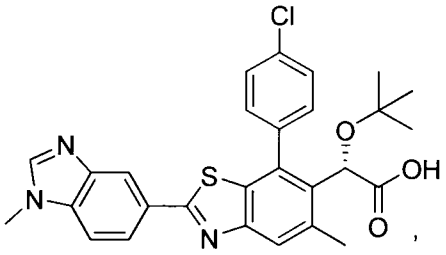

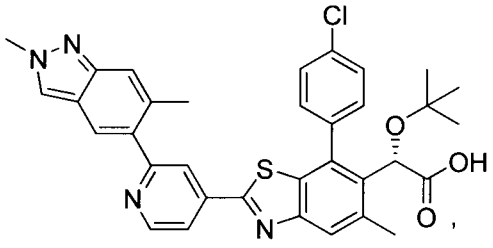

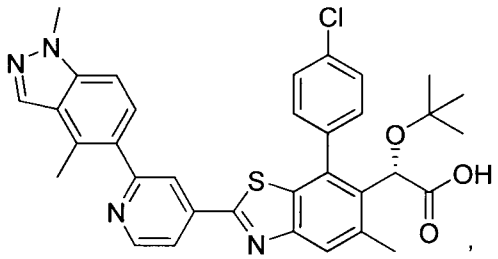

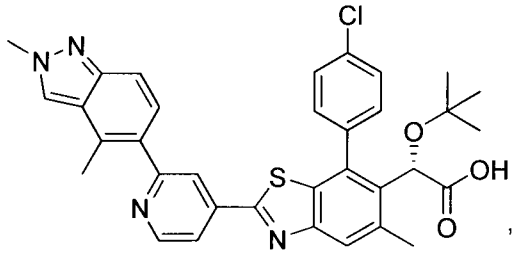

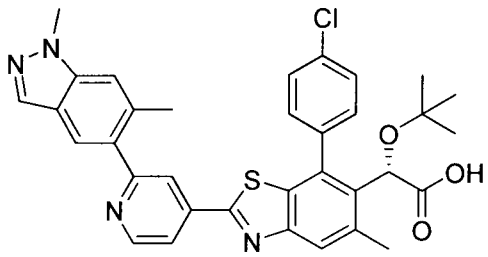

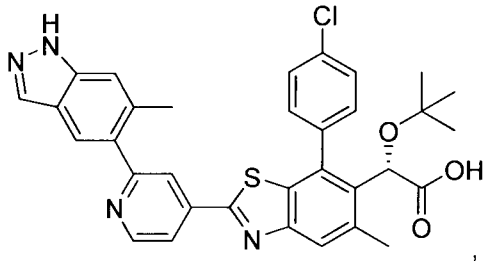

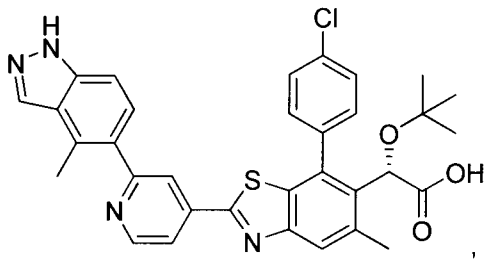

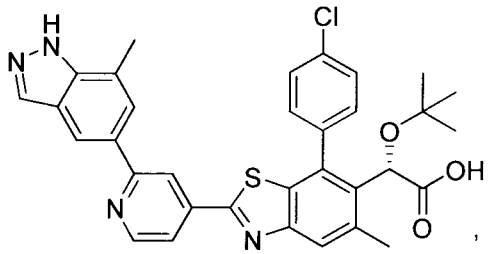

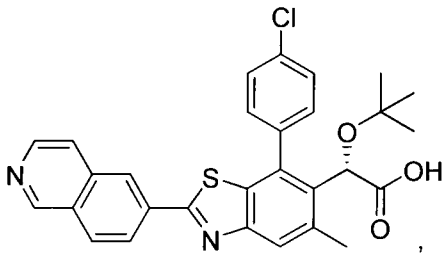

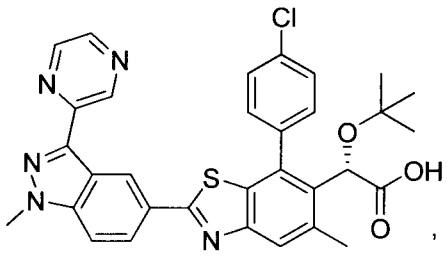

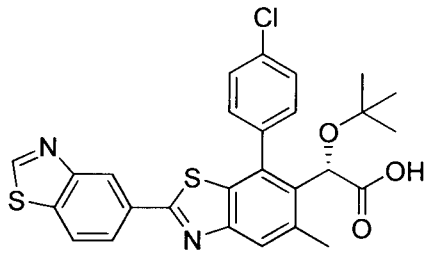

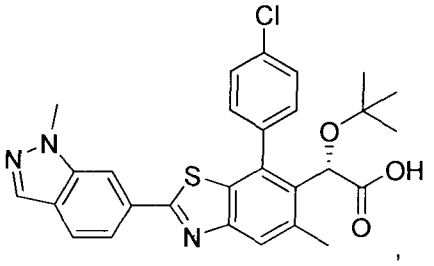

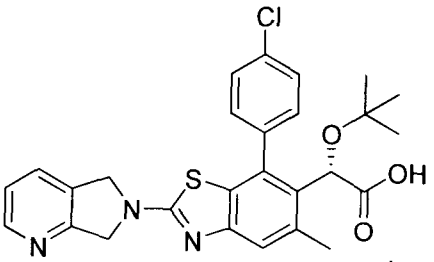

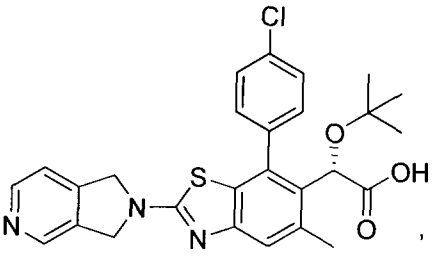

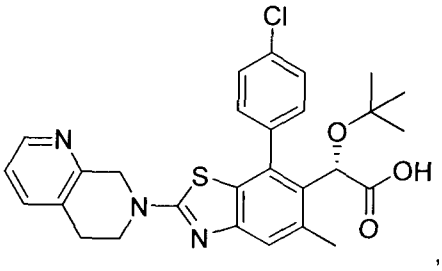

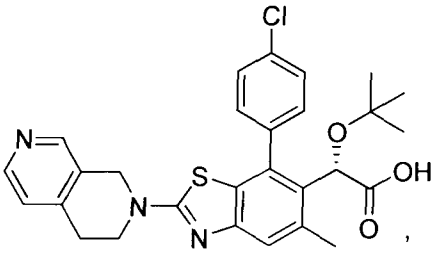

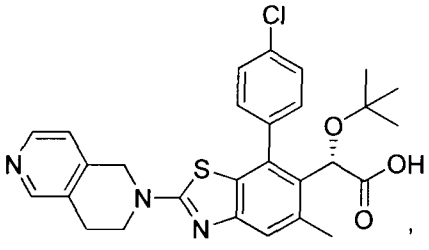

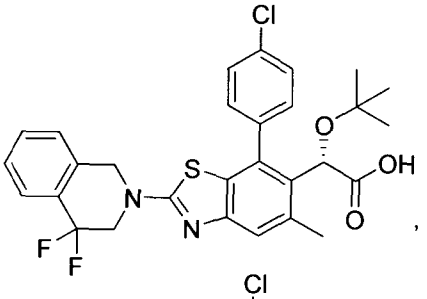

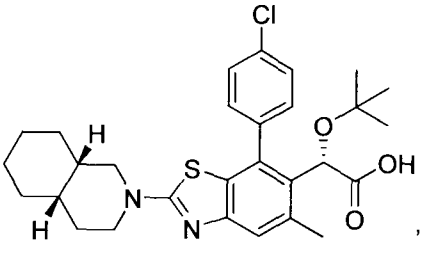

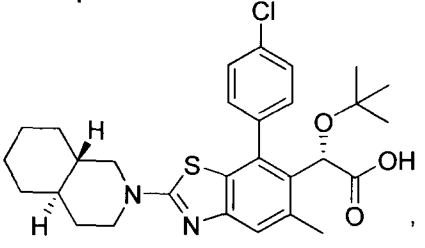

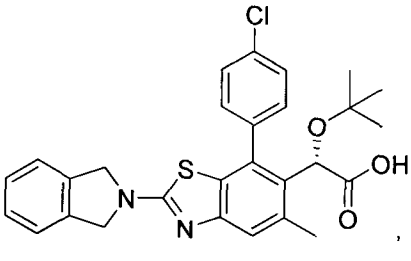

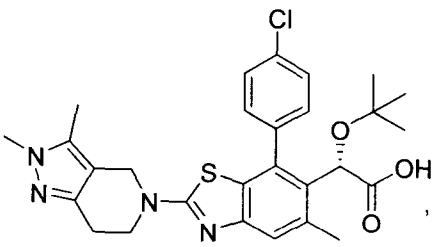

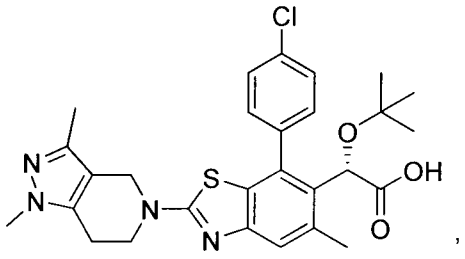

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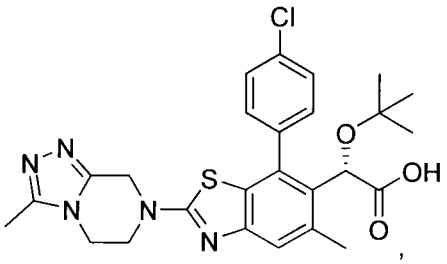

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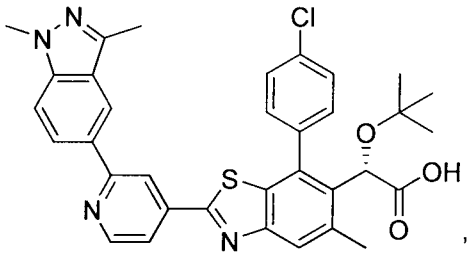

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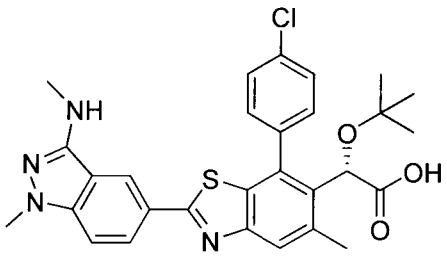

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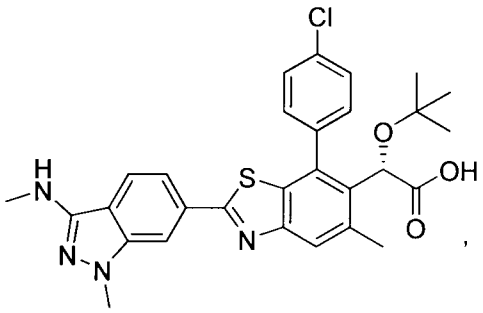

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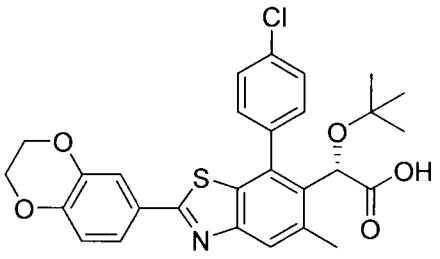

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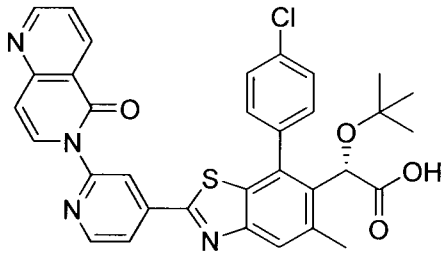

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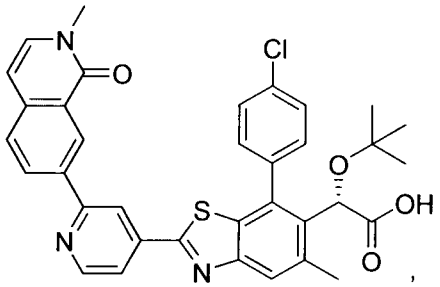

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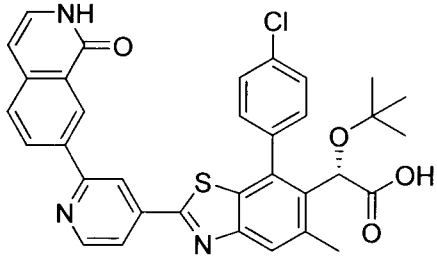

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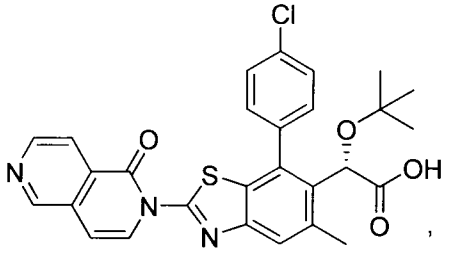

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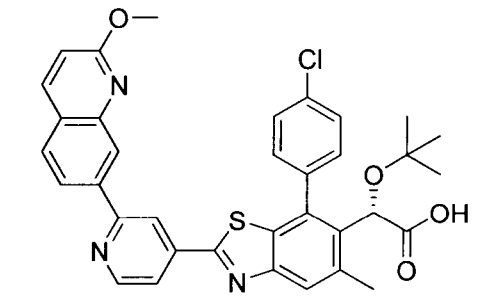
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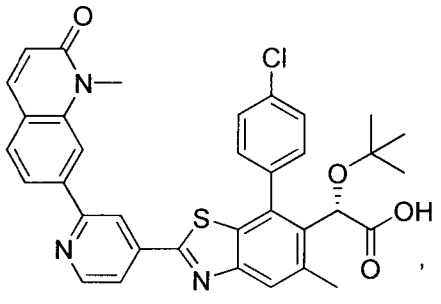
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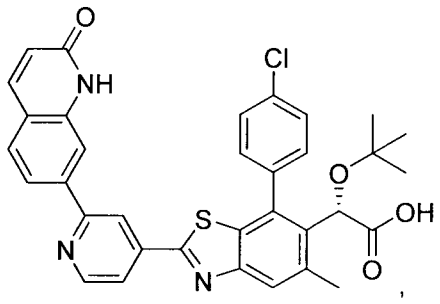
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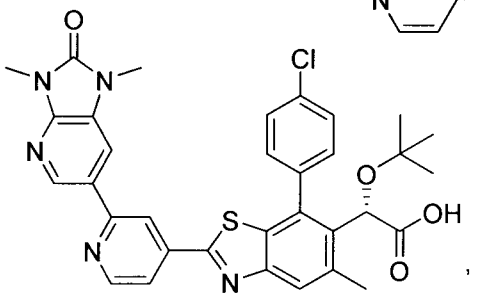
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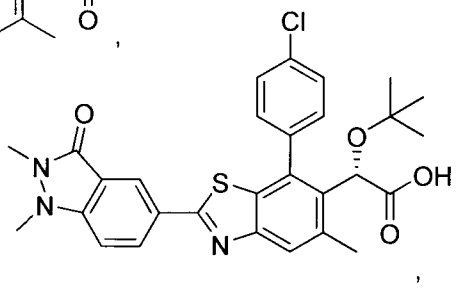
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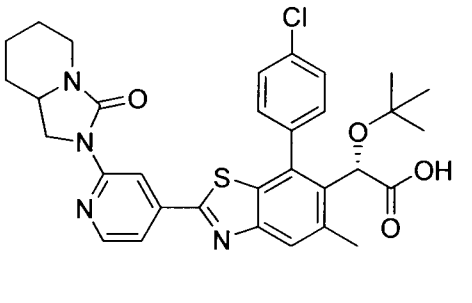
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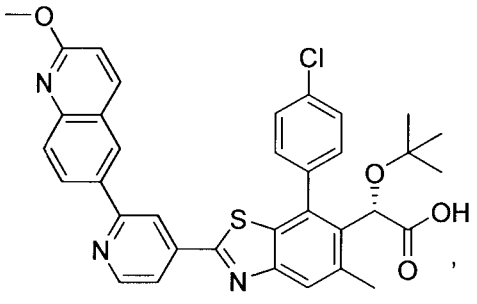
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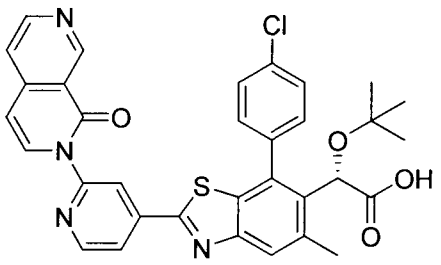

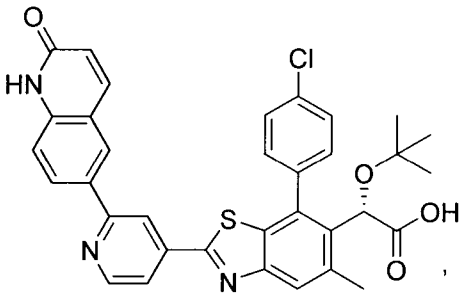

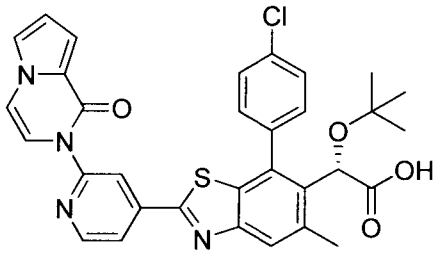

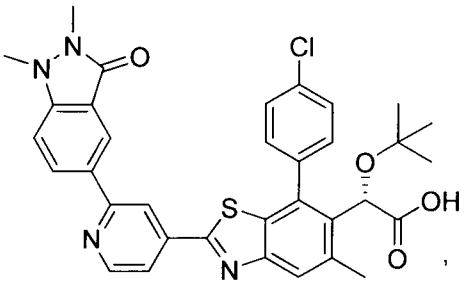

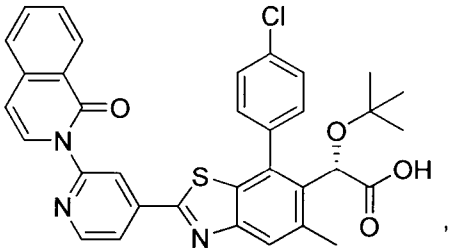

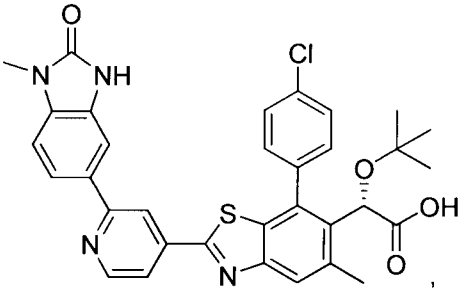

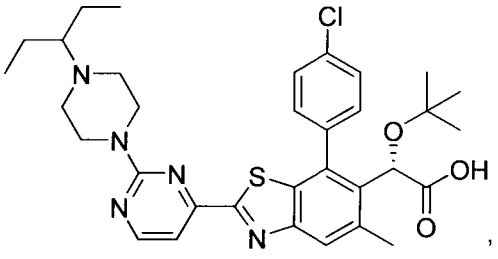

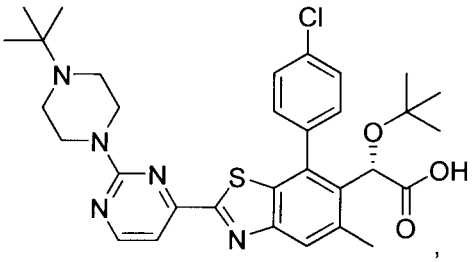

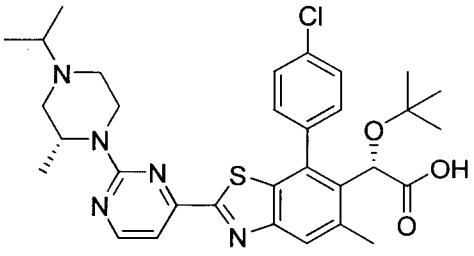

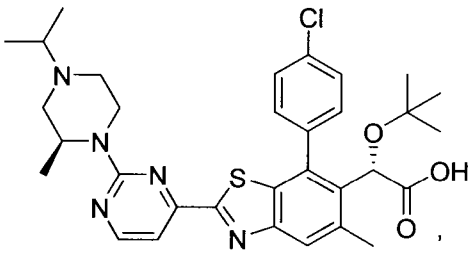

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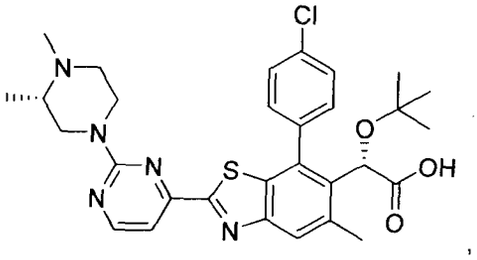

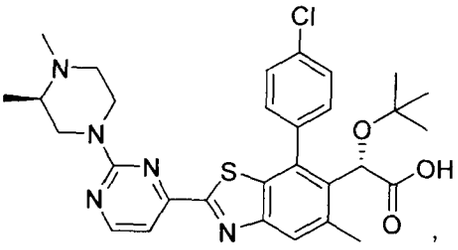

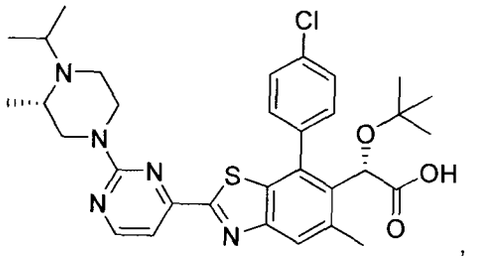

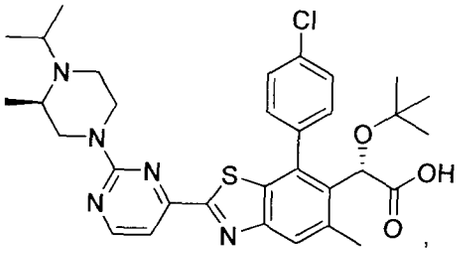

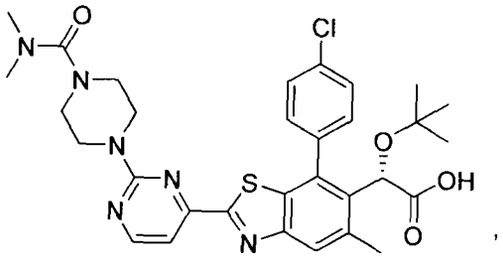

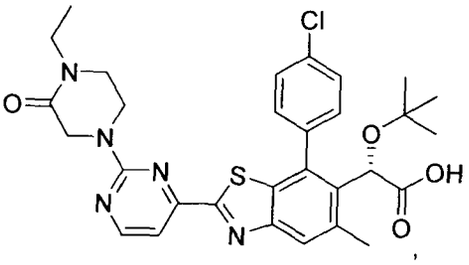

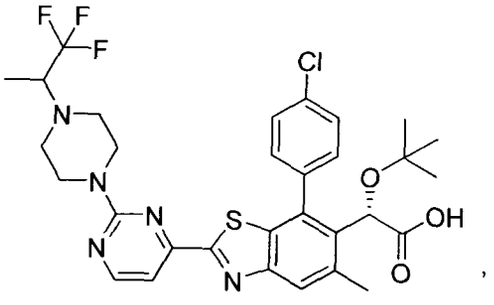

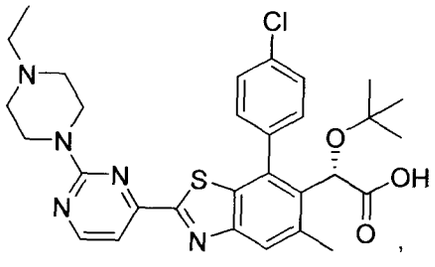

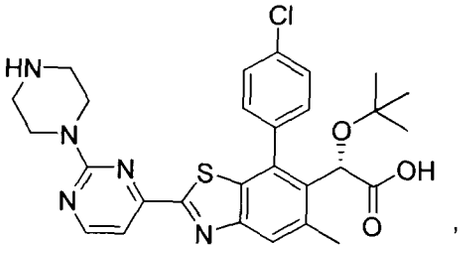

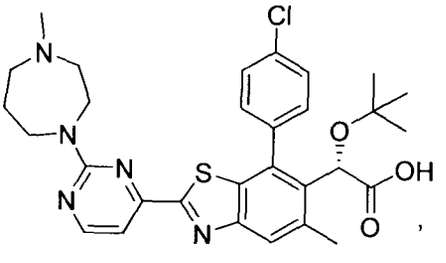

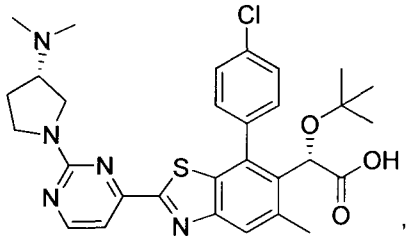

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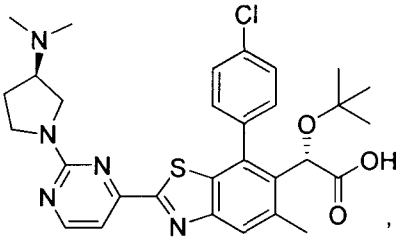

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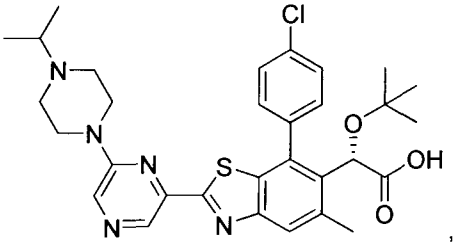

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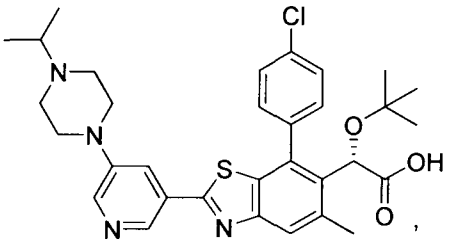

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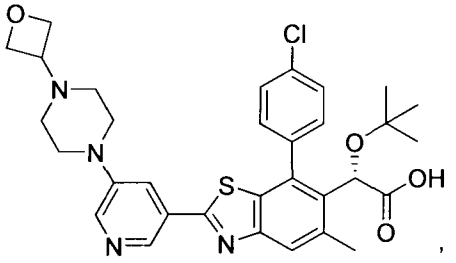

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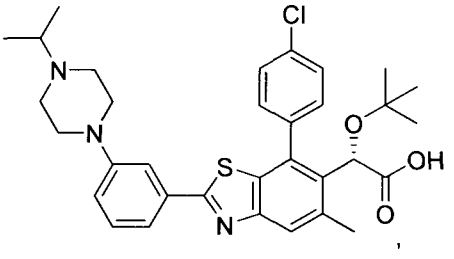

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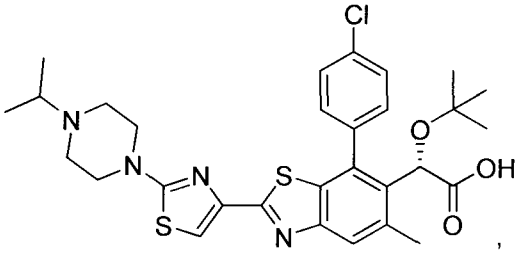

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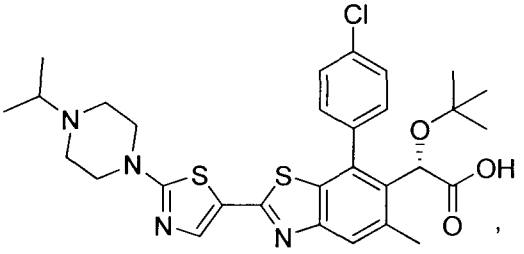

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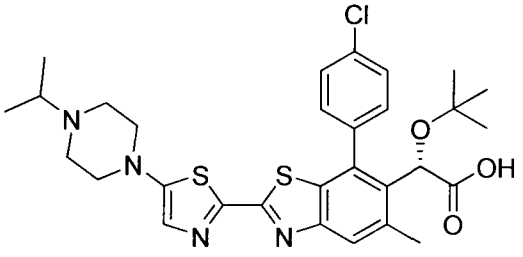

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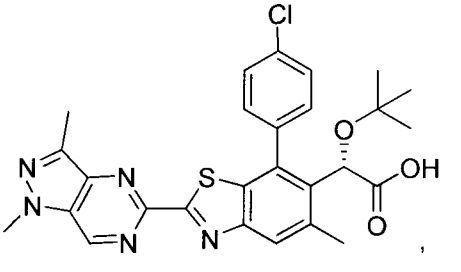

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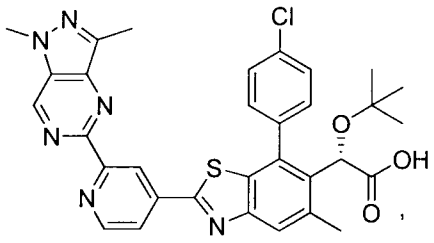

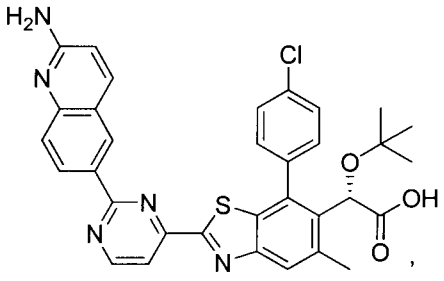

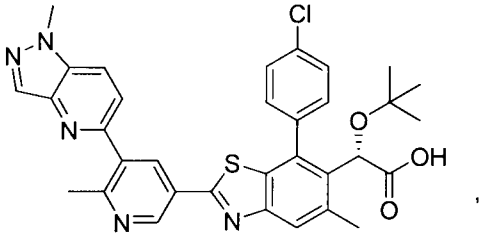

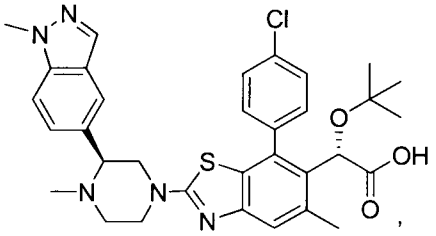

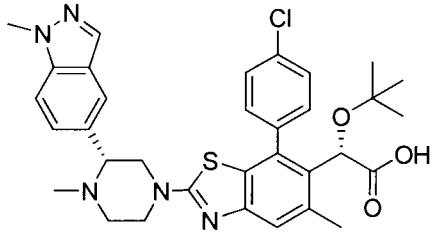

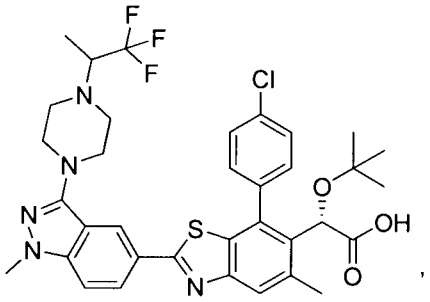

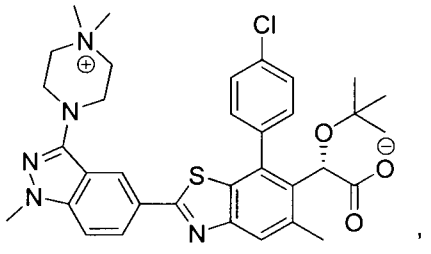

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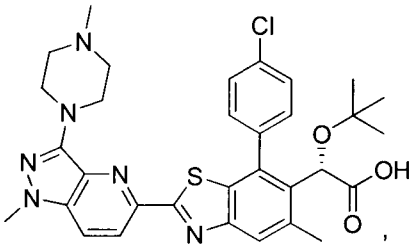

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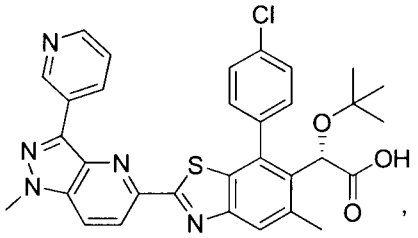

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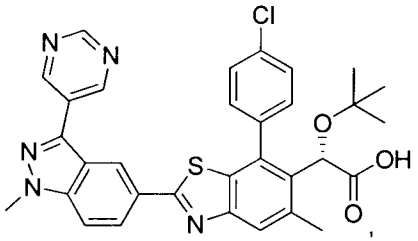

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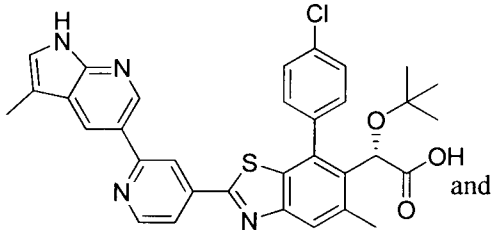

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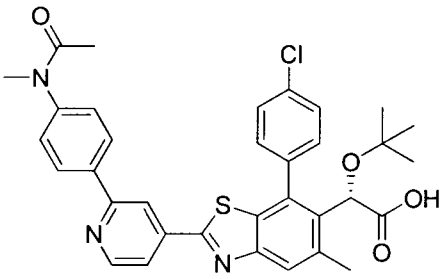
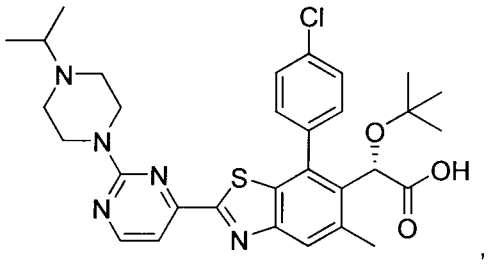


and pharmaceutically acceptable salts thereof.

In one embodiment a compound is selected from:



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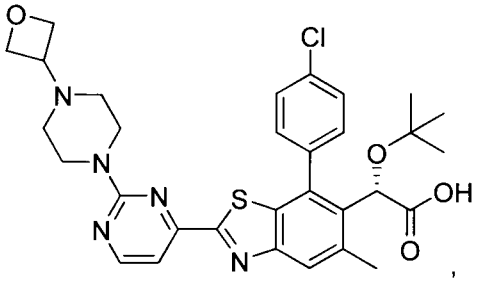

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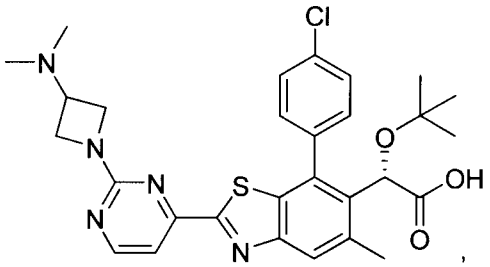

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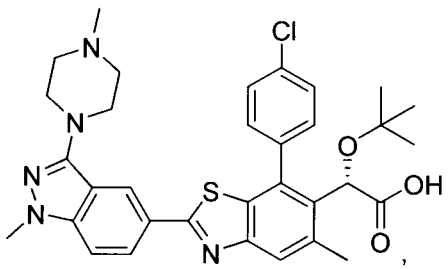

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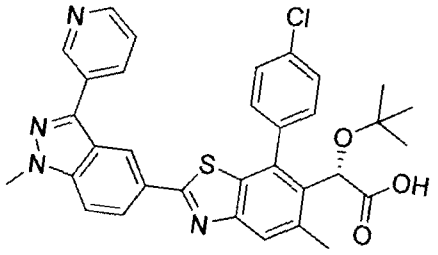

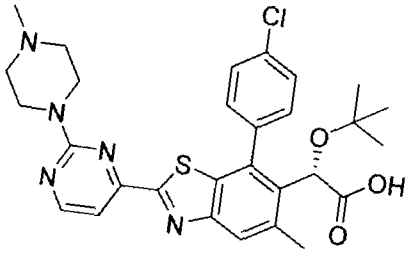

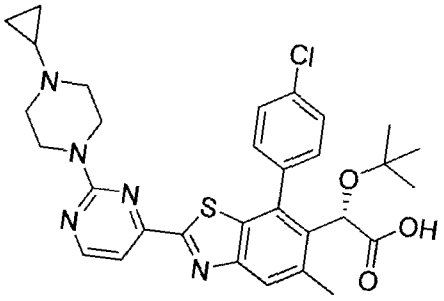

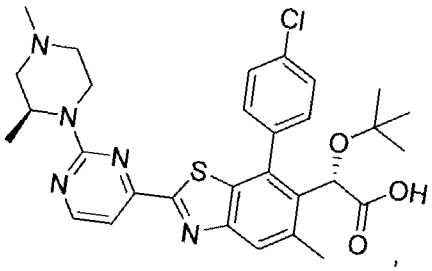

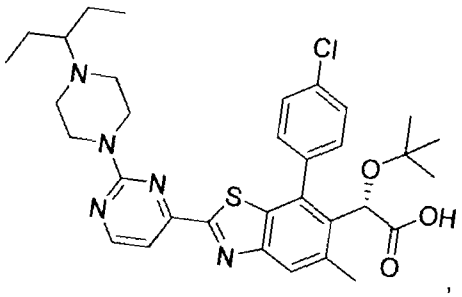

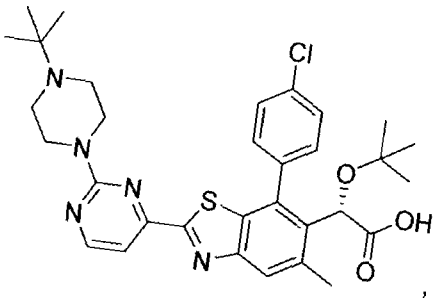

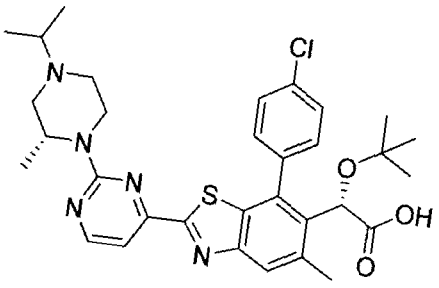

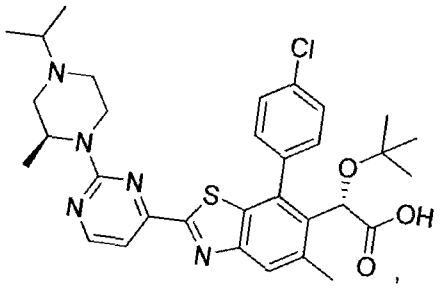

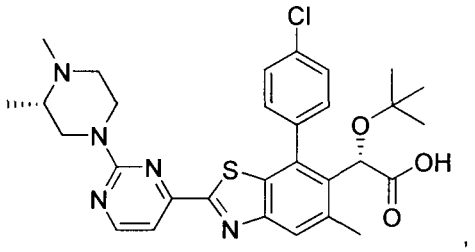
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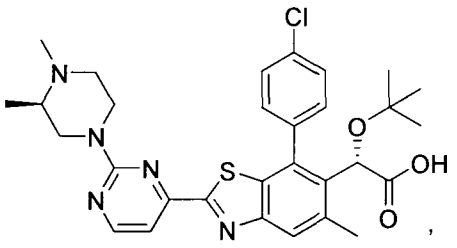
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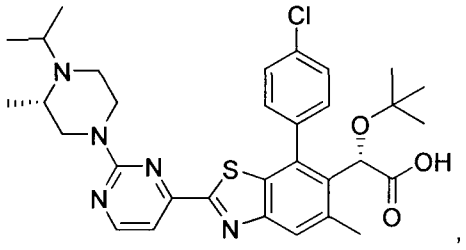
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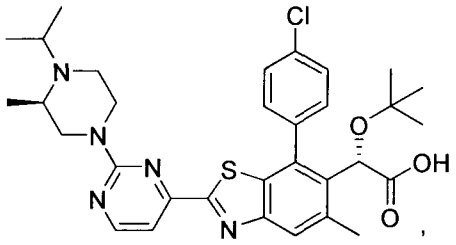
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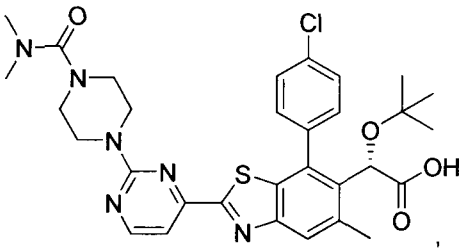
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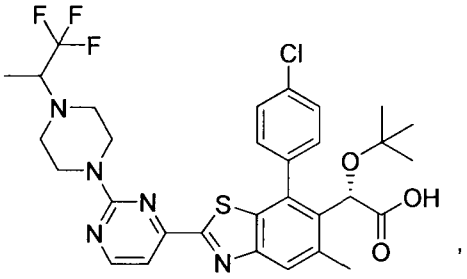
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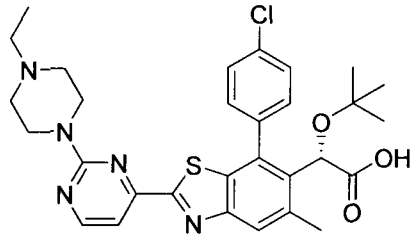
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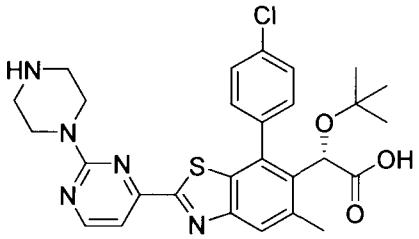
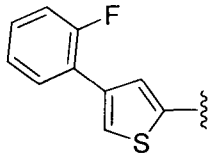


and pharmaceutically acceptable salts thereof.

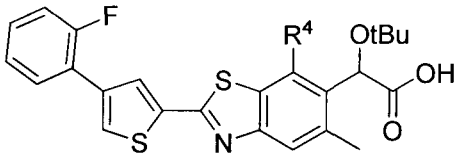
In one embodiment the compounds of the invention do not include compounds wherein A is thiophene.

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.

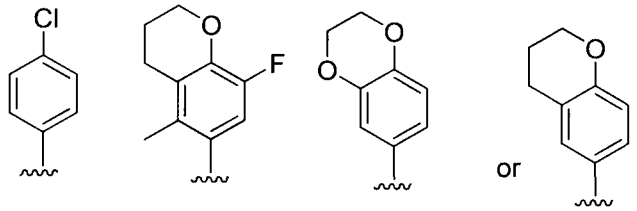
In another embodiment the compounds of the invention do not include compounds wherein A-B is:



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



wherein R^4 is:

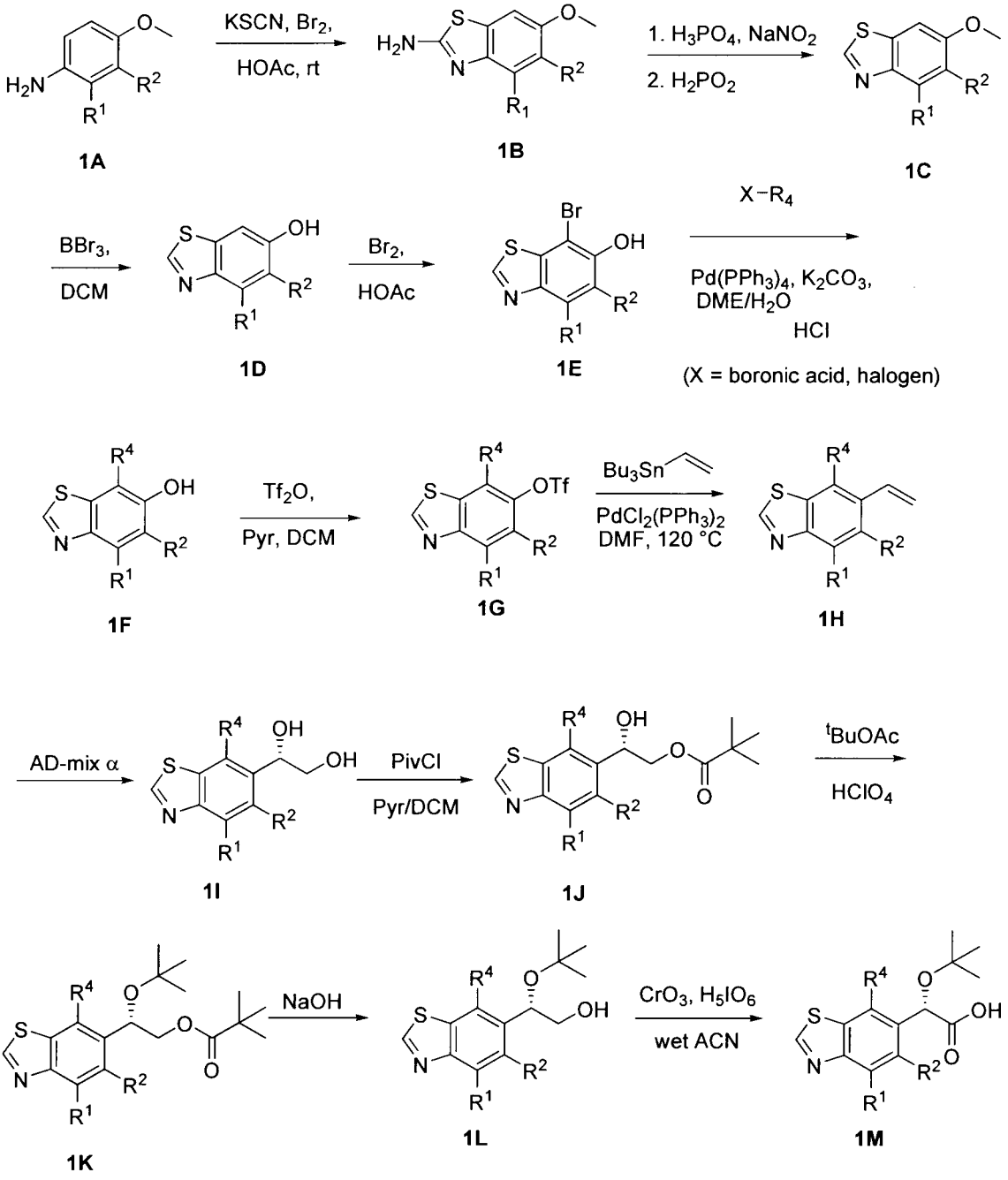


or salts thereof.

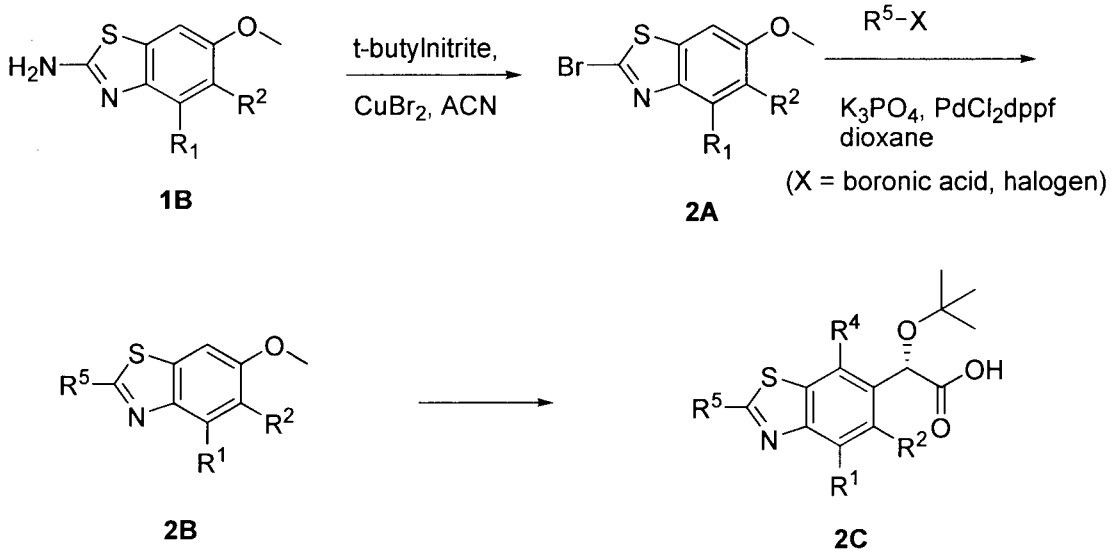
General Synthetic Procedures

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

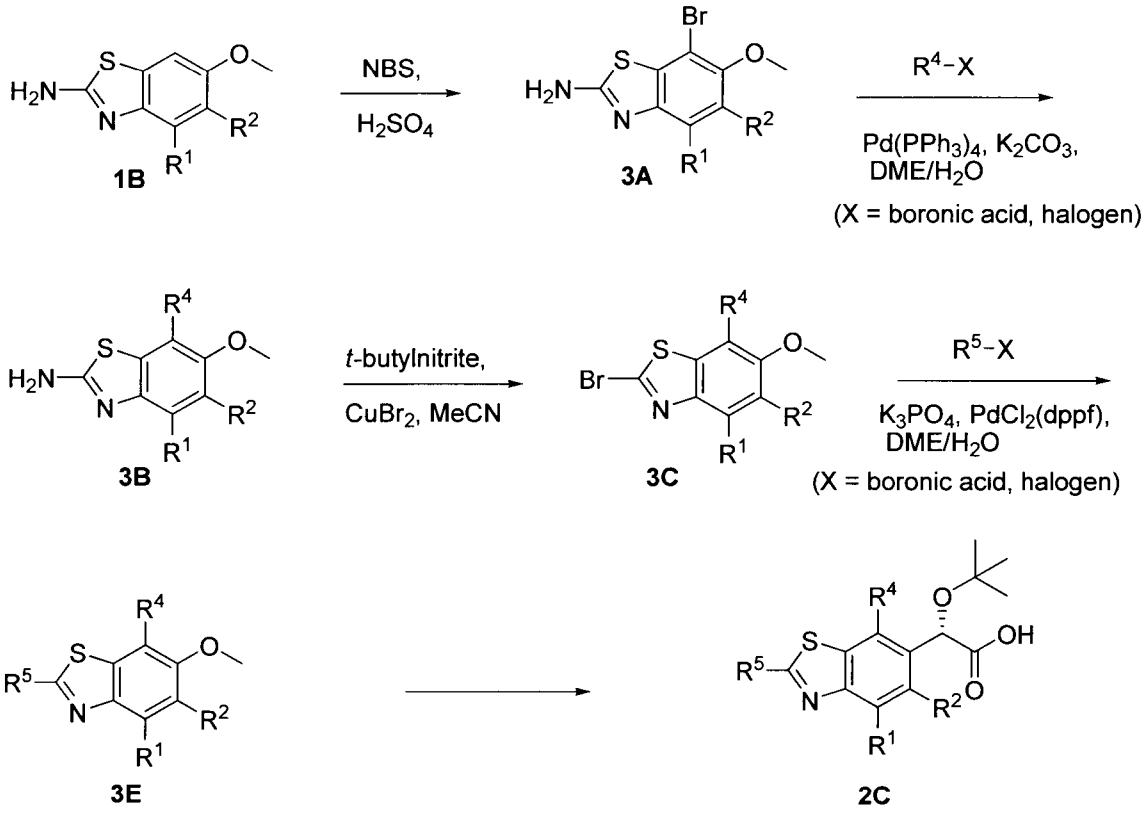

KSCN, Br2,
HOAc, rt
1. H3PO4, NaNO2
2. H2PO2
BBr3,
DCM
Br2,
HOAc
X−R4
Pd(PPh3)4, K2CO3,
DME/H2O
HCl
(X = boronic acid, halogen)
Tf2O,
Pyr, DCM
Bu3Sn
PdCl2(PPh3)2
DMF, 120 °C
AD-mix α
PivCl
Pyr/DCM
tBuOAc
HClO4
NaOH
CrO3, H5IO6
wet ACN
1A
1B
1C
1D
1E
1F
1G
1H
1I
1J
1K
1L
1M

Scheme 2



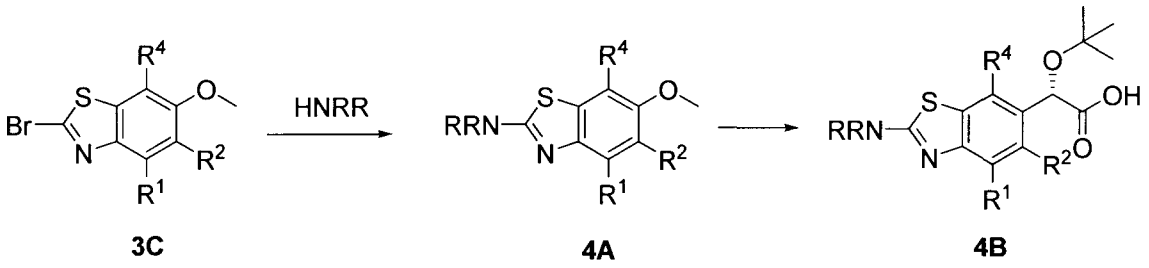
In certain embodiments, the benzothiazole intermediate **2B** is converted to the final compound **2C** by the methods used to convert **1C** to **1M** as outlined in Scheme 1.

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.

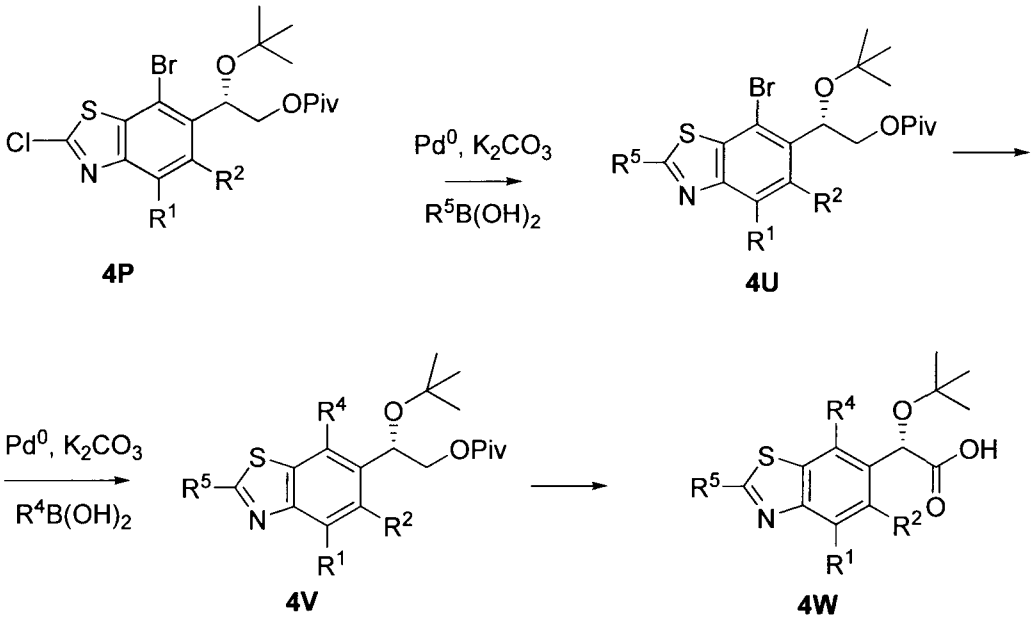
Scheme 4



3C 4A 4B

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).

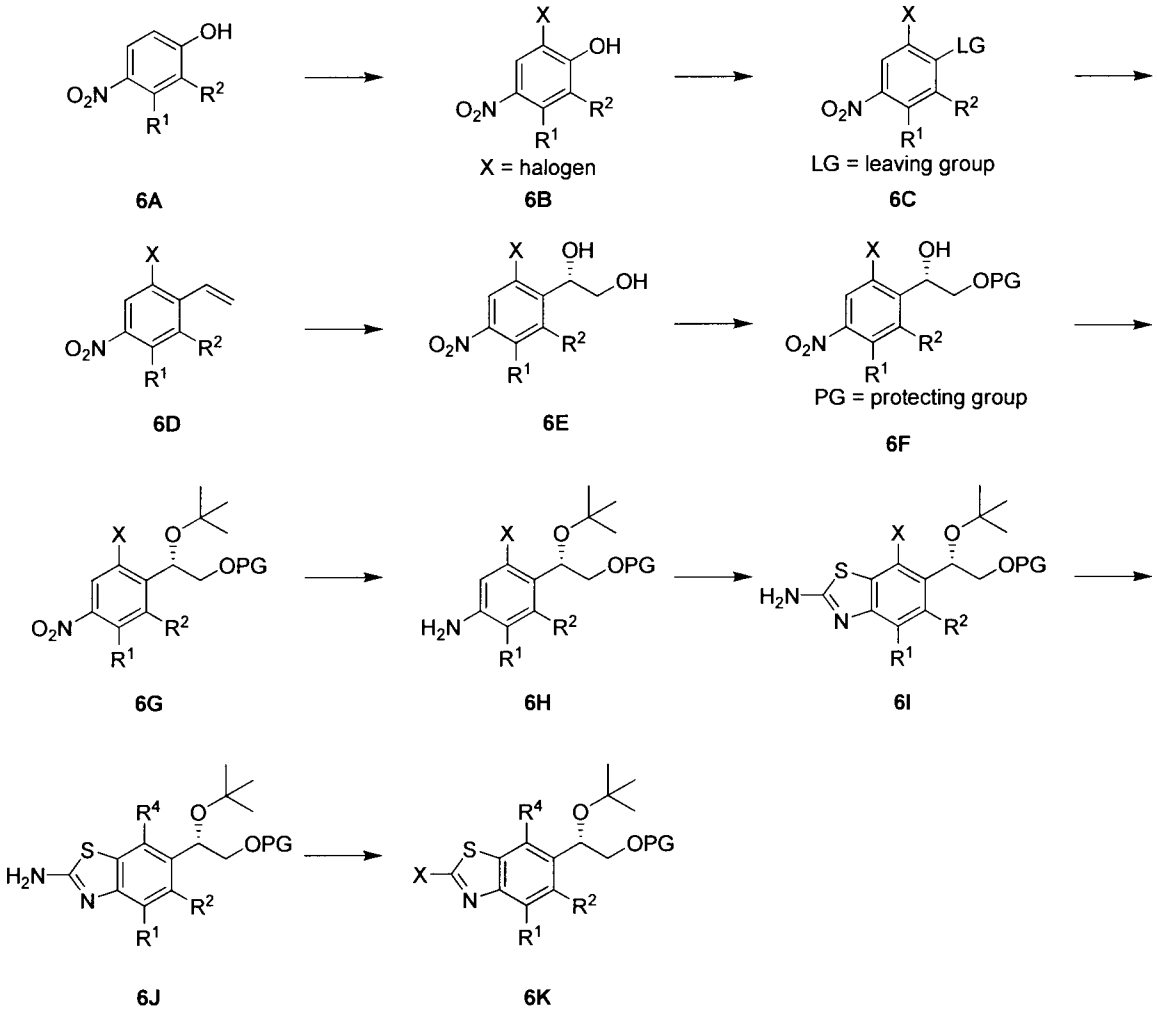
Scheme 5



4P 4U 4V 4W

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.

Scheme 6

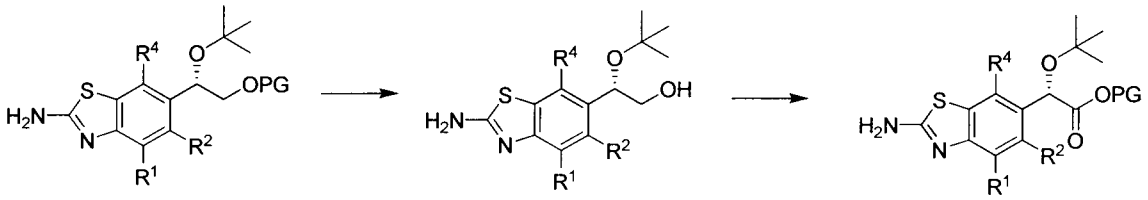


In certain embodiments, an appropriately substituted phenol **6A** is halogenated by the treatment of dihalide, for example bromine, in a suitable solvent such as, for example acetic acid. The phenol **6B** is converted to a leaving group (e.g., triflate) known to undergo cross-coupling reactions. The 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.

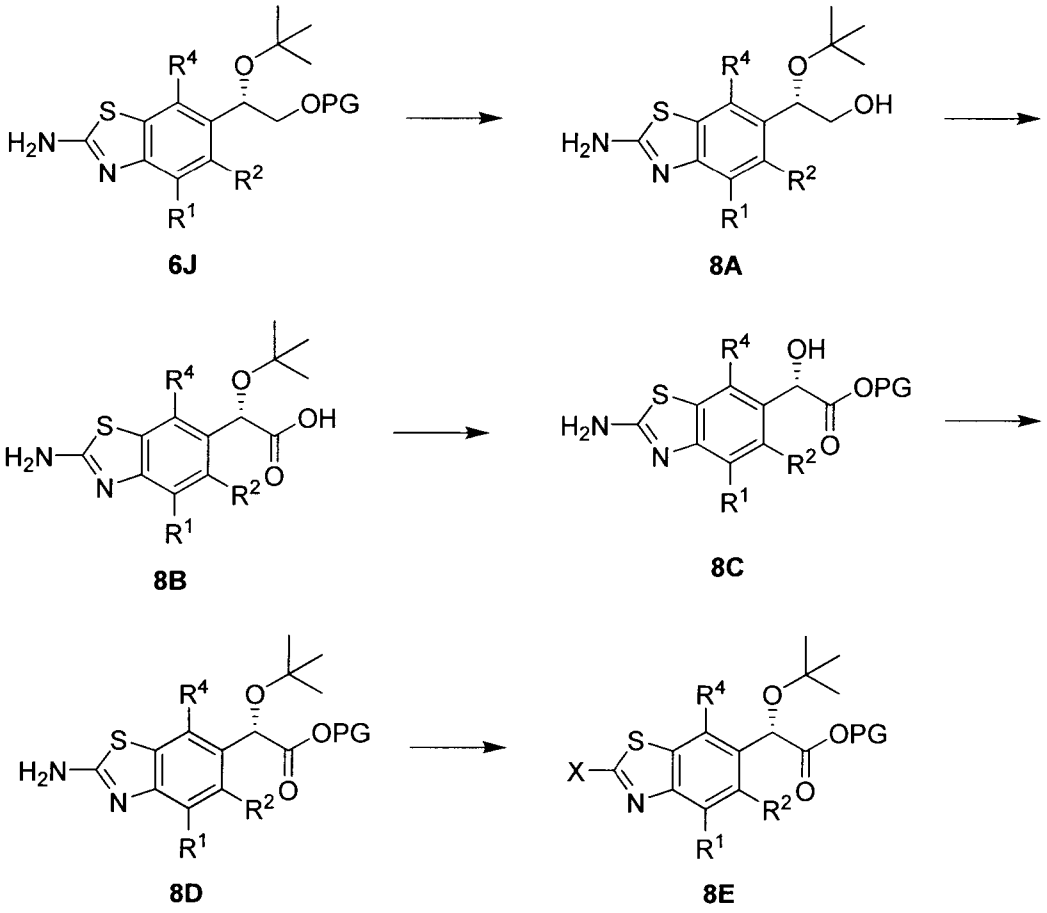
Benzothiazole **6I** is formed by methods known to those skilled in the art such as potassium thiocyanate and pyridinium perbromide, for example. The resulting benzothiazole undergoes cross-coupling reaction such as Suzuki cross-coupling using a boronic acid or ester and a palladium catalyst such as 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



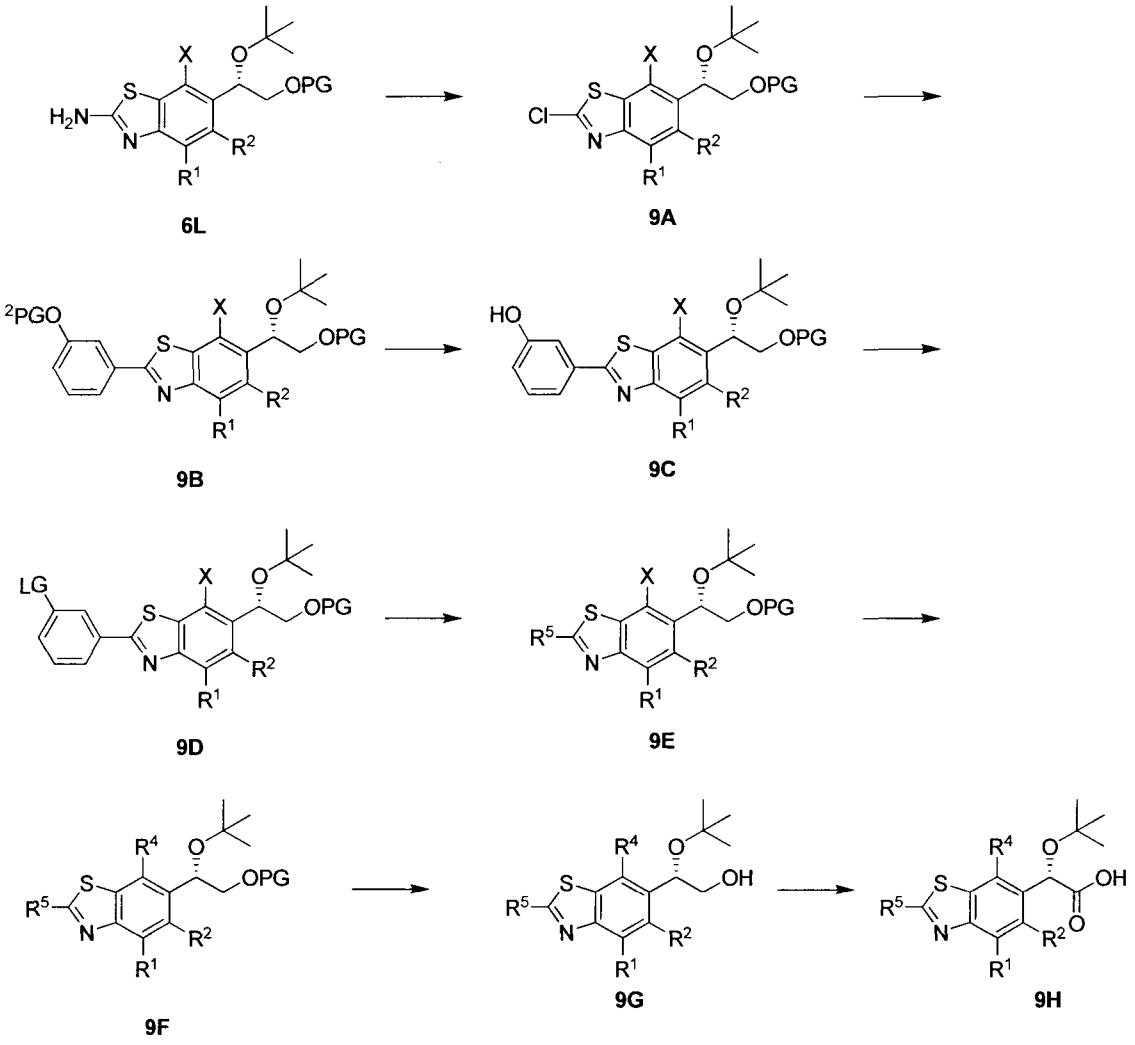
In certain embodiments the protected primary hydroxyl **6J** is deprotected by methods known to those skilled in the art such as the deprotection of a pivalate protecting group under basic conditions for example, using sodium hydroxide, to give the corresponding primary hydroxyl compound **7A**. The 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

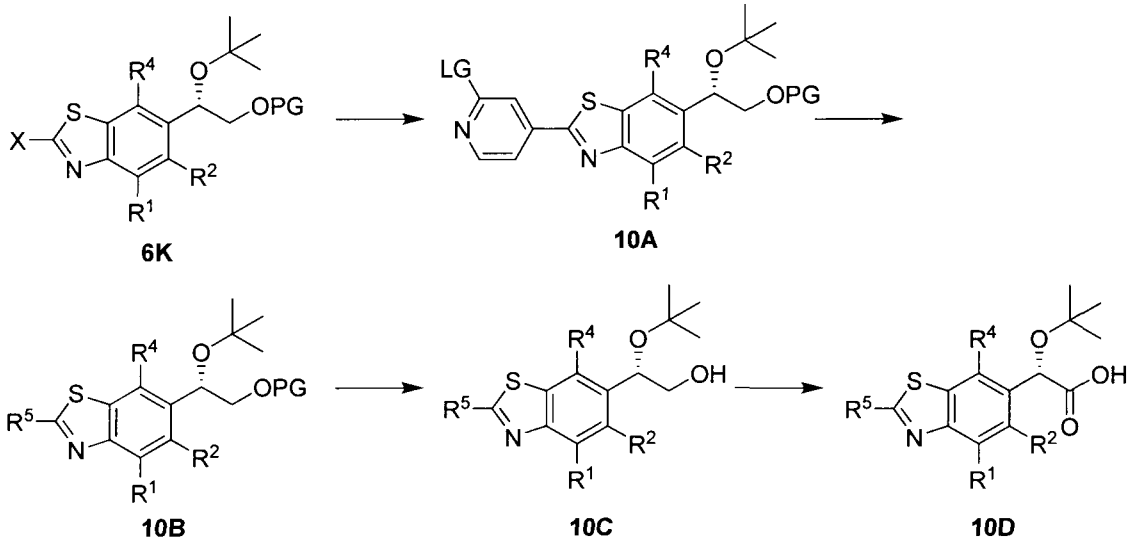


In certain embodiments chlorobenzothiazole **9A** is formed from **6J** by methods known to those skilled in the art such as *tert*-butyl nitrite and a copper(II)halide such as copper(II)bromide, for example. Selective palladium-catalyzed cross-coupling such as Suzuki or Stille with protected phenol boronic acid/ester or stannane, respectively, provides **9B.** Selective deprotection of PG^2 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, 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 R^4 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 **9F**. The protected primary hydroxyl **9F** is deprotected by methods known to those skilled in the

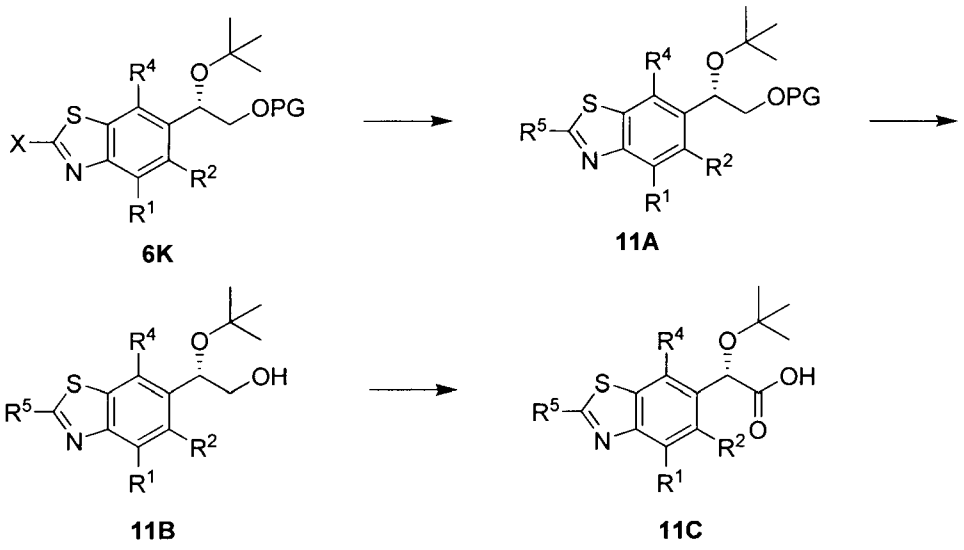
art such as the deprotection of a pivalate protecting group under basic conditions for example, using sodium hydroxide, to give the corresponding primary hydroxyl compound **9G**. The primary hydroxyl is oxidized to the corresponding carboxylic acid **9H** by periodic acid and chromium trioxide, for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

Scheme 10



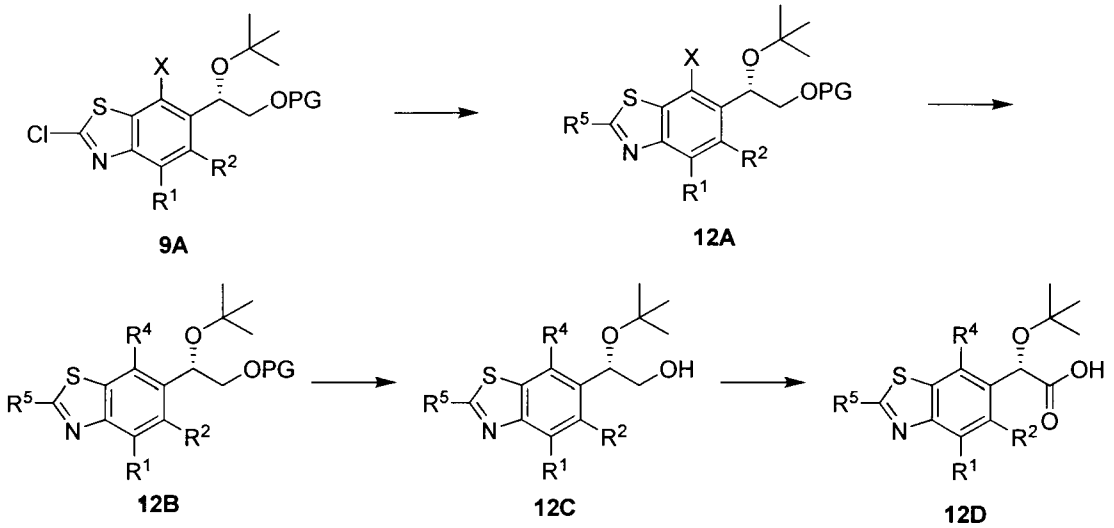
In certain embodiments halobenzothiazole **6K** undergoes selective palladium-catalyzed cross-coupling such as Suzuki or Stille with a boronic acid/ester or stannane that also contains a leaving group such as for example, a chloropyridylboronic acid, known to undergo cross-coupling reactions to give **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.

Scheme 11



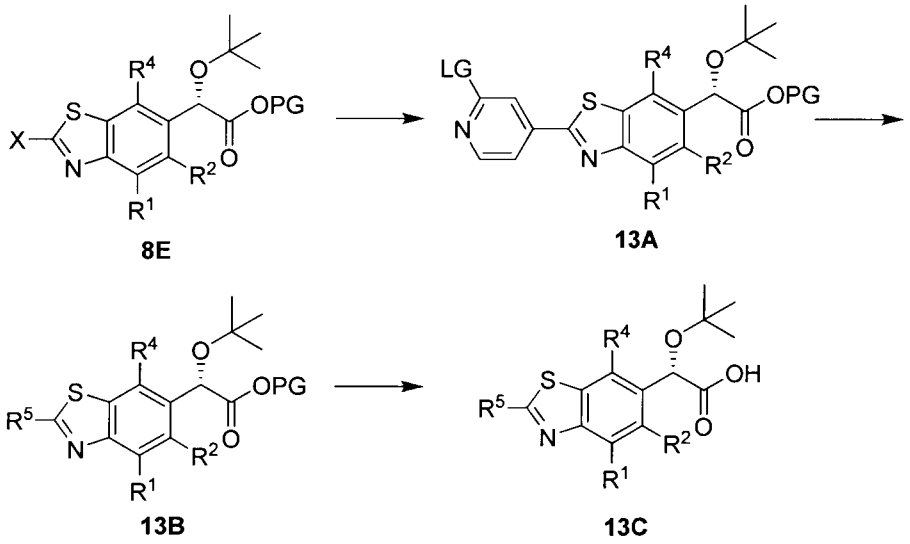
In certain embodiments halobenzothiazole **6K** undergoes palladium-catalyzed cross-coupling such as Suzuki with a boronic acid or ester; Stille with a stannane; palladium-catalyzed carbonylation using carbon monoxide, for example in the presence of an amine; copper(I)halide catalyzed or Buchwald-Hartwig amination; palladium-catalyzed amidation; S_NAr with an amine; to introduce the R^5 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



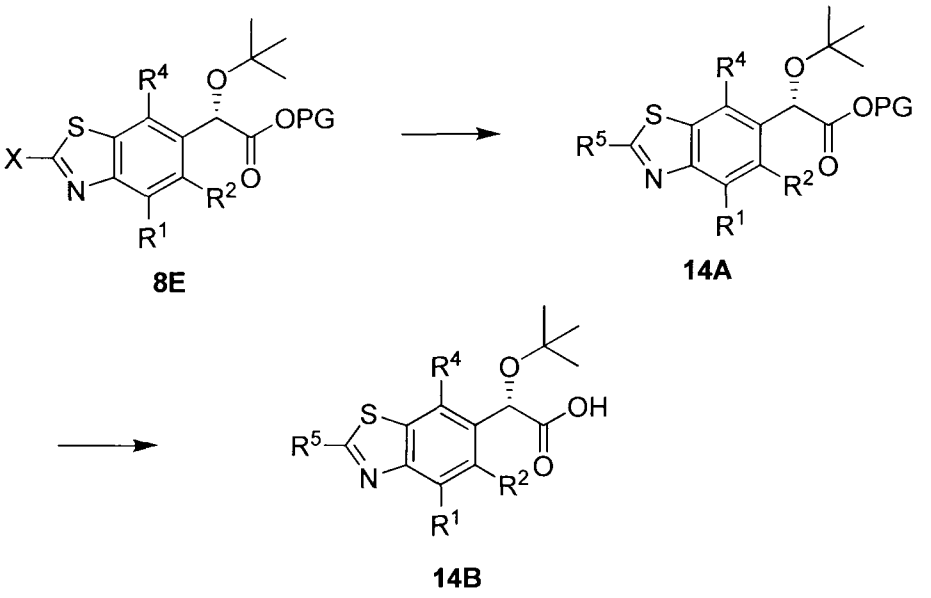
In certain embodiments chlorobenzothiazole **9A** undergoes selective palladium-catalyzed cross-coupling such as Suzuki or Stille with protected phenol boronic acid/ester or stannane, respectively, to provide **12A.** The R^4 moiety is introduced by cross-coupling reaction such as, for example Suzuki 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



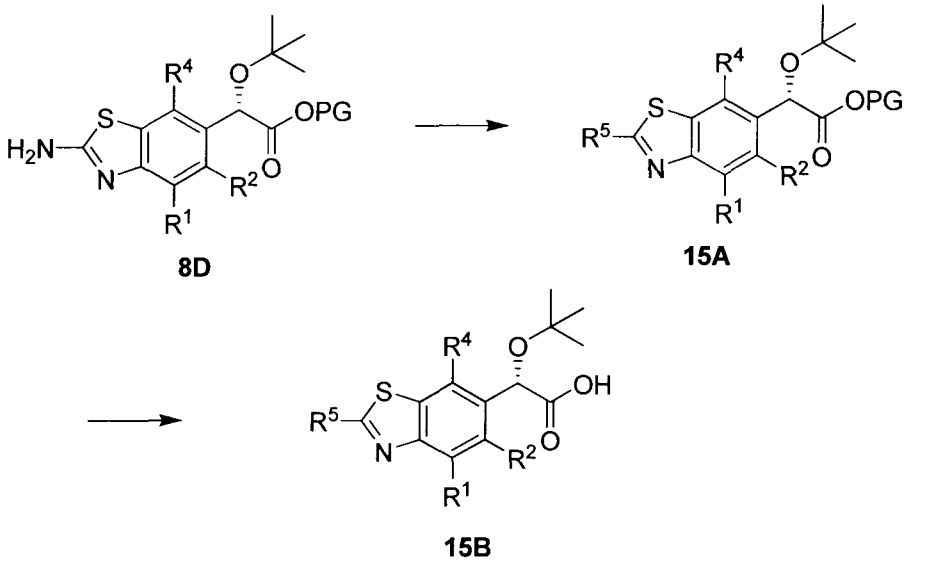
In certain embodiments halobenzothiazole **8E** undergoes selective palladium-catalyzed cross-coupling such as Suzuki or Stille with a boronic acid/ester or stannane that also contains a leaving group such as for example, a chloropyridylboronic acid, known to undergo cross-coupling reactions to give **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



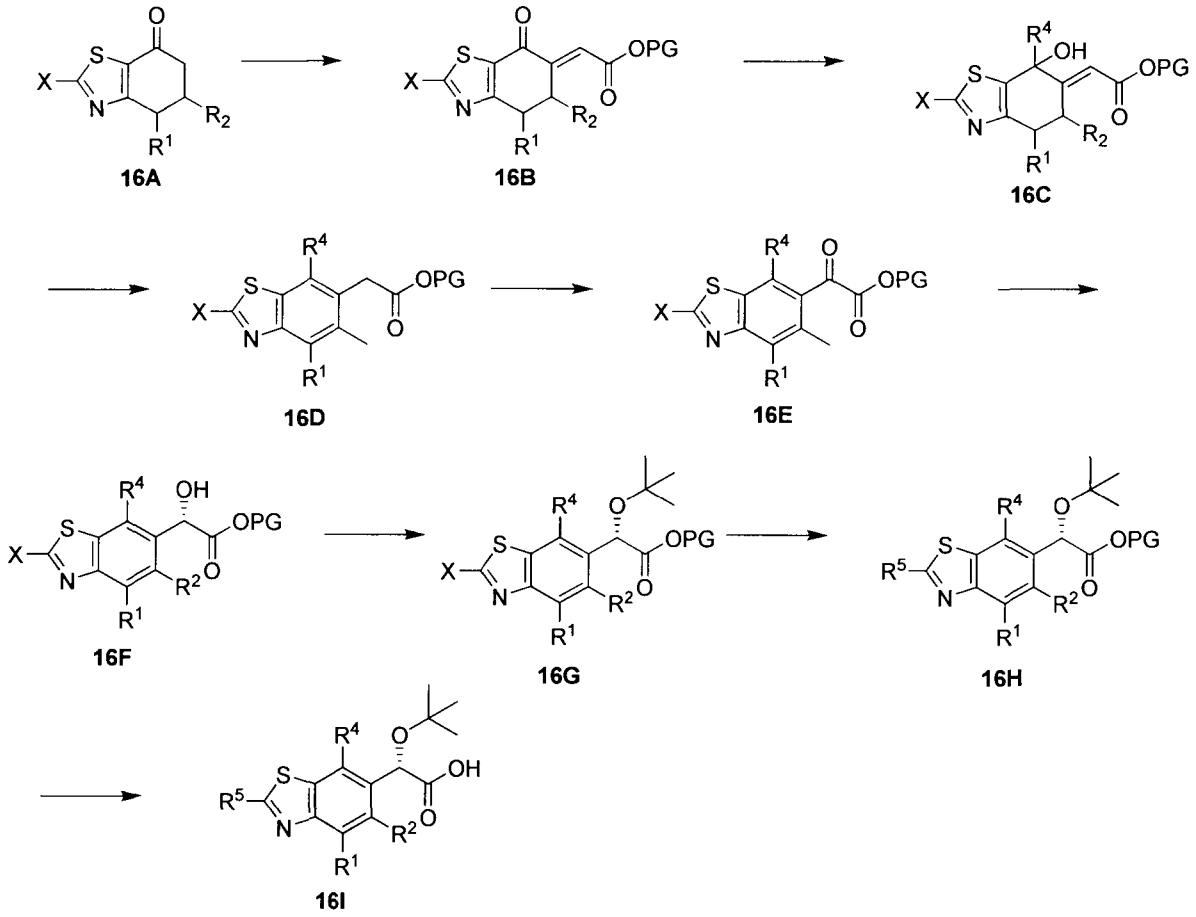
In certain embodiments halobenzothiazole **8E** undergoes palladium-catalyzed cross-coupling such as Suzuki with a boronic acid or ester; Stille with a stannane; palladium-catalyzed carbonylation using carbon monoxide, for example in the presence of an amine; copper(I)halide catalyzed or Buchwald-Hartwig 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**.

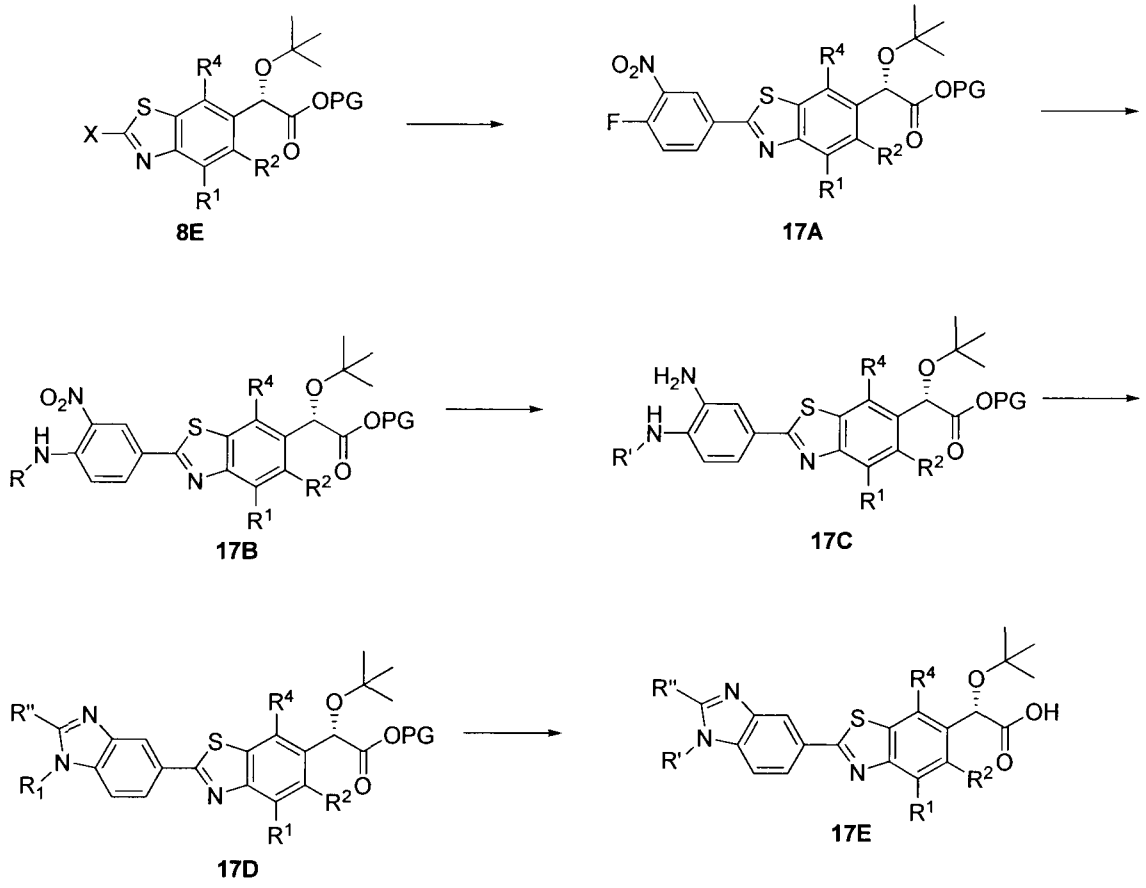
Scheme 16



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



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 SnAr reaction with nucleophiles, such as, for example methylamine, to give **17B**. Hydrogenation under platinium on carbon, for example provides the bis-aniline **17C**. 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 phosphases. 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 $-CH_2OC(=O)R^{99}$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^{99}$ 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) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

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. 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 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).

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 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 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 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 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, ±-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;

(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).

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:

(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, and RDEA806;

(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, ±-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, 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).

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 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 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.

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 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, KM023and 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, ±-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;

(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).

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, and RDEA806;

(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, ±-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, 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.

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 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 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 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 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, 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 μL of 189X test concentration of 3-fold serially diluted compound in DMSO was added to 40 μL 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 2x10e6 MT-4 cells were pre-infected for 1 and 3 hours respectively, @ 37°C with 25 uL (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 uL 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 μl 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 μM. In certain embodiments, the compounds demonstrate an EC50 of < 30 μM. In certain embodiments, the compounds demonstrate an EC50 of < 10 μM. In certain embodiments, the compounds demonstrate an EC50 of < 1 μM. In certain embodiments, the compounds demonstrate an EC50 of < 0.5 μM. In certain embodiments, the compounds demonstrate an EC50 of < 0.1 μM. In certain embodiments, the compounds demonstrate an EC50 of < 0.05 μM. In certain embodiments, the compounds demonstrate an EC50 of < 0.01 μM. 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 uL of 1 uM 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 °C for 0, 10, 25, 60 minutes. The reactions were quenched with 100 uL 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. Humun 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. Humun microsomal stability equal to C refers to a compound having a human microsomal stability half-life of less than 150 minutes.

Table 3

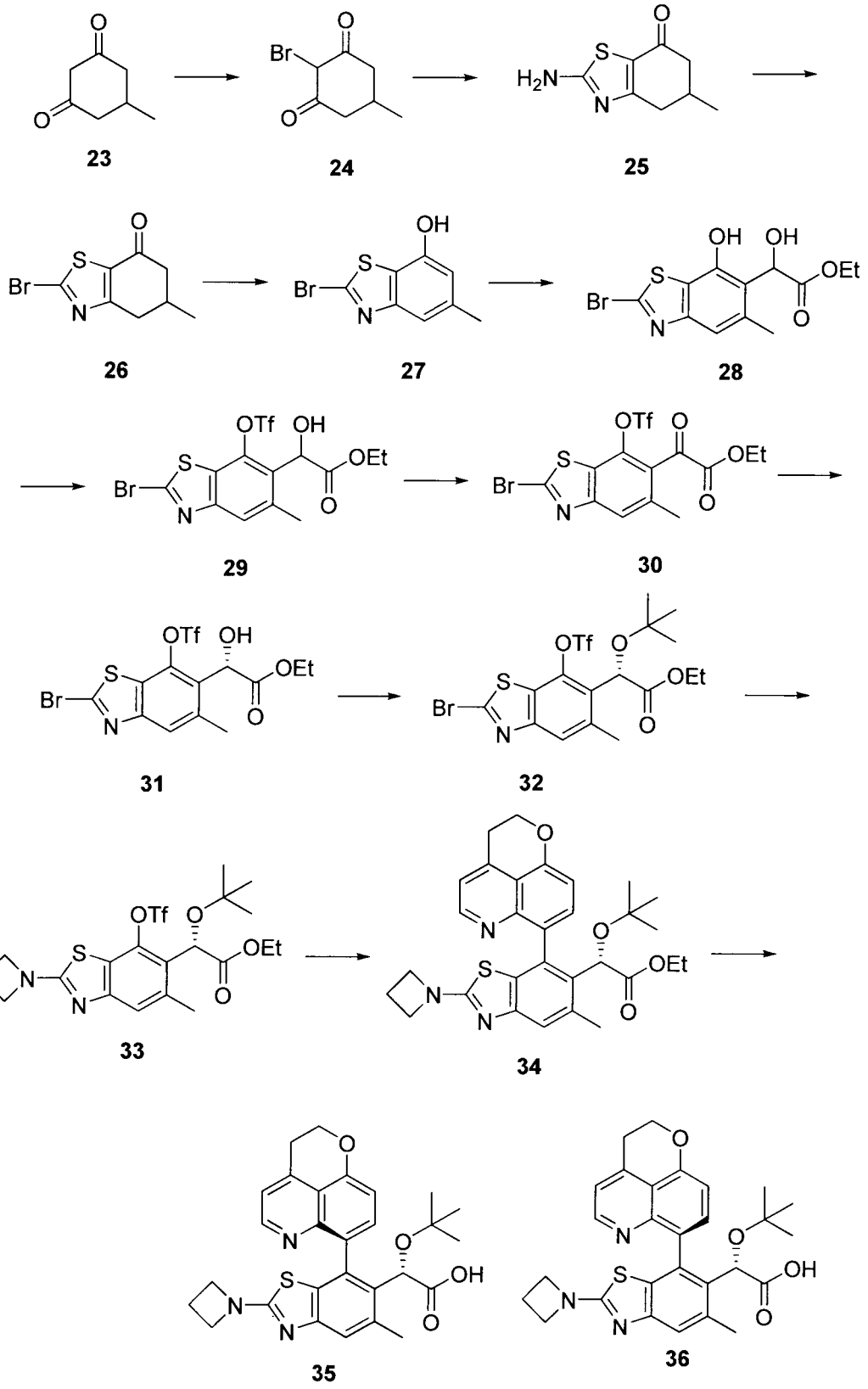
Compound Number	Human Microsomal stability
104	C
107	C
109	B
141	B
152	C
158	C
163	C
186	C
202	A
206	C
212	A
257	A
278	B
285	A
333	A
336	A
113a	A

The specific pharmacological responses observed may vary according to and depending 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 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 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 solution of NaOH (2 M, ~400 μL). The reaction mixture was heated at 70 °C for 4 h. The

reaction was brought to ~pH 5 with TFA and was then purified by reverse phase HPLC (ACN/H_2O containing 0.1% TFA) to give 6 mg of compound **35** and 10 mg of compound **36.**

Compound **35**: ^{1}H-NMR: 400 MHz, (CD_3OD) 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 $C_{28}H_{29}N_3O_4S$: 504.2 ($M+H^+$); Found: 504.0 ($M+H^+$).

Compound **36**: ^{1}H-NMR: 400 MHz, (CD_3OD) 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 $C_{28}H_{29}N_3O_4S$: 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 $C_8H_{11}N_2OS$: 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

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**. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 C_8H_9BrNOS: 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 CCl_4 (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 CH_2Cl_2 (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 CH_2Cl_2. 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**. ^{1}H-NMR: 400 MHz, (CD_3OH) δ: 7.25 (s, 1H), 6.69 (s, 1H), 2.40 (s, 3H). LCMS-ESI$^+$: calc'd for C_8H_7BrNOS: 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 CH_2Cl_2 (80 mL) at 0 °C was added triethylamine (2.45 mL, 16.8 mmol) then a solution of titanium tetrachloride in CH_2Cl_2 (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 CH_2Cl_2. 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**. ^{1}H-NMR: 400 MHz, (CD_3OH) 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 $C_{12}H_{13}BrNO_4S$: 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**

(2.42 g, 7.00 mmol) in CH_2Cl_2 (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 NH_4Cl 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**. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 $C_{13}H_{12}BrF_3NO_6S_2$: 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 CH_2Cl_2 (100 mL) was added Dess-Martin periodinane (9.61 g, 22.6 mmol). After 30 min, water (75 mL) and saturated $Na_2S_2O_4$ solution (75 mL) was added. The mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. 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**. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 $C_{13}H_{10}BrF_3NO_6S_2$: 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 Na_2CO_3 was added (50 mL). The layers were separated, and the organic layer was washed with additional Na_2CO_3 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}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). LCMS-ESI$^+$: calc'd for $C_{17}H_{20}BrF_3NO_6S_2$: 534.0 ($M+H^+$); Found: 534.1 ($M+H^+$).

Step 10.

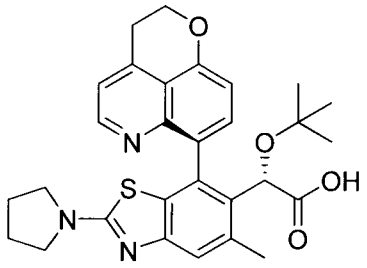
Preparation of (S)-ethyl 2-(2-(azetidin-1-yl)-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**33**). To a solution of **32** (50 mg, 0.094 mmol) in THF (1 mL) was added azetidine (20 μL). The reaction mixture was heated at 70 °C for 30 min. A saturated solution of 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 $C_{20}H_{25}F_3N_2O_6S_2$: 511.1 ($M+H^+$); Found: 511.0 ($M+H^+$).

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'-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 mmmol). The reaction mixture was heated in the microwave at 110 °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 crude material was purified by column chromatography (EtOAc/hexanes) to give 21 mg of **34.** LCMS-ESI$^+$: calc'd for $C_{30}H_{33}N_3O_4S$: 532.2 ($M+H^+$); Found: 532.0 ($M+H^+$).

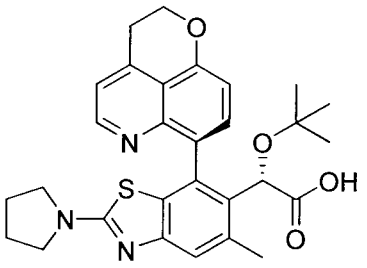
Example 2. Preparation of (S)-2-tert-butoxy-2-((S)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methyl-2-(pyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (**50**) and (S)-2-tert-butoxy-2-((R)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methyl-2-(pyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (**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}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*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_4S$: 518.21 ($M+H^+$); Found: 517.99, 518.97 ($M+H^+$).

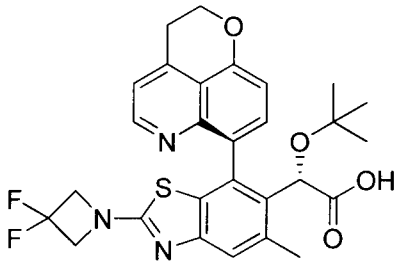


51

Compound **51**: ^{1}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*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_4S$: 518.21 ($M+H^+$); Found: 518.07, 519.07 ($M+H^+$).

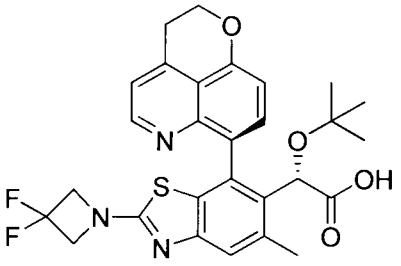
Example 3. Preparation of (S)-2-tert-butoxy-2-((S)-2-(3,3-difluoroazetidin-1-yl)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (**52**) and (S)-2-tert-butoxy-2-((R)-2-(3,3-difluoroazetidin-1-yl)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-5-methylbenzo[d]thiazol-6-yl)acetic 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}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*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_4S$: 540.18 ($M+H^+$); Found: 539.96, 540.96 ($M+H^+$).

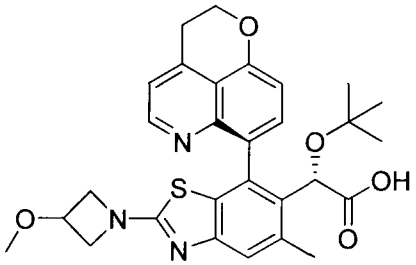


53

Compound **53**: ^{1}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*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_4S$: 540.18 ($M+H^+$); Found: 539.98, 541.02 ($M+H^+$).

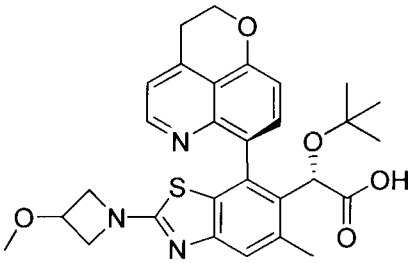
Example 4. Preparation of (S)-2-tert-butoxy-2-((S)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-2-(3-methoxyazetidin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (**54**) and (S)-2-tert-butoxy-2-((R)-7-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)-2-(3-methoxyazetidin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetic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



54

Compound **54**: ^{1}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*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_5S$: 534.21 ($M+H^+$); Found: 533.95, 534.97 ($M+H^+$).

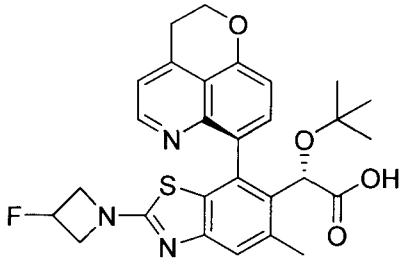


55

Compound **55**: ^{1}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*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_5S$: 534.21 ($M+H^+$); Found: 534.03, 535.08 ($M+H^+$).

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.



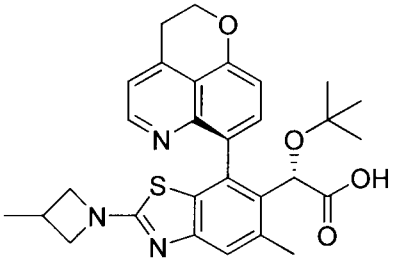
56

Compound **56**: ^{1}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).

LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{29}FN_3O_4S$: 522.19 ($M+H^+$); Found: 521.97, 523.02 ($M+H^+$).

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**).

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.

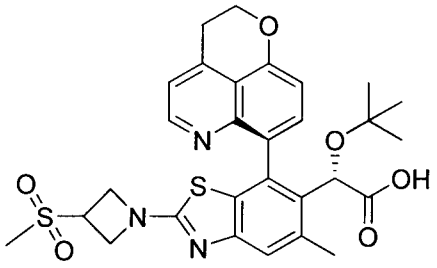


57

Compound **57**: ^{1}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*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_4S$: 518.21($M+H^+$); Found: 518.09, 519.12($M+H^+$).

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**).

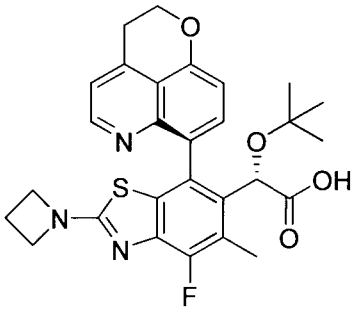
Compound **58** was prepared from compound **32** according to the procedure used to prepare compound **35** (except that 2-methylsulfonylazetidine was used instead of azetidine) in Example 1.



58

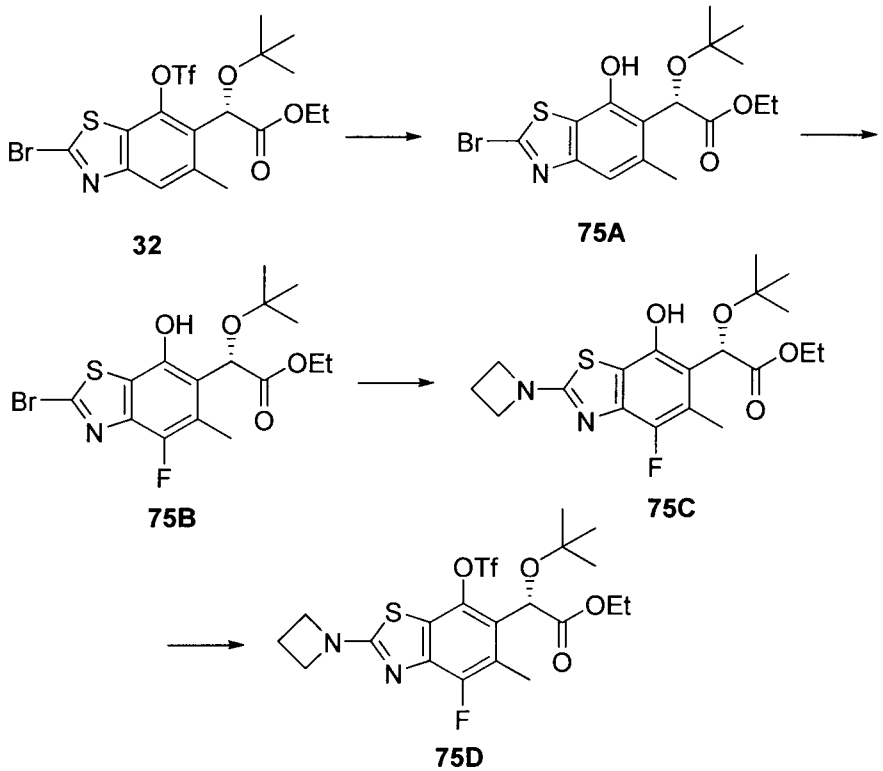
Compound **58**: ^{1}H-NMR: 400 MHz, (CD_3OD) δ: ^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (d, J = 5.3 Hz, 1H), 7.89 (t, J = 6.7 Hz, 2H), 7.61 (s, 1H), 7.44 (d, J = 8.1 Hz, 1H), 5.18 (s, 1H), 4.72 (dd, J = 9.0, 6.2 Hz, 2H), 4.59 – 4.35 (m, 5H), 3.01 (s, 3H), 2.72 (s, 3H), 0.92 (s, 9H). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_6S$: 582.17 ($M+H^+$); Found: 581.95, 583.02($M+H^+$).

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**).



76

Compound **76**: ^{1}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*): $[M+H]^+$ calcd for $C_{28}H_{29}FN_3O_4S$: 522.19 ($M+H^+$); Found: 521.99, 523.00($M+H^+$).



32 **75A** **75B** **75C** **75D**

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 H_2O (20 mL) and HOAc(200 ul), extracted by EtOAc, the organic phase was washed by sat. $NaHCO_3$, dried over $MgSO_4$, 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 $C_{16}H_{20}BrNO_4S$: 402.0 ($M+H^+$); Found: 401.9 ($M+H^+$).

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 KH_2PO_4, extracted by EtOAc, the organic phase was dried over $MgSO_4$, 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 $C_{16}H_{19}FNO_4S$: 420.0 ($M+H^+$); Found: 420.1 ($M+H^+$).

Step 3.

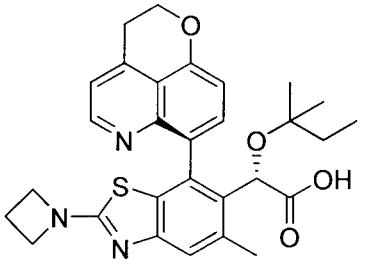
Preparation of (S)-ethyl 2-(2-(azetidin-1-yl)-4-fluoro-7-hydroxy-5methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**75C**): Prepared by the similar method to make (S)-ethyl 2-(2-(azetidin-1-yl)-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**33**) in Example 10. LCMS-ESI$^+$: calc'd for $C_{19}H_{25}FN_2O_4S$: 397.2 ($M+H^+$); Found: 397.0 ($M+H^+$).

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-5methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (**75C**) (50 mg, 0.126 mmol), N-phenyl triflate (90 mg, 0.252 mmol), Cs_2CO_3 (82 mg, 0.126 mmol) in THF (2 mL) was stirred at rt. After the reaction finished, the reaction was washed by sat $NaHCO_3$, extracted by EtOAc, the organic phase was dried over $MgSO_4$, 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 $C_{20}H_{24}F_4N_2O_6S_2$: 529.1 ($M+H^+$); Found: 529.0 ($M+H^+$).

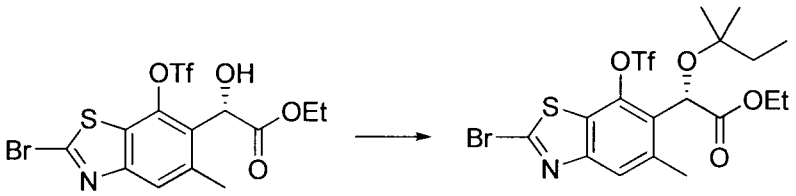
The remainder of the synthesis of compound **76** is analogous to the preparation of compound **35** from compound **33** in example 1.

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**).



89

Compound **89**: ^{1}H 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

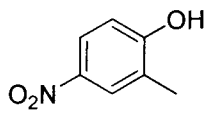


31 **90**

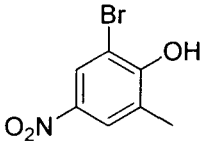
Preparation of **90**: A slurry of **31** (740 mg, 1.55 mmol) in tert-amyl acetate (7.0 mL) was treated with 70% aq. $HClO_4$ (5 µL) was added at 23 °C. Reaction became cloudy, but LCMS analysis indicated minimal conversion. More 70% aq. $HClO_4$ (50 µL) was introduced. After 2 h, the reaction was added 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**. ^{1}H-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**.

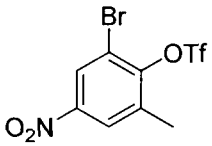
Example 10. Preparation of *(S)*-2-(2-amino-7-bromo-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (100).



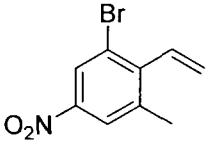
2-methyl-4-nitrophenol



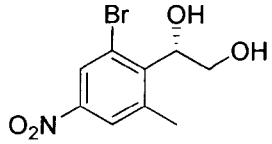
2-bromo-6-methyl-4-nitrophenol



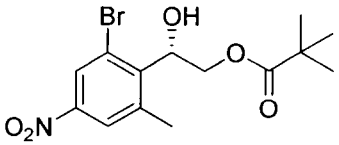
2-bromo-6-methyl-4-nitrophenyl trifluoromethanesulfonate



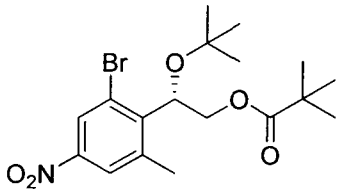
1-bromo-3-methyl-5-nitro-2-vinylbenzene



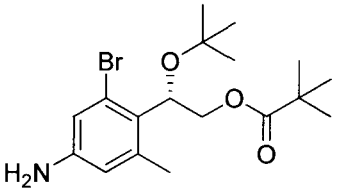
(*S*)-1-(2-bromo-6-methyl-4-nitrophenyl)ethane-1,2-diol



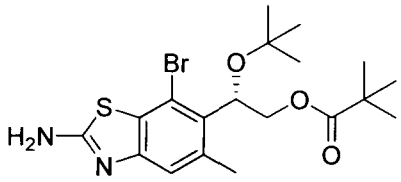
(*S*)-2-(2-bromo-6-methyl-4-nitrophenyl)-2-hydroxyethyl pivalate



(*S*)-2-(2-bromo-6-methyl-4-nitrophenyl)-2-*tert*-butoxyethyl pivalate



(*S*)-2-(4-amino-2-bromo-6-methylphenyl)-2-*tert*-butoxyethyl pivalate



(*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: Br_2 (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 $NaHSO_3$ (3 x 500 mL). The EtOAc layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford 2-bromo-6-methyl-4-nitrophenol (110 g, 80%) as yellow solid. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 Et_3N (62.3 g, 0.616 mol) and Tf_2O (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 Na_2SO_4, 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. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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)Cl_2 (673 mg, 0.92 mmol) and DMF (50 mL) was stirred at 70 °C for 3 h under N_2. 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 $NaHCO_3$ (100 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, 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. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 $K_2OsO_4 \cdot 2\ H_2O$; 1.389 g of $(DHQ)_2PHAL$; 51.038 g of K_2CO_3 and 120.99 g of

$K_4Fe(CN)_6$), $MeSO_2NH_2$ (11.8 g, 0.124 mol) in *t*-BuOH (250 mL) and H_2O (250 mL) was stirred at 0 °C for 3 days. Na_2SO_3 (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 Na_2SO_4, 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. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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).

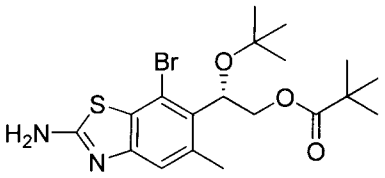
Preparation of *(S)*-2-(2-Bromo-6-methyl-4-nitrophenyl)-2-hydroxyethyl pivalate: To a suspension of *(S)*-1-(2-Bromo-6-methyl-4-nitrophenyl)ethane-1,2-diol (17.0 g, 61.6 mmol) in DCM (435 mL) at 0 °C was added pyridine (18.6 g, 235.4 mmol) and PivCl (13.4 g, 110.8 mmol) slowly. After stirring at 0 °C 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 $NaHCO_3$ (500 mL), and the resulting system was extracted with DCM (2 x 200 mL). The combined organic layer was dried over anhydrous Na_2SO_4, 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. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 $HClO_4$ (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 $NaHCO_3$ until the pH of solution > 8. The mixture was extracted with EtOAc (3 x 1 L). The combined organic layers were dried over anhydrous Na_2SO_4, 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. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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).

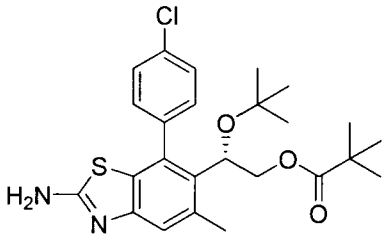
Preparation of *(S)*-2-(4-amino-2-bromo-6-methylphenyl)-2-*tert*-butoxyethyl pivalate: To a solution of *(S)*-2-(2-Bromo-6-methyl-4-nitrophenyl)-2-*tert*-butoxyethyl pivalate (9 g, 0.022 mol) in EtOH (50 mL) and EtOAc (50 mL) was added Pt/C (1.4 g), and the reaction was fitted with a balloon of H_2. 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. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 $NaHCO_3$ solution, then extracted with EtOAc (3 x 600 mL). The combined organic layers were dried over anhydrous Na_2SO_4, 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 $C_{19}H_{27}BrN_2O_3S$: 443.1 and 445.1 ($M+H^+$); found: 443.1 and 445.1 ($M+H^+$). ^{1}H-NMR: 400 MHz, (CD_3OD) 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).

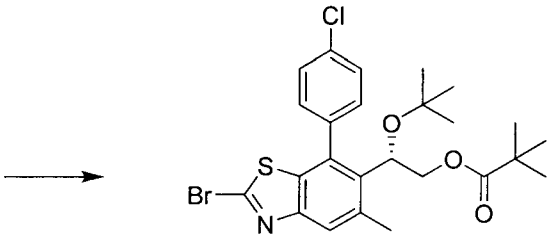
Example 11. Preparation of *(S)*-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (101).



(*S*)-2-(2-amino-7-bromo-5-methylbenzo [*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate



(*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate



(*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate

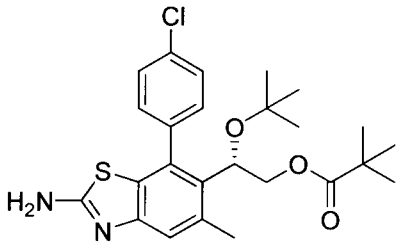
101

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), K_2CO_3 (960 mg, 6.96 mmol), 4-chlorophenylboronic acid (325 mg, 2.09 mmol), $Pd(PPh_3)_4$ (200 mg, 0.174 mmol), dioxane (8.0 mL), and H_2O (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. H_2O (50 mL) was added, and the system was extracted with EtOAc (3 x 50 mL). The combined extracts were dried (Na_2SO_4), 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 $C_{25}H_{31}ClN_2O_3S$: 475.2 and 477.2 ($M+H^+$); found: 475.3 and 477.3 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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).

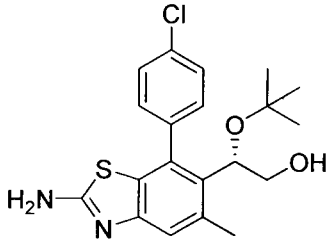
Preparation of *(S)*-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate: At 23 °C, in a water bath, a solution of *(S)*-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (1.13 g, 2.37 mmol) in CH_3CN (22 mL) was treated with solid anhydrous $CuBr_2$ (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 CH_3CN (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 H_2O (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 (Na_2SO_4), 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 $C_{25}H_{29}BrClNO_3S$: 538.1, 540.1, and 542.1.1 ($M+H^+$); found: 538.2, 540.2, and 542.2 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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).

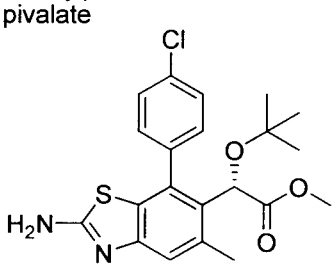
Example 12. Preparation of *(S)*-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (102).



(*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate



(*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethanol



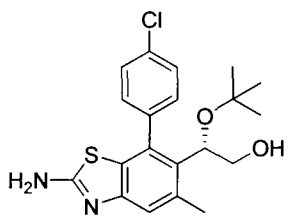
(*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

102

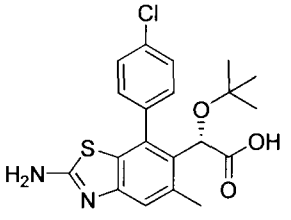
Preparation of *(S)*-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethanol: A flask was charged with *(S)*-2-(2-Amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (2.15 g, 4.52 mmol), LiOH monohydrate (2.00 g, 47.4 mmol), H_2O (4 mL), EtOH (absolute, 4.0 mL), and THF (8.0 mL). The reaction was placed under N_2 and heated to 100 °C. After 2 h, the reaction was cooled to 23 °C, diluted with H_2O, and extracted with EtOAc several times. The combined organic phases were dried (Na_2SO_4), 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 $C_{20}H_{23}ClN_2O_2S$: 391.1 and 393.1 ($M+H^+$); found: 391.2 and 393.2 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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).

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 CH_3CN (40 mL) and H_2O (10 mL) was treated with H_5IO_6 (2.00 g, 8.77 mmol) at 0 °C. Then solid CrO_3 (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. Na_2HPO_4 until the pH was ~8. Then 1.0 M aq. NaH_2PO_4 was added to pH = 5. The resulting system was extracted with DCM (50 mL). The organic phase was dried (Na_2SO_4), 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. Na_2HPO_4 (50 mL) was added. The organic phase was collected, and the aq. layer was extracted with DCM. Combined organic layers were dried (Na_2SO_4), 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 $C_{21}H_{23}ClN_2O_3S$: 419.1 and 421.1 ($M+H^+$); found: 419.2 and 421.2 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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).

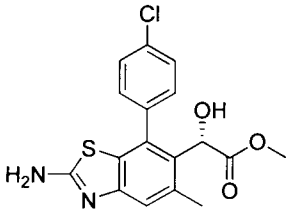
Example 13. Preparation of *(S)*-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (103).



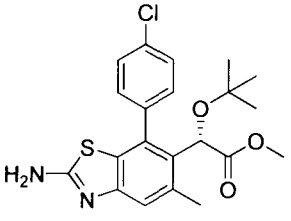
(*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethanol



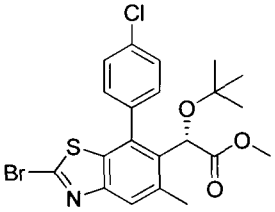
(*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid



(*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-hydroxyacetate



(*S*)-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

103

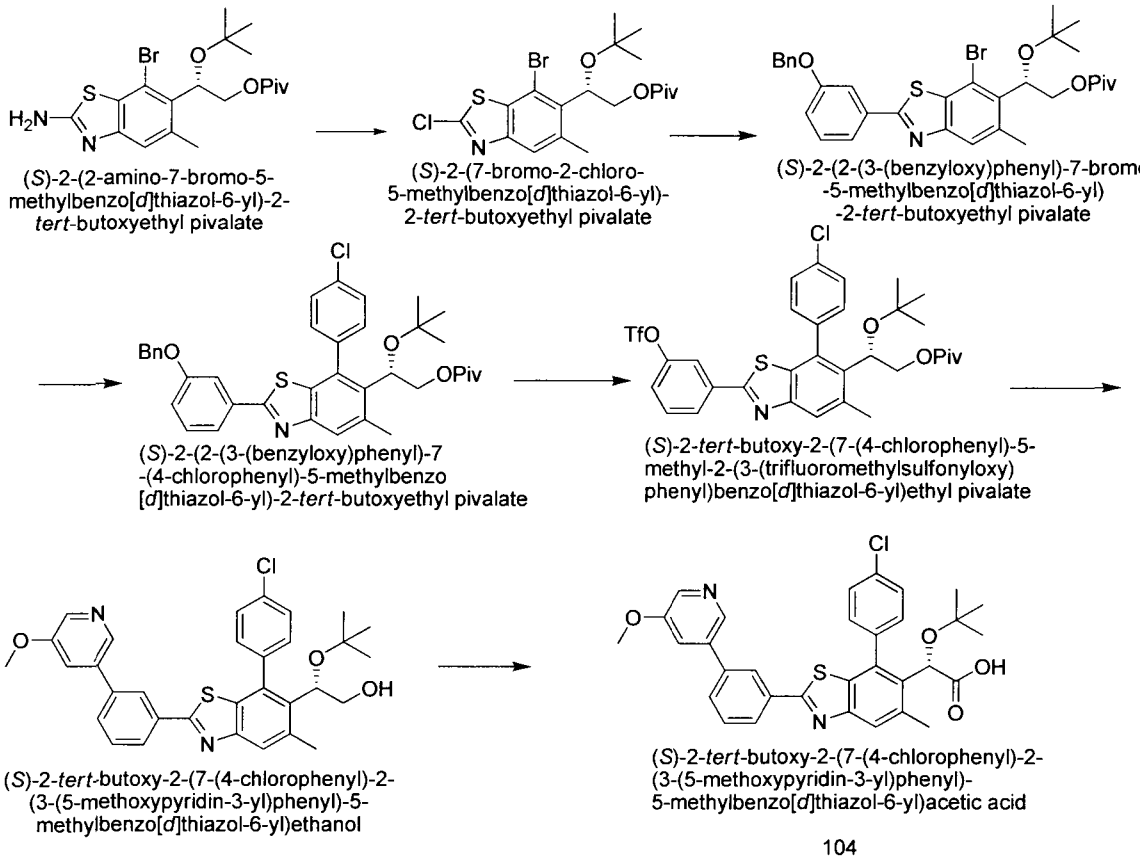
Preparation of *(S)*-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid. To a solution of *(S)*-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethanol (1.95 g, 5.00 mmol) in acetonitrile (25 mL) and water (1 mL) was added H_5IO_6 (1.37 g, 6.00 mmol) and CrO_3 (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 Na_2SO_3 (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc. The crude material was taken on without further purification. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 H_2SO_4 (200 μL). The reaction mixture was stirred at overnight. EtOAc (20 mL) and saturated

$NaHCO_3$ 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 μL). 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 $NaHCO_3$ solution (50 mL) were added. The layers were separated, dried, filtered, and concentrated *in vacuo*. LCMS-ESI$^+$: calc'd for $C_{21}H_{23}ClN_2O_3S$: 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 $CuBr_2$ (1.1 g, 5.0 mmol) and *t*-butyl nitrite (600 μL, 5.0 mmol). The reaction was stirred at room temperature for 30 min, and then a saturated solution of Na_2SO_3 (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 $C_{21}H_{21}BrClNO_3S$: 482.0 and 484.0 ($M+H^+$); found: 482.1 and 484.1 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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).



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 μL, 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 silca gel column, eluting be 0-50% EtOAc in hexanes to give the product (850 mg, 81%). LCMS-ESI$^+$: calc'd for $C_{19}H_{25}BrClNO_3S$: 462.0 ($M+H^+$); Found: 462.14 ($M+H^+$).

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), $Pd(PPh_3)_4$ (16 mg, 0.014 mmol), 2N K_2CO_3 (700 μL). 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 $C_{32}H_{36}BrNO_4S$: 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-cholorophenylboronic acid (38 mg, 0.246 mmol), 2N K_2CO_3 (400μL), $Pd(PPh_3)_4$ (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. $NaHCO_3$, extracted by EtOAc, the organic phase was dried over $MgSO_4$, 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 $C_{38}H_{40}ClNO_4S$: 642.2 ($M+H^+$); Found: 642.3 ($M+H^+$).

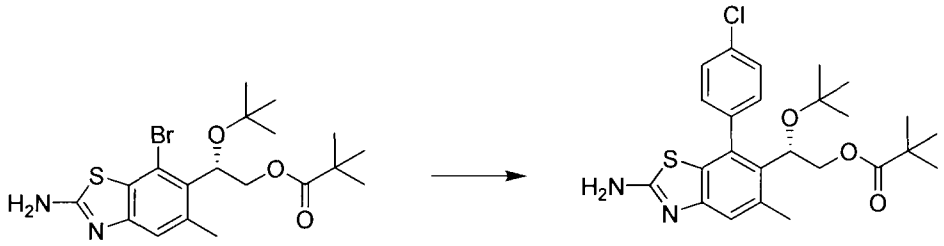
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethylsulfonyloxy)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate: To a solution of *(S)*-2-(2-(3-(benzyloxy)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (410 mg, 0.638 mmol) in EtOH/EtOAc (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), Tf_2O (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. $NaHCO_3$, extracted by DCM, dried over $MgSO_4$, 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 $C_{32}H_{33}ClF_3NO_6S_2$: 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 K_2CO_3 (70 μL), $Pd(PPh_3)_4$ (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. $NaHCO_3$,

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 $C_{32}H_{31}ClN_2O_3S$: 559.2 ($M+H^+$); Found: 559.2 ($M + H^+$).

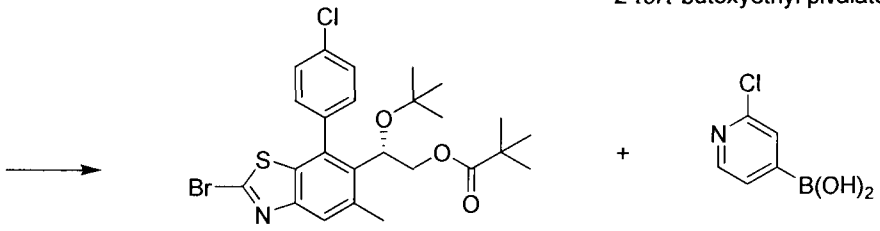
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(5-methoxypyridin-3-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(5-methoxypyridin-3-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)ethanol (10 mg, 0.0179 mmol) in wet acetonitrile (0.75 w% H_2O, 1 mL), was added stock solution of H_5IO_6/CrO_3 (0.439 M in 0.75% H_2O in acetonitrile, 400 µL) at 0 °C for ½ hour. The reaction 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 $C_{32}H_{29}ClN_2O_4S$: 573.2 ($M+H^+$); Found: 573.2 ($M + H^+$). 1H NMR (400 MHz, CD3OD): 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).

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).



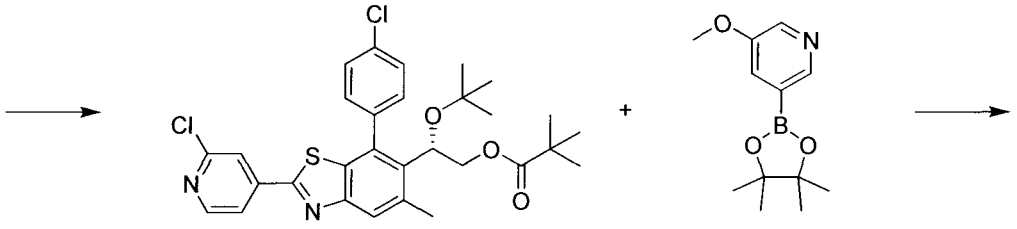
(*S*)-2-(2-amino-7-bromo-5-methylbenzo [*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate

(*S*)-2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate



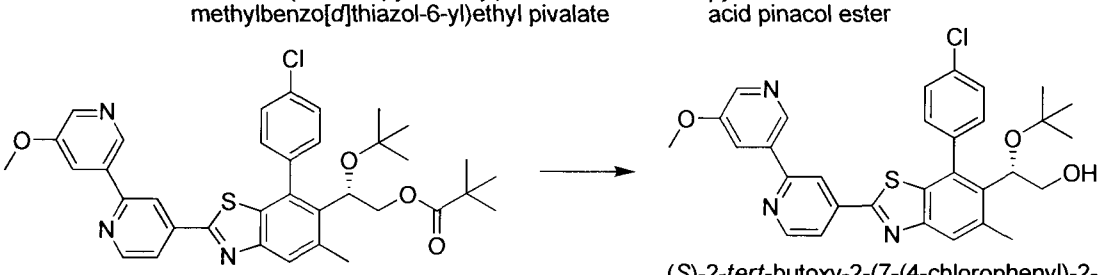
(*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate

2-chloropyridinyl-4-boronic acid



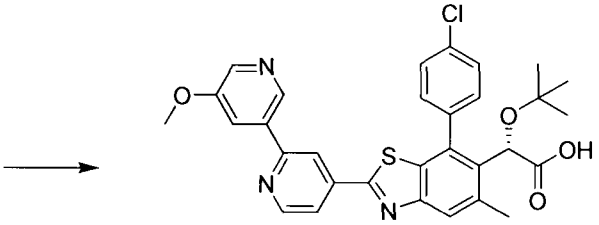
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)ethyl pivalate

5-methoxy-3-pyridineboronic acid pinacol ester



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)ethyl pivalate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)ethanol



(*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

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), K_2CO_3 (960 mg, 6.96 mmol), 4-chlorophenylboronic acid (325 mg, 2.09 mmol), $Pd(PPh_3)_4$ (200 mg, 0.174 mmol), dioxane (8.0 mL), and H_2O (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. H_2O (50 mL) was added, and the system was extracted with EtOAc (3 x 50 mL). The combined extracts were dried (Na_2SO_4), 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 $C_{25}H_{31}ClN_2O_3S$: 475.2 and 477.2 ($M+H^+$); found: 475.3 and 477.3 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 CH_3CN (22 mL) was treated with solid anhydrous $CuBr_2$ (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 CH_3CN (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 H_2O (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 (Na_2SO_4), 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 $C_{25}H_{29}BrClNO_3S$: 538.1, 540.1, and 542.1.1 ($M+H^+$); found: 538.2, 540.2, and 542.2 ($M+H^+$). ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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-

methylbenzo[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 $Pd(PPh_3)_4$ (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 Na_2SO_4, and concentrated. Purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the final compound. LCMS-ESI$^+$: calc'd for $C_{30}H_{33}Cl_2N_2O_3S$: 571.2 ($M+H^+$); Found: 571.1 ($M + H^+$); ^1H NMR (400 MHz, $CDCl_3$) 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).

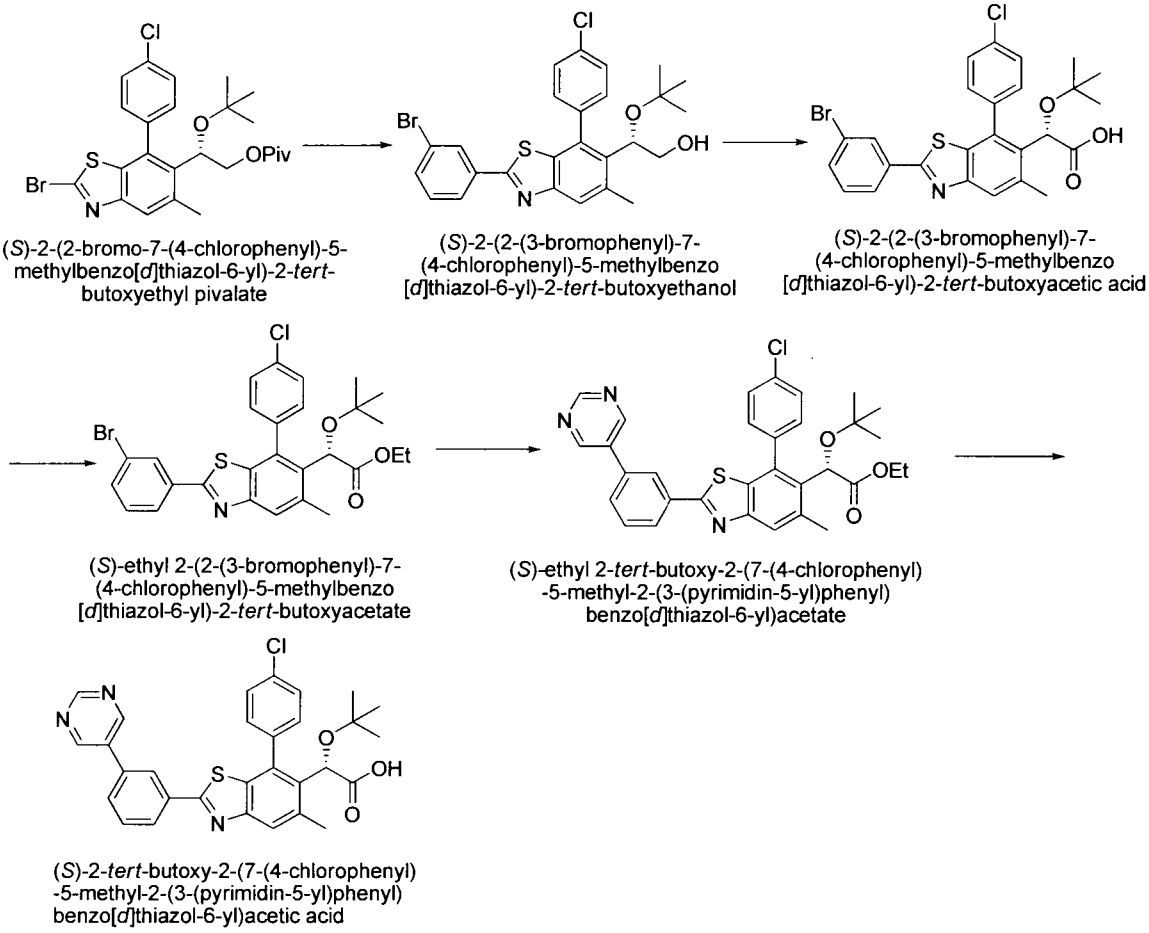
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)ethyl pivalate: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)ethyl pivalate (40.0 mg, 0.070 mmol), 5-methoxy-3-pyridineboronic acid pinacol ester (19.7 mg, 0.084 mmol), potassium carbonate (29.0 mg, 0.210 mmol), and $Pd(PPh_3)_4$ (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 Na_2SO_4, and concentrated. Purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the product. LCMS-ESI$^+$: calc'd for $C_{36}H_{39}ClN_3O_4S$: 644.2 ($M+H^+$); Found: 644.1 ($M + H^+$); ^1H NMR (400 MHz, $CDCl_3$) 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-methylbenzo[*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-methylbenzo[*d*]thiazol-6-yl)ethyl pivalate

(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 NH_4Cl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated to give the crude product which was used without further purification. LCMS-ESI$^+$: calc'd for $C_{31}H_{31}ClN_3O_3S$: 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 periodic acid (11.4 g, 50.0 mmol) and chromium trioxide (23 mg, 1.2 mol %) in wet acetonitrile (0.75% H_2O) 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 CrO_3/H_5IO_6 (0.72 mL, 0.439 M solution) and CrO_3 (9.4 mg, 0.094 mmol) at room temperature. The reaction was stirred for 1 h and quenched with aqueous Na_2SO_3 (10% w/v). When the reaction mixture turned green, it was extracted 3 times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, 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 the product. ^1H NMR (400 MHz, CD_3OD) 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 $C_{31}H_{29}ClN_3O_4S$: 574.1 ($M+H^+$); Found: 574.0 ($M + H^+$).

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).



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), $Ph(PPh_3)_4$ (33 mg, 0.029 mmol) 2N K_2CO_3 (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 $MgSO_4$, 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 $C_{26}H_{25}BrClNO_2S$: 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% H_2O, 2.5 mL), was added H_5IO_6/CrO_3 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.

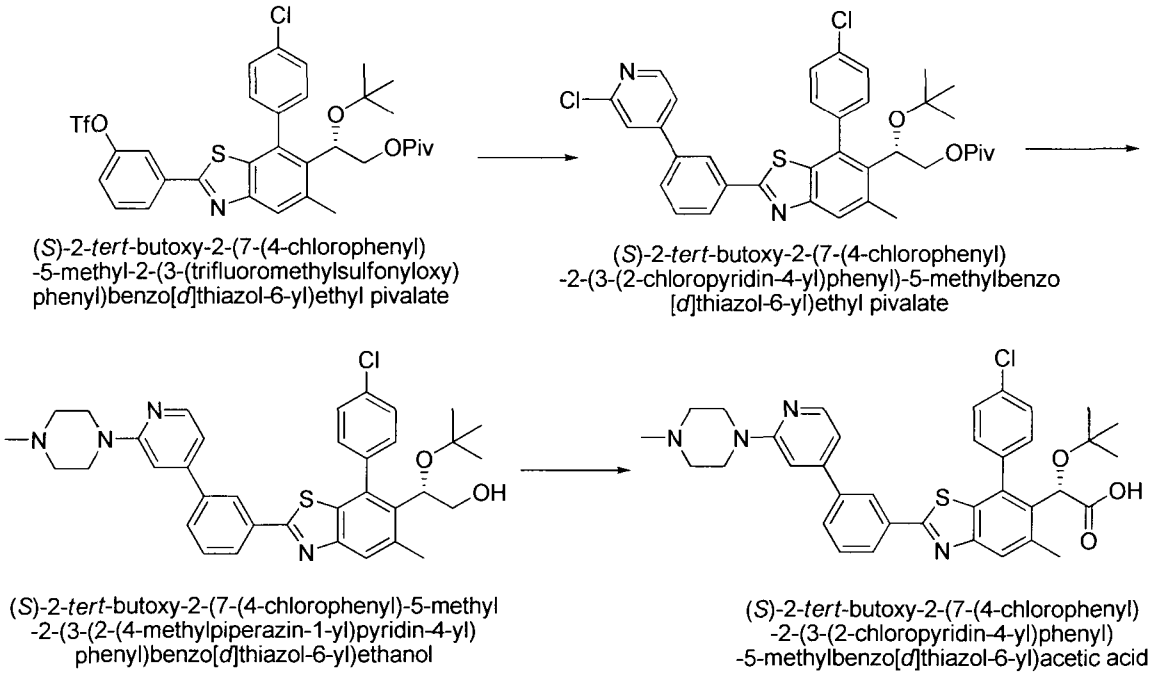
$NaHCO_3$, extracted by EtOAc, the organic phase was dried over $MgSO_4$, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{26}H_{23}BrClNO_3S$: 544.0 ($M+H^+$); Found: 544.1 ($M+H^+$).

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 Cs_2CO_3 (152 mg, 0.467 mmol), ethyl iodide (30 μL, 0.343 mmol). The reaction was stirred at room temperature for 2hs. The reaction mixture was washed by sat. $NaHCO_3$, extracted by EtOAc, dry over $MgSO_4$, filtered, purified by silica gel column, eluting by 0-50% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{28}H_{27}BrClNO_3S$: 572.1 ($M+H^+$); Found: 572.2 ($M+H^+$).

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 K_2CO_3 (60 μL), $Pd(PPh_3)_4$ (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. $NaHCO_3$, 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. LCMS-ESI$^+$: calc'd for $C_{32}H_{30}ClN_3O_3S$: 572.2 ($M+H^+$); Found: 572.2 ($M+H^+$).

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 H_2O with 0.1% TFA to give the product. LCMS-ESI$^+$: calc'd for $C_{30}H_{26}ClN_3O_3S$: 544.1 ($M+H^+$); Found: 544.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD): 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).



107

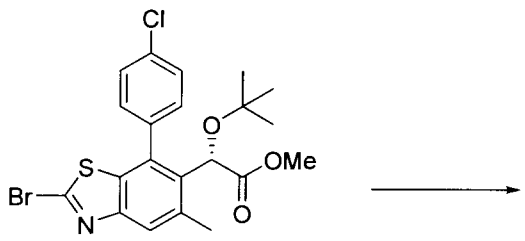
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2-chloropyridin-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate: The reaction mixture of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethylsulfonyloxy)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate (30 mg, 0.0438 mmol), 2-chloropyridine-4-boronic acid (10 mg, 0.0657 mmol), 2N K_2CO_3 (100 μL), $Pd(PPh_3)_4$ (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. $NaHCO_3$, extracted by EtOAc, dried by $MgSO_4$, 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 $C_{36}H_{36}Cl_2N_2O_3S$: 647.2 ($M+H^+$); Found: 647.3 ($M + H^+$).

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. $NaHCO_3$, extracted by EtOAc, the organic phase was dried over $MgSO_4$, 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 $NaHCO_3$, extracted by EtOAc, the organic phase was

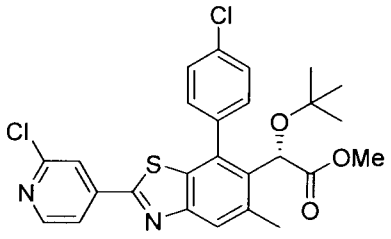
dried over $MgSO_4$, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{36}H_{39}ClN_4O_2S$: 627.2 ($M+H^+$); Found: 627.3 ($M+H^+$).

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 temperature overnight. The mixture was washed by sat. $NaHCO_3$, 1M $Na_2S_2O_3$, extracted by DCM, dried over $MgSO_4$, filtered, concentrated down. To the residue was added t-BuOH (600 μL), 1M NaH_2PO4 (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 for $C_{36}H_{37}ClN_4O_3S$: 641.2 ($M+H^+$); Found: 641.2 ($M+H^+$).

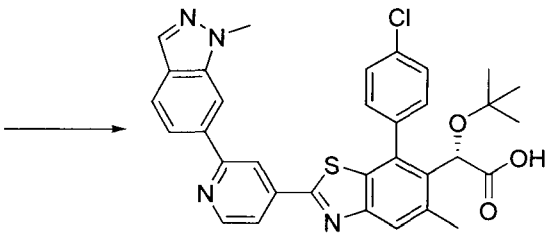
Example 18. Method F: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-6-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (108).



(*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



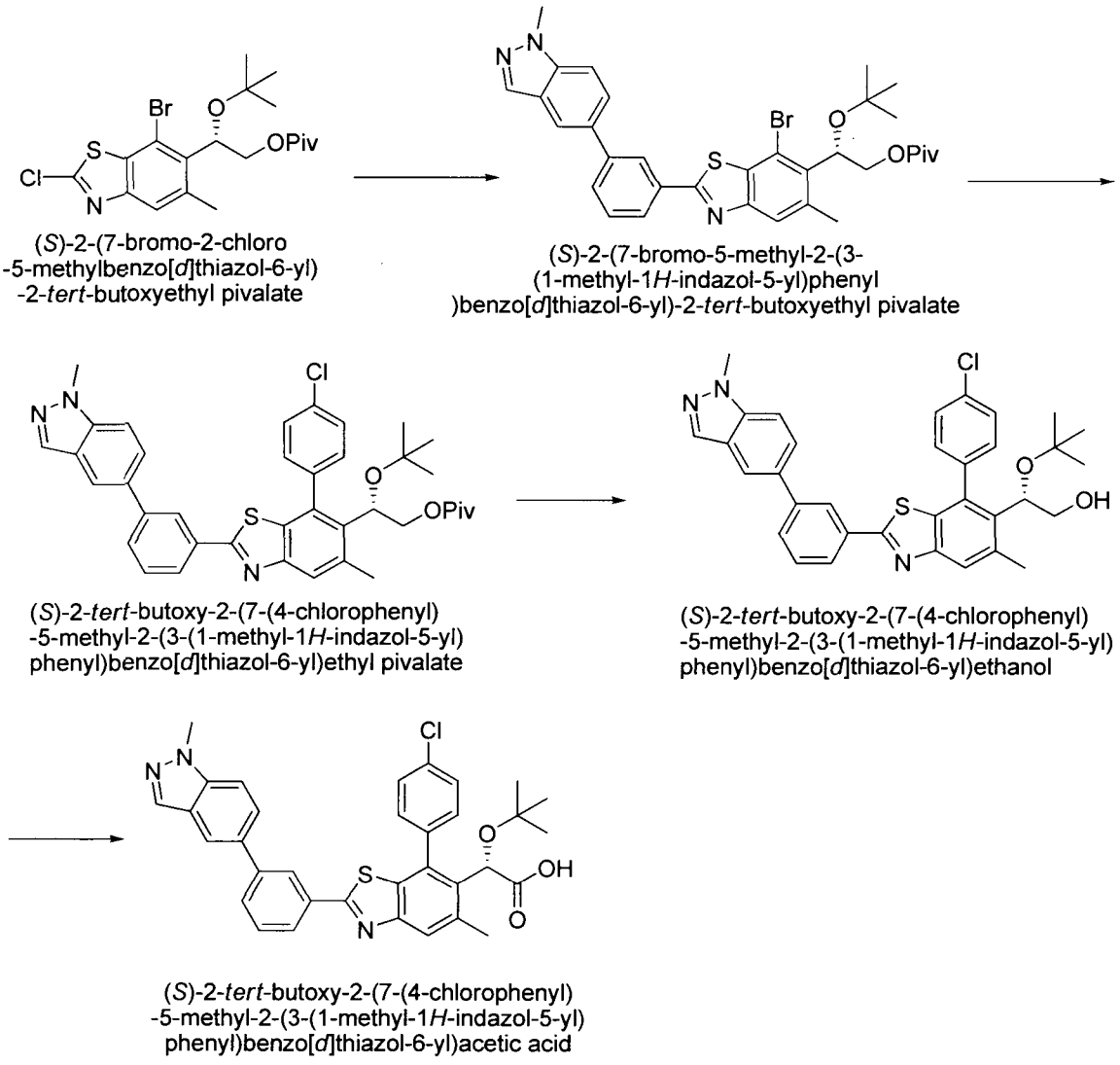
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

108

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 mol), 2-chloropyridine-4-boronic acid (157 mg, 0.99 mmol), 2N K_2CO_3 (1.9 mL), $Pd(PPh_3)_4$ (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. $NaHCO_3$, 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. LCMS-ESI$^+$: calc'd for $C_{26}H_{24}Cl_2N_2O_3S$: 515.1 ($M+H^+$); Found: 515.1 ($M + H^+$).

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-1*H*-indazole-6-boronic acid (10.3 mg, 0.058 mmol), 2N K_2CO_3 (100 μL, 0.19 mmol), $Pd(PPh_3)_4$ (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 H_2O with 0.1% TFA to give the product. LCMS-ESI$^+$: calc'd for $C_{33}H_{29}ClN_4O_3S$: 597.2 ($M+H^+$); Found: 597.2 ($M + H^+$). ^{1}H NMR (400 MHz, CD_3OD): 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).

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)-1*H*-indazole (260 mg, 0.78 mmol), $Pd(PPh_3)_4$ (75 mg, 0.065 mmol), 2N K_2CO_3 (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. $NaHCO_3$, 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. LCMS-ESI$^+$: calc'd for $C_{33}H_{36}BrN_3O_3S$: 634.2 ($M+H^+$); Found: 634.1 ($M+H^+$).

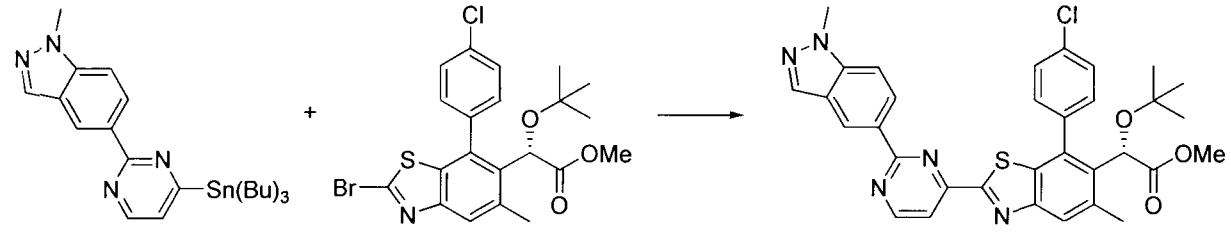
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate: The mixture of *(S)*-2-(7-bromo-5-

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 $NaHCO_3$ (100 μL), $Pd(PPh_3)_4$ (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. $NaHCO_3$, 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. LCMS-ESI$^+$: calc'd for $C_{39}H_{40}ClN_3O_3S$: 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 μL) in THF/MeOH (1:1, 1mL) was heated at 40 °C. After reaction finished, the reaction mixture was diluted by EtOAc, washed by sat. $NaHCO_3$, 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. LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_3O_2S$: 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% H_2O, 1 mL), was added stock solution of H_5IO_6/CrO_3 (0.439 M in wet acetonitrile, 150 μL) at 0 °C for ½ hour. The reaction mixture was filtered and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA give the product. LCMS-ESI$^+$: calc'd for $C_{34}H_{30}ClN_3O_3S$: 596.2 ($M+H^+$); Found: 596.2 ($M + H^+$). ^1H NMR (300 MHz, CD_3OD): 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).

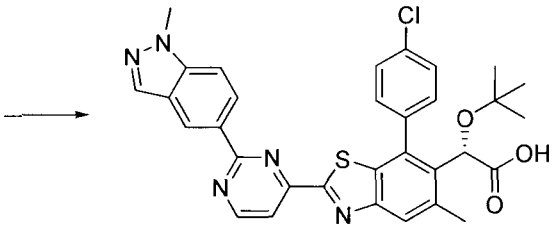
Example 20. Method H: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid (110).



1-methyl-5-(4-(tributylstannyl)pyrimidin-2-yl)-1*H*-indazole

(*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-5-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-5-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

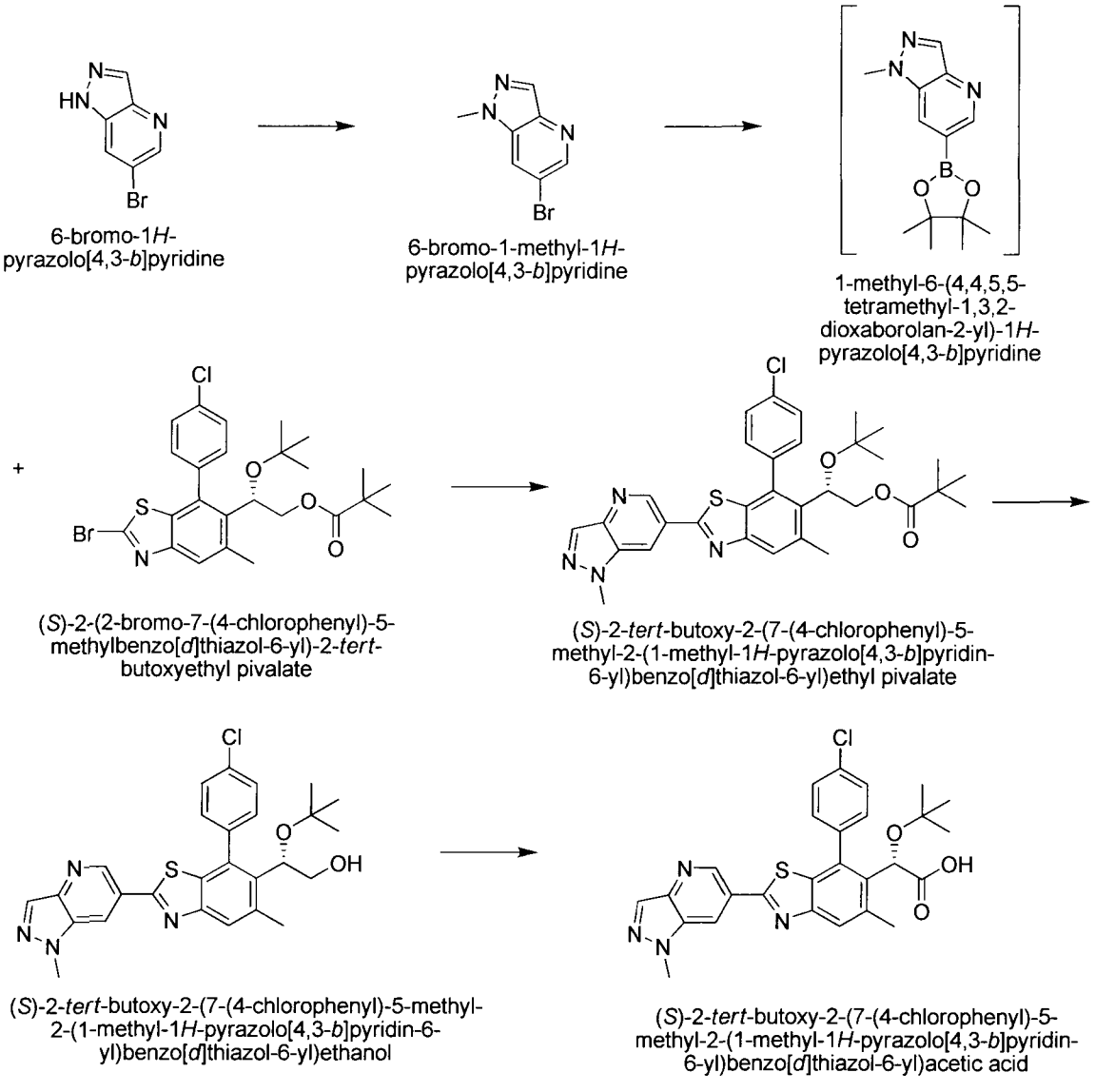
110

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), $Pd(PPh_3)_4$ (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 $C_{33}H_{31}ClN_5O_3S$: 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. ^{1}H NMR (400 MHz, CD_3OD) 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 =

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 $C_{32}H_{29}ClN_5O_3S$: 598.2 ($M+H^+$); Found: 598.3 ($M + H^+$).

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 ($MgSO_4$), 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 $C_7H_6BrN_3$: 211.98 (M+H$^+$); Found: 212.1 (M + H$^+$).

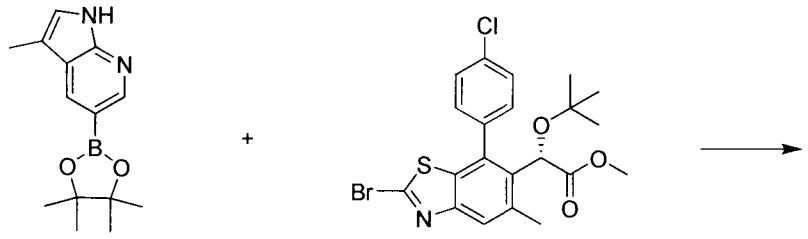
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine-6-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate: To a solution of 6-bromo-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (20 mg, 0.094 mmol) in dioxane (2 mL) was added bis(pinacolato)diboron (29 mg, 0.113 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 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), K_2CO_3 (33 mg, 0.23 mmol) and water (0.3 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 Na_2SO_4, filtered and concentrated to give crude product which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{32}H_{35}ClN_4O_3S$: 591.22 (M+H$^+$); Found: 591.2 (M + H$^+$).

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/CH_3OH (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 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 $C_{27}H_{27}ClN_4O_2S$: 507.16 (M+H$^+$); Found: 507.2 (M + H$^+$).

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 CrO_3/H_5IO_6 (0.439M, 1.1 mL, 0.483mmol) and CrO_3 (20 mg, 0.198 mmol). The reaction solution was stirred

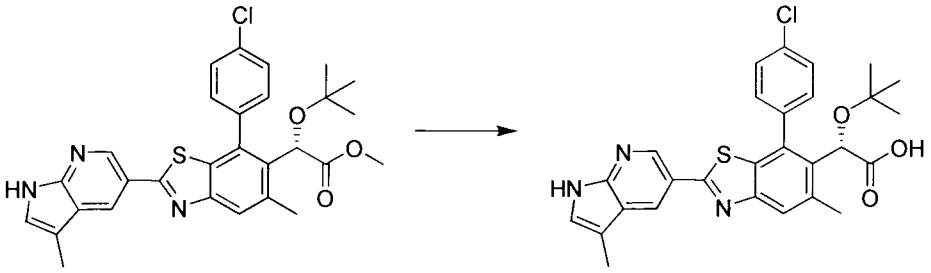
at room temperature for 1 h and quenched with 5% $Na_2S_2O_3$ solution. The mixture was extracted with ethyl acetate, washed with water and brine. The organic solution was dried and concentrated to give crude which was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{27}H_{25}ClN_4O_3S$: 521.14 ($M+H^+$); Found: 521.2 ($M + H^+$), ^1H NMR (400 MHz, CD_3OD) 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).

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).



3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine

(*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*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

(*S*)-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

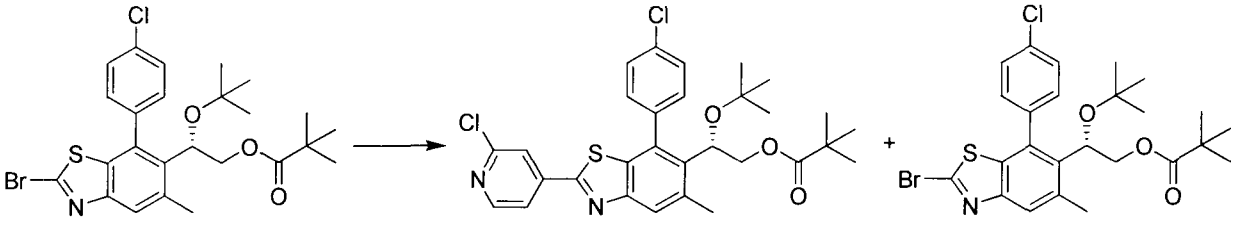
112

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), K_2CO_3 (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 Na_2SO_4, filtered and concentrated to give crude which was purified by chromatographic column to afford

the desired product. LCMS-ESI$^+$: calc'd for $C_{29}H_{28}ClN_3O_3S$: 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/CH_3OH (0.5 mL/0.5 mL) was added 2N NaOH (75μL, 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 $C_{28}H_{26}ClN_3O_3S$: 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).

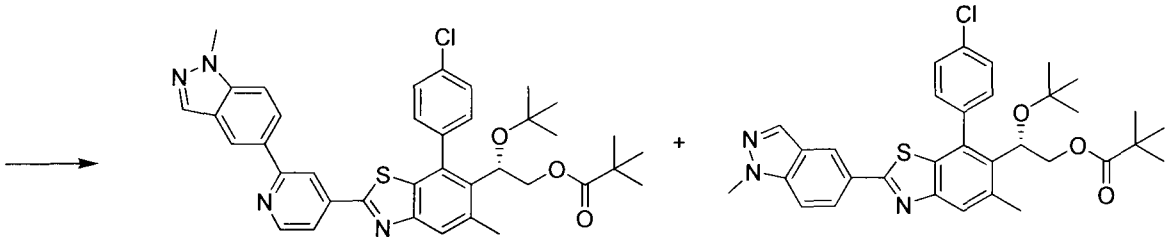
Example 23. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (113a) and (*S*)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (113b) .



(*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate

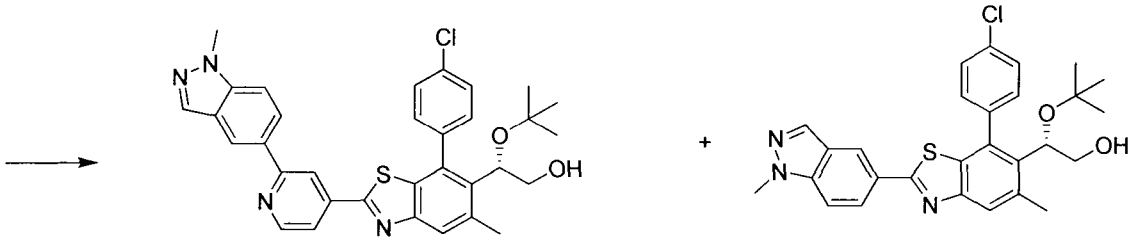
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)ethyl pivalate

(*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate



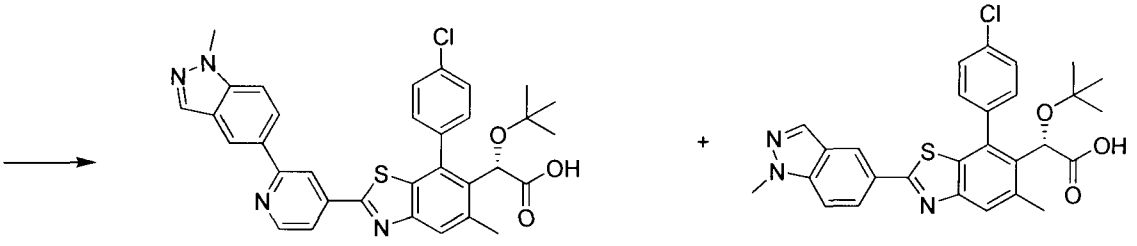
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate



(*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)ethanol

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)ethanol



(*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

(*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

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), 2-chloropyridin-4-ylboronic acid (0.66 g, 0.42 mmol), $Pd(PPh_3)_4$ (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 $C_{30}H_{33}Cl_2N_2O_3S$: 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 $C_{25}H_{29}BrClNO_3S$: 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-1*H*-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 $C_{38}H_{40}ClN_4O_3S$: 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 $C_{33}H_{36}ClN_3O_3S$: 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 ($MgSO_4$), 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 $C_{33}H_{32}ClN_4O_2S$: 583.2 ($M+H^+$); found: 583.2 ($M+H^+$).

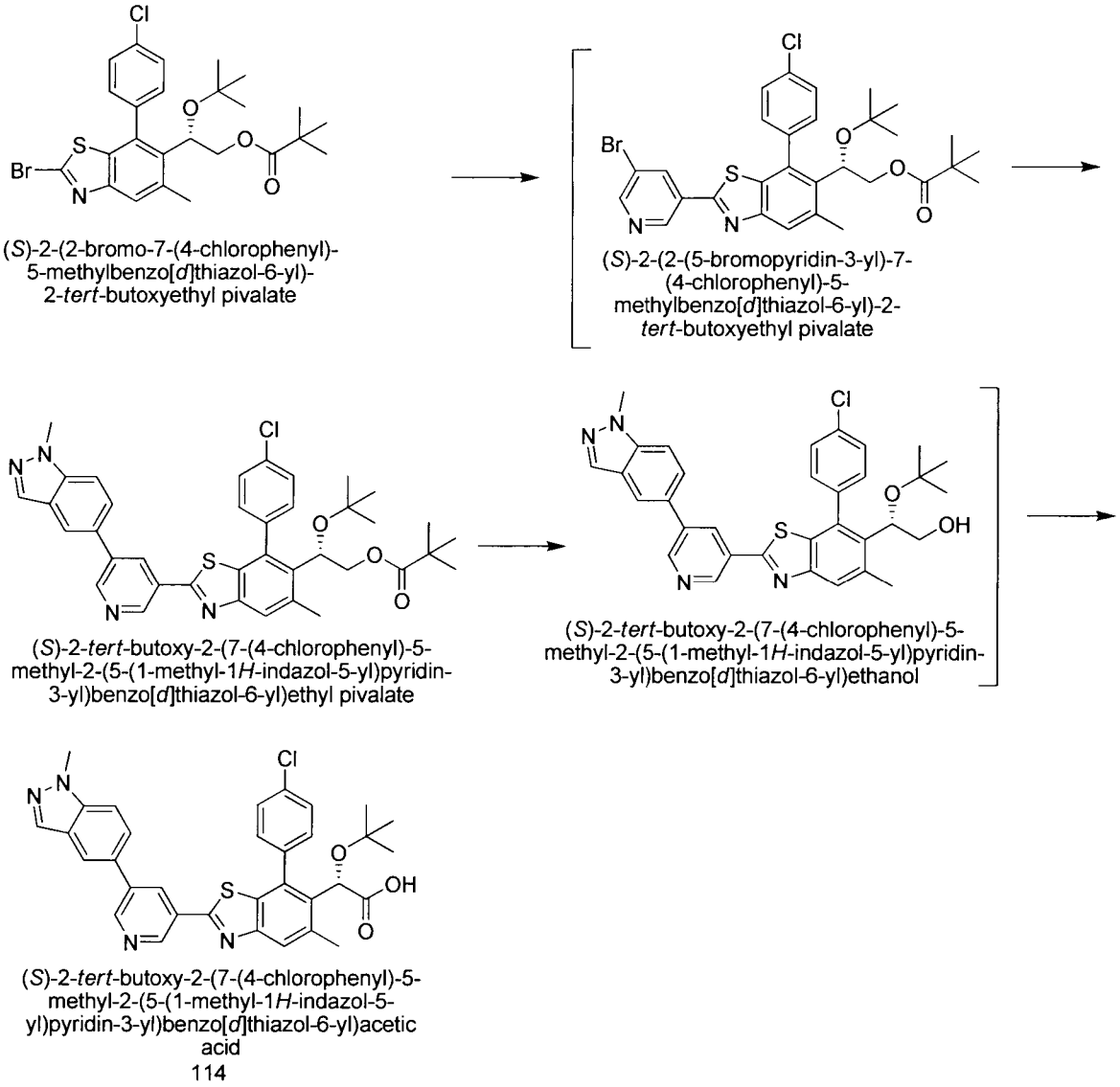
(S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)ethanol was also isolated.

LCMS-ESI$^+$: calc'd for $C_{28}H_{29}ClN_3O_2S$: 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% H_2O) 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 Na_2SO_3 solution and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, concentrated and purified by reverse phase HPLC (H_2O/ACN + 0.1% TFA) to give the desired product after lyophilization. LCMS-ESI$^+$: calc'd for $C_{33}H_{30}ClN_4O_3S$: 597.2 ($M+H^+$); found: 597.2, 599.2. ^1H NMR (400 MHz, CD_3OD) 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 $C_{33}H_{30}ClN_4O_3S$: 520.05 ($M+H^+$); found: 520.2, 522.1. ^1H NMR (400 MHz, CD_3OD) 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), $Pd(PPh_3)_4$ (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 $C_{30}H_{32}BrClN_2O_3S$: 617.1 (M+H$^+$); found: 617.2 (M+H$^+$).

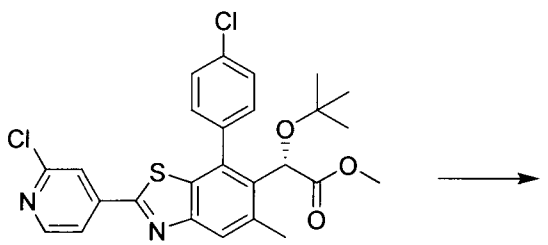
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)ethyl pivalate:*(S)*-2-(2-(5-bromopyridin-3-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate was telescoped into the subsequent reaction. 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 H_2O, 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 $C_{38}H_{40}ClN_4O_3S$: 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 ($MgSO_4$), 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 $C_{33}H_{32}ClN_4O_2S$: 583.2 (M+H$^+$); found: 583.3 (M+H$^+$).

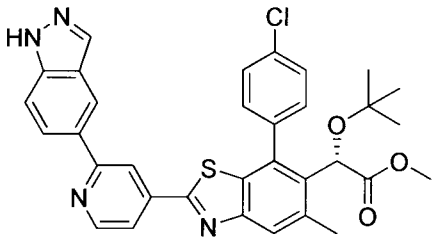
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid: A stock solution of periodic acid/chromium trioxide was prepared according to WO 99/52850 by dissolving periodic acid (11.4 g, 50.0 mmol) and chromium trioxide (23 mg, 1.2 mol %) in wet acetonitrile (0.75% H_2O) 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% H_2O in ACN (3 mL). The reaction mixture was stirred at room temperature for 45 minutes, quenched with saturated Na_2SO_3 solution and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, concentrated and purified by reverse phase HPLC (H_2O/ACN + 0.1% TFA) to give the desired

product after lyophilization. LCMS-ESI$^+$: calc'd for $C_{33}H_{30}ClN_4O_3S$: 597.2 ($M+H^+$); found: 597.2, 599.2. ^1H NMR (400 MHz, CD_3OD) 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).

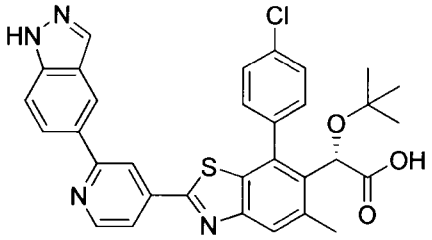
Example 25. Preparation of *(S)*-2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (115).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*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



(*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

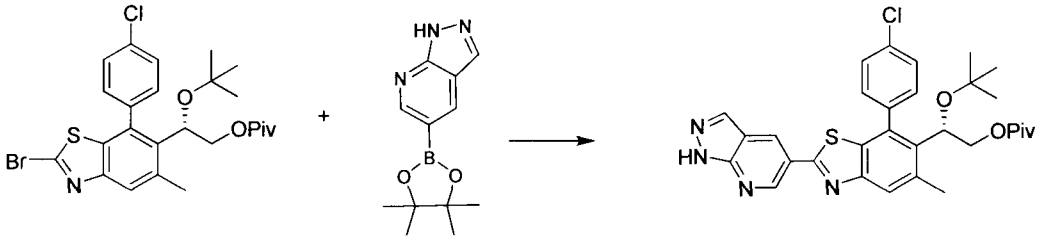
115

Preparation of *(S)*-methyl 2-(2-(2-(1H-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)-1H-indazole (14.2 mg, 58.2 μmol), $Pd(PPh_3)_4$ (5.6 mg, 4.86μmol), K_2CO_3 (27 mg, 0.19 mmol), H_2O (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)-1H-indazole (10 mg, 41 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 K_2CO_3 (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 $C_{33}H_{29}ClN_4O_3S$: 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), H_2O (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 H_2O / CH_3CN 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 $C_{32}H_{27}ClN_4O_3S$: 583.2 and 585.2 ($M+H^+$); Found: 583.3 and 585.3 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) 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).

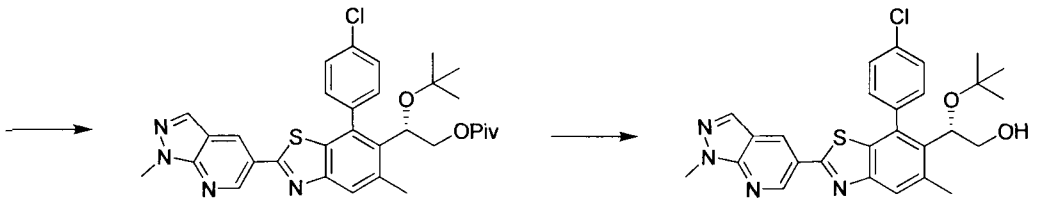
Example 26. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetic acid (116).



(*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate

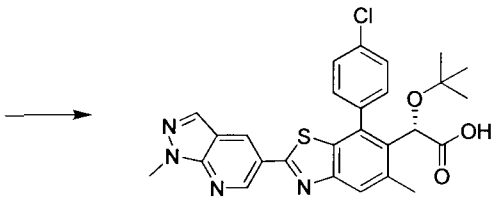
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)ethanol



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

116

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 μL) and water (25 μL) was added aqueous K_2CO_3 (95 μL of a 2.0 M solution) and tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol). The reaction mixture was heated at 100 °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 ($M + H^+$).

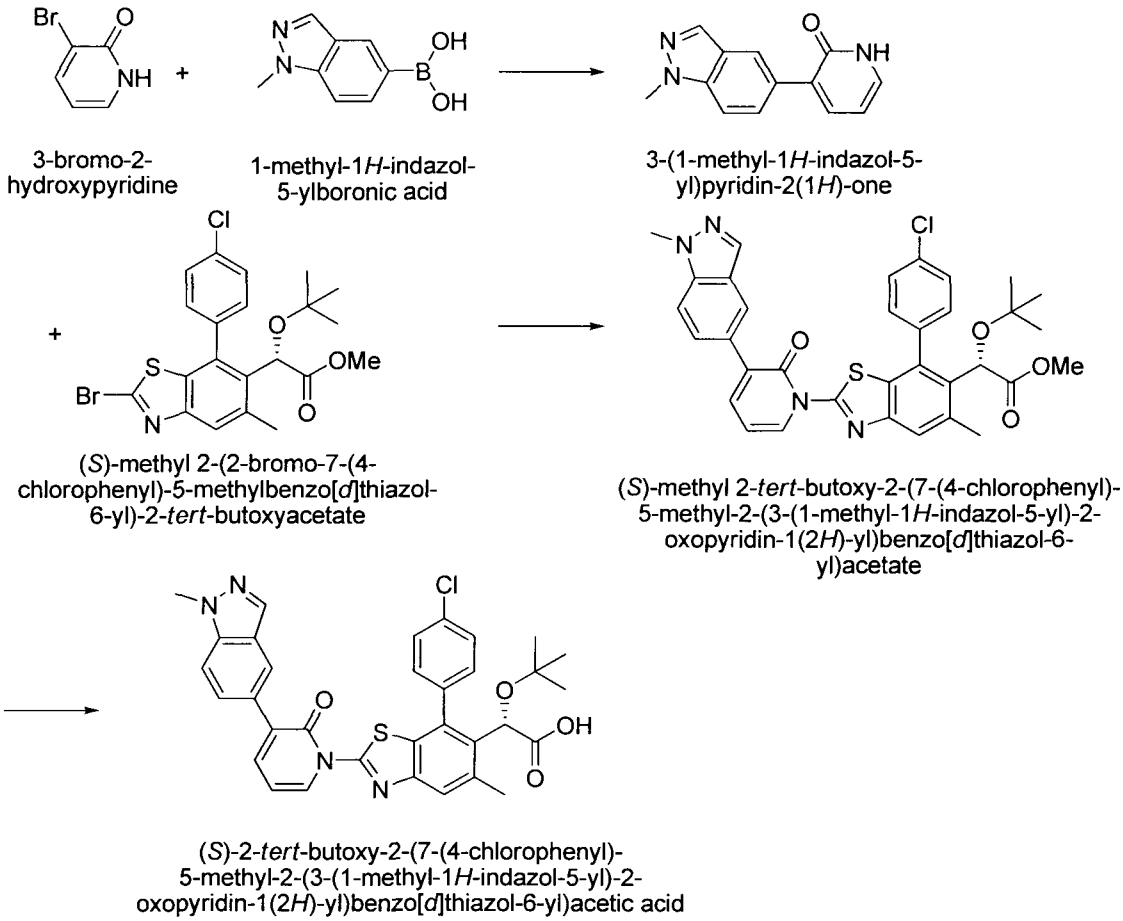
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)benzo[d]thiazol-6-yl)ethyl pivalate: To a solution of the crude

material from the previous reaction (assume 0.095 mmol) in dry DMF (1.0 mL) was added Cs_2CO_3 (60 mg, 0.185 mmol) at room temperature. After 15 min, neat methyl iodide (12 μL, 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 Na_2SO_4 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 $C_{32}H_{36}ClN_4O_3S$: 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 NH_4Cl 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 $C_{27}H_{28}ClN_4O_2S$: 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 CrO_3/H_5IO_6 (296 μL, 0.439 M solution) and CrO_3 (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 $C_{27}H_{26}ClN_4O_3S$: 521.1 ($M+H^+$); 521.2 ($M + H^+$); 1H NMR (400 MHz, CD_3OD): 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).



117

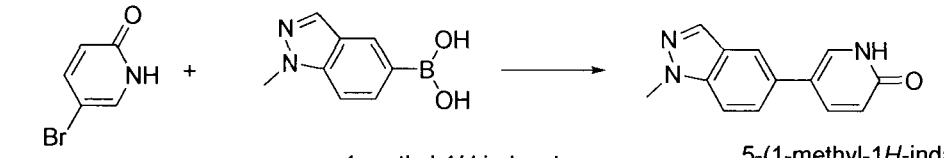
Preparation of 3-(1-methyl-1H-indazol-5-yl)pyridin-2(1H)-one: The suspension of 3-bromo-2-hydroxypyridine (80 mg, 0.46 mmol), 1-methyl-1H-indazol-5-ylboronic acid (121 mg, 0.69 mmol) and sodium carbonate (146 mg, 1.38 mmol) in DMF (2.0 mL) and H_2O (0.4 mL) was degassed with N_2 for 5 minutes. To the 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/H_2O + 0.1% TFA) to give the product. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{12}N_3O$: 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-*N*1,*N*2-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 N_2 for 5 minutes and then heated at 110 °C for 3 h. The mixture was then

diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, 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 $C_{34}H_{32}ClN_4O_4S$: 627.18; Found: 627.2.

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 stirred at 37 °C for 6 h. The reaction mixture was purified by reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give the product. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{30}ClN_4O_4S$: 613.17; Found: 613.2; ^{1}H-NMR: 400 MHz, (CD_3OD) 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).

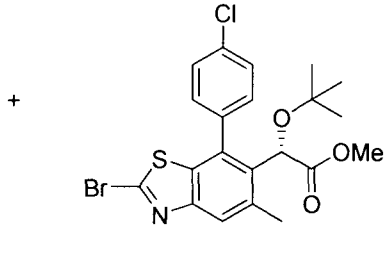
Example 28. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid (118).



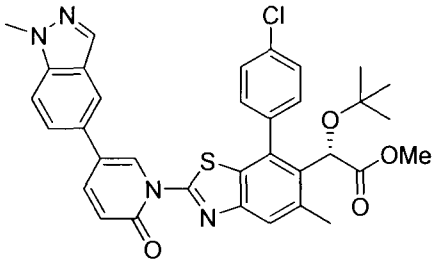
5-bromo-2-hydroxypyridine

1-methyl-1*H*-indazol-5-ylboronic acid

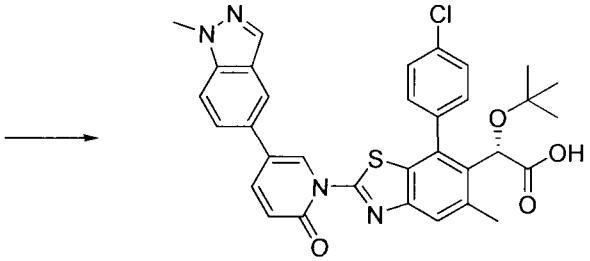
5-(1-methyl-1*H*-indazol-5-yl)pyridin-2(1*H*)-one



(*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1*H*-indazol-5-yl)-2-oxopyridin-1(2*H*)-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1*H*-indazol-5-yl)-2-oxopyridin-1(2*H*)-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 N_2 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 CH_2Cl_2, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by reverse phase HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give the product. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{12}N_3O$: 226.25; Found: 226.3.

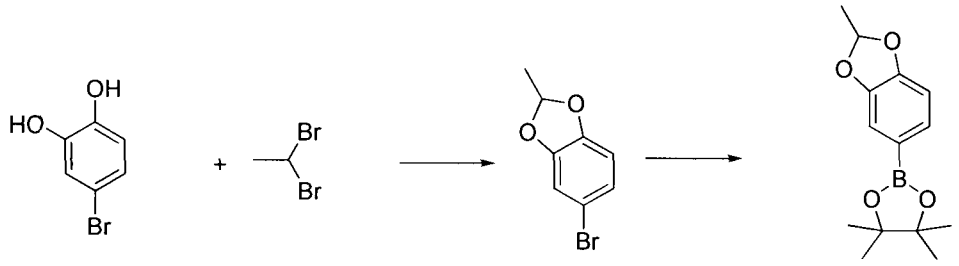
Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(1-methyl-1H-indazol-5-yl)-2-oxopyridin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate:

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 $C_{34}H_{32}ClN_4O_4S$: 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. ^{1}H-NMR: 400 MHz, (CD_3OD) 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 $C_{33}H_{30}ClN_4O_4S$: 613.17; Found: 613.2.

Example 29. 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 (119).

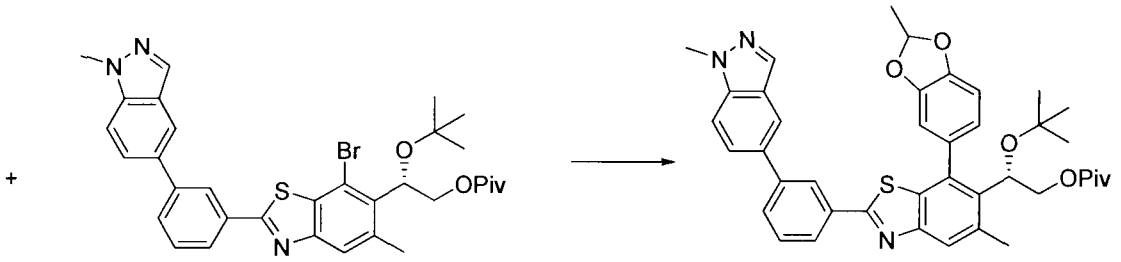


4-bromobenzene-1,2-diol

1,1-dibromoethane

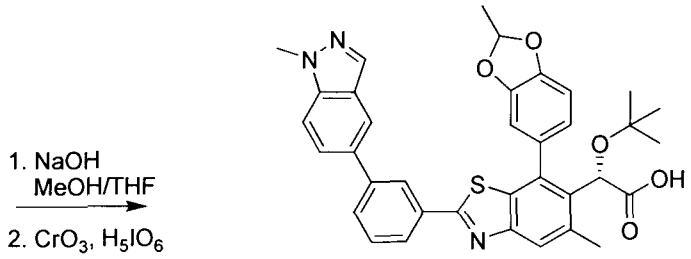
5-bromo-2-methylbenzo[*d*][1,3]dioxole

4,4,5,5-tetramethyl-2-(2-methylbenzo[*d*][1,3]dioxol-5-yl)-1,3,2-dioxaborolane



(*S*)-2-(7-bromo-5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)phenyl)benzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate

(2*S*)-2-*tert*-butoxy-2-(5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)phenyl)-7-(2-methylbenzo[*d*][1,3]dioxol-5-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate



(2*S*)-2-*tert*-butoxy-2-(5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)phenyl)-7-(2-methylbenzo[*d*][1,3]dioxol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

119

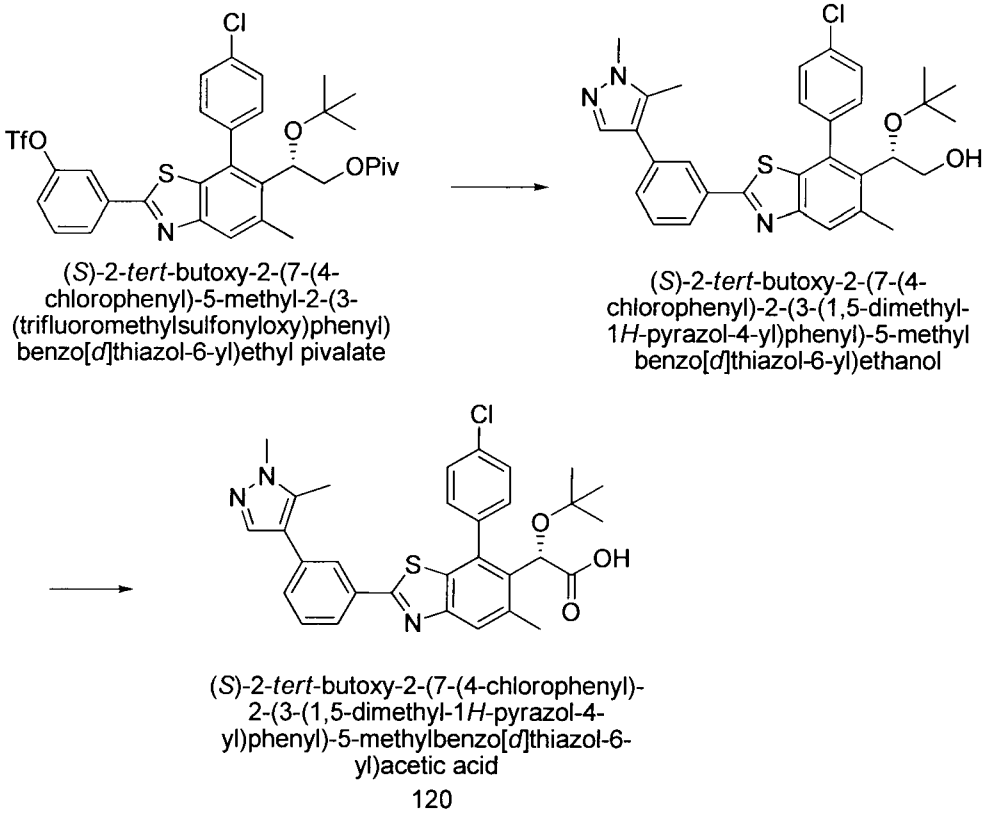
Preparation of 5-bromo-2-methylbenzo[d][1,3]dioxole: To a solution of 4-bromobenzene-1,2-diol (500 mg, 2.65 mmol) in acetone (4 mL) was added cesium carbonate (1.90 g, 5.82 mmol) and 1,1-dibromoethane (1.09 g, 5.82 mmol). The mixture was microwaved to 120 °C for 3 h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 10% ethyl acetate/hexanes) to give the product. ^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 N_2 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.^{1}H-NMR: 400 MHz, ($CDCl_3$) 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 $Pd(PPh_3)_4$ (4 mg, 3.1 x 10^{-3} mmol) and 2M K_2CO_3 (66 µL, 0.133 mmol). The reaction was degassed for 5 minutes with N_2 and then heated to 110°C for 1 h. After cooling, the reaction mixture was diluted with EtOAc, extracted with saturated $NaHCO_3$, brine, dried over Na_2SO_4, 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 $C_{41}H_{44}N_3O_5S$: 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 $C_{36}H_{34}N_3O_5S$: 620.2; Found: 620.3; ^{1}H-NMR: 400 MHz, (CD_3OD) 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, 1 H), 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).

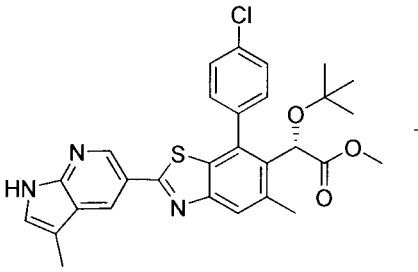


Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethylsulfonyloxy)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate: The reaction mixture of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethylsulfonyloxy)phenyl)benzo[d]thiazol-6-yl)ethyl pivalate (20 mg, 0.029 mmol), 1,5-dimethyl-1H-pyrazole-5-boronic acid pinnacle ester (13 mg, 0.058 mmol), 2N K_2CO_3 (80 μL), $Pd(PPh_3)_4$ (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 overnight. Then reaction mixture was washed by sat. $NaHCO_3$, 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 desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{32}ClN_3O_2S$: 546.2 ($M+H^+$); Found: 546.3 ($M+H^+$).

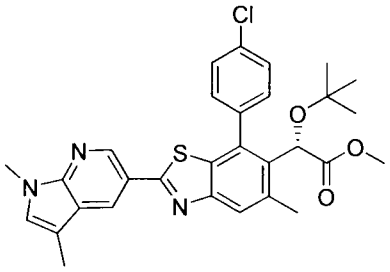
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-2-*tert*-butoxy-2-(7-(4-

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% H_2O, 1 mL), was added stock solution of H_5IO_6/CrO_3 (0.439 M in wet acetonitrile, 400 μL) at 0 °C for ½ hour. The reaction mixture was filtered and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA give the product. LCMS-ESI$^+$: calc'd for $C_{31}H_{30}ClN_3O_3S$: 560.2 ($M+H^+$); Found: 560.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD): 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).

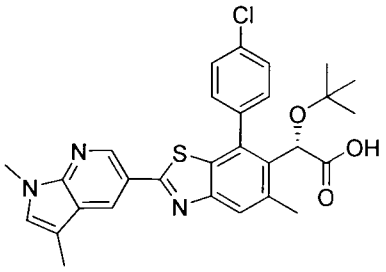
Example 31. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (121).



(*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



(*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



(*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

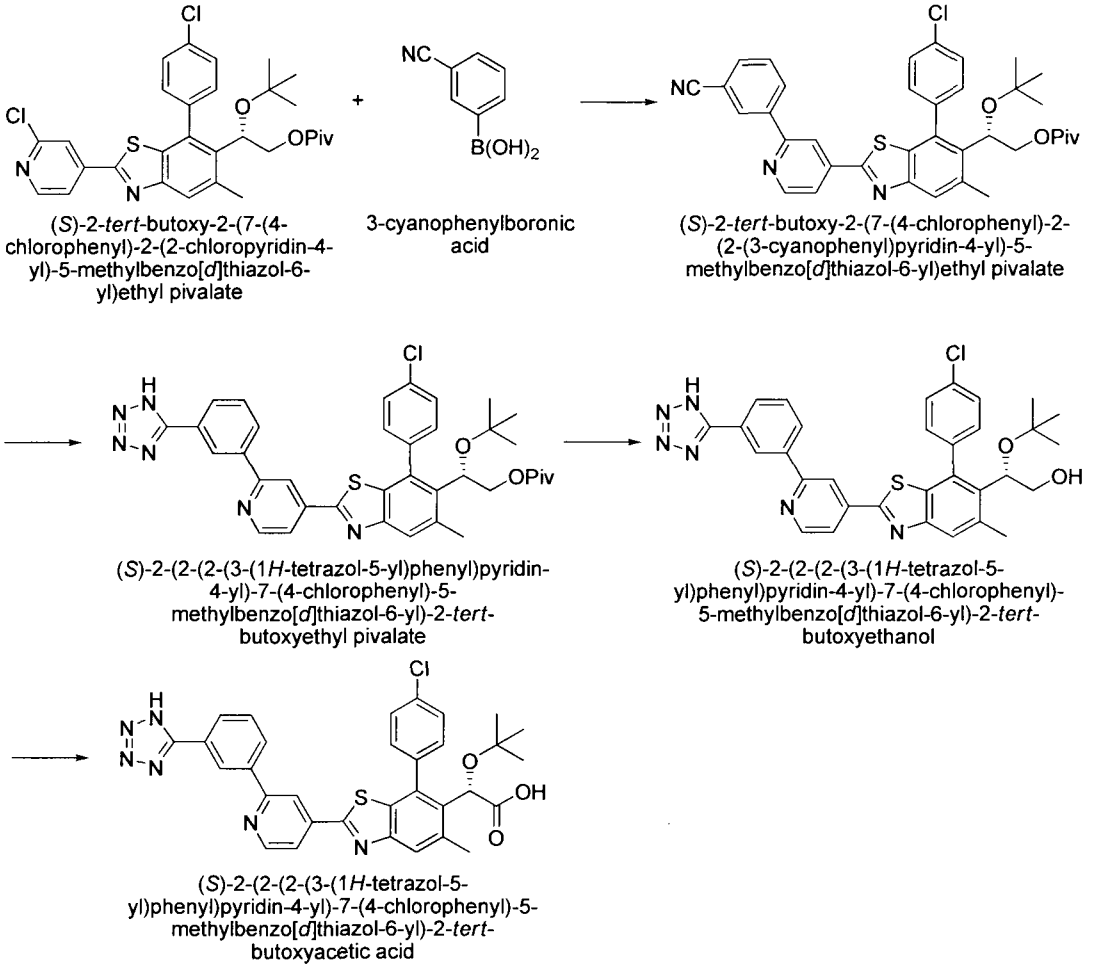
121

Preparation *(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: 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 (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

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 ($MgSO_4$), filtered and concentrated to give crude product which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{30}H_{30}ClN_3O_3S$: 548.17 ($M+H^+$); Found: 548.4 ($M+H^+$).

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/CH_3OH (0.5 mL/0.5 mL) was added 2N NaOH (37uL, 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 H_2O with 0.1% TFA to give desired product. LCMS-ESI$^+$: calc'd for $C_{29}H_{28}ClN_3O_3S$: 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-(1H-tetrazol-5-yl)phenyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (122).



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

3-cyanophenylboronic acid

(*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-(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

(*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*-butoxyethanol

(*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

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), $Pd(PPh_3)_4$, and K_2CO_3 (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 $C_{37}H_{37}ClN_3O_3S$: 638.2 ($M+H^+$); Found: 637.9 ($M + H^+$).

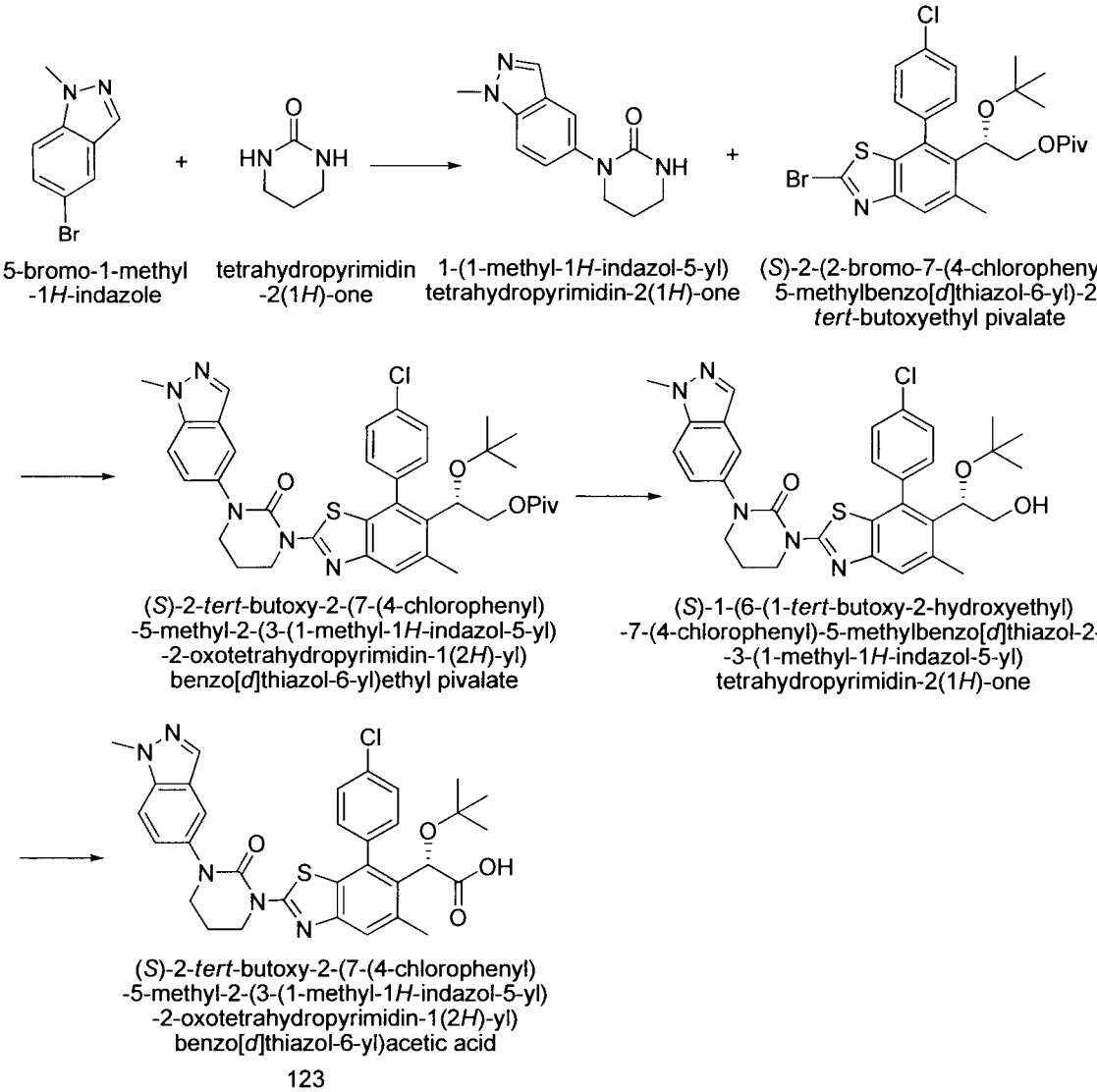
Preparation of *(S)*-2-(2-(2-(3-(1H-tetrazol-5-yl)phenyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate: To a solution of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-cyanophenyl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethyl

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 $C_{37}H_{38}ClN_6O_3S$: 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 NH_4Cl (sat. aq.), and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product which was used without further purification. LCMS-ESI$^+$: calc'd for $C_{32}H_{30}ClN_6O_2S$: 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 CrO_3/H_5IO_6 (0.27 mL, 0.439 M solution) and CrO_3 (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. ^{1}H NMR (400 MHz, CD_3OD) 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 $C_{32}H_{28}ClN_6O_3S$: 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).



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 $Pd_2(dba)_3$ (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 $C_{12}H_{14}N_4O$: 231.2 ($M+H^+$); Found: 231.2 ($M+H^+$).

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

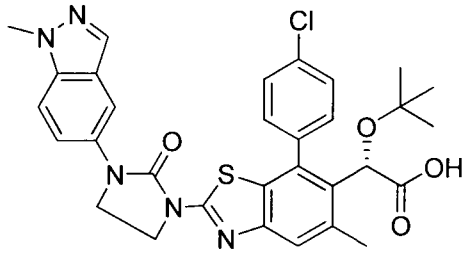
pivalate (27 mg, 0.05 mmol) in 1,4-dioxane (1.5 mL) was added 1-(1-methyl-1H-indazol-5-yl)tetrahydropyrimidin-2(1H)-one (23 mg, 0.1 mmol), followed by $Pd_2(dba)_3$ (5 mg, 0.006 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (10 mg, 0.02 mmol) and cesium carbonate (60 mg, 0.18 mmol). The reaction 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 Na_2SO_4 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 $C_{37}H_{42}ClN_5O_4S$: 688.3 ($M+H^+$); Found: 688.4($M+H^+$).

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 $C_{32}H_{34}ClN_5O_3S$: 604.2 ($M+H^+$); Found: 604.3 ($M+H^+$).

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)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% H_2O, 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% H_2O) 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 $C_{32}H_{32}ClN_5O_4S$: 618.2 ($M+H^+$); Found: 618.3 ($M+H^+$), 615.8 ($M+H^+$); ^{1}H-NMR 400 MHz, (CD_3OD) 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),

5.20 (s, 1 H), 4.40 (m, 2 H), 4.07 (s, 3 H), 3.85 (m, 2 H), 2.55 (s, 3 H), 2.34 (m, 2 H), 0.94 (s, 9 H).

Example 34. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxoimidazolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (124).

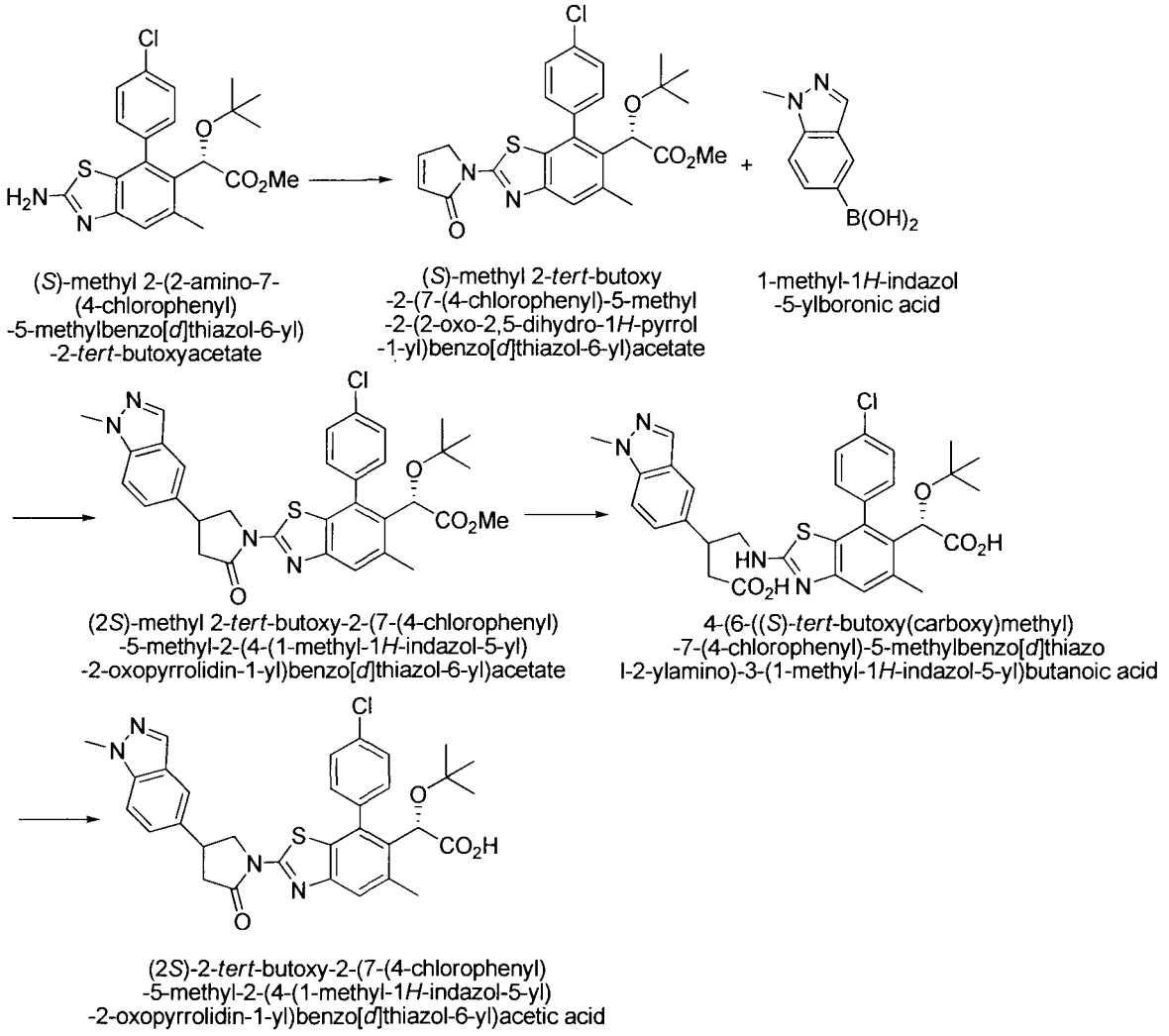


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)-2-oxoimidazolidin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid

124

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxoimidazolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxoimidazolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (1.3 mg) was prepared in a similar manner as compound *(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 except using imidazolidin-2-one instead of tetrahydropyrimidin-2(1H)-one. LCMS-ESI$^+$: calc'd for $C_{31}H_{30}ClN_5O_4S$: 604.2 (M+H$^+$); Found: 604.2 (M + H$^+$); ^{1}H-NMR 400 MHz, (CD_3OD) δ 7.99 (s, 1 H), 7.82 (m, 1 H), 7.66 (m, 1 H), 7.60-7.48 (m, 5 H), 7.42 (m, 1H), 5.21 (s, 1 H), 4.33 (m, 1 H), 4.22 (m, 2 H), 4.06 (s, 3 H), 3.64 (m, 1 H), 2.55 (s, 3 H), 0.96 (s, 9 H).

Example 35. Preparation of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)-2-oxopyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (125).



125

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-methyl 2-(2-amino-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (40 mg, 0.1 mmol) in acetonitrile (1 mL) was added 2,5-dimethoxy-2,5-dihydrofuran (26 μL, 0.2 mmol), followed by hydrochloric acid (0.2 N, 0.8 mL, 0.16 mmol). The mixture was stirred for 24 hours, and was diluted with EtOAc and quenched with saturated sodium bicarbonate solution. The organic layer was separated, and was washed with water and brine, dried with sodium sulfate and filtered. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{25}H_{25}ClN_2O_4S$: 485.1 ($M+H^+$); Found: 485.2 ($M + H^+$).

Preparation of (2S)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)-2-oxopyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-

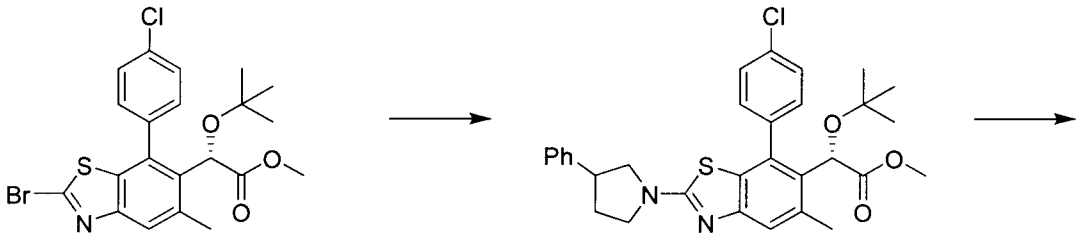
methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)benzo[d]thiazol-6-yl)acetate (12 mg, 0.025 mmol) in 1,4-dioxane/water (0.5 mL/50 μL) was added 1-methyl-1H-indazol-5-ylboronic acid (8 mg, 0.050 mmol), followed by chloro(1,5-cyclooctadiene)rhodium (I) dimer (1 mg), BINAP (5 mg), and potassium carbonate solution (2 N, 6 μL). The mixture was purged with nitrogen and heated at 80 °C for 24 hours. The mixture was diluted with EtOAc, and was washed with water and brine, dried with sodium sulfate and filtered. Concentration and purification by flash column chromatography (hexanes/EtOAc) gave (2S)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)-2-oxopyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{33}H_{33}ClN_4O_4S$: 617.2 (M + H$^+$); Found: 617.2 (M + H$^+$).

Preparation of 4-(6-((*S*)-*tert*-butoxy(carboxy)methyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-ylamino)-3-(1-methyl-1H-indazol-5-yl)butanoic acid: To a solution of (2S)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)-2-oxopyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetate (5 mg) in THF/MeOH (0.5 mL/0.5 mL) was added sodium hydroxide solution (1.0 N, 0.5 mL). The mixture was stirred at 25 °C for 2 hours and heated at 50 °C for 16 hours. The mixture was cooled and neutralized with 0.1 N hydrochloric acid until pH = 5. The reaction mixture was freeze-dried and used for next step without further purification. LCMS-ESI$^+$: calc'd for $C_{32}H_{33}ClN_4O_5S$: 621.2 (M + H$^+$); Found: 621.2 (M + H$^+$).

Preparation of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)-2-oxopyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of 4-(6-((*S*)-*tert*-butoxy(carboxy)methyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-ylamino)-3-(1-methyl-1H-indazol-5-yl)butanoic acid in DMF (1 mL) was added di-isopropylethylamine (86 μL), followed by N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (19 mg). The mixture was stirred for 2 hours and purified with reverse phase HPLC to give an intermediate (6 mg). The intermediate was dissolved in pyridine (1 mL), water (1 mL) and 1-hydroxybenzotriazole hydrate (1 mg) were added. The mixture was heated at 100 °C for 48 hours. Concentration and purification by reverse phase HPLC gave (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)-2-oxopyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid. LCMS-ESI$^+$: calc'd for $C_{32}H_{31}ClN_4O_4S$: 603.2 (M+H$^+$); Found: 603.4 (M + H$^+$); ^{1}H-NMR 400 MHz, (CD_3OD) δ 7.97 (m, 1 H), 7.74 (m, 1 H), 7.60-7.47 (m, 7 H), 5.22 (s, 1

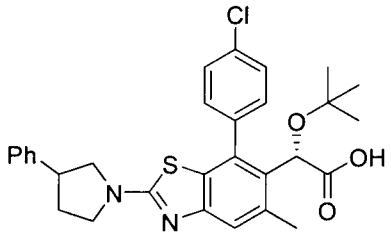
H), 4.68 (m, 1 H), 4.19 (m, 1 H), 4.06 (m, 3 H), 4.0 (m, 1 H), 3.10 (m, 1 H), 2.95 (m, 1 H), 2.55 (s, 3 H), 0.95 (s, 9 H).

Example 36. Preparation of *(2S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-phenoxypyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid (126).



(*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(2*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-phenylpyrrolidin-1-yl)benzo[*d*]thiazol-6-yl)acetate



(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-phenylpyrrolidin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid

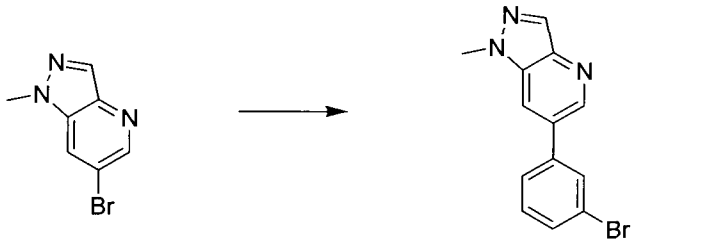
126

Preparation of (*2S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-phenylpyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetate: To a solution of (*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (46.1 mg, 0.095 mmol) in THF (2 mL) was added 3-phenylpyrrolidine (16.9 mg, 0.115 mmol) and diethylpropylamine (24.8 µL, 0.143 mmol). The resulting reaction mixture was heated at 50 °C for 16 hr then evaporated to dryness. The residue was purified via chromatography on silica gel (4 g "gold" ISCO column; 0-60% EtOAc/Hex) to give (*2S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-phenylpyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{31}H_{34}ClN_2O_3S$: 548.2 550.2 ($M+H^+$); found: 549.3, 551.3 ($M+H^+$).

Preparation of *(2S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-phenoxypyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of (*2S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-phenylpyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetate (29.3 mg, 0.653 mmol) in CH_3OH (1 mL) was added NaOH (1N, 1 mL, 1 mmol), the resulting mixture was heated at 50 C for 10 hr. The mixture was acidified to pH 3 and evaporated to a

small volume, and the residue was partitioned between CH_2Cl_2 and brine. The organic layer was separated, dried, filtered and evaporated to dryness. The residue was purified on TLC (50% EtOAc/Hex) to give *(2S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-phenoxypyrrolidin-1-yl)benzo[d]thiazol-6-yl)acetic acid. LCMS-ESI$^+$: calc'd for $C_{30}H_{32}ClN_2O_3S$: 534.2, 536.2 ($M+H^+$); found: 535.2, 537.2 ($M+H^+$).^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.63 (dd, J = 2.0, 7.2 Hz, 1H), 7.49-7.52 (m, 3H), 7.30-7.34 (m, 5H),7.24 (m, 1H), 5.13 (s, 1H), 3.94 (m, 1H), 3.70 (m, 1H), 3.52-3.63 (m, 4H), 2.48 (s, 3H), 2.46 (m, 1H), 2.20 (m, 1H), 0.94 (s, 9H).

Example 37. Preparation of 6-(3-bromophenyl)-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine: To a solution of 6-bromo-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (127).



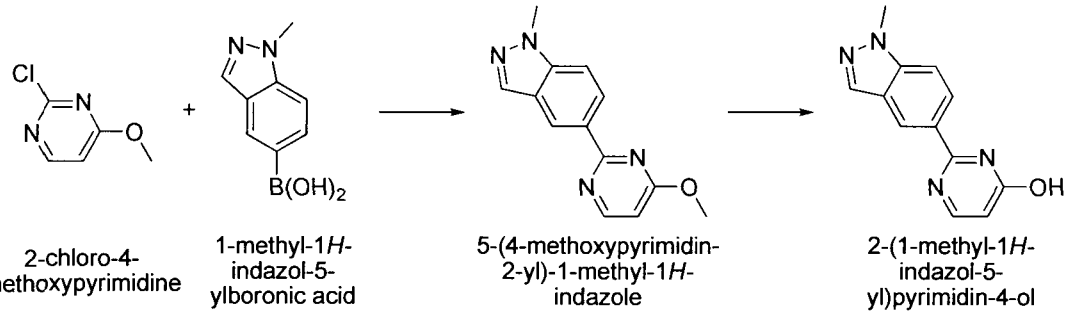
6-bromo-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine

6-(3-bromophenyl)-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine

127

Preparation of 6-(3-bromophenyl)-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine: To a solution of 6-bromo-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (120 mg, 0.566 mmol) and 3-bromophenylboronic acid(136 mg, 0.679 mmol) in degassed 1,4-dioxane (6mL) and water (2 mL) was added K_2CO_3 (391 mg, 2.83 mmol) and tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.028 mmol). 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 Na_2SO_4 and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{13}H_{10}BrN_3$: 288.01 ($M+H^+$); Found: 288.2 ($M + H^+$).

Example 38. Representative procedure for the synthesis of stannane intermediates used in Method H. Preparation of 1-methyl-5-(4-(tributylstannyl)pyrimidin-2-yl)-1H-indazole (128).

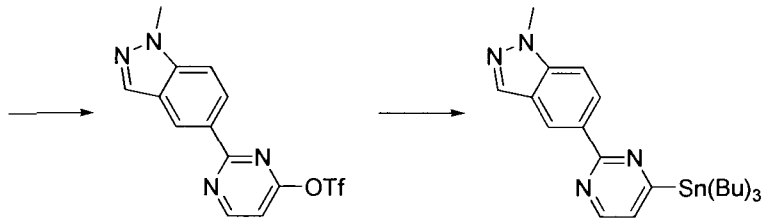


2-chloro-4-methoxypyrimidine

1-methyl-1*H*-indazol-5-ylboronic acid

5-(4-methoxypyrimidin-2-yl)-1-methyl-1*H*-indazole

2-(1-methyl-1*H*-indazol-5-yl)pyrimidin-4-ol



2-(1-methyl-1*H*-indazol-5-yl)pyrimidin-4-yl trifluoromethanesulfonate

1-methyl-5-(4-(tributylstannyl)pyrimidin-2-yl)-1*H*-indazole

128

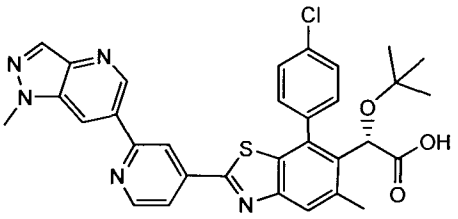
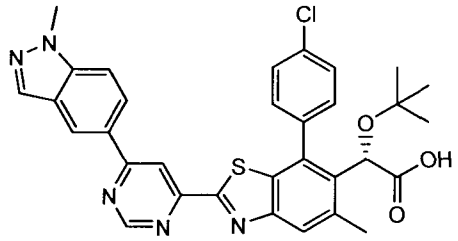
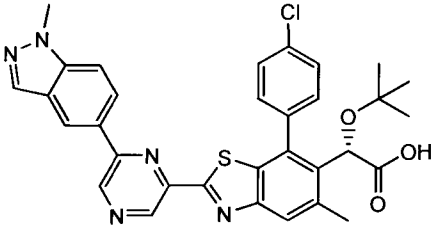
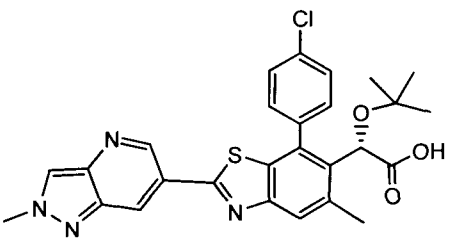
Preparation of 5-(4-methoxypyrimidin-2-yl)-1-methyl-1H-indazole: 2-chloro-4-methoxypyrimidine (100.0 mg, 0.69 mmol), 1-methyl-1H-indazol-5-ylboronic acid (133.9 mg, 0.76 mmol), $Pd(PPh_3)_4$ (79.9 mg, 0.069 mmol), and K_2CO_3 (286.8 mg, 2.075 mmol) were taken in a microwave vial and the vial was vacuum pumped and flushed with argon three times. To this mixture was added degassed toluene (2.5 mL) and DMF (0.28 mL). The reaction mixture was heated in a microwave at 185 °C for 30 min, 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. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.56 (dd, J = 8.9, 1.3 Hz, 1H), 8.52 (d, J = 5.8 Hz, 1H), 8.10 (s, 1H), 7.47 (d, J = 8.9 Hz, 1H), 6.64 (d, J = 5.8 Hz, 1H), 4.14 (s, 3H), 4.12 (s, 3H). LCMS-ESI$^+$: calc'd for $C_{13}H_{13}N_4O$: 241.1 ($M+H^+$); Found: 241.2 ($M + H^+$).

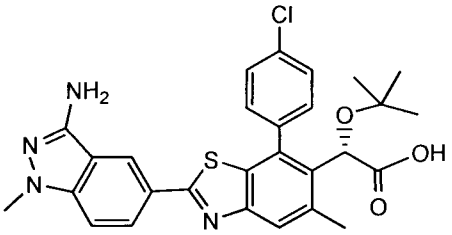
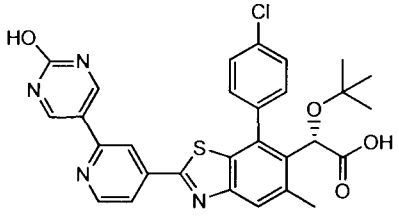
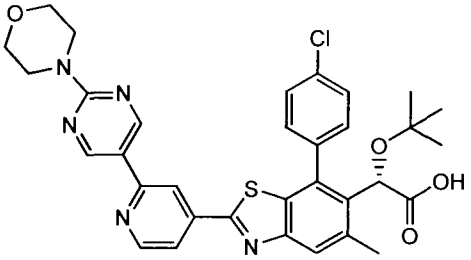
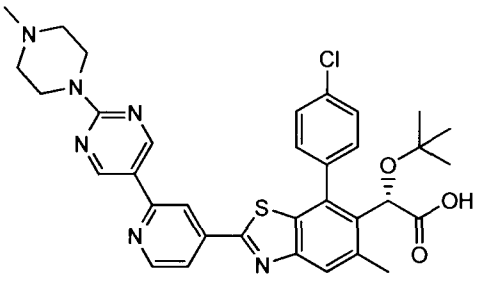
Preparation of 2-(1-methyl-1H-indazol-5-yl)pyrimidin-4-ol: 5-(4-methoxypyrimidin-2-yl)-1-methyl-1H-indazole (30.2 mg, 0.126 mmol) was suspended in hydrochloric acid (1.25 mL of a 2N solution) and heated at 85 °C for 14 h, cooled, and neutralized by dropwise addition of NaOH (2N solution). The mixture was extracted six times with 1:1 chloroform/isopropanol and the combined organic layers were dried over Na_2SO_4 and concentrated to provide the crude product which was used without further purification. LCMS-ESI$^+$: calc'd for $C_{12}H_{11}N_4O$: 227.1 ($M+H^+$); Found: 227.2 ($M + H^+$).

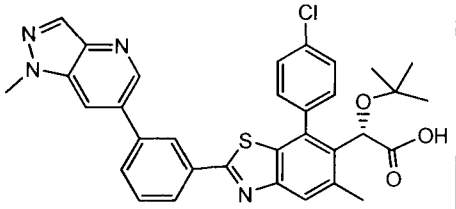
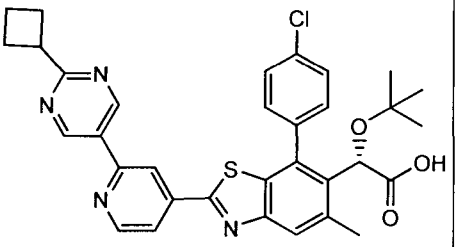
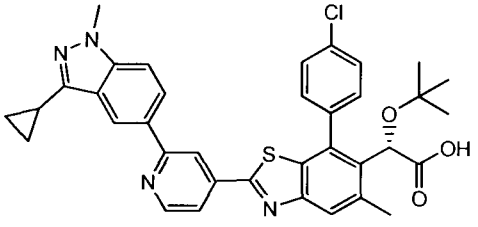
Preparation of 2-(1-methyl-1H-indazol-5-yl)pyrimidin-4-yl trifluoromethanesulfonate: To a solution of crude 2-(1-methyl-1H-indazol-5-yl)pyrimidin-4-ol (41.5 mg, 0.183 mmol) in DCM (2.0 mL) was added triethylamine (0.15 mL, 1.101 mmol) followed by trifluoromethanesulfonic anhydride (91.3 μL, 0.550 mmol) at -78 °C. The reaction mixture was stirred for 16 h and allowed to slowly warm to room temperature during this time then concentrated. Purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 5.4 Hz, 1H), 8.90 (s, 1H), 8.49 (dd, J = 8.9, 1.5 Hz, 1H), 8.13 (s, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.00 (d, J = 5.4 Hz, 1H), 4.13 (s, 3H). LCMS-ESI$^+$: calc'd for $C_{13}H_{10}F_3N_4O_3S$: 359.0 ($M+H^+$); Found: 359.1 ($M + H^+$).

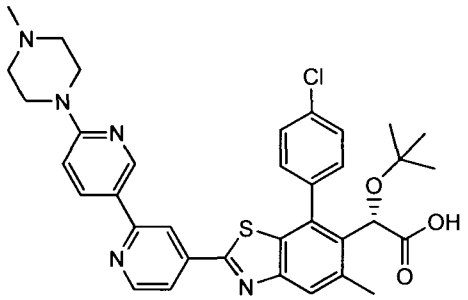
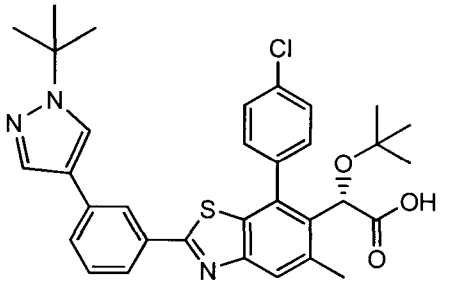
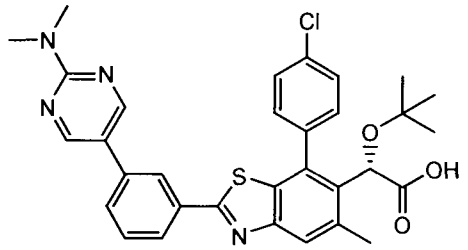
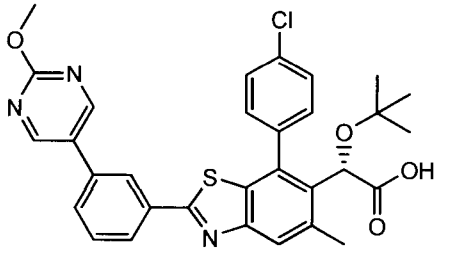
Preparation of 1-methyl-5-(4-(tributylstannyl)pyrimidin-2-yl)-1H-indazole: 2-(1-methyl-1H-indazol-5-yl)pyrimidin-4-yl trifluoromethanesulfonate (43.4 mg, 0.121 mmol), $Pd(PPh_3)_4$ (7.0 mg, 0.006 mmol), and lithium chloride (25.6 mg, 0.604 mmol) were taken in a microwave vial and the vial was vacuum pumped and flushed with argon three times. To this mixture was added degassed toluene (2.0 mL) and bis(tributyltin) (61 μL, 0.121 mmol). The reaction mixture was heated at 110 °C for 16 h, cooled, quenched with water, and diluted with ethyl acetate. The aqueous layer was removed and twice extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the product. LCMS-ESI$^+$: calc'd for $C_{24}H_{37}N_4Sn$: 501.2 ($M+H^+$); Found: 501.3 ($M + H^+$).

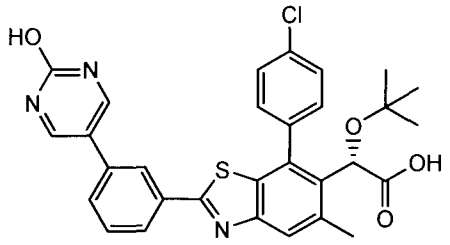
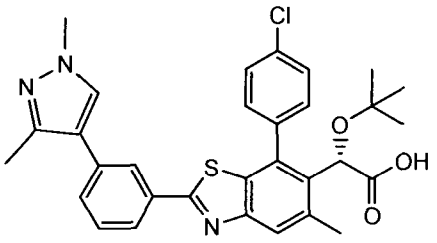
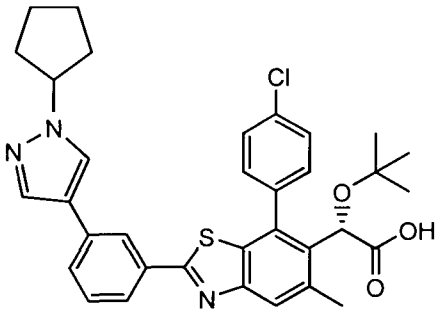
Example 39. The compounds in the table below were prepared by the general method noted (Method B (example 14), Method C (example 15), Method D (example 16), Method E (example 17), Method F (example 18), Method G (example 19), Method H (example 20), Method I (example 21) and Method J (example 22)).

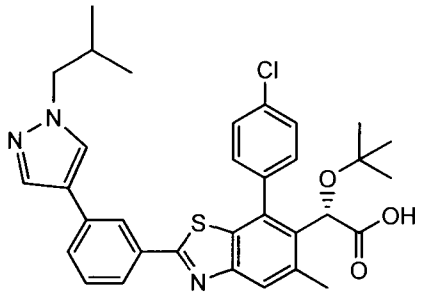
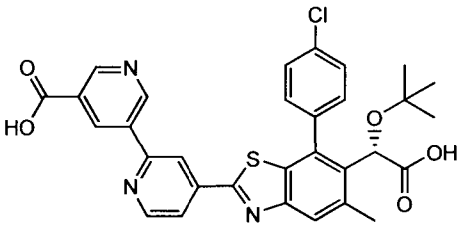
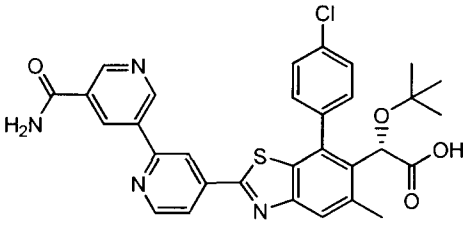
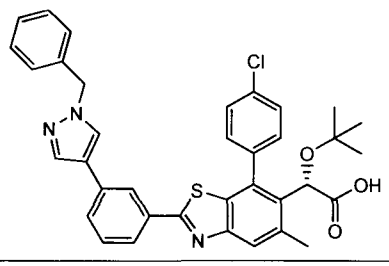
Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
129		C	598.1	598.2	^{1}H NMR (400 MHz, CD_3OD): δ 9.31 (s, 1H), 8.85-8.84 (m, 2H), 8.64 (s, 1H), 8.25(s, 1H), 8.01-7.954 (m, 2H), 7.71-7.60 (m, 4H), 5.28 (s, 1H), 4.22 (d, J = 1 Hz, 3H), 2.64 (s, 3H), 0.97 (s, 9H)
130		H	598.1	597.9	^{1}H NMR (400 MHz, CD_3OD) δ 9.19 (d, J = 0.9 Hz, 1H), 8.84 (d, J = 1.0 Hz, 1H), 8.78 (s, 1H), 8.38 (dd, J = 8.9, 1.6 Hz, 1H), 8.21 (s, 1H), 7.98 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.72 – 7.69 (m, 1H), 7.65 – 7.59 (m, 3H), 5.30 (s, 1H), 4.14 (s, 3H), 2.65 (s, 3H), 0.98 (s, 9H).
131		H	598.1	598	^{1}H NMR (400 MHz, CD_3OD) δ 9.37 (s, 1H), 9.29 (s, 1H), 8.62 (s, 1H), 8.28 (dd, J = 8.9, 1.6 Hz, 1H), 8.16 (s, 1H), 7.94 (s, 1H), 7.73 – 7.72 (m, 1H), 7.71 – 7.69 (m, 1H), 7.67 – 7.60 (m, 3H), 5.29 (s, 1H), 4.11 (s, 3H), 2.64 (s, 3H), 0.99 (s, 9H).
132		I	521	521.3	^{1}H NMR (400 MHz, CD_3OD) δ 9.23 (d, J = 1 Hz, 1H), 8.65 (s, 1H), 8.54 (s, 1H), 7.90 (s, 1H), 7.71 – 7.59 (m, 4H), 5.27 (s, 1H), 4.31 (s,

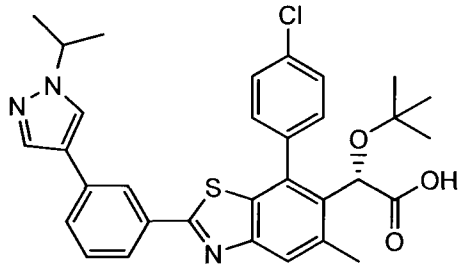
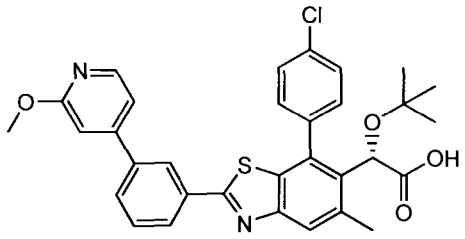
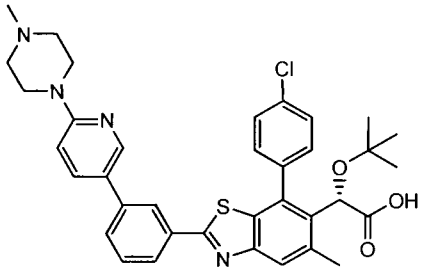
Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
					3H), 2.62 (s, 3H), 0.97 (s, 9H).
133		J	535.1	535.3	^{1}H NMR (400 MHz, CD_3OD): δ 8.40 (s, 1H), 8.09-8.07 (m, 1H), 7.79 (s, 1H), 7.69 (d, J = 4.2 Hz, 1H), 7.60-7.41 (m, 4H), 5.25 (s, 1H), 3.83 (s, 3H), 2.60 (s, 3H), 0.97 (s, 9H).
134		F	561.13	561.1	^{1}H NMR (400 MHz, CD_3OD): δ 9.13 (bs, 2H), 8.72 (bs, 1H), 8.36 (bs, 1H), 7.92-7.90 (m, 2H), 7.69-7.56 (m, 4H), 5.27 (s, 1H), 2.62 (s, 3H), 0.97 (s, 9H).
135		F	630.29	630.2	^{1}H NMR (400 MHz, CD_3OD): δ 9.03 (s, 2H), 8.71 (d, J= 2.4 Hz, 1H), 8.43 (s, 1H), 7.95-7.93 (m, 2H), 7.70-7.68 (m, 1H), 7.60 (s, 3H), 5.27 (s, 1H), 3.92-3.89 (m, 4H), 3.78-3.75 (m, 4H), 2.63 (s, 3H), 0.97 (s, 9H).
136		F	643.22	643.2	^{1}H NMR (400 MHz, CD_3OD): δ 9.10(s, 2H), 8.72 (d, J = 2.6 Hz, 1H), 8.38 (s, 1H), 7.92 (s, 1H), 7.87-7.7.86 (m, 1H), 7.70-7.68 (m, 1H), 7.62-7.58 (m, 3H), 5.27 (s, 1H), 5.10-5.04 (m, 2H), 3.61-3.34 (m, 4H), 3.29-3.18 (m, 2H), 2.97 (s, 3H), 2.62 (s,

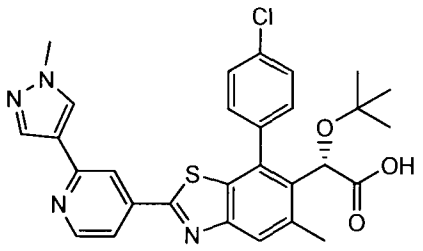
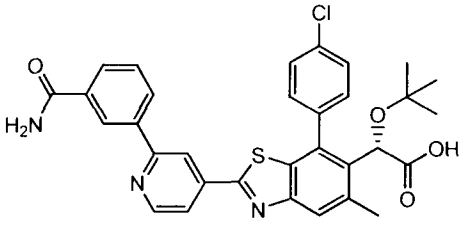
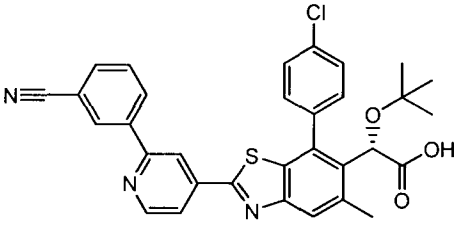
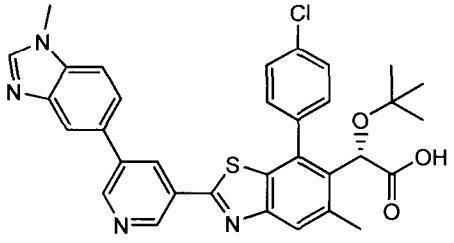
Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
					3H), 0.97 (s, 9H).
137		I	597.1	597.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (s, 1H), 8.51-8.45 (m, 2H), 8.25 (s, 1H), 8.10-7.94 (m, 2H), 7.87 – 7.58 (m, 6H), 5.26 (s, 1H), 4.20 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).
138		F	599.15	599.1	^{1}H NMR (400 MHz, CD_3OD): δ 9.43 (s, 2H), 8.83 (d, J = 2.4 Hz, 1H), 8.57 (s, 1H), 8.02-8.8.00 (m, 1H), 7.95 (s, 1H), 7.70-7.68 (m, 1H), 7.60-7.59 (m, 3H), 5.27 (s, 1H), 3.92-3.31 (m, 1H), 2.63 (s, 3H), 2.59-2.42 (m, 4H), 2.20-2.2.12 (m, 2H), 2.03-1.97 (m, 2H), 0.97 (s, 9H).
139		F	637.2	637.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.60 (d, J = 2.6 Hz, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 7.93-7.91 (m, 1H), 7.86-7.83 (m, 2H), 7.61-7.59 (m, 1H), 7.50-7.45 (m, 4H), 5.28 (s, 1H), 3.86 (s, 3H), 2.53 (s, 3H), 2.24-2.21 (m, 1H), 0.99-0.97 (m, 4H), 0.88 (s, 9H).

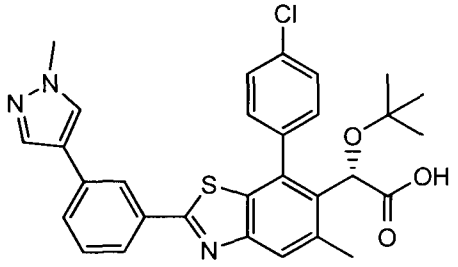
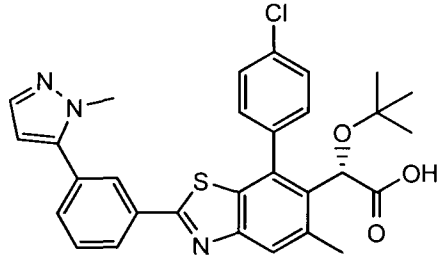
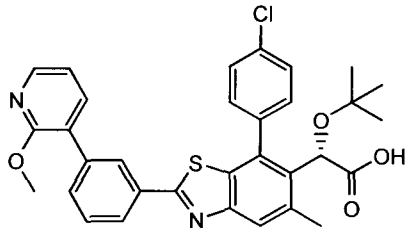
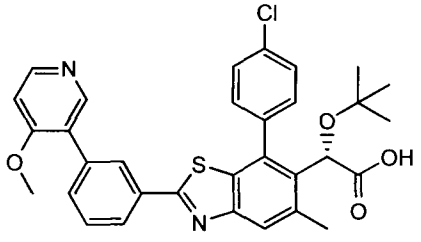
Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
140		F	642.22	642.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.79 (d, J = 1.2 Hz, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.29 (s, 1H), 8.23-8.21 (m, 1H), 7.83 (s, 1H), 7.77-7.76 (m, 1H), 7.61-7.58 (m, 1H), 7.52-7.48 (m, 3H), 6.98 (d, J = 4.4 Hz, 1H), 5.18 (s, 1H), 4.55-4.52 (m, 2H), 3.39-3.21 (m, 6H), 2.88 (s, 3H), 2.53 (s, 3H), 0.87 (s, 9H).
141		B	588.17	588.3	^{1}H NMR (400 MHz, CD_3OD): δ (8.23-8.22 (m, 2H), 7.93 (s, 1H), 7.83-7.80 (m, 2H), 7.74-7.67 (m, 2H), 7.58 (m, 3H), 7.48-7.45 (m, 1H), 5.25 (s, 1H), 2.61 (s, 3H), 1.64 (s, 9H), 0.97 (s, 9H).
142		D	587.14	587.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.57 (s, 2H), 8.10 (s, 1H), 7.81 (d, J = 4Hz, 1H), 7.72 (s, 1H), 7.58 (d, J = 4Hz, 1H), 7.47-7.42 (m, 4H), 5.16 (s, 1H), 3.14 (s, 6H), 2.61 (s, 3H), 0.97 (s, 9H).
143		D	574.1	574.2	^{1}H NMR (400 MHz, CD_3OD): δ 0.89 (s, 2H), 8.29 (s, 1H), 8.02 (d, J = 3.8 Hz, 1H), 7.85 (s, 1H), 7.78 (d, J = 4 Hz, 1H), 7.68 (d, J = 4.2 Hz, 1H), 7.63-7.58 (m, 4H), 5.26 (s, 1H), 4.06 (s,

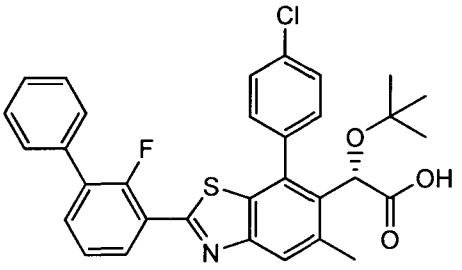
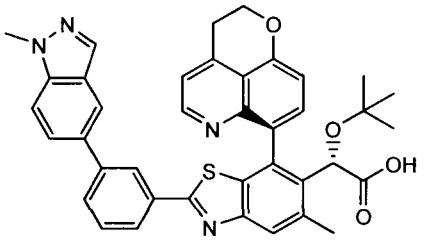
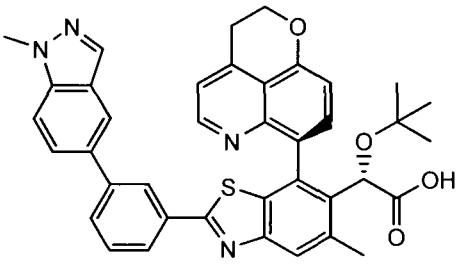
Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
					3H), 2.61 (s, 3H), 0.97 (s, 9H).
144		D	560.07	560.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.65 (s, 2H), 8.14 (s, 1H), 7.91 (d, J = 4 Hz, 1H), 7.74 (s, 1H), 7.65-7.46 (m, 6H), 5.26 (s, 1H), 2.51 (s, 3H), 0.87 (s, 9H).
145		B	560.12	560.2	^{1}H NMR (400 MHz, CD_3OD): δ 7.98 (s, 1H), 7.79-7.73 (m, 3H), 7.60-7.587 (m, 3H), 7.50-7.48 (m, 4H), 7.43-7.39 (m, 1H), 5.16 (s, 1H), 3.78 (s, 3H), 2.52 (s, 3H), 2.31 (s, 3H), 0.88 (s, 9H).
146		B	600.18	600.2	1H NMR (400 MHz, CD3OD): δ 8.22 (s, 1H), 8.15 (s, 1H), 7.92 (s, 1H), 7.85-7.82 (m, 2H), 7.73-7.7.67 (m, 2H), 7.60-7.58 (m, 3H), 7.50-7.46 (m, 1H), 5.26 (s, 1H), 4.76-4.72 (m, 1H), 2.62 (s, 3H), 2.22-2.19 (m, 2H), 2.07-2.03 (m, 2H), 1.93-1.91 (m, 2H), 1.78-1.73 (m, 2H), 0.97 (s, 9H).

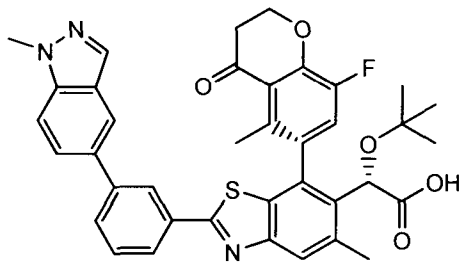
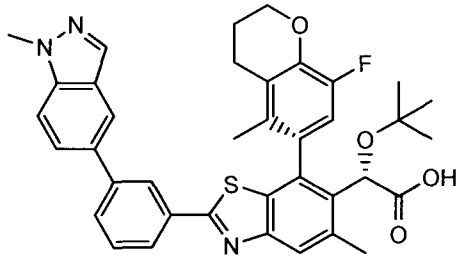
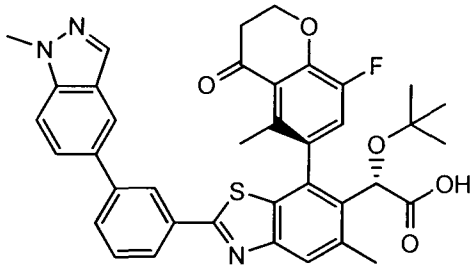
Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
147		B	588.17	588.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.21 (s, 1H), 8.09 (s, 1H), 7.92 (s, 1H), 7.83-7.81 (m, 2H), 7.72-7.67 (m, 2H), 7.59-7.58 (m, 3H), 7.49-7.45 (m, 1H), 5.25 (s, 1H), 3.98 (d, J = 3.6 Hz, 2H), 2.61 (s, 3H), 2.24-2.20 (m, 1H), 0.97 (s, 9H), 0.94 (d, J = 3.4 Hz, 6H).
148		C	588.08	588.1	^{1}H NMR (400 MHz, CD_3OD) δ 9.49 (s, 1H), 9.22 (s, 1H), 9.14 – 9.10 (m, 1H), 8.86 (d, *J* = 5.1 Hz, 1H), 8.62 (s, 1H), 8.02 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.97 (s, 1H), 7.73 – 7.68 (m, 1H), 7.64 – 7.59 (m, 3H), 5.28 (s, 1H), 2.64 (s, 3H), 0.98 (s, 9H).
149		C	587.1	587.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.49 (s, 1H), 9.14 (s, 1H), 9.10 (s, 1H), 8.86 (d, *J* = 5.1 Hz, 1H), 8.63 (s, 1H), 8.04 (d, *J* = 5.2 Hz, 1H), 7.95 (s, 1H), 7.73 – 7.67 (m, 1H), 7.63 – 7.58 (m, 3H), 5.28 (s, 1H), 2.64 (s, 3H), 0.99 (s, 9H).
150		B	622.19	622.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.21 (s, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 7.83-7.28 (m, 13H), 5.38 (s, 2H), 5.25 (s, 1H), 2.61 (s,

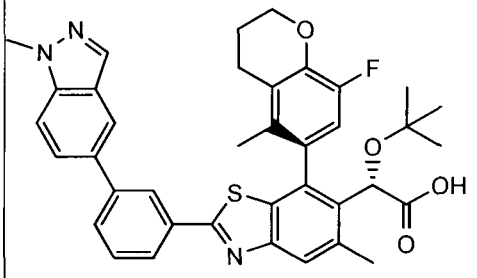
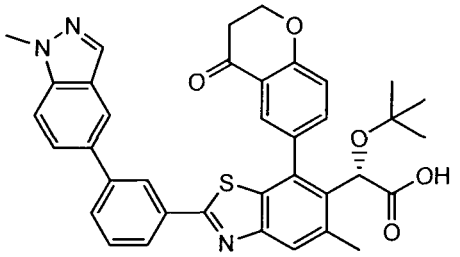
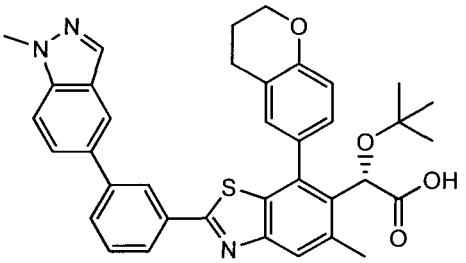
Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
					3H), 0.97 (s, 9H).
151		B	574.14	574.2	1H NMR (400 MHz, CD3OD): δ 8.22 (s, 1H), 8.16 (s, 1H), 7.92 (s, 1H), 7.84-7.82 (m, 2H), 7.73-7.59 (m, 5H), 7.50-7.46 (m, 1H), 5.26 (s, 1H), 4.59-4.55 (m, 1H), 2.61 (s, 3H), 1.54 (d, J = 3.2 Hz, 6H), 0.97 (s, 9H).
152		B	573.11	573.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.38 (s, 1H), 8.22 (d, J = 2.8 Hz, 1H), 8.08-8.06 (m, 1H), 7.89-7.87 (m, 2H), 7.70-7.58 (m, 5H), 7.35-7.34 (m, 1H), 7.18 (s, 1H), 5.26 (s, 1H), 3.99 (s, 3H), 2.62 (s, 3H), 0.97 (s, 9H).
153		B	641.23	641.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.54 (d, J = 1 Hz, 1H), 8.27 (s, 1H), 8.02-7.94 (m, 2H), 7.87 (s, 1H), 7.77-7.68 (m, 2H), 7.60-7.58 (m, 4H), 7.07 (d, J = 4.4 Hz), 5.26 (s, 1H), 4.0-4.50 (m, 2H), 3.65-3.55 (m, 2H), 3.3-3.15 (m, 4H), 2.98 (s, 3H), 2.62 (s, 3H), 0.97 (s, 9H).

Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
154		C	547.08	547.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.64 (d, J = 5.7 Hz, 1H), 8.41 (s, 1H), 8.40 (s, 1H), 8.18 (s, 1H), 8.02 (d, J = 5.5 Hz, 1H), 7.98 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.65 – 7.58 (m, 3H), 5.28 (s, 1H), 3.99 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H).
155		C	586.11	586.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (d, J = 5.3 Hz, 1H), 8.57 (s, 1H), 8.53 (s, 1H), 8.26 (d, J = 7.7 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.94 (s, 1H), 7.72 – 7.68 (m, 1H), 7.67 – 7.58 (m, 4H), 5.28 (s, 1H), 2.63 (s, 3H), 0.98 (s, 9H).
156		C	568.1	568.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.77 (d, J = 5.2 Hz, 1H), 8.47 (s, 1H), 8.45 (s, 1H), 8.36 (d, J = 7.9 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.62 – 7.57 (m, 3H), 5.28 (s, 1H), 2.63 (s, 3H), 0.98 (s, 9H).
157			597.14	597.2, 599.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.48 (s, 1H), 9.26 (s, 1H), 9.07 (s, 1H), 8.82 (s, 1H), 8.24 (s, 1H), 8.10 (s, 2H), 7.93 (s, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.60 (d, J = 6.0 Hz, 3H), 5.27 (s, 1H),

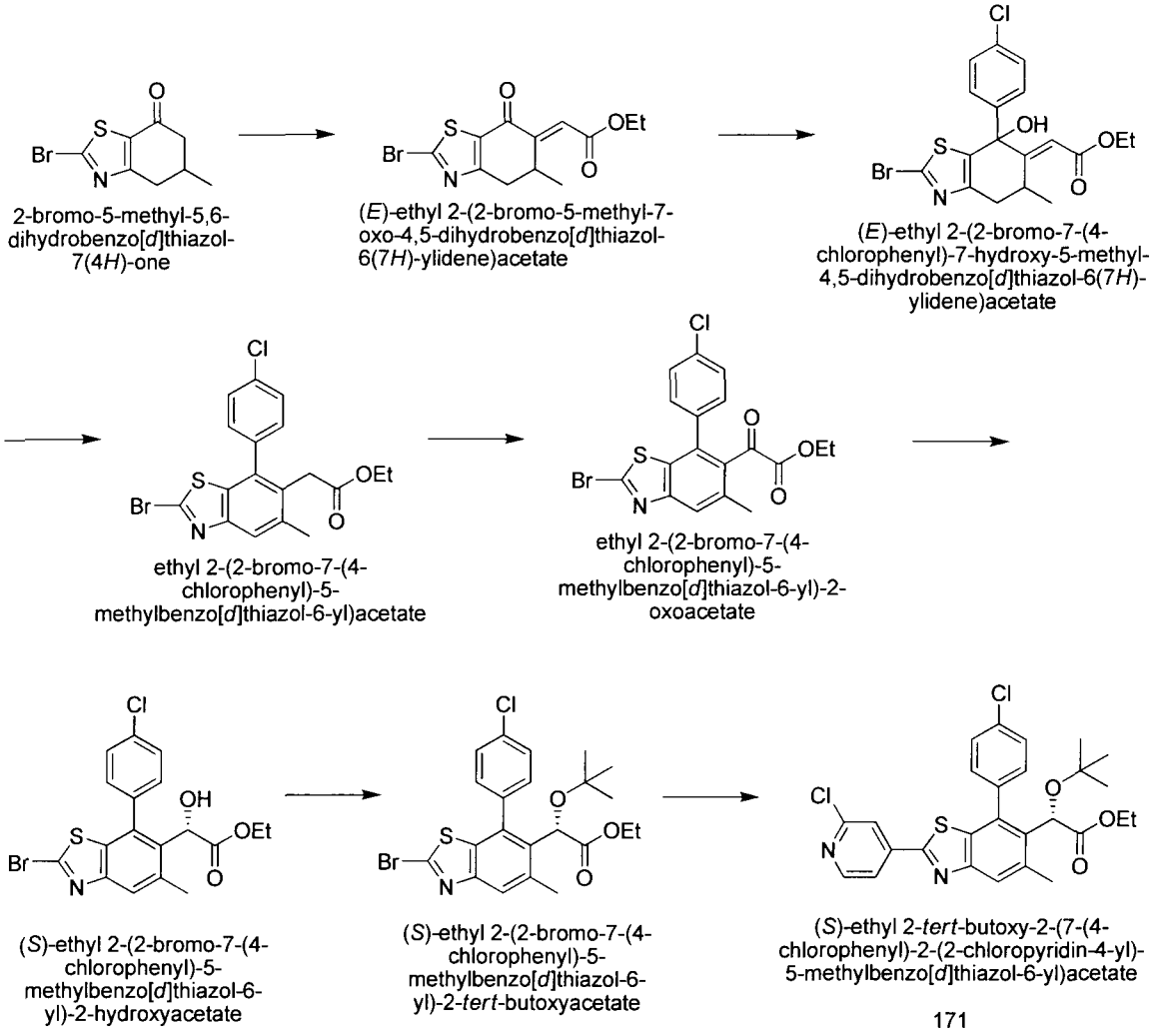
Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
					4.21 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).
158		B	546.09	546.1	^{1}H NMR (400 MHz, CD_3OD): δ8.20 (s, 1H), 8.06 (s, 1H), 7.90 (s, 1H), 7.84-7.82 (m, 2H), 7.71-7.59 (m, 5H), 7.50-7.48 (s, 1H), .5.26 (s, 1H), 3.94 (s, 3H), 2.61 (s, 3H), 0.97 (s, 9H).
159		B	546.09	546.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.16 (s, 1H), 8.07 (d, J = 3.6 Hz, 1H), 7.86 (s, 1H), 7.69-7.854 (m, 7H), 6.47 (d, J = 0.8 Hz, 1H), 5.25 (s, 1H), 3.92 (s, 3H), 2.61 (s, 3H), 0.97 (s, 9H).
160		B	573.11	573.1	^{1}H NMR (400 MHz, CD_3OD): δ 8.21-8.16 (m, 3H), 7.99-7.85 (m, 2H), 7.79-7.67 (m, 3H), 7.59-7.53 (m, 4H), 7.10-7.07 (m, 1H), 5.25 (s, 1H), 3.96 (s, 3H), 2.61 (s, 3H), 0.97 (s, 9H).
161		B	573.11	573.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.63-8.60 (m, 2H), 8.16 (s, 1H), 8.03 (d, J = 4Hz, 1H), 7.77 (s, 1H), 7.66-7.49 (m, 7H), 5.16 (s, 1H), 4.07 (s, 3H), 2.52 (s, 3H), 0.88 (s, 9H).

Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
162		G	560.09	560.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.22 (t, J = 7.2Hz, 1H), 7.82 (s, 1H), 7.60-7.48 (m, 7H), 7.40-7.311 (m, 4H), 5.17 (s, 1H), 2.35 (s, 3H), 0.87 (s, 9H).
163		G	654.79	655.1	^{1}H NMR (400 MHz, CD_3OD): δ 8.77 (d, J = 2.8 Hz, 1H), 8.27-8.26 (m, 1H), 8.09 (s, 1H), 8.05 (d, J = 0.4 Hz, 1H), 8.03-8.02 (m, 1H), 7.94-7.90 (m, 2H), 7.84-7.82 (m, 1H), 7.78-7.73 (m, 2H), 7.65-7.63 (m, 1H), 7.58-7.54 (m, 1H), 7.41 (d, J = 4.2 Hz, 1H), 5.26 (s, 1H), 4.71-4.70 (m, 2H), 4.09 (s, 3H), 3.63 (t, J = 5.8Hz, 2H), 2.79 (s, 3H), 0.93 (s, 9H).
164		G	654.79	655.1	^{1}H NMR (400 MHz, CD_3OD): δ 8.64 (d, J = 2.6 Hz, 1H), 8.24-8.18 (m, 2H), 8.05-8.04 (m, 2H), 8.013-8.01 (m, 2H), 7.90-7.88 (m, 1H), 7.82-7.80 (m, 1H), 7.75-7.72 (m, 1H), 7.64-7.62 (m, 2H), 7.57-7.53 (m, 1H), 7.40 (d, J = 4.2 Hz, 1H), 5.31 (s, 1H), 4.67-4.66 (m, 2H), 4.09 (s, 3H), 3.57-3.56 (m, 2H), 2.74 (s, 3H), 0.91 (s, 9H).

Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
165		G	663.77	664.2	^{1}H NMR (400 MHz, CD_3OD): δ8.32 (s, 1H), 8.08 (s, 2H), 7.97-7.7.79 (m, 4H), 7.65-7.53 (m, 3H), 5.20 (s, 1H), 4.71 (t, J = 6.4 Hz, 2H), 4.11 (s, 3H), 2.94 (t, J = 6.4 Hz, 2H), 2.67 (s, 3H), 2.30 (s, 3H), 1.06 (s, 9H).
166		G	649.78	650.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.32(s, 1H), 8.09 (s, 2H), 7.97 (d, J = 4 Hz, 1H), 7.85-7.79 (m, 3H), 7.68-7.57 (m, 2H), 7.17 (d, J = 5.8 Hz, 1H), 5.27 (s, 1H), 4.30-4.25 (m, 2H), 4.11 (s, 3H), 2.78-2.69 (s, 2H), 2.63 (s, 3H), 2.16-2.13 (m, 2H), 1.92 (s, 3H), 1.02 (s, 9H).
167		G	663.77	664.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.21 (s, 1H), 7.98-7.97 (m, 2H), 7.85 (d, J = 3.8 Hz, 1H), 7.80 (s, 1H), 7.75-7.68 (m, 2H), 7.57-7.50 (m, 2H), 7.10 (d, J = 5.4 Hz), 5.11 (s, 1H), 4.60 (t, J = 6.6 Hz, 2H), 4.01 (s, 3H), 2.85 (t, J = 6.4 Hz, 2H), 2.63 (s, 3H), 2.24 (s, 3H), 1.04 (s, 9H).

Compound Number	Structure	Method	Parent MW	LCMS-ESI+	1H NMR
168		G	649.78	650.2	^{1}H NMR (400 MHz, CD_3OD): δ 8.31 (s, 1H), 8.08-8.07 (m, 2H), 7.95 (d, J = 4Hz), 7.85-7.78 (m, 3H), 7.67-7.58 (m, 2H), 6.81 (d, J = 5.6 Hz), 5.19 (s, 1H), 4.27 (t, J = 2.6Hz, 2H), 4.10 (s, 3H), 2.77-2.75 (m, 2H), 2.69 (s, 3H), 2.15-2.14 (m, 2H), 1.91 (s, 3H), 1.14 (s, 9H).
169		G	631.75	632.2	^{1}H NMR (300 MHz, CD_3OD): δ 8.30 (s, 1H), 8.19-7.94 (m, 3H), 7.85-7.7.57 (m, 6H), 7.22-7.19 (m, 1H) 5.28 (s, 0.5H), 5.24 (s, 0.5H), 4.66-4.64 (m, 2H), 4.01 (s, 3H), 2.90-2.88 (m, 2H), 2.63 (s, 3H), 0.99 (s, 9H).
170		G	617.77	618.2	^{1}H NMR (300 MHz, CD_3OD): δ 8.23 (s, 1H), 7.98 (s, 2H), 7.81-7.70 (m, 3H), 7.57-7.48 (m, 2H), 7.28-7.16 (m, 2H), 6.82 (s, 1H), 5.30 (s, 1H), 4.17-1.15 (m, 2H), 4.01 (s, 3H), 2.78-2.74 (m, 2H), 2.50 (s, 3H), 1.97 (M, 2H), 0.88 (s, 9H).

Example 40. Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (171).



Preparation of (E)-ethyl 2-(2-bromo-5-methyl-7-oxo-4,5-dihydrobenzo[d]thiazol-6(7H)-ylidene)acetate: A 3.0 L round-bottom flask was charged with 2-bromo-5-methyl-5,6-dihydrobenzo[d]thiazol-7(4H)-one (75.0 g, 305 mmol, 1.00 equiv), anhydrous THF (750 mL), and a 50% w/v solution of ethylglyoxylate in toluene (211 mL, 1.07 mol, 3.50 equiv). The resulting solution was placed in a water bath. Solid lithium *tert*-butoxide (48.9 g, 610 mmol, 2.0 equiv) was steadily added over a 1 min period. The reaction was capped and stirred for 4.5 h. TLC (20% EtOAc/80% hexane indicated full consumption of 2-bromo-5-methyl-5,6-dihydrobenzo[d]thiazol-7(4H)-one). Saturated aqueous NH_4Cl (750 mL) was added quickly. The reaction was stirred for 15 min. H_2O (250 mL) was added. Most of the solids dissolved. 1.0 M aqueous HCl (180 mL) was added over a 5 min period. After a short time the pH of the aqueous layer was ~3.5. The organic phase was collected, and the aqueous layer was extracted with EtOAc (2 x 375 mL). Combined organic layers were washed with brine (500 mL), dried ($MgSO_4$), filtered, and concentrated to a minimum volume with a bath temperature of 50-60 °C and 10 mmHg vacuum. DCM (40 mL) was added. The resulting solution was transferred to a

Combiflash XL solid loading cartridge by gravity loading. The solid cartridge was assembled in line with a 1.5 kg Combiflash XL silica gel column equilibrated with hexane. The following gradient elution sequence was used: [100% Hexane (5 column volumes, isocratic) → 10% EtOAc / 90% Hexane (10 column volumes, linear gradient) → 10% EtOAc / 90% Hexane (7 column volumes, isocratic)) → 100% EtOAc (8 column volumes, isocratic)]. Fractions containing product were combined, concentrated, and dried under high vacuum to give desired product. LCMS-ESI$^+$ calc'd for $C_{12}H_{12}BrNO_3S$: 330.0 and 332.0 ($M+H^+$); found: 330.0 and 332.0 ($M+H^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (s, 1H), 4.60-4.53 (m, 1H), 4.30-4.21 (m, 2H), 3.23 (dd, J = 17.6, 5.8 Hz, 1H), 3.07 (d, J = 5.8 Hz, 1H), 1.33 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H).

Preparation of (E)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-7-hydroxy-5-methyl-4,5-dihydrobenzo[d]thiazol-6(7H)-ylidene)acetate: A 3-liter flask equipped with a mechanical stirrer, addition funnel, and nitrogen inlet was charged with (E)-ethyl 2-(2-bromo-5-methyl-7-oxo-4,5-dihydrobenzo[d]thiazol-6(7H)-ylidene)acetate (24.1 g, 73 mmol, 1.0 equiv) and then diluted with THF (800 mL). To the resulting solution was added 0.6M $LaCl_3$•2LiCl (243 mL, 146 mmol, 2.0 equiv) and then the reaction mixture was cooled to -65 °C by the aid of a dry-ice acetone bath. The addition funnel was then charged with 1.0M 4-chlorophenylmagnesium bromide (146 mL, 146 mmol, 2.0 equiv) and then slowly added to the reaction mixture over a 25 minute period. Upon completion of the addition, TLC analysis showed full consumption of the starting material (TLC of the starting material in 20% EtOAc/Hex has Rf = 0.50; TLC of the product in 20% EtOAc/Hex has Rf = 0.38), and the reaction was quenched with saturated NH_4Cl (100 mL) and then diluted with EtOAc (1 L) and H_2O (1.5 L). The cooling bath was removed and the mixture was allowed to warm to room temperature with stirring. The layers were separated and the aqueous extract was washed with EtOAc (1 L). The combined organics were dried over Na_2SO_4, filtered through a small plug of silica gel eluting with EtOAc, and then concentrated in vacuo. The resulting crude residue was chromatographed using a 330 g RediSep normal phase silica gel cartridge (EtOAc/Hex, 5%→15%) on a CombiFlash system to afford desired product. TLC (20% EtOAc/Hex) Rf = 0.38; ^{1}H NMR (400 MHz, CDCl3) δ 7.31 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 5.62 (s, 1H), 4.57 – 4.40 (m, 1H), 4.22 – 4.04 (m, 2H), 3.03 (qd, J = 16.6, 3.8 Hz, 2H), 2.61 (br s, 1H), 1.38 (d, J = 7.2 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H).

Preparation of ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate: Polyphosphoric acid (PPA) (140 g) and THF (210 mL) were heated to 75°C in a 1 L

recovery flask. (E)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-7-hydroxy-5-methyl-4,5-dihydrobenzo[d]thiazol-6(7H)-ylidene)acetate (31.0 g, 70.0 mmol) was added via addition funnel in THF (70 mL) over 2 min. The funnel was rinsed with THF (20 mL). The reaction mixture was heated at 80 °C for 2.5 h. After cooling to rt, the mixture was poured onto a 1 M K_2HPO_4 (1.5 L) solution followed by EtOAc (700 mL). The layers were separated, and the organic layer was washed with brine (500 mL). The organic layer was dried, filtered, and concentrated in vacuo to give desired product that was used without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.45 (d, 2H, J = 8 Hz), 7.29 (d, 2H, J = 8 Hz), 4.13 (q, 2H, J = 7 Hz), 3.57 (s, 2H), 2.45 (s, 3H), 1.23 (t, 3H, J = 7 Hz).

Preparation of ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-oxoacetate: To a solution of the ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate (15.4 g, 36.4 mmol) in THF (146 mL) at -78 °C was added a solution of KHMDS (1 M in THF, 43.6 mmol, 43.6 mL) over 5 min. After 30 min, a solution of 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (11.4 g, 43.6 mmol) in THF (29 mL) was added. After 1 h, a saturated solution of NH_4Cl was added (200 mL). The reaction mixture was warmed to rt. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated in vacuo and were used without further purification.

To the above residue was added CH_2Cl_2 (240 mL) followed by Dess-Martin periodinane (16.9 g, 40.0 mmol). After 2 h, a saturated solution of $Na_2S_2O_3$ (150 mL) and a saturated solution of $NaHCO_3$ (150 mL) and water (100 mL) were added. The mixture was stirred at room temperature for 2 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated in vacuo. A mixture of hexanes/EtOAc (9:1) was added. The mixture was filtered, the solids were washed with additional hex/EtOAc (9:1), and the filtrate was concentrated. The crude oil was purified by column chromatography (5%-10% EtOAc/hex) to give desired product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.45 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 3.91 (q, 2H, J = 7 Hz), 2.52 (s, 3H), 1.08 (t, 3H, J = 7 Hz).

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

Catalyst Preparation: A 25 mL flask was charged with dichloro(pentamethylcyclopentadienyl)rhodium(III) dimer (94 mg, 0.15 mmol, 1.0 equiv) and the ligand N-((1S,2S)-2-amino-1,2-diphenylethyl)-4-nitrobenzenesulfonamide (153 mg, 0.39

mmol, 2.6 equiv) and sealed with a rubber septum. The flask was purged with argon and then ACN (1.5 mL) and NEt_3 (0.15 mL) were added to the flask and an additional septum was fitted. The resulting red solution was stirred at room temperature under argon for a minimum of 45 minutes, but not more than 6 hours, which resulted in a heterogeneous orange suspension.

A 100 mL flask was charged with ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-oxoacetate (2.4 g, 5.5 mmol, 1.0 equiv) and sealed with a rubber septum. The flask was purged with argon and to this was charged ACN (11 mL) and NEt_3 (1.9 mL, 13.6 mmol, 2.5 equiv) and stirring was initiated. The solution was cooled to 0 °C and then HCO_2H (0.63 mL, 16.7 mmol, 3.0 equiv) was added to the solution at a rate to maintain an internal temperature not more than 20 °C. Upon completion of the addition, the solution was allowed to cool back to 0 °C. Argon was then bubbled through the solution using a porous gas dispersion unit. To the stirring solution at 0 °C was charged the prepared catalyst solution (0.5 mL, 0.05 equiv) from the catalyst preparation above. The solution was stirred at 0 °C with the bubbling of argon through the solution until TLC indicated complete consumption of starting material (10-18 h). The reaction was quenched with H_2O then diluted with EtOAc and allowed to warm to room temperature. The layers were separated and the organic extract was washed once more with H_2O. The organic extract was then dried over Na_2SO_4, filtered through a small pad of silica gel eluting with EtOAc, and concentrated in vacuo. The resulting crude residue was chromatographed using a 80 g RediSep normal phase silica gel cartridge (EtOAc/Hex, 5%→20%) on a CombiFlash system to give the desired product. TLC (20% EtOAc/Hex) Rf = 0.27; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.53 – 7.43 (m, 2H), 7.37 (m, 2H), 5.23 (d, J = 2.2 Hz, 1H), 4.19 (m, 2H), 3.29 (d, J = 2.2 Hz, 1H), 2.48 (d, J = 0.5 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H).

Alternative preparation of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-hydroxyacetate: A solution of ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-oxoacetate (10.60 g, 25.0 mmol) in PhMe (100 mL) was cooled to –30 °C. (R)-Me-CBS catalyst (1.39 g, 5.00 mmol) was added, followed immediately by distilled catecholborane (4.00 mL, 37.5 mmol). At 1.2 h, additional (R)-Me-CBS catalyst (1.39 g, 5.00 mmol) was added. After another 1 h had passed, additional (R)-Me-CBS catalyst (700 mg, 2.50 mmol) was added. After 30 min, the reaction was quenched with EtOAc (30 mL). Saturated aqueous $NaHCO_3$ (50 mL) was added, and the reaction was warmed to 23 °C and stirred for an additional 30 min. The organic phase was collected, washed with saturated aqueous $NaHCO_3$ (1x), dried ($MgSO_4$), filtered, and concentrated. Benzene was added

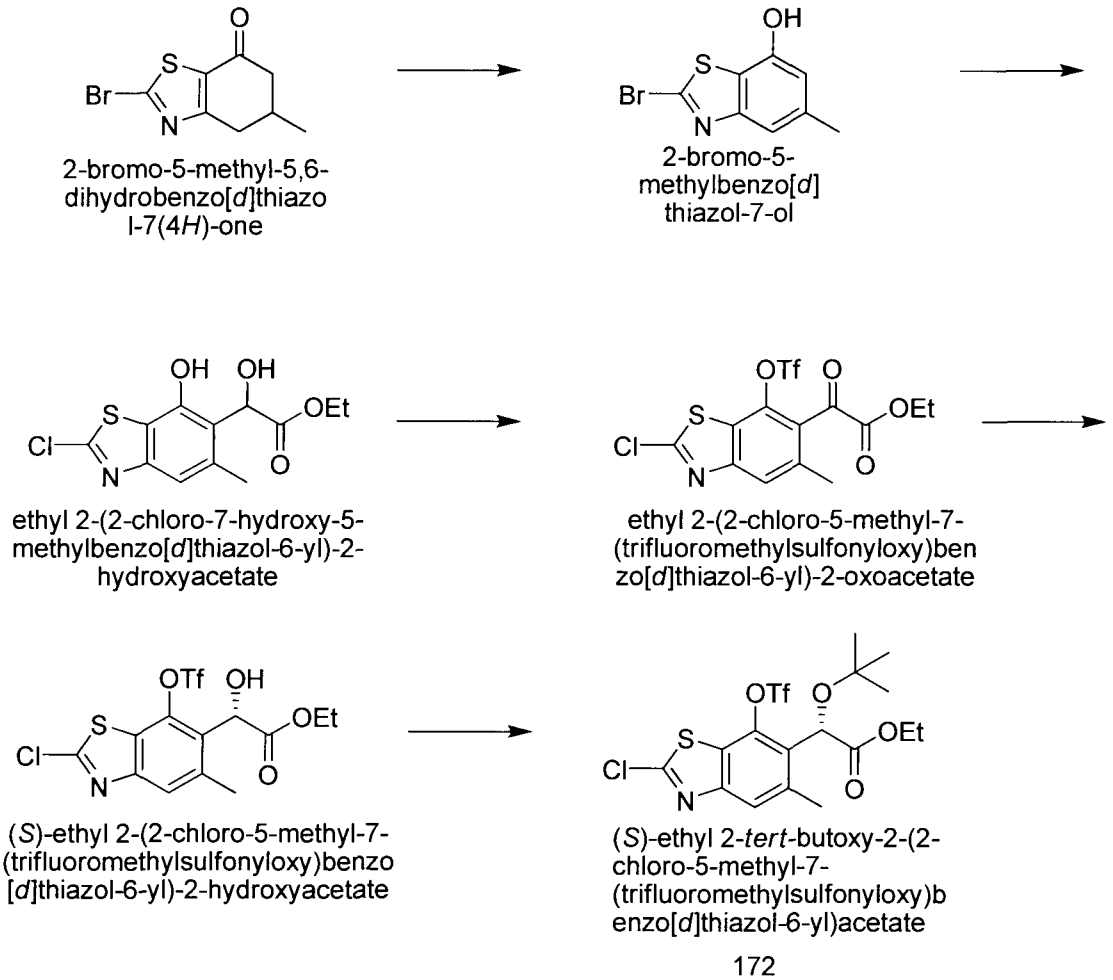
and the resulting solution was purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{18}H_{15}BrClNO_3S$: 440.0, 442.0, 440.0 ($M+H^+$); Found: 440.2, 442.1, 444.1 ($M+H^+$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (s, 1H), 7.54 – 7.43 (m, 2H), 7.42 – 7.32 (m, 2H), 5.23 (s, 1H), 4.31 – 4.12 (m, 2H), 2.47 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H).

Preparation of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: A suspension of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-hydroxyacetate (7.20 g, 16.9 mmol) in neat t-BuOAc (100 mL) was cooled to 0 °C in an ice bath. 70% w/v aqueous $HClO_4$ (293 μL, 3.4 mmol) was added dropwise over 5 min. The reaction was warmed to 23 °C, then stirred for 2.3 h. At this point the reaction was transferred to an addition funnel. The reaction was added to a 23 °C solution of sat aqueous $NaHCO_3$ (400 mL) over 30 min. Once addition was complete, the reaction was stirred for another 15 min. The resulting system was extracted with EtOAc (2 x 150 mL). Combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Some residual t-BuOAc remained. Hexane (200 mL) was added and the slurry was concentrated once more. The resulting residue (reasonably free of t-BuOAc) was treated with Benzene and loaded onto a 330 g "gold" ISCO silica gel column. The following gradient elution sequence was used: [100% Hexane (5 column volumes, isocratic) → 10% EtOAc / 90% Hexane (5 column volumes, linear gradient → 10% EtOAc / 90% Hexane (5 column volumes, isocratic (*(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate elutes)) → 100% EtOAc (10 column volumes, isocratic, (unreacted *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-hydroxyacetate elutes))]. Product-containing fractions were pooled, concentrated, co-evarporated with Et_2O (100 mL) to give desired product. LCMS-ESI+ calc'd for $C_{22}H_{23}BrClNO_3S$: 496.0, 498.0 and 500.0 (M+H+); found: 496.2, 498.2, and 500.1 (M+H+). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.48 (m, 3H), 7.37 (m, 1H), 5.12 (s, 1H), 4.20 (m, 2H), 2.57 (s, 3H), 1.24 (t, 3H, J = 7 Hz), 0.96 (s, 9H).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate (858 mg, 1.733 mmol) and 2-chloropyridine-4-boronic acid (327 mg, 2.080 mmol) in dioxane (14.6 mL) was added $Pd(PPh_3)_4$ (160 mg, 0.139 mmol) and 2N K_2CO_3 (3.6 mL, 7.280 mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 90°C for 6 h. After cooling, the reaction mixture was diluted with

EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{27}H_{27}Cl_2N_2O_3S$: 529.1; found: 529.2.

Example 41. Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(2-chloro-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)acetate (172).



Preparation of 2-bromo-5-methylbenzo[d]thiazol-7-ol: To a solution of 2-bromo-5-methyl-5,6-dihydrobenzo[d]thiazol-7(4H)-one (17.5 g, 71.24 mmol) in acetic acid (142 mL) at 80°C was added dropwise bromine (3.30 mL, 64.12 mmol) over 30 minutes. Reaction mixture was stirred for 1h at 80°C, cooled to room temperature and resulting solid collected by filtration. The filter cake was partitioned between dichloromethane/saturated sodium bicarbonate solution. The organic layer was washed with saturated sodium bicarbonate solution, brine, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in dichloromethane (250 mL) and added dropwise over 2.5 h to a solution of 1,8-Diazabicyclo[5.4.0]undec-7-ene (19.5 mL, 130 mmol) in dichloromethane (1.5 L) at 0°C. Reaction mixture was stirred for 30 minutes, quenched with 1N HCl and stirred for 5 minutes. The organic layer was washed with brine,

dried ($MgSO_4$), filtered and concentrated. Purification by CombiFlash (220g, 5 to 40% EtOAc/Hex) gave impure product. Recystallization from hot EtOAc/Hex gave pure product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H), 6.65 (s, 1H), 2.44 (s, 3H).

Preparation of ethyl 2-(2-chloro-7-hydroxy-5-methylbenzo[d]thiazol-6-yl)-2-hydroxyacetate: To a mixture of 2-bromo-5-methylbenzo[d]thiazol-7-ol (2.48 g, 10.16 mmol) in dichloromethane (100 mL) at 0°C was added triethylamine (1.42 mL, 10.16 mmol) to give a clear solution. Titaniuim(IV) chloride (1.0M in CH_2Cl_2, 10.67 mL, 10.67 mmol) was added slowly to give an orange reaction mixture that was stirred for 30 minutes. A solution of cracked ethyl glyoxalate (1.04 g, 10.16 mmol) in CH_2Cl_2 (1 mL) was added over 2 minutes and reaction mixture was stirred at room temperature for 2.5 h. Reaction mixture was quenched with Rochelle's salt and stirred at room temperature for 2 h, diluted with CH_2Cl_2, and aqueous layer extracted with CH_2Cl_2 (2x). The combined organic layer was dried ($MgSO_4$), filtered and concentrated. Purification by CombiFlash (40g, 0 to 30% EtOAc/Hex) gave product contaminated with ethyl 2-(2-bromo-7-hydroxy-5-methylbenzo[d]thiazol-6-yl)-2-hydroxyacetate. LCMS-ESI$^+$: calc'd for $C_{12}H_{13}ClNO_3S$: 302.8 ($M+H^+$); Found: 302.1 ($M + H^+$).

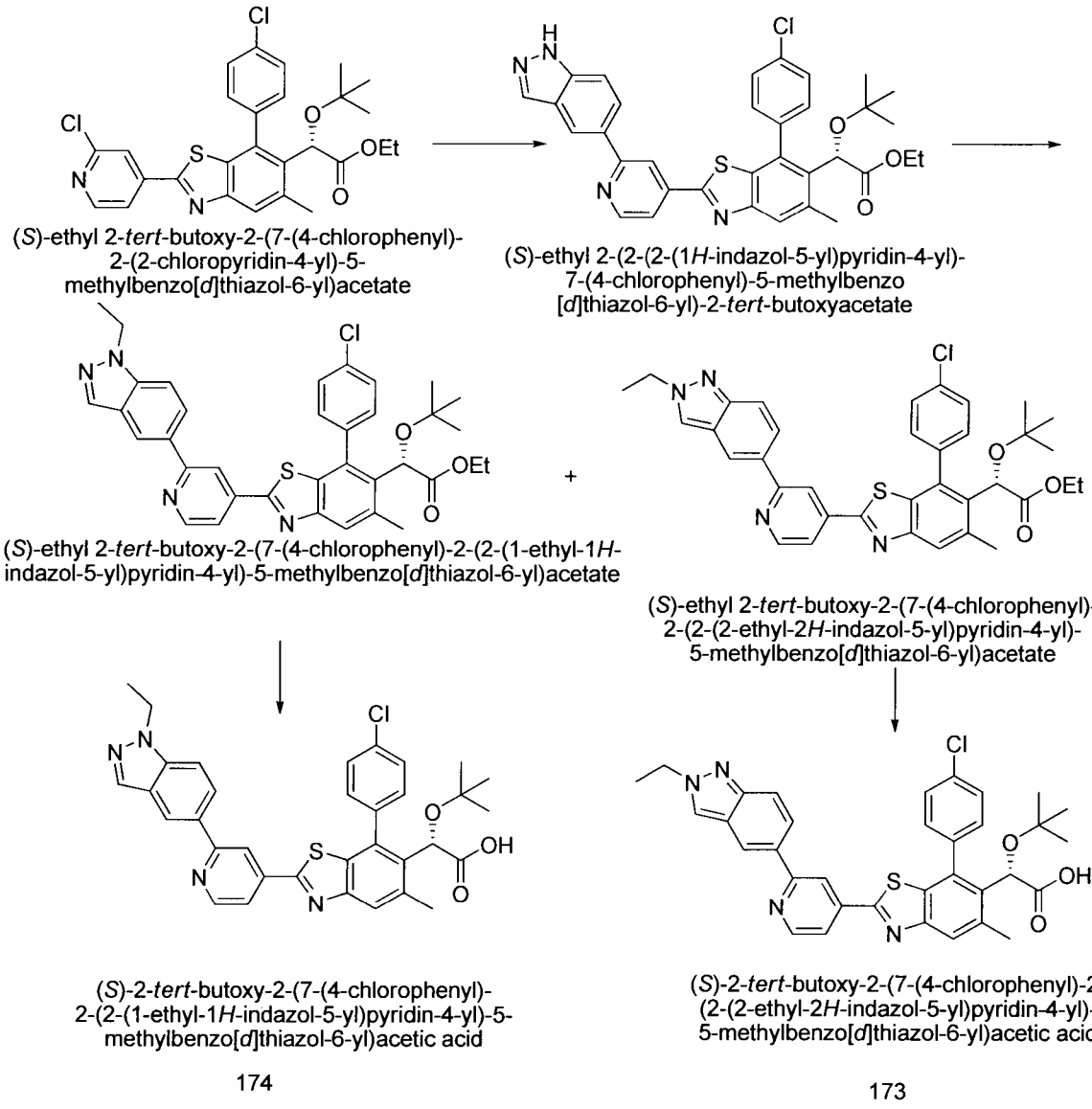
Preparation of ethyl 2-(2-chloro-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-oxoacetate: To a solution of ethyl 2-(2-chloro-7-hydroxy-5-methylbenzo[d]thiazol-6-yl)-2-hydroxyacetate (1.006 g, 3.33 mmol) in CH_2Cl_2 (33 mL) at -78°C was added 2,6-lutidine (0.846 mL, 7.33 mmol). Reaction mixture was stirred for 1h, then trifluoromethanesulfonyl anhydride (0.616 mL, 3.66 mmol) was added over 15 minutes. Reaction was stirred for 1h, then more trifluoromethanesulfonyl anhydride was added (0.062 mL, 3.66 mmol) and reaction continued for 30 minutes. Reaction mixture was quenched with brine, stirred for 5 minutes, diluted with CH_2Cl_2, washed with 1N HCl/brine. Organic layer was dried ($MgSO_4$), filtered, concentrated and used in next step without further purification.

The above residue was dissolved in CH_2Cl_2 (33 mL), cooled to 0°C and Dess-Martin periodinane (2.54 g, 5.99 mmol) was added portion-wise. After stirring for 2 h, more Dess-Martin periodinane (0.25 g, 5.99 mmol) was added. After 1 h, reaction was quenched with $Na_2S_2O_3$ solution and stirred for 30 minutes. The mixture was diluted with CH_2Cl_2, washed with water, saturated sodium bicarbonate solution, brine and dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 20% EtOAc/Hex) to give product contaminated with ethyl 2-(2-bromo-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-oxoacetate . ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 4.42 (q, J = 7.2 Hz, 2H), 2.49 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H).

Preparation of *(S)*-ethyl 2-(2-chloro-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-hydroxyacetate: To a solution of ethyl 2-(2-chloro-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-oxoacetate (0.6621 g, 1.53 mmol), and (R)-2-methyl-CBS-oxazaborolidine (0.098 g, 0.35 mmol) in toluene (6 mL) was added a solution of distilled catecholborane (0.254 g, 2.39 mmol) in toluene (1 mL) over 15 minutes, then stirred for another 45 minutes. The reaction was quenched with saturated sodium carbonate solution and stirred at room temperature for 15 minutes. Product extracted with EtOAc and organic layer washed with saturated sodium carbonate (3x), brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 25% EtOAc/Hex) to give product contaminated with *(S)*-ethyl 2-(2-bromo-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-hydroxyacetate. LCMS-ESI$^+$: calc'd for $C_{13}H_{12}ClF_3NO_6S_2$: 434.0 ($M+H^+$); Found: 433.9 ($M + H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(2-chloro-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-chloro-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-hydroxyacetate (0.5691 g, 1.31 mmol) in *tert*-butyl acetate (65 mL) was added 70% perchloric acid (65 µL, 1.57 mmol). Reaction mixture was stirred for 1.5 h and quenched with solid sodium bicarbonate. Saturated sodium bicarbonate solution was carefully added until basic and mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 15% EtOAc/Hex) to give product contaminated with *(S)*-ethyl 2-*tert*-butoxy-2-(2-bromo-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)acetate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 5.59 (s, 1H), 4.4 – 4.1 (m, 2H), 2.55 (s, 3H), 1.20 (s, 9H), 1.16 (t, J = 7.2 Hz, 3H).

Example 42. (Method K): Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-ethyl-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (173) and (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-ethyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (174).



Preparation of *(S)*-ethyl 2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: *(S)*-ethyl 2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)ethyl pivalate in method C. LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_4O_3S$: 611.2 ($M+H^+$); found: 611.2.

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-ethyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate and *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-ethyl-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (32 mg, 0.052 mmol) in DMF (1 mL), was added Cs_2CO_3 (34 mg, 0.104 mmol), iodoethane (5 μL, 0.062 mmol). The reaction was reacted

at room temperature. After the reaction finished, the reaction mixture was washed by water, extracted by EtOAc, the organic phase was dried over $MgSO_4$, filtered, concentrated down, purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-ethyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{36}H_{35}ClN_4O_3S$: 639.2 ($M+H^+$); found: 639.4;

(S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-ethyl-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate was also isolated. LCMS-ESI$^+$: calc'd for $C_{36}H_{35}ClN_4O_3S$: 639.2 ($M+H^+$); found: 639.3.

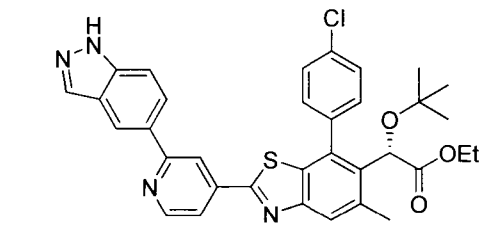
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-ethyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-ethyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in method D. LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_4O_3S$: 611.2 ($M+H^+$); found: 611.2.

^{1}H NMR (400 MHz, CD_3OD) δ:8.74 (s, 2.6 Hz, 1H), 8.56 (s, 1H), 8.45 (s, 1H), 8.17 (s, 1H), 8.09-8.03 (M, 2H), 7.94 (s, 1H), 7.76-7.69 (m, 2H), 7.61-7.59 (m, 3H), 5.28 (s, 1H), 4.53-4.48 (m, 2H), 2.63 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H), 0.98 (s, 9H).

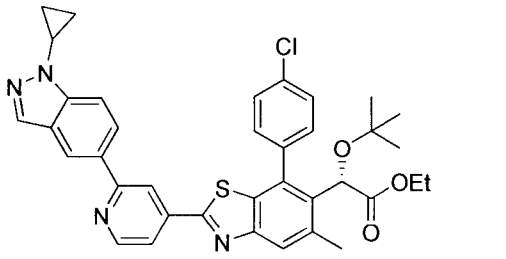
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-ethyl-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-ethyl-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in method D. LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_4O_3S$: 611.2 ($M+H^+$); found: 611.2.

^{1}H NMR (400 MHz, CD_3OD) δ: 8.70 (d, J = 2.8 Hz, 1H), 8.50 (d, 1H), 8.41-8.40 (m, 2H), 7.99-7.91 (m, 2H), 7.76-7.68 (m, 2H), 7.60-7.58 (m, 3H), 5.27 (s, 1H), 4.53-4.50 (m, 2H), 2.62 (s, 3H), 1.62 (t, J = 6.8 Hz, 3H), 0.97 (s, 9H).

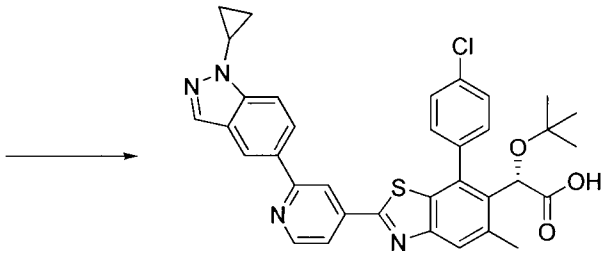
Example 43. Method L: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-cyclopropyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (175).



(*S*)-ethyl 2-(2-(2-(1*H*-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-cyclopropyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



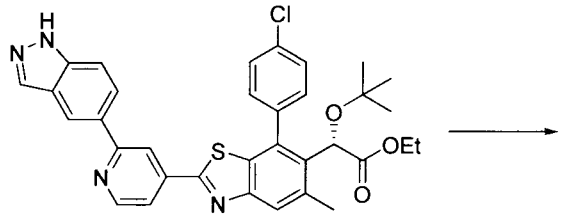
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-cyclopropyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

175

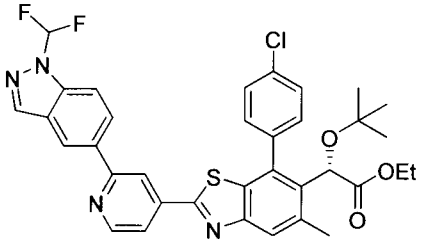
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-cyclopropyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (30 mg, 0.049 mmol) in dichloroethane (1 mL) was added $Cu(OAc)_2$ (9 mg, 0.049 mmol), 2-2'-dipyridyl (7.7 mg, 0.049 mmol), cyclopropylboronic acid (8.4 mg, 0.1 mmol), Na_2CO_3 (10.4 mg, 0.1 mmol). The reaction mixture was heated at 70 °C for 3 hours under air. The reaction mixture was washed by water, extracted by EtOAc, the organic phase was dried over $MgSO_4$, filtered, concentrated down, purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{37}H_{35}ClN_4O_3S$: 651.2 ($M+H^+$); found: 651.3.

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-cyclopropyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-cyclopropyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in method D. LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_4O_3S$: 623.2 ($M+H^+$); found: 623.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.73 (d, J = 2.6 Hz, 1H), 8.49 (s, 1H), 8.43 (s, 1H), 8.15-8.10 (m, 2H), 7.93-7.92 (m, 2H), 7.82 (d, J = 4.6 Hz, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.61-7.60 (m, 3H), 5.28 (s, 1H), 3.67-3.72 (m, 1H), 2..63 (s, 3H), 1.23-1.20 (m, 4H), 0.98 (s, 9H).

Example 44. Method M: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(difluoromethyl)-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (176) and (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-(difluoromethyl)-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (177).

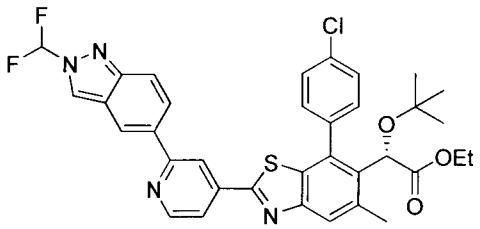


(*S*)-ethyl 2-(2-(2-(1*H*-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

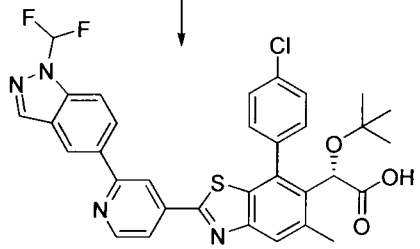


(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-(difluoromethyl)-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

+

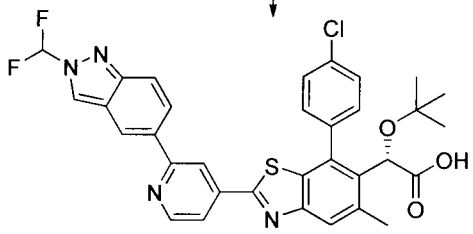


(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(difluoromethyl)-2*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-(difluoromethyl)-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

177



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(difluoromethyl)-2*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

176

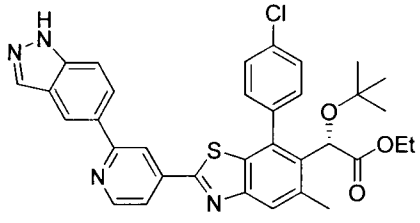
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-(difluoromethyl)-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (20 mg, 0.0327 mmol) in DMF (1 mL) was added Cs_2CO_3 (53 mg, 0.163 mmol), methyl 2-chloro-2,2-difluoroacetate (4 μL, 0.039 mmol). The reaction mixture was heated at 60 °C overnight. Then more methyl 2-chloro-2,2-difluoroacetate (6 μL, 0.058 mmol) was added and heated at 60 °C for 1 day. The reaction mixture was washed by water, extracted by EtOAc, the organic phase was dried over $MgSO_4$, filtered, concentrated down, purified by silica gel column, eluting by 0-50% EtOAc in hexanes to give *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-

chlorophenyl)-2-(2-(1-(difluoromethyl)-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate LCMS-ESI$^+$: calc'd for $C_{35}H_{31}ClF_2N_4O_3S$: 661.2 (M+H$^+$); found: 661.2; and *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(difluoromethyl)-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{35}H_{31}ClF_2N_4O_3S$: 661.2 (M+H$^+$); found: 661.3.

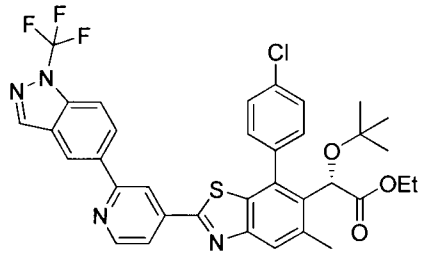
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-(difluoromethyl)-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1-(difluoromethyl)-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in method D. LCMS-ESI$^+$: calc'd for $C_{33}H_{27}ClF_2N_4O_3S$: 633.2 (M+H$^+$); found: 633.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.77 (d, J = 2.8 Hz, 1H), 8.56 (s, 1H), 8.52 (s, 1H), 8.34 (s, 1H), 8.28 (d, J = 4.4 Hz, 1H), 7.96-7.60 (m, 8H), 5.28 (s, 1H), 2.64 (s, 3H), 0.98 (s, 9H). ^{19}F NMR (400 MHz, CD3OD) δ: -97.70 (dm J = 27.8 Hz, 2F).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(difluoromethyl)-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(difluoromethyl)-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in method D. LCMS-ESI$^+$: calc'd for $C_{33}H_{27}ClF_2N_4O_3S$: 633.2 (M+H$^+$); found: 633.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.83 (s. 1H), 8.76 (d, J = 2.6 Hz, 1H), 8.54 (d, J = 0.4 Hz, 1H), 8.49 (s, 1H), 8.08-7.84 (m, 5H), 7.71-7.60 (m, 4H), 5.28 (s, 1H), 2.63 (s, 3H), 0.98 (s, 9H). ^{19}F NMR (400 MHz, CD_3OD) δ: -97.17 (d, J = 31.6 Hz, 2F).

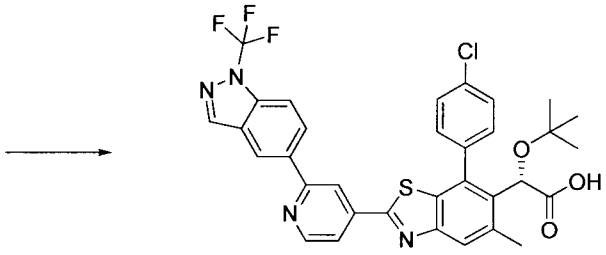
Example 45. Method N: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-(trifluoromethyl)-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (178).



(*S*)-ethyl 2-(2-(2-(1*H*-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-(trifluoromethyl)-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-(trifluoromethyl)-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

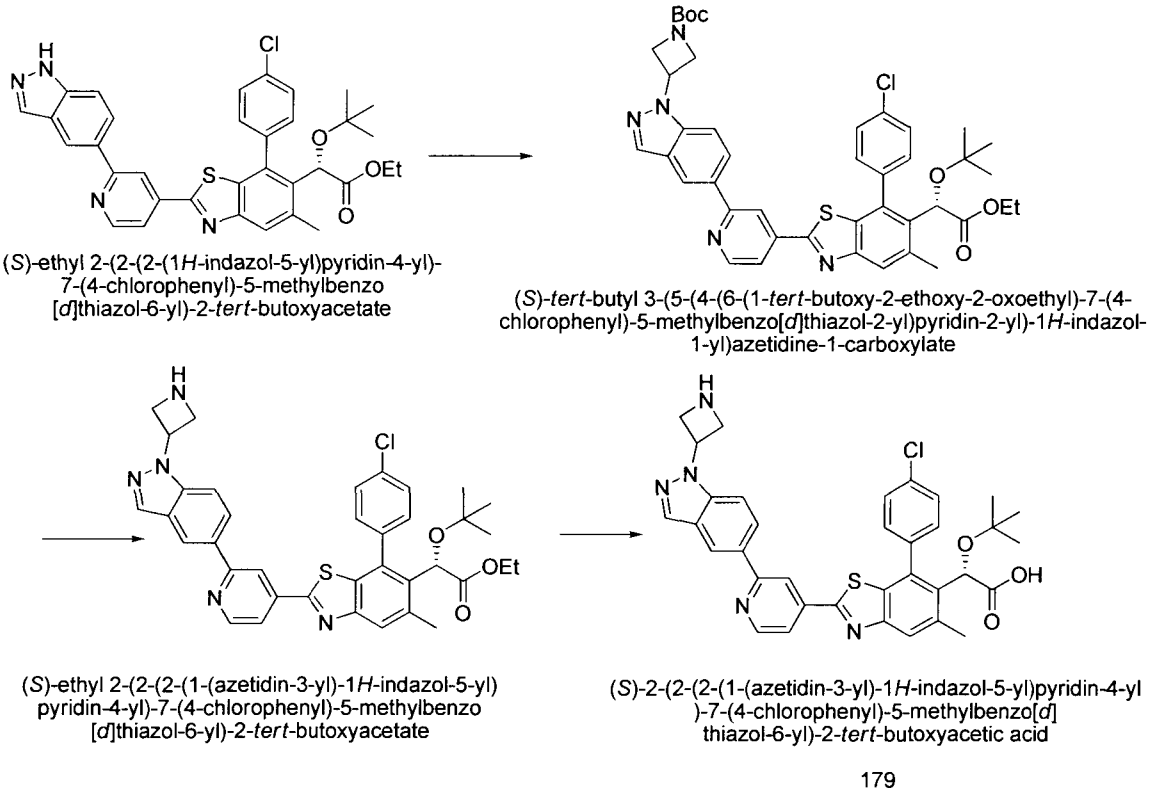
178

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-(trifluoromethyl)-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (40 mg, 0.065 mmol) in CS_2 (1.5 mL), was added 1-Trifluoromethyl-3,3-dimethyl-1,2-benziodoxole (64 mg, 0.195 mmol), bis(trifluoromethane)sulfonimide (27 mg, 0.0975 mmol). The reaction mixture was heated at 60 °C in sealed microwave vial for 1d. The reaction mixture was washed by saturated $NaHCO_3$, extracted by EtOAc, the organic phase was dried over $MgSO_4$, filtered, concentrated down, purified by silica gel column, eluting by 0-50% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{35}H_{30}ClF_3N_4O_3S$: 679.2 ($M+H^+$); found: 679.2.

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-(trifluoromethyl)-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-(trifluoromethyl)-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in method D. LCMS-ESI$^+$: calc'd for $C_{33}H_{26}ClF_2N_4O_3S$: 651.1 ($M+H^+$); found: 651.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.96 (s, 1H), 8.77(d, J = 2.6 Hz, 1H), 8.50 (s, 2H), 8.20-8.17 (m, 1H),

7.93-7.92 (m, 2H), 7.85-7.65 (m, 2H), 7.61 (s, 3H), 5.28 (s, 1H), 2.63 (s, 3H), 0.98 (s, 9H). ^{19}F NMR (400 MHz, CD_3OD) δ: -62.05 (s, 3F).

Example 46. Method O: Preparation of *(S)*-2-(2-(2-(1-(azetidin-3-yl)-1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (179).



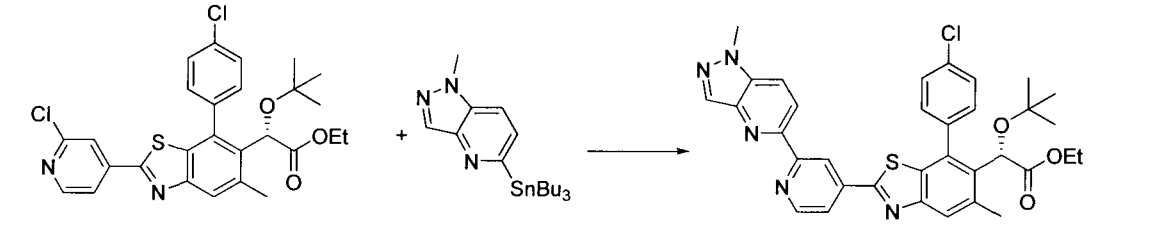
Preparation of *(S)-tert*-butyl 3-(5-(4-(6-(1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)pyridin-2-yl)-1H-indazol-1-yl)azetidine-1-carboxylate: To a solution of *(S)*-ethyl 2-(2-(2-(1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (110 mg, 0.18 mmol) in DMF (3 mL) was added Cs_2CO_3 (117 mg, 0.36 mmol) and 1-Boc-3-iodoazetidine (76 mg, 0.27 mmol). The reaction mixture was heated at 60 °C overnight. The reaction mixture was washed by saturated $NaHCO_3$, extracted by EtOAc, the organic phase was dried over $MgSO_4$, filtered, concentrated down, purified by silica gel column, eluting by 0-60% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{42}H_{44}ClN_5O_5S$: 766.3 ($M+H^+$); found: 766.3.

Preparation of *(S)*-ethyl 2-(2-(2-(1-(azetidin-3-yl)-1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: To a solution of *(S)-tert*-butyl 3-(5-(4-(6-(1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-

methylbenzo[d]thiazol-2-yl)pyridin-2-yl)-1H-indazol-1-yl)azetidine-1-carboxylate (54 mg, 0.070 mmol) in isopropanol (3 mL) was added HCl in Dioxane (3 mL, 4 N in dioxane). The reaction mixture was stirred at room temperature. After the reaction finished, the reaction mixture was diluted by EtOAc, washed by saturated $NaHCO_3$, back-extracted by EtOAc, the organic phase was dried over $MgSO_4$, filtered, concentrated down, purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{37}H_{36}ClN_5O_3S$: 666.2 ($M+H^+$); found: 666.3.

Preparation of *(S)*-2-(2-(2-(1-(azetidin-3-yl)-1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid: *(S)*-2-(2-(2-(1-(azetidin-3-yl)-1H-indazol-5-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in method D. LCMS-ESI$^+$: calc'd for $C_{35}H_{32}ClN_5O_3S$: 638.2 ($M+H^+$); found: 638.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.75 (d, J = 2.6 Hz), 8.50 (s, 2H), 8.37 (s, 1H), 8.20-8.18 (m, 1H), 7.94-7.90 (m, 2H), 7.74-7.69 (m, 2H), 7.61 (m, 3H), 5.92-5.88 (m, 1H), 5.28 (s, 1H), 4.67 (d, J = 3.8 Hz, 4H), 2.63 (s, 3H), 0.98 (s, 9H).

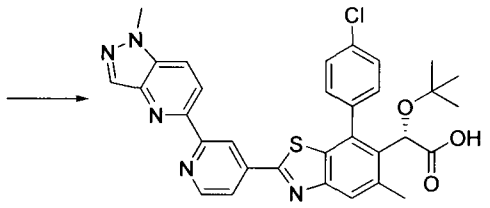
Example 47. Method P: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (180).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

1-methyl-5-(tributylstannyl)-1*H*-pyrazolo[4,3-*b*]pyridine

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

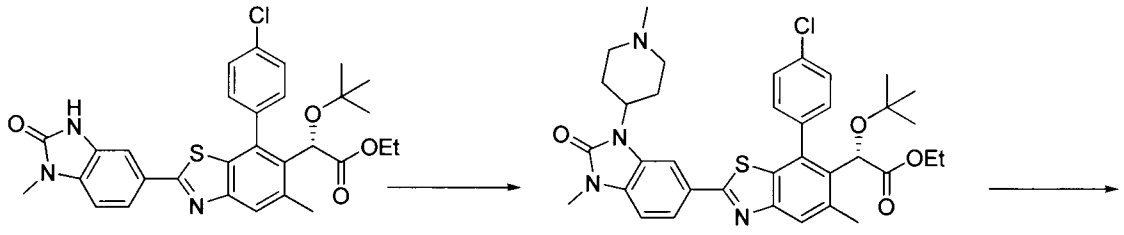
180

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-

(2-(1-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate : To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (48 mg, 0.091 mmol) in microwave vial, was added 1-methyl-5-(tributylstannyl)-1H-pyrazolo[4,3-b]pyridine (47 mg, 0.111 mmol), copper(I) iodide (9 mg, 0.045 mmol), lithium chloride (11 mg, 0.27 mmol), $Pd(PPh_3)_4$ (10 mg, 0.009 mmol). The reaction mixture was heated at 120 °C for 4 hours. Then the mixture was washed by saturated $NaHCO_3$, extracted by EtOAc, the organic phase was dried over $MgSO_4$, filtered, concentrated down, purified by silica gel column, eluting by 0-60% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_5O_3S$: 626.2 ($M+H^+$); found: 626.3.

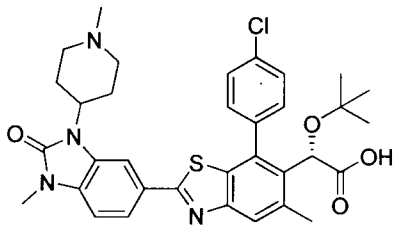
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in method D. LCMS-ESI$^+$: calc'd for $C_{32}H_{28}ClN_5O_3S$: 598.2 ($M+H^+$); found: 598.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.77 (s, 1H), 8.60 (d, J = 2.6 Hz, 1H), 8.32 (d, J = 4.6 Hz, 1H), 8.15 (s, 1H), 7.99 (d, J = 4.2 Hz, 1H), 7.84 (d, J = 2.4Hz, 1H), 7.76 (s, 1H), 7.61 (d, J= 4.4 Hz, 1H), 7.52-7.19 (m, 3H), 5.19 (s, 1H), 3.98 (s, 3H), 2.52 (s, 3H), 0.89 (s, 9H).

Example 48. Method Q: Preparation of *(S)*-2-*tert*-butoxy-2-(4-(4-chlorophenyl)-1,6-dimethyl-3-(1-methylpiperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)acetic acid (181).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methylpiperidin-4-yl)-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methylpiperidin-4-yl)-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

181

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methylpiperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)benzo[d]thiazol-6-yl)acetate (47 mg, 0.083mmol) in DMF (1 mL), pyridine (0.5 mL), was added N-methyl-4-bromopiperidine (26 mg, 0.146 mmol). The reaction was stirred at 85 °C overnight. Then Cs_2CO_3 (54 mg) was added, raised temp to 100 °C and stirred overnight. More N-methyl-4-bromopiperidine (50 mg 0.28 mmol), the mixture was heated at 100 °C for 2 days. The reaction was quenched by adding water, extracted by EtOAc, dried by $MgSO_4$, filtered, concentrated down and purified by silica gel column, first 0-100% EtOAc in hexanes to elute *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)benzo[d]thiazol-6-yl)acetate , then switched to 0-20% MeOH in DCM to elute the product. LCMS-ESI$^+$: calc'd for $C_{36}H_{41}ClN_4O_4S$: 661.2 ($M+H^+$); found: 661.3.

Preparation of *(S)*-2-*tert*-butoxy-2-(4-(4-chlorophenyl)-1,6-dimethyl-3-(1-methylpiperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(4-(4-chlorophenyl)-1,6-dimethyl-3-(1-methylpiperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)acetic acid was made by the similar method to make *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid in

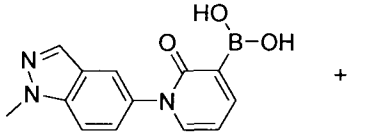
method D. LCMS-ESI$^+$: calc'd for $C_{34}H_{37}ClN_4O_4S$: 633.2 ($M+H^+$); found: 633.2. ^1H NMR (400 MHz, CD_3OD) δ: 7.84 (s, 1H), 7.5-7.70 (m, 2H), 7.60-7.57 (m, 1H), 7.51-7.49 (m, 3H), 7.17 (d, J = 4.2 Hz), 5.15 (s, 1H), 4.56-4.53 (m, 1H), 3.61-3.57 (m, 2H), 3.34 (s, 3H), 3.19-3.15 (m, 2H), 2.86 (s, 3H), 2.75-2.72 (m, 2H), 2.51 (s, 3H), 2.05-2.02 (m, 2H), 0.88 (s, 9H).

Example 49. Method U: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methyl-1H-indazol-5-yl)-2-oxo-1,2-dihydropyridin-3-yl)benzo[*d*]thiazol-6-yl)acetic acid (182).

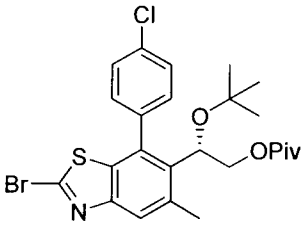
5-bromo-1-methyl-1*H*-indazole

3-bromo-2-hydroxypyridine

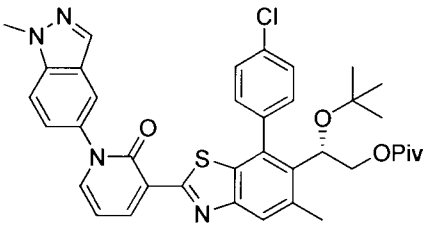
3-bromo-1-(1-methyl-1*H*-indazol-5-yl)pyridin-2(1*H*)-one



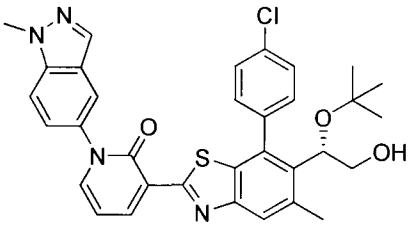
1-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2-dihydropyridin-3-ylboronic acid



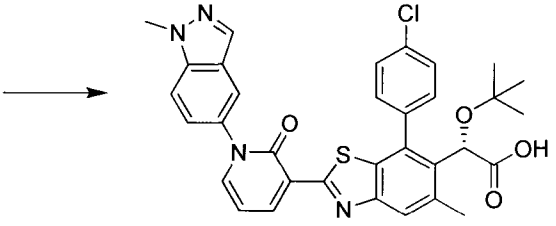
(*S*)-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2-dihydropyridin-3-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate



(*S*)-3-(6-(1-*tert*-butoxy-2-hydroxyethyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-2-yl)-1-(1-methyl-1*H*-indazol-5-yl)pyridin-2(1*H*)-one



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2-dihydropyridin-3-yl)benzo[*d*]thiazol-6-yl)acetic acid

182

Preparation of 3-bromo-1-(1-methyl-1*H*-indazol-5-yl)pyridin-2(1*H*)-one: To a solution of 3-bromo-2-hydroxypyridine (600 mg, 3.448 mmol) in anhydrous DMF (4.0 mL) was added 5-bromo-1-methyl-1*H*-indazole (1455 mg, 6.896 mmol), CuI (394 mg, 2.069 mmol), trans-N_1,N_2-dimethylcyclohexane-1,2-diamine (1.09 mL, 6.896 mmol) and K_2CO_3 (1191 mg, 8.621 mmol). The reaction mixture was heated to 110 °C for 15 min. The reaction mixture was purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the TFA salt of the desired product (135 mg, 16%). Then the product was diluted with EtOAc, extracted with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated to give the free base of the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{13}H_{11}BrN_3O$: 304.0; found: 304.2.

Preparation of 1-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2-dihydropyridin-3-ylboronic acid: To a stirred and cooled (-78 °C) solution of 3-bromo-1-(1-methyl-1*H*-indazol-5-yl)pyridin-2(1*H*)-one (87 mg, 0.287 mmol) and trimethylborate (137 µL, 1.234 mmol) in anhydrous THF (5.0 mL) was added *n*-BuLi (2.5 M in hexane, 0.71 mL) for 10 min. Quenched the reaction by water and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{13}H_{13}BN_3O_3$: 270.1; found: 270.2.

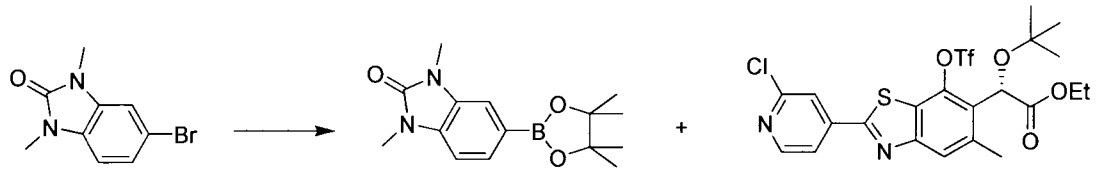
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methyl-1H-indazol-5-yl)-2-oxo-1,2-dihydropyridin-3-yl)benzo[*d*]thiazol-6-yl)ethyl pivalate: To a solution of *(S)*-2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyethyl pivalate (20.8 mg, 0.039 mmol) and 1-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2-dihydropyridin-3-ylboronic acid (22.2 mg, 0.082 mmol) in DME (0.6 mL) and EtOH (0.6 mL) was added $Pd(PPh_3)_4$ (2.0 mg, 0.002 mmol) and 2N K_2CO_3 (58 µL, 0.116 mmol). The reaction was degassed for 5 minutes with N_2 and then microwaved to 100°C for 1h. After cooling, the reaction mixture was diluted with EtOAc, extracted with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{38}H_{40}ClN_4O_4S$: 683.3; found: 683.4.

Preparation of *(S)*-3-(6-(1-*tert*-butoxy-2-hydroxyethyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-2-yl)-1-(1-methyl-1*H*-indazol-5-yl)pyridin-2(1*H*)-one: To a stirred

solution of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2-dihydropyridin-3-yl)benzo[d]thiazol-6-yl)ethyl pivalate (15.0 mg, 0.022 mmol) in THF (1.0 mL) and methanol (0.6 mL) was added 1N NaOH solution (0.4 mL, excess). The reaction mixture was stirred at 50 °C for 4h. The reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{33}H_{32}ClN_4O_3S$: 599.2; found: 599.3.

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methyl-1*H*-indazol-5-yl)-2-oxo-1,2-dihydropyridin-3-yl)benzo[*d*]thiazol-6-yl)acetic acid: To the solution of *(S)*-3-(6-(1-*tert*-butoxy-2-hydroxyethyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-2-yl)-1-(1-methyl-1*H*-indazol-5-yl)pyridin-2(1H)-one (7.0 mg, 0.012 mmol) in wet acetonitrile (0.75 w% H_2O, 0.8 mL), was added stock solution of H_5IO_6/CrO_3 (0.439 M in wet acetonitrile, 0.6 mL) at 0 °C for 40 min. The reaction mixture was filtered and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{33}H_{30}ClN_4O_4S$: 613.2; found: 613.2. 1H NMR (400 MHz, CD3OD) δ 8.84 (dd, J = 7.2, 2.0 Hz, 1H), 8.09 (s, 1H), 7.89 (dd, J = 6.8, 2.0 Hz, 1H), 7.84 (s, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.69 – 7.63 (m, 2H), 7.54 – 7.43 (m, 4H), 6.68 (t, J = 6.8 Hz, 1H), 5.26 (s, 1H), 4.12 (s, 3H), 2.62 (s, 3H), 0.95 (s, 9H).

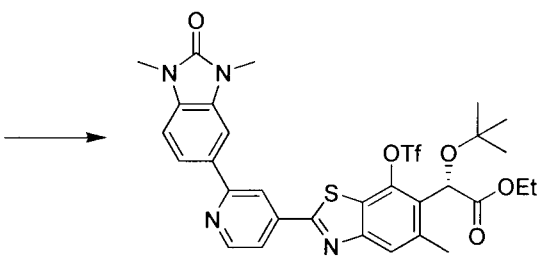
Example 50. Method V: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (183).



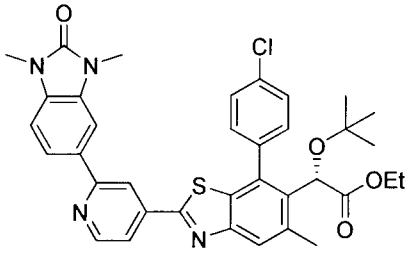
5-bromo-1,3-dimethyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one

1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one

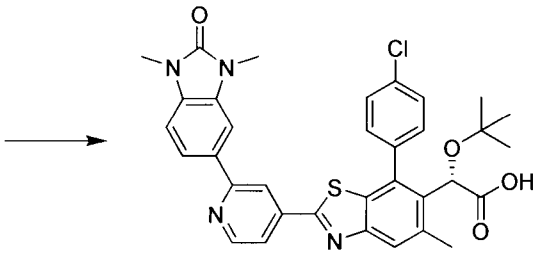
(*S*)-ethyl 2-*tert*-butoxy-2-(2-(2-chloropyridin-4-yl)-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(2-(2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)pyridin-4-yl)-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

183

Preparation of 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one: A solution of 5-bromo-1,3-dimethyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (200 mg, 0.830 mmol), bis(pinacolato)diboron (253 mg, 0.996 mmol) and potassium acetate (244 mg, 2.490 mmol) in dioxane (8.2 mL) was degassed for 5 min with N_2, then treated with Pd(dppf)Cl_2 · DCM (34 mg, 0.041 mmol). The resulting mixture was heated at 90 °C overnight. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{15}H_{22}BN_2O_3$: 289.2; found: 289.3.

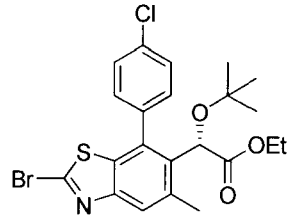
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(2-(2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)pyridin-4-yl)-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[*d*]thiazol-6-yl)acetate: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(2-(2-chloropyridin-4-yl)-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[*d*]thiazol-6-yl)acetate (26.0 mg, 0.046 mmol), 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[d]imidazol-2(3*H*)-one (20.0 mg, 0.069 mmol) and K_3PO_4 (29.2 mg, 0.138 mmol) in dioxane (1.0 mL) and H_2O (0.1 mL) was degassed for 5 min, treated with $PdCl_2$(dppf) (5.0 mg, 0.007 mmol). The resulting mixture was heated at 100 °C for 8 min. The reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{31}H_{32}F_3N_4O_7S_2$: 693.2; found: 693.1.

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(2-(2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)pyridin-4-yl)-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[*d*]thiazol-6-yl)acetate (15.3 mg, 0.022 mmol), 4-chlorophenylboronic acid (4.0 mg, 0.026 mmol) and K_2CO_3 (9.0 mg, 0.066 mmol) in DME (0.5 mL) was added $Pd(PPh_3)_4$ (2.0 mg, 1.73 x 10^{-3} mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 120°C for 6 h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{36}H_{36}ClN_4O_4S$: 655.2; found: 655.3.

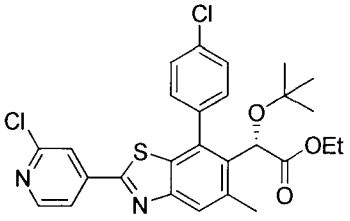
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a stirred solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (7.0 mg, 0.011 mmol) in THF (0.5 mL) and methanol (0.5 mL) was added 1N NaOH solution (0.5 mL, excess). The reaction mixture was stirred at 50 °C for 2h and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{34}H_{32}ClN_4O_4S$: 627.2; found: 627.3. ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (d, J = 6.0 Hz, 1H), 8.47 (s, 1H), 7.98 (dd, J = 5.6, 1.6 Hz, 1H), 7.93 (s,

1H), 7.80 (d, J = 1.6 Hz, 1H), 7.78 (s, 1H), 7.71 – 7.68 (m, 1H), 7.62 – 7.58 (m, 3H), 7.24 (d, J = 8.4 Hz, 1H), 5.28 (s, 1H), 3.47 (s, 3H), 3.42 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).

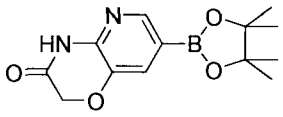
Example 51. Method W: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid (184).



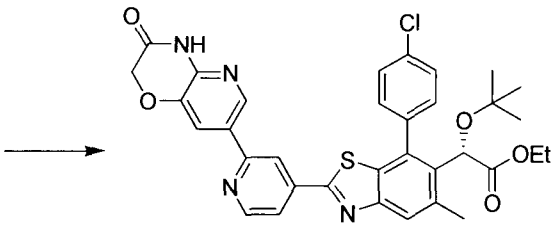
(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



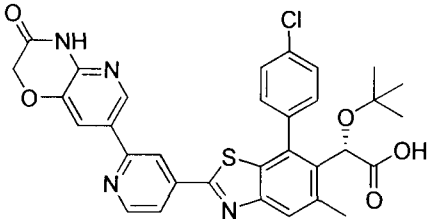
(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

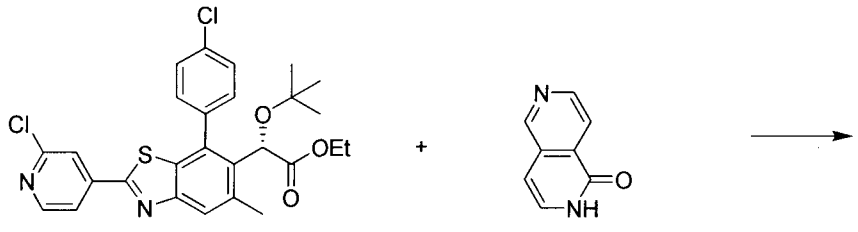
184

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate (858 mg, 1.73 mmol) and 2-chloropyridine-4-boronic acid (327 mg, 2.08 mmol) in dioxane (14.6 mL) was added $Pd(PPh_3)_4$ (160 mg, 0.139 mmol) and 2N K_2CO_3 (3.6 mL, 7.28 mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 90°C for 6 h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{27}H_{27}Cl_2N_2O_3S$: 529.1; found: 529.2.

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (32.0 mg, 0.061 mmol) and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one (20.0 mg, 0.073 mmol) in dioxane (0.5 mL) was added $Pd(PPh_3)_4$ (3.5 mg, 0.003 mmol) and 2N K_2CO_3 (127 µL, 0.255 mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 100°C for 10 h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{34}H_{32}ClN_4O_5S$: 643.2; found: 643.3.

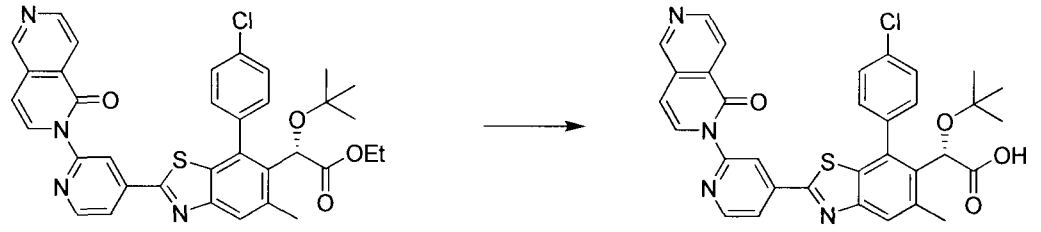
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-3,4-dihydro-2H-pyrido[3,2-*b*][1,4]oxazin-7-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a stirred solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (17.1 mg, 0.027 mmol) in THF (1.1 mL) and methanol (1.1 mL) was added 1N NaOH solution (0.8 mL, excess). The reaction mixture was stirred at 50 °C for 2h and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-3,4-dihydro-2H-pyrido[3,2-*b*][1,4]oxazin-7-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{32}H_{28}ClN_4O_5S$: 615.2; found: 615.2. ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (d, J = 4.8 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.43 (s, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.94 (s, 1H), 7.91 (dd, J = 5.2, 1.6 Hz, 1H), 7.71 – 7.68 (m, 1H), 7.62 – 7.59 (m, 3H), 5.28 (s, 1H), 4.72 (s, 2H), 2.63 (s, 3H), 0.97 (s, 9H).

Example 52. Method Y: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-oxo-2,6-naphthyridin-2(1*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid (186).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

2,6-naphthyridin-1(2*H*)-one



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-oxo-2,6-naphthyridin-2(1*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-oxo-2,6-naphthyridin-2(1*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

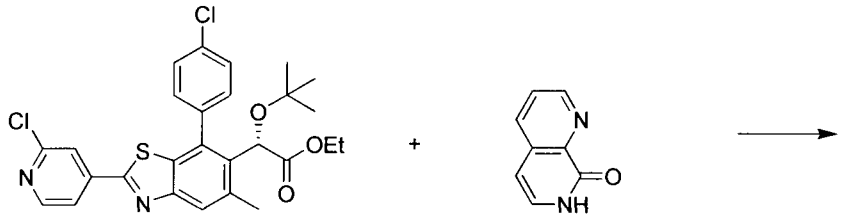
186

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-oxo-2,6-naphthyridin-2(1*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (26.0 mg, 0.049 mmol) in anhydrous THF (0.6 mL) was added 2,6-naphthyridin-1(2*H*)-one (11.0 mg, 0.074 mmol), Xantphos (4.0 mg, 0.006 mmol), Cs_2CO_3 (27.0 mg, 0.084 mmol) and $Pd_2(dba)_3$ (2.0 mg, 0.002 mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 100°C overnight. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography (silica gel, 0 to 90% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{35}H_{32}ClN_4O_4S$: 639.2; found: 639.3.

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-oxo-2,6-naphthyridin-2(1*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-oxo-2,6-naphthyridin-2(1*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (15.5 mg, 0.024 mmol) in pyridine (0.8 mL) was added LiI (100 mg, excess). The reaction mixture was heating in a microwave at 170 °C for 90 min. The mixture was concentrated in vacuo and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{33}H_{28}ClN_4O_4S$: 611.2; found: 611.2. ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.81

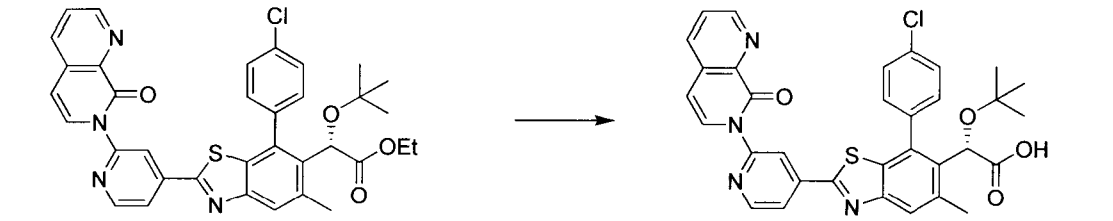
(d, J = 6.0 Hz, 1H), 8.75 – 8.71 (m, 2H), 8.60 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 3.6 Hz, 1H), 7.94 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.53 – 7.48 (m, 3H), 6.94 (d, J = 8.0 Hz, 1H), 5.32 (s, 1H), 2.59 (s, 3H), 1.00 (s, 9H).

Example 53. Method Z: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(8-oxo-1,7-naphthyridin-7(8*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid (187).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

1,7-naphthyridin-8(7*H*)-one



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(8-oxo-1,7-naphthyridin-7(8*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(8-oxo-1,7-naphthyridin-7(8*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

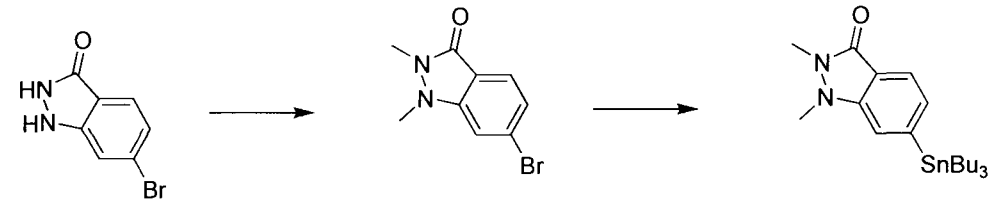
187

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(8-oxo-1,7-naphthyridin-7(8*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate: A suspension of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (27.0 mg, 0.051 mmol), 1,7-naphthyridin-8(7*H*)-one (22.4 mg, 0.153 mmol) and Cs_2CO_3 (66.5 mg, 0.204 mmol) in anhydrous DMF (1.0 mL) was heated in a microwave at 150°C for 50 min. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 90% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{35}H_{32}ClN_4O_4S$: 639.2; found: 639.3.

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(8-oxo-1,7-naphthyridin-7(8*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(8-oxo-1,7-naphthyridin-7(8*H*)-yl)pyridin-4-

yl)benzo[*d*]thiazol-6-yl)acetate (7.9 mg, 0.012 mmol) in pyridine (0.6 mL) was added LiI (75 mg, excess). The reaction mixture was heating in a microwave at 170 °C for 90 min. The mixture was concentrated in vacuo and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{33}H_{28}ClN_4O_4S$: 611.2; found: 611.2. ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 2.8 Hz, 1H), 8.68 (d, J = 5.2 Hz, 1H), 8.62 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.99 – 7.92 (m, 3H), 7.76 – 7.69 (m, 2H), 7.55 – 7.49 (m, 3H), 6.66 (d, J = 7.6 Hz, 1H), 5.34 (s, 1H), 2.58 (s, 3H), 1.01 (s, 9H).

Example 54. Method AA: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (188).

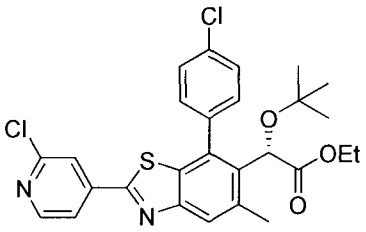


6-bromo-1*H*-indazol-3(2*H*)-one

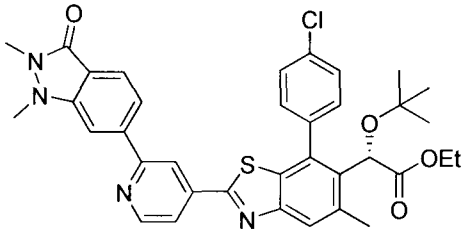
6-bromo-1,2-dimethyl-1*H*-indazol-3(2*H*)-one

1,2-dimethyl-6-(tributylstannyl)-1*H*-indazol-3(2*H*)-one

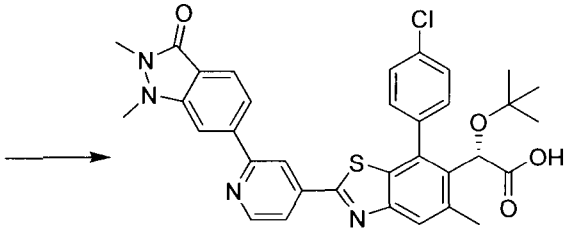
\+



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

188

Preparation of 6-bromo-1,2-dimethyl-1*H*-indazol-3(2*H*)-one: To a solution of 6-bromo-1*H*-indazol-3(2*H*)-one (300 mg, 1.41 mmol) in 1N NaOH (4.2 mL) was added dimethyl sulfate (0.4 mL, 4.22 mmol). The reaction mixture was stirred at room temperature for 6 h and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_9H_{10}BrN_2O$: 241.0; found: 241.2.

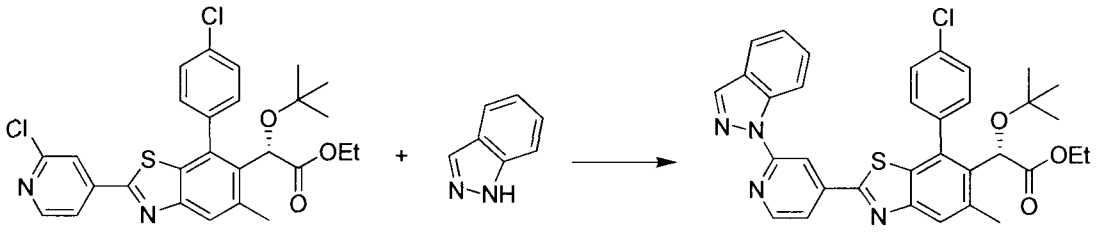
Preparation of 1,2-dimethyl-6-(tributylstannyl)-1*H*-indazol-3(2*H*)-one: To a solution of 6-bromo-1,2-dimethyl-1*H*-indazol-3(2*H*)-one (51.0 mg, 0.212 mmol) and bis(tributyltin) (0.12 mL, 0.319 mmol) in toluene (2.0mL) was added $Pd(PPh_3)_4$ (17.0 mg, 0.015 mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 100 °C overnight. After cooling, the reaction mixture was diluted with EtOAc, treated with KF solution and stirred at room temperature for 1h. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, filtered

and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{21}H_{37}N_2OSn$: 453.2; found: 453.3

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (32.0mg, 0.061 mmol) and 1,2-dimethyl-6-(tributylstannyl)-1*H*-indazol-3(2*H*)-one (33.0 mg, 0.073 mmol) in dioxane (0.8 mL) was added $Pd(PPh_3)_4$ (4.0 mg, 0.003 mmol) and CuI (4.0 mg, 0.018 mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 100°C for 2 days. Concentrated in vacuo and then purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{36}H_{36}ClN_4O_4S$: 655.2; found: 655.3.

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a stirred solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (9.4 mg, 0.014 mmol) in THF (0.5 mL) and methanol (0.5 mL) was added 1N NaOH solution (0.5 mL, excess). The reaction mixture was stirred at 50 °C for 2 h and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{34}H_{32}ClN_4O_4S$: 627.2; found: 627.2. ^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (d, J = 5.2 Hz, 1H), 8.49 (s, 1H), 8.06 (s, 1H), 7.96 (dd, J = 5.2, 1.2 Hz, 1H), 7.90 (s, 1H), 7.85 (q, J = 8.4 Hz, 2H), 7.70 – 7.67 (m, 1H), 7.61 – 7.56 (m, 3H), 5.27 (s, 1H), 3.51 (s, 3H), 3.47 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).

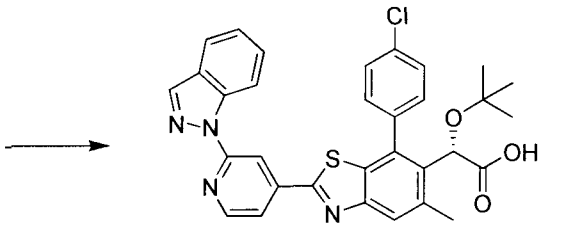
Example 55. Method AE: Preparation of *(S)*-2-(2-(2-(1*H*-indazol-1-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid (189).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

1*H*-indazole

(*S*)-ethyl 2-(2-(2-(1*H*-indazol-1-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-2-(2-(2-(1*H*-indazol-1-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid

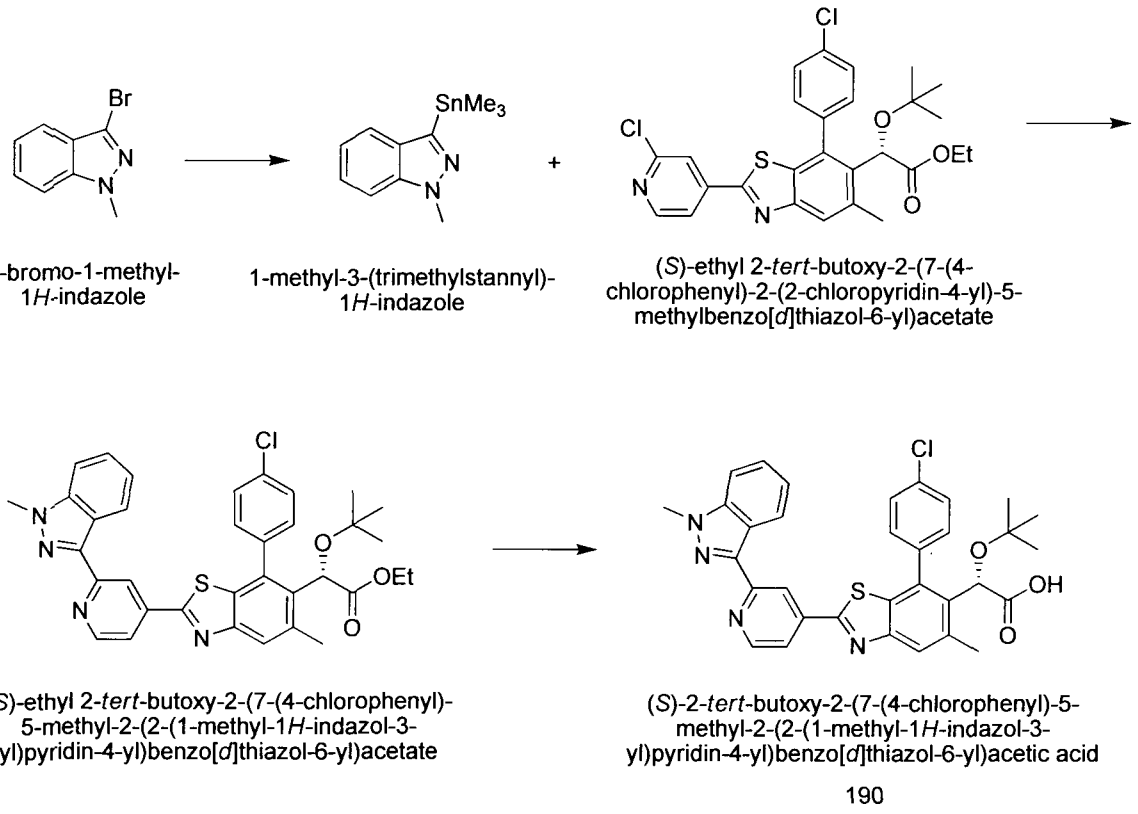
189

Preparation of *(S)*-ethyl 2-(2-(2-(1*H*-indazol-1-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (30 mg, 0.057 mmol) and 1*H*-indazole (6.0 mg, 0.052 mmol) in DMF (0.5 mL) was added K_2CO_3 (16.0 mg, 0.117 mmol) and 18-crown-6 (0.1 mg, 5.1 x 10^{-4} mmol). The reaction mixture was heated in a microwave at 160°C for 1h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 60% ethyl acetate/hexanes) and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{34}H_{32}ClN_4O_3S$: 611.2; found: 611.3.

Preparation of *(S)*-2-(2-(2-(1*H*-indazol-1-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid: To a stirred solution of *(S)*-ethyl 2-(2-(2-(1*H*-indazol-1-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate (6.8 mg, 0.011 mmol) in THF (0.4 mL) and methanol (0.4 mL) was added 1N NaOH solution (0.4 mL, excess). The reaction mixture was stirred at 50 °C for 2h and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{32}H_{28}ClN_4O_3S$: 583.2; found: 583.3. ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 8.8 Hz, 1H), 8.63 (d, J = 4.8 Hz, 1H), 8.57 (s, 1H),

8.23 (s, 1H), 7.97 (s, 1H), 7.81 – 7.77 (m, 2H), 7.73 (d, J = 7.6 Hz, 1H), 7.58 – 7.50 (m, 4H), 7.30 (t, J = 7.2 Hz, 1H), 5.35 (s, 1H), 2.61 (s, 3H), 1.02 (s, 9H).

Example 56. Method AF: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-3-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid (190).



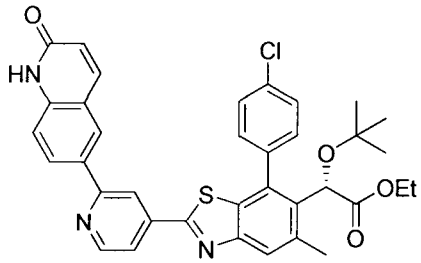
Preparation of 1-methyl-3-(trimethylstannyl)-1*H*-indazole: To a solution of 3-bromo-1-methyl-1*H*-indazole (100 mg, 0.476 mmol) and hexamethylditin (203 mg, 0.619 mmol) in toluene (3.5 mL) was added $Pd(PPh_3)_4$ (198 mg, 0.171 mmol). The reaction was heated at 110°C for 1h. After cooling, the reaction mixture was diluted with EtOAc, treated with KF solution and stirred at room temperature for 1h. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 60% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{11}H_{17}N_2Sn$: 297.0; found: 297.0.

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-3-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (35.0mg, 0.066 mmol) and 1-methyl-3-(trimethylstannyl)-1*H*-indazole (24.0 mg, 0.079 mmol) in dioxane (0.9 mL) was added $Pd(PPh_3)_4$ (4.0 mg, 3.03 x 10^{-3} mmol) and CuI (4.0 mg, 0.018

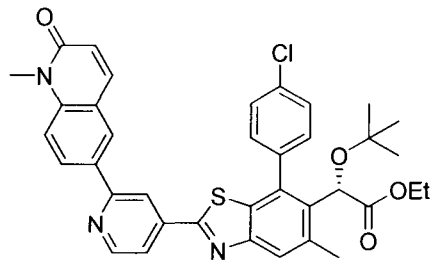
mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 100°C overnight. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 70% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{35}H_{34}ClN_4O_3S$: 625.2; found: 625.3.

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-3-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a stirred solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-3-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (13.5 mg, 0.022 mmol) in THF (0.5 mL) and methanol (0.5 mL) was added 1N NaOH solution (0.5 mL, excess). The reaction mixture was stirred at 50 °C for 2h and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{33}H_{30}ClN_4O_3S$: 597.2; found: 597.2. 1H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, J = 5.6 Hz, 1H), 8.93 (s, 1H), 8.59 (d, J = 7.6 Hz, 1H), 8.22 (d, J = 5.2 Hz, 1H), 8.07 (s, 1H), 7.75 (d, J = 6.8 Hz, 1H), 7.60 – 7.46 (m, 6H), 5.36 (s, 1H), 4.29 (s, 3H), 2.65 (s, 3H), 1.02 (s, 9H).

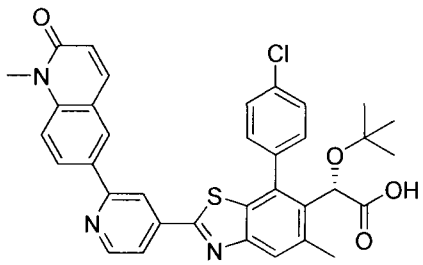
Example 57. Method AG: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid (191).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

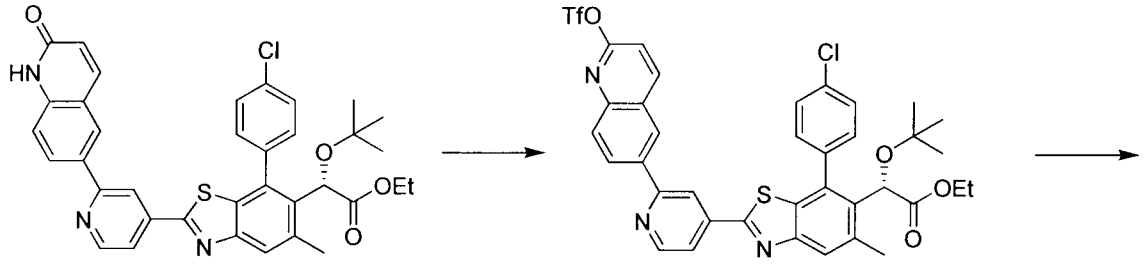
191

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (13.0 mg, 0.020 mmol) in DMF (0.8 mL) was added Cs_2CO_3 (13.0 mg, 0.041 mmol) and methyl iodide (3.0 μL, 0.050 mmol). The reaction mixture was heated at 80°C for 3h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{37}H_{35}ClN_3O_4S$: 652.2; found: 652.3.

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a stirred solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (5.2 mg, 0.008 mmol) in THF (0.4 mL) and methanol (0.4 mL) was added 1N NaOH solution (0.4 mL, excess). The reaction mixture was stirred at 50 °C for 2h and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{35}H_{31}ClN_3O_4S$: 624.2; found: 624.2. ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 5.2

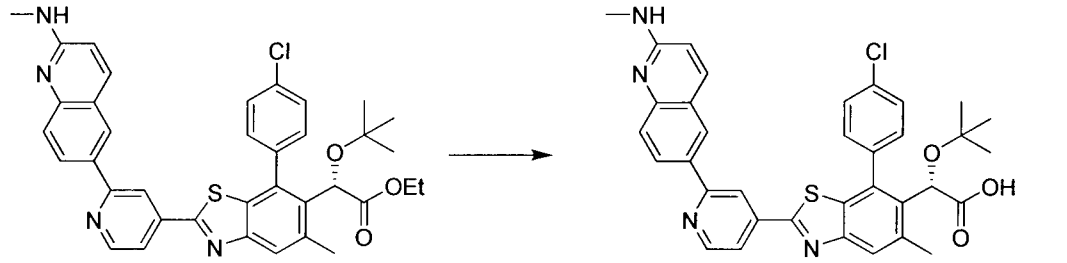
Hz, 1H), 8.49 (s, 1H), 8.41 (s, 1H), 8.36 (d, J = 7.6 Hz, 1H), 8.00 (s, 1H), 7.94 (s, 1H), 7.85 (d, J = 9.6 Hz, 1H), 7.74 (d, J = 6.8 Hz, 1H), 7.58 – 7.47 (m, 4H), 6.81 (d, J = 9.6 Hz, 1H), 5.35 (s, 1H), 3.79 (s, 3H), 2.63 (s, 3H), 1.03 (s, 9H).

Example 58. Method AH: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(methylamino)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid (192).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(trifluoromethylsulfonyloxy)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(methylamino)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(methylamino)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

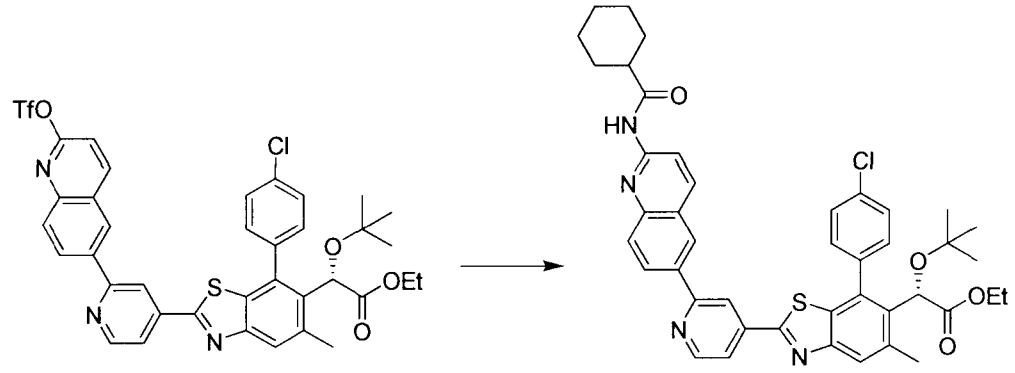
192

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(trifluoromethylsulfonyloxy)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate: To a stirred and cooled (-78 °C) solution *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-oxo-1,2-dihydroquinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (110 mg, 0.172 mmol) in CH_2Cl_2 (2.0 mL) was added pyridine (70 µL, 0.863 mmol), followed by trifluoromethanesulfonic anhydride (116 µL, 0.691 mmol). The solution was warmed to 0 °C over period of 2h. Quenched the reaction by water and diluted with EtOAc, extracted with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{37}H_{32}ClF_3N_3O_6S_2$: 770.1; found: 770.1.

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(methylamino)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate: *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(trifluoromethylsulfonyloxy)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (28.0 mg, 0.036 mmol) and 1.0 mL of methylamine at 2M in THF were heating at 80 °C for 3 days. Concentrated in vacuo and then purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{37}H_{36}ClN_4O_3S$: 651.2; found: 651.3.

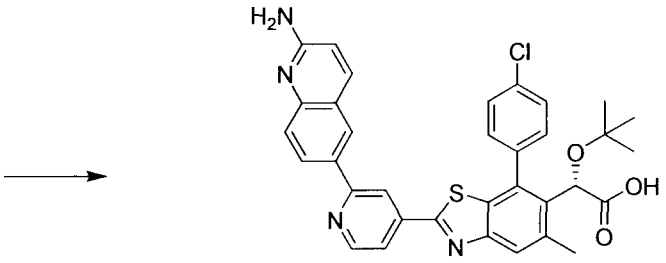
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(methylamino)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a stirred solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(methylamino)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (4.1 mg, 0.006 mmol)) in pyridine (0.4 mL) was added LiI (50 mg, excess). The reaction mixture was heating in a microwave at 170 °C for 90 min. The mixture was concentrated in vacuo and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{35}H_{32}ClN_4O_3S$: 623.2; found: 623.2. ^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (d, J = 5.2 Hz, 1H), 8.60 (s, 1H), 8.57 (s, 1H), 8.53 (d, J = 8.8 Hz, 1H), 8.34 (d, J = 9.6 Hz, 1H), 8.22 – 7.20 (m, 3H), 7.70 (d, J = 9.2 Hz, 1H), 7.61 (s, 3H), 7.07 (d, J = 8.4 Hz, 1H), 5.28 (s, 1H), 3.24 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H).

Example 59. Method AI: Preparation of *(S)*-2-(2-(2-(2-aminoquinolin-6-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid (193).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(trifluoromethylsulfonyloxy)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(cyclohexanecarboxamido)quinolin-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-(2-(2-(2-aminoquinolin-6-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid

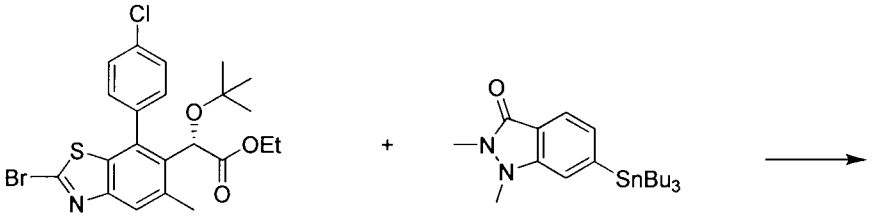
193

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(cyclohexanecarboxamido)quinolin-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-(trifluoromethylsulfonyloxy)quinolin-6-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (28.4 mg, 0.037 mmol) in anhydrous dioxane (0.6 mL) was added cyclohexanecarboxamide (7.0 mg, 0.055 mmol), Xantphos (2.0 mg, 0.004 mmol), Cs_2CO_3 (36.0 mg, 0.111 mmol) and $Pd_2(dba)_3$ (2.0 mg, 0.002 mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 100°C for 2h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{43}H_{44}ClN_4O_4S$: 747.3; found: 747.2.

Preparation of *(S)*-2-(2-(2-(2-aminoquinolin-6-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid: To a stirred solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(cyclohexanecarboxamido)quinolin-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (12.0 mg, 0.016 mmol) in THF (0.4 mL) and methanol (0.4 mL) was added 1N NaOH solution (0.4 mL, excess). The reaction mixture was stirred at 50 °C

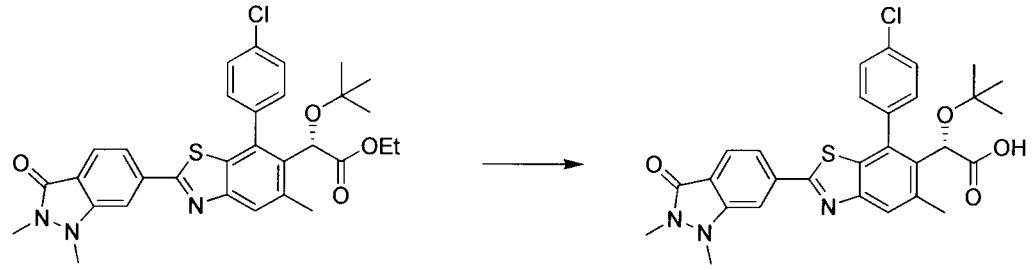
for 2h and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{34}H_{30}ClN_4O_3S$: 609.2; found: 609.2. 1H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 5.6 Hz, 1H), 8.51 (s, 1H), 8.45 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.06 (d, J = 0.8 Hz, 1H), 8.00 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.59 – 7.45 (m, 3H), 6.94 (d, J = 8.8 Hz, 1H), 5.36 (s, 1H), 2.62 (s, 3H), 1.03 (s, 9H).

Example 60. Method AJ: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-3-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid (194).



(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

1,2-dimethyl-6-(tributylstannyl)-1*H*-indazol-3(2*H*)-one



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

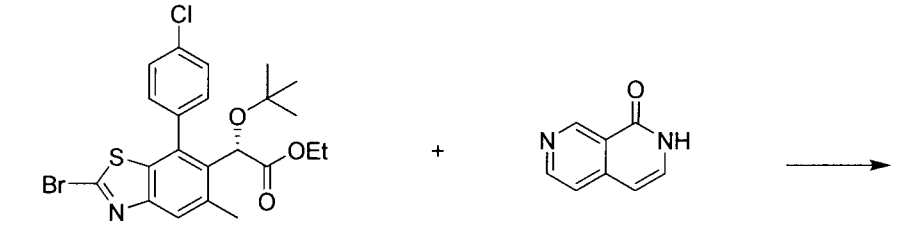
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

194

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate (30.0mg, 0.060 mmol) and 1,2-dimethyl-6-(tributylstannyl)-1*H*-indazol-3(2*H*)-one (32.5 mg, 0.072 mmol) in dioxane (0.7 mL) was added $Pd(PPh_3)_4$ (7.0 mg, 0.006 mmol), CuI (4.0 mg, 0.018 mmol) and LiCl (8.0 mg, 0.182 mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 100°C for 7h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{31}H_{33}ClN_3O_4S$: 578.2; found: 578.3.

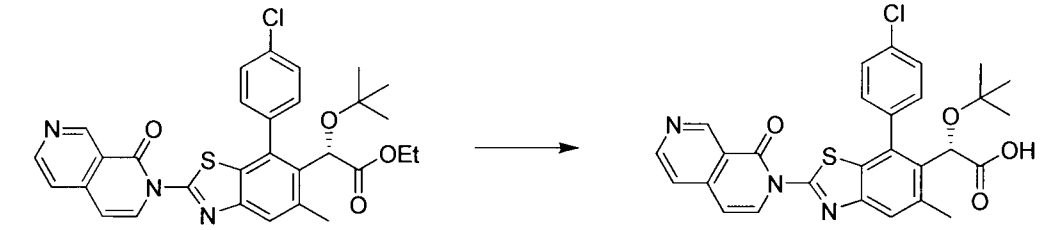
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a stirred solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-3-oxo-2,3-dihydro-1*H*-indazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (27.2 mg, 0.047 mmol) in THF (1.0 mL) and methanol (1.0 mL) was added 1N NaOH solution (0.5 mL, excess). The reaction mixture was stirred at 50 °C for 2h and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{29}H_{29}ClN_3O_4S$: 550.2; found: 550.2. ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.96 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.93 (dd, J = 8.0, 0.8 Hz, 2H), 7.55 – 7.49 (m, 3H), 5.33 (s, 1H), 3.50 (s, 3H), 3.39 (s, 3H), 2.60 (s, 3H), 1.01 (s, 9H).

Example 61. Method AK: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxo-2,7-naphthyridin-2(1*H*)-yl)benzo[*d*]thiazol-6-yl)acetic acid (195).



(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

2,7-naphthyridin-1(2*H*)-one



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxo-2,7-naphthyridin-2(1*H*)-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxo-2,7-naphthyridin-2(1*H*)-yl)benzo[*d*]thiazol-6-yl)acetic acid

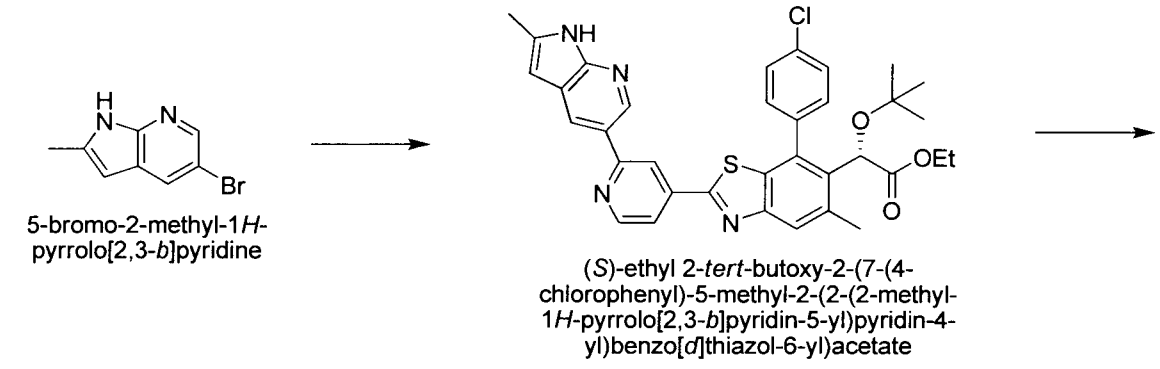
195

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxo-2,7-naphthyridin-2(1*H*)-yl)benzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate (36.7 mg, 0.076 mmol) and 2,7-naphthyridin-1(2*H*)-one (14.0 mg, 0.092 mmol) in DMF (0.9 mL) was added CuI (9.0 mg, 0.046 mmol) and trans-N_1,N_2-dimethylcyclohexane-1,2-diamine (15 μL, 0.092 mmol) and K_2CO_3 (21.0 mg, 0.152 mmol). The reaction was heated at 110°C for 2h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered

and concentrated and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{30}H_{29}ClN_3O_4S$: 562.2; found: 562.3.

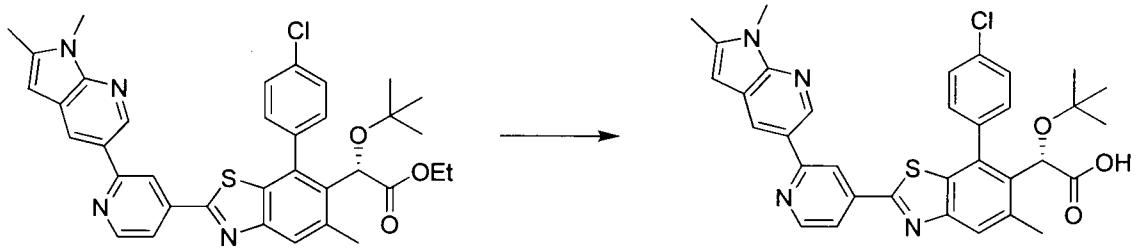
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxo-2,7-naphthyridin-2(1*H*)-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a stirred solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxo-2,7-naphthyridin-2(1*H*)-yl)benzo[*d*]thiazol-6-yl)acetate (18.8 mg, 0.034 mmol)) in pyridine (0.8 mL) was added LiI (100 mg, excess). The reaction mixture was heating in a microwave at 170 °C for 90 min. The mixture was concentrated in vacuo and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+ (m/z): [M+H]+ calcd for $C_{28}H_{25}ClN_3O_4S$: 534.1; found: 534.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 9.27 (d, J = 7.6 Hz, 1H), 8.93 (s, 1H), 7.89 (s, 1H), 7.79 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.58 – 7.50 (m, 3H), 6.93 (d, J = 7.6 Hz, 1H), 5.36 (s, 1H), 2.59 (s, 3H), 1.01 (s, 9H).

Example 62. Method AL: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (196).



5-bromo-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

196

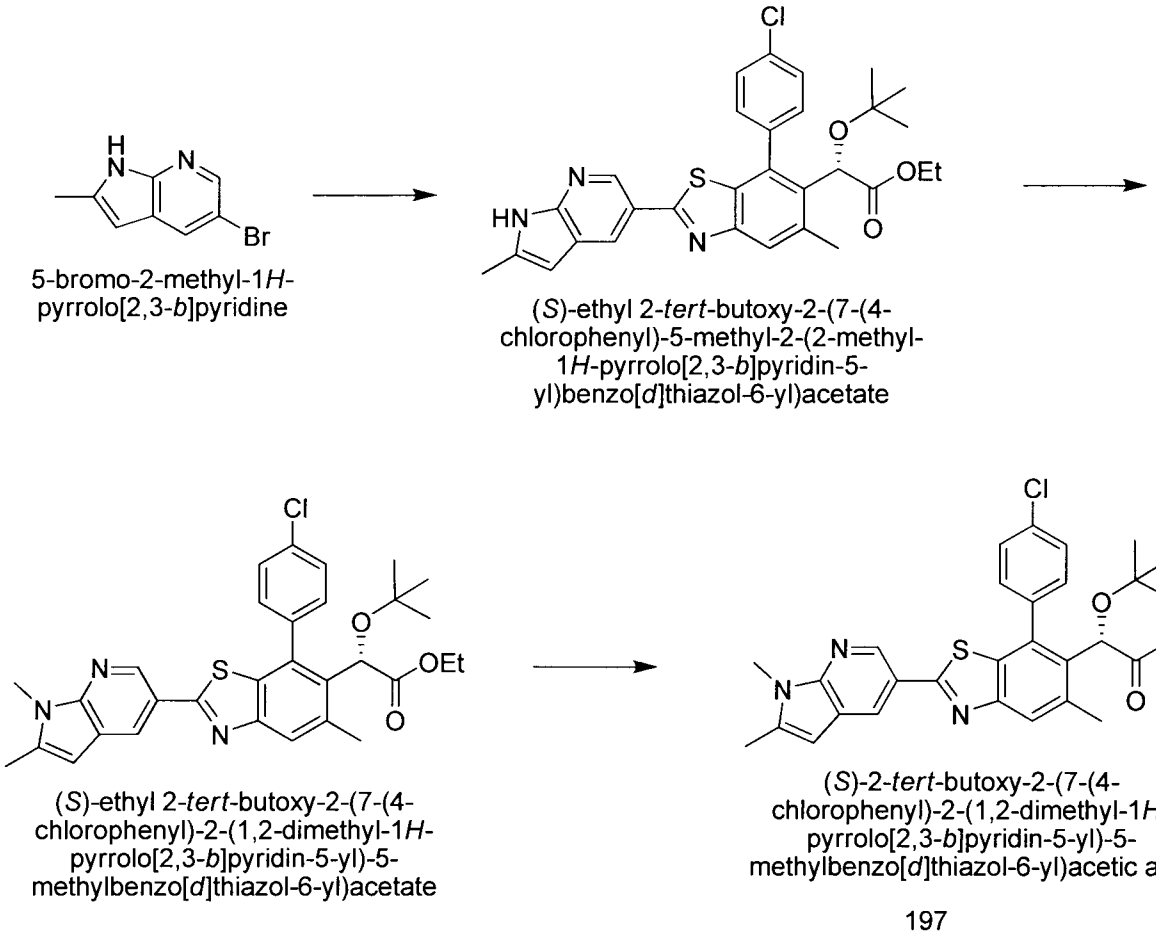
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)benzo[*d*]thiazol-6-yl)acetate: To a solution of 5-bromo-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (60 mg, 0.284 mmol) in dioxane (3 mL) was added bis(pinacolato)diboron (87 mg, 0.341 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (23 mg, 0.028 mmol), potassium acetate (84 mg, 0.852 mmol). The mixture was degassed and heated at 100 °C for 2 h. The mixture was cooled, and then added *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (100 mg, 0.189 mmol), tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.019 mmol), K_2CO_3 (131 mg, 0.948 mmol) and water (1 mL, degassed). The reaction mixture was heated at 110 °C for 1 h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4 and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{35}H_{33}ClN_4O_3S$: 625.2 ($M+H^+$); Found: 625.3 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)benzo[*d*]thiazol-6-yl)acetate (100 mg, 0.16 mmol) in DMF (5mL) was added cesium carbonate (68 mg, 0.208 mmol). The reaction solution was stirred at room temperature for 5 minutes, iodomethane (30 mg, 0.208mmol) was added. The reaction solution was stirred for 30 minutes and quenched with water. The mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{36}H_{35}ClN_4O_3S$: 639.2 ($M+H^+$); Found: 639.3 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (70 mg, 0.110 mmol) in THF/CH_3OH (1.0 mL/1.0 mL) was added 2N NaOH (0.55mL, 1.1 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 H_2O with 0.1% TFA to give the product.

LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_4O_3S$: 611.2 ($M+H^+$); Found: 612.2 ($M + H^+$), ^1H NMR (400 MHz, CD_3OD) δ 8.91 (s, 1H), 8.83 (d, J = 5.2 Hz, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.08 (d, J = 5.6 Hz, 1H), 8.04 (s, 1H), 7.80(d, J = 8.8 Hz, 1H), 7.71(s, 2H), 5.59 (s, 1H), 5.38 (s, 1H), 3.91 (s, 3H), 2.73 (s, 3H), 2.60(s, 3H), 1.08 (s, 9H).

Example 63. Method AM: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (197).



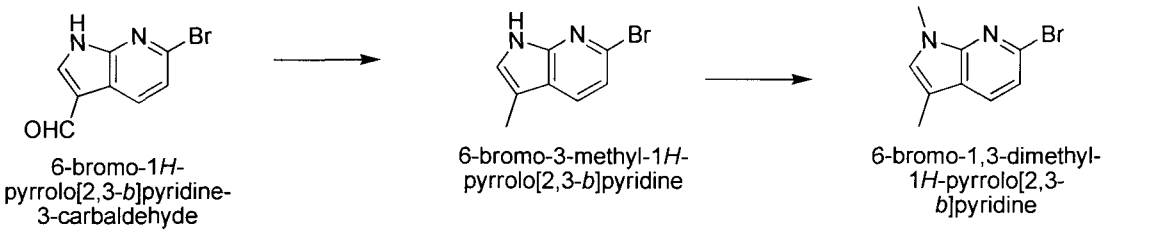
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetate: To a solution of 5-bromo-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (85 mg, 0.403 mmol) in dioxane (4 mL) was added bis(pinacolato)diboron (123 mg, 0.483 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (33 mg, 0.040 mmol), potassium acetate (120 mg, 1.21mmol). The mixture was degassed and heated at 100 °C for 2 h. The mixture was cooled, and then added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (100 mg, 0.201 mmol),

tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.02 mmol), K_2CO_3 (139 mg, 1.00 mmol) and water (1.3 mL, degassed). The reaction mixture was heated at 100 °C for 1 h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4 and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{30}H_{30}ClN_3O_3S$: 548.3 ($M+H^+$); Found: 548.3 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetate (70 mg, 0.128 mmol) in DMF (5 mL) was added cesium carbonate (54 mg, 0.166 mmol). The reaction solution was stirred at room temperature for 5 minutes, then iodomethane (24 mg, 0.166 mmol) was added. The reaction solution was stirred for 30 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 ($MgSO_4$) and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{32}ClN_3O_3S$: 562.3 ($M+H^+$); Found: 562.3 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: (49 mg, 0.09 mmol) in THF/CH_3OH (1.0 mL/1.0 mL) was added 2N NaOH (0.44mL, 0.9 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 H_2O with 0.1% TFA to give the product. LCMS-ESI$^+$: calc'd for $C_{29}H_{28}ClN_3O_3S$: 534.2 ($M+H^+$); Found: 534.2 ($M+H^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (d, J = 1.6 Hz, 1H), 8.41 (d, J = 2 Hz, 1H), 7.82 (s, 1H), 7.70-7.58 (m, 5H), 5.25 (s, 1H), 3.80 (s, 3H), 2.61 (s, 3H), 2.49 (s, 3H), 0.97 (s, 9H).

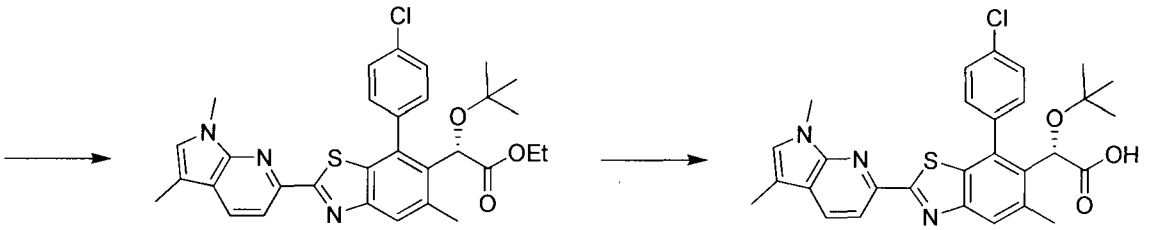
Example 64. Method AN: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (198).



6-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde

6-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine

6-bromo-1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

198

Preparation of 6-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine: LAH(1.0M in THF, 4.45 mL, 4.45 mmol) was added dropwise to refluxing 6-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (1000 mg, 4.45 mmol) in dry THF (16 mL). The mixture was refluxed for 1 h, allowed to attain room temperature, and quenched with water (0.34 mL), w/w 15% aq. NaOH (0.34 mL) and water (1mL). The resulting precipitation was filtered off, the filtrate concentrated and the residue was partitioned between aqueous NaOH and DCM. The organic layers were combined, dried and concentrated to give title compound. LCMS-ESI$^+$: calc'd for $C_8H_7BrN_2$: 211.2 ($M+H^+$); Found: 211.2 ($M+H^+$).

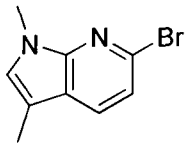
Preparation of 6-bromo-1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine: To a solution of 6-bromo-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (250 mg, 1.18 mmol) in DMF (6mL) was added cesium carbonate (502 mg, 1.54 mmol). The reaction solution was stirred at room temperature for 5 minutes, then iodomethane (219 mg, 1.54mmol) was added. The reaction solution was stirred for 30 minutes and quenched with water. The mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_9H_9BrN_2$ 225.2 ($M+H^+$); Found: 225.2 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of 6-bromo-1,3-

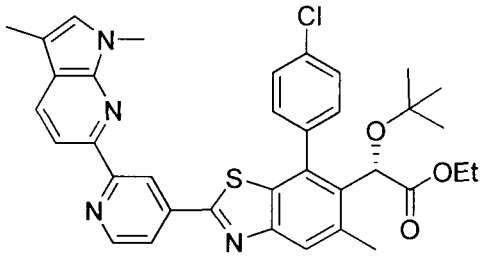
dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine (30 mg, 0.133 mmol) in dioxane (1.4 mL) was added bis(pinacolato)diboron (41 mg, 0.16 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (11 mg, 0.013 mmol), potassium acetate (39 mg, 0.4 mmol). The mixture was degassed and heated at 100 °C for 2 h. The mixture was cooled, and then added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (33 mg, 0.07 mmol), tetrakis(triphenylphosphine)palladium(0) (8 mg, 0.007 mmol), K_2CO_3 (48 mg, 0.35 mmol) and water (0.5 mL, degassed). The reaction mixture was heated at 100 °C for 1 h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4 and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{32}ClN_3O_3S$: 562.3 ($M+H^+$); Found: 562.3 ($M+H^+$).

Preparation of *(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)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: (37 mg, 0.066 mmol) in THF/CH_3OH (1.0 mL/1.0 mL) was added 2N NaOH (0.33mL, 0.66 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 H_2O with 0.1% TFA to give the product. LCMS-ESI$^+$: calc'd for $C_{29}H_{28}ClN_3O_3S$: 534.2 ($M+H^+$); Found: 534.2 ($M+H^+$); 1H NMR (400 MHz, CD_3OD) δ 8.06-8.00 (m, 2H), 7.82 (s, 1H), 7.70-7.60(m, 4H), 7.24 (s, 1H), 5.26 (s, 1H), 3.81 (s, 3H), 2.61 (s, 3H), 2.32 (s, 3H), 0.87 (s, 9H).

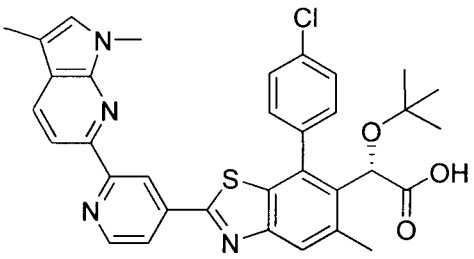
Example 65. Method AO: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (199).



6-bromo-1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



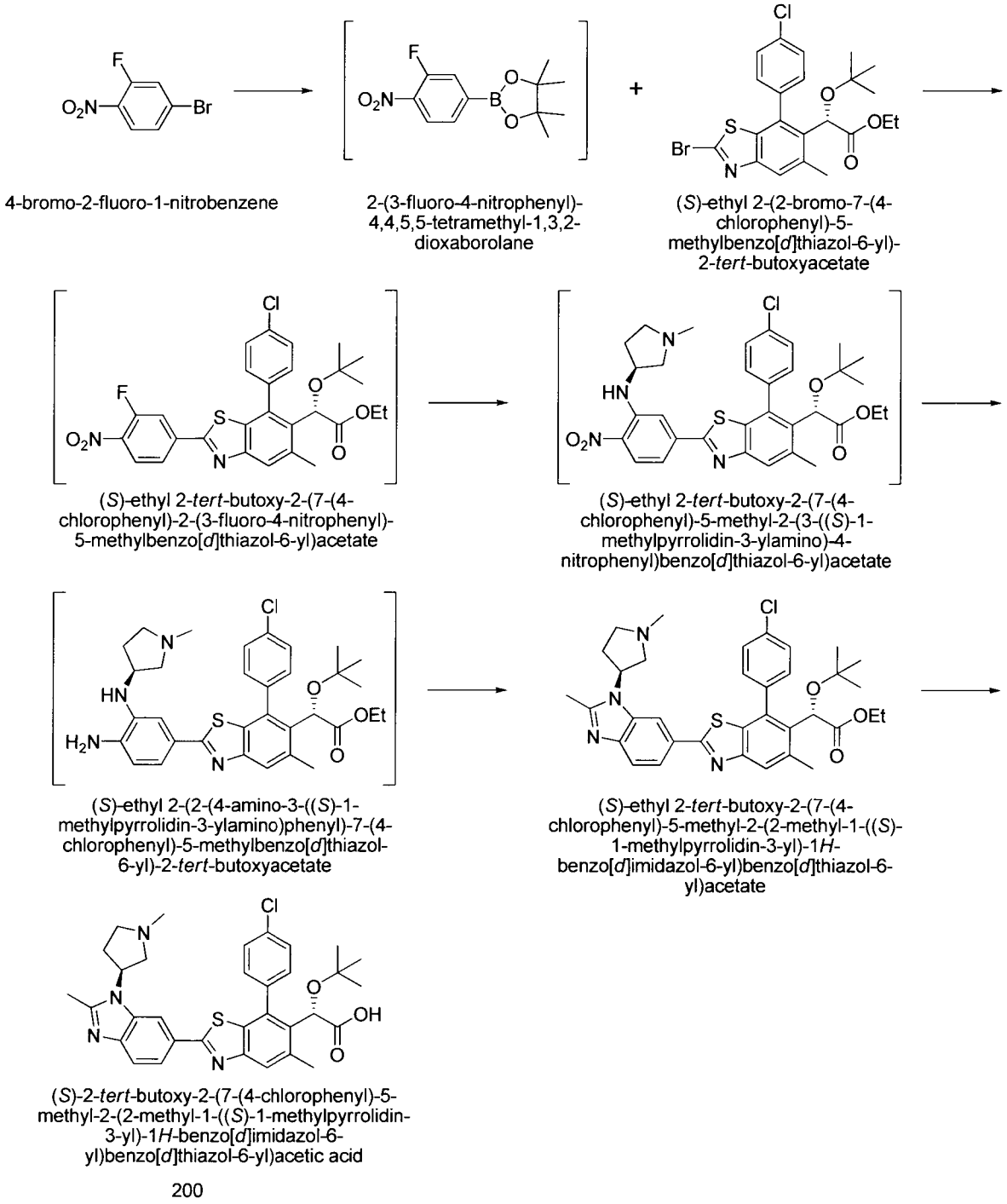
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

199

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl) -2-(2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of 6-bromo-1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine (15 mg, 0.067 mmol) in dioxane (1 mL) was added bis(pinacolato)diboron (20 mg, 0.080 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (5.5 mg, 0.0067 mmol), potassium acetate (20 mg, 0.201 mmol). The mixture was degassed and heated at 100 °C for 2 h. The mixture was cooled, and then added (R)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (24 mg, 0.045 mmol), tetrakis(triphenylphosphine)palladium(0) (5 mg, 0.0045 mmol), K_2CO_3 (31 mg, 0.227 mmol) and water (0.3 mL, degassed). The reaction mixture was heated at 110 °C for 1 h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4 and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{36}H_{35}ClN_4O_3S$: 639.3 ($M+H^+$); Found: 639.3 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3 -dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl) -2-(2-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridine-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: (28 mg, 0.044 mmol) in THF/CH_3OH (1.0 mL/1.0 mL) was added 2N NaOH (0.22mL, 0.44mmol). 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 H_2O with 0.1% TFA to give the product.
LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_4O_3S$: 611.2($M+H^+$); Found: 611.2 ($M + H^+$); ^1H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.79 (d, J = 5.6 Hz, 1H), 8.18-7.64 (m, 8H), 7.32(s, 1H), 5.29 (s, 1H), 3.96 (s, 3H), 2.66 (s, 3H), 2.34(s, 3H), 0.99 (s, 9H).

Example 66. Method AP: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(*(S)*-1-methylpyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid (200).



Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-fluoro-4-nitrophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate: A microwave vial was charged with 4-bromo-2-fluoro-1-nitrobenzene (690 mg, 3.14 mmol), bis(pinacolato)diboron (946 mg, 3.73 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (242 mg, 0.30 mmol), then KOAc (926 mg, 9.44 mmol). The vial was flushed with argon, diluted with dioxane (11 mL), sealed, then heated to 100 °C for 1 hour. The reaction mixture was allowed to cool to room temperature and then a portion of this cooled solution (6.1 mL, 1.74 mmol) was added to a vial that was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (437 mg, 0.88 mmol) and

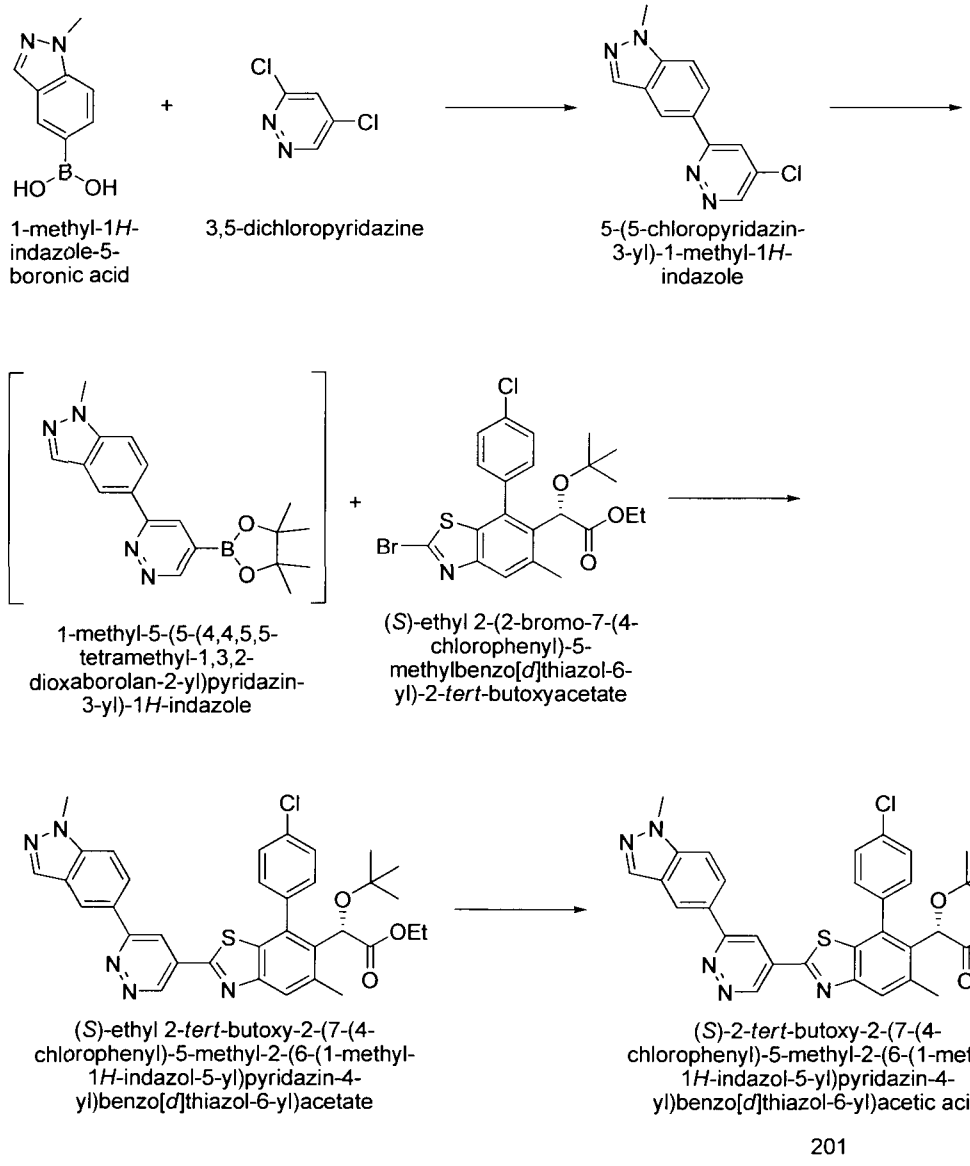
$Pd(PPh_3)_4$ (102 mg, 0.09 mmol). The mixture was diluted with dioxane (2 mL) and to this was added 2M aqueous K_2CO_3 (1.50 mL, 3.00 mmol). The vial was sealed, heated to 100 °C for 1 hour, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (5-30% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{28}H_{27}ClFN_2O_5S$: 557.1 (M + H$^+$); Found: 557.1 (M + H$^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(*(S)*-1-methylpyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate: A flask containing *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-fluoro-4-nitrophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate (83 mg, 0.15 mmol) was charged with Cs_2CO_3 (267 mg, 0.82 mmol) and then diluted with DMF (2 mL). The reaction mixture was then treated with (3*S*)-1-methylpyrrolidin-3-amine (52 mg, 0.52 mmol) at room temperature and allowed to stir for 30 minutes. The mixture was diluted with EtOAc and H_2O, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a crude residue. The flask containing the crude residue was charged with 5 wt% Pt/C (23 mg) and then diluted with 2:1 EtOH/EtOAc (3 mL). The flask was evacuated then backfilled with H_2 (3 cycles) and stirred under a hydrogen atmosphere for 20 minutes, at which time, the flask was purged with N_2, filtered through a pad of Celite, and concentrated *in vacuo* to provide a crude residue. The crude residue was taken up in AcOH (3 mL) and $MeC(OEt)_3$ (0.3 mL) was added at room temperature and stirred for 15 minutes. The solution was concentrated *in vacuo* and the crude residue was purified by reverse phase column chromatography (5-100% ACN/H_2O/0.1% TFA gradient) to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd $C_{35}H_{40}ClN_4O_3S$: 631.3 (M + H$^+$); Found: 631.2 (M + H$^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(*(S)*-1-methylpyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetate (4 mg, 0.006 mmol) in 2:1 MeOH/THF (1.2 mL) was added 2M aqueous NaOH (0.3 mL, 0.6 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O/0.1% TFA gradient). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.09 (dd, J = 8.6, 1.4 Hz,

1H), 7.90 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.75 – 7.67 (m, 1H), 7.67 – 7.53 (m, 3H), 5.85 – 5.61 (br m, 1H), 5.27 (s, 1H), 4.35 – 3.98 (br m, 2H), 3.99 – 3.81 (br m, 1H), 3.65 (br s, 1H), 3.19 (s, 3H), 3.04 – 2.74 (br m, 2H), 2.88 (s, 3H), 2.65 (s, 3H), 0.99 (s, 9H). LCMS-ESI$^+$: calc'd $C_{33}H_{36}ClN_4O_3S$: 603.2 (M + H$^+$); Found: 603.3 (M + H$^+$).

Example 67. Method AR: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridazin-4-yl)benzo[d]thiazol-6-yl)acetic acid (201).



Preparation of 5-(5-chloropyridazin-3-yl)-1-methyl-1H-indazole: 3,5-dichloropyridazine (200 mg, 1.34 mmol), 1-methyl-1*H*-indazole-5-boronic acid (260 mg, 1.48 mmol), K_2CO_3 (556.6 mg, 4.03 mmol), and tetrakis(triphenylphosphine)palladium(0) (233, 0.20 mmol) were taken 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 (10 mL) and degassed water (2.5 mL). The reaction mixture was heated at 95 °C for 2 h then cooled to room temperature. The reaction

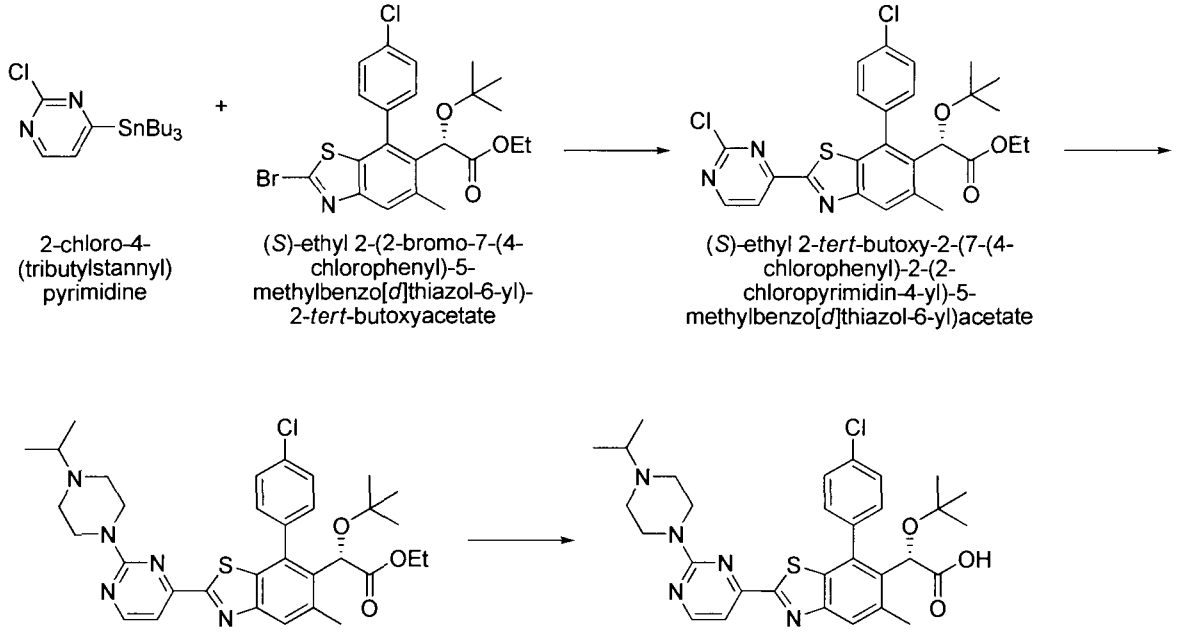
mixture was filtered through Celite (ethyl acetate eluent) and concentrated. Purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the product. LCMS-ESI$^+$: calc'd for $C_{14}H_{10}ClN_4$: 245.1 (M+H$^+$); Found: 245.2 (M + H$^+$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.15 (d, *J* = 2.2 Hz, 1H), 8.44 (s, 1H), 8.21 (dd, *J* = 8.8, 1.5 Hz, 1H), 8.11 (s, 1H), 7.97 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 4.14 (s, 3H).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridazin-4-yl)benzo[d]thiazol-6-yl)acetate: 5-(5-chloropyridazin-3-yl)-1-methyl-1H-indazole (75.0 mg, 0.307 mmol), bis(pinacolato)diboron (101.2 mg, 0.398 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (37.5 mg, 0.046 mmol), and potassium acetate (90.2 mg, 0.920 mmol) were taken in a microwave vial, and the vial was vacuum pumped and flushed with argon three times. To this mixture was added degassed DMF (3 mL). The reaction mixture was heated at 110 °C for 2 h then cooled. To the cooled reaction mixture was added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (180.0 mg, 0.368 mmol), tetrakis(triphenylphosphine)palladium(0) (53.1 mg, 0.046 mmol), K_2CO_3 (127.1 mg, 0.920 mmol) and degassed water (0.5 mL). The reaction mixture was heated to 110 °C for 2 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 $C_{34}H_{33}ClN_5O_3S$ (M + H$^+$): 626.2; Found: 625.5 (M+H$^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridazin-4-yl)benzo[d]thiazol-6-yl)acetic acid: To *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridazin-4-yl)benzo[d]thiazol-6-yl)acetate (92.2 mg, 0.147 mmol) in THF (1.2 mL) and methanol (1.2 mL) was added NaOH (1.2 mL of a 2N solution). The reaction mixture was heated at 45 °C for 5 h, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. The product was taken in THF (0.5 mL) and methanol (0.5 mL), then made basic by addition of NaOH (0.5 mL of a 2N solution). The mixture was purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water. Fractions containing the product were pooled and lyophilized to provide the sodium salt of the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{29}ClN_5O_3S$ (M + H$^+$): 598.2; Found: 598.1 (M+H$^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 9.72 (d, J = 1.8 Hz, 1H), 8.66 (s, 1H), 8.62 (s, 1H), 8.34 – 8.27 (m, 1H), 8.18 (s, 1H), 8.01 – 7.94 (m, 2H), 7.76 (d, J

= 7.6 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.62 – 7.54 (m, 2H), 5.17 (s, 1H), 4.14 (s, 3H), 2.70 (s, 3H), 0.95 (s, 9H).

Example 68. Method AS: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (202).



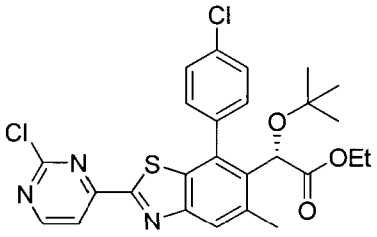
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (500 mg, 1.01 mmol), tetrakis(triphenylphosphine)palladium(0) (174 mg, 0.15 mmol), lithium chloride (128 mg, 3.02 mmol), and copper(I) iodide (57.5 mg, 0.3 mmol) were taken in a microwave vial, and the vial was vacuum pumped and flushed with argon three times. To this mixture was added 2-chloro-4-(tributyl)stannyl pyrimidine (447 mg, 1.11 mmol) in 1,4-dioxane (10 mL). The reaction mixture was heated at 90 °C overnight, then 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 $C_{26}H_{26}Cl_2N_3O_3S$ (M + H$^+$): 530.1; Found: 529.5 (M+H$^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (250 mg, 0.471

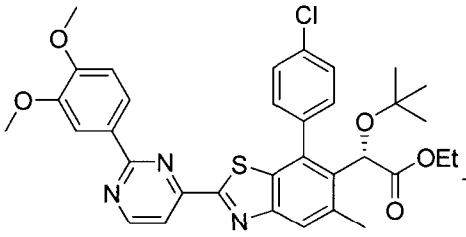
mmol) in 1,4-dioxane (5 mL) was added 1-isopropylpiperazine (302 mg, 2.36 mmol). The reaction mixture was stirred at room temperature for 2.5 h and concentrated to give the product which was used without further purification. LCMS-ESI$^+$ calc'd for $C_{33}H_{41}ClN_5O_3S$ (M + H^+): 622.3; Found: 622.2 (M+H^+).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To crude *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (2.5 mL) and methanol (2.5 mL) was added NaOH (2.63 mL of a 2N solution). The reaction mixture was heated at 45 °C for 1.5 h then 50 °C for 1.5 h, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{31}H_{37}ClN_5O_3S$ (M + H^+): 594.2; Found: 593.9 (M+H^+). ^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (d, J = 5.0 Hz, 1H), 7.92 (s, 1H), 7.69 – 7.64 (m, 1H), 7.64 – 7.47 (m, 4H), 5.25 (s, 1H), 5.02 (br d, J = 13.7 Hz, 2H), 3.66 – 3.51 (m, 3H), 3.29 – 3.14 (m, 4H), 2.63 (s, 3H), 1.40 (d, J = 6.7 Hz, 6H), 0.98 (s, 9H).

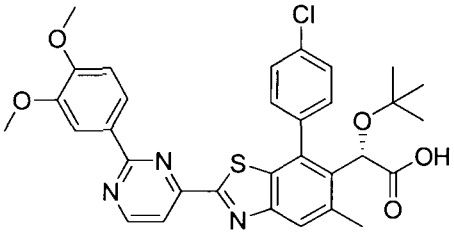
Example 69. Method AT: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3,4-dimethoxyphenyl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (203).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3,4-dimethoxyphenyl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3,4-dimethoxyphenyl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

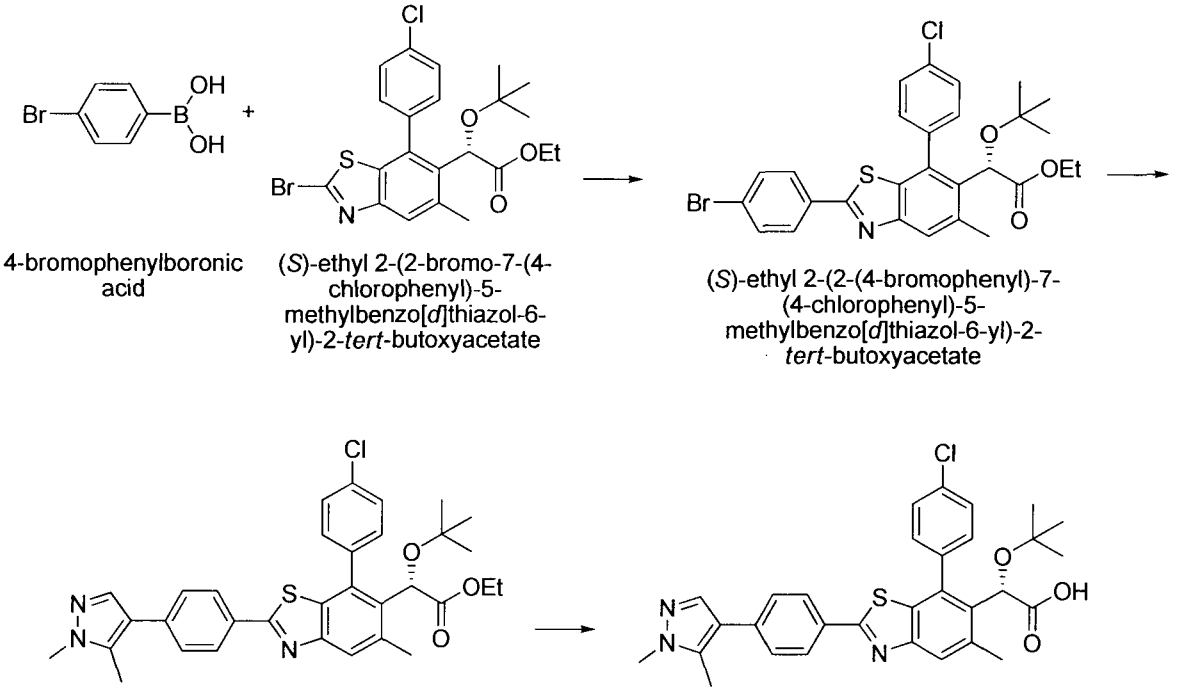
203

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3,4-dimethoxyphenyl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (50.0 mg, 0.094 mmol), 3,4-dimethoxyphenylboronic acid (20.6 mg, 0.113 mmol), tetrakis(triphenylphosphine)palladium(0) (16.4 mg, 0.014 mmol), and K_2CO_3 (39.2 mg, 0.283 mmol) were taken 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 (1 mL) and degassed water (0.25 mL). The reaction mixture was stirred at 110 °C for 1.5 h, 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 $C_{34}H_{35}ClN_3O_5S$ (M + H^+): 632.2; Found: 632.2 (M+H^+).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3,4-dimethoxyphenyl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3,4-dimethoxyphenyl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (51.2 mg, 0.081 mmol) in THF (0.85 mL) and methanol (0.85 mL) was added NaOH (0.85 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100%

acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{31}ClN_3O_5S$ (M + H$^+$): 604.2; Found: 604.1 (M+H$^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (d, J = 5.1 Hz, 1H), 8.12 (dd, J = 8.5, 2.0 Hz, 1H), 8.08 (d, J = 5.1 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.95 (s, 1H), 7.75 – 7.68 (m, 1H), 7.67 – 7.61 (m, 3H), 7.09 (d, J = 8.6 Hz, 1H), 5.29 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.65 (s, 3H), 0.98 (s, 9H).

Example 70. Method AU: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (204).

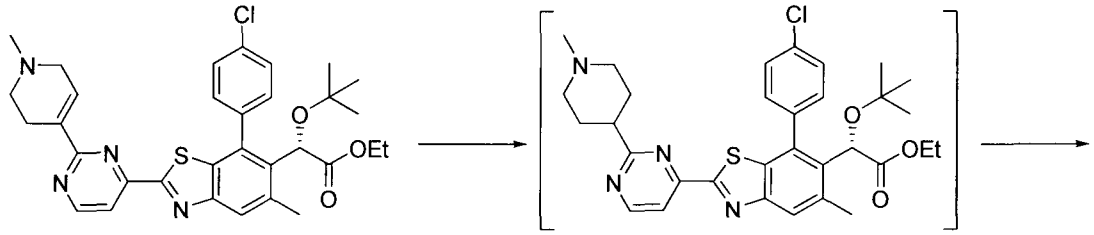


Preparation of *(S)*-ethyl 2-(2-(4-bromophenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (200 mg, 0.403 mmol), 4-bromophenylboronic acid (113 mg, 0.564 mmol), tetrakis(triphenylphosphine)palladium(0) (69.8 mg, 0.060 mmol), and K_2CO_3 (167 mg, 1.208 mmol) were taken 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 (4 mL) and degassed water (1 mL). The reaction mixture was stirred at 75 °C for 5 h, 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 $C_{28}H_{28}BrClNO_3S$ (M + H$^+$): 572.1 and 573.9; Found: 574.2 (M+H$^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetate: *(S)*-ethyl 2-(2-(4-bromophenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (50.0 mg, 0.087 mmol), 1,5-Dimethyl-1H-pyrazole-4-boronic acid, pinacol ester (24.7 mg, 0.105 mmol), tetrakis(triphenylphosphine)palladium(0) (15.1 mg, 0.013 mmol), and K_2CO_3 (36.2 mg, 0.262 mmol) were taken 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 degassed water (0.2 mL). The reaction mixture was stirred at 100 °C for 2.5 h, 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 $C_{33}H_{35}ClN_3O_3S$ (M + H^+): 588.2; Found: 588.3 (M+H^+).

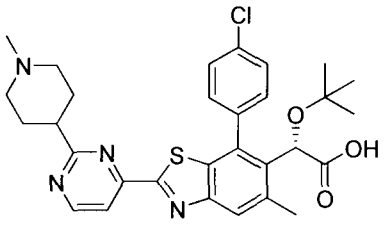
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.5 mL) and water (0.5 mL) was added NaOH (0.5 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{31}H_{31}ClN_3O_3S$ (M + H^+): 560.2; Found: 560.1 (M+H^+). ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 – 8.03 (m, 2H), 7.83 (s, 1H), 7.71 – 7.67 (m, 2H), 7.64 – 7.51 (m, 5H), 5.26 (s, 1H), 3.86 (s, 3H), 2.61 (s, 3H), 2.46 (s, 3H), 0.98 (s, 9H).

Example 71. Method AV: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methylpiperidin-4-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid (205).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methylpiperidin-4-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetate

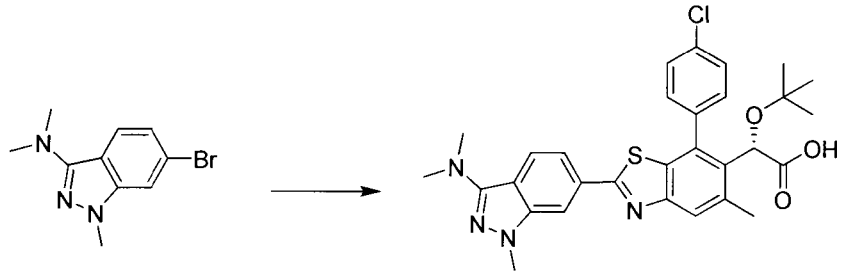


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methylpiperidin-4-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

205

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methylpiperidin-4-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid: To *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate (14.4 mg, 0.024 mmol) in ethanol (0.5 mL) was added rhodium on alumina (2.5 mg, 5 wt.% loading material). The reaction flask was evacuated and flushed with hydrogen three times, then left under a balloon of hydrogen. After 4 h, additional rhodium on alumina (5.0 mg) was added, and the reaction flask evacuated and flushed with hydrogen three additional times. After another 3 h, additional rhodium on alumina (5.0 mg) was added, and the reaction flask evacuated and flushed with hydrogen three additional times. The reaction mixture was stirred under a balloon of hydrogen for 2 days. Upon completion of the reduction, as indicated by LC/MS, the hydrogen balloon was removed. To the crude reaction mixture was added THF (0.5 mL) and NaOH (0.5 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{30}H_{34}ClN_4O_3S$ (M + H^+): 565.2; Found: 565.1 (M+H^+). ^{1}H NMR (400 MHz, CD_3OD) δ 8.94 (d, J = 5.3 Hz, 1H), 8.18 (d, J = 5.2 Hz, 1H), 7.95 (s, 1H), 7.72 – 7.65 (m, 1H), 7.65 – 7.51 (m, 3H), 5.27 (s, 1H), 3.63 (br d, J = 12.2 Hz, 2H), 3.25 – 3.14 (m, 3H), 2.91 (s, 3H), 2.64 (s, 3H), 2.38 (br d, J = 16.0 Hz, 2H), 2.12 (br d, J = 12.3 Hz, 2H), 0.98 (s, 9H).

Example 72. Method AW: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(dimethylamino)-1-methyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (206).



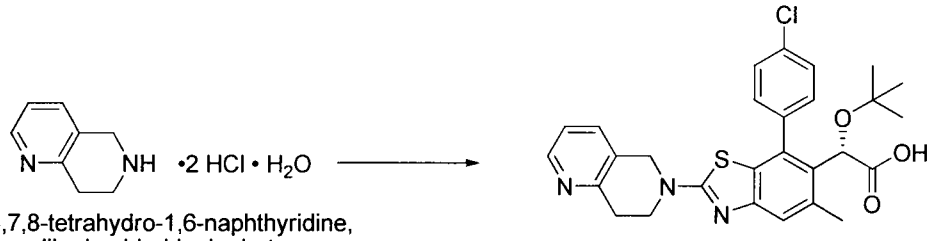
6-bromo-N,N,1-trimethyl-1H-indazol-3-amine

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(dimethylamino)-1-methyl-1*H*-indazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

206

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(dimethylamino)-1-methyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A vial was charged with 6-bromo-N,N,1-trimethyl-1H-indazol-3-amine (102 mg, 0.402 mmol), bis-pinacolatodiboron (112 mg, 0.442 mmol), $PdCl_2(dppf)\cdot DCM$ (33 mg, 40 μmol), glacial AcOH (25 μL, 0.44 mmol), KOAc (130 mg, 1.33 mmol), and dioxane (2.0 mL). The reaction was heated to 100 °C for 30 min. To this reaction was added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (150 mg, 0.302 mmol), 2 M aq K_2CO_3 (884 μL), and $Pd(PPh_3)_4$ (46 mg, 40 μmol). The reaction was heated for another 1 h at 100 °C. Finally, EtOH (absolute, 1.7 mL) and 2 M aqueous NaOH (884μL) were added. The reaction was heated to 100 °C for another 1 h. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{30}H_{31}ClN_4O_3S$: 563.2, 565.2 ($M+H^+$); Found: 563.2, 565.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.01 (s, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.84 (s, 1H), 7.69 (dd, J = 6.3, 3.2 Hz, 1H), 7.65 (dd, J = 8.6, 1.2 Hz, 1H), 7.62 – 7.56 (m, 3H), 5.26 (s, 1H), 3.90 (s, 3H), 3.12 (s, 6H), 2.61 (d, J = 4.8 Hz, 3H), 0.98 (d, J = 4.1 Hz, 9H).

Example 73. Method AX: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (207).



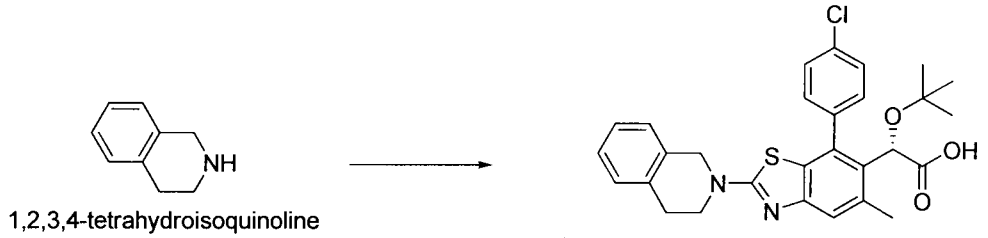
5,6,7,8-tetrahydro-1,6-naphthyridine, dihydrochloride, hydrate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

207

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A vial was charged with 5,6,7,8-tetrahydro-1,6-naphthyridine, dihydrochloride, hydrate (125 mg), DCM (1.5 mL), and 50% w/v aq KOH (200 µL). The vial was shaken. Then H_2O (1.3 mL) was added. The organic phase was collected, dried with a small amount of Na_2SO_4, decanted, and concentrated to give the free base. N,N-dimethylacetamide (500 µL), and *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (25 mg, 50 µmol) were added. The vessel was sealed and heated to 100 °C for 30 min. Then THF (1 mL), EtOH (absolute, 500 µL), and 5 M aq NaOH (500 µL) were added. The reaction was heated to 100 °C for 30 min. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{28}H_{28}ClN_3O_3S$: 522.2, 524.2 (M+H$^+$); Found: 522.3, 524.2 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 8.62 (d, J = 5.6 Hz, 1H), 8.29 (d, J = 8.1 Hz, 1H), 7.78 (dd, J = 7.9, 5.6 Hz, 1H), 7.63 (dd, J = 8.5, 1.9 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.52 – 7.44 (m, 1H), 7.38 (app. s, 1H), 5.15 (s, 1H), 4.96 (s, broad, 2H), 4.03 (t, J = 5.9 Hz, 2H), 3.31 – 3.23 (m, 2H), 2.51 (s, 3H), 0.95 (s, 9H).

Example 74. Method AY: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3,4-dihydroisoquinolin-2(1H)-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (208).



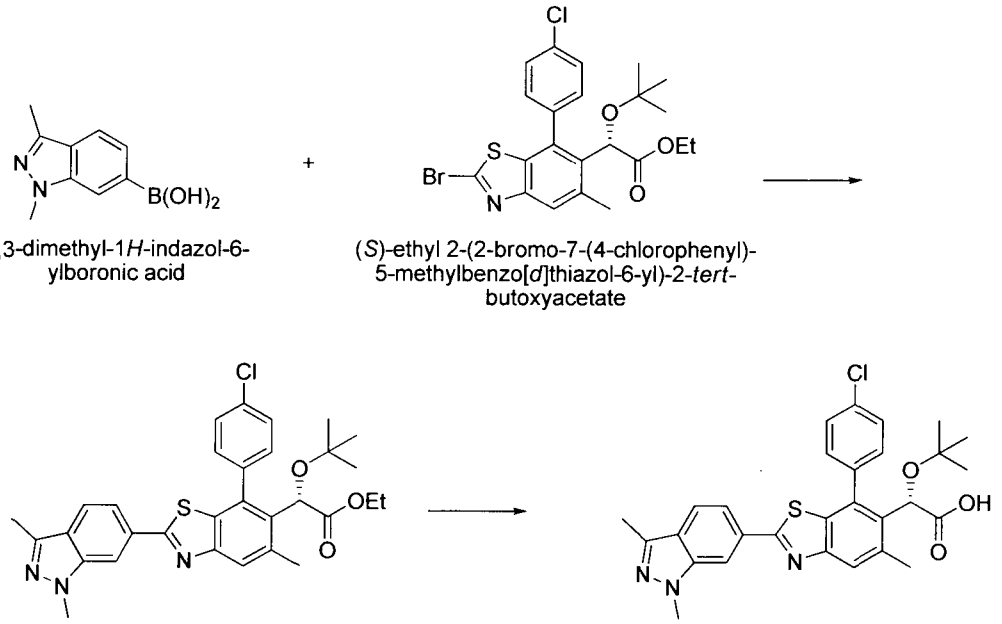
1,2,3,4-tetrahydroisoquinoline

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

208

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3,4-dihydroisoquinolin-2(1H)-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (25 mg, 50 μmol), N,N-dimethylacetamide and 1,2,3,4-tetrahydroisoquinoline (50 μL). The reaction was heated to 100 °C for 30 min. Then THF (1 mL), EtOH (absolute, 500 μL), and 5 M aq NaOH (500 μL) were introduced. The reaction was heated for another 30 min at 100 °C. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{29}H_{29}ClN_2O_3S$: 521.2, 523.2 (M+H$^+$); Found: 521.2, 523.2 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 7.71 – 7.47 (m, 4H), 7.38 (s, 1H), 7.30 – 7.22 (m, 4H), 5.17 (s, 1H), 4.79 (s, 2H), 3.84 (t, J = 6.0 Hz, 2H), 3.09 (t, J = 6.0 Hz, 2H), 2.54 (s, 3H), 0.96 (s, 9H).

Example 75. Method AZ: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (209).



1,3-dimethyl-1*H*-indazol-6-ylboronic acid

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-indazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-indazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

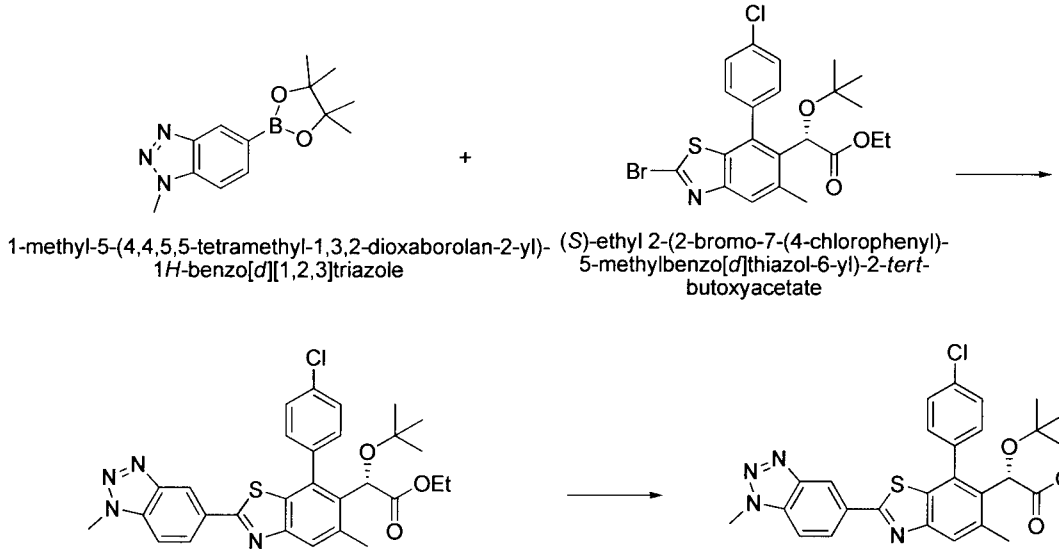
209

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a vial flushed with argon was added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (100 mg, 0.202 mmol), 1,3-dimethyl-1H-indazol-6-ylboronic acid (76 mg, 0.4 mmol), $Pd(PPh_3)_4$ (23 mg, 20 μmol), and K_2CO_3 (83 mg, 0.6 mmol). De-gassed dioxane (1.6 mL) and water (0.4 mL) were then added, and the reaction was heated to 100 °C for 1 h. After cooling to 23 °C, the

reaction was filtered over a plug of Celite, concentrated, and purified by column chromatography (gradient 0 to 30% EtOAc in hexanes) to give the product. LCMS-ESI$^+$: calc'd for $C_{31}H_{33}ClN_3O_3S$: 562.2 ($M+H^+$); Found: 562.3 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a vial was dissolved *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (100 mg, 0.178 mmol) in THF (4 mL) and EtOH (2 mL). 1M NaOH (2 mL) was added, and the mixture was heated to 50 °C overnight. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was was purified by reverse phase HPLC, eluting with 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{29}H_{29}ClN_3O_3S$: 534.1 ($M+H^+$); Found: 534.2 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 8.04 (s, 1H), 7.77 (s, 1H), 7.70 (q, J = 8.7 Hz, 3H), 7.57 (d, J = 6.1 Hz, 3H), 5.25 (s, 1H), 3.98 (s, 3H), 2.59 (s, 3H), 2.51 (s, 3H), 0.97 (s, 9H).

Example 76. Method BA: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (210).



1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*][1,2,3]triazole

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

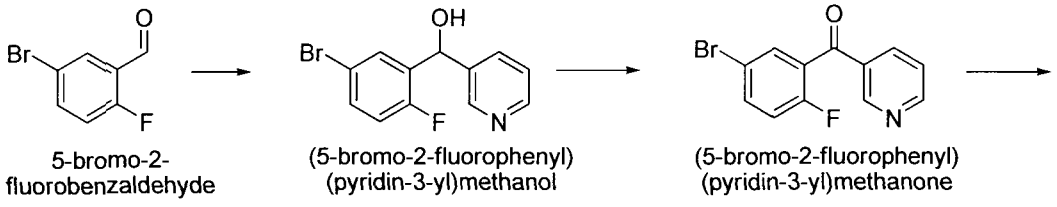
210

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetate: To a vial flushed with argon was added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (100 mg, 0.202 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole (62 mg, 0.24 mmol), $Pd(PPh_3)_4$ (23 mg, 20 μmol), and K_2CO_3 (83 mg,

0.6 mmol). De-gassed dioxane (2 mL) and water (0.5 mL) were then added, and the reaction was heated to 100 °C for 1 h. After cooling to 23 °C, the reaction was filtered over a plug of Celite, concentrated, and purified by column chromatography (gradient 0 to 35% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.31 (dd, J = 8.7, 1.4 Hz, 1H), 7.90 (s, 1H), 7.66 – 7.44 (m, 5H), 5.17 (s, 1H), 4.33 (s, 3H), 4.26 – 4.16 (m, 2H), 2.61 (s, 3H), 1.30 – 1.22 (m, 3H), 0.98 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetic acid: To a vial was dissolved *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetate (100 mg, 0.182 mmol) in THF (3 mL) and EtOH (1.5 mL). 1M NaOH (1.5 mL) was added, and the mixture was heated to 50 °C overnight. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was was purified by reverse phase HPLC, eluting with 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{27}H_{26}ClN_4O_3S$: 521.0 ($M+H^+$); Found: 521.2 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.26 (dd, J = 8.8, 1.5 Hz, 1H), 7.87 (d, J = 9.0 Hz, 2H), 7.70 (dd, J = 7.4, 2.4 Hz, 1H), 7.65 – 7.56 (m, 3H), 5.26 (s, 1H), 4.35 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).

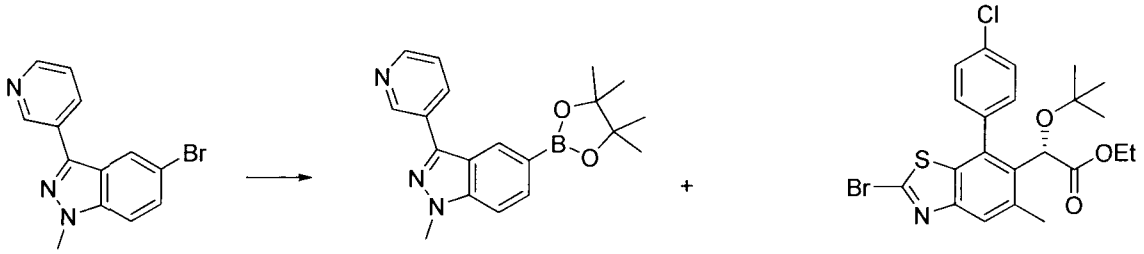
Example 78. Method BC: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (212).



5-bromo-2-fluorobenzaldehyde

(5-bromo-2-fluorophenyl)(pyridin-3-yl)methanol

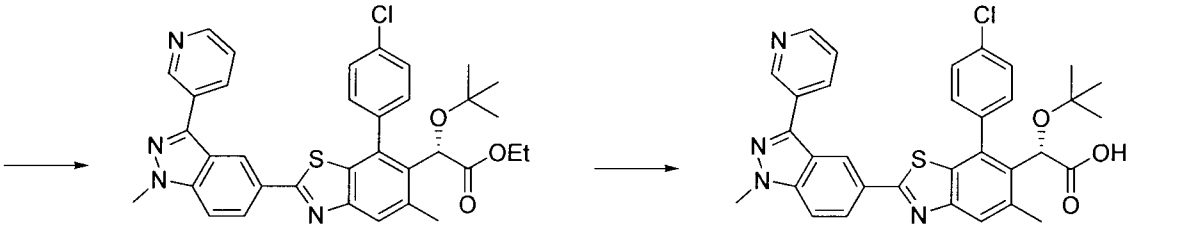
(5-bromo-2-fluorophenyl)(pyridin-3-yl)methanone



5-bromo-1-methyl-3-(pyridin-3-yl)-1*H*-indazole

1-methyl-3-(pyridin-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

212

Preparation of (5-bromo-2-fluorophenyl)(pyridin-3-yl)methanol: To an oven-dried flask was added anhydrous THF (20 mL) and 3-bromopyridine (2 mL, 20 mmol). Isopropylmagnesium chloride in THF (11 mL, 2.0 M solution) was then added dropwise over several minutes. The mixture was stirred at room temperature for 1 hour, and then 5-bromo-2-fluorobenzaldehyde (2.4 mL, 20 mmol) was added. After stirring for 1 further hour at room temperature, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, dried over $MgSO_4$, and purified by column chromatography (gradient 0 to 50% EtOAc in hexanes) to afford the product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.9 Hz, 1H), 8.41 (dd, J = 4.8, 1.5 Hz, 1H), 7.78 – 7.68 (m, 2H), 7.38 (ddd, J = 8.7, 4.6, 2.6 Hz, 1H), 7.27 (dd, J = 8.6, 4.2 Hz, 1H), 6.95 – 6.85 (m, 1H), 6.10 (s, 1H), 4.22 (br s, 1H).

Preparation of (5-bromo-2-fluorophenyl)(pyridin-3-yl)methanone: To a stirring solution of (5-bromo-2-fluorophenyl)(pyridin-3-yl)methanol (3.75 g, 13.3 mmol) in DCM (50 mL) was added Dess-Martin periodinane (6.21 g, 14.6 mmol) portion-wise over several minutes. The reaction was then quenched with saturated 1:1 $Na_2S_2O_3$/$NaHCO_3$ solution (140 mL) and stirred

until gas evolution ceased. The aqueous layer was extracted with DCM, dried over $MgSO_4$, and purified by column chromatography (gradient 0 to 30% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.83 (dd, J = 4.9, 1.7 Hz, 1H), 8.14 (dd, J = 7.9, 0.6 Hz, 1H), 7.73 (dd, J = 6.0, 2.5 Hz, 1H), 7.68 (ddd, J = 8.7, 4.5, 2.6 Hz, 1H), 7.47 (dd, J = 8.0, 4.9 Hz, 1H), 7.09 (t, J = 9.0 Hz, 1H).

Preparation of 5-bromo-1-methyl-3-(pyridin-3-yl)-1H-indazole: A heavy wall pressure flask was charged with (5-bromo-2-fluorophenyl)(pyridin-3-yl)methanone (3.417 g, 12.2 mmol) and dioxane (30 mL). Methylhydrazine (1.4 mL, 26.6 mmol) was then added, and the mixture was heated to 100 °C for 16 hours. The crude mixture was concentrated, and purified by column chromatography (gradient 0 to 55% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, J = 2.1 Hz, 1H), 8.65 (dd, J = 4.9, 1.5 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.54 (dd, J = 8.9, 1.7 Hz, 1H), 7.49 (dd, J = 8.0, 4.9 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 4.15 (s, 3H).

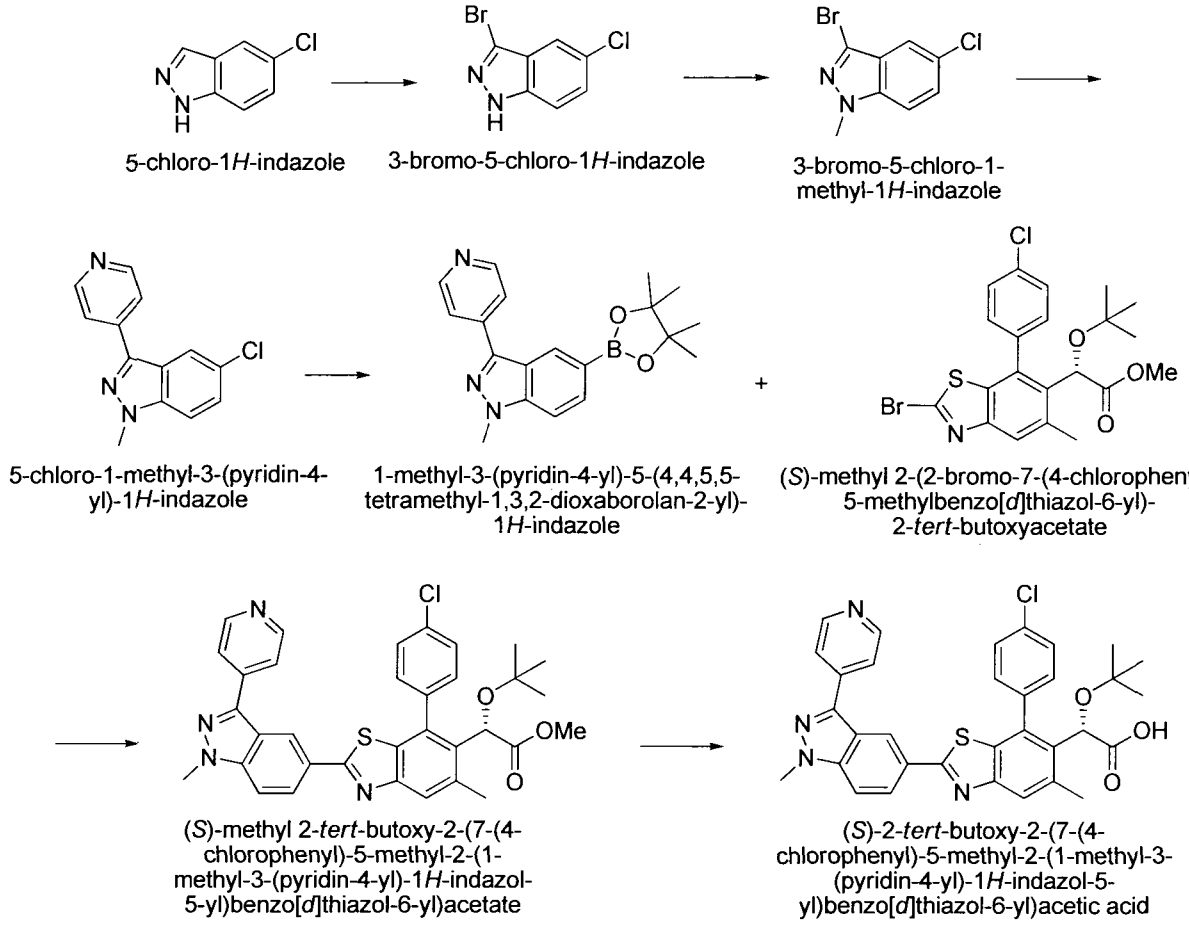
Preparation of 1-methyl-3-(pyridin-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole: To a vial flushed with argon was added 5-bromo-1-methyl-3-(pyridin-3-yl)-1H-indazole (432 mg, 1.5 mmol), $PdCl_2$(dppf)·DCM (123 mg, 0.15 mmol), bis(pinacolato)diboron (419 mg, 1.65 mmol), and KOAc (442 mg, 4.5 mmol). Anhydrous dioxane (8 mL) was added, and the mixture was heated to 90 °C for 3 hours. After cooling to room temperature, the crude reaction was filtered over a plug of Celite, concentrated, and purified by column chromatography (gradient 0 to 60% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, J = 1.6 Hz, 1H), 8.64 (dd, J = 4.8, 1.4 Hz, 1H), 8.50 (s, 1H), 8.30 (dt, J = 7.8, 1.8 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.49 – 7.39 (m, 2H), 4.14 (s, 3H), 1.38 (s, 12H).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate: To a vial flushed with argon was added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (75 mg, 0.15 mmol), 1-methyl-3-(pyridin-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (60.4 mg, 0.18 mmol), $Pd(PPh_3)_4$ (17.4 mg, 15 μmol), and K_2CO_3 (62.2 mg, 0.45 mmol). De-gassed dioxane (1.6 mL) and water (0.4 mL) were then added, and the reaction was heated to 100 °C for 1 h. After cooling to 23 °C, the reaction was filtered over a plug of Celite, concentrated, and purified by column chromatography (gradient 0 to 70%

EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.67 (d, *J* = 3.6 Hz, 1H), 8.58 (s, 1H), 8.33 (d, *J* = 7.7 Hz, 1H), 8.19 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.87 (s, 1H), 7.60 – 7.45 (m, 6H), 5.17 (s, 1H), 4.34 – 4.08 (m, 5H), 2.61 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.99 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid: To a vial was dissolved *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate (69 mg, 0.11 mmol) in THF (2 mL) and EtOH (1 mL). 1M NaOH (1 mL) was added, and the mixture was heated to 50 °C for 15 hours. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was was purified by reverse phase HPLC, eluting with 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product as a light yellow powder. LCMS-ESI$^+$: calc'd for $C_{33}H_{30}ClN_4O_3S$: 597.1 ($M+H^+$); Found: 597.2 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 9.32 (s, 1H), 8.89 (d, *J* = 8.1 Hz, 1H), 8.72 (d, *J* = 4.5 Hz, 1H), 8.66 (s, 1H), 8.09 (dd, *J* = 8.9, 1.4 Hz, 1H), 7.95 (dd, *J* = 7.9, 5.5 Hz, 1H), 7.79 (s, 1H), 7.76 – 7.67 (m, 2H), 7.63 – 7.52 (m, 3H), 5.26 (s, 1H), 4.17 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).

Example 79. Method BD: Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-4-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (213).



213

Preparation of 3-bromo-5-chloro-1H-indazole: A flask was charged with 5-chloro-1H-indazole (4.9 g, 32.11 mmol) and DMF (30 mL). It was then cooled to 0 °C, and a solution of bromine (2.4 mL, 46.86 mmol) in DMF (30 mL) was added over several minutes. After addition was complete, the flask was warmed to rt and stirred for 4 hours. Additional bromine (0.89mL, 16 mmol) was added, and the reaction stirred at room temperature for 20 minutes. The reaction was poured into 600 mL of ice-cold 1% (w/v) $Na_2S_2O_3$ solution, and the precipitated product was filtered off. The product was redissolved in EtOAc (500 mL), washed with saturated aqueous $NaHCO_3$ then brine, dried over Na_2SO_4, and concentrated to afford the product. ^1H NMR (400 MHz, DMSO-d_6) δ 13.60 (br s, 1H), 7.68 – 7.54 (m, 2H), 7.44 (dd, J = 9.0, 1.8 Hz, 1H).

Preparation of 3-bromo-5-chloro-1-methyl-1H-indazole: 3-bromo-5-chloro-1H-indazole (7.5 g, 32.4 mmol) was dissolved in anhydrous DMF (60 mL) then cooled to 0°C. With vigorous stirring, cesium carbonate (13.36 g, 41 mmol) was added in one portion followed by dropwise addition of iodomethane (2.55 mL, 41 mmol). The reaction was then stirred at 0° C for 1 hour. The reaction was diluted with distilled water (80 mL), and extracted with EtOAc (3 x 60 mL).

The organic extracts were washed with brine (2x), dried over Na_2SO_4, and purified by column chromatography (gradient 0 to 15% EtOAc/hexanes) to afford the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.8 Hz, 1H), 7.38 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 4.04 (s, 3H).

Preparation of 5-chloro-1-methyl-3-(pyridin-4-yl)-1H-indazole: To a pressure flask was added 3-bromo-5-chloro-1-methyl-1H-indazole (0.737 g, 3 mmol), pyridine-4-boronic acid (0.996 g, 8.1 mmol), $PdCl_2$(dppf)·DCM (0.490 g, 0.6 mmol), and K_3PO_4 (3.184 g, 15 mmol). The flask was flushed with argon for 5 minutes, then dry DME (15 mL) was added and the flask sealed under argon. The reaction was then heated to 90 °C for 4 hours. Additional $PdCl_2$(dppf)·DCM (0.245 g, 0.3 mmol) and pyridine-4-boronic acid (0.370 g, 3 mmol) were added, and heating was continued for another 14 h at 90 °C. After cooling to room temperature, the crude reaction was filtered over a plug of Celite, concentrated, dissolved in DCM, and purified by column chromatography (gradient 0 to 75% EtOAc/hexanes) to afford the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 6.0 Hz, 2H), 8.02 (d, J = 0.6 Hz, 1H), 7.87 (d, J = 6.1 Hz, 2H), 7.53 – 7.32 (m, 2H), 4.15 (s, 3H).

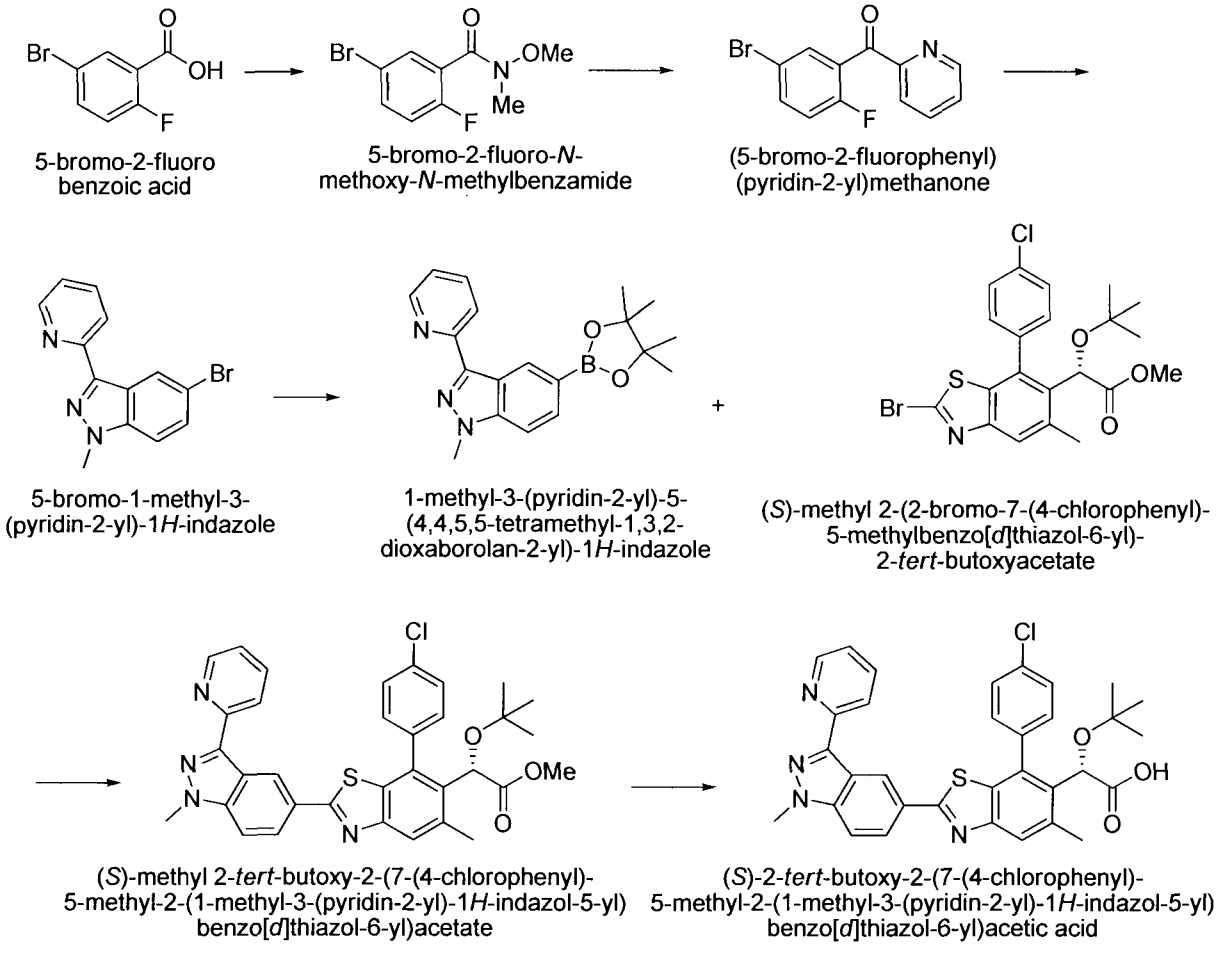
Preparation of 1-methyl-3-(pyridin-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole: To a microwave tube was added 5-chloro-1-methyl-3-(pyridin-4-yl)-1H-indazole (171 mg, 0.7 mmol), bis(pinacolato)diboron (533 mg, 2.1 mmol), $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), X-Phos (13 mg, 0.028 mmol), and KOAc (206 mg, 2.1 mmol). The tube was flushed with argon for 5 minutes, anhydrous dioxane (5 mL) was then added, and the reaction heated to 110 °C for 1 hour. After cooling to room temperature, the crude reaction was filtered over a plug of Celite, concentrated, and purified by column chromatography (gradient 0 to 70% EtOAc/hexanes) to afford the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 6.2 Hz, 2H), 8.53 (s, 1H), 8.05 (d, J = 5.3 Hz, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.53 – 7.39 (m, 1H), 4.14 (s, 3H), 1.39 (s, 12H).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-4-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate: To a vial flushed with argon was added (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (100 mg, 0.207 mmol), 1-methyl-3-(pyridin-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (53 mg, 0.16 mmol), $Pd(PPh_3)_4$ (18 mg, 16 μmol), and K_2CO_3 (66 mg, 0.47 mmol). De-gassed dioxane (2 mL) and water (0.5 mL) were then added, and the

reaction was heated to 100 °C for 1 h. After cooling to 23 °C, the reaction was filtered over a plug of Celite, concentrated, and purified by column chromatography (gradient 0 to 75% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 5.9 Hz, 2H), 8.64 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 5.9 Hz, 2H), 7.89 (s, 1H), 7.61 – 7.39 (m, 5H), 5.21 (s, 1H), 4.18 (s, 3H), 3.75 (s, 3H), 2.60 (s, 3H), 0.99 (s, 9H).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-4-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid: In a vial was dissolved (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(2-methylpyridin-3-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate (100 mg, 0.16 mmol) in THF (3 mL) and EtOH (1.5 mL). 1M NaOH (1.5 mL) was added, and the mixture was heated to 50 °C overnight. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was was purified by reverse phase HPLC, eluting with 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI+: calc'd for $C_{33}H_{30}ClN_4O_3S$: 597.2 (M+H+); Found: 597.2 (M+H+). ^{1}H NMR (400 MHz, CD_3OD) δ 8.77 (d, J = 6.1 Hz, 2H), 8.73 (s, 1H), 8.47 (d, J = 6.3 Hz, 2H), 8.06 (d, J = 8.9 Hz, 1H), 7.78 – 7.70 (m, 3H), 7.60 (dt, J = 11.1, 7.5 Hz, 3H), 5.26 (s, 1H), 4.18 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).

Example 80. Method BE: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-2-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (214).



214

Preparation of 5-bromo-2-fluoro-N-methoxy-N-methylbenzamide: To a suspension of 5-bromo-2-fluorobenzoic acid (29 g, 132 mmol) in anhydrous DCM (500 mL) was added oxalyl chloride (16.8 mL, 199 mmol) and 5 drops of DMF. The suspension was stirred at room temperature for 2 hours. The solvent and excess oxalyl chloride were removed by rotary evaporation, and the residue was dissolved in anhydrous DCM (500 mL). With vigorous stirring, N,O-dimethylhydroxylamine hydrochloride (16.8 g, 172.3 mmol) was added in one portion, followed by triethylamine (80 mL, 574 mmol). The thick suspension was stirred for 1 hour at room temperature and then filtered. The organic layer was washed sequentially with 1M HCl, 1M NaOH, and water, dried over Na_2SO_4, and concentrated to afford the product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 5.7, 2.5 Hz, 1H), 7.50 (ddd, J = 8.7, 4.6, 2.5 Hz, 1H), 7.00 (t, J = 8.8 Hz, 1H), 3.56 (s, 3H), 3.34 (s, 3H).

Preparation of (5-bromo-2-fluorophenyl)(pyridin-2-yl)methanone: An oven-dried flask was cooled under argon, then charged with anhydrous THF (40 mL) and 2-bromopyridine (1.76 mL, 18 mmol). Isopropylmagnesium chloride in tetrahydrofuran (2.0 M in THF, 11 mL) was then added dropwise at room temperature. The mixture was then stirred at room temperature for

2 hours, then cooled to 0 °C, whereupon a THF solution (5 mL) of 5-bromo-2-fluoro-N-methoxy-N-methylbenzamide (3.93 g, 15 mmol) was added. The mixture was then allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched with saturated NH_4Cl, extracted with EtOAc, washed with 10% HCl, dried over Na_2SO_4, and purified by column chromatography (gradient 0 to 10% EtOAc/hexanes) to afford the product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 4.6 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.92 (t, J = 7.7 Hz, 1H), 7.79 (dd, J = 5.8, 1.4 Hz, 1H), 7.67 – 7.59 (m, 1H), 7.52 (dd, J = 7.4, 4.9 Hz, 1H), 7.04 (t, J = 9.0 Hz, 1H).

Preparation of 5-bromo-1-methyl-3-(pyridin-2-yl)-1H-indazole: A heavy wall pressure flask was charged with (5-bromo-2-fluorophenyl)(pyridin-2-yl)methanone (0.98 g, 3.5 mmol) and dioxane (10 mL). Methylhydrazine (0.4 mL, 7.7 mmol) was then added, and the mixture was heated to 100 °C for 15 hours. The crude mixture was concentrated, and purified by column chromatography (gradient 0 to 20% EtOAc in hexanes) to give the product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 7.3 Hz, 1H), 4.12 (s, 3H).

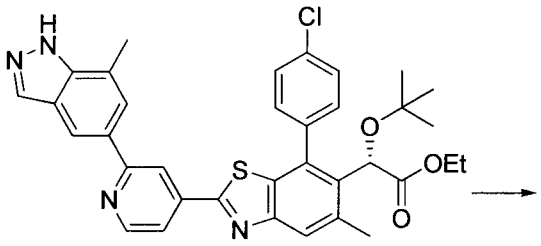
Preparation of 1-methyl-3-(pyridin-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole: To a vial flushed with argon was added 5-bromo-1-methyl-3-(pyridin-2-yl)-1H-indazole (576 mg, 2 mmol), $PdCl_2(dppf)\cdot DCM$ (163 mg, 0.2 mmol), bis(pinacolato)diboron (559 mg, 2.2 mmol), and KOAc (589 mg, 6 mmol). Anhydrous dioxane (10 mL) was added, and the mixture was heated to 90 °C for 3 hours. After cooling to room temperature, the crude reaction was filtered over a plug of Celite, concentrated, and purified by column chromatography (gradient 0 to 25% EtOAc in hexanes) to give the product. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.85 (dd, J = 8.5, 0.6 Hz, 1H), 7.77 (td, J = 7.7, 1.8 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.25 – 7.22 (m, 1H), 4.15 (s, 3H), 1.38 (s, 12H).

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-2-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate: To a vial flushed with argon was added *(S)*-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (100 mg, 0.207 mmol), 1-methyl-3-(pyridin-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (83.3 mg, 0.25 mmol), $Pd(PPh_3)_4$ (24 mg, 21 μmol), and K_2CO_3 (86 mg, 0.62 mmol). De-gassed dioxane (2 mL) and water (0.5 mL) were then added, and the

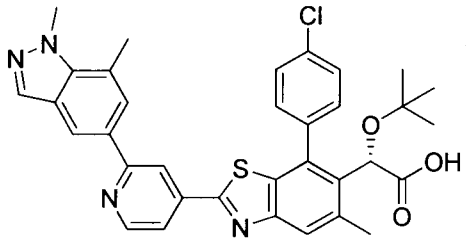
reaction was heated to 100 °C for 1 h. After cooling to rt, the reaction was filtered over a plug of Celite, concentrated, and purified by column chromatography (gradient 0 to 40% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 – 9.15 (m, 1H), 8.84 – 8.77 (m, 1H), 8.25 (dd, *J* = 8.8, 1.7 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H), 7.59 – 7.49 (m, 4H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.29 – 7.24 (m, 1H), 5.21 (s, 1H), 4.17 (s, 3H), 3.75 (s, 3H), 2.59 (s, 3H), 0.98 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-2-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid: To a vial was dissolved *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-2-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate (122 mg, 0.2 mmol) in THF (3 mL) and EtOH (1.5 mL). 1M NaOH (1.5 mL) was added, and the mixture was heated to 50 °C overnight. The reaction was cooled to rt, and filtered (0.45 micron teflon syringe filter). The filtrate was was purified by reverse phase HPLC, eluting with 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product as a bright yellow powder. LCMS-ESI$^+$: calc'd for $C_{33}H_{30}ClN_4O_3S$: 597.1 ($M+H^+$); Found: 597.2 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 8.66 (d, *J* = 4.7 Hz, 1H), 8.33 (d, *J* = 8.1 Hz, 1H), 8.23 (dd, *J* = 11.1, 4.5 Hz, 1H), 8.02 (dd, *J* = 8.9, 1.3 Hz, 1H), 7.76 (s, 1H), 7.75 – 7.68 (m, 1H), 7.65 – 7.53 (m, 5H), 5.26 (s, 1H), 4.14 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).

Example 81. Method BF: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,7-dimethyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (215) and *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2,7-dimethyl-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (216).

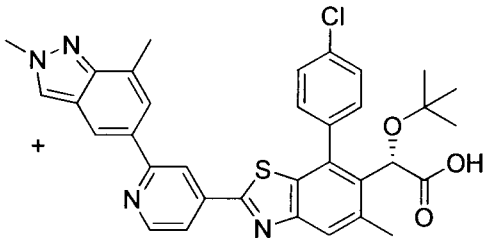


(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(7-methyl-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,7-dimethyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

215



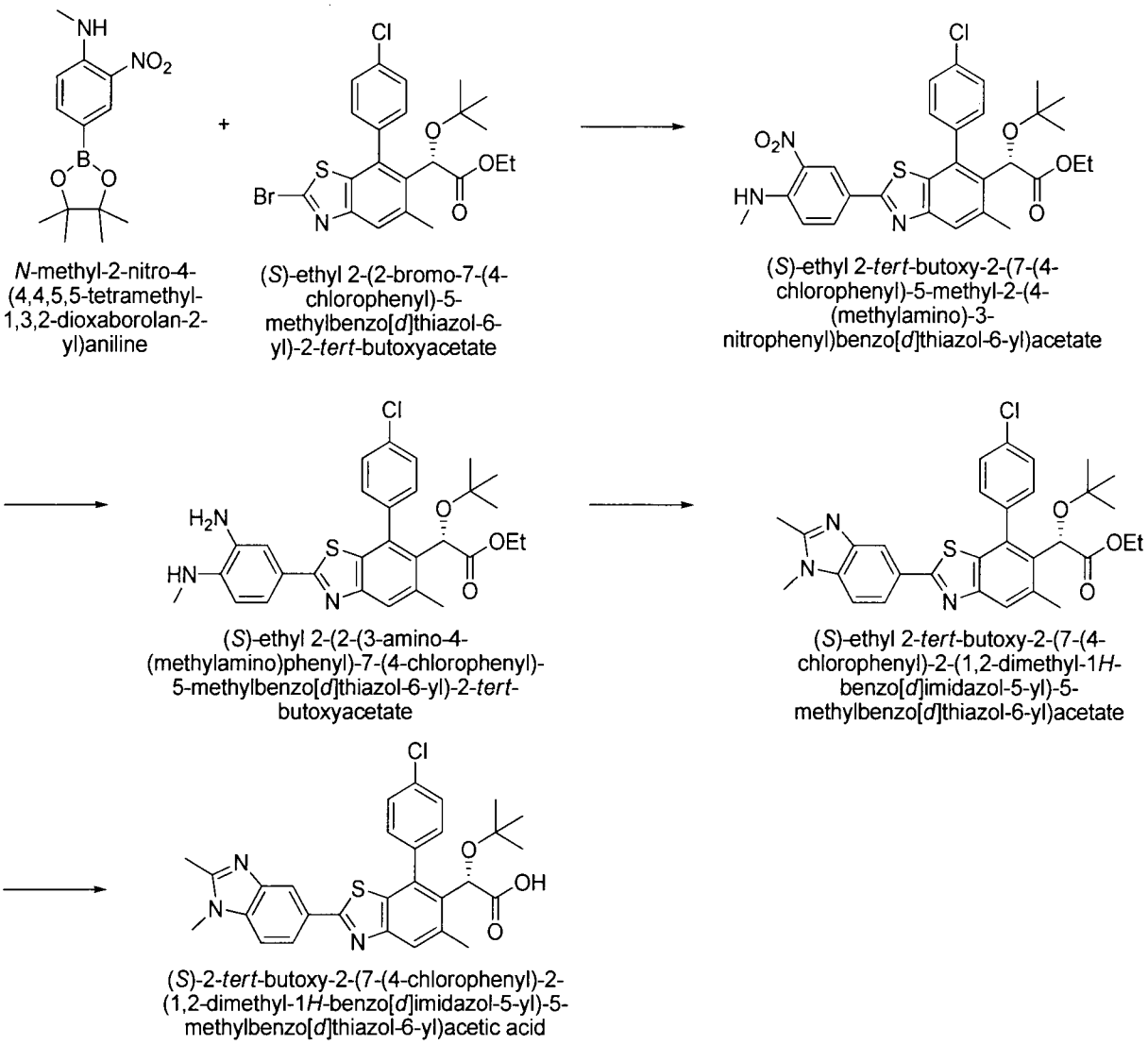
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2,7-dimethyl-2*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

216

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,7-dimethyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid and *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2,7-dimethyl-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(7-methyl-1H-indazol-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate, prepared according to Method F (100 mg, 0.16 mmol) in DMF (2 mL) was added sodium hydride (60%, 7.7 mg, 0.19 mmol). After 30 min, iodomethane (~100 μL) was added. After 2 h, a saturated solution of NH_4Cl was added and EtOAc. The layers were separated, and the organic layer was washed with brine. The organic layer was dried, filtered, and concentrated *in vacuo*. MeOH (2 mL) and THF (2 mL) were added followed by sodium hydroxide solution (2 M aqueous, 500 μL). The reaction mixture was stirred at 50 °C for 4 h. The mixture was purified using reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the products. *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,7-dimethyl-1H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_4O_3S$: 611.2 ($M+H^+$); Found: 611.2 ($M + H^+$); ^1H NMR (400 MHz, CD_3OD): δ 8.63 (d, J = 6.0 Hz, 1H), 8.48 (s, 1H), 8.15 (s, 1H), 8.01 (m, 2H), 7.87 (s, 1H), 7.67 (s, 1H), 7.61 (m, 1H), 7.52 (m, 3H), 5.20 (s, 1H), 4.23 (s, 3H), 2.77 (s, 3H), 2.55 (s, 3H), 0.89 (s, 9H).

(S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2,7-dimethyl-2H-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_4O_3S$: 611.2 ($M+H^+$); Found: 611.2 ($M+H^+$); ^1H NMR (400 MHz, CD_3OD): δ 8.64 (d, J = 5.6 Hz, 1H), 8.56 (s, 1H), 8.31 (s, 1H), 8.18 (s, 1H), 8.12 (dd, J = 5.6, 1.6 Hz, 1H), 7.90 (s, 1H), 7.61 (m, 1H), 7.53 (m, 4H), 5.20 (s, 1H), 4.17 (s, 3H), 2.57 (s, 3H), 2.56 (s, 3H), 0.89 (s, 9H).

Example 82. Method BG: Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (217).



N-methyl-2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(methylamino)-3-nitrophenyl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-(2-(3-amino-4-(methylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-benzo[*d*]imidazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-benzo[*d*]imidazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

217

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(methylamino)-3-nitrophenyl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (497 mg, 1.00

mmol) in 1,4-dioxane (6 mL) was added N-methyl-2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (417 mg, 1.50 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and potassium carbonate solution (2 M aqueous, 1.5 mL, 3.0 mmol). The reaction mixture was stirred at 105 °C for 3 h and was then cooled to rt. EtOAc and H_2O were added. The layers were separated, and the organic layer was dried, filtered, and concentrated *in vacuo*. The crude mixture was purified by CombiFlash (EtOAc/Hex) to give *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(methylamino)-3-nitrophenyl)benzo[d]thiazol-6-yl)acetate. ^1H NMR (400 MHz, CD_3OD): δ 8.71 (s, 1H), 8.40 (m, 1H), 8.05 (dd, J = 8.8, 2.4 Hz, 1H), 7.73 (s, 1H), 7.51-7.58 (m, 4H), 7.06 (d, J = 8.8 Hz, 1H), 5.22 (s, 1H), 4.22 (m, 2H), 3.05 (d, J = 4.8 Hz, 3H), 2.55 (s, 3H), 1.22 (t, J = 7 Hz, 3H), 0.97 (s, 9H).

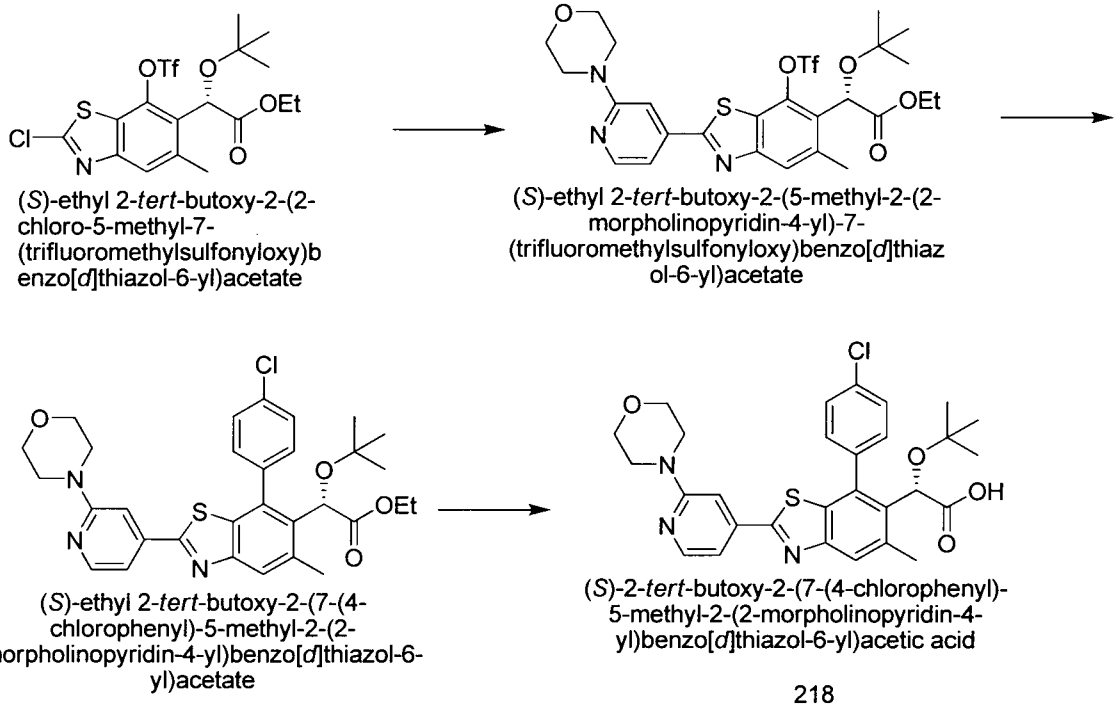
Preparation of *(S)*-ethyl 2-(2-(3-amino-4-(methylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(methylamino)-3-nitrophenyl)benzo[d]thiazol-6-yl)acetate (510 mg) in EtOH (4 mL) and EtOAc (2 mL) was added 5% Pt/C (150 mg). The reaction mixture was flushed with hydrogen gas and stirred under hydrogen atmosphere (using a balloon) for 1.5 h. The mixture was filtered through celite and concentrated *in vacuo* and *(S)*-ethyl 2-(2-(3-amino-4-(methylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate was used without further purification. LCMS-ESI^+: calc'd for $C_{29}H_{33}ClN_3O_3S$: 538.2 ($M+H^+$); Found: 538.2 ($M + H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-(3-amino-4-(methylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (40 mg, 0.07 mmol) in acetic acid (2 mL) was added triethyl orthoacetate (~200 μL). After 30 min, MeOH (20 mL) was added and the mixture was concentrated *in vacuo* and *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate was used without further purification. LCMS-ESI^+: calc'd for $C_{31}H_{33}ClN_3O_3S$: 562.2 ($M+H^+$); Found: 562.2 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1H-benzo[d]imidazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in MeOH (2 mL) and THF (2 mL) was added a sodium

hydroxide solution (2 M aqueous, 500 μL). The reaction mixture was stirred at 50 °C for 4 h. The mixture was purified using reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the product. LCMS-ESI$^+$: calc'd for $C_{29}H_{29}ClN_3O_3S$: 534.2 ($M+H^+$); Found: 534.2 ($M+H^+$); ^1H NMR (400 MHz, CD_3OD): δ 8.38 (s, 1H), 8.23 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.87 (s, 1H), 7.69 (m, 1H), 7.60 (m, 3H), 5.26 (s, 1H), 4.00 (s, 3H), 2.87 (s, 3H), 2.62 (s, 3H), 0.97 (s, 9H).

Example 83. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-morpholinopyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (218).



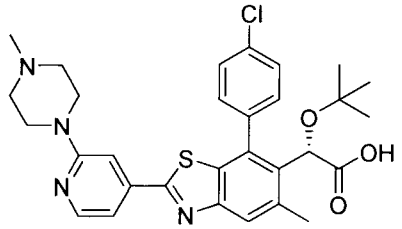
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(5-methyl-2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)acetate: A mixture of *(S)*-ethyl 2-*tert*-butoxy-2-(2-chloro-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)acetate (16 mg, 0.0327 mmol), 2-morpholinopyridine-4-boronic acid (10 mg, 0.049 mmol), $PdCl_2$(dppf) (2.7 mg, 0.00327 mmol) and powdered potassium carbonate (18 mg, 0.131 mmol) in anhydrous dimethoxyethane (0.5 mL) was sparged with nitrogen for 10 minutes, then heated overnight at 80°C. Reaction mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 60% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{26}H_{31}F_3N_3O_7S_2$: 618.2 ($M+H^+$); Found: 618.1 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-morpholinopyridin-4-yl)benzo[d]thiazol-6-yl)acetate: A mixture of *(S)*-ethyl 2-*tert*-butoxy-2-(5-

methyl-2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)acetate (20 mg, 0.0324 mmol), 4-chlorophenyboronic acid (10 mg, 0.063 mmol), SPhos precatalyst (3.3 mg, 0.0049 mmol) and powdered potassium carbonate (18 mg, 0.129 mmol) in anhydrous dimethoxyethane (0.75 mL) was sparged with nitrogen for 5 minutes, then heated in microwave at 120°C for 1.5 h. Added more 4-chlorophenyboronic acid and SPhos precatalyst (3.3 mg, 0.0049 mmol) and continued reaction. Reaction mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 40% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{31}H_{35}ClN_3O_4S$: 580.2 ($M+H^+$); Found: 580.3 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-morpholinopyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-morpholinopyridin-4-yl)benzo[d]thiazol-6-yl)acetate (4.2 mg, 0.00724 mmol) 5M NaOH (29 µL) in methanol (0.2 mL) and THF (1.0 mL) was stirred at 40°C overnight. Acetic acid (1 drop) and DMF (0.3 mL) were added and mixture concentrated to ~ 0.5 mL, diluted with DMF/H_2O, filtered and purified by Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give product after lyophilization. LCMS-ESI$^+$: calc'd for $C_{29}H_{31}ClN_3O_4S$: 552.2 ($M+H^+$); Found: 552.3 ($M + H^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 6.2 Hz, 1H), 7.94 (s, 1H), 7.69 (s, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.59 (dd, J = 4.2, 2.1 Hz, 2H), 7.47 (dd, J = 6.2, 1.5 Hz, 1H), 5.26 (s, 1H), 3.91 – 3.79 (m, 4H), 3.74 – 3.62 (m, 4H), 2.63 (s, 3H), 0.97 (s, 9H).

Example 84. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (219).

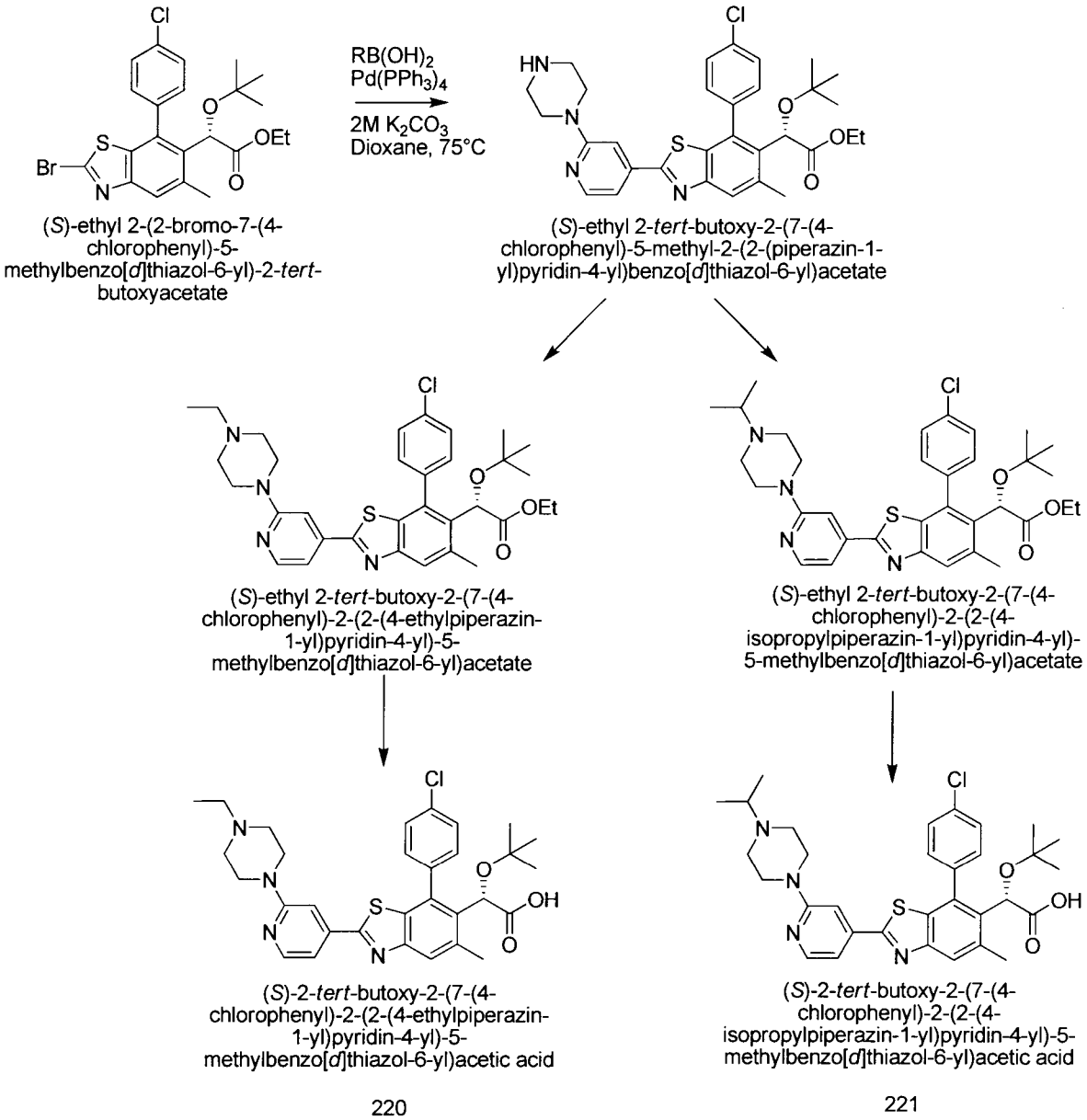


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

219

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: Prepared in a manner similar to *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-morpholinopyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid except 2-(4-methylpiperazino)pyridine-4-pyridine boronic acid using instead of 2-morpholinopyridine-4-boronic acid. LCMS-ESI$^+$: calc'd for $C_{30}H_{34}ClN_3O_3S$: 565.2 ($M+H^+$); Found: 565.3 ($M + H^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (d, J = 4.8 Hz, 1H), 7.89 (s, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.64 – 7.47 (m, 4H), 7.34 (d, J = 5.1 Hz, 1H), 5.26 (s, 1H), 4.77 – 4.38 (m, 2H), 3.78 – 3.04 (m, 2H), 2.97 (s, 3H), 2.62 (s, 3H), 0.97 (s, 9H).

Example 85. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (220) and *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (221).



Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(piperazin-1-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate: A mixture of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (106.5 mg, 0.214 mmol), 2-(1-piperazinyl)-pyridine-4-boronic acid, pinacol ester (93 mg, 0.322 mmol), $Pd(PPh_3)_4$ (25 mg, 0.02147 mmol) and 2M potassium carbonate (0.321 mL, 0.642 mmol) in anhydrous dioxane (1.0 mL) was sparged with nitrogen for 5 minutes, then heated in microwave for 1h at 100°C. Reaction mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), filtered, concentrated and used in next step without further purification. LCMS-ESI$^+$: calc'd for $C_{36}H_{36}ClN_4O_3S$: 579.2 ($M+H^+$); Found: 579.1 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of crude *(S)*-ethyl 2-*tert*-

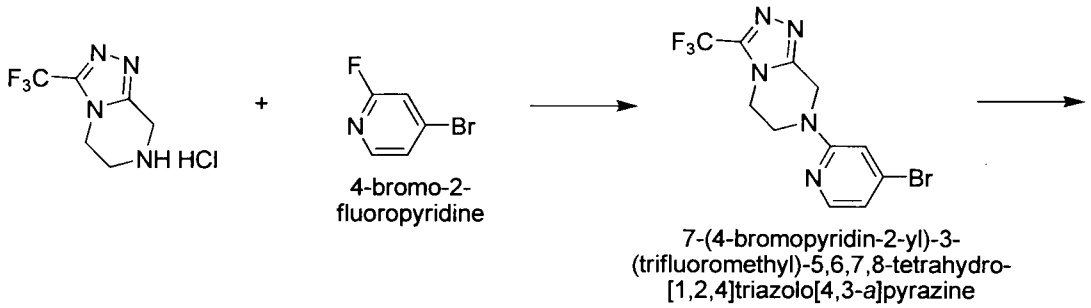
butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(piperazin-1-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate (~0.144 mmol) in DMF (1.5 mL) was added cesium carbonate (0.094 g, 0.288 mmol), followed by iodoethane (12.6 μL, 0.158 mmol). Reaction mixture was stirred for 1h, then more iodoethane (5 μL) was added and reaction mixture stirred for 2h. LC/MS showed incomplete reaction, so more iodoethane (5 μL) was added and reaction mixture stirred overnight. Reaction mixture was diluted with ethyl acetate, washed with 5% lithium chloride solution (2x), brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 10% MeOH/CH_2Cl_2) to give product. LCMS-ESI$^+$: calc'd for $C_{33}H_{40}ClN_4O_3S$: 607.2 ($M+H^+$); Found: 607.3 ($M + H^+$).

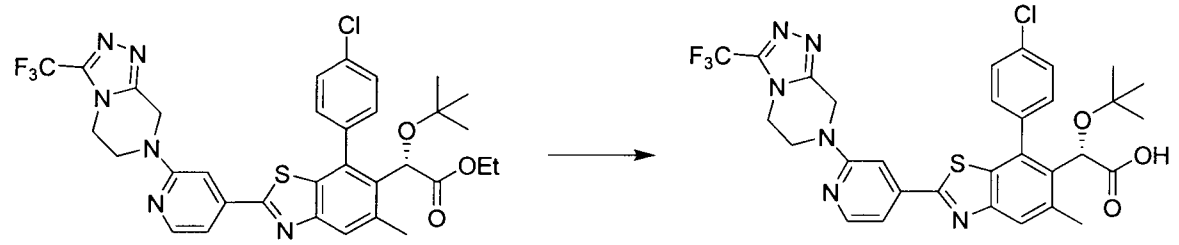
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (26.7 mg, 0.044 mmol), 5M NaOH (176 μL, 0.879 mmol)) in methanol (0.2 mL) and THF (1.0 mL) was stirred at 45°C for 2h, then stirred overnight at rt. Acetic acid (1 drop) and DMF (0.3 mL) were added and mixture concentrated to ~ 0.3 mL, diluted with methanol, filtered and purified by Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give product after lyophilization. LCMS-ESI$^+$: calc'd for $C_{31}H_{36}ClN_4O_3S$: 579.2 ($M+H^+$); Found: 579.3 ($M + H^+$); ^1H NMR (400 MHz, CD_3OD) δ 8.27 (d, J = 5.4 Hz, 1H), 7.84 (s, 1H), 7.66 (dd, J = 8.5, 1.7 Hz, 1H), 7.63 – 7.52 (m, 3H), 7.50 (s, 1H), 7.32 (dd, J = 5.4, 1.3 Hz, 1H), 5.25 (s, 1H), 4.81 – 4.18 (m, 2H), 4.81 – 4.18 (m, 2H), 3.7 – 2.99 (m, 4H), 3.27 (dd, J = 14.8, 7.5 Hz, 3H), 2.59 (s, 3H), 1.39 (t, J = 7.3 Hz, 3H), 0.96 (s, 9H).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of crude *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(piperazin-1-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate (~0.144 mmol) in ethanol(2.0 mL) was added acetone (0.21 mL) and acetic acid (12 μL, 0.21 mmol) at 0°C. Reaction mixture was stirred for 15 minutes, then sodium cyanoborohydride (10 mg, 0.158 mmol) was added and reaction mixture was warmed to room temperature over 2h. Reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate/brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 10% MeOH/CH_2Cl_2) to give product. LCMS-ESI$^+$: calc'd for $C_{34}H_{42}ClN_4O_3S$: 622.2 ($M+H^+$); Found: 621.3 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (36.7 mg, 0.059 mmol), 5M NaOH (236 μL, 1.18 mmol)) in methanol (0.2 mL) and THF (1.0 mL) was stirred at 45°C for 2h, then stirred overnight at rt. Acetic acid (1 drop) and DMF (0.3 mL) were added and mixture concentrated to ~ 0.3 mL, diluted with DMF/methanol, filtered and purified by Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give product after lyophilization. LCMS-ESI$^+$: calc'd for $C_{32}H_{38}ClN_4O_3S$: 593.2 ($M+H^+$); Found: 593.3 ($M + H^+$); ^1H NMR (400 MHz, CD_3OD) δ 8.26 (d, J = 5.5 Hz, 1H), 7.84 (s, 1H), 7.66 (dd, J = 8.5, 1.8 Hz, 1H), 7.61 – 7.48 (m, 4H), 7.33 (dd, J = 5.4, 1.3 Hz, 1H), 5.24 (s, 1H), 4.77 – 4.40 (m, J = 33.2 Hz, 2H), 3.58 (td, J = 13.2, 6.6 Hz, 1H), 3.50 – 3.14 (m, 2H), 2.58 (s, 3H), 1.41 (d, J = 6.7 Hz, 6H), 0.95 (s, 9H).

Example 86. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (222).





222

Preparation of 7-(4-bromopyridin-2-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine: A mixture of 4-bromo-2-fluoropyridine (0.216 mL, 2.1 mmol), 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (0.399 g, 1.75 mmol) and potassium carbonate (0.482 g, 3.49 mmol) in anhydrous DMF (7.0 mL) was heated at 100°C for 16 h. Reaction mixture was cooled, diluted with ethyl acetate, washed with 5% lithium chloride solution (2x), brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 50% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{11}H_{10}BrF_3N_5$: 348.0. ($M+H^+$); Found: 348.2 ($M + H^+$).

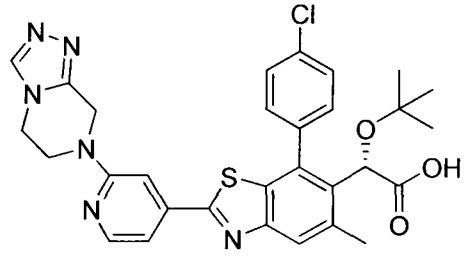
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate: A mixture of 7-(4-bromopyridin-2-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (22.7 mg, 0.065 mmol), bis(pinacolato)diboron (33 mg, 0.13 mmol), potassium acetate (32 mg, 0.325 mmol) and $PdCl_2$(dppf) (4.8 mg, 0.0065 mmol) in anhydrous dioxane (1.0 mL) was heated at 120°C for 30 minutes. Cooled to room temperature and used directly in the next step.

To the above reaction mixture were added *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (38.8 mg, 0.078 mmol), 2M potassium carbonate solution (0.13 mL, 0.26 mmol), and $Pd(PPh_3)_4$ (7.5 mg, 0.0065 mmol). Reaction mixture was heated at 95°C overnight, diluted with ethyl acetate, and washed with brine. Aqueous layer was back-extracted with ethyl acetate and combined organic layer was dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 40% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{33}H_{33}ClF_3N_6O_3S$: 685.2. ($M+H^+$); Found: 685.3 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate (35 mg, 0.052 mmol) and 5M sodium hydroxide (0.21 mL, 1.04 mmol) in methanol (0.3 mL) and THF (1.0 mL) was heated 45°C for 2h. Acetic acid (1 drop) and DMF (0.3 mL) were added and mixture concentrated to ~ 0.3 mL, diluted with methanol, filtered and purified by Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give product after lyophilization. LCMS-ESI$^+$: calc'd for $C_{31}H_{29}ClF_3N_6O_3S$: 657.2 ($M+H^+$); Found: 657.3 ($M + H^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (d, J = 5.5 Hz, 1H), 7.81 (s, 1H),

7.66 (dd, J = 8.7, 1.8 Hz, 1H), 7.62 – 7.49 (m, J = 10.0, 7.3 Hz, 4H), 7.32 (dd, J = 5.5, 1.3 Hz, 1H), 5.24 (s, 1H), 5.07 (s, 2H), 4.36 (t, J = 5.2 Hz, 2H), 4.20 (t, J = 5.3 Hz, 2H), 2.57 (s, 3H), 0.95 (s, 9H).

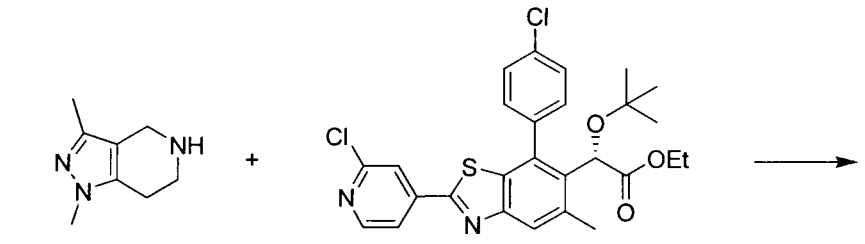
Example 87. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (223).



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid
223

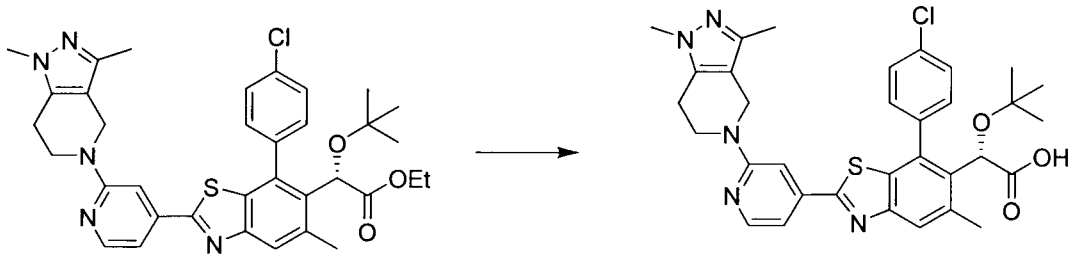
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid was prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid except starting with 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride instead of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride. LCMS-ESI$^+$: calc'd for $C_{30}H_{30}ClN_6O_3S$: 589.2 ($M+H^+$); Found: 589.3 ($M+H^+$); ^1H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.28 (d, J = 5.4 Hz, 1H), 7.85 (s, 1H), 7.67 (dd, J = 8.5, 1.7 Hz, 1H), 7.63 – 7.51 (m, 4H), 7.34 (d, J = 5.3 Hz, 1H), 5.25 (s, 1H), 5.15 (s, 2H), 4.40 (t, J = 5.3 Hz, 2H), 4.22 (t, J = 5.4 Hz, 2H), 2.60 (s, 3H), 0.96 (s, 9H).

Example 88. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-6,7-dihydro-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (224).



1,3-dimethyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-5(4*H*)-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-5(4*H*)-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

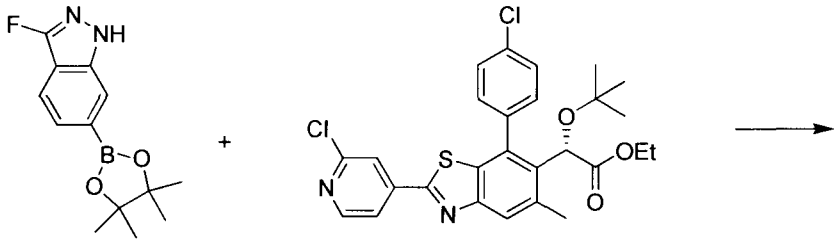
224

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-6,7-dihydro-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of 1,3-dimethyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (47.6 mg, 0.315 mmol), *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (32 mg, 0.060 mmol) in anhydrous NMP (1.0 mL) was heated at 90-110°C for 40 h. Reaction mixture was cooled to room temperature, filtered through a syringe filter and purified by Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product-containing fractions were diluted with ethyl acetate, washed with saturated sodium bicarbonate solution. Aqueous layer was back-extracted with ethyl acetate and the combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give product. LCMS-ESI$^+$: calc'd for $C_{35}H_{39}ClN_5O_3S$: 644.2 ($M+H^+$); Found: 644.3 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-6,7-dihydro-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-6,7-dihydro-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of 1,3-dimethyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (7.7 mg, 0.012 mmol) and 5M sodium hydroxide (47 μL, 0.24 mmol) in methanol (0.1 mL) and THF (0.5 mL) was heated 45°C for 2h. Acetic acid (1 drop) and DMF (0.3 mL) were added and mixture concentrated to ~ 0.3 mL, diluted with methanol, filtered and purified by Gilson HPLC (Gemini, 5 to 100%

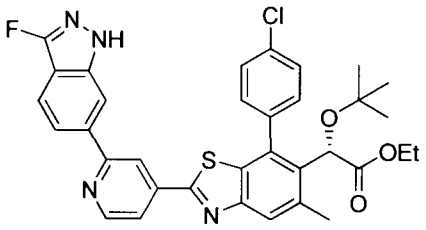
ACN/H_2O + 0.1% TFA) to give product after lyophilization. LCMS-ESI$^+$: calc'd for $C_{32}H_{34}ClN_5O_3S$: 616.2 ($M+H^+$); Found: 616.3 ($M + H^+$); ^1H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 6.3 Hz, 1H), 7.96 (s, 1H), 7.83 (s, 1H), 7.68 (dd, J = 8.5, 1.7 Hz, 1H), 7.67 – 7.54 (m, 3H), 7.47 (dd, J = 6.3, 1.3 Hz, 1H), 5.27 (s, 1H), 4.63 (s, 2H), 4.07 (t, J = 5.7 Hz, 2H), 3.72 (s, 3H), 2.93 (t, J = 5.5 Hz, 2H), 2.64 (s, 3H), 2.24 (s, 3H), 0.97 (s, 9H).

Example 89. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-fluoro-1-methyl-1H-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (225).

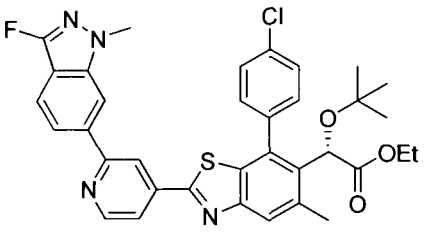


3-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole

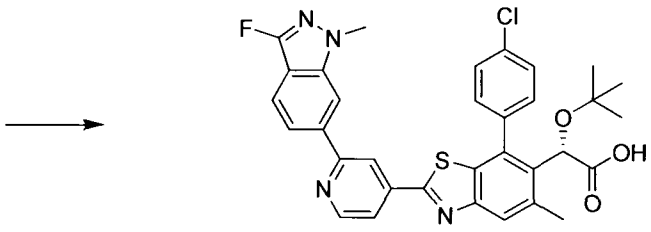
(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-fluoro-1*H*-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-fluoro-1-methyl-1*H*-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-fluoro-1-methyl-1*H*-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

225

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-fluoro-1H-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of 3-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (prepared according to WO201059658, 48 mg, 0.184 mmol), *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-

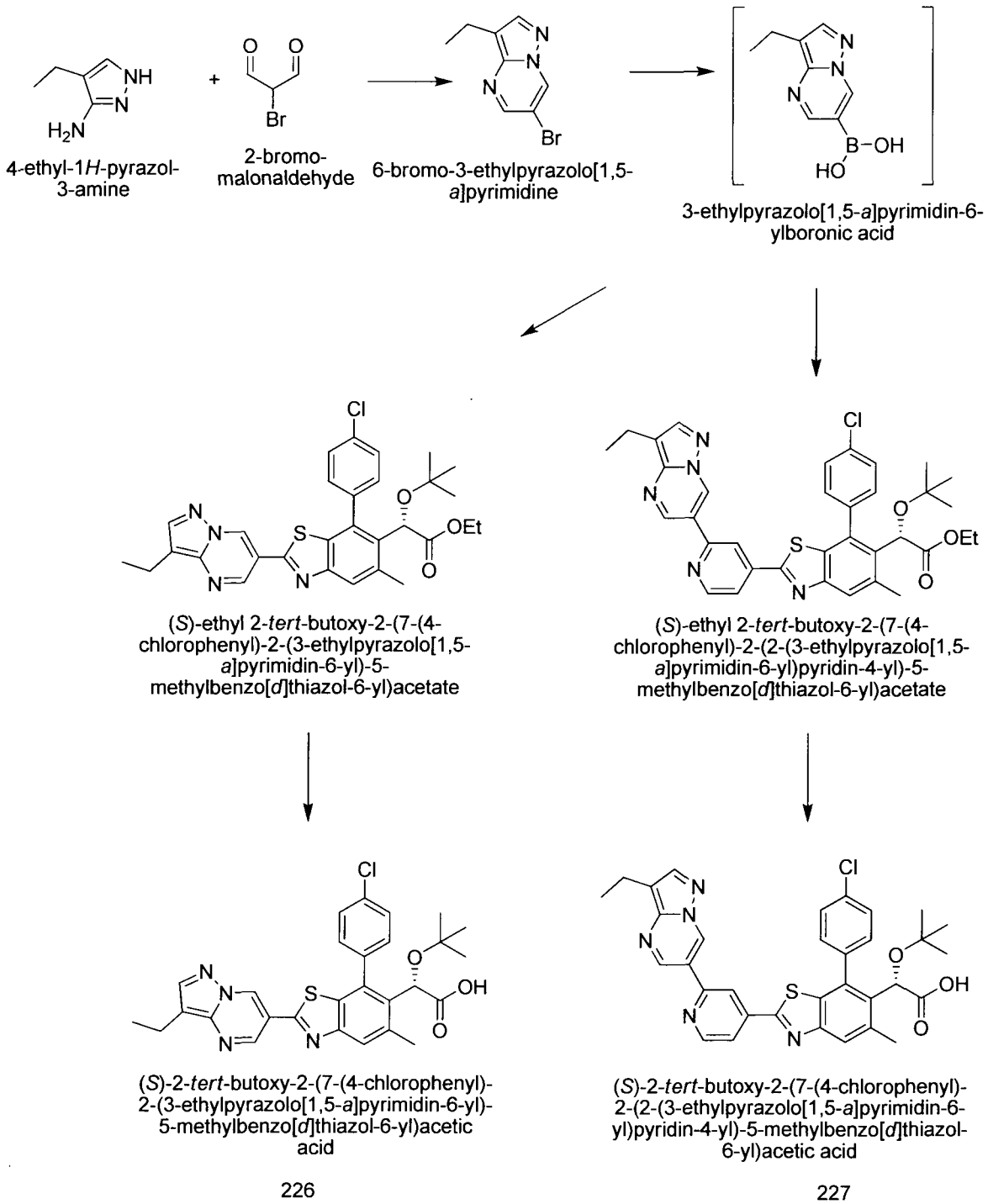
methylbenzo[d]thiazol-6-yl)acetate (75 mg, 0.142 mmol) and 2M potassium carbonate solution (0.28 mL, 0.568 mmol) in dioxane (1.0 mL) was sparged with nitrogen for 10 minutes, $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) was added and reaction mixture was heated in microwave at 100°C for 1h. Reaction mixture was diluted with ethyl acetate, washed with brine. The aqueous layer was back extracted with ethyl acetate and the combined organic layer was dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 40% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClFN_4O_3S$: 629.2 ($M+H^+$); Found: 629.3 ($M + H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-fluoro-1-methyl-1H-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a mixture of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-fluoro-1H-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (39.7 mg, 0.0631 mmol) and cesium carbonate (62 mg, 0.189 mmol) in anhydrous DMF (1.0 mL) at 0°C was added iodomethane (5.9 µL, 0.0947 mmol) and reaction stirred for 1 h. More iodomethane (3.0 µL) was added and reaction was stirred for 30 minutes, and stored in freezer overnight. Reaction mixture was diluted with ethyl acetate, washed with 5% lithium chloride solution (3x), brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 40% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{35}H_{33}ClFN_4O_3S$: 643.2 ($M+H^+$); Found: 643.2 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-fluoro-1-methyl-1H-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-fluoro-1-methyl-1H-indazol-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (37 mg, 0.058 mmol) and 5M NaOH (0.23 mL, 1.15 mmol) in MeOH (0.5 mL) and THF (2 mL) was stirred at 45°C for 2 hours. DMF (0.3 mL) and acetic acid (73 µL) were added and reaction mixture was concentrated to ~0.3 mL, filtered using a syringe filter, diluted with methanol. Purified using Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) and lyophilized to give product. LCMS-ESI$^+$: calc'd for $C_{33}H_{29}ClFN_4O_3S$: 615.2 ($M+H^+$); Found: 615.2 ($M + H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (d, J = 5.4 Hz, 1H), 8.58 (s, 1H), 8.20 (s, 1H), 8.02 (dd, J = 5.3, 1.6 Hz, 1H), 7.95 (s, 1H), 7.83 (dd, J = 28.4, 8.6 Hz, 2H), 7.76 – 7.67 (m, 1H), 7.60 (br s, 3H), 5.28 (s, 1H), 4.01 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H).

Example 90. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-ethylpyrazolo[1,5-a]pyrimidin-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (226) and *(S)*-2-*tert*-

butoxy-2-(7-(4-chlorophenyl)-2-(3-ethylpyrazolo[1,5-a]pyrimidin-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (227).



Preparation of 6-bromo-3-ethylpyrazolo[1,5-a]pyrimidine: To a solution of 4-ethyl-1H-pyrazol-3-amine (0.50 g, 4.50 mmol) and 2-bromo-malonaldehyde (1.47 g, 9.72 mmol) in ethanol (8.0 mL) was added acetic acid (1.21 mL, 21.2 mmol). The reaction mixture was refluxed for 4 h, then stored in a freezer overnight. The mixture was warmed to rt, the resulting precipitate was removed by filtration and the filtrate concentrated. The resulting residue was

portioned between ethyl acetate and 1M sodium hydroxide and the organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 50% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_8H_9BrN_3$: 226.0 ($M+H^+$); Found: 226.1 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-ethylpyrazolo[1,5-a]pyrimidin-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of 6-bromo-3-ethylpyrazolo[1,5-a]pyrimidine (415 mg, 1.84 mmol), bis(pinacolato)diboron (932 mg, 3.67 mmol), potassium acetate (902 mg, 9.2mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (150 mg, 0.184 mmol) in anhydrous dioxane (10.0 mL) was sparged with nitrogen for 10 minutes, then heated in a microwave at 100°C for 1 h. LC/MS showed clean conversion to 3-ethylpyrazolo[1,5-a]pyrimidin-6-ylboronic acid that was used crude.

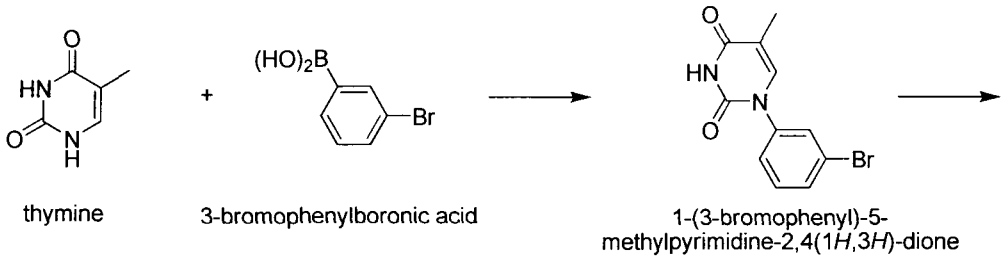
To a mixture of the above crude 3-ethylpyrazolo[1,5-a]pyrimidin-6-ylboronic acid in dioxane (~0.18M, 0.68 mL, 0.123 mmol) was added *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (50 mg, 0.0944 mmol), $Pd(PPh_3)_4$ (11 mg, 0.0094 mmol) and 2M potassium carbonate (0.19 mL, 0.378 mmol) was heated in a microwave at 110°C for 1 h. Reaction mixture was stored overnight at rt, diluted with ethyl acetate and washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 40% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{35}H_{35}ClN_5O_3S$: 640.2 ($M+H^+$); Found: 640.3 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-ethylpyrazolo[1,5-a]pyrimidin-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A mixture of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-ethylpyrazolo[1,5-a]pyrimidin-6-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (31 mg, 0.048 mmol) and lithium iodide (200 mg) in pyridine (0.5 mL) was heated in microwave at 170°C for 1 h. Reaction mixture was diluted with ethyl acetate, washed with 5% acetic acid solution, brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 10% $MeOH/CH_2Cl_2$). Lyophilization gave desired product. LCMS-ESI$^+$: calc'd for $C_{33}H_{31}ClN_5O_3S$: 612.2 ($M+H^+$); Found: 612.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD) δ 9.33 (d, J = 2.1 Hz, 1H), 9.02 (d, J = 2.1 Hz, 1H), 8.60 (d, J = 5.1 Hz, 1H), 8.56 – 8.49 (m, 2H), 8.29 (s, 1H), 8.02 (s, 1H), 7.85 (tt, J = 7.7, 1.8 Hz, 1H), 7.77 – 7.61 (m, 4H), 7.61 – 7.49 (m, 3H), 7.43 (ddd, J = 7.7, 4.4, 1.5 Hz, 2H), 5.24 (s, 1H), 2.78 (q, J = 7.6 Hz, 2H), 2.56 (s, 3H), 1.30 (t, J = 7.6 Hz, 3H), 0.96 (d, J = 6.8 Hz, 9H).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-ethylpyrazolo[1,5-a]pyrimidin-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a mixture of the crude 3-ethylpyrazolo[1,5-a]pyrimidin-6-ylboronic acid in dioxane (~0.18M, 0.68 mL, 0.123 mmol) was added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (50 mg, 0.101 mmol), $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) and 2M potassium carbonate (0.20 mL, 0.404 mmol) was heated in a microwave at 110°C for 1 h. Reaction mixture was stored overnight at rt, diluted with ethyl acetate and washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 30% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{30}H_{32}ClN_4O_3S$: 563.2 ($M+H^+$); Found: 563.3 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-ethylpyrazolo[1,5-a]pyrimidin-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A mixture of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-ethylpyrazolo[1,5-a]pyrimidin-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (24.9 mg, 0.044 mmol) and lithium iodide (200 mg) in pyridine (0.5 mL) was heated in microwave at 170°C for 1 h. Reaction mixture was diluted with ethyl acetate, washed with 5% acetic acid solution, brine, dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 30% MeOH/CH_2Cl_2). Lyophilization gave desired product. LCMS-ESI$^+$: calc'd for $C_{28}H_{28}ClN_4O_3S$: 535.2. ($M+H^+$); Found: 535.2 ($M + H^+$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (dd, J = 2.8, 1.6 Hz, 1H), 8.95 (dd, J = 2.8, 1.6 Hz, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.58 – 7.37 (m, 3H), 5.31 (s, 1H), 2.86 (q, J = 7.6 Hz, 2H), 2.58 (s, 3H), 1.34 (dd, J = 7.8, 7.3 Hz, 3H), 0.99 (s, 9H).

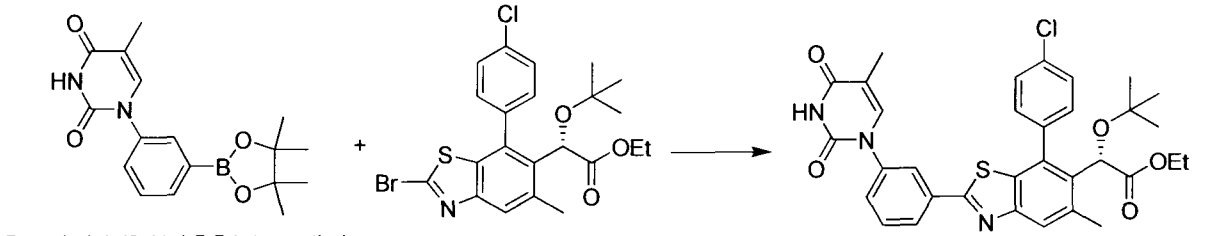
Example 91. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid (228).



thymine

3-bromophenylboronic acid

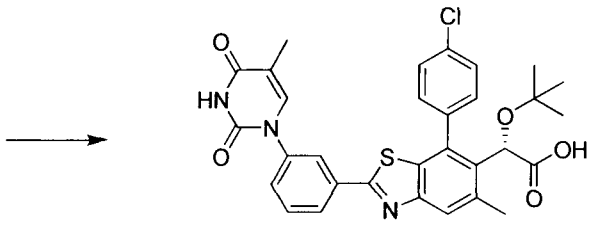
1-(3-bromophenyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione



5-methyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrimidine-2,4(1*H*,3*H*)-dione

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)phenyl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)phenyl)benzo[*d*]thiazol-6-yl)acetic acid

228

Preparation of 1-(3-bromophenyl)-5-methylpyrimidine-2,4(1H,3H)-dione: A 500 mL round bottom flask was charged with thymine (0.314 g, 2.49 mmol), 3-bromophenylboronic acid (1.00 g, 4.98 mmol), tetramethylethyldiamine (0.75 mL, 4.98 mmol), copper(II) acetate monohydrate (0.497 g, 2.49 mmol), methanol (200 mL), and H_2O (50 mL). The blue reaction mixture was stirred for 48 h, concentrated and purified by CombiFlash (0 to 8% MeOH/CH_2Cl_2) to give desired product. LCMS-ESI$^+$: calc'd for $C_{11}H_9BrN_2O_2$: 281.0 ($M+H^+$); Found: 281.1 ($M + H^+$).

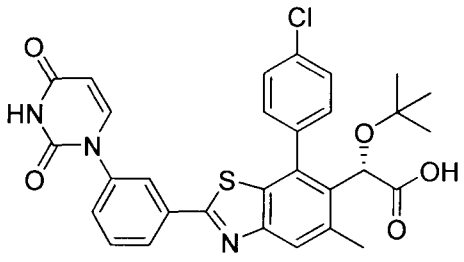
Preparation of 5-methyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrimidine-2,4(1H,3H)-dione: A mixture of 1-(3-bromophenyl)-5-methylpyrimidine-2,4(1H,3H)-dione (163 mg, 0.58 mmol), bis(pinacolato)diboron (294 mg, 1.16 mmol), potassium acetate (284 mg, 2.90 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (47 mg, 0.058 mmol) in anhydrous dioxane (6.0 mL) was sparged with nitrogen for 20 minutes, then heated at 100°C for

0.5 h. Reaction mixture was concentrated, dissolved in dichloromethane, adsorbed onto silica gel and purified by CombiFlash (0 to 8% MeOH/CH_2Cl_2) to give desired product. LCMS-ESI$^+$: calc'd for $C_{17}H_{22}BN_2O_4$: 329.2 ($M+H^+$); Found: 329.1 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)benzo[d]thiazol-6-yl)acetate: A mixture 5-methyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrimidine-2,4(1H,3H)-dione (50 mg, 0.154 mmol), *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (51 mg, 0.103 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01034 mmol) and 2M potassium carbonate (0.15 mL, 0.309 mmol) was heated at 105-120°C for 5 h. Reaction mixture was stirred over the weekend at rt, diluted with ethyl acetate and washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product-containing fractions were diluted with ethyl acetate, washed with saturated sodium bicarbonate solution/brine. Organic layer was dried ($MgSO_4$), filtered, and concentrated to give desired product. LCMS-ESI$^+$: calc'd for $C_{33}H_{33}ClN_3O_5S$: 618.2 ($M+H^+$); Found: 618.2 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)benzo[d]thiazol-6-yl)acetate (12.9 mg, 0.0212 mmol) and 5M NaOH (85 µL, 0.424 mmol) in MeOH (0.1 mL) and THF (1.2 mL) was stirred at 50°C for 1.5 hours. DMF (0.3 mL) and acetic acid (75 µL) were added and reaction mixture was concentrated to ~0.3 mL, filtered using a syringe filter, diluted with methanol. Purified using Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) and lyophilized to give product. LCMS-ESI$^+$: calc'd for $C_{31}H_{29}ClN_3O_5S$: 590.1 ($M+H^+$); Found: 590.2 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (d, J = 8.5 Hz, 1H), 7.94 (dd, J = 1.8, 1.8 Hz, 1H), 7.84 (s, 1H), 7.71 – 7.47 (m, 5H), 7.43 – 7.22 (m, 2H), 5.25 (s, 1H), 2.60 (s, 3H), 1.92 (d, J = 5.2Hz, 3H), 1.34 (s, 3H), 0.96 (s, 9H).

Example 92. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (229).

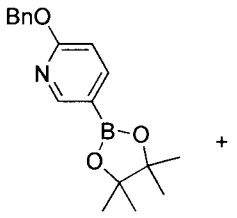


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)phenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

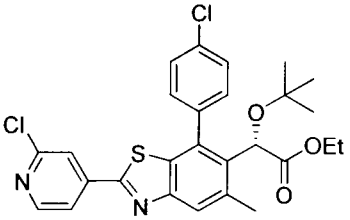
229

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: Prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid, except starting with uracil instead of thymine. LCMS-ESI$^+$: calc'd for $C_{30}H_{279}ClN_3O_5S$: 576.1 ($M+H^+$); Found: 576.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD) δ 8.10 – 8.02 (m, 1H), 7.95 (t, J = 1.8 Hz, 1H), 7.83 (s, 1H), 7.72 – 7.54 (m, 6H), 7.50 (d, J = 7.7 Hz, 1H), 7.44 – 7.37 (m, 1H), 5.81 (d, J = 7.7 Hz, 1H), 5.25 (s, 1H), 2.60 (s, 3H), 0.96 (s, 9H).

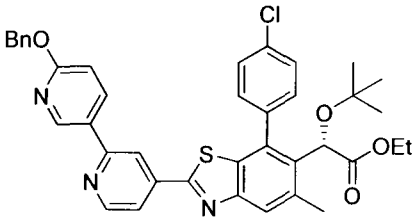
Example 93. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(6-oxo-1,6-dihydropyridin-3-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (230).



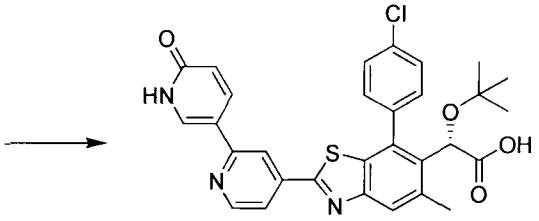
2-(benzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-(2-(6'-(benzyloxy)-2,3'-bipyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(6-oxo-1,6-dihydropyridin-3-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

230

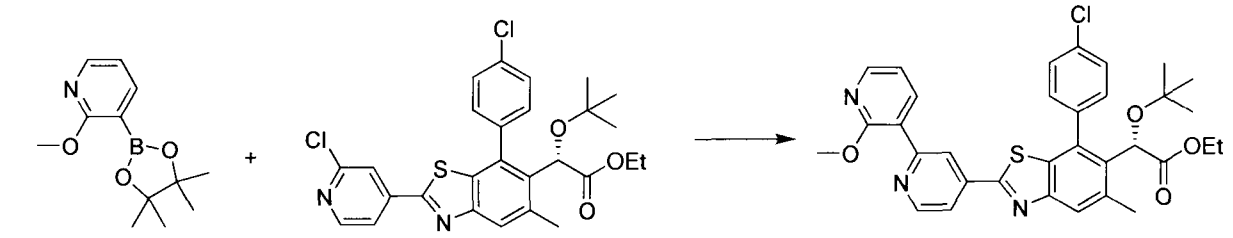
Preparation of *(S)*-ethyl 2-(2-(6'-(benzyloxy)-2,3'-bipyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: A mixture of 2-(benzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (15 mg, 0.048 mmol), *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (17 mg, 032 mmol) and 2M potassium carbonate solution (48 μL, 0.096 mmol) in dioxane (0.5 mL) was sparged with nitrogen for 10 minutes, $Pd(PPh_3)_4$ (3.7 mg, 0.0032 mmol) was added and reaction mixture was heated at 100°C for 4h. Reaction mixture was diluted with ethyl acetate, washed with brine. The aqueous layer was back extracted with ethyl acetate and the combined organic layer was dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 20% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{39}H_{37}ClN_3O_4S$: 678.2 ($M+H^+$); Found: 678.3 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(6-oxo-1,6-dihydropyridin-3-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: A mixture of *(S)*-ethyl 2-(2-(6'-(benzyloxy)-2,3'-bipyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (21.2 mg, 0.031 mmol) and 5% rhodium on alumina (61 mg) in absolute ethanol (5.0 mL) was placed under vacuum for 5 minutes, back-filled with hydrogen and stirred under hydrogen balloon for 3 h to give ~70% conversion based on LC/MS. Reaction mixture was filtered through a pad of Celite, concentrated and used in next step without further purification.

A solution of above residue and 5M NaOH (0.12 mL, 0.62 mmol) in methanol (0.2 mL) and THF (1.5 mL) was stirred at 50°C for 2 h. Acetic acid (21 equivalents) and DMF (0.3 mL) were added and reaction mixture was concentrated to ~0.3 mL, filtered using a syringe filter, diluted with methanol and purified using Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA). Product containing fractions were pooled, diluted with ethyl acetate and washed with saturated sodium bicarbonate solution/brine. Aqueous layer was back-extracted with ethyl acetate (3x) and combined organic layer was dried ($MgSO_4$), filtered and concentrated. Product suspended in acetonitrile/H_2O, acidified with TFA and lyophilized to give desired product. LCMS-ESI$^+$: calc'd for $C_{30}H_{27}ClN_3O_4S$: 560.1 ($M+H^+$); Found: 560.2 ($M + H^+$). ^1H NMR of Na salt (400 MHz, CD_3OD) δ 8.64 (d, J = 5.2 Hz, 1H), 8.30 (dd, J = 9.6, 2.6 Hz, 1H), 8.24 – 8.16 (m, 2H), 7.87 – 7.74 (m, 3H), 7.57 (s, 2H), 7.56 (d, J = 9.9 Hz, 1H), 6.64 (d, J = 9.6 Hz, 1H), 5.20 (s, 1H), 2.63 (s, 3H), 0.95 (s, 9H).

Example 94. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-oxo-1,2-dihydropyridin-3-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (232) and *(S)*-2-*tert*-butoxy-2-

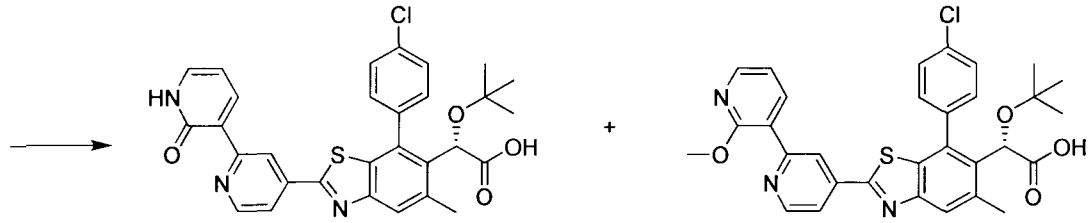
(7-(4-chlorophenyl)-2-(2'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (233) was also isolated.



2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-oxo-1,2-dihydropyridin-3-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

232

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

233

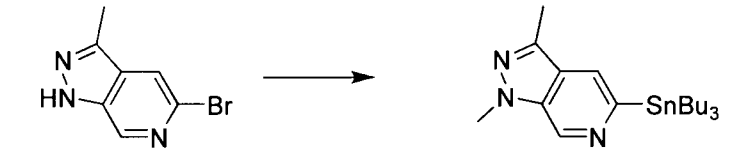
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (13 mg, 0.0878 mmol), *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (31 mg, 0585 mmol) and 2M potassium carbonate solution (88 µL, 0.178 mmol) in dioxane (0.5 mL) was sparged with nitrogen for 10 minutes. $Pd(PPh_3)_4$ (6.9 mg, 0.0059 mmol) was added and reaction mixture was heated in microwave at 100°C for 1h . Reaction mixture was diluted with ethyl acetate, washed with brine. The aqueous layer was back extracted with ethyl acetate and the combined organic layer was dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 40% EtOAc/Hex) to give product. LCMS-ESI$^+$: calc'd for $C_{33}H_{33}ClN_3O_4S$: 602.1 ($M+H^+$); Found: 602.3 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(2-oxo-1,2-dihydropyridin-3-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: A mixture of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (24.2 mg, 0.040 mmol) and lithium iodide (150 mg) in pyridine (2.0 mL) was heated in microwave at 170°C for 3.5 hours. Reaction mixture was cooled to room temperature and

allowed to stand for 14 days, diluted with ethyl acetate. Organic layer was washed with 5% AcOH solution (3x), brine, dried ($MgSO_4$), filtered, concentrated, and purified using Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) to give desired product. LCMS-ESI$^+$: calc'd for $C_{30}H_{27}ClN_3O_4S$: 560.1 ($M+H^+$); Found: 560.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD) δ 8.99 (s, 1H), 8.78 (dd, J = 11.1, 6.9 Hz, 2H), 8.28 (d, J = 6.0 Hz, 1H), 7.94 (s, 1H), 7.85 (d, J = 6.1 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.64 – 7.53 (m, 3H), 6.73 (dd, J = 6.8 Hz, 1H), 5.28 (s, 1H), 2.62 (s, 3H), 0.97 (s, 9H).

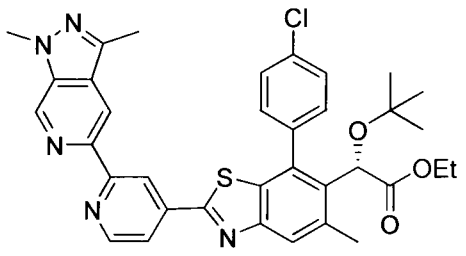
(S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2'-methoxy-2,3'-bipyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid was also isolated: LCMS-ESI$^+$: calc'd for $C_{31}H_{29}ClN_3O_4S$: 574.2 ($M+H^+$); Found: 574.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD) δ 9.05 (s, 1H), 8.81 (d, J = 6.2 Hz, 1H), 8.72 (d, J = 7.9 Hz, 1H), 8.32 (d, J = 6.2 Hz, 1H), 8.08 (d, J = 6.4 Hz, 1H), 8.00 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.6 Hz, 3H), 6.71 (dd, J = 6.5, 6.5 Hz, 1H), 5.28 (s, 1H), 3.75 (s, 3H), 2.65 (s, 3H), 0.98 (s, 9H).

Example 95. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (234) and *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (235).

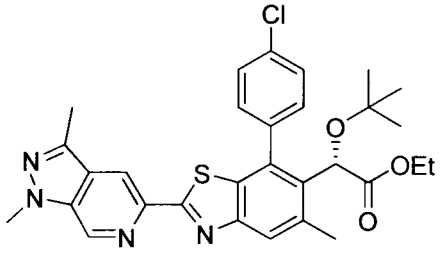


5-bromo-3-methyl-1*H*-pyrazolo[3,4-*c*]pyridine

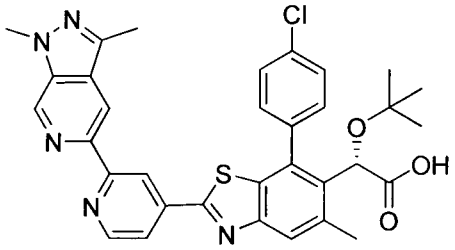
1,3-dimethyl-5-(tributylstannyl)-1*H*-pyrazolo[3,4-*c*]pyridine



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1*H*-pyrazolo[3,4-*c*]pyridin-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

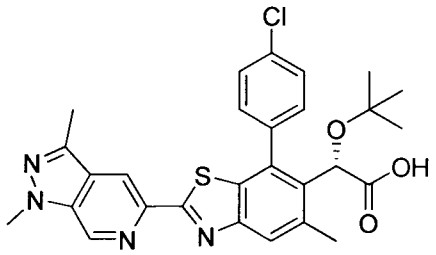


(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrazolo[3,4-*c*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1*H*-pyrazolo[3,4-*c*]pyridin-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

234



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrazolo[3,4-*c*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

235

Preparation of 1,3-dimethyl-5-(tributylstannyl)-1H-pyrazolo[3,4-c]pyridine: To a solution of 5-bromo-3-methyl-1H-pyrazolo[3,4-c]pyridine (0.5 g, 2.36 mmol) in DMF (12 mL) at 0°C was added cesium carbonate (2.305 g, 7.074 mmol), followed by iodomethane (0.22 mL, 3.537 mmol). After stirring for 1h, LC/MS showed reaction was complete. Reaction mixture was diluted with ethyl acetate, washed with 5% lithium chloride solution (3x), brine and dried (MgSO4). Filtration and concentration gave product that was used in the next step without further purification.

The above residue was dissolved in toluene (10 mL) and hexabutylditin (1.239 mL, 2.473 mmol) was added, followed by tetrakis(triphenylphosphine)palladium(0) (0.22 g, 0.19 mmol). The yellow reaction mixture was stirred at 140 °C in a sealed reaction vessel for 2 hours. Temperature was increased to 170°C and stirred for 45 min to give a black mixture. Reaction mixture was cooled to rt, diluted with diethyl ether and added aqueous KF solution and stirred vigorously for 1 hr. The biphasic mixture was filtered through a pad of Celite, diluted with ethyl acetate and washed with aqueous KF solution, brine, dried ($MgSO_4$), filtered and concentrated to give a yellow solid. Dissolved solid in DCM, adsorbed onto silica gel and purified by Combiflash (0 to 50% EtOAc/Hex) to give desired product. LCMS-ESI$^+$: calc'd for $C_{20}H_{36}N_3Sn$: 438.2 ($M+H^+$); Found: 438.2 ($M + H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of 1,3-dimethyl-5-(tributylstannyl)-1H-pyrazolo[3,4-c]pyridine (31 mg,0.071 mmol), *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (30.1 mg, 0.057 mmol), copper(I) iodide (13.5 mg, 0.071 mmol) and lithium chloride (15.1 mg, 0.355 mmol) in dioxane (0.5 mL) was sparged with nitrogen for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (8.9 mg, 0.0008 mmol) and trans-dichlorobis(triphenylphosphine)palladium (II) (5.2 mg, 0.007 mmol) were added and reaction mixture was heated at 120°C for 5 hours. Reaction mixture was cooled to rt, diluted with dichloromethane, adsorbed onto silica gel and purified by CombiFlash (0 to 70% EtOAc/Hex) to give product contaminated with tributylstannane impurity. LCMS-ESI$^+$: calc'd for $C_{35}H_{35}ClN_5O_3S$: 640.2 ($M+H^+$); Found: 640.4 ($M + H^+$).

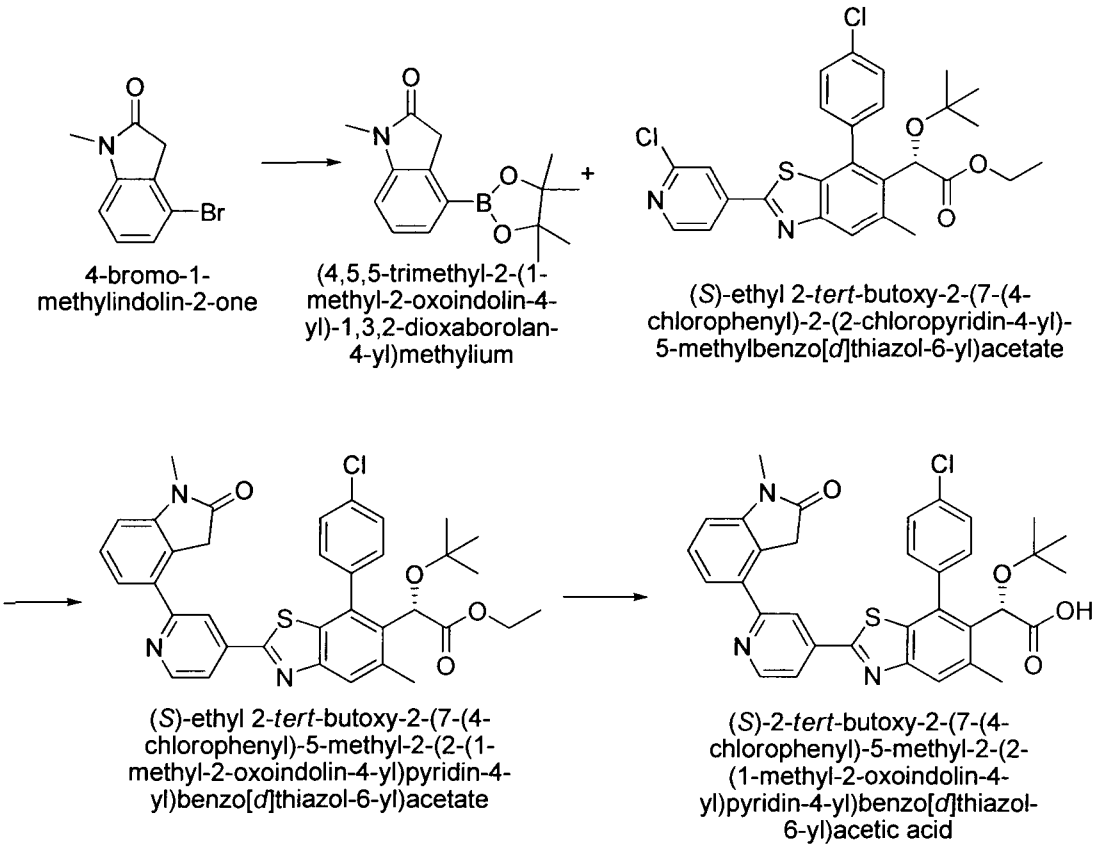
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (5.6 mg, 0.009 mmol)and 5M NaOH (0.035 mL, 0.175 mmol) in MeOH (0.1 mL) and THF (0.5 mL) was stirred at 50°C for 3 hours, then stored in freezer overnight. DMF (0.3 mL) and acetic acid (0.011 mL) were added and reaction mixture was concentrated to ~0.3 mL, filtered using a syringe filter, diluted with methanol. Purified using Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) and lyophilized to give desired product. LCMS-ESI$^+$: calc'd for $C_{33}H_{31}ClN_5O_3S$: 612.2 ($M+H^+$);

Found: 612.3 (M + H^+); ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (s, 2H), 7.8 - 7.6 (m, 8H), 5.26 (s, 1H), 4.13 (s, 3H), 2.69 (s, 3H), 2.64 (s, 3H), 0.97 (s, 9H).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of 1,3-dimethyl-5-(tributylstannyl)-1H-pyrazolo[3,4-c]pyridine (31 mg,0.071 mmol), *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (42 mg, 0.085 mmol), copper(I) iodide (14 mg, 0.071 mmol) and lithium chloride (15 mg, 0.355 mmol) in dioxane (0.5 mL) was sparged with nitrogen for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (9 mg, 0.0008 mmol) and trans-dichlorobis(triphenylphosphine)palladium (II) (5 mg, 0.007 mmol) were added and reaction mixture was heated at 120°C for 5 hours. Reaction mixture was cooled to rt, diluted with dichloromethane, adsorbed onto silica gel and purified by CombiFlash (0 to 70% EtOAc/Hex) to give product contaminated with tributylstannane impurity. LCMS-ESI$^+$: calc'd for $C_{35}H_{35}ClN_5O_3S$: 640.2 (M+H^+); Found: 640.4 (M + H^+).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (17.9 mg, 0.032 mmol)and 5M NaOH (0.127 mL, 0.636 mmol) in MeOH (0.2 mL) and THF (1.2 mL) was stirred at 50°C for 3 hours, then stored in freezer overnight. DMF (0.3 mL) and acetic acid (0.011 mL) were added and reaction mixture was concentrated to ~0.3 mL, filtered using a syringe filter, diluted with methanol. Purified using Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) and lyophilized to give desired product. LCMS-ESI$^+$: calc'd for $C_{28}H_{28}ClN_4O_3S$: 535.2 (M+H^+); Found: 535.3 (M + H^+); ^{1}H NMR (400 MHz, CD_3OD) δ 8.83 (s, 1H), 8.45 (s, 1H), 7.73 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.57 (s, 1H), 5.26 (s, 1H), 4.02 (s, 3H), 2.59 (s, 3H), 2.53 (s, 3H), 0.97 (s, 9H).

Example 96. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-4-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (236).



236

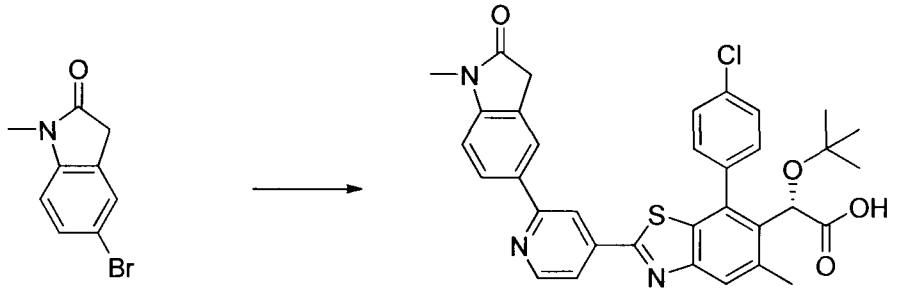
Preparation of (4,5,5-trimethyl-2-(1-methyl-2-oxoindolin-4-yl)-1,3,2-dioxaborolan-4-yl)methylium: To a solution of 4-bromo-1-methylindolin-2-one (154 mg, 0.68 mmol) in anhydous dioxane (4 mL, degassed) was added $Pd(dppf)Cl_2$ (74 mg, 0.15 eq.), bis(pinacolato)diboron (173 mg, 1 eq.) and KOAc (200 mg, 3 eq.). The reaction mixture was heated at 110 °C for 40 minutes, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give crude product which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{15}H_{20}BNO_3$: 274.2 ($M+H^+$); Found: 274.2 ($M + H^+$).

Preparation of Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (20 mg, 0.038 mmol) in dioxane (1.2 mL, degassed) was added (4,5,5-trimethyl-2-(1-methyl-2-oxoindolin-4-yl)-1,3,2-dioxaborolan-4-yl)methylium (16 mg, 1.5 eq.), $Pd(PPh_3)_4$ (6 mg, 0.05 eq.), K_2CO_3 (16 mg, 2 eq.) and water (0.1 mL). The reaction mixture was heated at 110 °C for 2 h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give crude

which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{36}H_{35}ClN_3O_4S$: 640.2 (M+H$^+$); Found: 640.3 (M + H$^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-4-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-4-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate (11 mg, 0.017 mmol) in pyridine (2 mL) was added ethyl iodide (100 mg, excess). The reaction mixture was heated at 170 °C in microwave reactor for 90 minutes and the crude was concentrated and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the product as TFA salt. LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_3O_4S$: 612.1 (M+H$^+$); Found: 612.2 (M + H$^+$); ^{1}H NMR (400 MHz, CD_3OD): δ 8.77 (d, 1H), 8.35 (s, 1 H), 7.93-7.92 (m, 2H), 7.70-7.68(m, 1H), 7.61-7.59 (m, 3H), 7.55-7.53 (m, 1H), 7.50-7.46(m, 1H), 7.08(d, 1H), 5.27 (s, 1H), 3.89 (s, 2H), 3.25 (s, 3H), 2.63(s, 3H), 0.97(s, 9H).

Example 97. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (237).



5-bromo-1-methylindolin-2-one

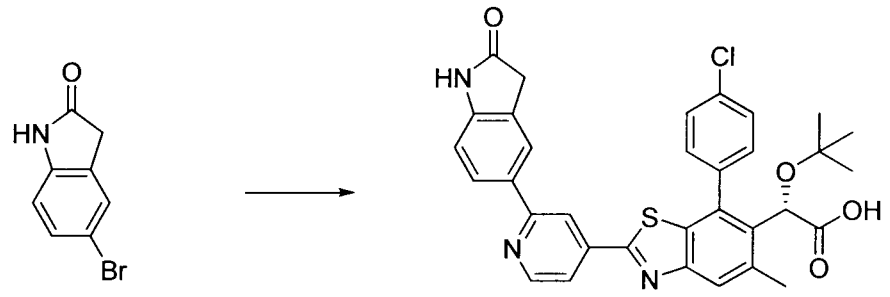
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

237

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid was prepared using in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-4-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid, except 5-bromo-1-methylindolin-2-one was used instead of 4-bromo-1-methylindolin-2-one. LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_3O_4S$: 612.1 (M+H$^+$); Found: 612.2 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD) δ: 8.61 (d, 1H), 8.36 (s, 1 H), 7.94 (d, 1H), 7.89 (m, 1H),

7.84 (m, 2H), 7.61-7.59 (m, 1H), 7.54-7.50(m, 3H), 7.03(d, 1H), 5.18 (s, 1H), 3.55(s, 2H), 3.14 (s, 3H), 2.53 (s, 3H), 0.89 (s, 9H).

Example 98. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (238).



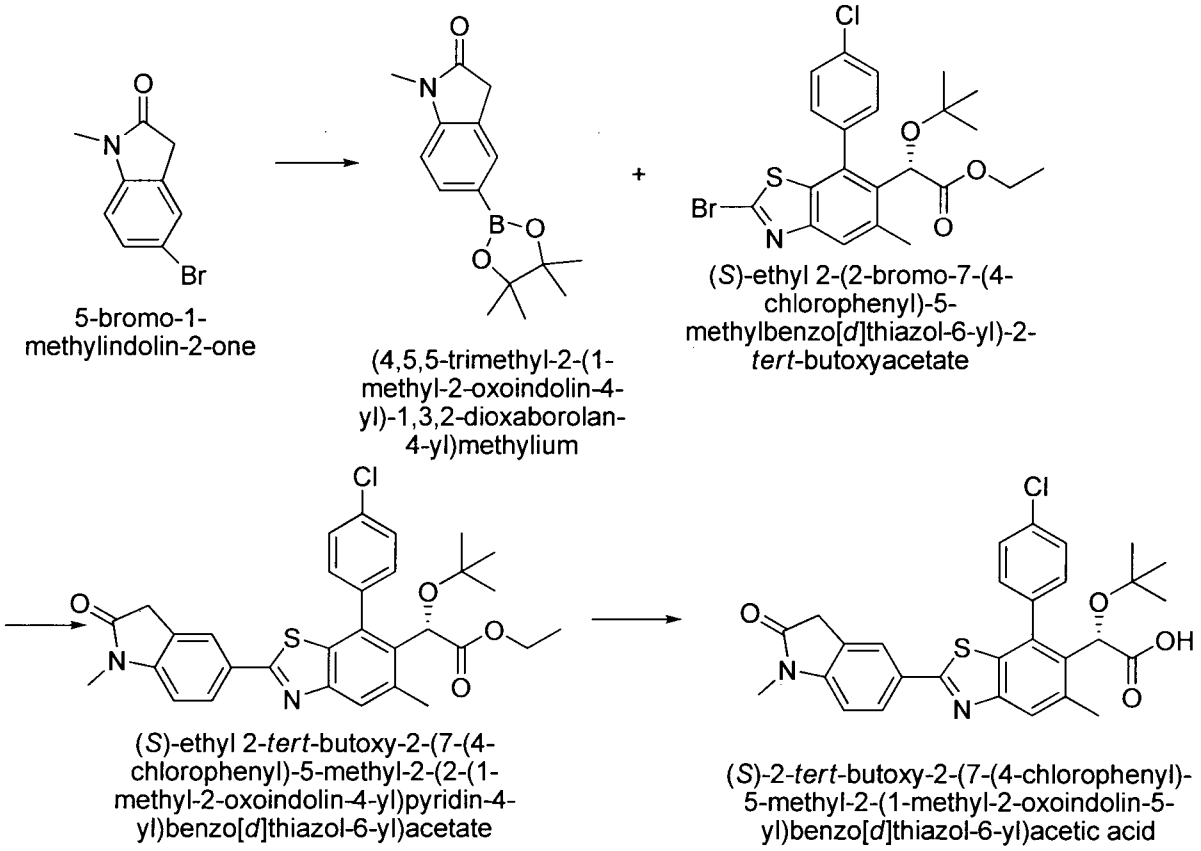
5-bromoindolin-2-one

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

238

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid was prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-4-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid except 5-bromoindolin-2-one was used instead of 4-bromo-1-methylindolin-2-one. LCMS-ESI$^+$: calc'd for $C_{33}H_{29}ClN_3O_4S$: 598.2 ($M+H^+$); Found: 598.3 ($M+H^+$); ^{1}H NMR (400 MHz, CD_3OD) δ: 8.71 (d, 1H), 8.45 (s, 1 H), 8.01 (d, 1H), 8.00-7.91 (m, 3H), 7.68 (m, 1H), 7.60(m, 3H), 7.06 (d, 1H), 5.27 (s, 1H), 3.63 (s, 2 H), 2.63 (s, 3H), 2.35 (s, 3H), 0.98 (s, 9H).

Example 99. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid (239).



239

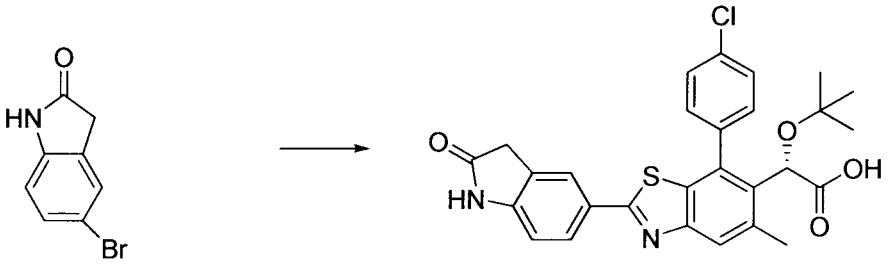
Preparation of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one: To a solution of 5-bromo-1-methylindolin-2-one (79 mg, 0.35 mmol) in anhydous dioxane (4 mL, degassed) was added $Pd(dppf)Cl_2$ (38 mg, 0.15 eq.), bis(pinacolato)diboron (89 mg, 1 eq.) and KOAc (69 mg, 3 eq.). The reaction mixture was heated at 110 °C for 40 minutes, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{15}H_{21}BNO_3$: 274.2 ($M+H^+$); Found: 274.2 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-4-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (50 mg, 0.1 mmol) in dioxane (1.2 mL, degassed) was added 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (30 mg, 1.1 eq.), $Pd(PPh_3)_4$ (17 mg, 0.05 eq.), K_2CO_3 (42 mg, 2 eq.) and water (0.1 mL). The reaction mixture was heated at 110 °C for 2 h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give crude which was purified by chromatographic column to afford

the desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{32}ClN_2O_4S$: 563.2 (M+H$^+$); Found: 563.3 (M + H$^+$).

Preparation *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-2-oxoindolin-4-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate (11 mg, 0.017 mmol) in pyridine (2 mL) was added ethyl iodide (100 mg, excess). The reaction mixture was heated at 170 °C in microwave reactor for 90 minutes and the crude was concentrated and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the product as TFA salt. LCMS-ESI$^+$: calc'd for $C_{29}H_{28}ClN_2O_4S$: 535.1 (M+H$^+$); Found: 535.2 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.96-7.84 (m, 2 H), 7.67 (s, 1H), 7.59-7.56 (m, 2H), 7.49-7.47 (m, 2H), 6.95(d, 1H), 5.14 (s, 1H), 3.52 (s, 2 H), 3.13 (s, 3H), 2.50 (s, 3H), 0.87(s, 9H).

Example 100. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid (240).

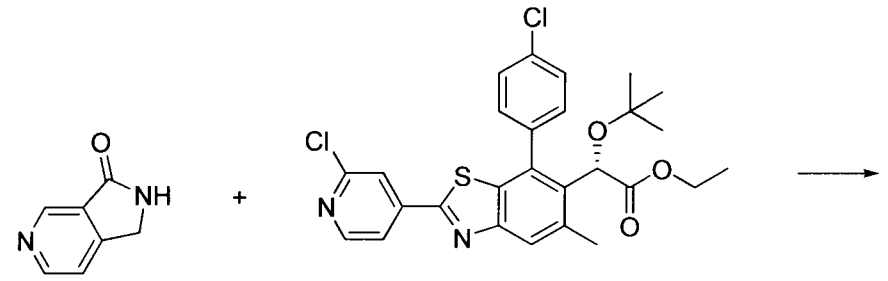


5-bromoindolin-2-one

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxoindolin-5-yl)benzo[*d*]thiazol-6-yl)acetic acid
240

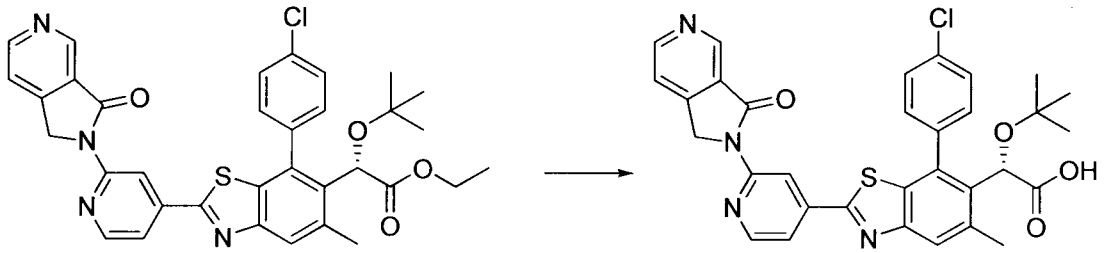
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid was prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid except 5-bromoindolin-2-one was used instead of 5-bromo-1-methylindolin-2-one. LCMS-ESI$^+$: calc'd $C_{28}H_{26}ClN_2O_4S$: 521.1 (M+H$^+$); Found: 521.2 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.91-7.88 (m, 2 H), 7.77 (s, 1H), 7.66 (m, 1H), 7.59-7.56 (m, 2H), 6.99(d, 1H), 5.23 (s, 1H), 3.61 (s, 2 H), 2.63 (s, 3H), 2.59 (s, 3H), 0.96 (s, 9H).

Example 101. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (241).



1*H*-pyrrolo[3,4-*c*]pyridin-3(2*H*)-one

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-1*H*-pyrrolo[3,4-*c*]pyridin-2(3*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-1*H*-pyrrolo[3,4-*c*]pyridin-2(3*H*)-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

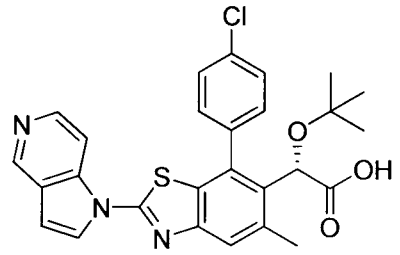
241

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (28 mg, 0.053 mmol) in anhydous THF (1.2 mL, degassed) was added $Pd_2(dba)_3$ (3 mg, 0.05 eq.), XantPhos (5 mg, 0.15 eq.), 1H-pyrrolo[3,4-c]pyridin-3(2H)-one (14 mg, 2 eq.) and Cs_2CO_3 (35 mg, 2 eq.). The reaction mixture was heated at 100 °C for 2 h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_4O_4S$: 627.2 ($M+H^+$); Found: 627.3 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-1H-pyrrolo[3,4-c]pyridin-

2(3H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate (28 mg, 0.044 mmol) in pyridine (2 mL) was added ethyl iodide (200 mg, excess). The reaction mixture was heated at 170 °C in microwave reactor for 90 minutes and the crude was concentrated and purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{28}ClN_4O_4S$: 599.1 ($M+H^+$); Found: 599.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD) δ: 8.80 (s, 1H), 8.58 (s, 2H), 8.18 (d, 1H), 7.57 (m, 2H), 7.50-7.43 (m, 4H), 7.33 (s, 1H), 5.14 (s, 1H), 4.68 (d, 2 H), 2.33 (s, 3H), 0.90 (s, 9H).

Example 102. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid (242).

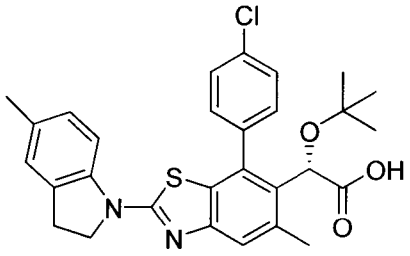


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxoindolin-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

242

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid was prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid except (S)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate was used instead of (S)-ethyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate, 1H-pyrrolo[3,2-c]pyridine was used instead 1H-pyrrolo[3,4-c]pyridin-3(2H)-one and $Pd(P\text{-}tBu_3)_2$ was used instead of $Pd_2(dba)_3$. LCMS-ESI$^+$: calc'd $C_{27}H_{25}ClN_3O_3S$: 506.0 ($M+H^+$); Found: 506.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD) δ: 9.31 (s, 1H), 9.18 (d, 1H), 8.66 (d, 1H), 8.31 (d, 1H), 7.90 (s, 1H), 7.72-7.70 (m, 1H), 7.63-7.61 (m, 3H), 7.32 (d, 1H), 5.26 (s, 1H), 2.63 (s, 3H), 0.98 (s, 9H).

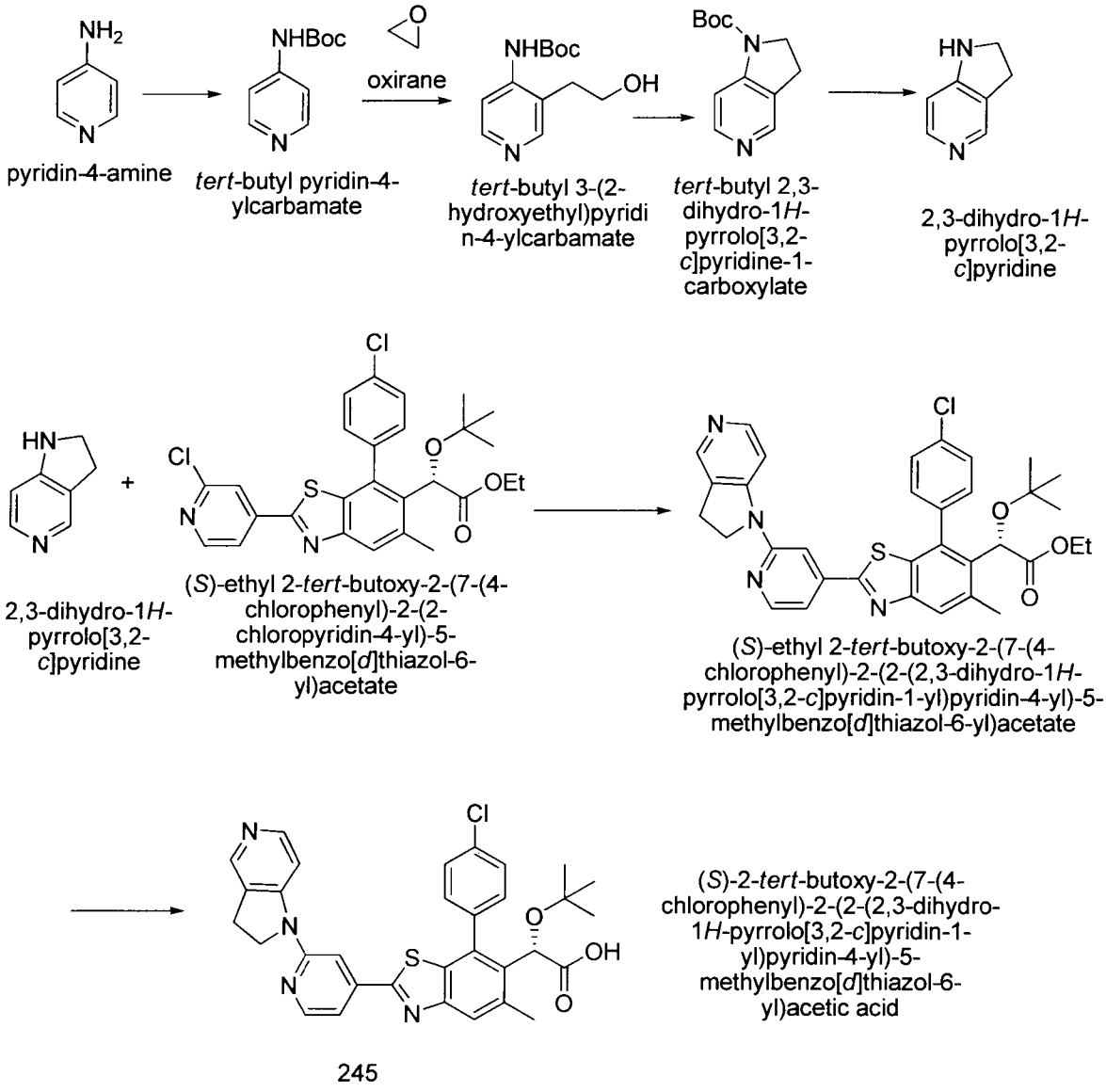
Example 103. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methylindolin-1-yl)benzo[d]thiazol-6-yl)acetic acid (243).



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methylindolin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid
243

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methylindolin-1-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methylindolin-1-yl)benzo[d]thiazol-6-yl)acetic acid was prepared in similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-oxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid except (S)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate was used instead of (S)-ethyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate, 5-Methylindoline was used instead 1H-pyrrolo[3,4-c]pyridin-3(2H)-one and Pd(P-$tBu_3)_2$ was used instead of $Pd_2(dba)_3$. LCMS-ESI$^+$: $C_{29}H_{30}ClN_2O_3S$: 521.2 ($M+H^+$); Found: 521.2 ($M + H^+$); ^1H NMR (400 MHz, CD_3OD) δ: 7.75 (s, 1H), 7.67-7.64 (m, 1H), 7.57-7.50 (m, 3H), 7.44(s, 1H), 7.12 (d, 1H), 6.84(d, 1H), 5.17 (s, 1H), 4.07 (dd, 2 H), 3.19 (dd, 2H), 2.53 (s, 3H), 2.35 (s, 3H), 0.95 (s, 9H).

Example 105. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (245).



Preparation of *tert*-butyl 2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxylate: Followed reference procedure (Spivey, Alan C. et al. *J. Org. Chem.* 1999, *64(26)*, 9430-9443) using pyridin-4-amine. LCMS-ESI$^+$: calc'd for $C_{12}H_{17}N_2O_2$: 221.1 ($M+H^+$); Found: 221.0 ($M+H^+$).

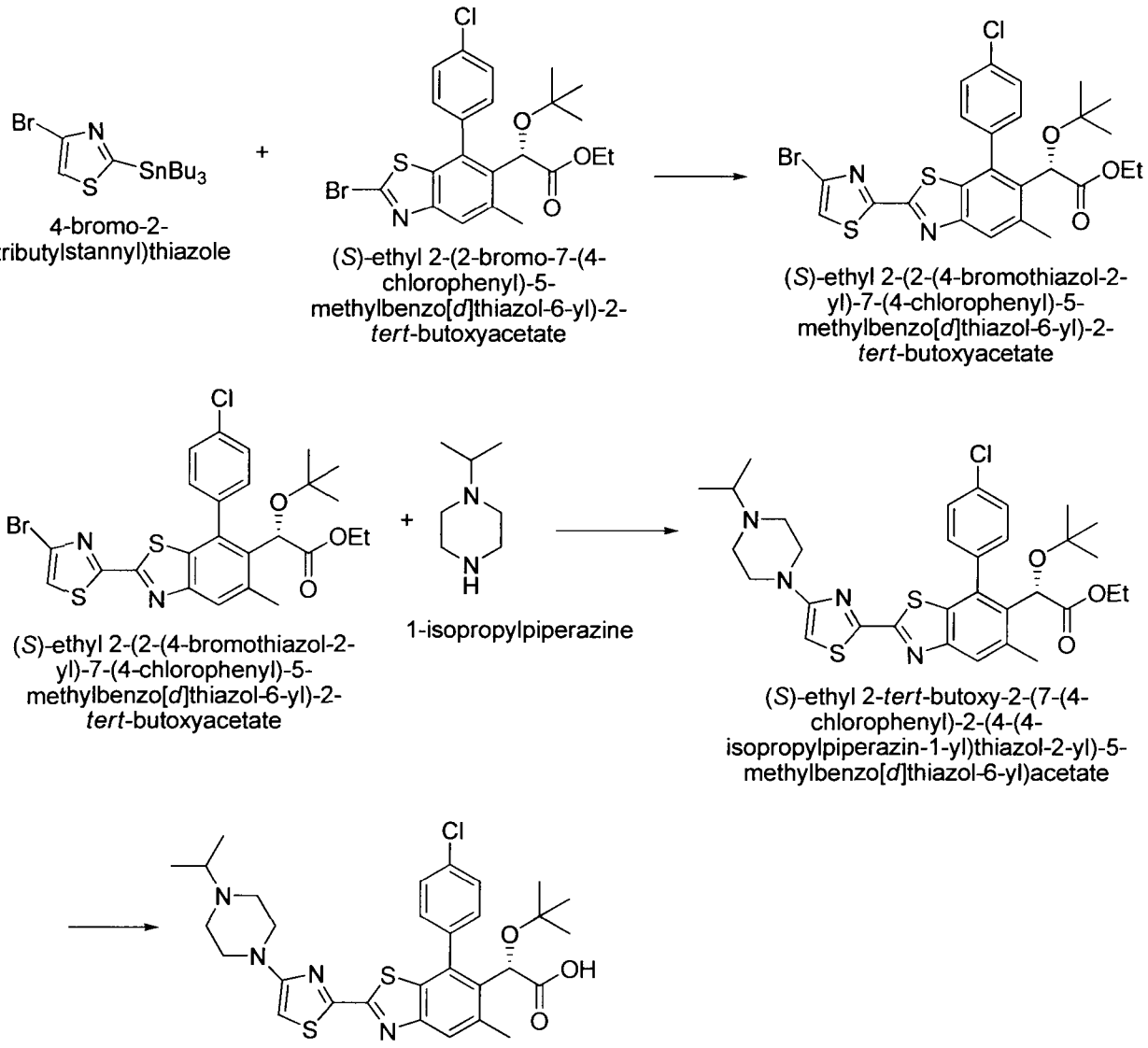
Preparation 2,3-dihydro-1H-pyrrolo[3,2-c]pyridine: *tert*-Butyl 2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxylate (280 mg) was dissolved in 5 mL DCM. TFA (1mL) was added room temperature. The reaction was stirred at room temperature for 1 hour. Concentrated down the reaction mixture and the crude material was used in next step without purification. Crude ^{1}H NMR (400 MHz, CD_3OD): δ 8.43 (d, 1H), 8.37 (s, 1 H), 8.07 (d, 1H), 4.22 (dd, 2 H), 3.36 (m, 2H).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: In a 5 mL

microwave reaction tube, 2,3-dihydro-1H-pyrrolo[3,2-c]pyridine TFA salt (excess), *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (26 mg, 0.05 mmol), bis(tri-*tert*-butylphosphine)palladium (0) (4 mg, 15%), cetyltrimethylammonium bromide (3 mg) were charged with 1 mL toluene, then 1 drop of 50% KOH aqueous solution was added. The reaction was heated to 105 °C for 1 hour. LC-MS of the reaction crude show desired product. The reaction crude was extracted using ethyl acetate form brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{34}H_{34}ClN_4O_3S$: 613.1 ($M+H^+$); Found: 613.3 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (18 mg, 0.017 mmol) in THF (0.3 mL) and methanol (0.3 mL) was added NaOH (0.1 mL of 2N solution). The reaction mixture was heated at 45 °C for 2 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. LCMS-ESI$^+$: calc'd for $C_{32}H_{30}ClN_4O_3S$: 585.1 ($M+H^+$); Found: 585.2 ($M+H^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.62(d,1H), 8.58(d, 1H), 8.33 (d, 1H), 8.23(s, 1H), 7.87 (s, 1H), 7.66-7.61(m, 3), 7.59– 7.49(m, 3H), 5.24(s, 1H), 4.43 (m, 2H), 3,42(m, 2H), 2.61 (s, 3H), 0.98(s, 9H).

Example 106. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(4-isopropylpiperazin-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl) acetic acid (246).



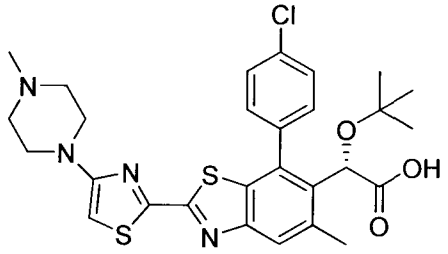
246

Preparation of *(S)*-ethyl 2-(2-(4-bromothiazol-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: In a 5 mL microwave reaction tube, *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (240 mg, 0.5 mmol), 4-bromo-2-(tributylstannyl)thiazole (0.25 mL, 1.5 eq.), $Pd(PPh_3)_4$ (84 mg, 15%) and CuI (14 mg, 15%) were charged, then 4 mL dioxane was added. The reaction mixture was purged N_2, then heated to 100 °C for 3 hour. LC-MS of reaction crude showed desired product mass. The reaction crude was partitioned using ethyl acetate and brine. The organic layer was concentrated and purified via CombiFlash column (0-50% ethyl acetate / hexane) to give desired product. LCMS-ESI$^+$: calc'd for $C_{25}H_{25}BrClN_2O_3S_2$: 565.9, found. 567.0 ($M + H^+$).

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: In a 5 mL microwave reaction tube, *(S)*-methyl 2-(2-(4-bromothiazol-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (50 mg, 0.08 mmol), isopropylpiperazine (34 mg, 3 eq.), Bis(tri-t-butylphosphine)palladium (0) (3 mg, 15%), cetyltrimethylammonium bromide (4 mg, 0.5 eq.) were charged with 1 mL toluene, then 1 drop of 50% KOH aqueous solution (excess) was added. The reaction was heated to 105 °C for 1 hour. Reaction mixture was purified by HPLC (0.1% TFA in ACN and water) to give desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{38}ClN_4O_3S_2$: 613.2 ($M+H^+$); Found: 613.4 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (4 mg) in THF (0.3 mL) and methanol (0.3 mL) was added NaOH (0.1 mL of a 2N solution). The reaction mixture was heated at 50 °C for 2 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. LCMS-ESI$^+$: calc'd for $C_{30}H_{36}ClN_4O_3S_2$: 599.2 ($M+H^+$); Found: 599.1. ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 8.68-7.66(m, 1H), 7.60-7.56 (m, 3H), 6.65 (s, 1H), 5.25 (s, 1H), 3.60-3.56 (m, 4H), 3.30-3.10 (m, 5H), 2.63(s, 3H), 1.41 (d, 6H), 0.99 (s, 9H).

Example 107. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (247).



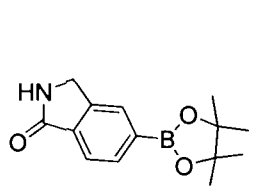
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

247

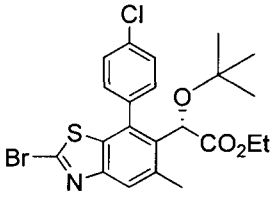
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid was prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid except using 1-methylpiperazine instead of 1-isopropylpiperazine. LCMS-ESI$^+$: calc'd for $C_{28}H_{32}ClN_4O_3S_2$:

571.2 ($M+H^+$); Found: 570.9. ($M + H^+$). ^1H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 8.68-7.66(m, 1H), 7.60-7.56 (m, 3H), 6.65 (s, 1H), 5.25 (s, 1H), 3.56-3.30 (m, 8H), 2.96 (s, 3H), 2.61 (s, 3H), 0.96 (s, 9H).

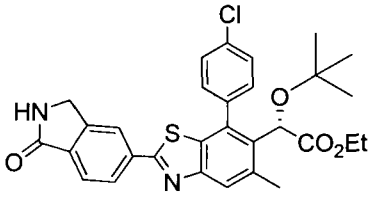
Example 108. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-oxoisoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid (248).



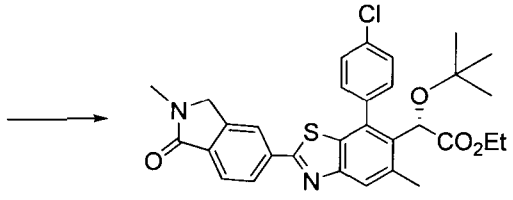
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one



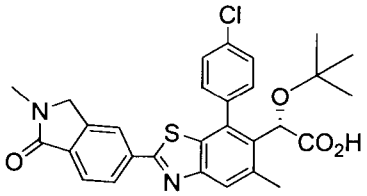
(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxoisoindolin-5-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-oxoisoindolin-5-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-oxoisoindolin-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

248

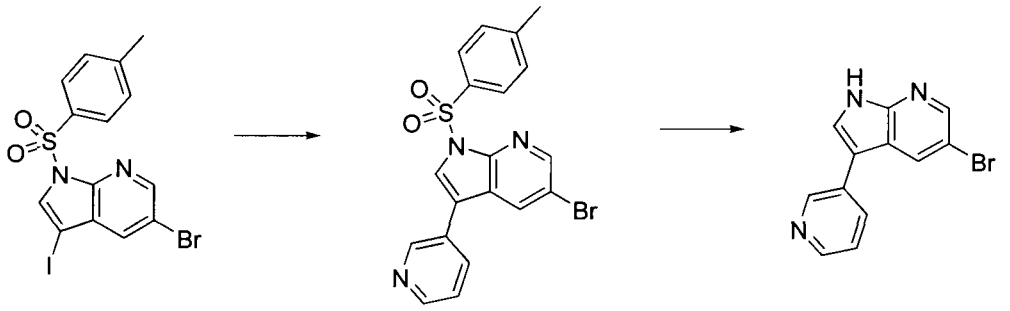
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxoisoindolin-5-yl)benzo[d]thiazol-6-yl)acetate: *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxoisoindolin-5-yl)benzo[d]thiazol-6-yl)acetate was prepared in a similar manner as *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetate in Method J, except using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one. LCMS-ESI$^+$: calc'd for $C_{30}H_{29}ClN_2O_4S$: 549.2 ($M+H^+$); found: 549.2 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-oxoisoindolin-5-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-oxoisoindolin-5-yl)benzo[d]thiazol-6-yl)acetate (94 mg, 0.171 mmol) in DMF (2.0 mL) was added NaH (~10 mg, 60% oil dispersion) at 0 °C. After 15 min, iodomethane (0.016 mL, 0.256 mmol) was added and after 30 min the reaction was allowed to

warm to room temperature. Satd. aqueous NH_4Cl was added and the reaction was diluted with EtOAc, washed sequentially with 5% aqueous LiCl and brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography on silica gel using EtOAc to provide the title compound. LCMS-ESI$^+$: calc'd for $C_{31}H_{31}ClN_2O_4S$: 563.2 ($M+H^+$); found: 563.2 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-oxoisoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-oxoisoindolin-5-yl)benzo[d]thiazol-6-yl)acetate (36 mg, 0.064 mmol) dissolved in THF/MeOH (1.25 mL/1.25 mL) and 2N NaOH (0.160 mL) was heated at 50 °C for 2 h and the crude was purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the title compound. LCMS-ESI$^+$: calc'd for $C_{29}H_{27}ClN_2O_4S$: 535.1 ($M+H^+$); found: 535.2 ($M+H^+$). ^1H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.65-7.51 (m, 4H), 5.03 (s, 1H), 4.46 (s, 2H), 3.03 (s, 3H), 2.48 (s, 3H), 0.83 (s, 9H).

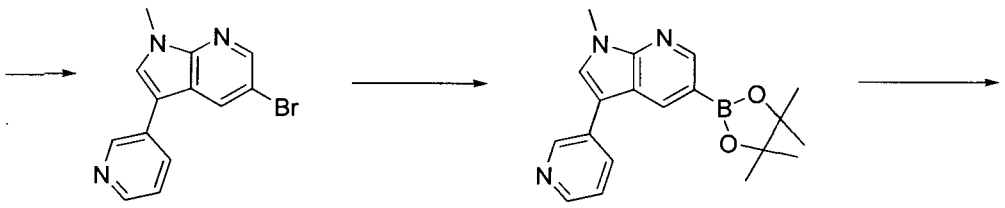
Example 109. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetic acid (249).



5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine

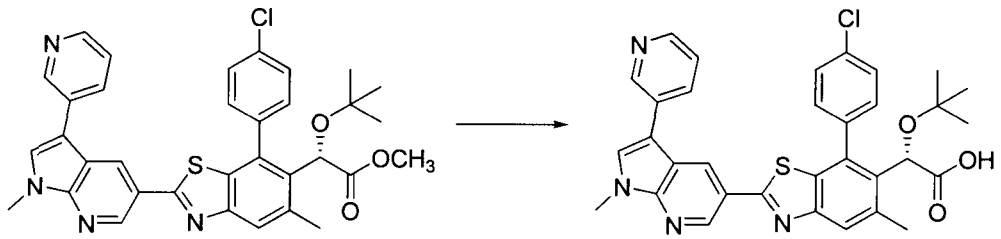
5-bromo-3-(pyridin-3-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine

5-bromo-3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine



5-bromo-1-methyl-3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine

1-methyl-3-(pyridin-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

249

Preparation of 5-bromo-3-(pyridin-3-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine: To a screw top reaction tube was placed 5-bromo-3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (1.2 g, 2.52 mmol, prepared according to WO2011/149950), pyridin-3-ylboronic acid (371 mg, 3.02 mmol) and trans-dichlorobis(triphenylphosphine)palladium (II) (177 mg, 0.25 mmol). Degassed acetonitrile (16 mL) and 1 N Na_2CO_3 (16 mL) was added and the reaction tube was purged with argon, sealed and heated at 60 °C for 2 h. The reaction was cooled, filtered through a Celite pad and concentrated under reduced pressure. The residue was partitioned between EtOAc/water and extracted. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give a solid. Trituration of the solid with hexanes and dichloromethane gave the desired compound. LCMS-ESI$^+$: calc'd for $C_{19}H_{14}BrN_3O_2S$: 428.0 ($M+H^+$); found: 428.2 ($M+H^+$).

Preparation of 5-bromo-3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine: To a solution of 5-bromo-3-(pyridin-3-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (662 mg, 1.55 mmol) in acetone (30 mL) and methanol (20 mL) was added 2N NaOH (1.8 mL). The reaction was heated in a 65 °C oil bath for 1h and then evaporated to near dryness. The crude reaction product was partitioned between EtOAc and 1N NaOH and extracted. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give product that was used for the next step without any further purification. LCMS-ESI$^+$: calc'd for $C_{12}H_8BrN_3$: 274.0 ($M+H^+$); found: 274.1 ($M+H^+$).

Preparation of 5-bromo-1-methyl-3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine: To a solution of the crude material (assume 0.43 mmol) from the previous reaction in DMF (15 mL) was added NaH (93 mg of a 60% oil dispersion, 2.32 mmol) in several portions at 0 °C. After 15 min, iodomethane (0.145 mL, 0.33 mmol) was added and the reaction allowed to slowly warm to room temperature and stirred for 2 h. The bulk of the DMF was removed under reduced pressure and the residue partitioned between EtOAc/water. The organic layer was separated and washed with 5% LiCl, brine, dried over Na_2SO_4 and concentrated to give a dark orange residue. The crude material was passed through a short column of silica gel eluting with 100% EtOAc to provide the desired product. LCMS-ESI$^+$: calc'd for $C_{13}H_{10}BrN_3$: 288.0 ($M+H^+$); found: 288.1 ($M+H^+$).

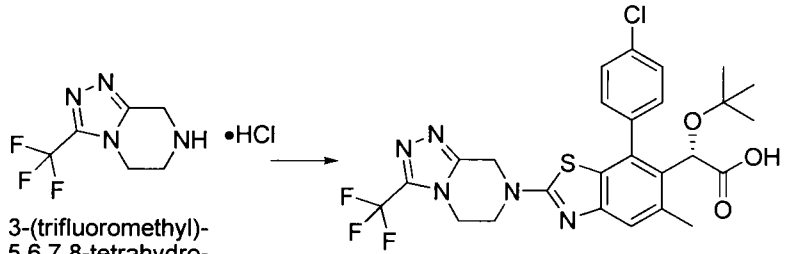
Preparation of 1-methyl-3-(pyridin-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine: To a large microwave vial was placed -bromo-1-methyl-3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (90 mg, 0.31 mmol), bis(pinacolato)diboron (87 mg, 0.34 mmol), dichloro 1,1-bis(diphenylphosphino)ferrocene palladium(II) dichloromethane (26 mg, 0.031 mmol) and potassium acetate (92 mg, 0.94 mmol). Degassed 1,4-dioxane (3.0 mL) was added and the vial was sealed after purging with argon and heated in a 90 °C oil bath for 2.5 h. The reaction was cooled, filtered through a short plug of silica gel on Celite using EtOAc and concentrated to give product that was used in the next step without any further purification. LCMS-ESI$^+$: calc'd for $C_{19}H_{22}BN_3O_2$: 336.2 ($M+H^+$); found: 336.2 ($M+H^+$).

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetate: To a microwave vial containing the crude material from the previous reaction (assume 0.31 mmol) was added *(S)*-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (136 mg, 0.28 mmol) and tetrakis(triphenylphosphine)palladium 936 mg, 0.03 mmol). Degassed 1,4-

dioxane (3.0 mL) and 2N K_2CO_3 (0.47 mL) was added and the vial was sealed after purging with argon and heated in a 100 °C oil bath for 2.5 h. The reaction was cooled, partitioned between EtOAc/water and extracted. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give the crude material. Purification of the residue by flash column chromatography on silica gel using a gradient of EtOAc to 30% MeOH in EtOAc provided the desired compound. LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_4O_3S$: 611.2 ($M+H^+$); found: 611.2 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetic acid: A solution of the material from the previous reaction was dissolved in THF/MeOH (4.0 mL/ 4.0 mL) and 2N NaOH (0.70 mL). The reaction was heated at 45 °C overnight and then evaporated to dryness. Water (~0.50 mL) was added followed by HOAc (~10 drops). Acetonitrile was added dropwise to produce a tan precipitate that was collected by filtration. The collected solid was washed with water/acetonitrile and dried under vacuum to give the desire product. LCMS-ESI$^+$: calc'd for $C_{33}H_{29}ClN_4O_3S$: 597.2 ($M+H^+$); found: 597.3 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 8.86 (bs, 2H), 8.71 (s, 1H), 8.44 (d, J = 4.7 Hz, 1H), 8.13 (d, J = 7.4 Hz, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.60 (s, 3H), 7.52-7.47 (m, 1H), 5.26 (s, 1H), 3.90 (s, 3H), 2.60 (s, 3H), 0.97 (s, 9H).

Example 110. *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)benzo[d]thiazol-6-yl)acetic acid (250).



3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride

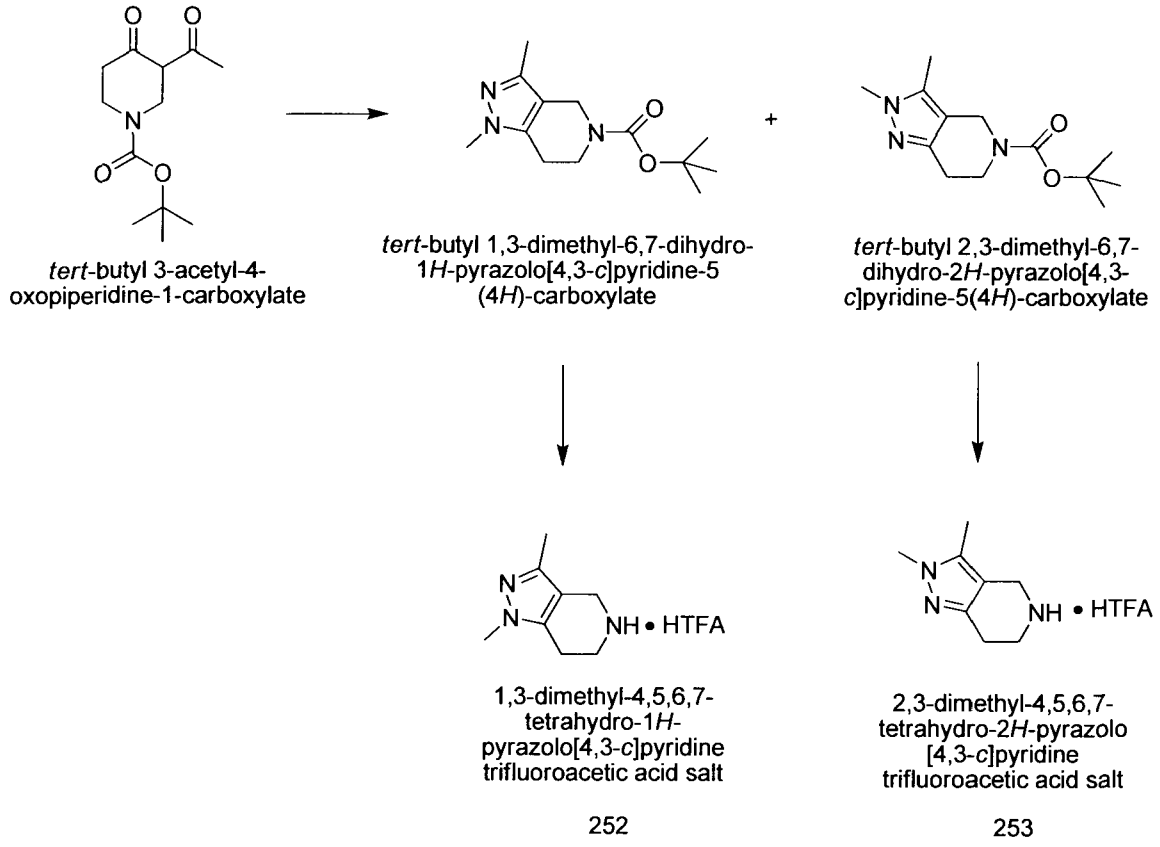
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)benzo[*d*]thiazol-6-yl)acetic acid

250

Prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid except using 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride instead of 5,6,7,8-tetrahydro-1,6-naphthyridine, dihydrochloride, hydrate. LCMS-ESI$^+$: calc'd for

$C_{26}H_{25}ClF_3N_5O_3S$: 580.1, 582.1 ($M+H^+$); Found: 580.2, 582.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD): δ 7.72 – 7.45 (m, 4H), 7.41 (s, 1H), 5.16 (s, 1H), 5.09 (s, 2H), 4.38 (t, J = 5.4 Hz, 2H), 4.11 (t, J = 5.5 Hz, 2H), 2.51 (s, 3H), 0.95 (s, 2H).

Example 111. Preparation of 1,3-dimethyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine trifluoroacetic acid salt (252) and 2,3-dimethyl-4,5,6,7-tetrahydro-2H-pyrazolo [4,3-c]pyridine trifluoroacetic acid salt (253).



252 253

Preparation of *tert*-butyl 1,3-dimethyl-6,7-dihydro-1H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate and *tert*-butyl 2,3-dimethyl-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate: A vial was charged with glacial AcOH (2.0 mL). N-Methylhydrazine (500 μL) was added dropwise over 3 min at an initial temperature of 23 °C. The reaction became warm. Once the reaction had cooled back to 23 °C, a solution of *tert*-butyl 3-acetyl-4-oxopiperidine-1-carboxylate (500 mg, 2.07 mmol) in glacial AcOH (500 μL) was added. The reaction was heated to 80 °C for 1 h. The reaction was carefully added to saturated aq $NaHCO_3$ (100 mL)(bubbling). The system was extracted with EtOAc (1x). The extract was dried over Na_2SO_4, filtered, and concentrated. The residue was treated with DCM and purification by flash column chromatography on silica gel (DCM to DCM/MeOH 4:1, detection at 210 nM) provided the two title compounds.

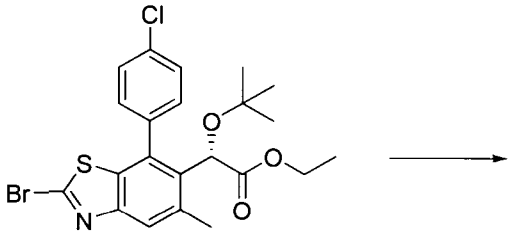
tert-butyl 1,3-dimethyl-6,7-dihydro-1H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate: LCMS-ESI$^+$: calc'd for $C_{13}H_{21}N_3O_2$: 252.2 (M+H$^+$); Found: 252.0 (M + H$^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38 – 4.22 (m, broad, 2H), 3.68 (s, 3H), 3.68 (s, broad, 2H) 2.63 (dd, broad, J = 13.1, 7.6 Hz, 2H), 2.17 (s, 3H), 1.49 (s, 9H).

tert-butyl 2,3-dimethyl-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate: LCMS-ESI$^+$: calc'd for $C_{13}H_{21}N_3O_2$: 252.2 (M+H$^+$); Found: 252.0 (M + H$^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.42 – 4.25 (m, 2H), 3.72 (s, 3H), 3.67 (s, broad, 2H), 2.68 (dd, broad, J = 18.1, 12.6 Hz, 2H), 2.16 (s, 3H), 1.47 (s, 9H).

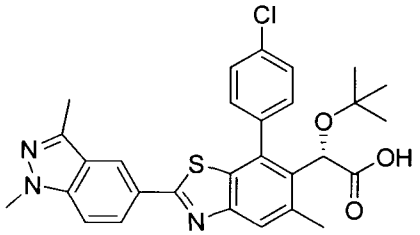
Preparation of 1,3-dimethyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine trifluoroacetic acid salt: A solution of *tert*-butyl 1,3-dimethyl-6,7-dihydro-1H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate (all of the product from the previous reaction above) in DCM (2.0 mL) was treated with TFA (500 μL), then stirred for 3 h at 23 °C. The reaction was then concentrated, giving the desired product in crude form. The material was immediately used in the next reaction. LCMS-ESI$^+$: calc'd for $C_8H_{13}N_3$: 152.1 (M+H$^+$); Found: 152.0 (M + H$^+$).

Preparation of 2,3-dimethyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine trifluoroacetic acid salt: Prepared in a manner similar to 1,3-dimethyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine trifluoroacetic acid salt, except using *tert*-butyl 2,3-dimethyl-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate instead of *tert*-butyl 1,3-dimethyl-6,7-dihydro-1H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate. LCMS-ESI$^+$: calc'd for $C_8H_{13}N_3$: 152.1 (M+H$^+$); Found: 152.0 (M + H$^+$).

Example 112. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (254).



(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

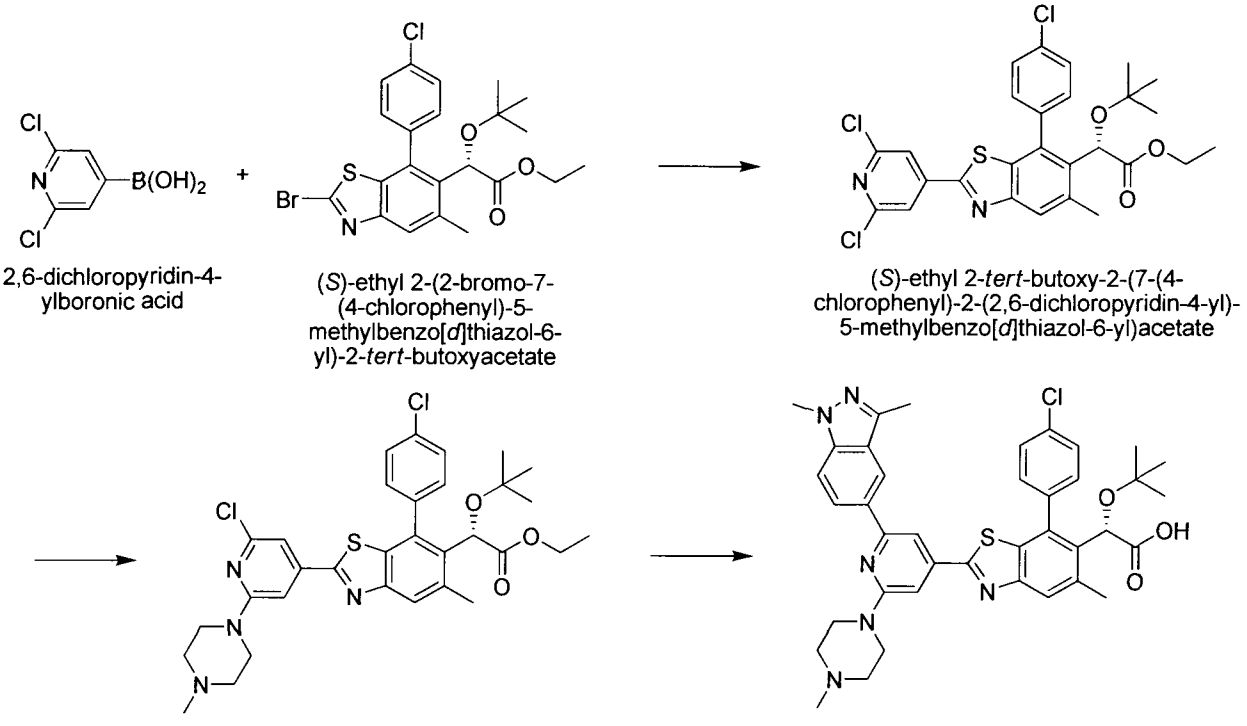


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-indazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

254

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (100 mg, 0.202 mmol), 1,3-dimethylindazole-5-boronic acid (42 mg, 0.22 mmol), $Pd(PPh_3)_4$ (23 mg, 20 μmol), 2 M aq K_2CO_3 (800 μL), and dioxane (3.2 mL). The reaction was heated to 100 °C for 2 h. The reaction was treated with absolute EtOH (1.6 mL) and 10 M aq NaOH (800 μL). After heating to 100 °C for 2 h, the reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{29}H_{28}ClN_3O_3S$: 534.2, 536.2 ($M+H^+$); Found: 534.3, 536.3 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.35 (s, 1H), 8.08 (dd, J = 8.9, 1.6 Hz, 1H), 7.81 (s, 1H), 7.75 – 7.64 (m, 1H), 7.62 – 7.52 (m, 4H), 5.26 (s, 1H), 4.01 (s, 3H), 2.61 (s, 3H), 2.57 (s, 3H), 0.98 (s, 9H).

Example 113. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-indazol-5-yl)-6-(4-methylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (255).



255

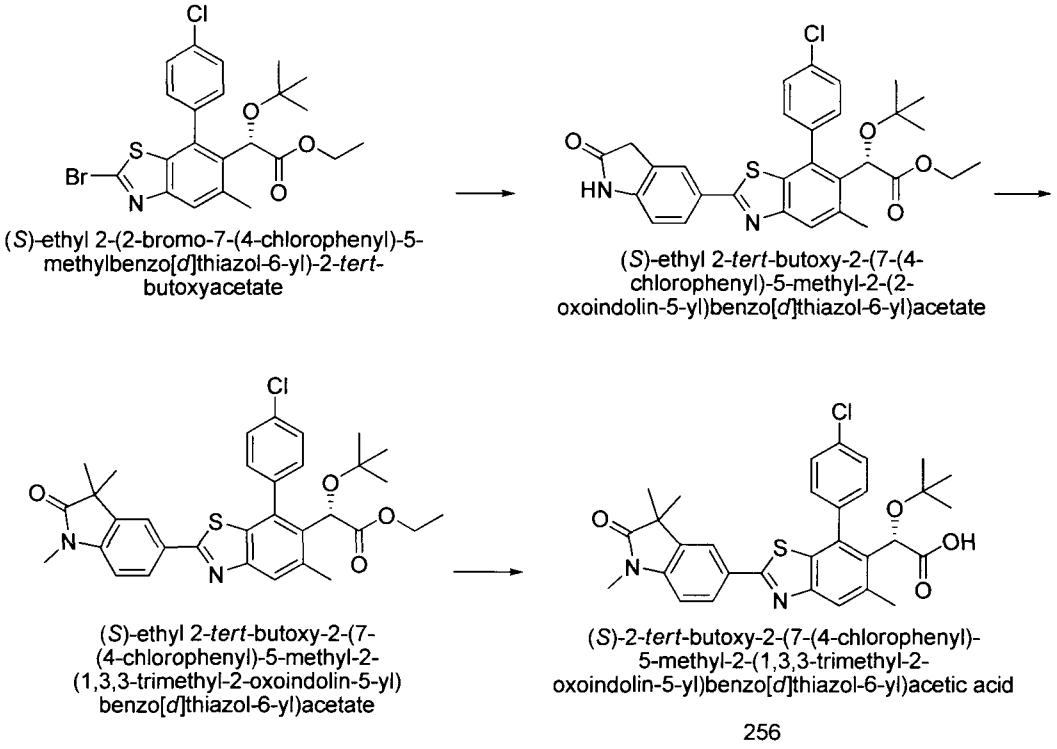
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2,6-dichloropyridin-4-

yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A microwave tube was charged with $Pd(PPh_3)_4$ (4 mg), *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (25 mg), the 2,6-dichloropyridin-4-ylboronic acid (10 mg), dioxane (250 μL) and 2M aq K_2CO_3 (100 μL). The vessel was sealed and heated to 100 °C overnight. At 16 h, the reaction had only reached ~60% conversion. The reaction was cooled to 23 °C, diluted with absolute EtOH (1.5 mL) and H_2O (500 μL), and was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{27}H_{25}Cl_3N_2O_3S$: 563.1, 565.1, 567.1 ($M+H^+$); Found: 563.1, 565.0, 567.1 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(2-(2-chloro-6-(4-methylpiperazin-1-yl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate: A solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2,6-dichloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (10 mg), *N*-methylpiperazine (10 mg), and DMA (250 μL) were combined in a microwave tube and heated to 100 °C for 30 min. Reaction was cooled to 23 °C and diluted with absolute ethanol and was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the title compound. LCMS-ESI$^+$: calc'd for $C_{32}H_{36}Cl_2N_4O_3S$: 627.2, 629.2 ($M+H^+$); Found: 627.2, 629.2 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-indazol-5-yl)-6-(4-methylpiperazin-1-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: Prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid. LCMS-ESI$^+$: calc'd for $C_{39}H_{42}ClN_6O_3S$: 709.3, 711.3 ($M+H^+$); Found: 709.4, 711.2. ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 8.44 (s, 1H), 8.23 (d, J = 9.1 Hz, 1H), 7.93 (app. s, 2H), 7.74 – 7.47 (m, 5H), 7.41 (s, 1H), 5.28 (s, 1H), 4.86 – 4.68 (m, 2H), 3.99 (s, 3H), 3.80 – 3.52 (m, 2H), 3.39 – 3.12 (m, 4H), 2.99 (s, 3H), 2.64 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).

Example 114. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1,3,3-trimethyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid (256).



256

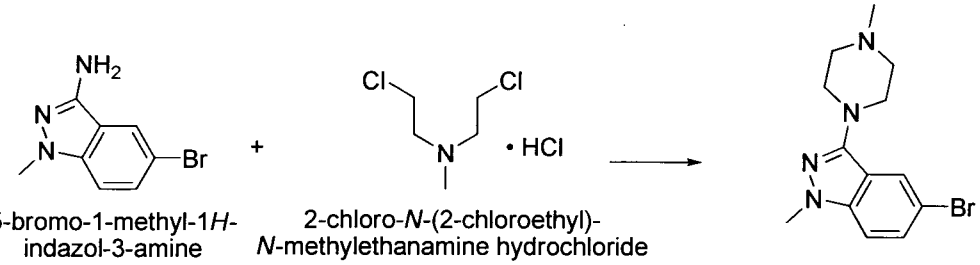
Preparation of: *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetate: A vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (100 mg, 0.202 mmol), 2-(oxindole-5'-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (58 mg, 0.221 mmol), $Pd(PPh_3)_4$ (23 mg, 20 μmol), solid K_2CO_3 (92 mg, 0.66 mmol), dioxane (1.6 mL), and H_2O (400 μL). The vessel was sealed and heated to 100 °C for 1.5 h. The reaction was diluted with water and extracted with EtOAc (2x). Combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was treated with benzene and purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the product. LCMS-ESI$^+$: calc'd for $C_{30}H_{29}ClN_2O_4S$: 549.2, 551.2 ($M+H^+$); Found: 549.3, 551.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3CN): δ 8.60 (s, broad, 1H), 7.92 – 7.77 (m, 2H), 7.76 (s, 1H), 7.62 – 7.42 (m, 4H), 6.91 (d, J = 8.1 Hz, 1H), 5.17 (s, 1H), 4.29 – 3.93 (m, 2H), 3.48 (s, 2H), 2.53 (s, 3H), 1.28 – 1.11 (m, 3H), 0.93 (s, 9H).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1,3,3-trimethyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetate: A vial was charged with *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetate (45 mg, 82 μmol), Cs_2CO_3 (134 mg, 0.410 mmol), iodomethane (51 μL, 0.82 mmol), and DMF (500 μL). The reaction was warmed to 50 °C for 2 h. The reaction was diluted with EtOAc and washed with 5% w/v aq LiCl (3x). The organic phase was dried (Na_2SO_4), filtered, and

concentrated, giving the product, which was immediately used in the next step. LCMS-ESI$^+$: calc'd for $C_{30}H_{29}ClN_2O_4S$: 591.2, 593.2 (M+H$^+$); Found: 591.3, 593.3 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3CN): δ 8.04 – 7.88 (m, 2H), 7.81 (s, 1H), 7.63 – 7.48 (m, 4H), 7.02 (d, J = 8.1 Hz, 1H), 5.18 (s, 1H), 4.32 – 4.06 (m, 2H), 3.15 (s, 3H), 2.51 (s, 3H), 1.41 (s, 6H), 1.27 – 1.12 (m, 3H), 0.94 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1,3,3-trimethyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetic acid: The crude *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1,3,3-trimethyl-2-oxoindolin-5-yl)benzo[d]thiazol-6-yl)acetate from the reaction above was treated with 1.0 M aq NaOH (2 mL), THF (4 mL), and absolute EtOH (2 mL). The reaction was heated to 50 °C for 19 h. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{31}ClN_2O_4S$: 563.2, 565.2 (M+H$^+$); Found: 563.3, 565.3 (M + H$^+$). $^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 8.05 – 7.94 (m, 2H), 7.81 (s, 1H), 7.73 – 7.64 (m, 1H), 7.64 – 7.54 (m, 3H), 7.14 (d, J = 8.2 Hz, 1H), 5.26 (s, 1H), 3.27 (s, 3H), 2.61 (s, 3H), 1.41 (s, 6H), 0.98 (s, 9H).

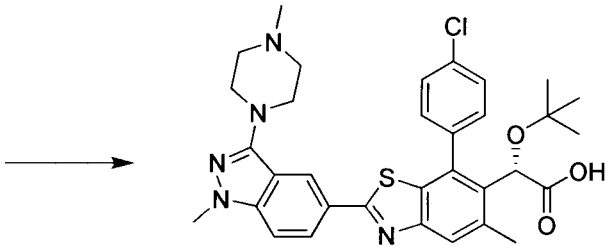
Example 115. *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (257).



5-bromo-1-methyl-1*H*-indazol-3-amine

2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine hydrochloride

5-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1*H*-indazole



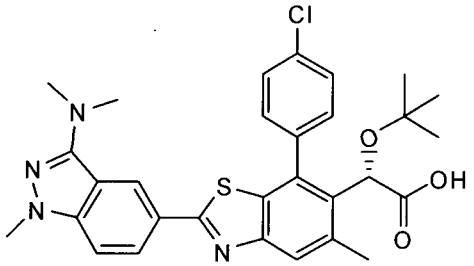
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

257

Preparation of 5-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazole: A vessel was charged with 5-bromo-1-methyl-1H-indazol-3-amine (250 mg, 1.10 mmol), 2-chloro-*N*-(2-chloroethyl)-N-methylethanamine hydrochloride (230 mg, 1.21 mmol), H_2O (250 μL), K_2CO_3 (500 mg, 3.63 mmol), and DMF (2.5 mL). The vessel was sealed and heated to 100 °C for 18 h. The reaction was poured into EtOAc and washed with 5% w/v aq LiCl (3x), dried (Na_2SO_4), filtered, and concentrated. The residue was treated with DCM and purification by flash column chromatography on silica gel (hexanes/ethyl acetate to remove side products; then DCM/MeOH eluent to elute product) provided 5-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazole. LCMS-ESI$^+$: calc'd for $C_{13}H_{17}BrN_4$: 309.1, 311.1 (M+H$^+$); Found: 309.2, 311.2 (M + H$^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid: A vial was charged with 5-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazole (64.0 mg, 0.208 mmol), bis-pinacolatodiboron (58 mg, 0.23 mmol), $PdCl_2$(dppf)·DCM (17 mg, 21 μmol), glacial AcOH (13 μL, 0.23 mmol), KOAc (67 mg, 0.69 mmol), and dioxane (1.6 mL). The reaction was heated to 100 °C for 2 h. To this reaction was added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (103 mg, 0.208 mmol), $KHCO_3$ (23 mg, 0.23 mmol), 2 M aq K_2CO_3 (400 μL), and $Pd(PPh_3)_4$ (24 mg, 21 μmol). The reaction was heated for another 1 h at 100 °C. Finally, EtOH (absolute, 800 μL) and 10 M aq NaOH (500 μL) were added. The reaction was heated to 100 °C for another 1 h. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{33}H_{36}ClN_5O_3S$: 618.2, 620.2 (M+H$^+$); Found: 618.4, 620.2 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 8.43 (s, 1H), 8.05 (d, J = 8.9 Hz, 1H), 7.80 (s, 1H), 7.68 (d, J = 9.1 Hz, 1H), 7.62 – 7.47 (m, 4H), 5.24 (s, 1H), 4.31 – 4.01 (m, 2H), 3.94 (s, 3H), 3.74 – 3.54 (m, 2H), 3.54 – 3.35 (m, 2H), 3.32 – 3.16 (m, 2H), 3.00 (s, 3H), 2.61 (s, 3H), 0.97 (s, 9H).

Example 116. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(dimethylamino)-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (258).

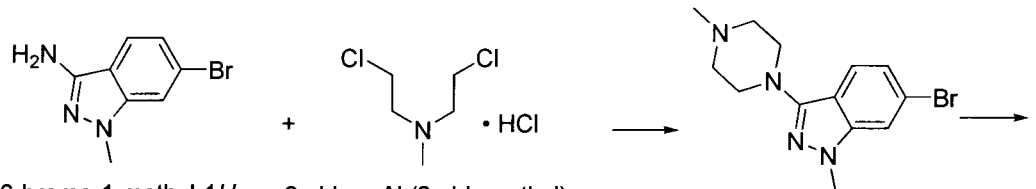


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(dimethylamino)-1-methyl-1*H*-indazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

258

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(dimethylamino)-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: Prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid, except using 5-bromo-N,N,1-trimethyl-1H-indazol-3-amine instead of 5-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazole. LCMS-ESI$^+$: calc'd for $C_{30}H_{31}ClN_4O_3S$: 563.2, 565.2 (M+H$^+$); Found: 563.2, 565.2 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 8.49 (s, 1H), 7.96 (dd, J = 8.9, 1.5 Hz, 1H), 7.78 (s, 1H), 7.74 – 7.64 (m, 1H), 7.62 – 7.52 (m, 3H), 7.41 (d, J = 8.9 Hz, 1H), 5.25 (s, 1H), 3.86 (s, 3H), 3.16 (s, 6H), 2.60 (s, 3H), 0.97 (s, 9H).

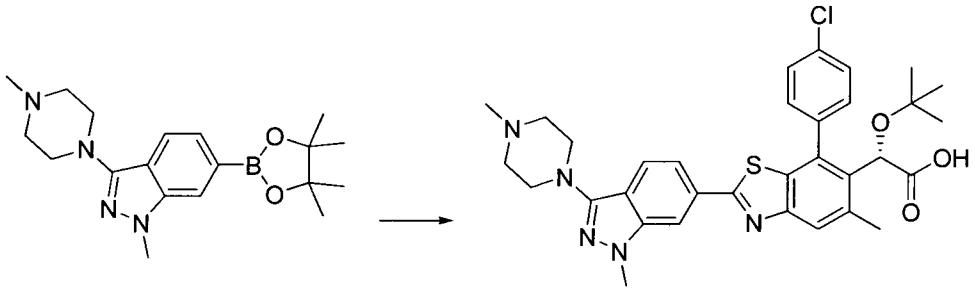
Example 117. *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazol-6-yl)benzo[d]thiazol-6-yl)acetic acid (259).



6-bromo-1-methyl-1*H*-indazol-3-amine

2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine hydrochloride

6-bromo-1-methyl-3-(4-methyl piperazin-1-yl)-1*H*-indazole



1-methyl-3-(4-methylpiperazin-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1*H*-indazol-6-yl)benzo[*d*]thiazol-6-yl)acetic acid

259

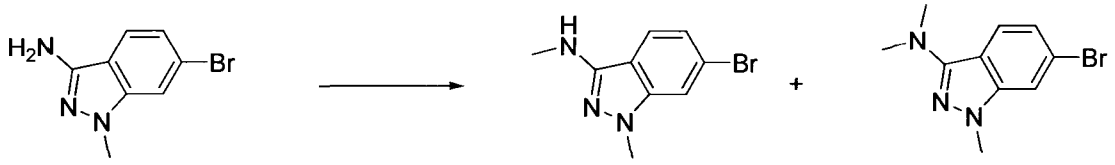
Preparation of 6-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazole: Prepared in a manner similar to 5-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazole but using 6-bromo-1-methyl-1H-indazol-3-amine instead of 5-bromo-1-methyl-1H-indazol-3-amine. LCMS-ESI$^+$: calc'd for $C_{13}H_{17}BrN_4$: 309.1, 311.1 (M+H$^+$); Found: 309.2, 311.2 (M + H$^+$).

Preparation of 1-methyl-3-(4-methylpiperazin-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole: A vial was charged with 6-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazole (200 mg, 0.649 mmol), glacial AcOH (41 μL, 0714 mmol), KOAc (210 mg, 2.14 mmol), $PdCl_2$(dppf)·DCM (53 mg, 65 μmol), bis-pinacolatodiboron (181 mg, 0.714 mmol), and dioxane (2.0 mL). The reaction was sealed and heated to 100 °C for 1 h. The reaction was cooled to 23 °C and diluted with water. The system was treated with EtOAc and filtered through Celite. The filtrate was extracted with EtOAc (2x). Combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was treated with benzene and purification by flash column chromatography on silica gel (hexanes/ethyl acetate (side products elute) then DCM/MeOH eluent to isolate product) provided 1-methyl-3-(4-methylpiperazin-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole. LCMS-ESI$^+$: calc'd for $C_{19}H_{29}BN_4O_2$: 357.2 (M+H$^+$); Found: 357.3 (M + H$^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazol-6-yl)benzo[d]thiazol-6-yl)acetic acid: A vial was charged

with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (75 mg, 0.151 mmol), $KHCO_3$ (15.2 mg, 0.151 mmol), K_2CO_3 (41.7 mg, 0.302 mmol), 1-methyl-3-(4-methylpiperazin-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (55 mg, 0.154 mmol), $Pd(PPh_3)_4$ (17 mg, 15 μmol), H_2O (400 μL), and dioxane (1.6 mL). The vessel was sealed and heated to 100 °C for 2 h. Then EtOH (absolute, 800 μL) and 2 M aq NaOH (400 μL) were added. Heating was continued at 100 °C for 3 h. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{33}H_{36}ClN_5O_3S$: 618.2, 620.2 ($M+H^+$); Found: 618.3, 620.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.10 (s, 1H), 7.93 – 7.83 (m, 2H), 7.79 – 7.65 (m, 2H), 7.64 – 7.55 (m, 3H), 5.16 (s, 2H), 4.09 (d, J = 12.9 Hz, 1H), 3.97 (s, 3H), 3.63 (d, J = 8.7 Hz, 2H), 3.39 (d, J = 11.5 Hz, 2H), 3.36 – 3.22 (m, 2H), 3.00 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).

Example 118. Preparation of 6-bromo-N,1-dimethyl-1H-indazol-3-amine (260) and 6-bromo-N,N,1-trimethyl-1H-indazol-3-amine (261).



6-bromo-1-methyl-1*H*-indazol-3-amine

6-bromo-*N*,1-dimethyl-1*H*-indazol-3-amine

260

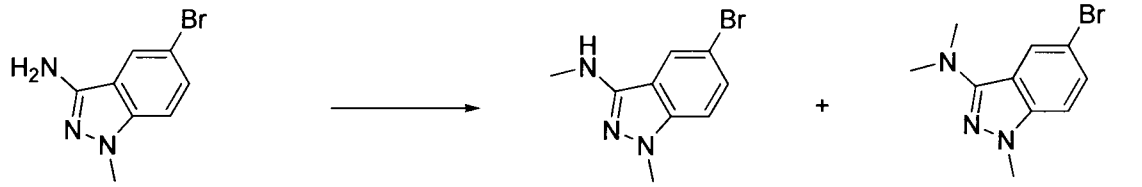
6-bromo-*N*,*N*,1-trimethyl-1*H*-indazol-3-amine

261

Preparation of 6-bromo-N,1-dimethyl-1H-indazol-3-amine and 6-bromo-N,N,1-trimethyl-1H-indazol-3-amine: A vial was charged with 6-bromo-1-methyl-1H-indazol-3-amine (500 mg, 2.21 mmol), $NaBH(OAc)_3$ (2.33 g, 11.0 mmol), DMF (5.0 mL), and glacial AcOH (630 μL, 11.0 mmol). The reaction was heated to 60 °C and sealed. Then 37% w/w aq formaldehyde (765 μL, 11.0 mmol formaldehyde) was added dropwise over 5 min. Pressure increased during the addition. At 5 h, the reaction was cooled to 23 °C and shaken with 1.0 M aq NaOH (50 mL). EtOAc (100 mL) was added. The organic phase was collected. It was washed with 5% aq LiCl (2 x 50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was treated with DCM/Benzene and purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) provided the two title products:
6-bromo-N,1-dimethyl-1H-indazol-3-amine. LCMS-ESI$^+$: calc'd for $C_9H_{10}BrN_3$: 240.0, 242.0 ($M+H^+$); Found: 240.1, 242.1 ($M + H^+$).

6-bromo-N,N,1-trimethyl-1H-indazol-3-amine. LCMS-ESI$^+$: calc'd for $C_{10}H_{12}BrN_3$: 254.0, 256.0 (M+H$^+$); Found: 254.2, 256.1 (M + H$^+$).

Example 119. 5-bromo-N,1-dimethyl-1H-indazol-3-amine (262) and 5-bromo-N,N,1-trimethyl-1H-indazol-3-amine (263).



5-bromo-1-methyl-1*H*-indazol-3-amine

5-bromo-*N*,1-dimethyl-1*H*-indazol-3-amine

262

5-bromo-*N*,*N*,1-trimethyl-1*H*-indazol-3-amine

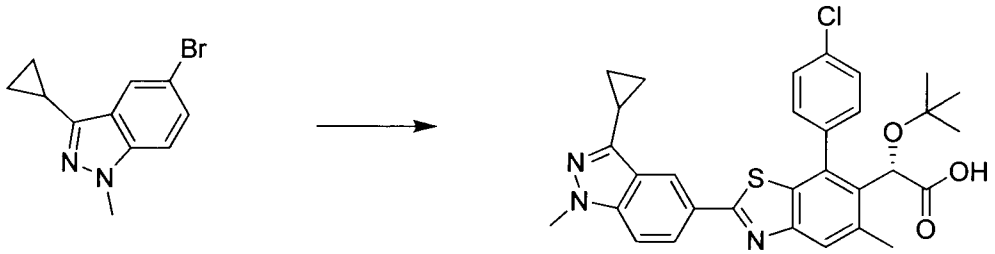
263

Preparation of 5-bromo-N,1-dimethyl-1H-indazol-3-amine and 5-bromo-N,N,1-trimethyl-1H-indazol-3-amine: Each was prepared in a manner similar to 6-bromo-N,1-dimethyl-1H-indazol-3-amine and 6-bromo-N,N,1-trimethyl-1H-indazol-3-amine, respectively except using 5-bromo-1-methyl-1H-indazol-3-amine instead of 6-bromo-1-methyl-1H-indazol-3-amine.

5-bromo-N,1-dimethyl-1H-indazol-3-amine. LCMS-ESI$^+$: calc'd for $C_9H_{10}BrN_3$: 240.0, 242.0 (M+H$^+$); Found: 240.1, 242.1 (M + H$^+$).

5-bromo-N,N,1-trimethyl-1H-indazol-3-amine. LCMS-ESI$^+$: calc'd for $C_{10}H_{12}BrN_3$: 254.0, 256.0 (M+H$^+$); Found: 254.1, 256.1 (M + H$^+$).

Example 120. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-cyclopropyl-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (264).



5-bromo-3-cyclopropyl-1-methyl-1*H*-indazole

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-cyclopropyl-1-methyl-1*H*-indazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

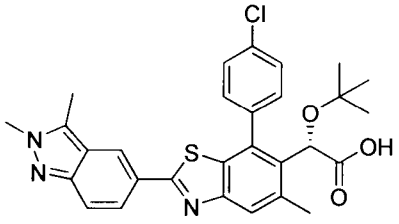
264

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-cyclopropyl-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A vial was charged with 5-bromo-3-cyclopropyl-1-methyl-1H-indazole (49 mg, 0.19 mmol), bis-pinacolatodiboron (53 mg, 0.21

mmol), $PdCl_2(dppf)\cdot DCM$ (15 mg, 19 μmol), KOAc (62 mg, 0.62 mmol), and dioxane (1.6 mL). The reaction was sealed and heated to 100 °C for 2 h. *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (94 mg, 0.190 mmol), $Pd(PPh_3)_4$ (22 mg, 19 μmol), and 2 M aq K_2CO_3 (400 μL) were added; the reaction was heated at 100 °C for 1.5 h. The reaction was treated with absolute EtOH (2 mL) and 10 M aq NaOH (2 mL). After heating to 100 °C for 1 h, the reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{30}ClN_3O_3S$: 560.2, 562.2 ($M+H^+$); Found: 560.2, 562.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.37 (s, 1H), 7.99 (dd, J = 8.8, 1.3 Hz, 1H), 7.77 (s, 1H), 7.72 – 7.66 (m, 1H), 7.58 (d, J = 3.2 Hz, 3H), 7.49 (d, J = 8.9 Hz, 1H), 5.25 (s, 1H), 3.93 (s, 3H), 2.59 (s, 3H), 2.26 (ddd, J = 13.1, 8.3, 5.2 Hz, 1H), 1.16 – 0.98 (m, 4H), 0.97 (s, 9H).

Example 121. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2,3-dimethyl-2H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (265).

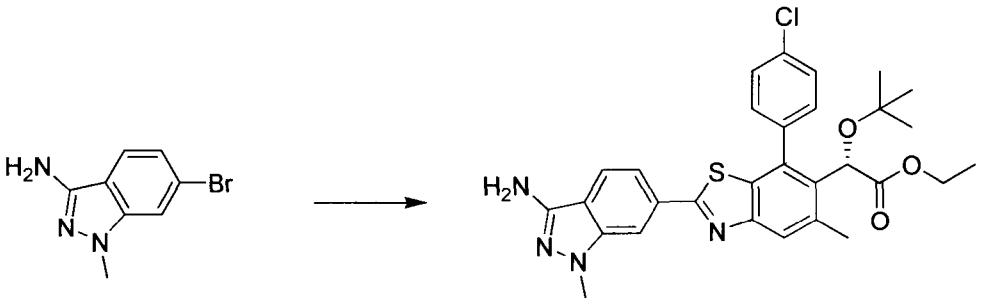
5-bromo-2,3-dimethyl-2*H*-indazole



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2,3-dimethyl-2*H*-indazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid
265

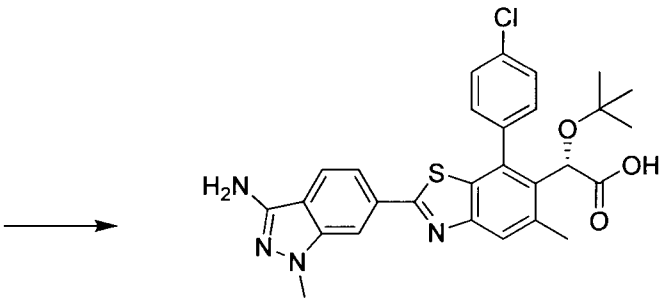
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2,3-dimethyl-2H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: prepared in a similar manner as the preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-cyclopropyl-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid except using 5-bromo-2,3-dimethyl-2H-indazole instead of 5-bromo-3-cyclopropyl-1-methyl-1H-indazole. LCMS-ESI$^+$: calc'd for $C_{29}H_{28}ClN_3O_3S$: 534.2, 536.2 ($M+H^+$); Found: 534.2, 536.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.37 (s, 1H), 7.99 (dd, J = 9.1, 1.7 Hz, 1H), 7.82 (s, 1H), 7.76 – 7.66 (m, 1H), 7.66 – 7.50 (m, J = 9.1, 4.8 Hz, 4H), 5.26 (s, 1H), 4.12 (s, 3H), 2.71 (s, 3H), 2.62 (s, 3H), 0.99 (s, 9H).

Example 122. Preparation of *(S)*-2-(2-(3-amino-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (266).



6-bromo-1-methyl-1*H*-indazol-3-amine

(*S*)-ethyl 2-(2-(3-amino-1-methyl-1*H*-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-2-(2-(3-amino-1-methyl-1*H*-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid

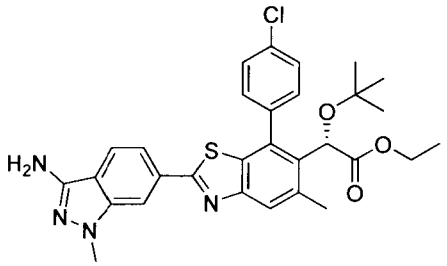
266

Preparation of *(S)*-ethyl 2-(2-(3-amino-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: A vessel was charged with 6-bromo-1-methyl-1H-indazol-3-amine (191 mg, 0.846 mmol), bis-pinacolatodiboron (236 mg, 0.930 mmol), $PdCl_2(dppf)\cdot DCM$ (69 mg, 85 μmol), glacial KOAc (273 mg, 2.79 mmol), and dioxane (3.2 mL). The reaction was heated to 100 °C for 1 h. To this reaction was added *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (420 mg, 0.846 mmol), 2 M aq K_2CO_3 (800 μL), and $Pd(PPh_3)_4$ (98 mg, 85 μmol). The reaction was heated for another 1 h at 100 °C. The reaction was diluted with water and extracted with EtOAc (3x). Combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was treated with benzene and purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) gave the title compound in semi-pure form. The mixture was treated with DCM and purification by flash column chromatography on silica gel (DCM/MeOH eluent) giving the title compound. LCMS-ESI$^+$: calc'd for $C_{30}H_{31}ClN_4O_3S$: 563.2, 565.2 ($M+H^+$); Found: 563.3, 565.3 ($M+H^+$).

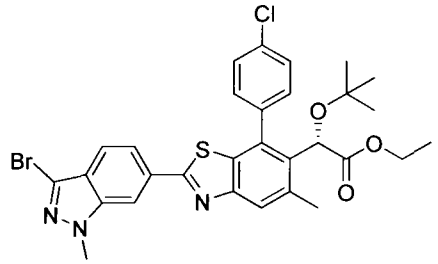
Preparation of *(S)*-2-(2-(3-amino-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid: A vial was charged with *(S)*-ethyl 2-(2-(3-amino-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-

butoxyacetate (60 mg), THF (1.5 mL), EtOH (absolute, 1 mL), and 2M aq NaOH (1 mL). The vessel was sealed and heated to 100 °C for 2 h. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{28}H_{27}ClN_4O_3S$: 535.2, 537.2 ($M+H^+$); Found: 535.2, 537.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.06 (s, 1H), 7.87 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.78 – 7.65 (m, 2H), 7.64 – 7.54 (m, 3H), 5.27 (s, 1H), 3.90 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).

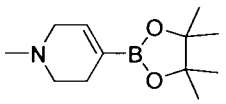
Example 123. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methylpiperidin-4-yl)-1H-indazol-6-yl)benzo[d]thiazol-6-yl)acetic acid (267).



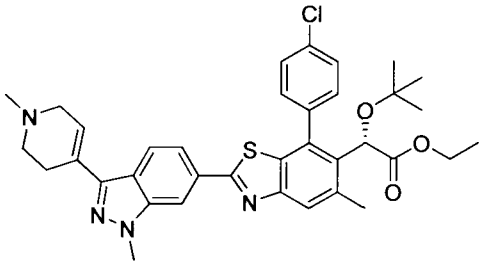
(*S*)-ethyl 2-(2-(3-amino-1-methyl-1*H*-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



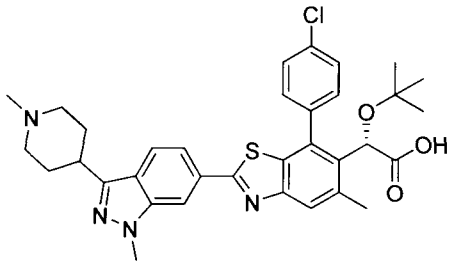
(*S*)-ethyl 2-(2-(3-bromo-1-methyl-1*H*-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazol-6-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methylpiperidin-4-yl)-1*H*-indazol-6-yl)benzo[*d*]thiazol-6-yl)acetic acid

267

Preparation of *(S)*-ethyl 2-(2-(3-bromo-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: A flask was charged with *(S)*-ethyl 2-(2-(3-

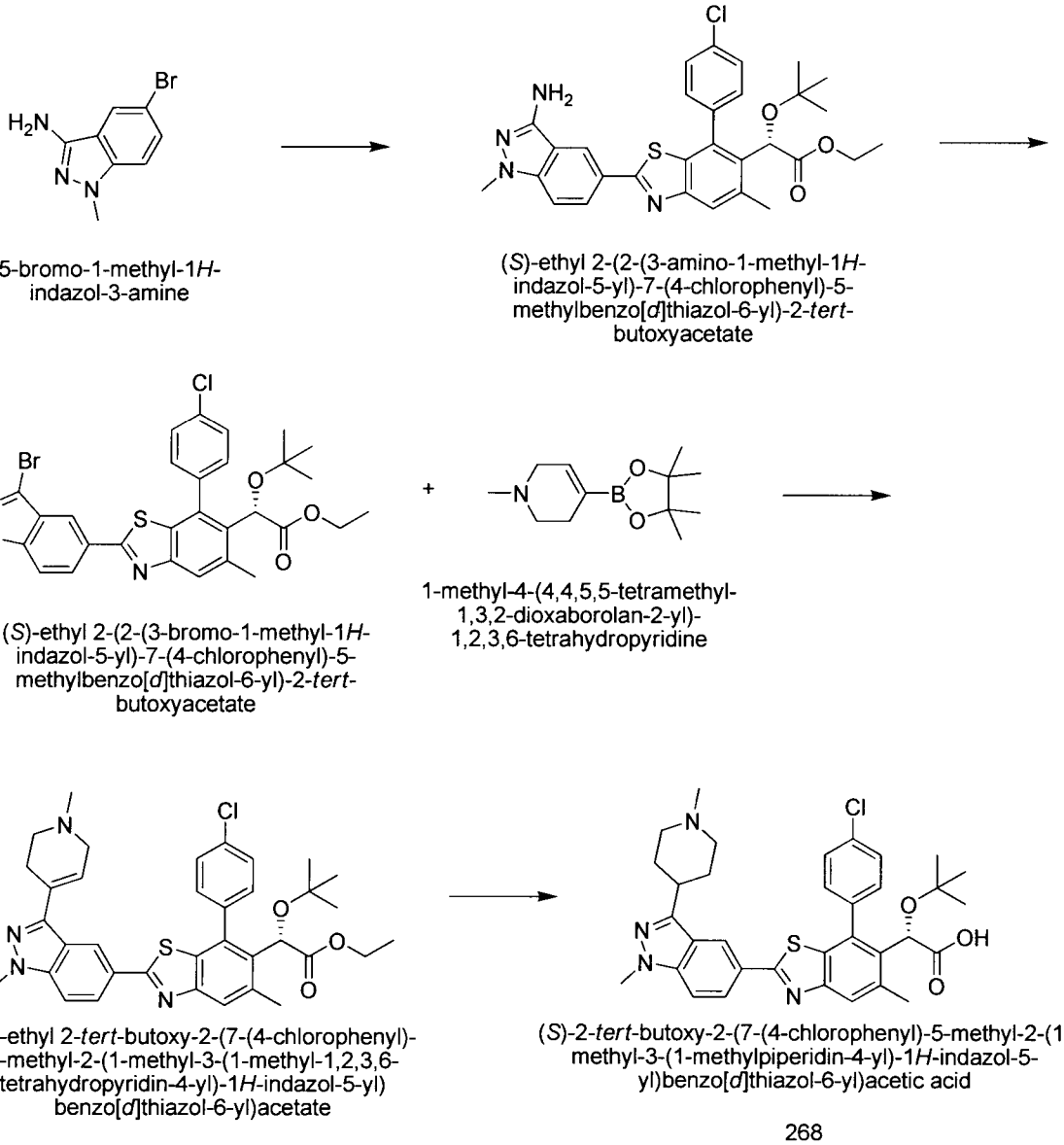
amino-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (227 mg, 0.403 mmol) and CH_3CN (4.0 mL). A solution of t-butyl nitrite (46 mg, 0.443 mmol) in CH_3CN (400 μL) was added, followed by $CuBr_2$ (anhydrous, 108 mg, 0.484 mmol). The reaction was fitted with a bubbler and stirred for 30 min at 23 °C. The reaction was diluted with water and EtOAc, then filtered through celite. The filtrate was extracted with EtOAc (2x). Combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was treated with benzene and purification by flash column chromatography on silica gel (hexanes/ethyl acetate eluent) gave the title compound. LCMS-ESI$^+$: calc'd for $C_{30}H_{29}BrClN_3O_3S$: 626.1, 628.1, 630.1 ($M+H^+$); Found: 626.1, 628.1, 630.2 ($M + H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazol-6-yl)benzo[d]thiazol-6-yl)acetate: A vial was charged with *(S)*-ethyl 2-(2-(3-bromo-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (36 mg, 57 μmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (13 mg, 57 μmol), $KHCO_3$ (6.3 mg, 63 μmol), $Pd(PPh_3)_4$ (6.7 mg, 5.7 μmol), 2 M aq K_2CO_3 (250 μL), and dioxane (1 mL). The vessel was sealed and heated to 100 °C for 1 h. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{36}H_{39}ClN_4O_3S$: 643.2, 645.2 ($M+H^+$); Found: 643.0, 645.0 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.27 (s, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.97 – 7.82 (m, 2H), 7.72 – 7.48 (m, 4H), 6.61 (s, 1H), 5.27 (s, 1H), 4.38 – 4.18 (m, 2H), 4.14 (s, 3H), 4.06 – 3.93 (m, 2H), 3.65 – 3.46 (m, 1H), 3.21 – 3.07 (m, 3H), 3.03 (s, 3H), 2.61 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.00 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methylpiperidin-4-yl)-1H-indazol-6-yl)benzo[d]thiazol-6-yl)acetic acid: A flask was charged with 5% w/w Rh/Al_2O_3 (20 mg, 9.6 μmol), *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazol-6-yl)benzo[d]thiazol-6-yl)acetate (22.3 mg), and EtOH (absolute, 2 mL). The reaction was evacuated (vacuum) and backfilled from a balloon of H_2, then stirred vigorously at 23 °C for 2.5 h. At this point, the reaction was treated with THF (1 mL), and 5 M aq NaOH (1 mL), then heated to 100 °C for 30 min. The reaction was cooled to 23 °C, and filtered (0.45 micron teflon syringe filter). The filtrate was purified by reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the desired product. LCMS-ESI$^+$: calc'd for $C_{34}H_{37}ClN_4O_3S$:

617.2, 619.2 ($M+H^+$); Found: 617.4, 619.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.22 (s, 1H), 7.98 – 7.78 (m, 3H), 7.71 (d, J = 8.4 Hz, 1H), 7.65 – 7.57 (m, 3H), 5.28 (s, 1H), 4.13 (s, 0.5 H, minor diastereomer), 4.09 (s, 2.5 H, major diastereomer), 3.73 – 3.60 (m, 2H), 3.54 – 3.37 (m, 2H), 3.29 – 3.18 (m, 2H), 2.97 (s, 2.5H, major diastereomer), 2.94 (s, 0.5H, minor diastereomer), 2.64 (s, 3H), 2.45 – 2.31 (m, 2H), 2.28 – 2.06 (m1H), 0.99 (s, 9H).

Example 124. *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methylpiperidin-4-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (268).



268

Preparation of *(S)*-ethyl 2-(2-(3-amino-1-methyl-1H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: Prepared in a manner similar to *(S)*-ethyl 2-(2-(3-amino-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate except using 5-bromo-1-methyl-1H-indazol-3-amine instead of 6-bromo-1-

methyl-1H-indazol-3-amine. LCMS-ESI$^+$: calc'd for $C_{30}H_{31}ClN_4O_3S$: 563.2, 565.2 (M+H$^+$); Found: 563.3, 565.2 (M + H$^+$).

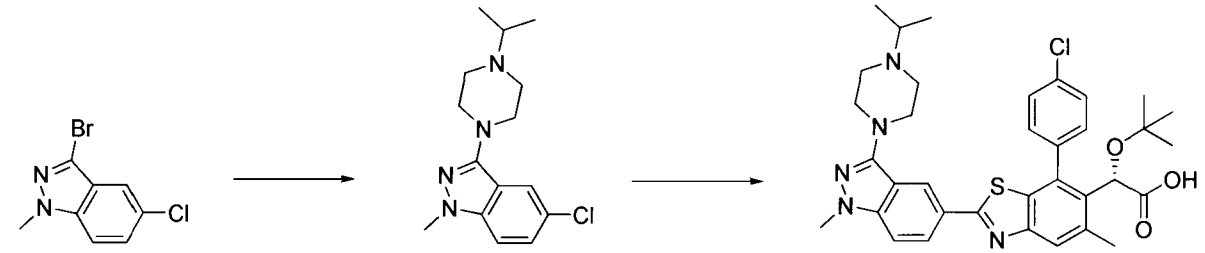
Preparation of *(S)*-ethyl 2-(2-(3-bromo-1-methyl-1H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: prepared in a manner similar to *(S)*-ethyl 2-(2-(3-bromo-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate except using *(S)*-ethyl 2-(2-(3-amino-1-methyl-1H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate instead of *(S)*-ethyl 2-(2-(3-amino-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate. LCMS-ESI$^+$: calc'd for $C_{30}H_{29}BrClN_3O_3S$: 626.1, 628.1, 630.1 (M+H$^+$); Found: 626.1, 628.1, 630.1 (M + H$^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate: Prepared in a manner similar to *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazol-6-yl)benzo[d]thiazol-6-yl)acetate except using *(S)*-ethyl 2-(2-(3-bromo-1-methyl-1H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate instead of *(S)*-ethyl 2-(2-(3-bromo-1-methyl-1H-indazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate. LCMS-ESI$^+$: calc'd for $C_{36}H_{39}ClN_4O_3S$: 643.2, 645.2 (M+H$^+$); Found: 643.1, 645.0 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 8.65 (s, 1H), 8.13 (dd, J = 8.9, 1.5 Hz, 1H), 7.84 (s, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.65 – 7.47 (m, 4H), 6.66 (s, 1H), 5.25 (s, 1H), 4.37 – 4.15 (m, 2H), 4.11 (s, 3H), 4.03 – 3.87 (m, 2H), 3.87 – 3.63 (m, 2H), 3.57 – 3.37 (m, 2H), 3.07 (s, 3H), 2.60 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.00 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methylpiperidin-4-yl)-1H-indazol-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-(1-methyl-3-(1-methylpiperidin-4-yl)-1H-indazol-6-yl)benzo[d]thiazol-6-yl)acetic acid except using *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate instead of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazol-6-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{34}H_{37}ClN_4O_3S$: 617.2, 619.2 (M+H$^+$); Found: 617.3, 619.2 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 8.47 (s, 1H), 8.13 (dd, J = 8.9,

1.5 Hz, 1H), 7.83 (s, 1H), 7.74 – 7.54 (m, 5H), 5.26 (s, 1H), 4.10 (s, 0.3H, minor diastereomer), 4.06 (s, 2.7H, major diastereomer), 3.76 – 3.60 (m, 2H), 3.58 – 3.39 (m, 2H), 3.30 – 3.19 (m, 2H), 2.97 (s, 2.7H, major diastereomer), 2.94 (s, 0.3H, minor diastereomer), 2.63 (s, 3H), 2.49 – 2.29 (m, 2H), 2.29 – 2.09 (m, 1H), 0.99 (s, 9H).

Example 125. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(4-isopropylpiperazin-1-yl)-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (269).



3-bromo-5-chloro-1-methyl-1*H*-indazole

5-chloro-3-(4-isopropylpiperazin-1-yl)-1-methyl-1*H*-indazole

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(4-isopropylpiperazin-1-yl)-1-methyl-1*H*-indazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

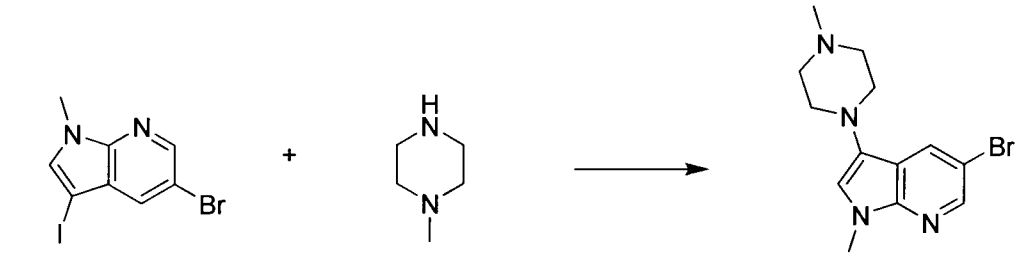
269

Preparation of 5-chloro-3-(4-isopropylpiperazin-1-yl)-1-methyl-1H-indazole: A solution of 3-bromo-5-chloro-1-methyl-1H-indazole (500 mg), N-isopropylpiperazine (287 mg), and Dioxane (5.00 mL) was prepared. NaOtBu (294 mg) and Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)][2-(2-aminoethyl)phenyl]Pd(II) (163 mg) were charged and the vessel was sealed and heated to 100 °C overnight. H_2O (3 mL) was added and the reaction was filtered (0.45 micron). The filtrate was directly purified on the Gilson C18 column (5 to 100 ACN/H_2O + 0.1% TFA) giving the title compound. LCMS-ESI$^+$: calc'd for $C_{15}H_{21}ClN_4$: 293.2, 295.1 ($M+H^+$); Found: 293.3, 295.2 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(4-isopropylpiperazin-1-yl)-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A microwave vial was charged with $Pd(OAc)_2$ (1.4 mg, trimeric), X-Phos ligand (5.9 mg), bis-pinacolatodiboron (37 mg), and KOAc (53 mg). The vessel was evacuated under vacuum and backfilled with argon. A solution of 5-chloro-3-(4-isopropylpiperazin-1-yl)-1-methyl-1H-indazole (50 mg) in Dioxane (1 mL) was introduced. The reaction was stirred briefly at 23 °C, then heated to 110 °C. After 1.5 h, The reaction was cooled to 23 °C and charged with *(S)*-methyl 2-(2-bromo-7-(4-

chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (83 mg), $KHCO_3$ (12 mg), $Pd(PPh_3)_4$(14 mg), and 2 M aq K_2CO_3 (500 μL). The reaction was heated to 100 °C for 1 h. EtOH (absolute, 1 mL) and 5 M aq NaOH (1 mL) were added. The reaction was heated at 100 °C for 30 min. The reaction was cooled to 23 °C and directly purified on the Gilson C18 column [5 to 100 ACN/H_2O + 0.1% TFA] giving the title compound. LCMS-ESI$^+$: calc'd for $C_{35}H_{40}ClN_5O_3S$: 646.3, 648.3 ($M+H^+$); Found: 646.4, 648.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.42 (s, 1H), 8.06 (d, J = 8.9 Hz, 1H), 7.80 (s, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.62 – 7.48 (m, 4H), 5.24 (s, 1H), 4.15 (d, J = 14.4 Hz, 2H), 3.94 (s, 3H), 3.70 – 3.52 (m, 3H), 3.47 (s, 2H), 3.35-3.25 (m, 2H), 2.60 (s, 3H), 1.44 (d, J = 6.6 Hz, 6H), 0.97 (s, 9H).

Example 126. Preparation of 5-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (270).



5-bromo-3-iodo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine

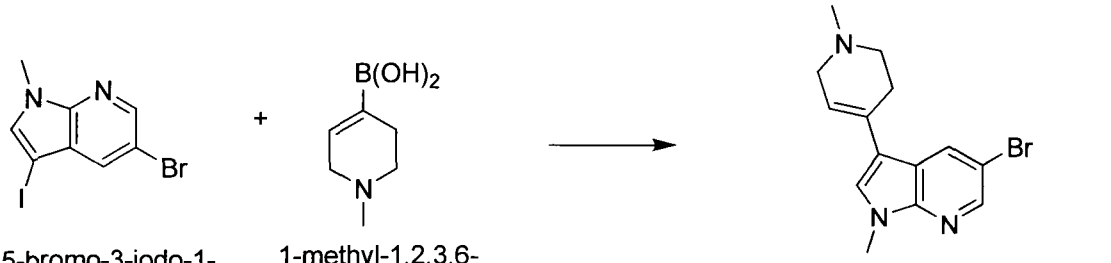
1-methylpiperazine

5-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine

270

Preparation of 5-bromo-1-methyl-3-(4-methylpiperazin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine: A solution of 5-bromo-3-iodo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (150 mg, 0.445 mmol), 1-methylpiperazine (356.7 mg, 3.56 mmol), copper(I) iodide (84.8 mg, 0.445 mmol), K_3PO_4 (378 mg, 1.78mmol), 1,2-ethanediol (138 mg, 2.225 mmol) in isopropyl alcohol (5 mL) in a sealed tubes was heated at 70 °C for 2 days. After cooling to room temperature, the reaction mixture was filtered through celite. The filtrate was concentrated in vacuo. The residue was taken up in EtOAc and the solution was washed with saturated $NaHCO_3$, dried and concentrated. Purification by flash chromatography afforded the title compound. LCMS-ESI$^+$: calc'd for $C_{13}H_{17}BrN_4$ 309.1 ($M+H^+$); Found: 309.1 ($M + H^+$).

Example 127. Preparation of 5-bromo-1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-pyrrolo-[2,3-*b*]pyridine (271).

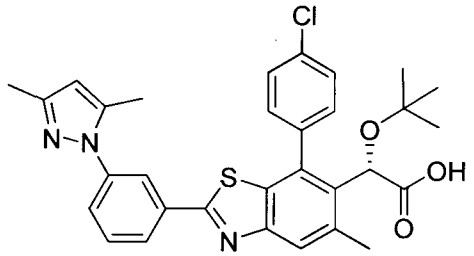


5-bromo-3-iodo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine + 1-methyl-1,2,3,6-tetrahydropyridin-4-ylboronic acid → 5-bromo-1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine

271

Preparation of 5-bromo-1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-pyrrolo-[2,3-*b*]pyridine: To a solution of 5-bromo-3-iodo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (180 mg, 0.534 mmol) and 1-methyl-1,2,3,6-tetrahydropyridin-4-boronic acid (155 mg, 0.694 mmol) in dioxane (5.4 mL, degassed) was added tetrakis(triphenylphosphine)palladium(0) (75mg, 0.064 mmol), K_2CO_3 (369 mg, 2.67mmol) and water (1.8 mL, degassed). The reaction mixture was heated at 40 °C for 15h, cooled and partitioned between ethyl acetate and brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give crude which was purified by chromatographic column to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{14}H_{16}BrN_3$: 306.2 ($M+H^+$); Found: 306.2($M+H^+$).

Example 128. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (272).



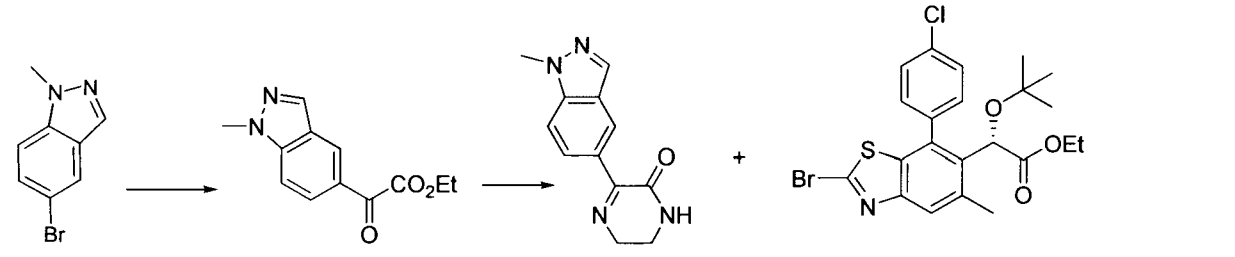
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

272

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: Prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-morpholinopyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid except 3-(3,5-dimethyl-1*H*-parazol-1-yl)phenylboronic acid used instead of 2-morpholinopyridine-4-boronic acid. LCMS-ESI$^+$: calc'd for $C_{31}H_{30}ClN_3O_3S$: 560.3 ($M+H^+$); Found: 560.3 ($M+H^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 8.05 (d, J = 7.3, 1H), 7.87

(s, 1H), 7.70-7.59 (m, 6H), 6.12 (s, 1H), 5.26 (s, 1H), 2.61 (s, 3H), 2.35 (s, 3H), 2.27 (s, 3H), 0.97 (s, 9H).

Example 129. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid (273).

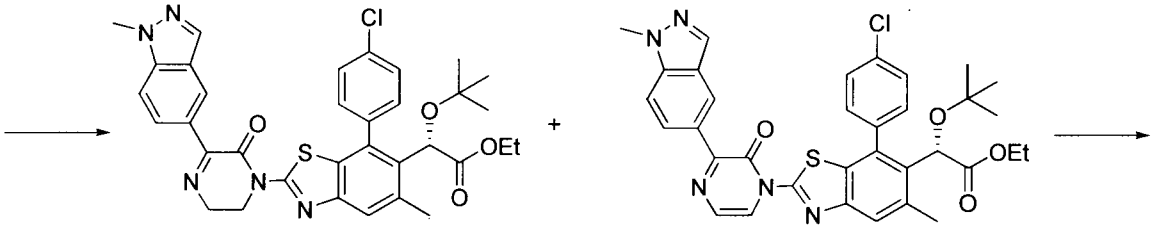


5-bromo-1-methyl-1*H*-indazole

ethyl 2-(1-methyl-1*H*-indazol-5-yl)-2-oxoacetate

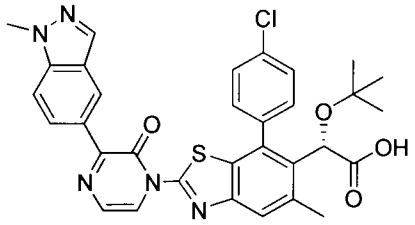
3-(1-methyl-1*H*-indazol-5-yl)-5,6-dihydropyrazin-2(1*H*)-one

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)-2-oxo-5,6-dihydropyrazin-1(2*H*)-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)-2-oxopyrazin-1(2*H*)-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)-2-oxopyrazin-1(2*H*)-yl)benzo[*d*]thiazol-6-yl)acetic acid

273

Preparation of ethyl 2-(1-methyl-1H-indazol-5-yl)-2-oxoacetate: To a solution of 5-bromo-1-methyl-1H-indazole (Aldrich, 1.06 g, 5 mmol) in THF (22 mL) at -78 °C was added n-butyllithium (2.2 mL, 2.5 M, 5.5 mmol) slowly. The mixture was stirred for 20 minutes, and the solution of diethyl oxalate (0.68 mL, 5.0 mmol) in THF (5 mL) was added over one minute period. The reaction was kept at -78 °C for 40 minutes, and was quenched with saturated ammonium chloride solution and warmed to 25 °C. The mixture was extracted with ethyl acetate, and the organic phase was washed with water, brine, and dried over sodium sulfate. Concentration and purification with flash column chromatography (hexanes/EtOAc) gave ethyl

2-(1-methyl-1H-indazol-5-yl)-2-oxoacetate. LCMS-ESI$^+$: calc'd for $C_{12}H_{13}N_2O_3$: 233.2 ($M+H^+$); Found: 233.0 ($M+H^+$).

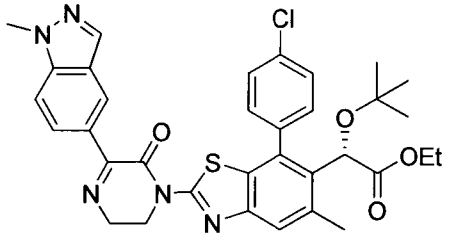
Preparation of 3-(1-methyl-1H-indazol-5-yl)-5,6-dihydropyrazin-2(1H)-one: The mixture of 2-(1-methyl-1H-indazol-5-yl)-2-oxoacetate (520 mg, 2.2 mmol), ethylenediamine (0.15 mL, 2.2 mmol), and sodium sulfate in toluene (9 mL) was heated at reflux for 12 hours. The reaction was cooled, and diluted with ethyl acetate. The mixture was filtered through a pad of celite and was washed with ethyl acetate. Concentration and purification with flash column chromatography (EtOAc) gave 3-(1-methyl-1H-indazol-5-yl)-5,6-dihydropyrazin-2(1H)-one. LCMS-ESI$^+$: calc'd for $C_{12}H_{13}N_4O$: 229.3 ($M+H^+$); Found: 229.2 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxo-5,6-dihydropyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate and *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate: The mixture of 3-(1-methyl-1H-indazol-5-yl)-5,6-dihydropyrazin-2(1H)-one (160 mg, 0.70 mmol), *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (500 mg, 1.05 mmol), tris(2-(2-methoxyethoxy)ethyl)amine (60 μL, 0.2 mmol), potassium carbonate (320 mg, 2.3 mmol), and copper(I) chloride (69 mg, 0.70 mmol) in xylene (16 mL) was degassed with nitrogen, and was heated at 140 °C for 16 hours. The reaction mixture was cooled and diluted with ethyl acetate. The mixture was filtered through a pad of celite and washed with ethyl acetate. The organic solution was washed with water and brine, and was dried over sodium sulfate. Concentration and purification with flash column chromatography (hexanes/EtOAc) gave *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxo-5,6-dihydropyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{34}H_{34}ClN_5O_4S$: 644.2 ($M+H^+$); Found: 644.3 ($M+H^+$); and *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate (40 mg). LCMS-ESI$^+$: calc'd for $C_{34}H_{33}ClN_5O_4S$: 642.2 ($M+H^+$); Found: 642.3 ($M+H^+$).

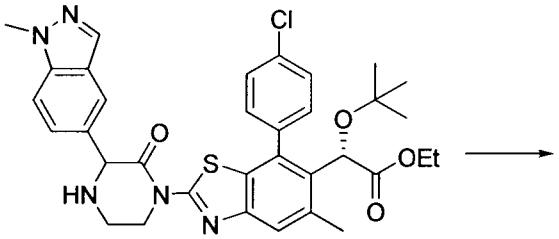
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid: The mixture of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate (6.4 mg) and lithium iodide (100 mg) in pyridine (0.8 mL) was heated at 170 °C for 75 minutes. The mixture was cooled and pyridine was removed under

reduced pressure. The mixture was co-evaporated with DMF and was purified with reverse phase HPLC to give *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid. LCMS-ESI$^+$: calc'd for $C_{32}H_{29}ClN_5O_4S$: 614.2 (M+H$^+$); Found: 614.2 (M + H$^+$); ^{1}H-NMR 400 MHz, ($CDCl_3$) δ 8.98 (s, 1 H), 8.72 (d, J = 4.7 Hz, 1 H), 8.34 (d, J = 8.6 Hz, 1 H), 8.06 (s, 1 H), 7.84 (s, 1 H), 7.70 (m, 2 H), 7.55-7.40 (m, 4 H), 5.36 (s, 1 H), 4.10 (s, 3 H), 2.60 (s, 3 H), 0.98 (s, 9 H).

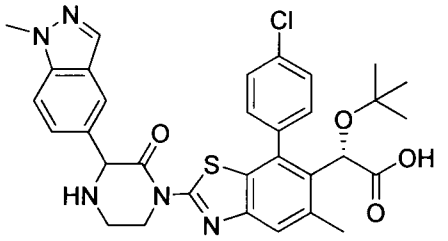
Example 130. Preparation of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (274) and (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (275).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)-2-oxo-5,6-dihydropyrazin-1(2*H*)-yl)benzo[*d*]thiazol-6-yl)acetate

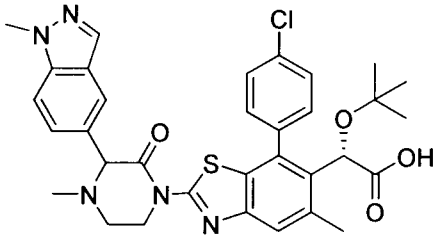


(2*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[*d*]thiazol-6-yl)acetate



(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid

274



(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1*H*-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid

275

Preparation of (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetate: To the solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxo-5,6-dihydropyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate (64 mg, 0.1 mmol) in THF (1 mL) was added acetic acid (6 μL, 0.1 mmol), followed by sodium cyanoborohydride (10 mg, 0.2 mmol). The mixture was stirred for 12 hours, and diluted with ethyl acetate. Sodium hydroxide solution (1 N, 5 mL) was added, and the mixture was stirred for 30 minutes. Organic phase was separated, and was washed water and brine, and was dried over sodium sulfate. Concentration

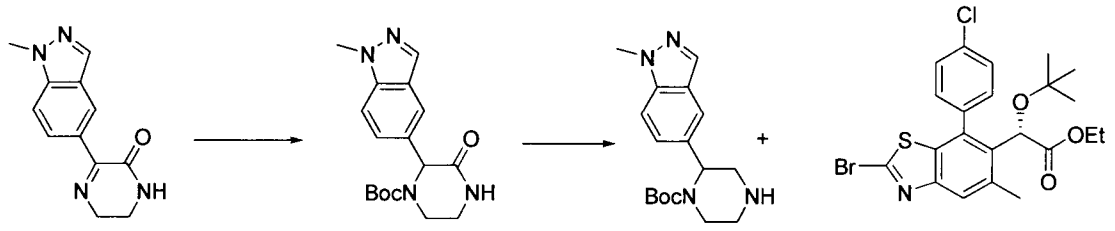
and purification with flash column chromatography (hexanes/EtOAc) gave (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for$C_{34}H_{37}ClN_5O_4S$: 646.2 (M+H$^+$); Found: 646.2 (M + H$^+$).

Preparation of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid: (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (5 mg) was prepared in a similar manner as compound *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetic acid except using (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetate instaed of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopyrazin-1(2H)-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{32}H_{33}ClN_5O_4S$: 618.2 (M+H$^+$); Found: 618.1 (M + H$^+$). ^{1}H-NMR 400 MHz, ($CDCl_3$) δ 7.99 (m, 1 H), 7.74-7.60 (m, 3 H), 7.43-7.35 (m, 4 H), 7.3-7.2 (m, 1 H), 5.31 (s, 1 H), 5.13 (m, 1 H), 4.62-4.35 (m, 2 H), 4.06 (s, 3 H), 3.3 (m, 2 H), 2.57 (s, 3 H), 0.98 (s, 9 H).

Preparation of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid: To the solution of : (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (3 mg) in methanol (0.5 mL) was added formaldehyde solution (20 μL, 37%), followed by acetic acid (10 μL) and sodium cyanoborohydride (12 mg). The mixture was stirred for 1 hour, and solvents were removed under reduced pressure. The remaining solid was dissolved with DMF/water (1 mL/0.5 mL), and was purified with reverse phase HPLC to give (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid. LCMS-ESI$^+$: calc'd for $C_{33}H_{35}ClN_5O_4S$: 632.2 (M+H$^+$); Found: 632.2 (M + H$^+$). ^{1}H-NMR 400 MHz, (CD_3OD) δ 8.0 (m, 1 H), 7.82 (m, 1 H), 7.68 (s, 1 H), 7.62-7.40 (m, 6 H), 5.21 (m, 1 H), 4.70 (m, 1 H), 4.6-4.3 (m, 2 H), 4.08/4.05 (s, 3 H), 3.5 (m, 2 H), 2.57 (s, 3 H), 2.40 (m, 3 H), 0.93 (s, 9 H).

Example 131. Preparation of (2S)-2-*tert*-butoxy-2-(2-(4-(*tert*-butoxycarbonyl)-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic (276) and

(2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (277).

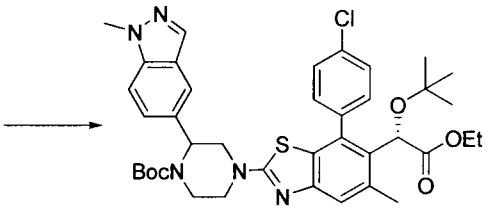


3-(1-methyl-1*H*-indazol-5-yl) -5,6-dihydropyrazin-2(1*H*)-one

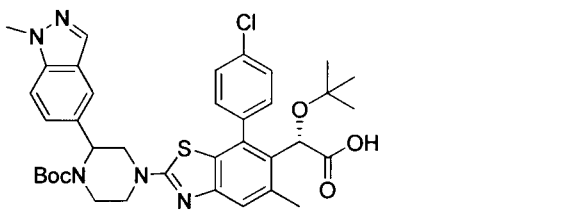
tert-butyl 2-(1-methyl-1*H* -indazol-5-yl)-3-oxopiperazine -1-carboxylate

tert-butyl 2-(1-methyl-1*H* -indazol-5-yl)piperazine -1-carboxylate

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl) -5-methylbenzo[*d*]thiazol-6-yl) -2-*tert*-butoxyacetate

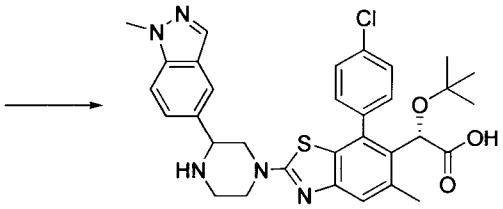


tert-butyl 4-(6-((*S*)-1-*tert*-butoxy-2-ethoxy -2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-2-yl)-2-(1-methyl-1*H*-indazol-5-yl) piperazine-1-carboxylate



(2*S*)-2-*tert*-butoxy-2-(2-(4-(*tert*-butoxycarbonyl) -3-(1-methyl-1*H*-indazol-5-yl)piperazin-1-yl) -7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

276



(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl) -5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl) piperazin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid

277

Preparation of *tert*-butyl 2-(1-methyl-1H-indazol-5-yl)-3-oxopiperazine-1-carboxylate: To the solution of 3-(1-methyl-1H-indazol-5-yl)-5,6-dihydropyrazin-2(1H)-one (23 mg, 0.1 mmol) in THF (1 mL) was added acetic acid (6 µl, 0.1 mmol), followed by sodium cyanoborohydride (10 mg, 0.2 mmol). The mixture was stirred for 12 hours, and diisopropylethylamine (35 µl, 0.2 mmol) and di-t-butyl dicarbonate (24 mg, 0.11 mmol) were added. The reaction mixture was stirred for another 16 hours, and was quenched with water. The mixture was diluted with ethyl acetate, and was basified with 1N sodium hydroxide. The organic phase was separated, and was washed with water and brine, and was dried with sodium sulfate. Concentration and purification with flash column chromatography (hexanes/EtOAc) gave *tert*-butyl 2-(1-methyl-1H-indazol-5-yl)-3-oxopiperazine-1-carboxylate. LCMS-ESI$^+$: calc'd for $C_{17}H_{23}N_4O_3$: 331.2 ($M+H^+$); Found: 330.9 ($M+H^+$).

Preparation of *tert*-butyl 2-(1-methyl-1H-indazol-5-yl)piperazine-1-carboxylate: To the solution of *tert*-butyl 2-(1-methyl-1H-indazol-5-yl)-3-oxopiperazine-1-carboxylate (10 mg) in THF (0.5 mL) at 0 °C was added borane in THF (1.0 N, 1 mL) slowly. The mixture was heated at 55 °C for 3 hours, and was cooled. The reaction was quenched with methanol (1 mL), and was stirred for 30 minutes. The mixture was diluted with ethyl acetate, and was made basic with 1 N sodium hydroxide solution. The organic phase was separated, and was washed with water and brine, and was dried with sodium sulfate. Concentration gave *tert*-butyl 2-(1-methyl-1H-indazol-5-yl)piperazine-1-carboxylate. LCMS-ESI$^+$: calc'd for $C_{17}H_{25}N_4O_2$: 317.2 (M+H$^+$); Found: 317.0 (M + H$^+$).

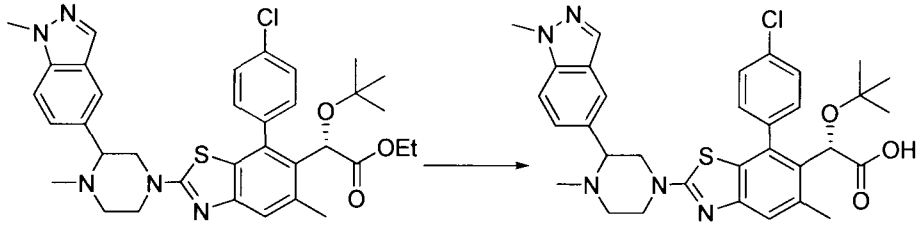
Preparation of *tert*-butyl 4-(6-((*S*)-1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-(1-methyl-1H-indazol-5-yl)piperazine-1-carboxylate: The mixture of *tert*-butyl 2-(1-methyl-1H-indazol-5-yl)piperazine-1-carboxylate (10 mg, 0.03 mmol), *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (15 mg; 0.03 mmol), and potassium carbonate (41 mg, 0.3 mmol) in DMF (0.5 mL) was heated at 140 °C for 4 hours. The mixture was cooled, and was quenched with water. The mixture was extracted with ethyl acetate, and the organic phase was washed with water and brine, and was dried with sodium sulfate. Concentration and purification by reverse phase HPLC gave *tert*-butyl 4-(6-((*S*)-1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-(1-methyl-1H-indazol-5-yl)piperazine-1-carboxylate. LCMS-ESI$^+$: calc'd for $C_{39}H_{47}ClN_5O_5S_2$: 732.3 (M+H$^+$); Found: 732.2 (M + H$^+$).

Preparation of (2S)-2-*tert*-butoxy-2-(2-(4-(*tert*-butoxycarbonyl)-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To the solution of *tert*-butyl 4-(6-((*S*)-1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-(1-methyl-1H-indazol-5-yl)piperazine-1-carboxylate (5 mg) in THF/MeOH (0.5 mL/0.5 mL) was added sodium hydroxide solution (0.4 mL, 1.0 N). The mixture was heated at 50 °C for 16 hours. The mixture was cooled, and was acidified with acetic acid (60 μL). Concentration and purification with reverse phase HPLC gave (2S)-2-*tert*-butoxy-2-(2-(4-(*tert*-butoxycarbonyl)-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid. LCMS-ESI$^+$: calc'd for $C_{37}H_{43}ClN_5O_5S$: 704.3 (M+H$^+$); Found: 704.1 (M + H$^+$); ^{1}H-NMR 400 MHz, (CD_3OD) δ 7.96 (s, 1H), 7.64 (m, 2 H), 7.49 (m, 3 H), 7.38 (m, 3 H), 5.46 (m, 1 H), 5.19 (s, 1 H), 4.4 (m, 1 H),

4.2 (m, 1 H), 4.07 (s, 3 H), 4.0-3.7 (m, 2 H), 3.5 (m, 2 H), 2.5 (s, 3 H), 1.40 (s, 9 H), 0.98 (s, 9 H).

Preparation of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid: To (2S)-2-*tert*-butoxy-2-(2-(4-(*tert*-butoxycarbonyl)-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (4 mg) was added hydrochloric acid in 2-propanol (3 mL, 0.5 N, 1.5 mmol). The mixture was stirred for 24 hours. Concentration and purification with reverse phase HPLC gave (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid. LCMS-ESI$^+$: calc'd for $C_{32}H_{35}ClN_5O_3S$: 604.2 ($M+H^+$); Found: 604.3 ($M+H^+$). ^{1}H-NMR 400 MHz, (CD_3OD) δ 8.10 (s, 1 H), 7.97 (s, 1 H), 7.72 (m, 1 H), 7.6-7.4 (m, 5 H), 7.38 (s, 1 H), 5.15 (s, 1 H), 4.7 (m, 1 H), 4.45 (m, 1 H), 4.26 (m, 1 H), 4.11 (s, 3 H), 3.8 (m, 1 H), 3.65-3.4 (m, 3 H), 2.50 (s, 3 H), 0.94 (s, 9 H);

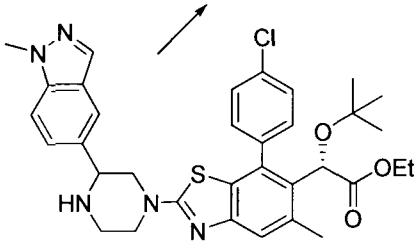
Example 132. Preparation of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (278) and of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-isopropyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (279).



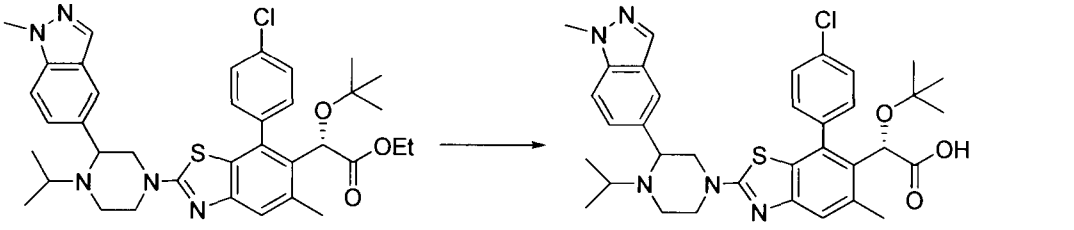
(2*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl) -5-methyl-2-(4-methyl-3-(1-methyl-1*H*-indazol -5-yl)piperazin-1-yl)benzo[*d*]thiazol-6-yl)acetate

(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl) -5-methyl-2-(4-methyl-3-(1-methyl-1*H*-indazol-5-yl) piperazin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid

278



(2*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl) -5-methyl-2-(3-(1-methyl-1*H*-indazol-5-yl) piperazin-1-yl)benzo[*d*]thiazol-6-yl)acetate



(2*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl) -2-(4-isopropyl-3-(1-methyl-1*H*-indazol-5-yl) piperazin-1-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl) -2-(4-isopropyl-3-(1-methyl-1*H*-indazol-5-yl) piperazin-1-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

279

Preparation of (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetate: (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetate (16 mg) was prepared in a similar manner as (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid except using (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetate instead of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid. LCMS-ESI$^+$: calc'd for $C_{35}H_{41}ClN_5O_3S$: 646.2 ($M+H^+$); Found: 646.3 ($M+H^+$).

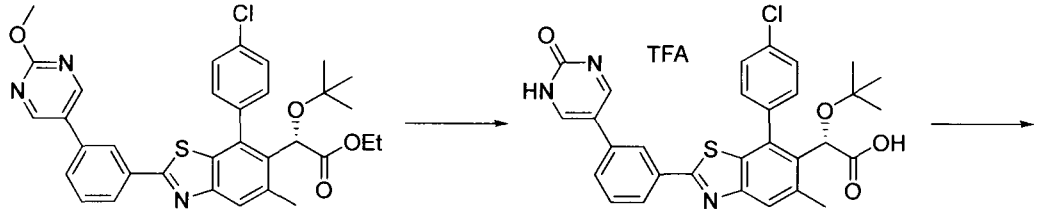
Preparation of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid: (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (12 mg) was prepared in a similar manner as compound (2S)-2-*tert*-butoxy-2-(2-(4-(*tert*-butoxycarbonyl)-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid except using (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetate instead of *tert*-butyl 4-(6-((*S*)-1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-(1-methyl-1H-indazol-5-yl)piperazine-1-carboxylate. LCMS-ESI$^+$: calc'd for $C_{33}H_{37}ClN_5O_3S$: 618.2 (M+H$^+$); Found: 618.4 (M + H$^+$). ^{1}H-NMR 400 MHz, (CD_3OD) δ 8.11 (m, 1 H), 7.98 (m, 1 H), 7.77 (m, 1 H), 7.60 (m, 1 H), 7.55-7.46 (m, 4 H), 7.38 (s, 1 H), 5.15 (s, 1 H), 4.40 (m, 2 H), 4.35 (m, 1 H), 4.11 (s, 3 H), 3.9-3.7 (m, 3 H), 3.45 (m, 1 H), 2.68 (s, 3 H), 2.50 (s, 3 H), 0.94 (s, 9 H).

Preparation of (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-isopropyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-isopropyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (16 mg) was prepared in a similar manner as (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid except using (2S)-ethyl 2-*tert*-butoxy2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetate, and acetone and 2,2-dimethoxypropane instead of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-1H-indazol-5-yl)-2-oxopiperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid and formaldehyde. LCMS-ESI$^+$: calc'd for $C_{37}H_{45}ClN_5O_3S$: 674.3 (M+H$^+$); Found: 674.3 (M + H$^+$).

Preparation of (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-isopropyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: (2S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-isopropyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (3.7 mg) was prepared in a similar manner as compound (2S)-2-*tert*-butoxy-2-(2-(4-(*tert*-butoxycarbonyl)-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid except using (2S)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-isopropyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)-5-methylbenzo[d]thiazol-6-yl)acetate instead of *tert*-butyl 4-(6-((*S*)-1-*tert*-butoxy-2-ethoxy-2-

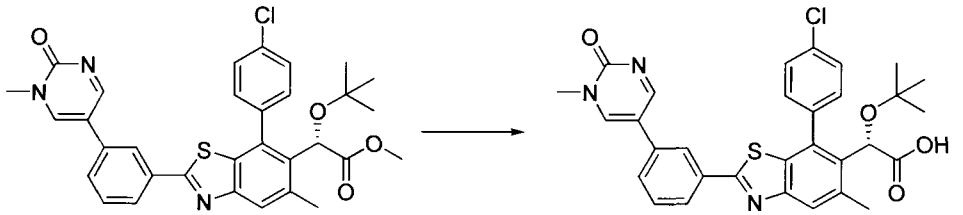
oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-(1-methyl-1H-indazol-5-yl)piperazine-1-carboxylate. LCMS-ESI$^+$: calc'd for $C_{35}H_{41}ClN_5O_3S$: 646.3 (M+H$^+$); Found: 646.3 (M + H$^+$). ^{1}H-NMR 400 MHz, (CD_3OD) δ 8.11 (m, 1 H), 8.04 (m, 1 H), 7.76 (m, 1 H), 7.60 (m, 2 H), 7.50 (m, 3 H), 7.36 (s, 1 H), 5.15 (s, 1 H), 4.37 (m, 2 H), 4.11 (s, 3 H), 4.1-3.7 (m, 3 H), 3.4 (m, 3 H), 2.49 (s, 3 H), 1.32 (d, J = 6.2 Hz, 3 H), 1.24 (d, J = 6.7 Hz, 3 H), 0.94 (s, 9 H).

Example 133. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid (280).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2-methoxypyrimidin-5-yl)phenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)benzo[*d*]thiazol-6-yl)acetic acid



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)benzo[*d*]thiazol-6-yl)acetic acid

280

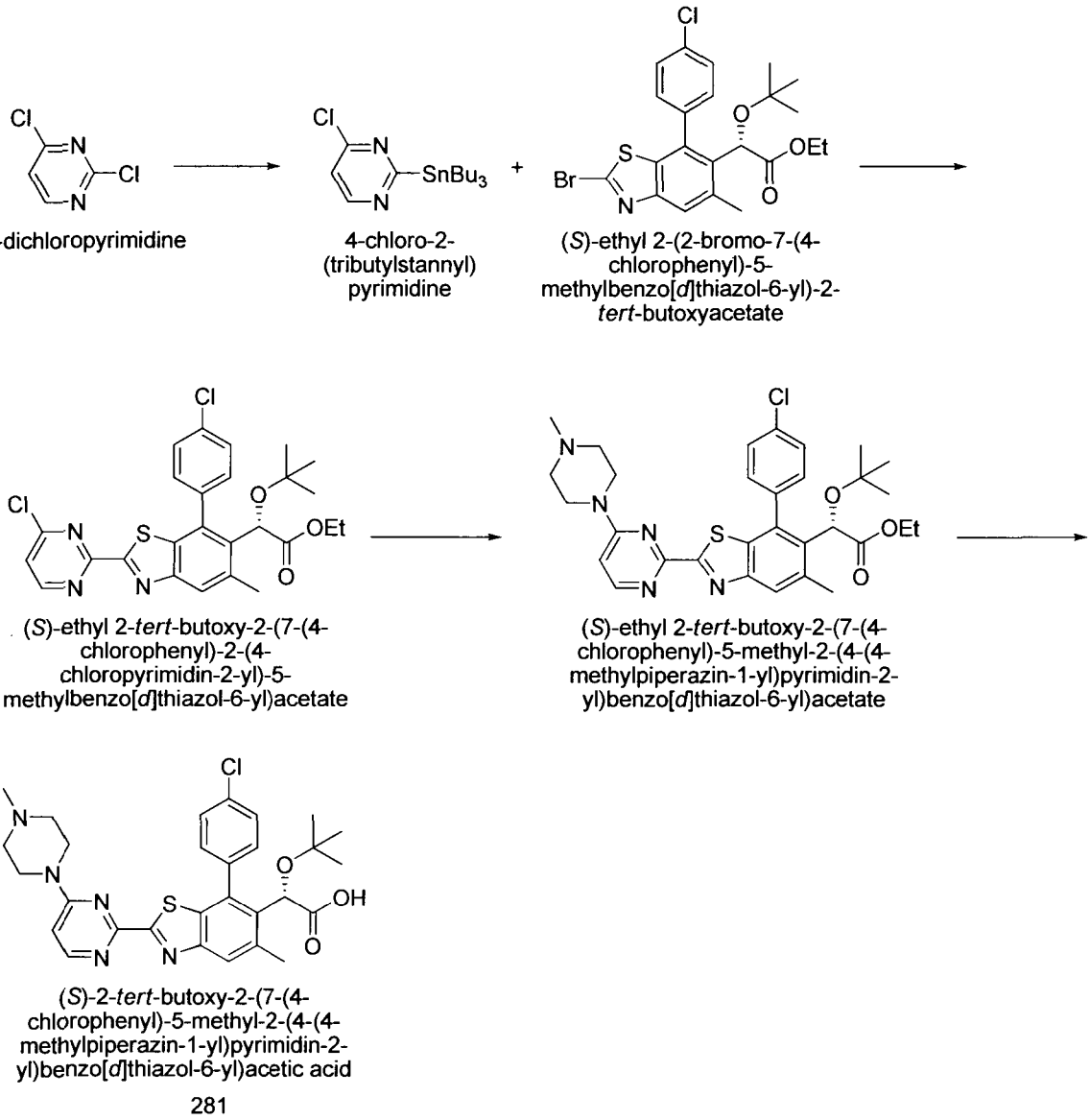
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid: To *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(2-methoxypyrimidin-5-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetate (168.5 mg, 0.280 mmol) in THF (2 mL) and water (2 mL) was added NaOH (1.4 mL of a 2N solution). The reaction mixture was heated at 40 °C overnight, cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{30}H_{27}ClN_3O_4S$ (M + H$^+$): 560.1; Found: 559.7 (M+H$^+$).

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetate: To the TFA salt of *(S)*-2-

tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid (94.8 mg, 0.141 mmol) in DMA (3.0 mL) was added K_2CO_3 (194.4 mg, 1.406 mmol) and methyl iodide (199.6 mg, 0.088 mL, 1.406 mmol). The reaction was stirred at room temperature for 45 minutes, filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$: calc'd for $C_{32}H_{31}ClN_3O_4S$ ($M + H^+$): 588.2; Found: 588.2 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid: To crude *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)benzo[d]thiazol-6-yl)acetate in THF (2.0 mL) and methanol (2.0 mL) was added NaOH (1 mL of a 2N solution). The reaction mixture was heated at 40 °C for 2 h, cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{31}H_{29}ClN_3O_4S$ ($M + H^+$): 574.1; Found: 574.2 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 9.02 (d, J = 3.2 Hz, 1H), 8.71 (d, J = 3.2 Hz, 1H), 8.27 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.65 – 7.57 (m, 4H), 5.26 (s, 1H), 3.71 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).

Example 134. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)benzo[d]thiazol-6-yl)acetic acid (281).



Preparation of 4-chloro-2-(tributylstannyl)pyrimidine: To a solution of 1.5M (in cyclohexane) lithium diisopropylamide (mono THF) (9.06 mmol, 6.04 mL) in THF (15 mL) at 0 °C was added tri-n-butyltin hydride (2.34 g, 8.05 mmol) in THF (2 mL) dropwise. The reaction mixture was stirred at 0 °C for 15 minutes, then cooled to -78 °C. To this solution was added 2,4-dichloropyrimidine (1 g, 6.71 mmol) in THF (7 mL) dropwise. The reaction mixture was stirred at -78 °C for 3 h, then warmed to 0 °C over 30 min. The reaction was quenched with saturated aqueous ammonium chloride (12 mL) at 0 °C, then warmed to room temperature and extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel (hexanes/DCM eluent) provided the product. LCMS-ESI$^+$ calc'd for $C_{16}H_{30}ClN_2Sn$ ($M + H^+$): 405.1; Found: 405.1 ($M+H^+$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 5.4, 1.3 Hz, 1H), 7.16 (dd, J = 5.4, 1.2 Hz, 1H), 1.67 - 1.49 (m, 6H), 1.38 - 1.27 (m, 6H), 1.26 - 1.10 (m, 6H), 0.88 (td, J = 7.5, 1.3 Hz, 9H).

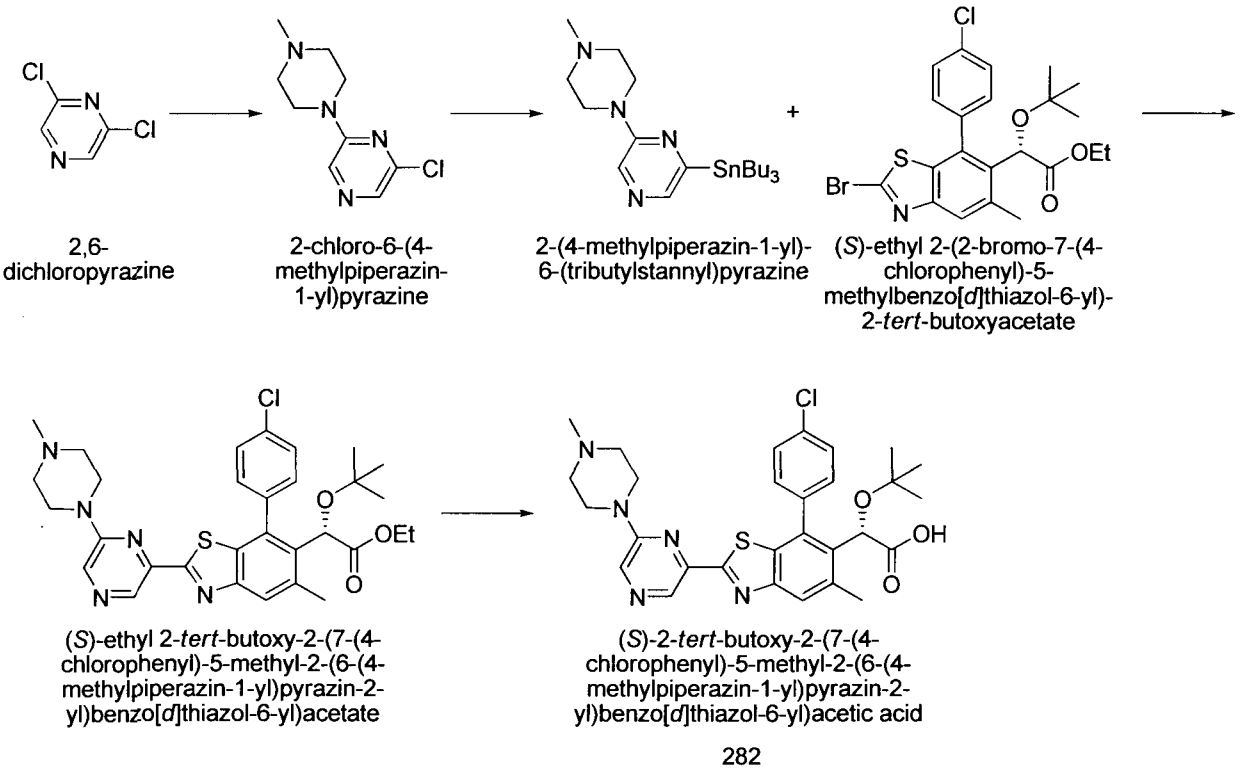
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-chloropyrimidin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (500 mg, 1.01 mmol), tetrakis(triphenylphosphine)palladium(0) (174 mg, 0.15 mmol), lithium chloride (128 mg, 3.02 mmol), and copper(I) iodide (58 mg, 0.3 mmol) were taken in a microwave vial, and the vial was vacuum pumped and flushed with argon three times. To this mixture was added 2-(tributylstannyl)-4-chloropyrimidine (447 mg, 1.11 mmol) in dioxane (12 mL) and the resulting mixture was stirred at 90 °C for 18 h. The reaction mixture was then 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 $C_{26}H_{26}Cl_2N_3O_3S$ (M + H$^+$): 530.1; Found: 530.0 (M+H$^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)benzo[d]thiazol-6-yl)acetate: To *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-chloropyrimidin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (30 mg, 0.06 mmol) in dioxane (1 mL) was added 1-methylpiperazine (56.7 mg, 0.063 mL, 0.566 mmol). The RM was stirred at room temperature for 20 minutes, concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{31}H_{37}ClN_5O_3S$ (M + H$^+$): 594.2; Found: 593.7 (M+H$^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)benzo[d]thiazol-6-yl)acetic acid: To crude *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)benzo[d]thiazol-6-yl)acetate in THF (0.5 mL) and methanol (0.5 mL) was added NaOH (0.5 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{29}H_{33}ClN_5O_3S$ (M + H$^+$): 566.2; Found: 566.1 (M+H$^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (d, J = 6.1 Hz, 1H), 7.96 (s, 1H), 7.72 – 7.65 (m, 1H), 7.60 (m, 3H), 7.00 (d, J = 5.7 Hz, 1H), 5.26 (s, 1H), 3.37 (br s, 8H), 2.97 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).

Example 135. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-

methylpiperazin-1-yl)pyrazin-2-yl)benzo[d]thiazol-6-yl)acetic acid (282).



2,6-dichloropyrazine

2-chloro-6-(4-methylpiperazin-1-yl)pyrazine

2-(4-methylpiperazin-1-yl)-6-(tributylstannyl)pyrazine

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-methylpiperazin-1-yl)pyrazin-2-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-methylpiperazin-1-yl)pyrazin-2-yl)benzo[*d*]thiazol-6-yl)acetic acid

282

Preparation of 2-chloro-6-(4-methylpiperazin-1-yl)pyrazine: To 2,6-dichloropyrazine (150 mg, 1.007 mmol) in 1,4-dioxane (1.0 mL) was added 1-methylpiperazine (121.0 mg, 0.13 mL, 1.208 mmol) followed by triethylamine (203.8 mg, 0.281 mL, 2.014 mmol). The reaction mixture was stirred at room temperature for 24 h then concentrated. Purification by flash column chromatography on silica gel using 100:5:1 EtOAc/MeOH/NH_4OH (0 to 100%) in EtOAc provided the product. LCMS-ESI$^+$ calc'd for $C_9H_{14}ClN_4$ (M + H^+): 213.1; Found: 213.2 (M+H^+).

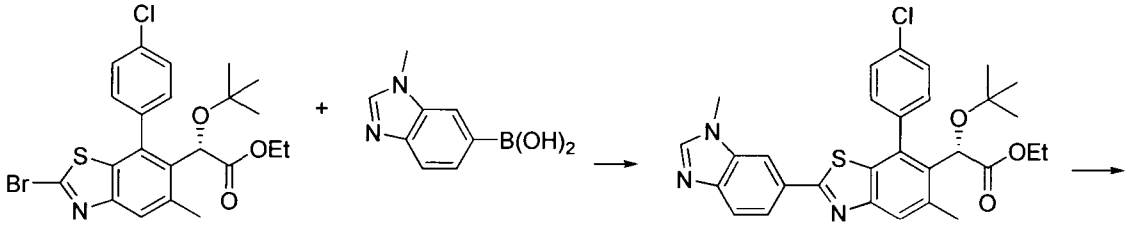
Preparation of 2-(4-methylpiperazin-1-yl)-6-(tributylstannyl)pyrazine: tetrakis(triphenylphosphine)palladium(0) (108 mg, 0.093 mmol) and LiCl (39.6 mg, 2.80 mmol) were taken in a microwave vial and the vial vacuum pumped and flushed with argon three times. To this mixture was added 2-chloro-6-(4-methylpiperazin-1-yl)pyrazine (199 mg, 0.933 mmol) and hexabutylditin (541 mg, 0.47 mL, 0.93 mmol) in toluene (10 mL). The reaction mixture was heated to 170 °C for 1.5 h, filtered through Celite, and concentrated. Purification by flash column chromatography on silica gel using 79:20:1 DCM/MeOH/NH_3 (0 to 100%) in DCM provided the product. LCMS-ESI$^+$ calc'd for $C_{21}H_{41}N_4Sn$ (M + H^+): 469.2; Found: 467.2 (M+H^+).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-

methylpiperazin-1-yl)pyrazin-2-yl)benzo[d]thiazol-6-yl)acetate: *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (50.0 mg, 0.101 mmol), tetrakis(triphenylphosphine)palladium(0) (17.4 mg, 0.015 mmol), lithium chloride (12.8 mg, 0.302 mmol), and copper(I) iodide (5.8 mg, 0.030 mmol) were taken in a microwave vial and the vial vacuum pumped and flushed with argon three times. To this mixture was added 2-(4-methylpiperazin-1-yl)-6-(tributylstannyl)pyrazine (56.4 mg, 0.121 mmol) in dioxane (1.0 mL), and the resulting mixture was stirred at 90 °C for 22 h. Purification by flash column chromatography on silica gel using 79:20:1 DCM/MeOH/NH_3 (0 to 100%) in DCM provided the product. LCMS-ESI$^+$ calc'd for $C_{31}H_{37}ClN_5O_3S$ (M + H^+):594.2; Found: 593.6 (M+H^+).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-methylpiperazin-1-yl)pyrazin-2-yl)benzo[d]thiazol-6-yl)acetic acid: To *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-methylpiperazin-1-yl)pyrazin-2-yl)benzo[d]thiazol-6-yl)acetate in THF (0.5 mL) and methanol (0.5 mL) was added NaOH (0.45 mL of a 2N solution). The reaction mixture was heated at 50 °C for 3 h, cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{29}H_{33}ClN_5O_3S$ (M + H^+): 566.2; Found: 566.1 (M+H^+). ^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (s, 1H), 8.46 (s, 1H), 7.91 (s, 1H), 7.72 – 7.64 (m, 1H), 7.64 – 7.50 (m, 3H), 5.24 (s, 1H), 4.62 (br s, 1H), 3.37 (br s, 7H), 2.97 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).

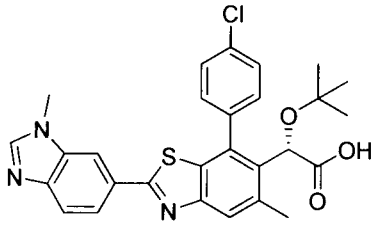
Example 136. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid (283).



(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

1-methyl-1*H*-benzo[*d*]imidazol-6-ylboronic acid

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)benzo[*d*]thiazol-6-yl)acetic acid

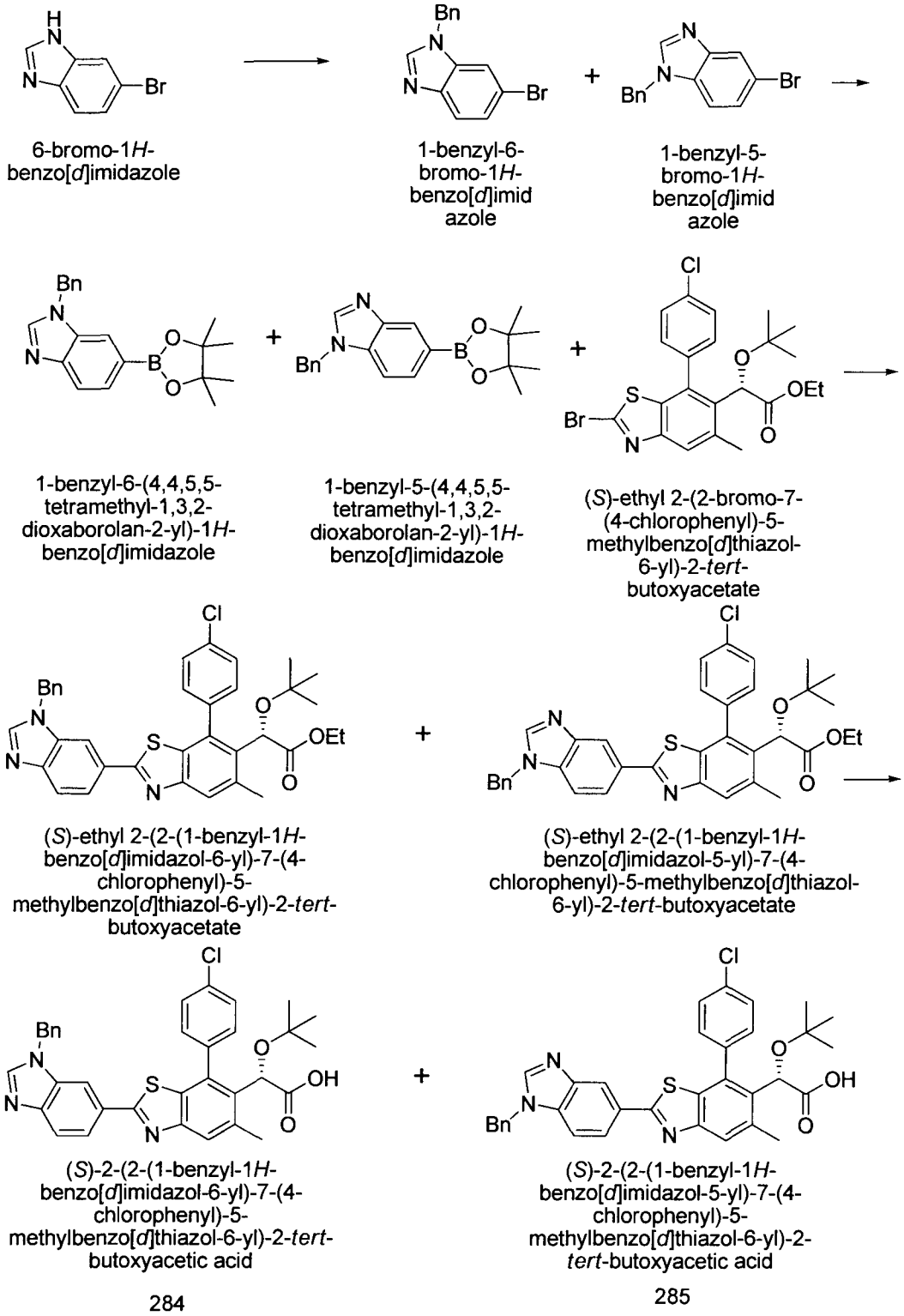
283

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate: A microwave vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (75 mg, 0.15 mmol), 1-methyl-1H-benzo[d]imidazol-6-ylboronic acid (34 mg, 0.19 mmol), then $Pd(PPh_3)_4$ (34 mg, 0.03 mmol). The vial was flushed with argon, diluted with dioxane (1.5 mL) and to this was added 2M aqueous K_2CO_3 (0.25 mL, 0.50 mmol). The vial was sealed, heated to 100 °C for 2 hours, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-10% $MeOH/CH_2Cl_2$ gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{30}H_{31}ClN_3O_3S$: 548.2 ($M+H^+$); Found: 548.3 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate (71 mg, 0.13 mmol) in 1:1 THF/MeOH (1.5 mL) was added 2M aqueous NaOH (0.35 mL, 0.7 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O/0.1% TFA gradient). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 9.34 (s, 1H), 8.55 (d, J = 1.0 Hz, 1H), 8.29 (dd, J = 8.7, 1.5 Hz, 1H), 7.93 (d, J = 8.7

Hz, 1H), 7.87 (s, 1H), 7.72 – 7.67 (m, 1H), 7.65 – 7.55 (m, 3H), 5.27 (s, 1H), 4.17 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H); LCMS-ESI$^+$: calc'd for $C_{28}H_{27}ClN_3O_3S$: 520.2 ($M+H^+$); Found: 520.2 ($M + H^+$).

Example 137. Preparation of *(S)*-2-(2-(1-benzyl-1H-benzo[d]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (284) and *(S)*-2-(2-(1-benzyl-1H-benzo[d]imidazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (285).



Preparation of 1-benzyl-6-bromo-1H-benzo[d]imidazole and 1-benzyl-5-bromo-1H-benzo[d]imidazole: A flask was charged with 6-bromo-1H-benzo[d]imidazole (595 mg, 3.0 mmol) and K_2CO_3 (1.3 g, 3.4 mmol) and then diluted with acetone (15 mL). To this was then added benzyl bromide (0.4 mL, 3.4 mmol) at room temperature and the resulting mixture was allowed to stir overnight. The reaction mixture was diluted with CH_2Cl_2 and H_2O and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic extracts

were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (20-60% EtOAc/Hex gradient) to afford the desired product as a 1:1 isomeric mixture. calc'd for $C_{14}H_{12}BrN_2$: 287.0 ($M+H^+$); Found: 582.3 ($M+H^+$).

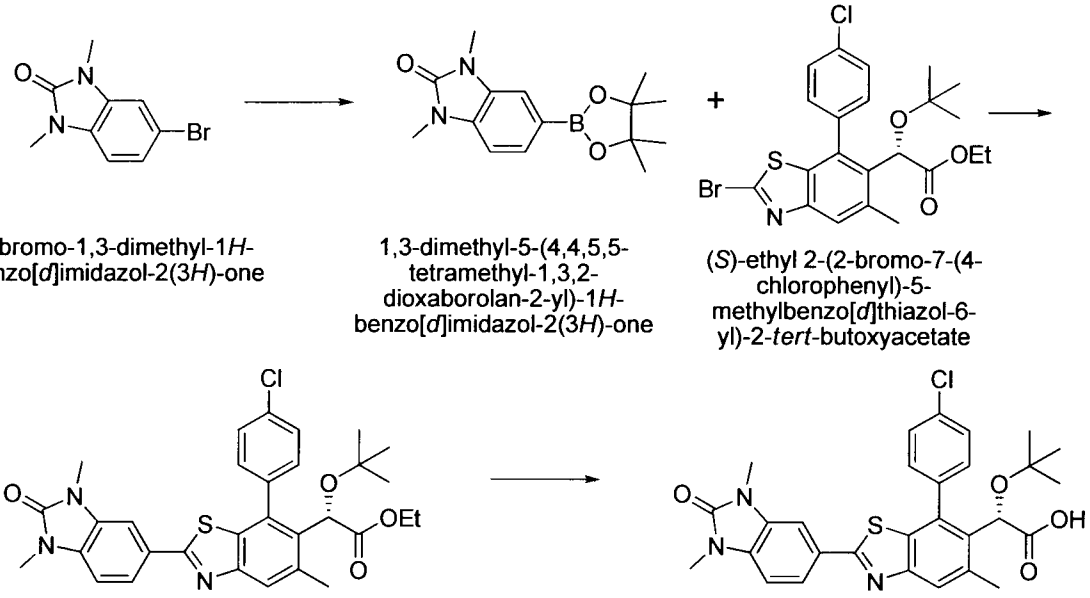
Preparation of 1-benzyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole and 1-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole: A microwave vial was charged with a 1:1 isomeric mixture of 1-benzyl-6-bromo-1H-benzo[d]imidazole and 1-benzyl-5-bromo-1H-benzo[d]imidazole (630 mg, 2.19 mmol), bis(pinacolato)diboron (835 mg, 3.29 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (171 mg, 0.21 mmol), then KOAc (646 mg, 6.58 mmol). The vial was flushed with argon, diluted with dioxane (11 mL), sealed, and then heated to 100 °C for 90 minutes. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, filtered through a pad of Celite, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (40-100% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{20}H_{24}BN_2O_2$: 335.2 ($M + H^+$); Found: 335.3 ($M+H^+$).

Preparation of *(S)*-ethyl 2-(2-(1-benzyl-1*H*-benzo[*d*]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-(*tert*-butoxy)acetate and *(S)*-ethyl 2-(2-(1-benzyl-1*H*-benzo[*d*]imidazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-(*tert*-butoxy)acetate: A microwave vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (150 mg, 0.30 mmol), a 1:1 mixture of 1-benzyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole and 1-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole (154 mg, 0.46 mmol), then $Pd(PPh_3)_4$ (37 mg, 0.03 mmol). The vial was flushed with argon, diluted with dioxane (3 mL) and to this was added 2M aqueous K_2CO_3 (0.5 mL, 0.10 mmol). The vial was sealed, heated to 100 °C for 2 hours, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-10% $MeOH/CH_2Cl_2$ gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{36}H_{35}ClN_3O_3S$: 624.2 ($M+H^+$); Found: 624.3 ($M+H^+$).

Preparation of *(S)*-2-(2-(1-benzyl-1H-benzo[d]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid and *(S)*-2-(2-(1-benzyl-1H-benzo[d]imidazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid: To a solution of a 1:1 mixture of *(S)*-ethyl 2-(2-(1-benzyl-1*H*-benzo[*d*]imidazol-6-yl)-7-(4-

chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-(*tert*-butoxy)acetate and *(S)*-ethyl 2-(2-(1-benzyl-1*H*-benzo[*d*]imidazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-(*tert*-butoxy)acetate (187 mg, 0.30 mmol) in 1:1 THF/MeOH (1.5 mL) was added 2M aqueous NaOH (0.35 mL, 0.7 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the isomeric mixture of products. *1:1 mixture of benzyl-isomers ^{1}H NMR (400 MHz, CD_3OD) δ 9.39 (s, 1H), 9.37 (s, 1H), 8.47 (s, 1H), 8.43 (s, 1H), 8.22 (dd, J = 8.7, 1.5 Hz, 1H), 8.17 (dd, J = 8.8, 1.5 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.87 – 7.80 (m, 3H), 7.72 – 7.65 (m, 2H), 7.63 – 7.53 (m, 6H), 7.51 – 7.35 (m, 9H), 5.76 (s, 2H), 5.72 (s, 2H), 5.25 (s, 2H), 2.60 (s, 6H), 0.97 (s, 18H). LCMS-ESI$^+$: calc'd for $C_{34}H_{31}ClN_3O_3S$: 596.2 ($M+H^+$); Found: 596.2 ($M+H^+$).

Example 138. Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (286).



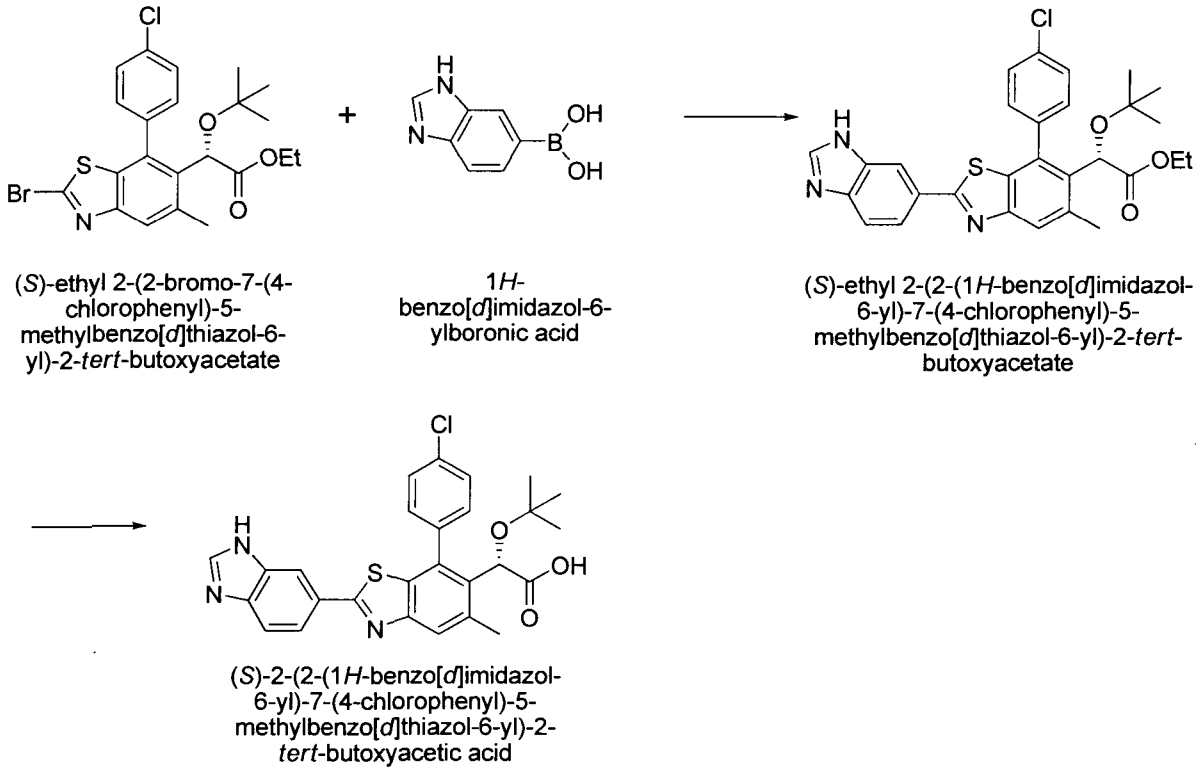
Preparation of 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one: A microwave vial was charged with 5-bromo-1,3-dimethyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (250 mg, 1.04 mmol), bis(pinacolato)diboron (395 mg, 1.56 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (84 mg, 0.10 mmol), then KOAc (316 mg, 3.22 mmol). The vial

was flushed with argon, diluted with dioxane (5 mL), sealed, then heated to 100 °C for 90 minutes. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, filtered through a pad of Celite, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (40-90% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{15}H_{22}BN_2O_3$: 289.2 (M + H^+); Found: 289.3 (M+H^+).

Preparation of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: A microwave vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (75 mg, 0.15 mmol), 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (182 mg, 0.63 mmol), then $Pd(PPh_3)_4$ (22 mg, 0.02 mmol). The vial was flushed with argon, diluted with dioxane (1.5 mL) and to this was added 2M aqueous K_2CO_3 (0.25 mL, 0.5 mmol). The vial was sealed, heated to 100 °C for 2 hours, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (40-100% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{33}ClN_3O_4S$: 578.2 (M+H^+); Found: 578.3 (M+H^+).

Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (82 mg, 0.14 mmol) in 1:1 THF/MeOH (1.5 mL) was added 2M aqueous NaOH (0.4 mL, 0.8 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 7.2 Hz, 3H), 7.68 (s, 1H), 7.59 (s, 3H), 7.25 (s, 1H), 5.25 (s, 1H), 3.48 (s, 3H), 3.45 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{29}H_{29}ClN_3O_4S$: 550.2 (M+H^+); Found: 550.2 (M+H^+).

Example 139. Preparation of *(S)*-2-(2-(1*H*-benzo[*d*]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-(*tert*-butoxy)acetic acid (287).



(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

1*H*-benzo[*d*]imidazol-6-ylboronic acid

(*S*)-ethyl 2-(2-(1*H*-benzo[*d*]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-2-(2-(1*H*-benzo[*d*]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid

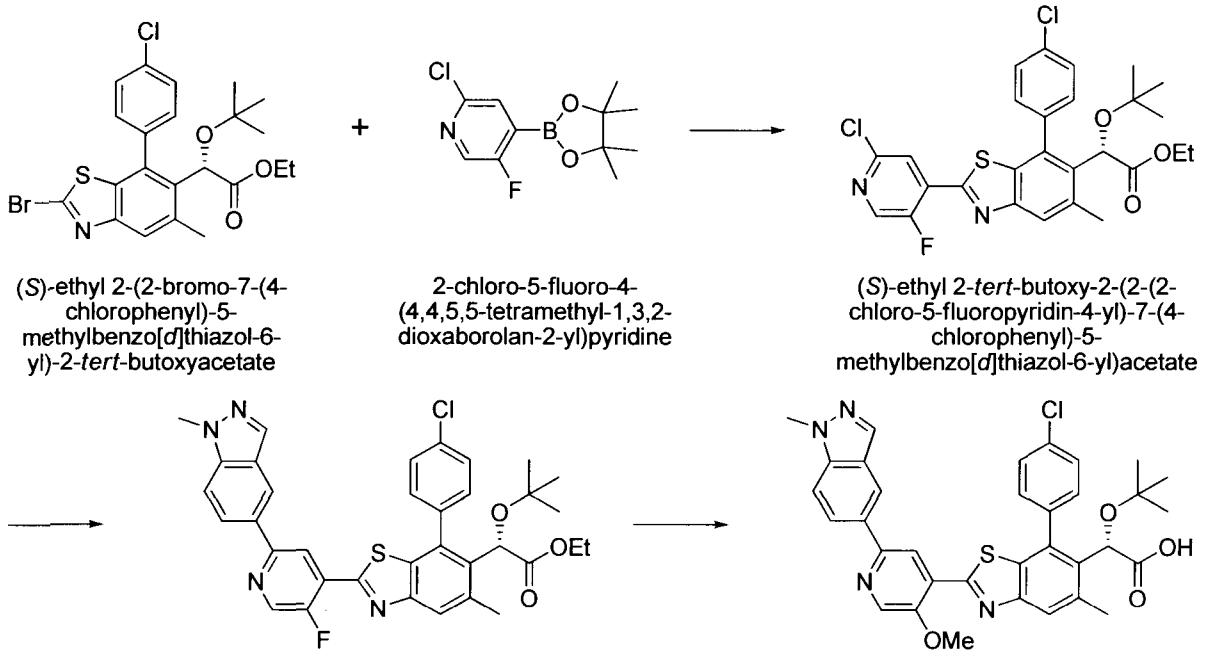
287

Preparation of *(S)*-ethyl 2-(2-(1*H*-benzo[*d*]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-(*tert*-butoxy)acetate: A microwave vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (78 mg, 0.16 mmol), (1*H*-benzo[*d*]imidazol-6-yl)boronic acid (44 mg, 0.27 mmol), then $Pd(PPh_3)_4$ (22 mg, 0.02 mmol). The vial was flushed with argon, diluted with dioxane (1.5 mL) and to this was added 2M aqueous K_2CO_3 (0.25 mL, 0.5 mmol). The vial was sealed, heated to 100 °C for 2 hours, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-20% $MeOH/CH_2Cl_2$ gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{29}H_{29}ClN_3O_3S$: 534.2 ($M+H^+$); Found: 534.3 ($M+H^+$).

Preparation of *(S)*-2-(2-(1*H*-benzo[*d*]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-(*tert*-butoxy)acetic acid: To a solution of *(S)*-ethyl 2-(2-(1*H*-benzo[*d*]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-(*tert*-butoxy)acetate (8 mg, 0.015 mmol) in 1:1 THF/MeOH (0.75 mL) was added 2M aqueous NaOH (0.2 mL, 0.4 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ

9.37 (s, 1H), 8.51 (s, 1H), 8.28 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.90 (s, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.66 – 7.57 (m, 3H), 5.27 (s, 1H), 2.63 (s, 3H), 0.98 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{27}H_{25}ClN_3O_3S$: 506.1 ($M+H^+$); Found: 506.2 ($M+H^+$).

Example 140. Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-methoxy-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (288).



(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

2-chloro-5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

(*S*)-ethyl 2-*tert*-butoxy-2-(2-(2-chloro-5-fluoropyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5-fluoro-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5-methoxy-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

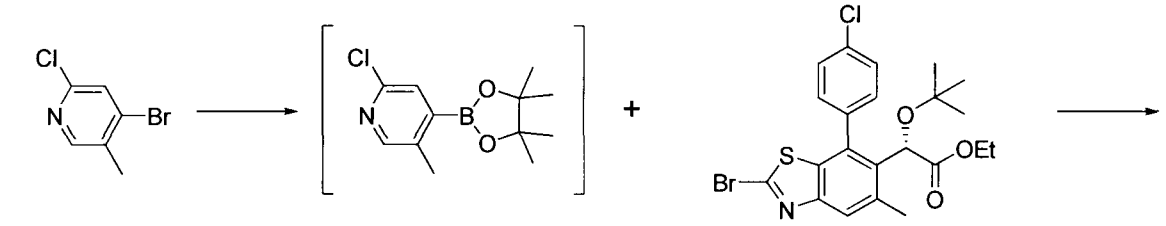
288

Preparation of *(S)*-ethyl 2-(*tert*-butoxy)-2-(2-(2-chloro-5-fluoropyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: A microwave vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (104 mg, 0.21 mmol), 2-Chloro-5-fluoropyridine-4-boronic acid pinacol ester (80 mg, 0.31 mmol), then $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The vial was flushed with argon, diluted with dioxane (2.0 mL) and to this was added 2M aqueous K_2CO_3 (0.30 mL, 0.60 mmol). The vial was sealed, heated to 100 °C for 2 hours, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-20% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{27}H_{26}Cl_2FN_2O_3S$: 547.1 ($M+H^+$); Found: 547.2 ($M+H^+$).

Preparation of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-fluoro-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: A microwave vial containing *(S)*-ethyl 2-(*tert*-butoxy)-2-(2-(2-chloro-5-fluoropyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (22 mg, 0.04 mmol) was charged with (1-methyl-1*H*-indazol-5-yl)boronic acid (19 mg, 0.11 mmol), then $Pd(PPh_3)_4$ (9 mg, 0.008 mmol). The vial was flushed with argon, diluted with dioxane (2.0 mL) and to this was added 2M aqueous K_2CO_3 (0.10 mL, 0.20 mmol). The vial was sealed, heated to 120 °C for 3 hours, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10-40% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{35}H_{33}ClFN_4O_3S$: 643.2 ($M+H^+$); Found: 643.2 ($M+H^+$).

Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-methoxy-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-fluoro-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (15 mg, 0.023 mmol) in 1:1 THF/MeOH (1.50 mL) was added 2M aqueous NaOH (0.25 mL, 0.5 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.95 (s, 1H), 8.60 (s, 1H), 8.39 (s, 1H), 8.16 (s, 1H), 8.06 (dd, J = 8.9, 1.6 Hz, 1H), 7.97 (s, 1H), 7.77 – 7.67 (m, 2H), 7.66 – 7.56 (m, 3H), 5.29 (s, 1H), 4.16 (s, 3H), 4.13 (s, 3H), 2.65 (s, 3H), 0.98 (s, 9H).LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_4O_4S$: 627.2 ($M+H^+$); Found: 627.2 ($M+H^+$).

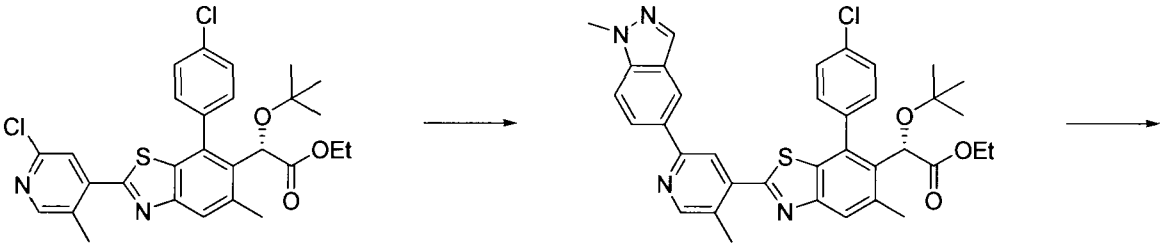
Example 141. Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid (289).



4-bromo-2-chloro-5-methylpyridine

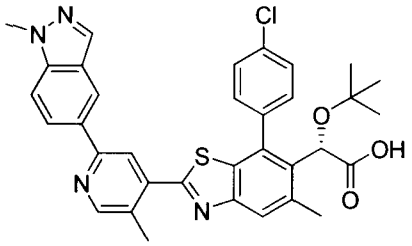
2-chloro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(2-(2-chloro-5-methylpyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

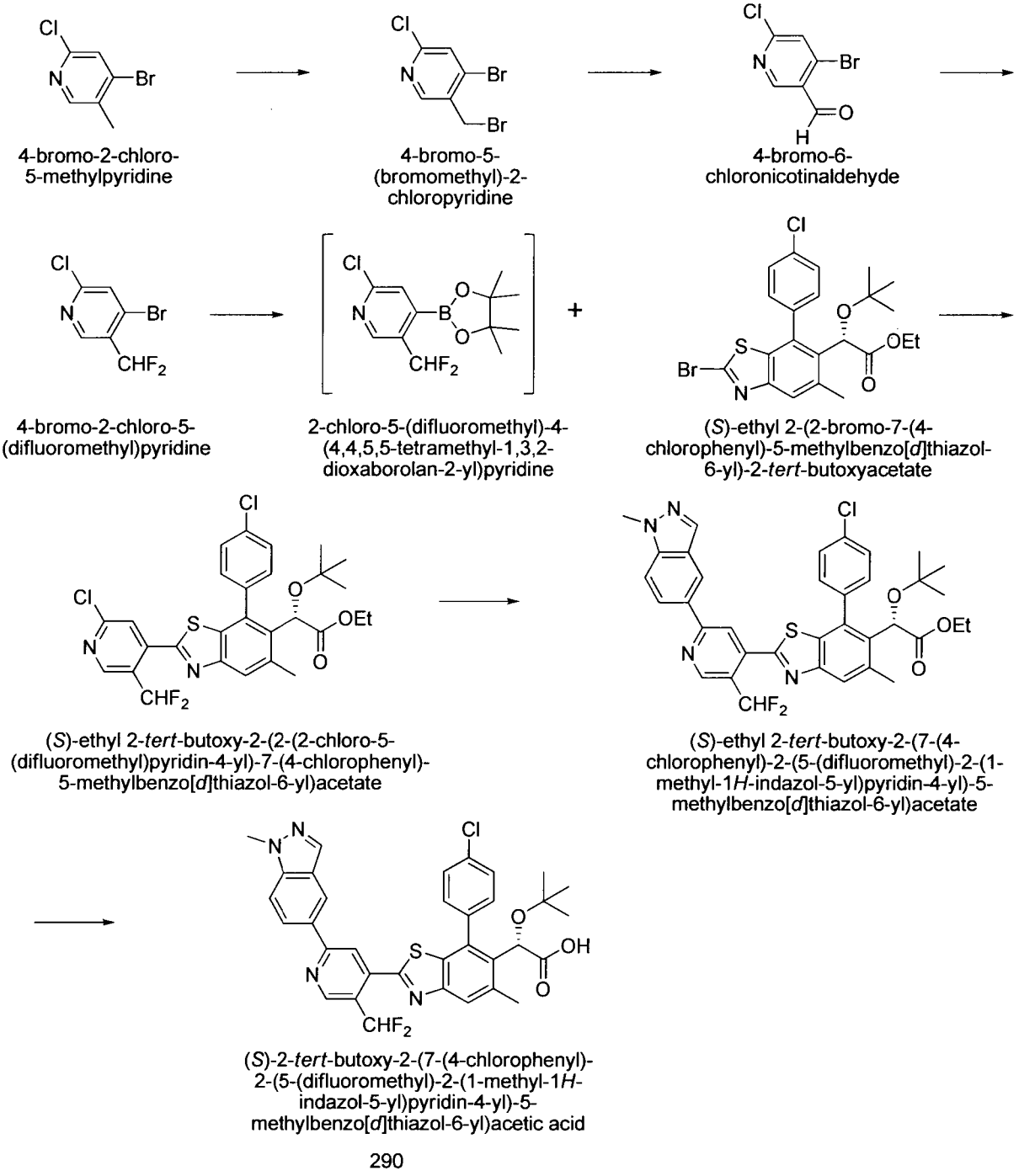
289

Preparation of *(S)*-ethyl 2-(*tert*-butoxy)-2-(2-(2-chloro-5-methylpyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: A microwave vial was charged with 4-bromo-2-chloro-5-methylpyridine (199 mg, 0.96 mmol), Bis(pinacolato)diboron (252 mg, 0.99 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (44 mg, 0.05 mmol), then KOAc (293 mg, 2.98 mmol). The vial was flushed with argon, diluted with dioxane (4 mL), sealed, then heated to 100 °C for 1 hour. The reaction mixture was allowed to cool to room temperature and then a portion of this cooled solution (0.7 mL, 0.17 mmol) was added to a vial that was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (80 mg, 0.16 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.01 mmol). The mixture was diluted with dioxane (2.0 mL) and to this was added 2M aqueous K_2CO_3 (0.30 mL, 0.60 mmol). The vial was sealed, heated to 100 °C for 1 hour, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-20% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{28}H_{29}Cl_2N_2O_3S$: 543.1 ($M + H^+$); Found: 543.2 ($M + H^+$).

Preparation of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate: A microwave vial containing *(S)*-ethyl 2-(*tert*-butoxy)-2-(2-(2-chloro-5-methylpyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (68 mg, 0.13 mmol) was charged with (1-methyl-1*H*-indazol-5-yl)boronic acid (44 mg, 0.25 mmol), then $Pd(PPh_3)_4$ (24 mg, 0.02 mmol). The vial was flushed with argon, diluted with dioxane (2.0 mL) and to this was added 2M aqueous K_2CO_3 (0.20 mL, 0.40 mmol). The vial was sealed, heated to 120 °C for 3 hours, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10-45% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{36}H_{36}ClN_4O_3S$: 639.2 ($M+H^+$); Found: 639.2($M+H^+$).

Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetate (63 mg, 0.023 mmol) in 1:1 THF/MeOH (1.50 mL) was added 2M aqueous NaOH (0.30 mL, 0.60 mmol) and stirred at 40 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 8.47 (s, 1H), 8.39 (s, 1H), 8.15 (s, 1H), 8.04 – 7.96 (m, 2H), 7.77 – 7.67 (m, 2H), 7.64 – 7.56 (m, 3H), 5.30 (s, 1H), 4.12 (s, 3H), 2.77 (s, 3H), 2.66 (s, 3H), 0.99 (s, 9H); LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_4O_3S$: 611.2 ($M+H^+$); Found: 611.2 ($M+H^+$).

Example 142. Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-(difluoromethyl)-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (290).



Preparation of 4-bromo-5-(bromomethyl)-2-chloropyridine: A flask was charged with 4-bromo-2-chloro-5-methylpyridine (513 mg, 2.48 mmol), $(PhCO_2)_2$ (32 mg, 0.13 mmol), and NBS (452 mg, 2.54 mmol) then diluted with CCl_4 (9 mL). The reaction mixture was heated to reflux for 2 hours and then allowed to cool to room temperature and diluted with CH_2Cl_2 and H_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-20% EtOAc/Hex gradient) to

afford the desired product. LCMS-ESI$^+$: calc'd for $C_6H_5Br_2ClN$ 283.9 ($M+H^+$); Found: 283.9 ($M+H^+$).

Preparation of 4-bromo-6-chloronicotinaldehyde: A flask was charged with 4-bromo-5-(bromomethyl)-2-chloropyridine (490 mg, 1.72 mmol), powdered 4 Å molecular sieves, and NMO (2.19 g, 18.74 mmol) then diluted with ACN (17 mL) and stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-20% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_6H_4BrClNO$ 219.9 ($M+H^+$); Found: 220.0 ($M+H^+$).

Preparation of 4-bromo-2-chloro-5-(difluoromethyl)pyridine: To a solution of 4-bromo-6-chloronicotinaldehyde (165 mg, 0.75 mmol) in CH_2Cl_2 at 0 °C was slowly added Deoxofluor (0.42 mL, 2.28 mmol) and stirred for 1 hour and then warmed to room temperature and stirred for 1 hour. The reaction mixture was then slowly diluted with saturated aqueous $NaHCO_3$ and then the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered through a small pad of silica gel, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-10% EtOAc/Hex gradient) to afford the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.65 (d, J = 0.3 Hz, 1H), 6.88 (t, J = 54.0 Hz, 1H).

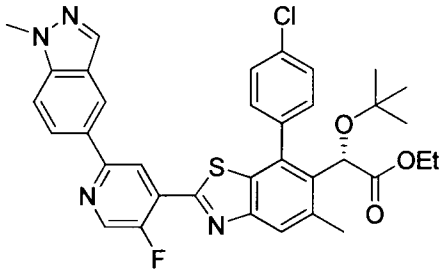
Preparation of *(S)*-ethyl 2-(*tert*-butoxy)-2-(2-(2-chloro-5-(difluoromethyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: A microwave vial was charged with 4-bromo-2-chloro-5-(difluoromethyl)pyridine (155 mg, 0.64 mmol), Bis(pinacolato)diboron (179 mg, 0.70 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (55 mg, 0.07 mmol), then KOAc (198 mg, 2.00 mmol). The vial was flushed with argon, diluted with dioxane (4 mL), sealed, then heated to 100 °C for 1 hour. The reaction mixture was allowed to cool to room temperature and then a portion of this cooled solution (1.2 mL, 0.19 mmol) was added to a vial that was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (58 mg, 0.12 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (19 mg, 0.02 mmol). The mixture was diluted with dioxane (0.8 mL) and to this was added 2M aqueous K_2CO_3 (0.20 mL, 0.40 mmol). The vial was sealed, heated to 100 °C for 1 hour, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-15% EtOAc/Hex gradient) to

afford the desired product. LCMS-ESI$^+$: calc'd $C_{28}H_{27}Cl_2F_2N_2O_3S$: 579.1 (M + H$^+$); Found: 579.1 (M + H$^+$).

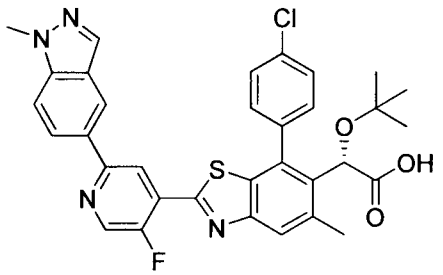
Preparation of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-(difluoromethyl)-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: A microwave vial containing *(S)*-ethyl 2-(*tert*-butoxy)-2-(2-(2-chloro-5-(difluoromethyl)pyridin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (44 mg, 0.076 mmol) was charged with (1-methyl-1*H*-indazol-5-yl)boronic acid (26 mg, 0.15 mmol), then $Pd(PPh_3)_4$ (18 mg, 0.02 mmol). The vial was flushed with argon, diluted with dioxane (1.0 mL) and to this was added 2M aqueous K_2CO_3 (0.15 mL, 0.30 mmol). The vial was sealed, heated to 120 °C for 3 hours, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10-40% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{36}H_{34}ClF_2N_4O_3S$: 675.2 (M+H$^+$); Found: 675.2 (M+H$^+$).

Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-(difluoromethyl)-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-(difluoromethyl)-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (21 mg, 0.03 mmol) in 1:1 THF/MeOH (1.50 mL) was added 2M aqueous NaOH (0.20 mL, 0.40 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 9.05 (s, 1H), 8.51 (s, 1H), 8.26 (s, 1H), 8.17 (dd, J = 8.9, 1.6 Hz, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.93 (t, J = 54.6 Hz, 1H), 7.75 – 7.56 (m, 5H), 5.29 (s, 1H), 4.10 (s, 3H), 2.65 (s, 3H), 0.99 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{34}H_{30}ClF_2N_4O_3S$: 647.2 (M+H$^+$); Found: 647.2 (M+H$^+$).

Example 143. Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-fluoro-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (291).



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5-fluoro-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

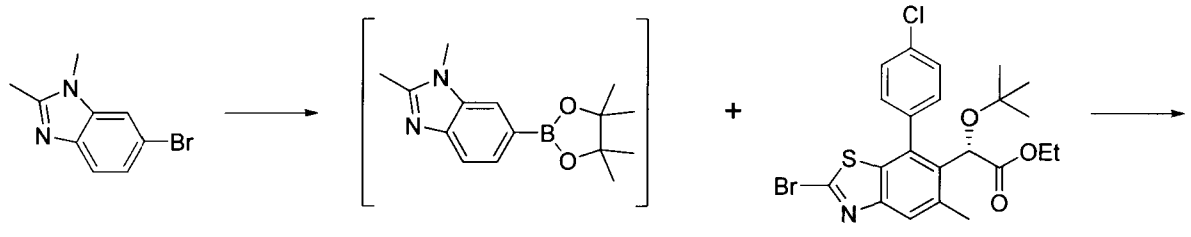


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5-fluoro-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

291

Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-fluoro-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(5-fluoro-2-(1-methyl-1*H*-indazol-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (27 mg, 0.04 mmol) in THF (1.50 mL) was added 2M aqueous NaOH (0.40 mL, 0.80 mmol) and stirred at 90 °C for 2 days. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.73 (d, J = 5.7 Hz, 1H), 8.66 (d, J = 2.3 Hz, 1H), 8.44 (d, J = 0.8 Hz, 1H), 8.14 (dd, J = 8.9, 1.7 Hz, 1H), 8.12 (d, J = 0.8 Hz, 1H), 7.95 (s, 1H), 7.78 – 7.50 (m, 5H), 5.29 (s, 1H), 4.10 (s, 3H), 2.64 (s, 3H), 0.99 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{33}H_{29}ClFN_4O_3S$: 615.2 ($M+H^+$); Found: 615.2 ($M+H^+$).

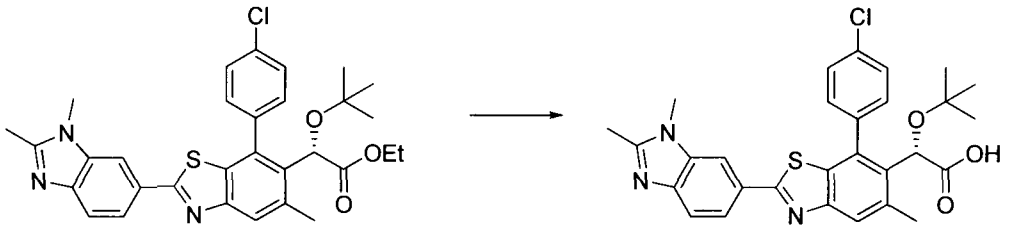
Example 144. Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-benzo[*d*]imidazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (292).



6-bromo-1,2-dimethyl-1*H*-benzo[*d*]imidazole

1,2-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-benzo[*d*]imidazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-benzo[*d*]imidazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

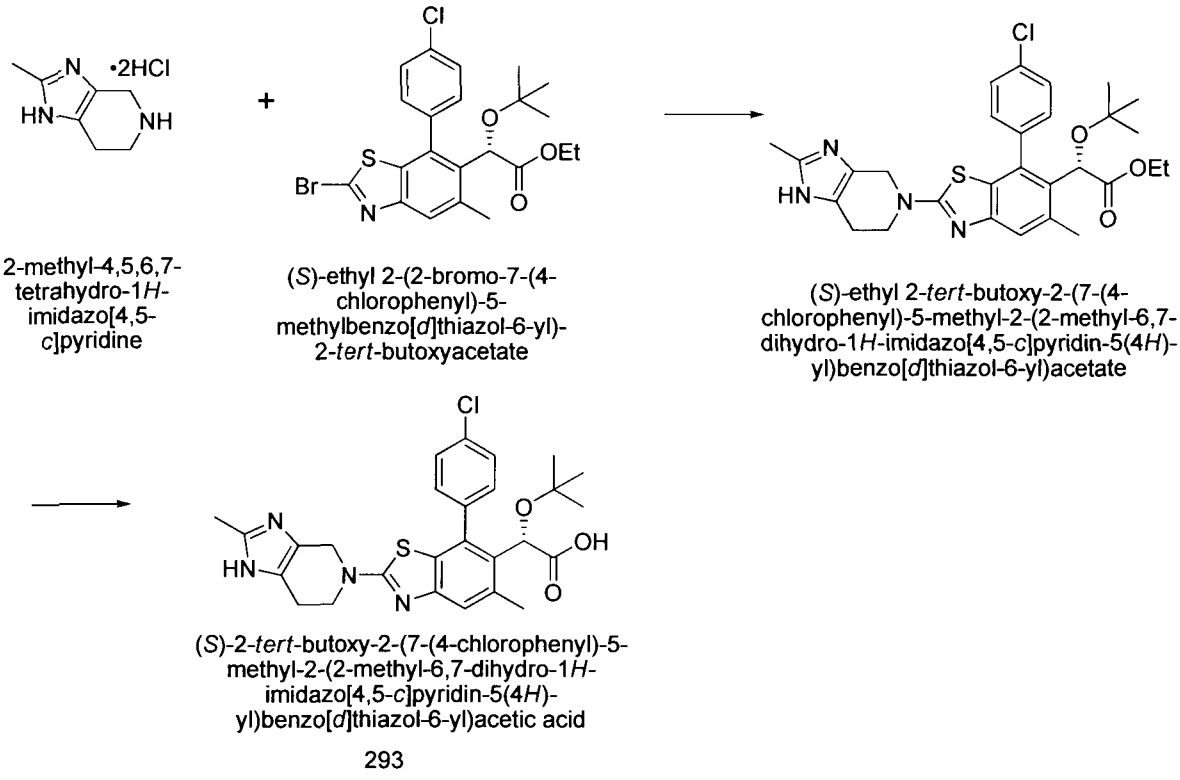
292

Preparation of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-benzo[*d*]imidazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: A microwave vial was charged with 6-bromo-1,2-dimethyl-1*H*-benzo[*d*]imidazole (150 mg, 0.67 mmol), Bis(pinacolato)diboron (189 mg, 0.74 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (55 mg, 0.07 mmol), then KOAc (221 mg, 2.25 mmol). The vial was flushed with argon, diluted with dioxane (3 mL), sealed, then heated to 100 °C for 45 minutes. The reaction mixture was allowed to cool to room temperature and then a portion of this cooled solution (1.0 mL, 0.22 mmol) was added to a vial that was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (55 mg, 0.10 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol). The mixture was diluted with dioxane (1.5 mL) and to this was added 2M aqueous K_2CO_3 (0.21 mL, 0.42 mmol). The vial was sealed, heated to 100 °C for 1 hour, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered through a small pad of silica gel, and concentrated *in vacuo* to afford the desired product. LCMS-ESI$^+$: calc'd $C_{31}H_{33}ClN_3O_3S$: 562.2 ($M + H^+$); Found: 562.3 ($M + H^+$).

Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-benzo[*d*]imidazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-benzo[*d*]imidazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (27 mg, 0.05 mmol) in 1:1 THF/MeOH (1.50 mL) was added 2M aqueous NaOH (0.15 mL, 0.30 mmol) and stirred at 50 °C overnight. The reaction

mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.26 (dd, J = 8.6, 1.5 Hz, 1H), 7.90 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.67 – 7.57 (m, 3H), 5.27 (s, 1H), 4.05 (s, 3H), 2.88 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).LCMS-ESI$^+$: calc'd for $C_{29}H_{29}ClN_3O_3S$: 534.2 ($M+H^+$); Found: 534.2 ($M+H^+$).

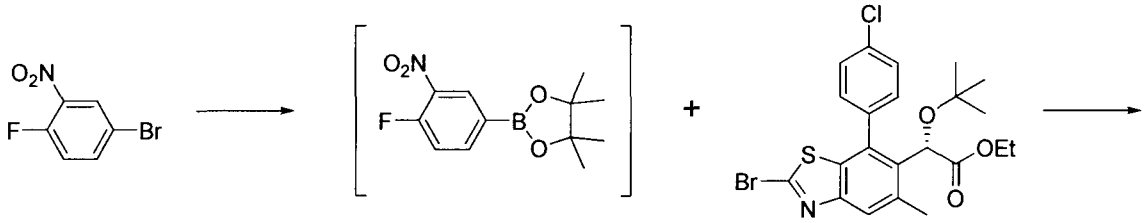
Example 145. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)benzo[d]thiazol-6-yl)acetic acid (293).



Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)benzo[d]thiazol-6-yl)acetate: A flask was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (100 mg, 0.20 mmol), 2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (85 mg, 0.40 mmol), Cs_2CO_3 (325 mg, 1.0 mmol), and then diluted with ACN (4 mL). The suspension was heated to 80 °C for 24 hours and then allowed to cool to room temperature. The resulting mixture was filtered and concentrated *in vacuo*. The crude residue was purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA)to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{29}H_{34}ClN_4O_3S$: 553.2 ($M+H^+$); Found: 553.2 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)benzo[d]thiazol-6-yl)acetate (21 mg, 0.04 mmol) in 1:1 THF/MeOH (1.5 mL) was added 2M aqueous NaOH (0.2 mL, 0.4 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 7.66 – 7.43 (m, 4H), 7.36 (s, 1H), 5.14 (s, 1H), 4.76 (br s, 2H), 3.94 (br t, J = 5.7 Hz, 2H), 2.87 (br t, J = 5.5 Hz, 2H), 2.61 (s, 3H), 2.50 (s, 3H), 0.94 (s, 9H); LCMS-ESI$^+$: calc'd for $C_{27}H_{30}ClN_4O_3S$: 525.2 ($M+H^+$); Found: 525.1 ($M+H^+$).

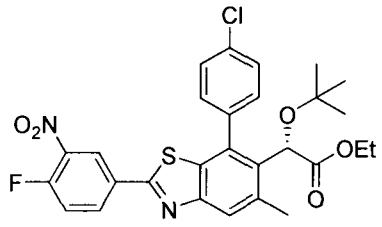
Example 146. Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid (294).



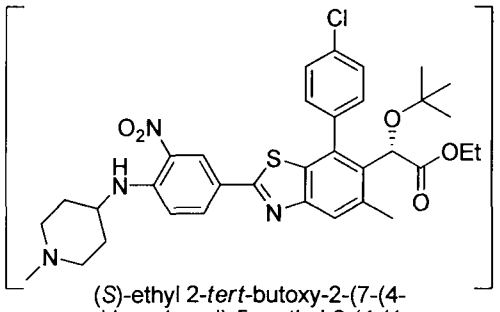
4-bromo-1-fluoro-2-nitrobenzene

2-(4-fluoro-3-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

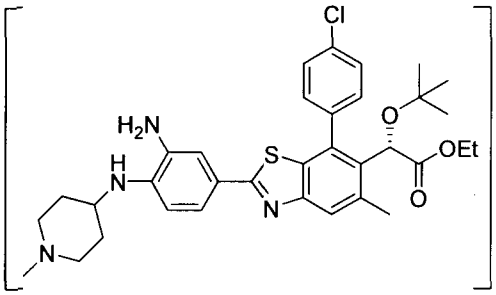
(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



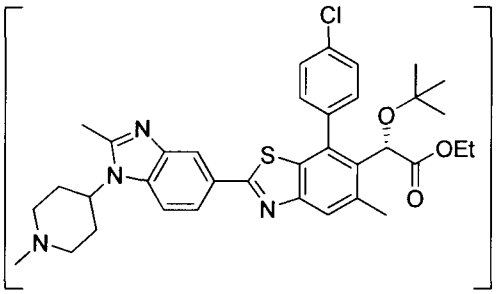
(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-fluoro-3-nitrophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



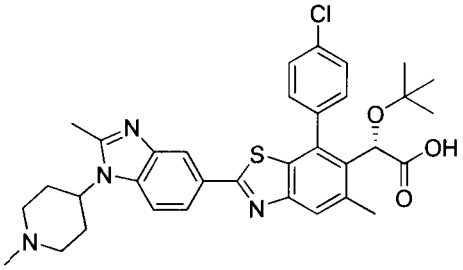
(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methylpiperidin-4-ylamino)-3-nitrophenyl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-(2-(3-amino-4-(1-methylpiperidin-4-ylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

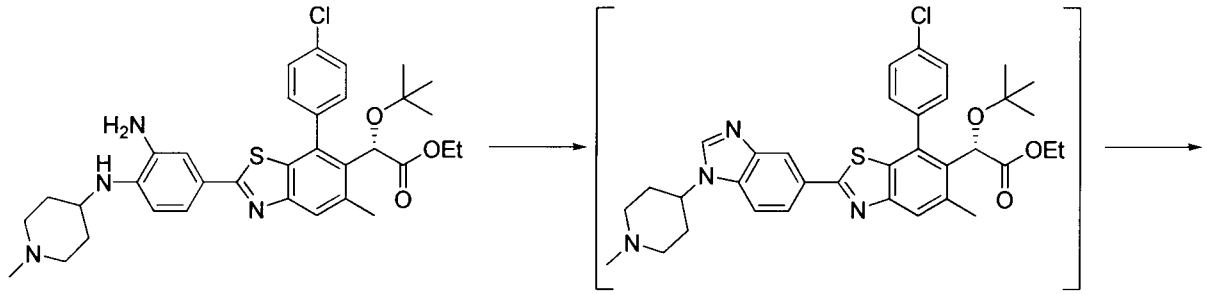
294

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-fluoro-3-nitrophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate: A microwave vial was charged with 4-bromo-1-fluoro-2-nitrobenzene (0.3 mL, 2.41 mmol), Bis(pinacolato)diboron (677 mg, 2.67 mmol),

$PdCl_2(dppf)•CH_2Cl_2$ (203 mg, 0.25 mmol), then KOAc (864 mg, 8.80 mmol). The vial was flushed with argon, diluted with dioxane (6 mL), sealed, then heated to 100 °C for 1 hour. The reaction mixture was allowed to cool to room temperature and then a portion of this cooled solution (1.3 mL, 0.52 mmol) was added to a vial that was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (130 mg, 0.26 mmol) and $Pd(PPh_3)_4$ (44 mg, 0.04 mmol). The mixture was diluted with dioxane (5.0 mL) and to this was added 2M aqueous K_2CO_3 (0.50 mL, 1.00 mmol). The vial was sealed, heated to 100 °C for 1 hour, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-25% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{28}H_{27}ClFN_2O_5S$: 557.1 (M + H$^+$); Found: 557.1 (M + H$^+$).

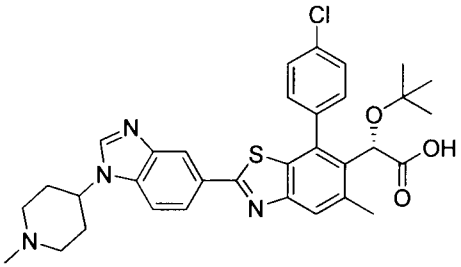
Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid: A flask containing *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(4-fluoro-3-nitrophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate (98 mg, 0.18 mmol) was charged with Cs_2CO_3 (124 mg, 0.38 mmol) and then diluted with DMF (4 mL). The reaction mixture was then treated with 4-amino-1-methylpiperidine (1.0 mL, 0.91 mmol) at room temperature and allowed to stir for 1 hour. The mixture was diluted with EtOAc and H_2O, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a crude residue. The flask containing the crude residue was then charged with 5 wt% Pt/C (33 mg) and diluted with 2:1 EtOH/EtOAc (5 mL). The flask was evacuated then backfilled with H_2 (3 cycles) and stirred under a hydrogen atmosphere for 45 minutes, at which time, the flask was purged with N_2, filtered through a pad of Celite, and concentrated *in vacuo* to provide a crude residue that was taken up in AcOH (5 mL). To this was added $MeC(OEt)_3$ (0.3 mL) at room temperature and allowed to stir for 15 minutes. The solution was concentrated *in vacuo* to provide a crude residue. The crude residue was taken up 1:1 THF/MeOH (1.5 mL) and to this was added 2M aqueous NaOH (0.2 mL, 0.4 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd $C_{34}H_{38}ClN_4O_3S$: 617.2 (M + H$^+$); Found: 617.3 (M + H$^+$).

Example 147. Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid (295).



(*S*)-ethyl 2-(2-(3-amino-4-(1-methylpiperidin-4-ylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetate

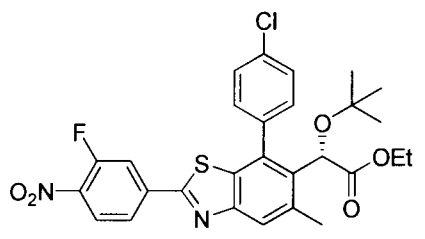


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

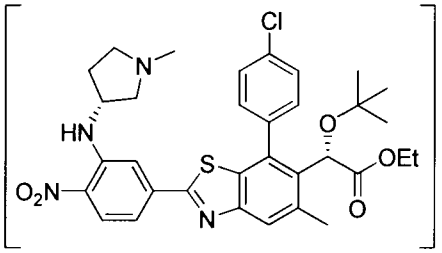
295

Preparation of *(S)*-2-(*tert*-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(1-methylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(2-(3-amino-4-((1-methylpiperidin-4-yl)amino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-(*tert*-butoxy)acetate (26 mg, 0.04 mmol) in AcOH (3 mL) was added $CH(OEt)_3$ (0.3 mL) at room temperature and stirred for 15 minutes. The solution was concentrated *in vacuo* to provide a crude residue that was taken up in 1:1 THF/MeOH (1.5 mL) was added 2M aqueous NaOH (0.2 mL, 0.4 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 8.42 (s, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.87 (s, 1H), 7.70 (d, J = 9.5 Hz, 1H), 7.60 (br s, 3H), 5.26 (s, 1H), 5.01 – 4.89 (m, 1H), 3.90 – 3.70 (m, 2H), 3.43 – 3.32 (m, 2H), 3.01 (s, 3H), 2.62 (s, 3H), 2.60 – 2.34 (m, 4H), 0.98 (s, 9H); LCMS-ESI$^+$: calc'd $C_{33}H_{36}ClN_4O_3S$: 603.2 (M + H^+); Found: 603.3 (M + H^+).

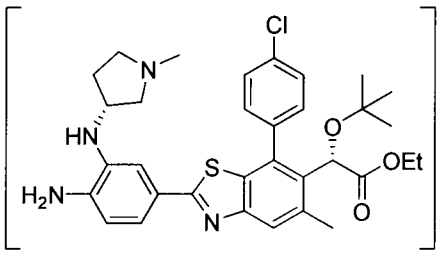
Example 148. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((R)-1-methylpyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid (296).



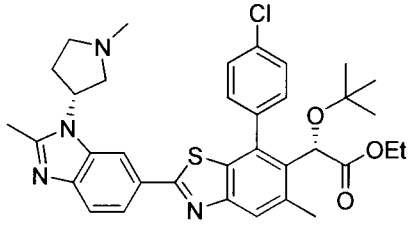
(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-fluoro-4-nitrophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



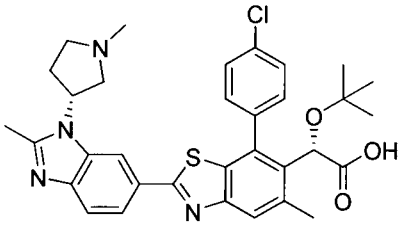
(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-((*R*)-1-methylpyrrolidin-3-ylamino)-4-nitrophenyl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-(2-(4-amino-3-((*R*)-1-methylpyrrolidin-3-ylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((*R*)-1-methylpyrrolidin-3-yl)-1*H*-benzo[*d*]imidazol-6-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((*R*)-1-methylpyrrolidin-3-yl)-1*H*-benzo[*d*]imidazol-6-yl)benzo[*d*]thiazol-6-yl)acetic acid

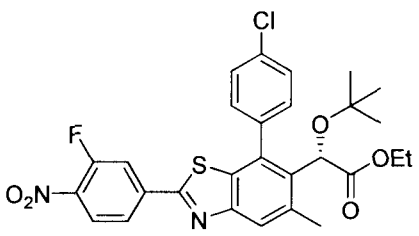
296

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((R)-1-methylpyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate: A flask containing *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-fluoro-4-nitrophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate (86 mg, 0.15 mmol) was charged with Cs_2CO_3 (252 mg, 0.77 mmol) and diluted with DMF (3 mL). The reaction mixture was treated with (3*R*)-1-methylpyrrolidin-3-amine (45 mg, 0.45 mmol) at room temperature and allowed to stir for 30 minutes. The mixture was diluted with EtOAc and H_2O, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a crude residue. The flask containing the crude residue was then charged with 5 wt% Pt/C (23 mg) and then diluted with 2:1 EtOH/EtOAc (3 mL). The flask was evacuated then backfilled with H_2 (3 cycles) and stirred under a hydrogen

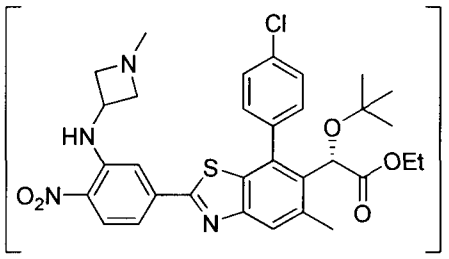
atmosphere for 20 minutes, at which time, the flask was purged with N_2, filtered through a pad of Celite, and concentrated *in vacuo* to provide a crude residue. The crude residue was then taken up in AcOH (2 mL) and $MeC(OEt)_3$ (0.2 mL) was added at room temperature and stirred for 15 minutes. The solution was concentrated *in vacuo* and the crude residue was purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA) to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd $C_{35}H_{40}ClN_4O_3S$: 631.3 (M + H^+); Found: 631.2 (M + H^+).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((R)-1-methylpyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((R)-1-methylpyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate (8 mg, 0.01 mmol) in 2:1 MeOH/THF (1.2 mL) was added 2M aqueous NaOH (0.3 mL, 0.6 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.04 (dd, J = 8.5, 1.4 Hz, 1H), 7.89 (s, 1H), 7.81 (d, J = 8.6 Hz, 1H), 7.74 – 7.66 (m, 1H), 7.66 – 7.54 (m, 3H), 5.81 – 5.60 (br m, 1H), 5.27 (s, 1H), 4.29 – 3.99 (br m, 2H), 3.99 – 3.84 (m, 1H), 3.60 (br s, 1H), 3.18 (s, 3H), 2.98 – 2.71 (m, 2H), 2.84 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H). LCMS-ESI$^+$: calc'd $C_{33}H_{36}ClN_4O_3S$: 603.2 (M + H^+); Found: 603.3 (M + H^+).

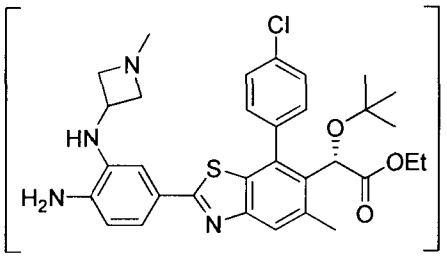
Example 149. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylazetidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid (297).



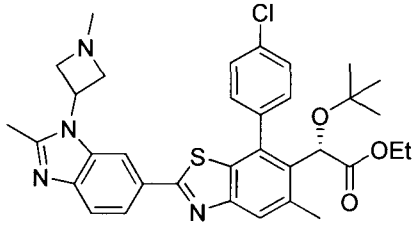
(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-fluoro-4-nitrophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



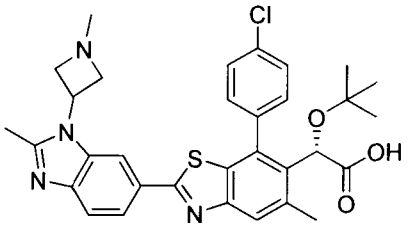
(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(1-methylazetidin-3-ylamino)-4-nitrophenyl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-(2-(4-amino-3-(1-methylazetidin-3-ylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylazetidin-3-yl)-1*H*-benzo[*d*]imidazol-6-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylazetidin-3-yl)-1*H*-benzo[*d*]imidazol-6-yl)benzo[*d*]thiazol-6-yl)acetic acid

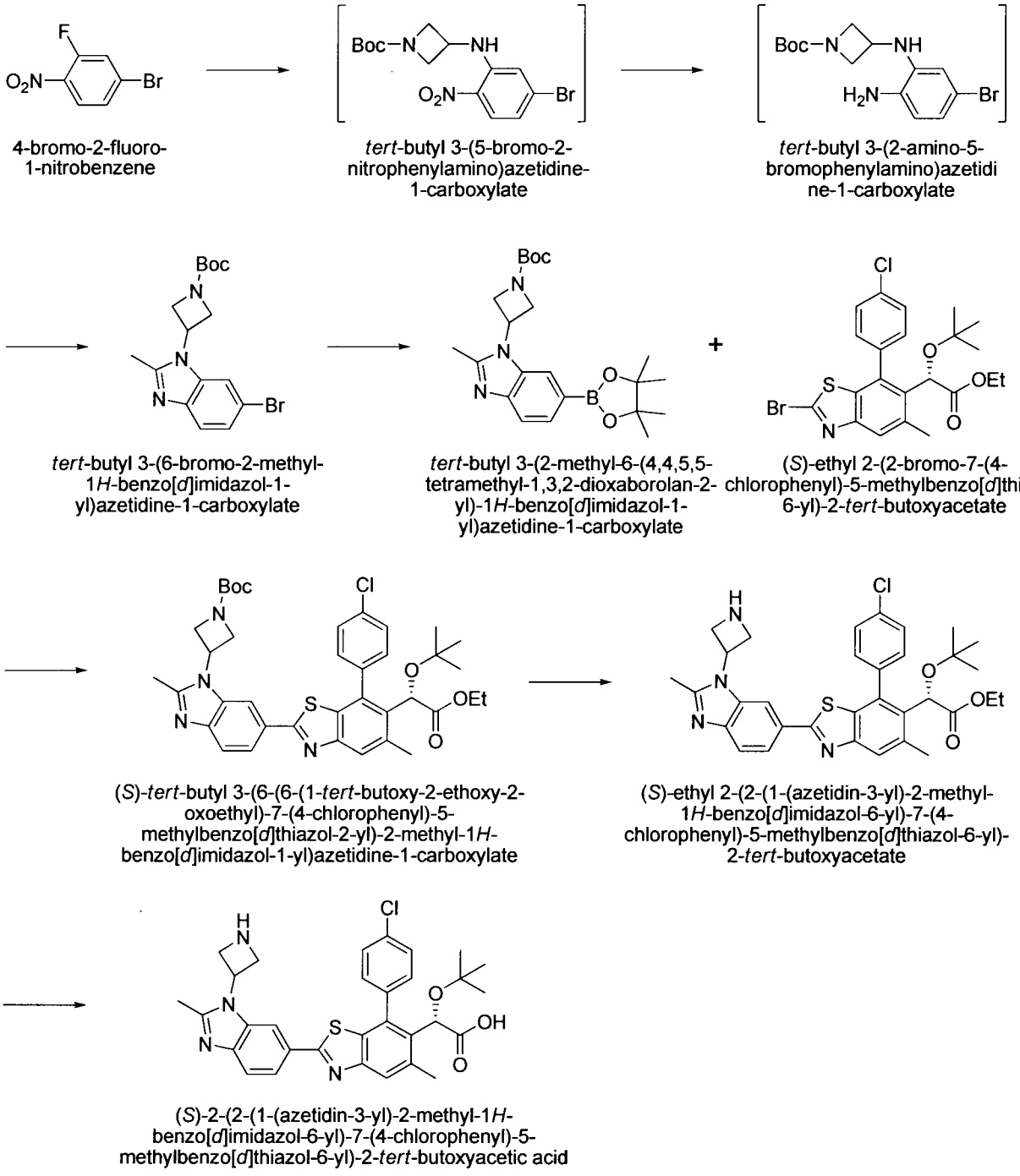
297

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylazetidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate: A flask containing *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-fluoro-4-nitrophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate (252 mg, 0.45 mmol) was charged with Cs_2CO_3 (736 mg, 2.26 mmol) and diluted with DMF (3 mL). The reaction mixture was then treated with 1-methylazetidin-3-amine (127 mg, 1.47 mmol) at room temperature and allowed to stir for 30 minutes. The mixture was diluted with EtOAc and H_2O, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a crude residue. The flask containing the crude residue was charged with 5 wt% Pt/C (46 mg) and diluted with 2:1 EtOH/EtOAc (4 mL). The flask was evacuated then backfilled with H_2 (3 cycles) and stirred under a hydrogen atmosphere for 20 minutes, at which time, the flask was purged with N_2, filtered through a pad of Celite, and concentrated *in vacuo* to provide a crude residue. The crude residue was taken up

in AcOH (3 mL) and $MeC(OEt)_3$ (0.3 mL) was added at room temperature and stirred for 15 minutes. The solution was concentrated *in vacuo* and the crude residue was purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA)to provide the TFA salt of the product. LCMS-ESI^+: calc'd $C_{34}H_{38}ClN_4O_3S$: 617.2 ($M + H^+$); Found: 617.3 ($M + H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylazetidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid:
To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(1-methylazetidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate (18 mg, 0.03 mmol) in 4:1 MeOH/THF (1.0 mL) was added 2M aqueous NaOH (0.3 mL, 0.6 mmol) and stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.13 (dd, J = 8.6, 1.4 Hz, 1H), 7.96 – 7.81 (m, 2H), 7.74 – 7.65 (m, 1H), 7.65 – 7.53 (m, 3H), 6.00 (br s, 1H), 5.27 (s, 1H), 5.22 (br s, 2H), 4.75 (br s, 2H), 3.25 (s, 3H), 2.84 (s, 3H), 2.64 (s, 3H), 0.99 (s, 9H); LCMS-ESI^+: calc'd $C_{32}H_{34}ClN_4O_3S$: 589.2 ($M + H^+$); Found: 589.2 ($M + H^+$).

Example 150. Preparation of *(S)*-2-(2-(1-(azetidin-3-yl)-2-methyl-1H-benzo[d]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (298).



298

Preparation of *tert*-butyl 3-(6-bromo-2-methyl-1H-benzo[d]imidazol-1-yl)azetidine-1-carboxylate: A flask was charged with 4-bromo-2-fluoro-1-nitrobenzene (529 mg, 2.41 mmol), Cs_2CO_3 (2.45 g, 7.52 mmol), and diluted with DMF (6 mL). To this was added *tert*-butyl 3-aminoazetidine-1-carboxylate (0.75 mL, 4.78 mmol) at room temperature and the reaction mixture was allowed to stir for 16 hours. The mixture was diluted with EtOAc and H_2O and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic

extracts were dried over Na_2SO_4, filtered through a small pad of silica gel eluting with 30% EtOAc/Hex, and concentrated *in vacuo* to afford a crude residue. The flask containing the crude residue was charged 5 wt% Pt/C (140 mg) and then diluted with 2:1 EtOH/EtOAc (30 mL). The flask was evacuated then backfilled with H_2 (3 cycles) and stirred under a hydrogen atmosphere for 20 minutes, at which time, the flask was purged with N_2, filtered through a pad of Celite, and concentrated *in vacuo* to provide a crude residue. The crude residue was taken up in AcOH (10 mL) and $MeC(OEt)_3$ (1 mL) was added at room temperature, stirred for 15 minutes, and then the solution was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (30-70% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{16}H_{21}BrN_3O_2$: 366.1 ($M + H^+$); Found: 366.1 ($M + H^+$).

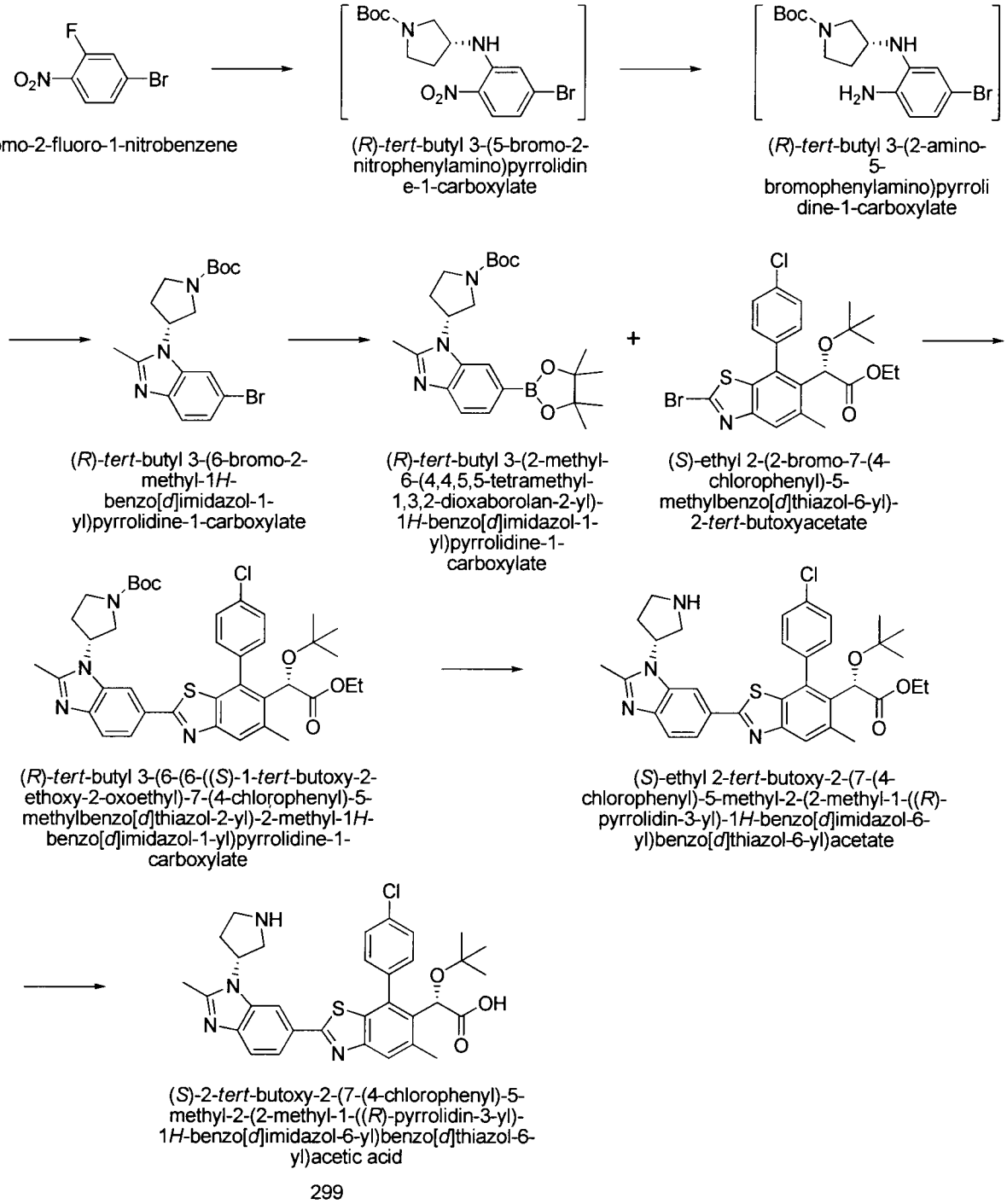
Preparation of *tert*-butyl 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-1-yl)azetidine-1-carboxylate: A microwave vial was charged with *tert*-butyl 3-(6-bromo-2-methyl-1H-benzo[d]imidazol-1-yl)azetidine-1-carboxylate (330 mg, 0.90 mmol), Bis(pinacolato)diboron (275 mg, 1.1 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (74 mg, 0.10 mmol), then KOAc (265 mg, 2.70 mmol). The vial was flushed with argon, diluted with dioxane (9 mL), sealed, and then heated to 100 °C for 90 minutes. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, filtered through a pad of Celite, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (50-100% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{22}H_{33}BN_3O_4$: 414.3 ($M + H^+$); Found: 414.2 ($M + H^+$).

Preparation of *(S)-tert*-butyl 3-(6-(6-(1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-methyl-1H-benzo[d]imidazol-1-yl)azetidine-1-carboxylate: A microwave vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (54 mg, 0.11 mmol), *tert*-butyl 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-1-yl)azetidine-1-carboxylate (181 mg, 0.44 mmol), then $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The vial was flushed with argon, diluted with dioxane (2 mL) and to this was added 2M aqueous K_2CO_3 (0.2 mL, 0.4 mmol). The vial was sealed, heated to 100 °C for 16 hours, and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-10% $MeOH/CH_2Cl_2$ gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{38}H_{44}ClN_4O_5S$ $C_{31}H_{33}ClN_3O_4S$: 703.3 ($M+H^+$); Found: 703.5 ($M+H^+$).

Preparation of *(S)*-ethyl 2-(2-(1-(azetidin-3-yl)-2-methyl-1H-benzo[d]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: A solution of *(S)*-*tert*-butyl 3-(6-(6-(1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-methyl-1H-benzo[d]imidazol-1-yl)azetidine-1-carboxylate (76 mg, 0.11 mmol) in 1.25 M HCl in *i*-PrOH (20 mL) was stirred at room temperature for 16 hours then at 45 °C for 3 hours. The solution was cooled to room temperature and concentrated *in vacuo* to provide the desired product. LCMS-ESI$^+$: calc'd for $C_{33}H_{36}ClN_4O_3S$: 603.2 ($M+H^+$); Found: 603.4 ($M+H^+$).

Preparation of *(S)*-2-(2-(1-(azetidin-3-yl)-2-methyl-1H-benzo[d]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid: To a solution of *(S)*-ethyl 2-(2-(1-(azetidin-3-yl)-2-methyl-1H-benzo[d]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (69 mg, 0.11 mmol) in 3:1 MeOH/THF (1.3 mL) was added 2M aqueous NaOH (0.3 mL, 0.6 mmol) and stirred at 90 °C for 3 hours. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.94 – 7.82 (m, 2H), 7.76 – 7.66 (m, 1H), 7.65 – 7.52 (m, 3H), 5.97 (p, J = 8.7 Hz, 1H), 5.27 (s, 1H), 5.14 – 5.01 (m, 2H), 4.74 – 4.62 (m, 2H), 2.87 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H); LCMS-ESI$^+$: calc'd $C_{31}H_{32}ClN_4O_3S$: 575.2 ($M + H^+$); Found: 575.3 ($M + H^+$).

Example 151. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((R)-pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid (299).



299

Preparation of (R)-*tert*-butyl 3-(6-bromo-2-methyl-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate: A flask was charged with 4-bromo-2-fluoro-1-nitrobenzene (531 mg, 2.41 mmol) and Cs_2CO_3 (2.37 g, 7.27 mmol) and diluted with DMF (6 mL). To this was added (R)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (0.85 mL, 5.01 mmol) at room temperature and the reaction mixture was allowed to stir for 16 hours. The mixture was diluted with EtOAc and H_2O and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4, filtered through a small pad

of silica gel eluting with 30% EtOAc/Hex, and concentrated *in vacuo* to afford a crude residue. The flask containing the crude residue was charged with 5 wt% Pt/C (200 mg) and then diluted with 2:1 EtOH/EtOAc (30 mL). The flask was evacuated then backfilled with H_2 (3 cycles) and stirred under a hydrogen atmosphere for 20 minutes, at which time, the flask was purged with N_2, filtered through a pad of Celite, and concentrated *in vacuo* to provide a crude residue. The crude residue was taken up in AcOH (10 mL) and $MeC(OEt)_3$ (1 mL) was added at room temperature, stirred for 15 minutes, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (30-70% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{17}H_{23}BrN_3O_2$: 380.1 (M + H$^+$); Found: 380.1 (M + H$^+$).

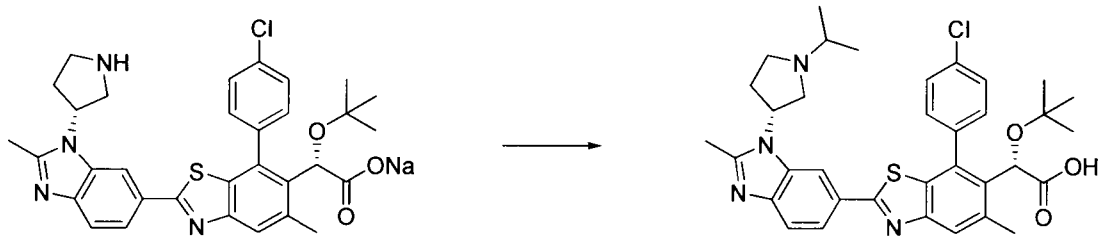
Preparation of (R)-*tert*-butyl 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate: A microwave vial was charged with (R)-*tert*-butyl 3-(6-bromo-2-methyl-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate (337 mg, 0.89 mmol), Bis(pinacolato)diboron (274 mg, 1.1 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (75 mg, 0.10 mmol), then KOAc (271 mg, 2.76 mmol). The vial was flushed with argon, diluted with dioxane (9 mL), sealed, and then heated to 100 °C for 90 minutes. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, filtered through a pad of Celite, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (50-100% EtOAc/Hex gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{23}H_{35}BN_3O_4$: 428.3 (M + H$^+$); Found: 428.2 (M + H$^+$).

Preparation of (R)-*tert*-butyl 3-(6-(6-((*S*)-1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-methyl-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate: A microwave vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (53 mg, 0.11 mmol), (R)-*tert*-butyl 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate (92 mg, 0.21 mmol), then $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The vial was flushed with argon, diluted with dioxane (2 mL) and to this was added 2M aqueous K_2CO_3 (0.2 mL, 0.4 mmol). The vial was sealed then heated to 100 °C for 16 hours and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (0-10% $MeOH/CH_2Cl_2$ gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{39}H_{46}ClN_4O_5S$: 717.3 (M+H$^+$); Found: 717.1(M+H$^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((R)-pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate: A solution of (R)-*tert*-butyl 3-(6-(6-(*(S)*-1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-methyl-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate (77 mg, 0.11 mmol) in 1.25 M HCl in *i*-PrOH (12 mL) was stirred at room temperature for 16 hours. The solution was then concentrated *in vacuo* to provide the desired product. LCMS-ESI$^+$: calc'd for $C_{34}H_{38}ClN_4O_3S$: 617.2 ($M+H^+$); Found: 617.2 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((R)-pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(2-(1-(azetidin-3-yl)-2-methyl-1H-benzo[d]imidazol-6-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (70 mg, 0.11 mmol) in 3:1 MeOH/THF (1.3 mL) was added 2M aqueous NaOH (0.6 mL, 1.2 mmol) and stirred at 90 °C for 3 hours. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.19 (dd, J = 8.6, 1.3 Hz, 1H), 7.98-7.79 (br m, 2H), 7.75 – 7.65 (br m, 1H), 7.65 – 7.52 (m, 3H), 5.69 (p, J = 9.4 Hz, 1H), 5.26 (s, 1H), 4.07 – 3.83 (m, 3H), 3.58 (td, J = 11.4, 7.0 Hz, 1H), 2.96 (s, 3H), 2.95 – 2.68 (m, 2H), 2.63 (s, 3H), 0.97 (s, 9H); LCMS-ESI$^+$: calc'd $C_{32}H_{34}ClN_4O_3S$: 589.2 ($M + H^+$); Found: 589.4 ($M + H^+$).

Example 152. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1-((R)-1-isopropylpyrrolidin-3-yl)-2-methyl-1H-benzo[d]imidazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (300).



sodium (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((*R*)-pyrrolidin-3-yl)-1*H*-benzo[*d*]imidazol-6-yl)benzo[*d*]thiazol-6-yl)acetate

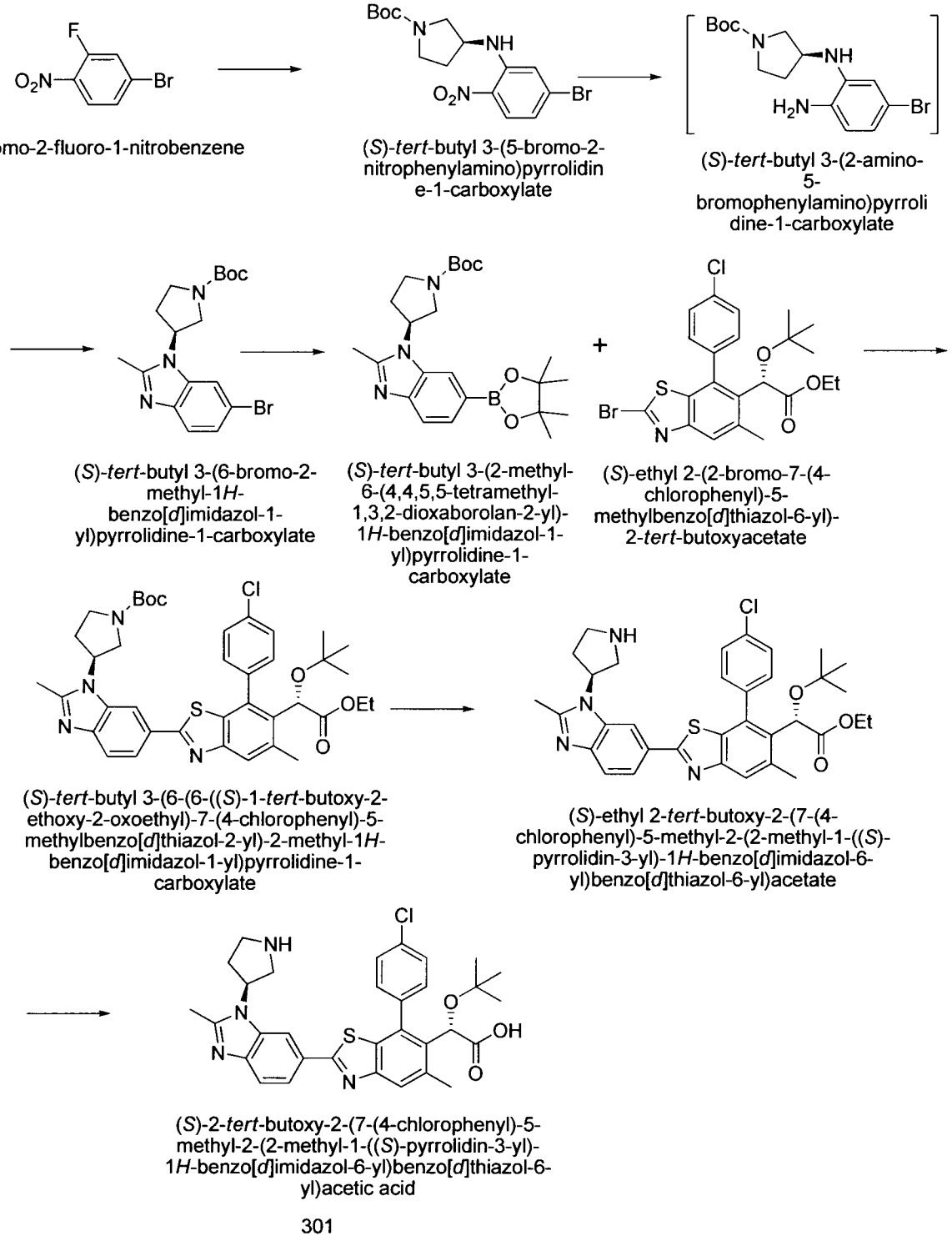
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1-((*R*)-1-isopropylpyrrolidin-3-yl)-2-methyl-1*H*-benzo[*d*]imidazol-6-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

300

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1-((R)-1-isopropylpyrrolidin-3-yl)-2-methyl-1H-benzo[d]imidazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: The

sodium salt of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((R)-pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid was prepared by dissolving the TFA salt in 1M aqueous NaOH and then filtering the solution through a small plug of reverse phase silica gel initially eluting with H_2O, then eluting with MeOH to obtain the desired sodium salt. A flask was then charged with sodium *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-((R)-pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate (13 mg, 0.02 mmol) and then diluted with DMF (1 mL). Sodium triacetoxyborohydride (32 mg, 0.15 mmol) and AcOH (20 μL, 0.27 mmol) were added sequentially and the reaction mixture was warmed to 60 °C, at which time acetone (20 μL, 0.35 mmol) was added and the resulting mixture was stirred for an additional 30 minutes at that temperature. The mixture was then cooled to room temperature, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.10 (dd, J = 8.6, 1.3 Hz, 1H), 7.90 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.76 – 7.67 (m, 1H), 7.67 – 7.56 (m, 3H), 5.66 (br s, 1H), 5.27 (s, 1H), 4.02 (br s, 3H), 3.70 (br s, 1H), 3.02 – 2.85 (m, 1H), 2.89 (s, 3H), 2.79 (br s, 1H), 2.64 (s, 3H), 1.50 (d, J = 6.4 Hz, 6H), 0.98 (s, 9H); LCMS-ESI$^+$: calc'd $C_{35}H_{40}ClN_4O_3S$: 631.3 (M + H^+); Found: 631.3 (M + H^+).

Example 153. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-*((S)*-pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid (301).



Preparation of *(S)-tert*-butyl 3-(6-bromo-2-methyl-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate: A flask was charged with 4-bromo-2-fluoro-1-nitrobenzene (531 mg, 2.41 mmol), Cs_2CO_3 (2.43 g, 7.46 mmol) and diluted with DMF (6 mL). The reaction mixture was then treated with *(S)-tert*-butyl 3-aminopyrrolidine-1-carboxylate (0.9 mL, 5.16 mmol) at room temperature and allowed to stir for 16 hours. The mixture was diluted with EtOAc and H_2O and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4, filtered through a small pad of silica

gel eluting with 30% EtOAc/Hex, and concentrated *in vacuo* to afford a crude residue. The flask containing the crude residue was charged with 5 wt% Pt/C (211 mg) and then diluted with 2:1 EtOH/EtOAc (16 mL). The flask was evacuated then backfilled with H_2 (3 cycles) and stirred under a hydrogen atmosphere for 20 minutes, at which time, the flask was purged with N_2, filtered through a pad of Celite, and concentrated *in vacuo* to provide a crude residue that was then taken up in AcOH (5 mL). To this was added $MeC(OEt)_3$ (0.5 mL) at room temperature and stirred for 15 minutes, at which time, the solution was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-50% THF/CH_2Cl_2 gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{17}H_{23}BrN_3O_2$: 380.1 (M + H^+); Found: 380.1 (M + H^+).

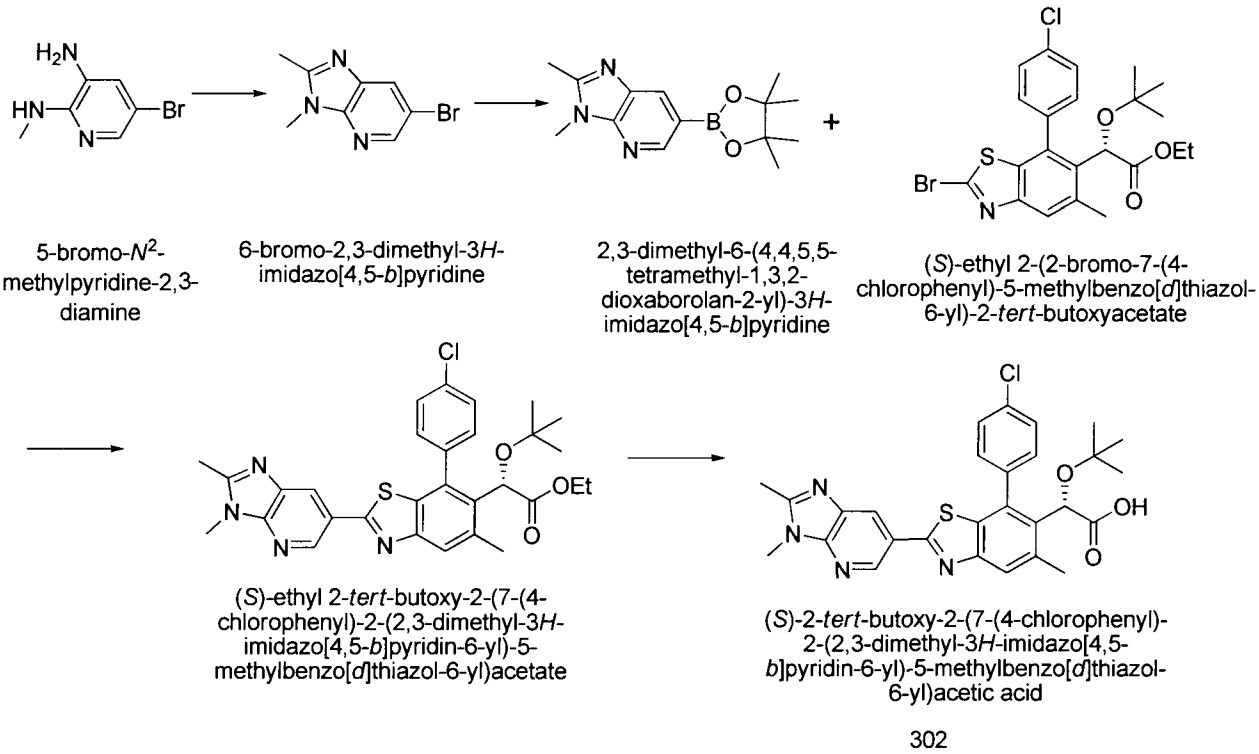
Preparation of *(S)-tert*-butyl 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate: A microwave vial was charged with *(S)-tert*-butyl 3-(6-bromo-2-methyl-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate (624 mg, 1.64 mmol), Bis(pinacolato)diboron (500 mg, 2.00 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (134 mg, 0.16 mmol), then KOAc (483 mg, 4.92 mmol). The vial was flushed with argon, diluted with dioxane (9 mL), sealed, and then heated to 100 °C for 90 minutes. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, filtered through a pad of Celite, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-50% THF/CH_2Cl_2 gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{23}H_{35}BN_3O_4$: 428.3 (M + H^+); Found: 428.2 (M + H^+).

Preparation of *(S)-tert*-butyl 3-(6-(6-(*(S)*-1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-methyl-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate: A microwave vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (50 mg, 0.10 mmol), *(S)-tert*-butyl 3-(2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate (181 mg, 0.42 mmol), then $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The vial was flushed with argon, diluted with dioxane (2 mL) and to this was added 2M aqueous K_2CO_3 (0.2 mL, 0.4 mmol). The vial was sealed then heated to 100 °C for 16 hours and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (0-100% THF/CH_2Cl_2 gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{39}H_{46}ClN_4O_5S$: 717.3 (M+H^+); Found: 717.1(M+H^+).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(*(S)*-pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate: A solution of *(S)*-*tert*-butyl 3-(6-(6-(*(S)*-1-*tert*-butoxy-2-ethoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)-2-methyl-1H-benzo[d]imidazol-1-yl)pyrrolidine-1-carboxylate (70 mg, 0.10 mmol) in 1.25 M HCl in *i*-PrOH (20 mL) was stirred at 35 °C for 4 hours. The solution was then concentrated *in vacuo* to provide the desired product. LCMS-ESI$^+$: calc'd for $C_{34}H_{38}ClN_4O_3S$: 617.2 ($M+H^+$); Found: 617.2 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(*(S)*-pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1-(*(S)*-pyrrolidin-3-yl)-1H-benzo[d]imidazol-6-yl)benzo[d]thiazol-6-yl)acetate (66 mg, 0.10 mmol) in 10:1 MeOH/THF (2.2 mL) was added 2M aqueous NaOH (0.9 mL, 1.8 mmol) and stirred at 100 °C for 5 hours. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.15 (dd, J = 8.6, 1.3 Hz, 1H), 7.90 (s, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.75 – 7.67 (m, 1H), 7.67 – 7.55 (m, 3H), 5.74 – 5.57 (m, 1H), 5.27 (s, 1H), 4.05 – 3.82 (m, 3H), 3.58 (td, J = 11.4, 6.9 Hz, 1H), 2.93 (s, 3H), 2.90 – 2.79 (m, 1H), 2.79 – 2.68 (m, 1H), 2.64 (s, 3H), 0.99 (s, 9H).LCMS-ESI$^+$: calc'd $C_{32}H_{34}ClN_4O_3S$: 589.2 ($M + H^+$); Found: 589.4 ($M + H^+$).

Example 154. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2,3-dimethyl-3H-imidazo[4,5-b]pyridin-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (302).



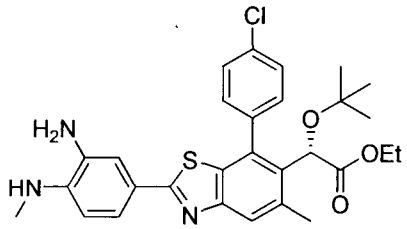
Preparation of 6-bromo-2,3-dimethyl-3H-imidazo[4,5-b]pyridine: To a suspension of 5-bromo-N^2-methylpyridine-2,3-diamine (510 mg, 2.51 mmol) in AcOH (20 mL) was added $MeC(OEt)_3$ (1 mL) and the solution was warmed to 80 °C for 2 hours. The reaction mixture was allowed to cool to room temperature and was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-25% THF/CH_2Cl_2 gradient) to afford the desired product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 1.8 Hz, 1H), 8.06 (d, J = 1.9 Hz, 1H), 3.80 (s, 3H), 2.65 (s, 3H).

Preparation of 2,3-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-imidazo[4,5-b]pyridine: A microwave vial was charged with 6-bromo-2,3-dimethyl-3H-imidazo[4,5-b]pyridine (300 mg, 1.32 mmol), Bis(pinacolato)diboron (387 mg, 1.52 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (117 mg, 0.14 mmol), then KOAc (408 mg, 4.16 mmol). The vial was flushed with argon, diluted with dioxane (6 mL), sealed, and then heated to 100 °C for 90 minutes. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, filtered through a pad of Celite, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0-50% THF/CH_2Cl_2 gradient) to afford the desired product. LCMS-ESI$^+$: calc'd $C_{14}H_{21}BN_3O_2$ 274.2 ($M + H^+$); Found: 274.2 ($M + H^+$).

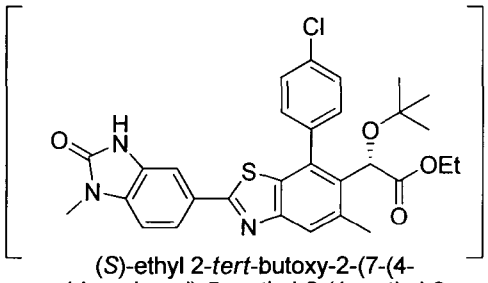
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2,3-dimethyl-3H-imidazo[4,5-b]pyridin-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A microwave vial was charged with *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (50 mg, 0.10 mmol), 2,3-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-imidazo[4,5-b]pyridine (102 mg, 0.37 mmol), then $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The vial was flushed with argon, diluted with dioxane (2 mL) and to this was added 2M aqueous K_2CO_3 (0.2 mL, 0.4 mmol). The vial was sealed then heated to 100 °C for 16 hours and then allowed to cool to room temperature. The mixture was diluted with EtOAc, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (0-100% THF/CH_2Cl_2 gradient) to afford the desired product. LCMS-ESI$^+$: calc'd for $C_{30}H_{32}ClN_4O_3S$: 563.2 ($M+H^+$); Found: 563.2 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2,3-dimethyl-3H-imidazo[4,5-b]pyridin-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2,3-dimethyl-3H-imidazo[4,5-b]pyridin-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (57 mg, 0.10 mmol) in 5:1 MeOH/THF (1.2 mL) was added 2M aqueous NaOH (0.3 mL, 0.6 mmol) and stirred at 50 °C for 16 hours. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 9.18 (s, 1H), 8.67 (s, 1H), 7.88 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.60 (br s, 3H), 5.27 (s, 1H), 3.99 (s, 3H), 2.86 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).LCMS-ESI$^+$: calc'd $C_{28}H_{28}ClN_4O_3S$: 535.2 ($M + H^+$); Found: 535.2 ($M + H^+$).

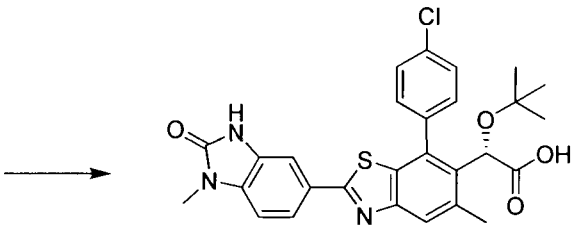
Example 155. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (303).



(*S*)-ethyl 2-(2-(3-amino-4-(methylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetate



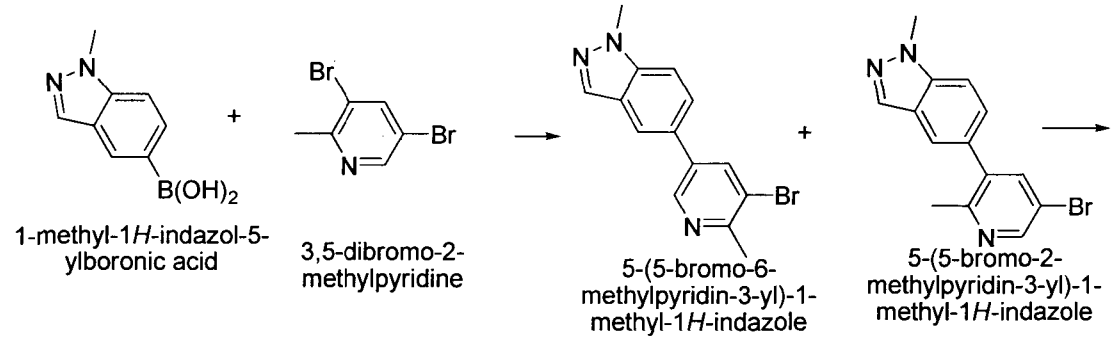
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

303

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-ethyl 2-(2-(3-amino-4-(methylamino)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (40 mg, 0.07 mmol) in THF (2 mL) was added carbonyldiimidazole (45 mg, 0.28 mmol). After 3 h, LCMS showed complete conversion to *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{30}H_{31}ClN_3O_4S$: 564.2 (M+H$^+$); Found: 564.2 (M + H$^+$).

MeOH (2 mL) was added to the mixture followed by a sodium hydroxide solution (2 M aqueous, 500 μL). The reaction mixture was stirred at 50 °C for 4 h. The mixture was purified using reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the product. LCMS-ESI$^+$: calc'd for $C_{28}H_{27}ClN_3O_4S$: 536.1 (M+H$^+$); Found: 536.2 (M + H$^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 7.74-7.79 (m, 3H), 7.67 (m, 1H), 7.58 (m, 3H), 7.18 (d, J = 8.0 Hz, 1H), 5.24 (s, 1H), 3.41 (s, 3H), 2.60 (s, 3H), 0.97 (s, 9H).

Example 157. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid (305).

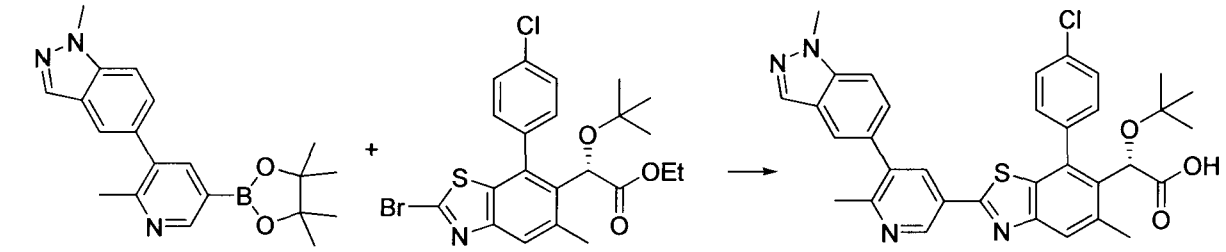


1-methyl-1*H*-indazol-5-ylboronic acid

3,5-dibromo-2-methylpyridine

5-(5-bromo-6-methylpyridin-3-yl)-1-methyl-1*H*-indazole

5-(5-bromo-2-methylpyridin-3-yl)-1-methyl-1*H*-indazole



1-methyl-5-(2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-1*H*-indazole

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1*H*-indazol-5-yl)pyridin-3-yl)benzo[*d*]thiazol-6-yl)acetic acid

305

Preparation of 5-(5-bromo-2-methylpyridin-3-yl)-1-methyl-1H-indazole and 5-(5-bromo-6-methylpyridin-3-yl)-1-methyl-1H-indazole: To a solution of 3,5-dibromo-2-methylpyridine (1.0 g, 3.99 mmol) and 5-(bromomethyl)-1-methyl-1H-indazole (772 mg, 4.38 mmol) in 1,4-dioxane (12 mL) was added $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) and potassium carbonate solution (2 M aqueous, 6 mL, 12 mmol). The reaction mixture was stirred at 105 °C in a sealed tube for 1.5 h. The mixture was diluted with water (15 mL) and EtOAc (20 mL). The layers were separated, and the organic layer was dried, filtered, and concentrated *in vacuo*. The crude material was purified by CombiFlash (EtOAc w/5% MeOH and Hexanes) to give 5-(5-bromo-2-methylpyridin-3-yl)-1-methyl-1H-indazole and 5-(5-bromo-6-methylpyridin-3-yl)-1-methyl-1H-indazole.

5-(5-bromo-2-methylpyridin-3-yl)-1-methyl-1H-indazole:

^{1}H NMR (400 MHz, CD_3OD): δ 8.54 (s, 1H), 8.00 (s, 1H), 7.69 (s, 1H), 7.62 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 4.10 (s, 3H), 2.43 (s, 3H).

5-(5-bromo-6-methylpyridin-3-yl)-1-methyl-1H-indazole:

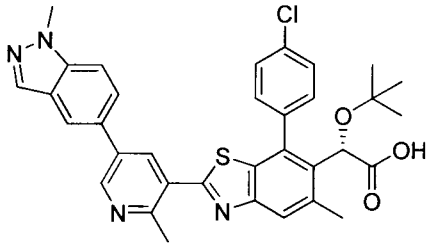
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 2 Hz, 1H), 8.06 (s, 1H), 8.04 (s, 1H), 7.88 (s, 1H), 7.56 (dd, J = 8.8 Hz, 1 H), 7.48 (d, J = 8.8 Hz, 1H), 4.10 (s, 3H), 2.71 (s, 3H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid: To a solution of 5-(5-bromo-2-methylpyridin-3-yl)-1-methyl-1H-indazole (80 mg, 0.27 mmol) in DMF (3 mL) was added potassium acetate (78 mg, 0.80 mmol), bis(pinacolato)diboron (99 mg, 0.40 mmol), and $PdCl_2dppf$ (9 mg, 0.013 mmol). The reaction mixture was stirred at 110 °C for 45 min. Brine (5 mL) was added and EtOAc (10 mL). The layers were separated, and the organic layer was dried, filtered, and concentrated *in vacuo*. The crude product was used without purification.

Dioxane (4 mL) was added followed by *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (45 mg, 0.091 mmol), $Pd(PPh_3)_4$ (5 mg, 0.005 mmol) and potassium carbonate solution (2 M aqueous, 200 μL, 0.40 mmol). The reaction mixture was stirred at 105 °C in a sealed tube for 2.5 h. The mixture was diluted with water (5 mL) and EtOAc (5 mL). The layers were separated, and the organic layer was dried, filtered, and concentrated *in vacuo*.

MeOH (2 mL) and THF (2 mL) were added to the crude material followed by a sodium hydroxide solution (2 M aqueous, 500 μL). The reaction mixture was stirred at 50 °C for 4 h. The mixture was purified using reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the product. LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_4O_3S$: 611.2 ($M+H^+$); Found: 611.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD): δ 9.17 (s, 1H), 8.59 (s, 1H), 8.11 (s, 1H), 7.91 (s, 1H), 7.89 (s, 1H), 7.69-7.74 (m, 2H), 7.58 (m, 3H), 7.53 (d, J = 9.6 Hz, 1H), 5.26 (s, 1H), 4.14 (s, 3H), 2.66 (s, 3H), 2.62 (s, 3H), 0.96 (s, 9H).

Example 158. Prepration of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid (306)



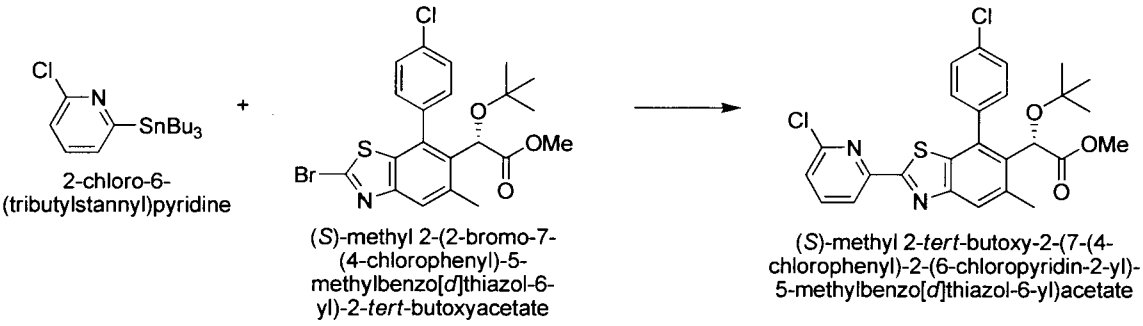
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-5-(1-methyl-1*H*-indazol-5-yl)pyridin-3-yl)benzo[*d*]thiazol-6-yl)acetic acid

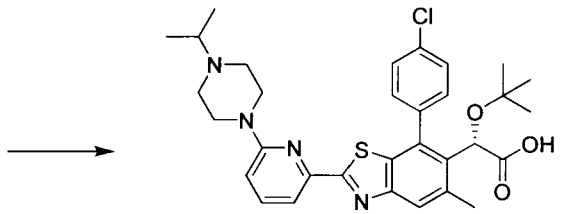
306

Prepration of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-

6-yl)acetic acid was prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid except using 5-(5-bromo-6-methylpyridin-3-yl)-1-methyl-1H-indazole instead of 5-(5-bromo-2-methylpyridin-3-yl)-1-methyl-1H-indazole. LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_4O_3S$: 611.2 ($M+H^+$); Found: 611.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD): δ 9.00 (s, 1H), 8.77 (s, 1H), 8.20 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.84 (m, 1H), 7.72 (m, 2H), 7.60 (m, 3H), 5.28 (s, 1H), 4.11 (s, 3H), 3.00 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H).

Example 159. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(6-(4-isopropylpiperazin-1-yl)pyridin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (307).





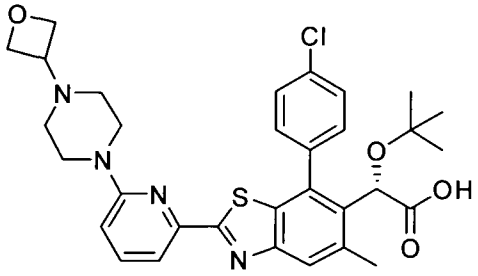
307

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(6-chloropyridin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (241.41 mg, 0.5 mmol) in DMF (2 mL) was added 2-chloro-6-(tributylstannyl)pyridine (241.55 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (28.89 mg, 0.03 mmol), copper (I) iodide (9.52 mg, 0.05 mmol), and lithium chloride (21.2 mg, 0.5 mmol). The reaction mixture was stirred at 95 °C for 4 h. Brine was added (5 mL) and EtOAc (10 mL). The layers were separated, and the organic layer was dried, filtered, and concentrated in vacuo. The crude material was purified by CombiFlash (EtOAc/Hexanes) to give *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(6-chloropyridin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{26}H_{25}Cl_2N_2O_3S$: 515.1 ($M+H^+$); Found: 515.1 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(6-(4-isopropylpiperazin-1-yl)pyridin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(6-chloropyridin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (75 mg, 0.14 mmol) in 1,4-dioxane (2 mL) and EtOH (2 mL) was added triethylamine (200 μL) and 1-isopropylpiperazine (93 mg, 0.73 mmol). The mixture was heated in the microwave at 160 °C for 5 h (the starting material is not all consumed). A saturated solution of NH_4Cl (4 mL) was added and EtOAc (5 mL). The layers were separated, and the organic layer was dried, filtered, concentrated *in vacuo* and used without further purification. LCMS-ESI$^+$: calc'd for $C_{33}H_{40}ClN_4O_3S$: 607.2 ($M+H^+$); Found: 607.3 ($M + H^+$).

MeOH (2 mL) and THF (2 mL) were added to the crude material followed by a sodium hydroxide solution (2 M aqueous, 500 μL). The reaction mixture was stirred at 50 °C for 4 h. The mixture was purified using reverse phase HPLC, eluting by 5-100% acetonitrile in H_2O with 0.1% TFA to give the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{38}ClN_4O_3S$: 593.2 ($M+H^+$); Found: 593.3 ($M + H^+$). ^{1}H NMR (400 MHz, CD_3OD): δ 7.73-7.82 (m, 3H), 7.69 (m, 1H), 7.53-7.60 (m, 3H), 7.05 (d, J = 8 Hz, 1H), 5.23 (s, 1H), 4.59 (br m, 2H), 3.58 (br m, 3H), 3.20 (br m, 4H), 2.61 (s, 3H), 1.39 (d, J = 7 Hz, 6H), 0.97 (s, 9H).

Example 160. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetic acid (308).



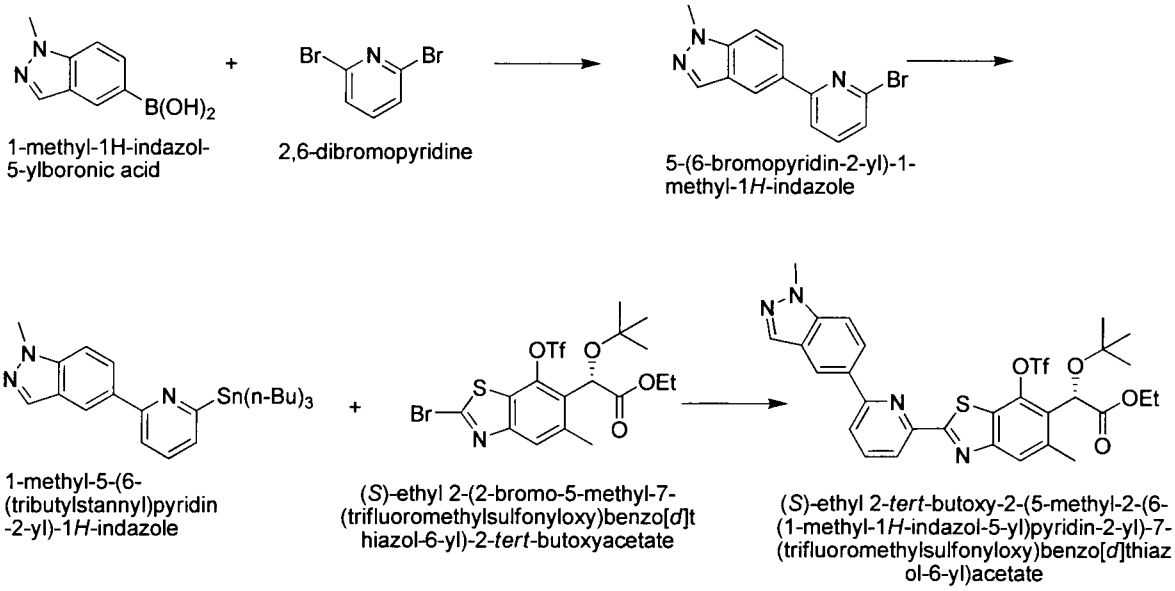
(S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetic acid

308

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetic acid was prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(6-(4-isopropylpiperazin-1-yl)pyridin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid, except using

1-(oxetan-3-yl)piperazine instead of 1-isopropylpiperazine. LCMS-ESI$^+$: calc'd for $C_{32}H_{36}ClN_4O_4S$: 607.2 ($M+H^+$); Found: 607.2 ($M + H^+$); 1H NMR (400 MHz, CD3OD): δ 7.70-7.81 (m, 3H), 7.64 (m, 1H), 7.49-7.56 (m, 3H), 7.04 (d, J = 8 Hz, 1H), 5.19 (s, 1H), 4.88 (br m, 2H), 4.77 (br m [under solvent], 4H), 4.35 (m, 1H), 3.80 (br m, 2H), 3.24 (m, [under solvent] 4H), 0.93 (s, 9H).

Example 161. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetic acid (309).



Preparation of 5-(6-bromopyridin-2-yl)-1-methyl-1H-indazole: In a 10-20 mL reaction vial, the 1-methyl-1H-indazol-5-ylboronic acid (500 mg, 2.73 mmol) and the 2,6-dibromopyridine (776 mg, 3.27 mmol) were dissolved in dioxane (7 mL) under argon atmosphere. The mixture was bubbled with argon for 5min and then potassium carbonate (754 mg, 5.46 mmol) and $PdCl_2$(dppf) catalyst were added sequentially. The resulting reaction mixture was then sealed and heated in oil bath at 110°C for 3 h. Reaction was then diluted with EtOAc (10 mL), filtered and the filtrate was collected and concentrated. Residue was purified on

silica gel column with 0-25% EtOAc/Hex to afford the title product. LCMS-ESI$^+$: calc'd for: $C_{13}H_{10}BrN_3$: 288.0, 290.0 ($M+H^+$); found: 288.2, 290.3 ($M+H^+$).

Preparation of 1-methyl-5-(6-(tributylstannyl)pyridin-2-yl)-1H-indazole: In a 10 mL reaction vial, 5-(6-bromopyridin-2-yl)-1-methyl-1H-indazole (130 mg, 0.453 mmol) was dissolved in dry toluene (5 mL) under argon atmosphere. The solution was bubbled with argon for 5min. Then $Sn_2(n\text{-}Bu)_6$ (415 mg, 0.358 mL, 0.68 mmol) and $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) were added sequentially. The resulting reaction mixture was sealed and heated in oil bath at 85°C for 17 h. Reaction mixture was then concentrated and purified on silica gel column with 0-20% EtOAc/Hex to afford a the title product. LCMS-ESI$^+$: calc'd for: $C_{25}H_{37}N_3Sn$: 500.2, 498.2, 499.2, 496.2, 497.2 ($M+H^+$); found: 500.1, 498.3, 499.5, 496.0, 497.0 ($M+H^+$)

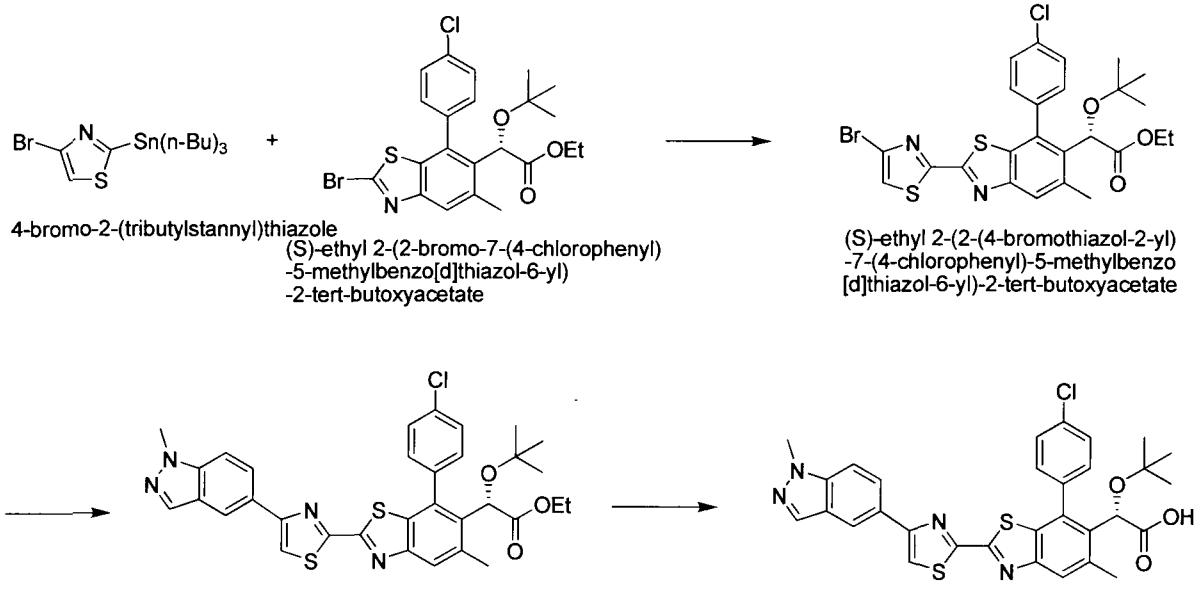
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)acetate: In a 10 mL reaction vial, *(S)*-ethyl 2-(2-bromo-5-methyl-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (50 mg, 0.0938 mmol) was dissolved in dry dioxane (1.5 mL) under argon atmosphere. The solution was bubbled with argon for 5 min. Then LiCl (11 mg, 0.256 mmol), CuI (5 mg, 0.026 mmol) and $Pd(PPh_3)_4$(10 mg, 0.0085 mmol) were added sequentially. A solution of 1-methyl-5-(6-(tributylstannyl)pyridin-2-yl)-1H-indazole (43mg, 0.0853mmol) in 1.4-dioxane (1.5 mL) was then added drop-wise. The resulting reaction mixture was then sealed and heated in oil bath at 100°C for 3 h. The resulting reaction mixture was diluted with EtOAc (5 mL), filtered and the filtrate was concentrated and purified on silica gel column with 0-40% EtOAc/Hex to afford the title product. LCMS-ESI$^+$: calc'd for: $C_{30}H_{29}F_3N_4O_6S_2$: 663.2, 664.2 ($M+H^+$); found: 663.1, 664.3 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetate: In a 10 mL reaction vial, *(S)*-ethyl 2-*tert*-butoxy-2-(5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)-7-(trifluoromethylsulfonyloxy)benzo[d]thiazol-6-yl)acetate (33 mg, 0.050 mmol) and p-chlorophenyl boronic acid (48 mg, 0.20 mmol) were dissolved in dioxane (2.5 mL) under argon atmosphere. The solution was bubbled with argon for 5min. Then potassium carbonate (45 mg, 0.32 mmol) and $Pd(PPh_3)_4$ (10mg, 0.0075 mmol) were added sequentially. The reaction mixture was sealed and heated in oil bath at 120 °C for 4.5 h. Reaction was then diluted with EtOAc (10 mL) and filtered to remove solid. The filtrate was concentrated and purified on silica gel column

with 0-40% EtOAc/Hex to afford product. LCMS-ESI$^+$: calc'd for: $C_{35}H_{33}ClN_4O_3S$: 625.2, 626.2, 627.2 (M+H$^+$); found: 625.1, 626.2, 627.1 (M+H$^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetic acid: In a 25 mL round bottom flask, *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetate (5 mg, 0.008 mmol) was dissolved in THF (0.4 mL) EtOH (0.2 mL) and water (0.1 mL). Then aqueous NaOH (2N) (0.1 mL) was added. The reaction mixture was stirred at 40 °C in oil bath for 17 h. The resulting reaction mixture was concentrated and purified on Gilson reverse phase preparative HPLC with 0-95% CH_3CN (with 0.1% TFA) in water (with 0.1% TFA) to afford the product as TFA salt. LCMS-ESI$^+$: calc'd for: $C_{33}H_{29}ClN_4O_3S$: 597.2, 599.2, 598.2 (M+H$^+$); found: 597.3, 599.3, 598.2 (M+H$^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, J = 1.6 Hz, 1H), 8.30 – 8.18 (m, 2H), 8.12 (s, 1H), 8.08 – 7.97 (m, 2H), 7.88 (s, 1H), 7.75 – 7.58 (m, 5H), 5.27 (s, 1H), 4.09 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).

Example 162. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)thiazol-2-yl)benzo[d]thiazol-6-yl)acetic acid (310).



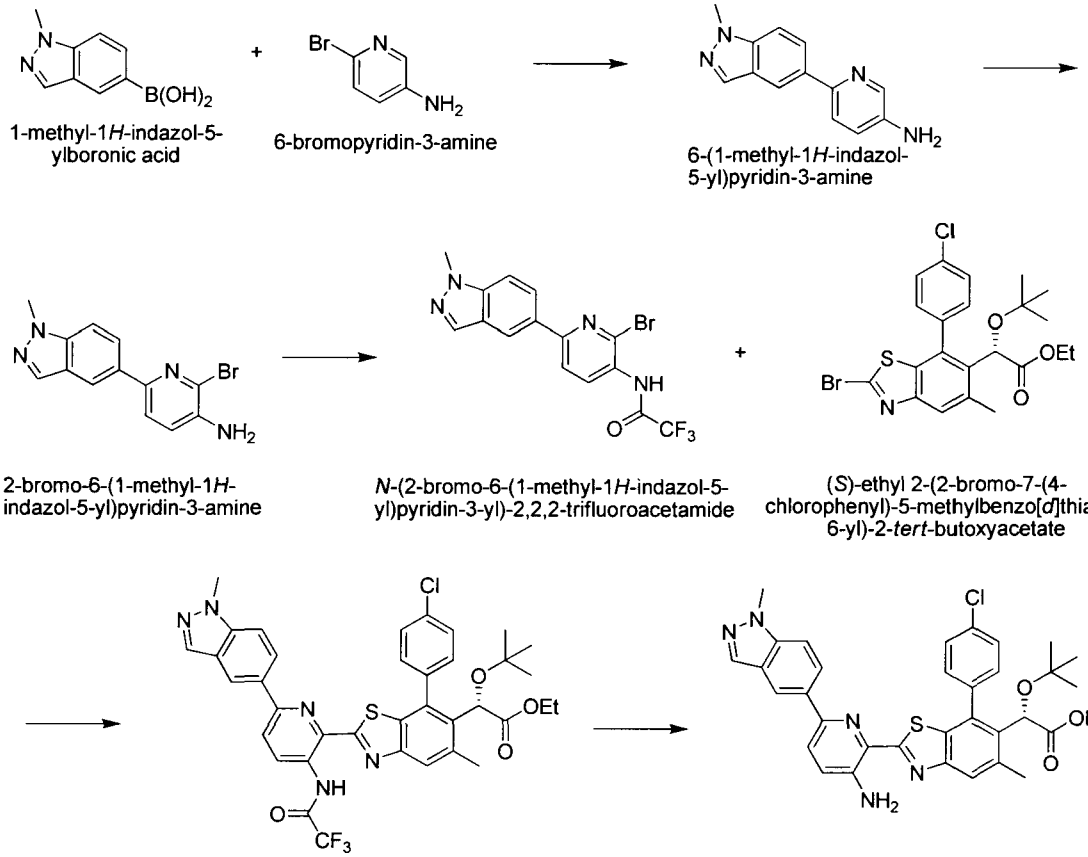
Preparation of *(S)*-ethyl 2-(2-(4-bromothiazol-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: In a 10 mL reaction vial, 4-bromo-2-(tributylstannyl)thiazole (125 mg, 0.251 mmol) and *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-

methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (114 mg, 0.251 mmol) were dissolved in dioxane (3 mL) at room temperature under argon atmosphere. The solution was bubbled with argon for 5 min. Then CuI (10.6 mg, 0.055 mmol), LiCl (31.7 mg, 0.753 mmol) and $Pd(PPh_3)_4$ (52.3 mg, 0.0417 mmol) were added sequentially. The reaction mixture was then sealed and heated in oil bath at 100°C for 3.5 h. The reaction mixture was then diluted with EtOAc (10 mL), filtered and the filtrate was concentrated and purified on silica gel column with 0-10% EtOAc/Hex to afford title compound. LCMS-ESI$^+$: calc'd for: $C_{25}H_{24}BrClN_2O_3S_2$: 581.0, 579.0, 582.0, 583.0, 580.0 ($M+H^+$); found: 581.1, 579.0, 582.2, 583.1, 580.3 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)thiazol-2-yl)benzo[d]thiazol-6-yl)acetate: In a 10 mL reaction vial, 1-methyl-1H-indazol-5-ylboronic acid (31 mg, 0.173 mmol) and *(S)*-ethyl 2-(2-(4-bromothiazol-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (100 mg, 0.173 mmol) were mixed with dioxane (5 mL) and water (1mL). The resulting reaction mixture was bubbled with argon for 5min. Then potassium carbonate (60 mg, 0.432 mmol) and $Pd(PPh_3)_4$ were added sequentially. The reaction mixture was sealed and heated in oil bath at 95°C for 2 h. The brown mixture was then diluted with EtOAc (20 mL), filtered and the filtrate was concentrated and purified on silica gel column with 0-30% EtOAc/Hex to afford the title compound. LCMS-ESI$^+$: calc'd for: $C_{33}H_{31}ClN_4O_3S_2$: 631.2, 633.2, 632.2 ($M+H^+$); found: 631.0, 633.1, 632.1 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)thiazol-2-yl)benzo[d]thiazol-6-yl)acetic acid: In a 25 mL round bottom flask, *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-(1-methyl-1H-indazol-5-yl)thiazol-2-yl)benzo[d]thiazol-6-yl)acetate (74 mg, 0.117 mmol) was dissolved in THF (3 mL) EtOH (2 mL) and water (1 mL). Then aqueous NaOH (2N) (1.17 mL) was added. The reaction mixture was stirred at 40°C in oil bath for 17 h. The resulting reaction mixture was concentrated and purified on Gilson reverse phase preparative HPLC with 0-95% acetonitrile (with 0.1% TFA) in water (with 0.1% TFA) to afford product as a TFA salt. LCMS-ESI$^+$: calc'd for: $C_{31}H_{27}ClN_4O_3S_2$: 603.1, 605.1, 604.1 ($M+H^+$); found: 603.2, 605.2, 604.0 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (d, J = 1.2 Hz, 1H), 8.06 – 7.98 (m, 3H), 7.82 (s, 1H), 7.70 (dd, J = 7.9, 2.4 Hz, 1H), 7.66 – 7.52 (m, 4H), 5.28 (s, 1H), 4.05 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).

Example 163. Preparation of *(S)*-2-(2-(3-amino-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (311).



311

Preparation of 6-(1-methyl-1H-indazol-5-yl)pyridin-3-amine: In a 10-20 mL reaction vial, the 1-methyl-1H-indazol-5-ylboronic acid (250 mg, 1.34 mmol) and the 6-bromopyridin-3-amine (250mg, 1.34 mmol) were dissolved in dioxane (7 mL) and water (1.5 mL) under argon atmosphere. The mixture was bubbled with argon for 5min and then potassium carbonate (368 mg, 2.67 mmol) and $Pd(PPh_3)_4$ (231mg, 0.2 mmol) were added sequentially. The resulting reaction mixture was then sealed and heated in oil bath at 110 °C for 3 h. Reaction was then partitioned between EtOAc (30 mL) and water (30 mL).The organic phase was washed with water (3 x 20 mL) and was concentrated. Residue was purified on silica gel column with 0-75% EtOAc/Hex to afford the title compound. LCMS-ESI$^+$: calc'd for: $C_{13}H_{12}N_4$: 225.1 ($M+H^+$); found: 225.2 ($M+H^+$).

Preparation of 2-bromo-6-(1-methyl-1H-indazol-5-yl)pyridin-3-amine: In a 50 mL round bottom flask, 6-(1-methyl-1H-indazol-5-yl)pyridin-3-amine (225mg, 1.00 mmol) was dissolved in DMF (8 mL) at room temperature and the solution was cooled down to 0°C for

5min under argon atmosphere. A solution of NBS (179 mg, 1.00 mmol) in DMF (6 mL) was added dropwise. The resulting reaction mixture was stirred at 0°C for 30min and then was poured onto saturated aq $NaHCO_3$ solution (30 mL). EtOAc (3x30 mL) was used for extraction. Organic phase was then washed with water (2x20 mL) and concentrated. Residue was purified on silica gel column with 0-30% to afford product. LCMS-ESI$^+$: calc'd for: $C_{13}H_{11}BrN_4$: 303.0, 305.0 ($M+H^+$); found: 303.1, 305.1 ($M+H^+$)

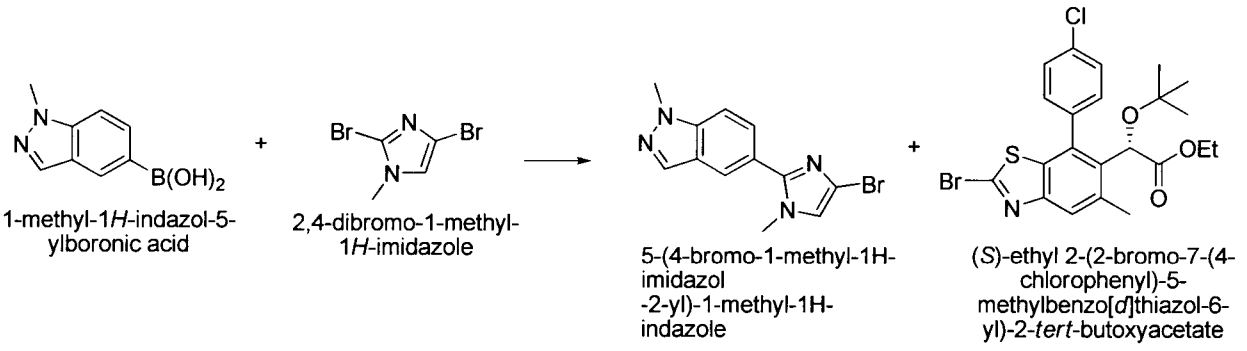
Preparation of N-(2-bromo-6-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)-2,2,2-trifluoroacetamide: In a 50m round bottom flask, 2-bromo-6-(1-methyl-1H-indazol-5-yl)pyridin-3-amine (34mg, 0.112mmol) was dissolved in DCM (5 mL) at room temperature under a argon atmosphere. Then a solution of trifluoroacetic anhydride (38.5 mg, 0.183 mmol) in DCM (1 mL) was added drop-wise. A few crystals of DMAP (catalytic amount) were added. The resulting reaction mixture was stirred under argon atmosphere for 17 h. The reaction mixture was concentrated and purified on silica gel column with 0-30% EtOAc/Hex to afford product. LCMS-ESI$^+$: calc'd for: $C_{15}H_{10}BrF_3N_4O$: 399.0, 401.0 ($M+H^+$); found: 399.0, 401.0 ($M+H^+$).

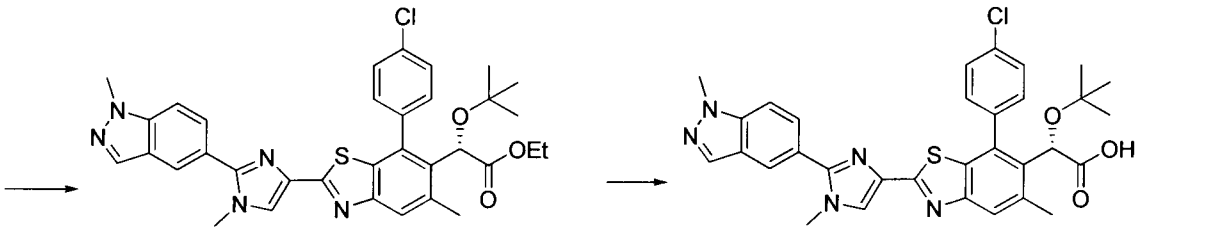
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-indazol-5-yl)-3-(2,2,2-trifluoroacetamido)pyridin-2-yl)benzo[d]thiazol-6-yl)acetate: In a 10 mL reaction vial, N-(2-bromo-6-(1-methyl-1H-indazol-5-yl)pyridin-3-yl)-2,2,2-trifluoroacetamide (24mg, 0.06mmol) was dissolved in dioxane (3 mL) at room temperature. The solution was bubbled with argon for 5min. Then $Sn_2(n\text{-}Bu)_6$ (0.057 mL, 0.108mmol), LiCl (30mg, 0.7mmol), $Pd(PPh_3)_2Cl_2$ (6.3mg, 0.009mmol) and $Pd(PPh_3)_4$ (10mg, 0.009mmol) were added sequentially. The resulting reaction mixture was sealed and heated to 90°C in oil bath. To this mixture, a solution of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (44mg, 0.09mmol) in dioxane (1.5mmol) was added slowly through syringe pump over 1.5 h. The resulting reaction mixture was stirred at 100°C in oil bath for 16 h. The reaction was then diluted with EtOAc (20 mL) and filtered to remove solid. The filtrate was concentrated and purified on silica gel column with 0-20% EtOAc/Hex to afford product. LCMS-ESI$^+$: calc'd for: $C_{37}H_{33}ClF_3N_5O_4S$: 736.2, 737.2, 738.2 ($M+H^+$); found: 736.1, 737.1, 738.1 ($M+H^+$).

Preparation of *(S)*-2-(2-(3-amino-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid: In a 25 mL round bottom flask, *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-(1-methyl-1H-

indazol-5-yl)-3-(2,2,2-trifluoroacetamido)pyridin-2-yl)benzo[d]thiazol-6-yl)acetate(9mg, 0.0122mmol) was dissolved in THF (1.5 mL) EtOH (0.5 mL) and water (0.5 mL). Then aqueous NaOH (2N) (0.2 mL) was added. The reaction mixture was stirred at 40°C in oil bath for 17 h. The resulting reaction mixture was concentrated and purified on Gilson reverse phase preparative HPLC with 0-95% acetonitrile (with 0.1% TFA) in water (with 0.1% TFA) to afford product as TFA salt. LCMS-ESI$^+$: calc'd for: $C_{33}H_{30}ClN_5O_3S$: 612.2, 613.2, 614.2 ($M+H^+$); found: 612.2, 613.2, 614.2 ($M+H^+$); ^1H NMR (400 MHz, CD_3OD) δ 8.28 (d, J = 1.5 Hz, 1H), 8.21 – 8.16 (m, 1H), 8.05 (s, 1H), 7.85 – 7.77 (m, 2H), 7.71 (d, J = 8.4 Hz, 1H), 7.65 – 7.56 (m, 4H), 7.34 (d, J = 8.7 Hz, 1H), 5.25 (s, 1H), 4.07 (s, 3H), 2.61 (s, 3H), 0.97 (s, 9H).

Example 164. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-(1-methyl-1H-indazol-5-yl)-1H-imidazol-4-yl)benzo[d]thiazol-6-yl)acetic acid (312).





312

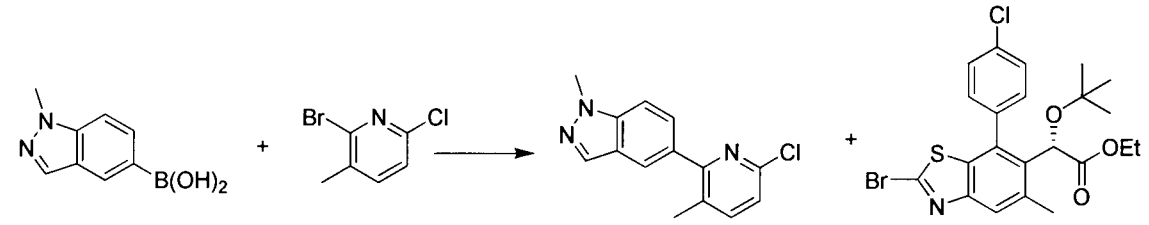
Preparation of 5-(4-bromo-1-methyl-1H-imidazol-2-yl)-1-methyl-1H-indazole: In a 10-20 mL reaction vial, the 1-methyl-1H-indazol-5-ylboronic acid (169 mg, 0.966 mmol) and the 2,4-dibromo-1-methyl-1H-imidazole (300 mg, 1.25 mmol) were dissolved in dioxane (4 mL) and water (1mL) under argon atmosphere. The mixture was bubbled with argon for 5min and then potassium carbonate (400 mg, 2.895mmol) and $Pd(PPh_3)_4$(167mg, 0.145mmol) were added sequentially. The resulting reaction mixture was then sealed and heated in oil bath at 110°C for 1.5 h. Reaction was then partitioned between EtOAc (30 mL) and water (30 mL).The organic

phase was washed with water (3x20 mL) and was concentrated. Residue was purified on silica gel column with 0-50% EtOAc/Hex to afford the desired product. LCMS-ESI$^+$: calc'd for: $C_{12}H_{11}BrN_4$: 291.0, 293.0 (M+H$^+$); found: 291.0, 293.0 (M+H$^+$)

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-(1-methyl-1H-indazol-5-yl)-1H-imidazol-4-yl)benzo[d]thiazol-6-yl)acetate: In a 10 mL reaction vial, 5-(4-bromo-1-methyl-1H-imidazol-2-yl)-1-methyl-1H-indazole (50mg, 0.172mmol) was dissolved in dioxane (3 mL) at rt. The solution was bubbled with argon for 5min. Then Sn_2(n-Bu)$_6$ (0.136 mL, 0.259 mmol), LiCl (60 mg, 1.4 mmol), $Pd(PPh_3)_2Cl_2$ (24 mg, 0.034 mmol) and $Pd(PPh_3)_4$ (40 mg, 0.0344 mmol) were added sequentially. The resulting reaction mixture was sealed and heated to 90°C in oil bath. To this mixture, a solution of *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (128 mg, 0.259 mmol) in dioxane (1.5mmol) was added slowly through syringe pump over 1.5 h. The resulting reaction mixture was stirred at 100°C in oil bath for 16 h. The reaction was then diluted with EtOAc (20 mL) and filtered to remove solid. The filtrate was concentrated and purified on silica gel column with 0-20% EtOAc/Hex to afford product. LCMS-ESI$^+$: calc'd for: $C_{34}H_{34}ClN_5O_3S$: 628.2, 629.2, 630.2 (M+H$^+$); found: 628.1, 629.1, 630.1 (M+H$^+$)

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-(1-methyl-1H-indazol-5-yl)-1H-imidazol-4-yl)benzo[d]thiazol-6-yl)acetic acid: In a 25 mL round bottom flask, *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-(1-methyl-1H-indazol-5-yl)-1H-imidazol-4-yl)benzo[d]thiazol-6-yl)acetate 15 mg, 0.024 mmol) was dissolved in THF (1.5 mL) EtOH (0.7 mL) and water (0.5 mL). Then aqueous NaOH (2 N) (0.4 mL) was added. The reaction mixture was stirred at 30°C in oil bath for 17 h. The resulting reaction mixture was concentrated. The residue was purified on Gilson reverse phase HPLC with CH_3CN and water (10 mL) to afford the product. LCMS-ESI$^+$: calc'd for: $C_{32}H_{30}ClN_5O_3S$: 600.2, 602.2, 601.2 (M+H$^+$); found: 600.3, 602.3, 601.3 (M+H$^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (d, J = 0.8 Hz, 1H), 7.99 (dd, J = 1.6, 0.8 Hz, 1H), 7.93 – 7.88 (m, 1H), 7.83 (s, 1H), 7.67 – 7.58 (m, 3H), 7.50 (dd, J = 8.6, 2.3 Hz, 1H), 7.42 (ddd, J = 8.3, 5.5, 2.2 Hz, 2H), 5.01 (s, 1H), 4.03 (d, J = 0.7 Hz, 3H), 3.75 (s, 3H), 2.55 (s, 3H), 0.82 (s, 9H).

Example 165. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetic acid (313).

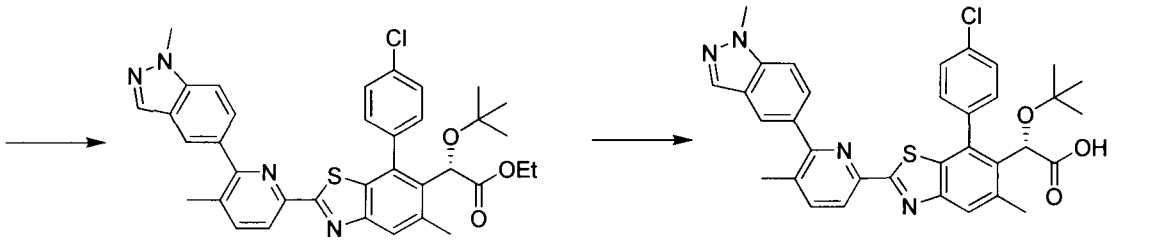


1-methyl-1H-indazol-5-ylboronic acid

2-bromo-6-chloro-3-methylpyridine

5-(6-chloro-3-methylpyridin-2-yl)-1-methyl-1H-indazole

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-6-(1-methyl-1*H*-indazol-5-yl)pyridin-2-yl)benzo[*d*]thiazol-6-yl)acetate

(S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetic acid

313

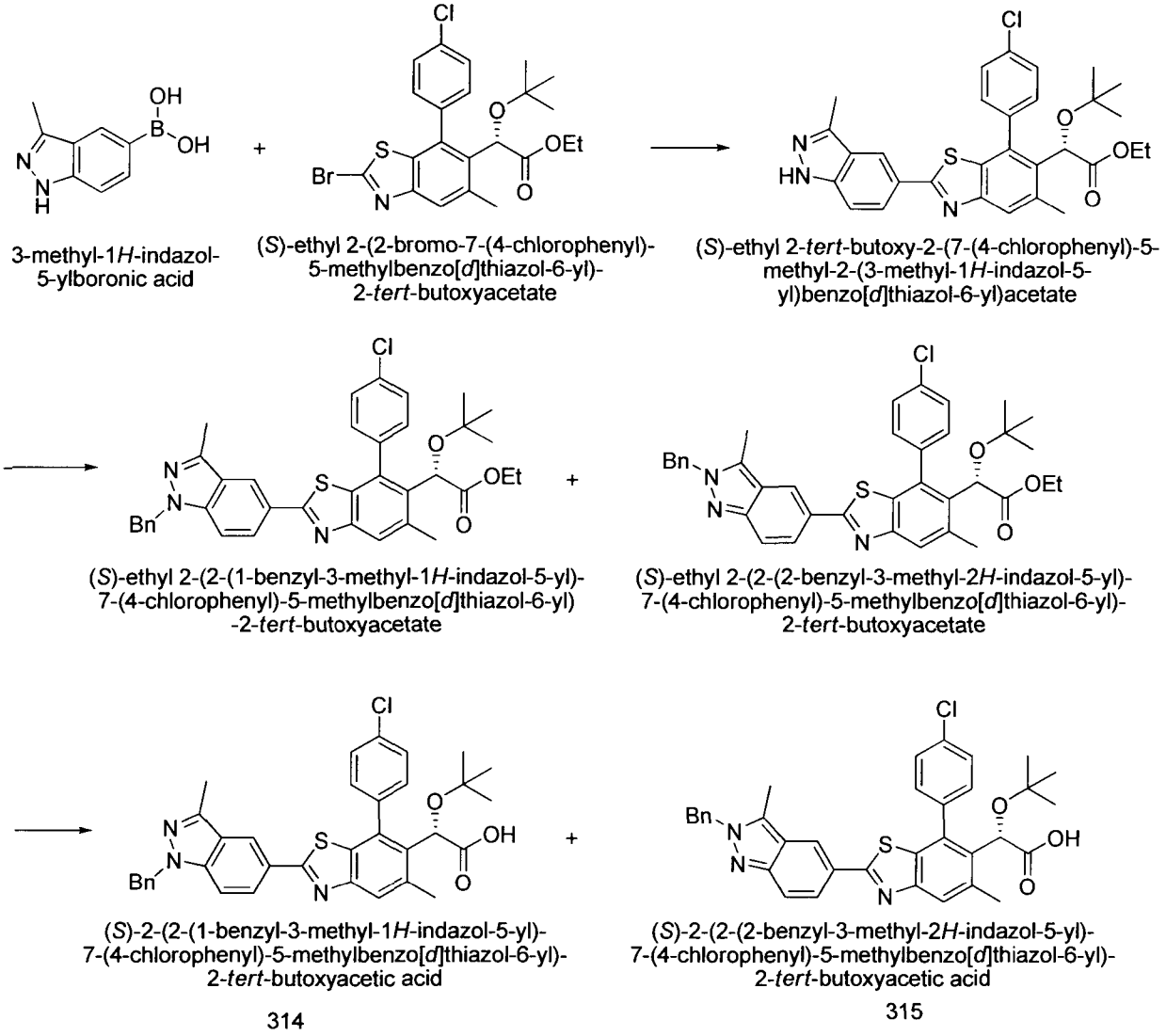
Preparation of 5-(6-chloro-3-methylpyridin-2-yl)-1-methyl-1H-indazole: In a 10 mL reaction vial, the 1-methyl-1H-indazol-5-ylboronic acid (500 mg, 2.84 mmol) and the 2-bromo-6-chloro-3-methylpyridine (585 mg, 2.84 mmol) were dissolved in dioxane (7 mL) and water (1.7 mL) under argon atmosphere. The mixture was bubbled with argon for 5min. Then potassium carbonate (979 mg, 7.1 mmol) and $Pd(PPh_3)_4$(49 3mg, 0.428 mmol) were added sequentially. The resulting reaction mixture was then sealed and heated in oil bath at 110°C for 2.5 h. Reaction was then partitioned between EtOAc (30 mL) and water (30 mL).The organic phase was washed with water (3x20 mL) and was concentrated. Residue was purified on silica gel column with 0-50% EtOAc/Hex to afford the title compound. LCMS-ESI$^+$: calc'd for: $C_{14}H_{12}ClN_3$: 258.1 and 260.1 ($M+H^+$); found: 258.0 and 260.0 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetate: In a 10 mL reaction vial, 5-(6-chloro-3-methylpyridin-2-yl)-1-methyl-1H-indazole (100 mg, 0.389 mmol) was dissolved in dioxane (5 mL) at rt. The solution was bubbled with argon for 5min. Then $Sn_2(n\text{-}Bu)_6$ (0.253 mL, 0.508 mmol), LiCl (100 mg, 2.38 mmol), $Pd(PPh_3)_2Cl_2$ (27 mg, 0.039 mmol) and $Pd(PPh_3)_4$ (45 mg, 0.039 mmol) were added sequentially. The resulting reaction mixture was sealed and heated to 90°C in oil bath. To this mixture, a solution of *(S)*-ethyl 2-(2-bromo-7-(4-

chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (289mg, 0.583mmol) in dioxane (5 mL) was added slowly through syringe pump over 1.5 h. The resulting reaction mixture was stirred at 100°C in oil bath for 16 h. The reaction was then diluted with EtOAc (20 mL) and filtered to remove solid. The filtrate was concentrated and purified on silica gel column with 0-20% EtOAc/Hex to afford product as. LCMS-ESI$^+$: calc'd for: $C_{36}H_{35}ClN_4O_3S$: 639.2, 640.2, 641.2 ($M+H^+$); found: 639.1, 640.1, 641.1 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-methyl-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl)benzo[d]thiazol-6-yl)acetic acid: In a 25 mL round bottom flask, *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-2-(1-methyl-1H-indazol-5-yl)-1H-imidazol-4-yl)benzo[d]thiazol-6-yl)acetate 49 mg, 0.768 mmol) was dissolved in THF (2 mL) EtOH (1 mL) and water (0.5 mL). Then aqueous NaOH (1N) (1 mL) was added. The reaction mixture was stirred at 30°C in oil bath for 17 h. The resulting reaction mixture was concentrated. The residue was triturated with CH_3CN (10 mL) and water (10 mL) and was filtered. Solid was collected to afford sodium salt of product. LCMS-ESI$^+$: calc'd for: $C_{34}H_{31}ClN_4O_3S$: 611.2, 612.2, 613.2 ($M+H^+$); found: 611.1, 612.1, 613.1 ($M+H^+$). ^{1}HNMR (400 MHz, CD_3OD) δ 8.16 (d, J = 7.9 Hz, 1H), 8.09 (d, J = 0.9 Hz, 1H), 8.05 – 8.01 (m, 1H), 7.98 (dd, J = 1.6, 0.9 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.79 (d, J = 0.9 Hz, 1H), 7.71 (dd, J = 8.8, 1.5 Hz, 1H), 7.64 (dt, J = 8.7, 0.9 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.52 – 7.46 (m, 2H), 5.09 (s, 1H), 4.11 (s, 3H), 2.67 (d, J = 0.8 Hz, 3H), 2.47 (s, 3H), 0.90 (s, 9H).

Example 166. Preparation of *(S)*-2-(2-(1-benzyl-3-methyl-1H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (314) and *(S)*-2-(2-(2-benzyl-3-methyl-2H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid (315).



Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate: Prepared in a manner similar to *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate, but using 3-methyl-1H-indazol-5-ylboronic acid instead of 1,3-dimethyl-1H-indazol-6-ylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.07 (dd, J = 8.8, 1.4 Hz, 1H), 7.86 (s, 1H), 7.59 – 7.44 (m, 5H), 5.17 (s, 1H), 4.22 (dtt, J = 10.8, 7.4, 3.7 Hz, 2H), 2.64 (s, 3H), 2.60 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.99 (s, 9H).

Preparation of *(S)*-ethyl 2-(2-(1-benzyl-3-methyl-1H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate and *(S)*-ethyl 2-(2-(2-benzyl-3-methyl-2H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate: To a stirring solution of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate (219 mg, 0.4 mmol) in ACN (5 mL) was added K_2CO_3 (166 mg, 1.2 mmol) and benzyl bromide (71 μL, 0.6 mmol). The reaction was then heated to 75 °C for 27 hours. After cooling to room temperature, the solids were filtered off, the crude

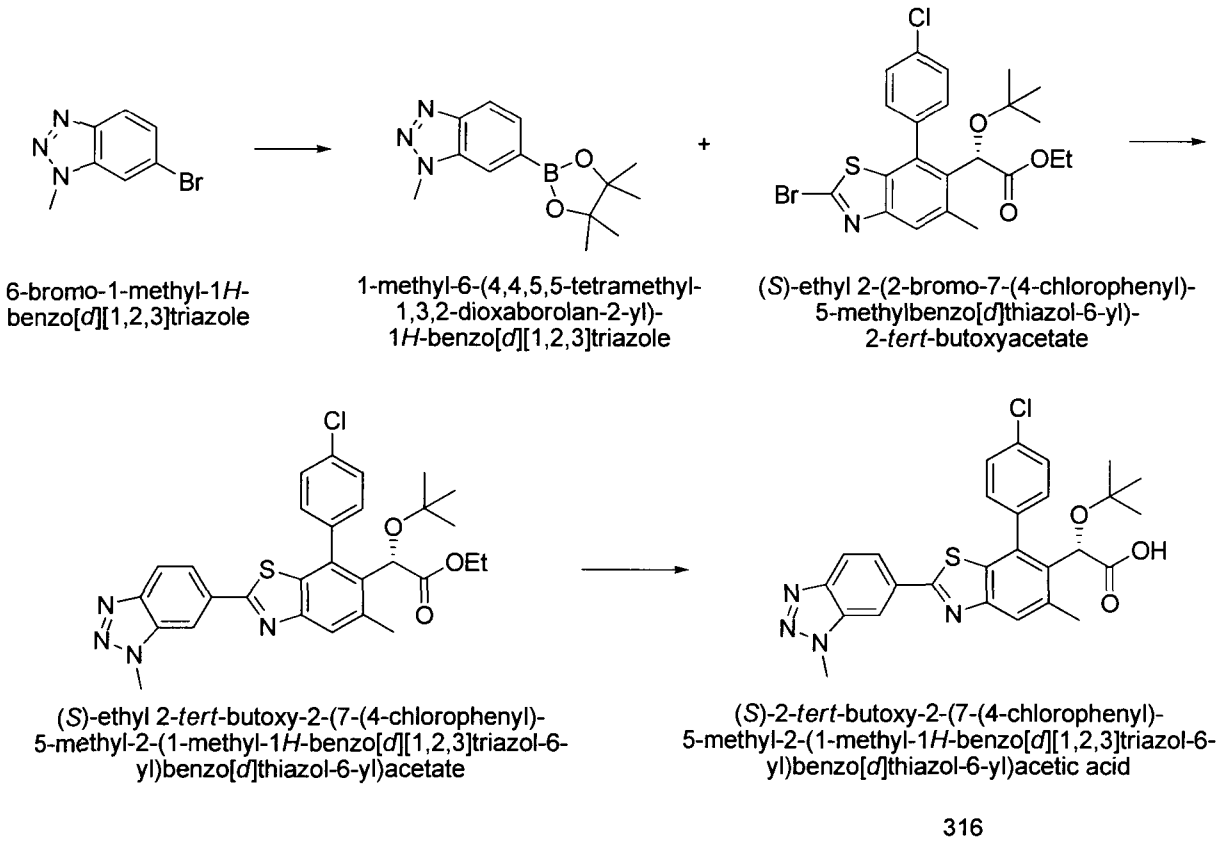
reaction was concentrated and purified by column chromatography (gradient 0 to 20% EtOAc in hexanes) to give *(S)*-ethyl 2-(2-(1-benzyl-3-methyl-1H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.05 (d, J = 8.9 Hz, 1H), 7.92 (s, 1H), 7.60 – 7.45 (m, 4H), 7.35 – 7.27 (m, 4H), 7.22 – 7.18 (m, 2H), 5.54 (s, 2H), 5.16 (s, 1H), 4.21 (dtt, J = 10.9, 7.4, 3.7 Hz, 2H), 2.63 (s, 3H), 2.60 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.98 (s, 9H).

(S)-ethyl 2-(2-(2-benzyl-3-methyl-2H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate was also isolated. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.92 (d, J = 9.4 Hz, 2H), 7.71 (d, J = 9.2 Hz, 1H), 7.62 – 7.43 (m, 4H), 7.36 – 7.28 (m, 3H), 7.17 (dd, J = 7.5, 1.0 Hz, 2H), 5.61 (s, 2H), 5.16 (s, 1H), 4.21 (ddt, J = 10.7, 7.0, 3.6 Hz, 2H), 2.61 (s, 3H), 2.60 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 0.98 (s, 9H).

Preparation of *(S)*-2-(2-(1-benzyl-3-methyl-1H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid: Prepared in a manner similar to *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid, but using *(S)*-ethyl 2-(2-(1-benzyl-3-methyl-1H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate instead of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{35}H_{33}ClN_3O_3S$: 610.2 ($M+H^+$); Found: 610.3 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.12 (dd, J = 7.6, 1.6 Hz, 1H), 7.89 (s, 1H), 7.78 (d, J = 10 Hz, 1H), 7.69 – 7.62 (m, 4H), 7.40 – 7.27 (m, 4H), 5.66 (s, 2H), 5.34 (s, 1H), 2.69 (s, 3H), 2.68 (s, 3H), 0.98 (s, 9H).

Preparation of *(S)*-2-(2-(2-benzyl-3-methyl-2H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetic acid: Prepared in a manner similar to *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid, but using *(S)*-ethyl 2-(2-(2-benzyl-3-methyl-2H-indazol-5-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate instead of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{35}H_{33}ClN_3O_3S$: 610.2 ($M+H^+$); Found: 610.3 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 7.99 (dd, J = 9.1, 1.6 Hz, 1H), 7.80 (s, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 9.1 Hz, 1H), 7.59 (t, J = 3.4 Hz, 3H), 7.38 – 7.26 (m, 3H), 7.17 (d, J = 7.0 Hz, 2H), 5.65 (s, 2H), 5.26 (s, 1H), 2.64 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).

Example 167. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)benzo[d]thiazol-6-yl)acetic acid (316).



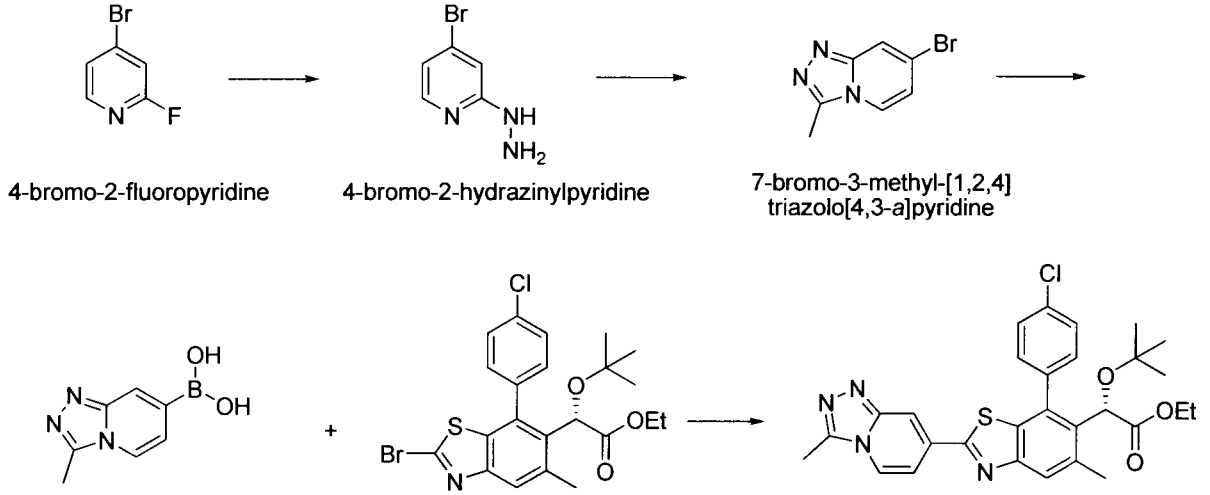
316

Preparation of 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole: Prepared in a manner similar to 1-methyl-3-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole, but using 6-bromo-1-methyl-1H-benzo[d][1,2,3]triazole instead of 5-bromo-1-methyl-3-phenyl-1H-indazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 6.8, 1.6 Hz, 2H), 7.79 (d, J = 8.6 Hz, 1H), 4.33 (s, 3H), 1.39 (s, 12H).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)benzo[d]thiazol-6-yl)acetate: Prepared in a manner similar to *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetate, but using 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole instead of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.60 – 7.45 (m, 4H), 5.18 (s, 1H), 4.39 (s, 3H), 4.28 – 4.17 (m, 2H), 2.63 (s, 3H), 1.26 (t, J = 8 Hz, 3H), 0.99 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)benzo[d]thiazol-6-yl)acetic acid: Prepared in a manner similar to *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetic acid, but using *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-6-yl)benzo[d]thiazol-6-yl)acetate instead of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{27}H_{26}ClN_4O_3S$: 521.0 ($M+H^+$); Found: 521.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.12 (dd, J = 8.8, 1.4 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.87 (s, 1H), 7.70 (d, J = 9.5 Hz, 1H), 7.64 – 7.57 (m, 3H), 5.27 (s, 1H), 4.39 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).

Example 168. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)benzo[d]thiazol-6-yl)acetic acid (317).



317

Preparation of 4-bromo-2-hydrazinylpyridine: To a stirring solution of hydrazine monohydrate (16 mL) was added 4-bromo-2-fluoropyridine (3.4 mL, 33.1 mmol). After stirring

for 23 hours at room temperature, 4M NaOH (15 mL) and water (30 mL) were added, and the thick suspension was stirred vigorously for 15 minutes. The precipitated solids were filtered off and dried to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 5.4 Hz, 1H), 6.97 (d, J = 1.3 Hz, 1H), 6.80 (dd, J = 5.4, 1.5 Hz, 1H), 6.05 (br s, 1H), 3.65 (br s, 2H).

Preparation of 7-bromo-3-methyl-[1,2,4]triazolo[4,3-a]pyridine: To a vial flushed with argon was added 4-bromo-2-hydrazinylpyridine (1.88 g, 10 mmol) and acetic acid (2.5 mL). The mixture was refluxed at 125 °C under argon for 16 hours. After cooling to room temperature, acetic acid was distilled off, and to the residue was added saturated $NaHCO_3$ (150 mL) and DCM (150 mL). The aqueous layer was extracted with DCM, the organic extracts were combined, dried over $MgSO_4$, and concentrated to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 1H), 7.73 (d, J = 7.3 Hz, 1H), 6.94 (dd, J = 7.3, 1.7 Hz, 1H), 2.74 (s, 3H).

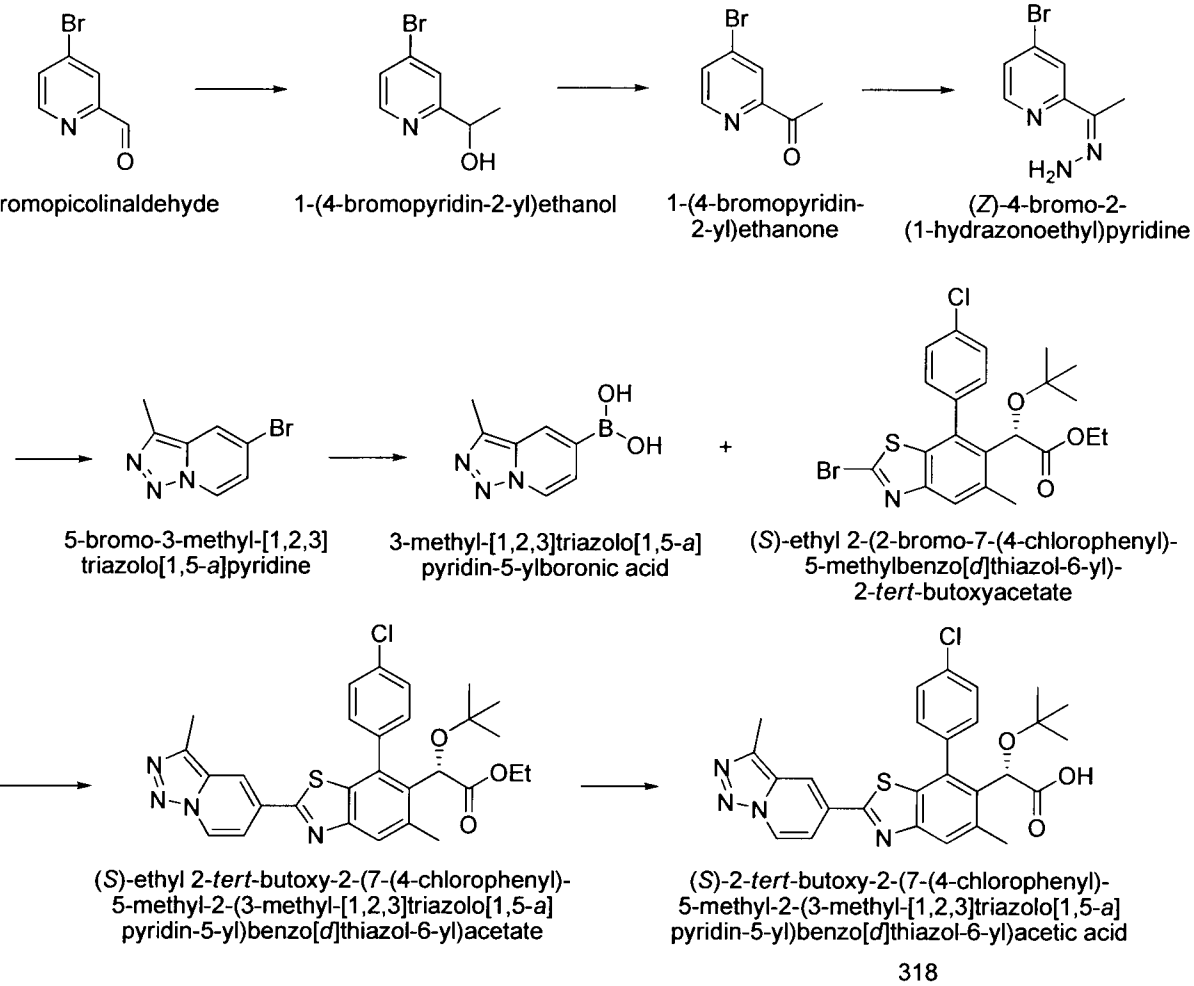
Preparation of 3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-ylboronic acid: To a vial flushed with argon was added 7-bromo-3-methyl-[1,2,4]triazolo[4,3-a]pyridine (318 mg, 1.5 mmol), $PdCl_2$(dppf)·DCM (245 mg, 0.3 mmol), bis(pinacolato)diboron (508 mg, 2 mmol), and KOAc (442 mg, 4.5 mmol). Anhydrous dioxane (8 mL) was added, and the mixture was heated to 100 °C for 3 hours. After cooling to room temperature, the mixture was filtered over a plug of Celite, and concentrated to provide the crude product, which was used directly without further purification. LCMS-ESI$^+$: calc'd for $C_7H_9BN_3O_2$: 178.1 ($M+H^+$); Found: 178.1 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)benzo[d]thiazol-6-yl)acetate: Prepared in a manner similar to *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate, but using 3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-ylboronic acid instead of 1,3-dimethyl-1H-indazol-6-ylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.94 (d, J = 6.0 Hz, 1H), 7.91 (s, 1H), 7.75 (s, 1H), 7.58 – 7.49 (m, 3H), 7.49 – 7.44 (m, 1H), 5.17 (s, 1H), 4.26 – 4.16 (m, 2H), 2.81 (s, 3H), 2.61 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.98 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)benzo[d]thiazol-6-yl)acetic acid: Prepared in a manner similar to *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-

methylbenzo[d]thiazol-6-yl)acetic acid, but using *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)benzo[d]thiazol-6-yl)acetate instead of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{27}H_{26}ClN_4O_3S$: 521.0 ($M+H^+$); Found: 521.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD) δ 8.61 (d, J = 7.3 Hz, 1H), 8.42 (s, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.74 – 7.67 (m, 1H), 7.66 – 7.58 (m, 3H), 5.28 (s, 1H), 2.85 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H).

Example 169. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-[1,2,3]triazolo[1,5-a]pyridin-5-yl)benzo[d]thiazol-6-yl)acetic acid (318).



Preparation of 1-(4-bromopyridin-2-yl)ethanol: An oven-dried flask was cooled under argon, and to it was added 4-bromopicolinaldehyde (2.98 g, 16 mmol) and anhydrous THF (50 mL). The mixture was cooled to -78 °C, and 3M methylmagnesium bromide in Et_2O (6.4 mL) was added dropwise. The mixture was then allowed to warm slowly to room temperature, whereupon it was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, concentrated, and purified by column chromatography

(gradient 0 to 60% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 5.3 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.38 (dd, J = 5.3, 1.4 Hz, 1H), 4.88 (q, J = 6.6 Hz, 1H), 3.84 (br s, 1H), 1.51 (d, J = 6.6 Hz, 3H).

Preparation of 1-(4-bromopyridin-2-yl)ethanone: To a stirring solution of 1-(4-bromopyridin-2-yl)ethanol (2.93 g, 14.5 mmol) in DCM (50 mL) was added Dess-Martin periodinane (12.93 g, 30.5 mmol) portion-wise over several minutes. The reaction was then quenched with saturated 1:1 $Na_2S_2O_3$/$NaHCO_3$ solution (200 mL) and stirred until gas evolution ceased. The aqueous layer was extracted with DCM, dried over $MgSO_4$, and purified by column chromatography (gradient 0 to 10% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 5.2 Hz, 1H), 8.20 (d, J = 1.9 Hz, 1H), 7.64 (dd, J = 5.2, 1.9 Hz, 1H), 2.71 (s, 3H).

Preparation of (Z)-4-bromo-2-(1-hydrazonoethyl)pyridine: To a stirring solution of 1-(4-bromopyridin-2-yl)ethanone (2.4 g, 12 mmol) in MeOH (40 mL) was added hydrazine monohydrate (2.9 mL, 60 mmol) in one portion. After stirring at room temperature for 2 hours, the mixture was concentrated to afford the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 5.3 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 7.33 (dd, J = 5.3, 1.8 Hz, 1H), 5.66 (br s, 2H), 2.23 (s, 3H).

Preparation of 5-bromo-3-methyl-[1,2,3]triazolo[1,5-a]pyridine: To a stirring solution of (Z)-4-bromo-2-(1-hydrazonoethyl)pyridine (2.53 g, 11.8 mmol) in DCM (40 mL) was added (diacetoxyiodo)benzene (3.8 g, 11.8 mmol) in small portions over several minutes and stirred at room temperature for 45 minutes. The reaction was quenched with saturated 1:1 $Na_2S_2O_3$/$NaHCO_3$ solution (40 mL) and stirred until gas evolution ceased. The aqueous layer was extracted with DCM, dried over $MgSO_4$, and purified by column chromatography (gradient 0 to 45% EtOAc in hexanes) to afford the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 6.9 Hz, 2H), 7.79 (s, 2H), 6.97 (d, J = 6.5 Hz, 2H), 2.57 (s, 7H).

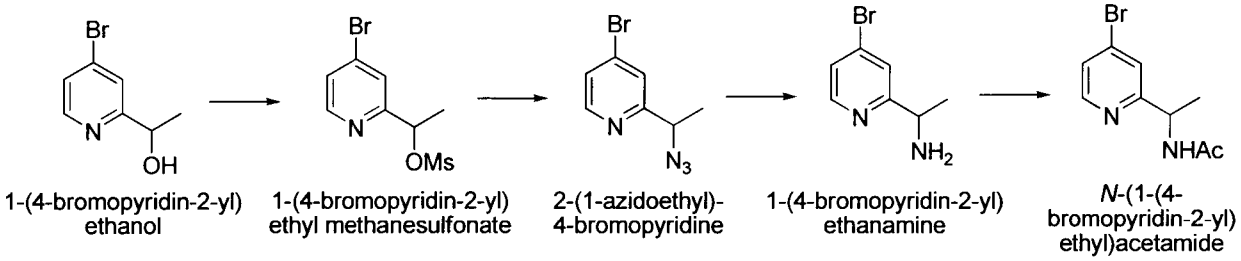
Preparation of 3-methyl-[1,2,3]triazolo[1,5-a]pyridin-5-ylboronic acid: To a vial flushed with argon was added 5-bromo-3-methyl-[1,2,3]triazolo[1,5-a]pyridine (424 mg, 2 mmol), $PdCl_2$(dppf)·DCM (327 mg, 0.4 mmol), bis(pinacolato)diboron (660 mg, 2.6 mmol), and KOAc (589 mg, 6 mmol). Anhydrous dioxane (10 mL) was added, and the mixture was heated to 100 °C for 3 hours. After cooling to room temperature, the mixture was filtered over a plug of Celite,

and concentrated to provide the crude product, which was used directly without further purification. LCMS-ESI$^+$: calc'd for $C_7H_9BN_3O_2$: 178.1 ($M+H^+$); Found: 178.04 ($M+H^+$).

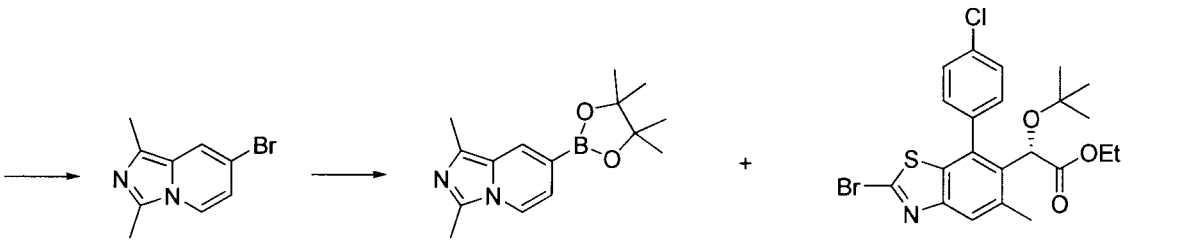
Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-[1,2,3]triazolo[1,5-a]pyridin-5-yl)benzo[d]thiazol-6-yl)acetate: Prepared in a manner similar to *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate, but using 3-methyl-[1,2,3]triazolo[1,5-a]pyridin-5-ylboronic acid instead of 1,3-dimethyl-1H-indazol-6-ylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 7.4 Hz, 1H), 8.21 (s, 1H), 7.91 (s, 1H), 7.66 (dd, J = 7.4, 1.6 Hz, 1H), 7.61 – 7.50 (m, 3H), 7.50 – 7.43 (m, 1H), 5.17 (s, 1H), 4.27 – 4.17 (m, 2H), 2.67 (s, 3H), 2.62 (s, 3H), 1.30 – 1.22 (m, 3H), 0.99 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-[1,2,3]triazolo[1,5-a]pyridin-5-yl)benzo[d]thiazol-6-yl)acetic acid: Prepared in a manner similar to *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid, but using *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-methyl-[1,2,3]triazolo[1,5-a]pyridin-5-yl)benzo[d]thiazol-6-yl)acetate instead of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-indazol-6-yl)-5-methylbenzo[d]thiazol-6-yl)acetate. LCMS-ESI$^+$: calc'd for $C_{27}H_{26}ClN_4O_3S$: 521.0 ($M+H^+$); Found: 521.2 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.87 (d, J = 7.4 Hz, 1H), 8.43 (s, 1H), 7.86 (s, 1H), 7.78 (dd, J = 7.4, 1.8 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.65 – 7.56 (m, 3H), 5.27 (s, 1H), 2.63 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).

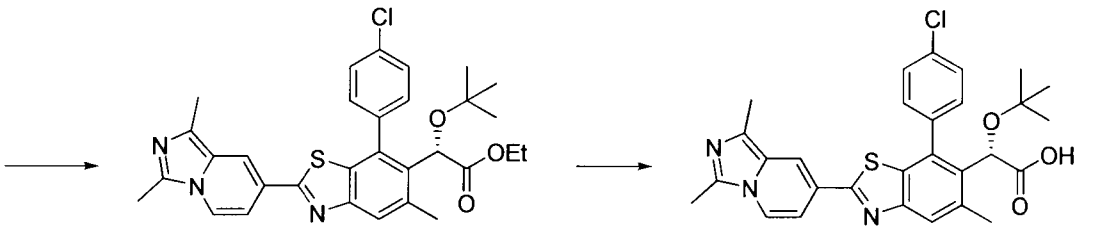
Example 170. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethylimidazo[1,5-a]pyridin-7-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (319).



1-(4-bromopyridin-2-yl) ethanol | 1-(4-bromopyridin-2-yl) ethyl methanesulfonate | 2-(1-azidoethyl)-4-bromopyridine | 1-(4-bromopyridin-2-yl) ethanamine | *N*-(1-(4-bromopyridin-2-yl) ethyl)acetamide



7-bromo-1,3-dimethylimidazo [1,5-*a*]pyridine | 1,3-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) imidazo[1,5-*a*]pyridine | (*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethylimidazo[1,5-*a*]pyridin-7-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate | (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethylimidazo[1,5-*a*]pyridin-7-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

319

Preparation of 1-(4-bromopyridin-2-yl)ethyl methanesulfonate: A stirring solution of the 1-(4-bromopyridin-2-yl)ethanol (3.72 g, 18.41 mmol and DMAP (4.5 g, 36.82 mmol) in 75 mL of dichloromethane was cooled to 0 °C. To it was added mesyl chloride (1.71 mL, 22.09 mmol) dropwise. The mixture was stirred at 0 °C for 10 minutes, then warmed to room temperature and stirred for 15 min. The reaction was quenched with 50 mL ice water, the layers were separated, and the aqueous layer was extracted with dichloromethane (50 mL). The organics were combined, washed with water and brine, dried over Na_2SO_4, and purified by column chromatography (gradient 0 to 45% EtOAc/hexanes) to afford the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 5.3 Hz, 1H), 7.64 (d, J = 1.6 Hz, 1H), 7.45 (dd, J = 5.3, 1.8 Hz, 1H), 5.75 (q, J = 6.6 Hz, 1H), 3.00 (s, 3H), 1.75 (d, J = 6.6 Hz, 3H).

Preparation of 2-(1-azidoethyl)-4-bromopyridine: To a stirring solution of 1-(4-bromopyridin-2-yl)ethyl methanesulfonate (4.68 g, 16.71 mmol) in anhydrous DMF (45 mL) DMF was added sodium azide (2.17 g, 33.41 mmol) and stirred at room temperature for 2 hours.

The reaction was then diluted with 80 mL of water, then extracted with EtOAc (2 x 75 mL). The organic extracts were combined, washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to give the crude product which was used directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 5.2 Hz, 1H), 7.55 (s, 1H), 7.41 (d, J = 5.2 Hz, 1H), 4.65 (q, J = 6.8 Hz, 1H), 1.60 (dd, J = 6.8, 0.8 Hz, 3H).

Preparation of 1-(4-bromopyridin-2-yl)ethanamine: To a solution of 2-(1-azidoethyl)-4-bromopyridine (4.08 g, 16.54 mmol) in THF (100 mL) and water (10 mL) was added polymer-bound triphenylphosphine (200-400 mesh, ~3 mmol/g loading; 10.97 g, 32.94 mmol).. The suspension was then stirred at room temperature for 7 hours. The reaction was filtered over a coarse frit twice, then concentrated to afford the crude product which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 5.2 Hz, 1H), 7.52 (s, 1H), 7.32 (dd, J = 5.2, 1.6 Hz, 1H), 4.13 (q, J = 6.7 Hz, 1H), 1.83 (br s, 2H), 1.41 (d, J = 6.7 Hz, 3H).

Preparation of N-(1-(4-bromopyridin-2-yl)ethyl)acetamide: To a solution of 1-(4-bromopyridin-2-yl)ethanamine (2.3 g, 11.44 mmol) in chloroform (30 mL) was added acetic anhydride (2.16 mL, 22.88 mmol) dropwise at 0 °C. The reaction was then quenched with ice water (40 mL) and extracted with chloroform (2 x 50 mL). The organic extracts were combined, then washed with 1M NaOH (50 mL), dried over Na_2SO_4, concentrated, and purified by column chromatography (gradient 0 to 5% MeOH/DCM) to afford the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 5.3 Hz, 1H), 7.42 (s, 1H), 7.36 (dd, J = 5.3, 1.7 Hz, 1H), 6.71 (br s, 1H), 5.10 (p, J = 7.0 Hz, 1H), 2.02 (s, 3H), 1.45 (d, J = 6.8 Hz, 3H).

Preparation of 7-bromo-1,3-dimethylimidazo[1,5-a]pyridine: N-(1-(4-bromopyridin-2-yl)ethyl)acetamide (2.28 g, 9.38 mmol) was suspended in anhydrous benzene (20 mL), then phosphorus oxychloride (2.2 mL, 23.6 mmol) was added and the reaction heated to reflux for 3 hours. The crude reaction was then added portion-wise to 1M potassium carbonate solution (60 mL) and stirred until gas evolution ceased. The pH was then adjusted to pH 10 with potassium carbonate. The aqueous layer was extracted with DCM (50 mL x 2), the organic were combined, dried over Na_2SO_4, and concentrated to afford the product, which was used without further purification. LCMS-ESI$^+$: calc'd for $C_9H_{10}BrN_2$: 225.1 ($M+H^+$); Found: 225.05 ($M+H^+$).

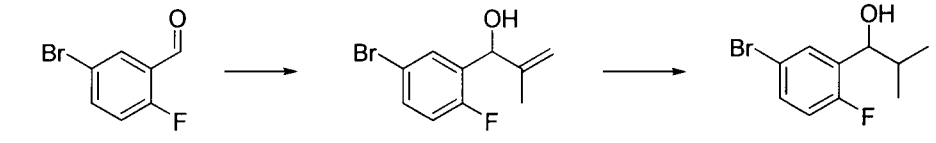
Preparation of 1,3-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)

imidazo[1,5-a]pyridine: To a vial flushed with argon was added 7-bromo-1,3-dimethylimidazo[1,5-a]pyridine (360 mg, 1.6 mmol), $PdCl_2(dppf)\cdot DCM$ (340 mg, 0.416 mmol), bis(pinacolato)diboron (609 mg, 2.4 mmol), and KOAc (628 mg, 6.4 mmol). Anhydrous dioxane (10 mL) was added, and the mixture was heated to 100 °C for 3 hours. After cooling to room temperature, the mixture was filtered over a plug of Celite, and concentrated to provide the crude product, which was used directly without further purification. LCMS-ESI^+: calc'd for $C_{15}H_{22}BN_2O_2$: 273.2 ($M+H^+$); Found: 273.21 ($M+H^+$).

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethylimidazo[1,5-a]pyridin-7-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: Prepared in manner similar to *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetate, but using 1,3-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,5-a]pyridine instead of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.82 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.51 (dt, J = 14.3, 7.8 Hz, 5H), 5.15 (s, 1H), 4.21 (dd, J = 5.9, 3.5 Hz, 2H), 2.67 (s, 3H), 2.59 (s, 3H), 2.54 (s, 3H), 1.25 (t, J = 6.0 Hz, 3H), 0.98 (s, 9H).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethylimidazo[1,5-a]pyridin-7-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: Prepared in a manner similar to *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetic acid, but using *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethylimidazo[1,5-a]pyridin-7-yl)-5-methylbenzo[d]thiazol-6-yl)acetate instead of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)benzo[d]thiazol-6-yl)acetate. LCMS-ESI^+: calc'd for $C_{29}H_{29}ClN_3O_3S$: 534.1 ($M+H^+$); Found: 534.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 8.28 (d, J = 7.7 Hz, 1H), 7.87 (s, 1H), 7.76 – 7.65 (m, 2H), 7.60 (d, J = 6.4 Hz, 3H), 5.27 (s, 1H), 2.86 (s, 3H), 2.65 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).

Example 171. Preparation of 1-(5-bromo-2-fluorophenyl)-2-methylpropan-1-ol (320).



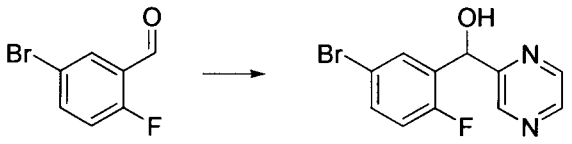
5-bromo-2-fluorobenzaldehyde

320

Preparation of 1-(5-bromo-2-fluorophenyl)-2-methylprop-2-en-1-ol: Prepared in a similar manner to (5-bromo-2-fluorophenyl)(phenyl)methanol, but using 0.5M isopropenylmagnesium bromide in THF instead of 1M phenylmagnesium bromide in THF. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 6.4, 2.6 Hz, 1H), 7.36 (ddd, J = 8.7, 4.5, 2.6 Hz, 1H), 6.96 – 6.88 (m, 1H), 5.42 (s, 1H), 5.17 (s, 1H), 4.99 (s, 1H), 2.10 (br s, 1H), 1.66 (s, 3H).

Preparation of 1-(5-bromo-2-fluorophenyl)-2-methylpropan-1-ol: A flask was charged with 1-(5-bromo-2-fluorophenyl)-2-methylprop-2-en-1-ol (5.39 g, 22 mmol), THF (120 mL), and water (120 mL). With vigorous stirring, p-toluenesulfonylhydrazide (20.5 g, 110 mmol) and NaOAc (18.05 g, 220 mmol) were added successively. The mixture was then refluxed at 70 °C for 20 hours. After cooling to room temperature, saturated K_2CO_3 solution was added, and the mixture stirred for 5 minutes. The aqueous layer was then extracted with Et_2O, dried over $MgSO_4$, and purified by column chromatography (gradient 0 to 15% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 6.3, 2.6 Hz, 1H), 7.34 (ddd, J = 8.5, 4.5, 2.6 Hz, 1H), 6.94 – 6.86 (m, 1H), 4.71 (d, J = 6.6 Hz, 1H), 1.97 (dq, J = 13.5, 6.7 Hz, 1H), 1.84 (br s, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H).

Example 172. Preparation of (5-bromo-2-fluorophenyl)(pyrazin-2-yl)methanol (321).



5-bromo-2-fluorobenzaldehyde

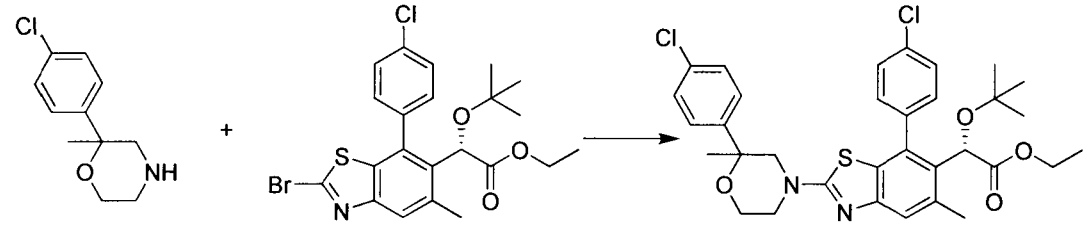
(5-bromo-2-fluorophenyl)(pyrazin-2-yl)methanol

321

Preparation of (5-bromo-2-fluorophenyl)(pyrazin-2-yl)methanol: To an oven-dried flask was added anhydrous THF (60 mL) and 2-iodopyrazine (3 mL, 20 mmol). The flask was cooeld to 0 °C, and 2M *n*-butylmagnesium chloride in THF (11 mL) was then added dropwise over several minutes. The mixture was stirred at 0 °C for 30 minutes, and then 5-bromo-2-fluorobenzaldehyde (2.4 mL, 20 mmol) was added. After stirring for 2 hours at 0 °C, the

reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, dried over $MgSO_4$, and purified by column chromatography (gradient 0 to 50% EtOAc in hexanes) to afford the product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.55 (s, 2H), 7.59 (dd, J = 6.4, 2.5 Hz, 1H), 7.46 – 7.35 (m, 1H), 6.98 (t, J = 9.2 Hz, 1H), 6.17 (s, 1H).

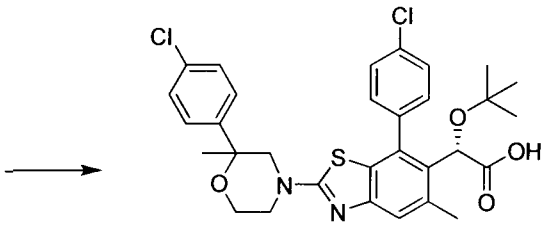
Example 173. Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[d]thiazol-6-yl)acetic acid (322).



2-(4-chlorophenyl)-2-methylmorpholine

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(2*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

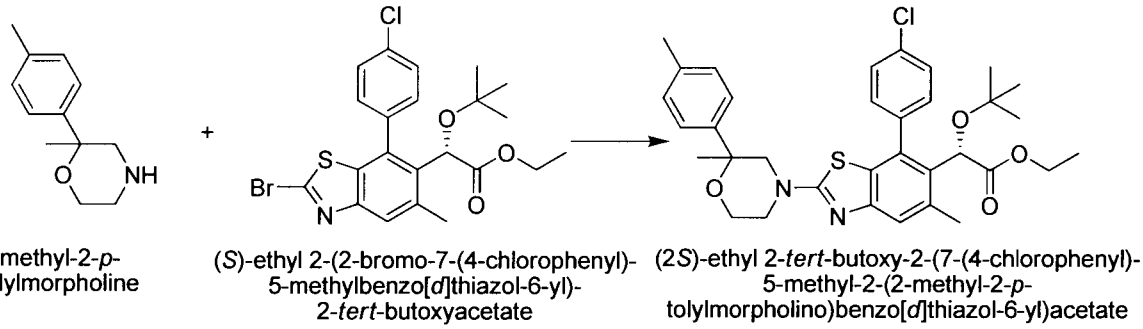
322

Preparation of (2S)-ethyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of (S)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate, 2-(4-chlorophenyl)-2-methylmorpholine and iPr_2NEt (20.1 mg, 0.156 mmol) in DMF was heated at 100 °C for 10 hours. The mixture was evaporated to dryness and separated on Combi Flash, eluting with 0-70% EtOAc/Hex to give title compound. LCMS-ESI$^+$: calc'd for $C_{33}H_{36}Cl_2N_2O_4S$: 627.2, 629.2 ($M+H^+$); found: 627.3, 629.3 ($M+H^+$).

Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (2S)-ethyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[d]thiazol-6-yl)acetate (63.7 mg, 0.101 mmol) in CH_3OH/THF (1:1, 4 mL) was added NaOH (2N, 1 mL, 2 mmol), the resulting mixture was heated at 50 °C for 14 hr. The mixture was evaporated to a small volume, acidified to pH 3 and taken into partitioned between

CH_2Cl_2 and brine. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified on Combi Flash (50% EtOAc/Hex) to give (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[d]thiazol-6-yl)acetic acid. LCMS-ESI$^+$: calc'd for $C_{31}H_{32}Cl_2N_2O_4S$: 599.2, 601.2 ($M+H^+$); found: 599.2, 601.2 ($M+H^+$).^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.62 (m, 1H), 7.44-7.53 (m, 5H), 7.32 (m, 3H), 5.13 (s, 1H), 4.31 (t, J = 14.4 Hz, 1H), 3.81 (m, 1H), 3.62 (m, 1H), 3.44-3.53 (m, 3H), 2.50 (s, 3H), 1.46 (s, 3H), 0.95 (s, 9H).

Example 174. Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-2-p-tolylmorpholino)benzo[d]thiazol-6-yl)acetic acid (323).



2-methyl-2-*p*-tolylmorpholine

(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

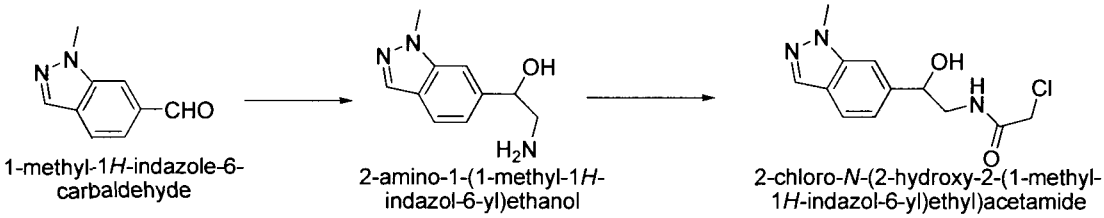
(2*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-2-*p*-tolylmorpholino)benzo[*d*]thiazol-6-yl)acetate

(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-2-*p*-tolylmorpholino)benzo[*d*]thiazol-6-yl)acetic acid

323

Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-2-p-tolylmorpholino)benzo[d]thiazol-6-yl)acetic acid: (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-2-p-tolylmorpholino)benzo[d]thiazol-6-yl)acetic acid was prepared using the similar procedure as (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[d]thiazol-6-yl)acetic acid except 2-(4-methylphenyl)-2-methylmorpholine was used instead of 2-(4-chlorophenyl)-2-methylmorpholine. LCMS-ESI$^+$: calc'd for $C_{32}H_{35}ClN_2O_4S$: 579.2, 581.2 ($M+H^+$); found: 579.4, 581.3 ($M+H^+$).^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.62 (m, 1H), 7.47-7.54 (m, 3H), 7.32 (m, 3H),7.14 (m, 2H), 5.14 (s, 1H), 4.31 (t, J = 12.8 Hz, 1H), 3.80 (m, 1H), 3.64 (m, 1H), 3.40-3.51 (m, 3H), 2.50 (s, 3H), 2.28 (s, 3H), 1.44 (s, 3H), 0.95 (s, 9H).

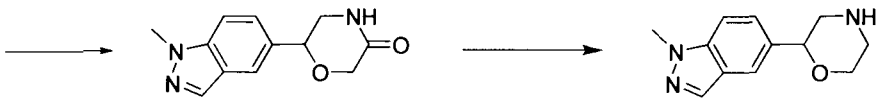
Example 175. Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid (324), (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((R)-2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid (325) and (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((S)-2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid (326).



1-methyl-1*H*-indazole-6-carbaldehyde

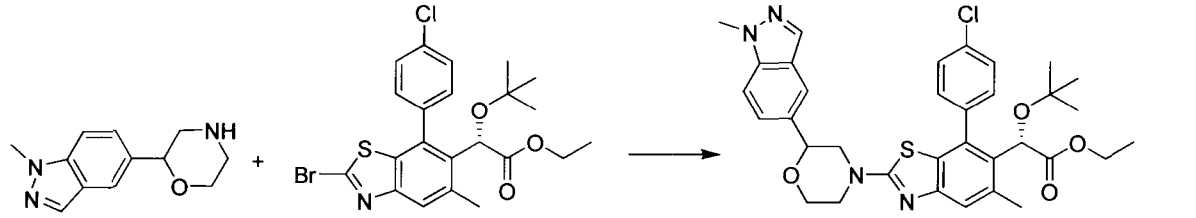
2-amino-1-(1-methyl-1*H*-indazol-6-yl)ethanol

2-chloro-*N*-(2-hydroxy-2-(1-methyl-1*H*-indazol-6-yl)ethyl)acetamide



6-(1-methyl-1*H*-indazol-5-yl)morpholin-3-one

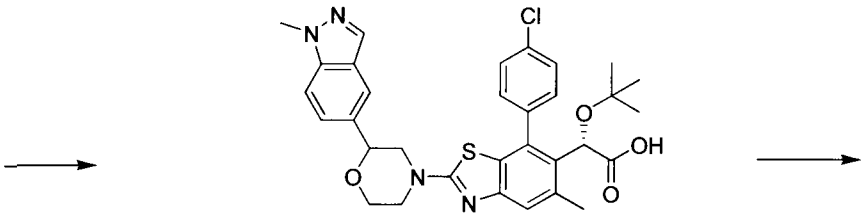
2-(1-methyl-1*H*-indazol-5-yl)morpholine



2-(1-methyl-1*H*-indazol-5-yl)morpholine

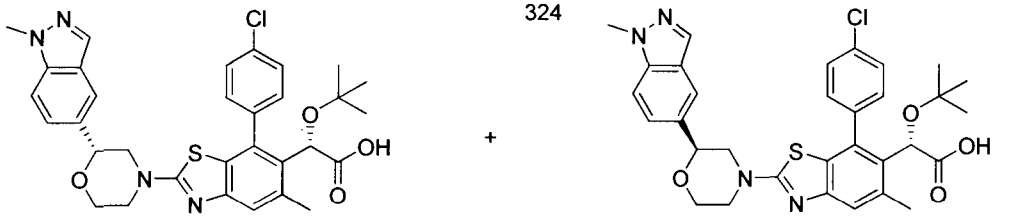
(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(2*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-5-yl)morpholino)benzo[*d*]thiazol-6-yl)acetate



(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1*H*-indazol-5-yl)morpholino)benzo[*d*]thiazol-6-yl)acetic acid

324



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((*R*)-2-(1-methyl-1*H*-indazol-5-yl)morpholino)benzo[*d*]thiazol-6-yl)acetic acid

325

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((*S*)-2-(1-methyl-1*H*-indazol-5-yl)morpholino)benzo[*d*]thiazol-6-yl)acetic acid

326

Preparation of 2-chloro-N-(2-hydroxy-2-(1-methyl-1H-indazol-6-yl)ethyl)acetamide: To a solution of 1-methyl-1H-indazole-6-carbaldehyde (532.8 mg, 3.3 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added ZnI_2 (106.1 mg, 0.33 mmol) and cyanotrimethylsilane (0.499 mL, 3.99 mmol), the resulting mixture was stirred at 0 °C for 2 hr, and LC/MS indicated the full formation of TMS-cyanohydrin. Around 3 mL of the above mixture was evaporated to dryness and then re-dissolved in THF, $LiAlH_4$ (2 mL, 1N in THF, 2 mmol) was added, the resulting mixture was stirred at room temperature for 2 hr. The mixture was quenched with EtOAc, added 0.075 mL H_2O, 0.075 mL NaOH (15%w/w), then 0.225 mL H_2O and then filtered through celite. The filtrate and washings were collected and evaporated to dryness to give crude compound. The crude material, containing around 50% of 2-amino-1-(1-methyl-1H-indazol-6-yl)ethanol, was used for the next step without purified or characterization.

To the crude material 2-amino-1-(1-methyl-1H-indazol-6-yl)ethanol (390.8 mg, ~50%, ~ 1mmol)in DMF was then added 2-chloroacetyl chloride (138.7 mg, 1.2 mmol) and iPr_2NEt (0.347 mL, 2 mmol). The resulting mixture was stirred at room temperature for 2 hr. The mixture was then taken into partition between EtOAc and brine. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified on Combi Flash (50% EtOAc/Hex) to give 2-chloro-N-(2-hydroxy-2-(1-methyl-1H-indazol-6-yl)ethyl)acetamide. LCMS-ESI$^+$: calc'd for $C_{12}H_{14}ClN_3O_2$: 268.1, 270.1 ($M+H^+$); found: 268.2, 270.2 ($M+H^+$).

Preparation of 6-(1-methyl-1H-indazol-5-yl)morpholin-3-one: To a solution of 2-chloro-N-(2-hydroxy-2-(1-methyl-1H-indazol-6-yl)ethyl)acetamide (70.1 mg, 0.26 mmol) in THF was added tBuOK (38.3 mg, 0.31mmol). The resulting mixture was stirred at room temperature for 7 hr. The mixture was taken into partition between CH_2Cl_2 and brine. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified on Combi Flash (50% EtOAc/Hex) to give 6-(1-methyl-1H-indazol-5-yl)morpholin-3-one. LCMS-ESI$^+$: calc'd for $C_{12}H_{13}N_3O$: 232.1 ($M+H^+$); found: 232.1 ($M+H^+$).

Preparation of 2-(1-methyl-1H-indazol-5-yl)morpholine: To a solution of 6-(1-methyl-1H-indazol-5-yl)morpholin-3-one (17.8 mg, 0.077 mmol) in THF was added BH_3 in THF (1M, mmol). The resulting mixture was stirred at room temperature for 10 hr. The crude compound was evaporated to dryness and used for the next step without further purification. LCMS-ESI$^+$: calc'd for $C_{12}H_{15}N_3O$: 218.1 ($M+H^+$); found: 218.2 ($M+H^+$).

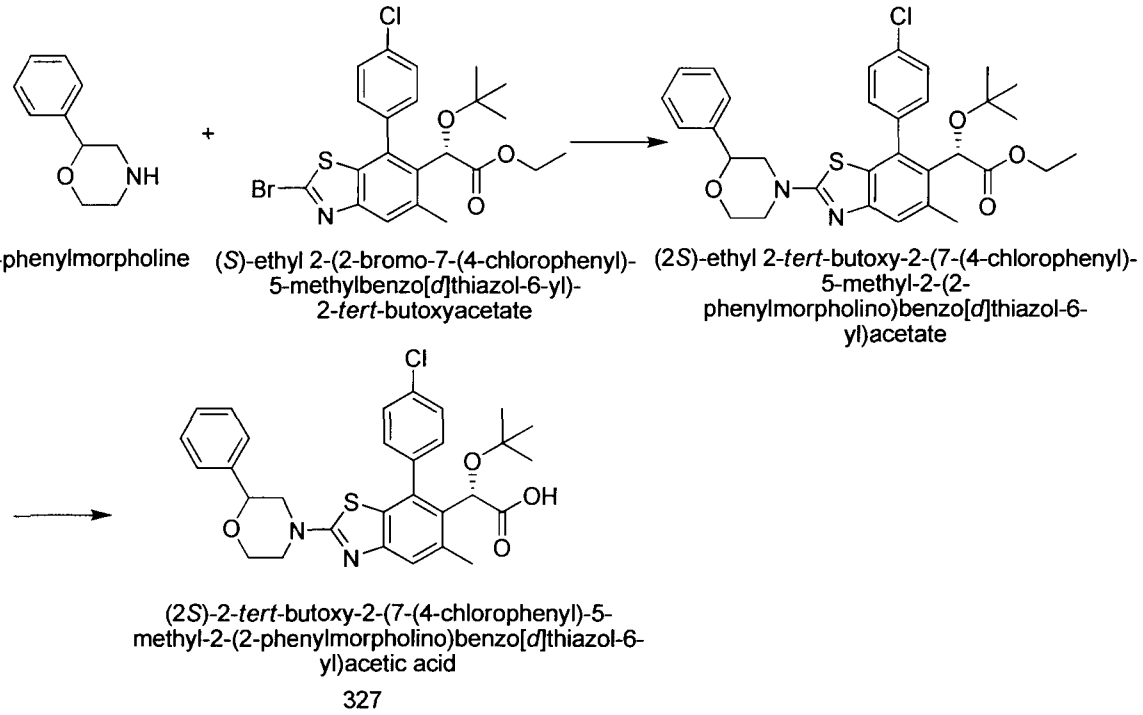
Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid: (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid was prepared using the similar procedure as (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[d]thiazol-6-yl)acetic acid except 2-(1-methyl-1H-indazol-5-yl)morpholine was used instead of 2-(4-chlorophenyl)-2-methylmorpholine. LCMS-ESI$^+$: calc'd for $C_{32}H_{33}ClN_4O_4S$: 605.2, 607.2 (M+H$^+$); found: 605.3, 607.3 (M+H$^+$).^{1}H-NMR: 400 MHz, (CD_3OD) δ: 7.99 (s, 1H), 7.82 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.49-7.56 (m, 5H), 7.32 (s, 1H), 5.13 (s, 1H), 4.72 (d, J = 7.2 Hz, 1H), 4.11 (m, 2H), 4.05 (s, 3H), 3.85 (m, 2H), 3.35 (m, 1H), 3.30 (t, J = 12 Hz, 1H), 2.50 (s, 3H), 0.94 (s, 9H).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((R)-2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid and (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((S)-2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid: The diastereomic mixture of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid was separated with 35% CH_3OH/SFC (containing 0.01%TFA) to give enantiomeric pure (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((R)-2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid and (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((S)-2-(1-methyl-1H-indazol-5-yl)morpholino)benzo[d]thiazol-6-yl)acetic acid respectively.

The fast eluting fraction: LCMS-ESI$^+$: calc'd for $C_{32}H_{33}ClN_4O_4S$: 605.2, 607.2 (M+H$^+$); found: 605.3, 607.3 (M+H$^+$).^{1}H-NMR: 400 MHz, (CD_3OD) δ: 8.00 (s, 1H), 7.83 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.47-7.57 (m, 5H), 7.34 (s, 1H), 5.15 (s, 1H), 4.76 (d, J = 10.8 Hz, 1H), 4.14 (m, 2H), 4.06 (s, 3H), 3.89 (m, 2H), 3.47-3.64 (m, 2H), 2.51 (s, 3H), 0.94 (s, 9H).

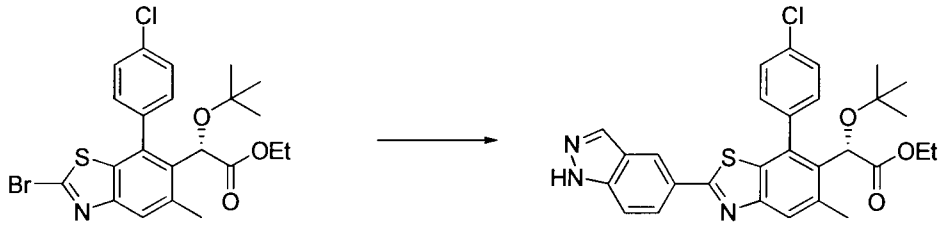
The slow eluting fraction: LCMS-ESI$^+$: calc'd for $C_{32}H_{33}ClN_4O_4S$: 605.2, 607.2 (M+H$^+$); found: 605.3, 607.3 (M+H$^+$).^{1}H-NMR: 400 MHz, (CD_3OD) δ: 8.00 (s, 1H), 7.84 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.47-7.57 (m, 5H), 7.34 (s, 1H), 5.14 (s, 1H), 4.76 (d, J = 10.8 Hz, 1H), 4.15 (t, J = 14.4 Hz, 2H), 4.06 (s, 3H), 3.88 (m, 2H), 3.46-3.64 (m, 2H), 2.51 (s, 3H), 0.94 (s, 9H).

Example 176. Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-phenylmorpholino)benzo[d]thiazol-6-yl)acetic acid (327).



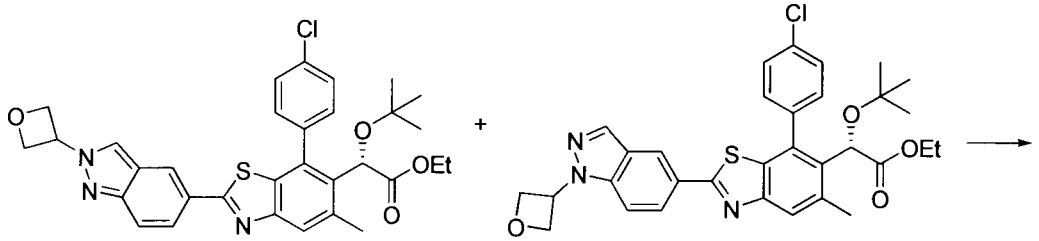
Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-phenylmorpholino)benzo[d]thiazol-6-yl)acetic acid: (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-phenylmorpholino)benzo[d]thiazol-6-yl)acetic acid was prepared using the similar procedure as (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-2-methylmorpholino)-5-methylbenzo[d]thiazol-6-yl)acetic acid except 2-(4-methylphenyl)-2-methylmorpholine was used instead of 2-(4-chlorophenyl)-2-methylmorpholine. LCMS-ESI$^+$: calc'd for $C_{30}H_{31}ClN_2O_4S$: 551.2, 553.2 ($M+H^+$); found: 551.3, 553.3 ($M+H^+$).^{1}H-NMR: 400 MHz, (CD_3Cl) δ: 7.62 (dd, J1 = 2.4 Hz, J2 = 10 Hz,, 1H), 7.49 (m, 3H), 7.3-7.4 (m, 6H), 5.13 (s, 1H), 4.58 (d, J = 10.8 Hz, 1H), 4.09 (m, 2H), 3.80 (m, 2H), 3.64 (m, 1H), 3.37 (m, 1H), 3.08 (dd, J1 = 12.8 Hz, J2 = 10.8 Hz,1H.50 (s, 3H), 2.49 (s, 3H), 0.93 (s, 9H).

Example 177. Method AQ: Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(oxetan-3-yl)-2H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (328) and (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(oxetan-3-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (329).



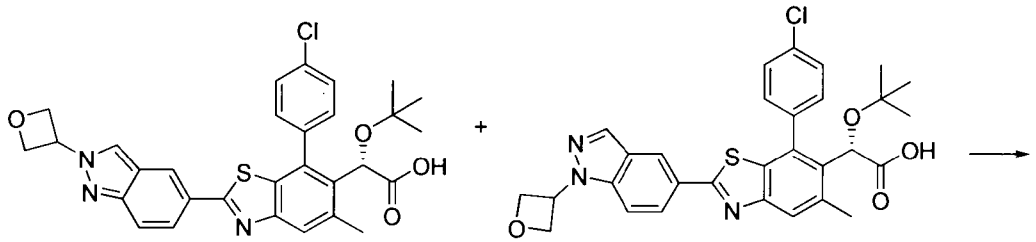
(*S*)-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1*H*-indazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(oxetan-3-yl)-2*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(oxetan-3-yl)-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(oxetan-3-yl)-2*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

328

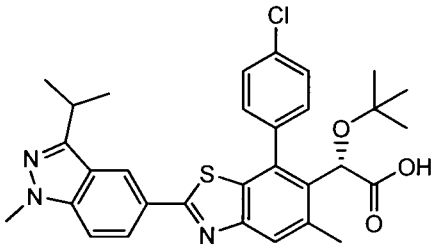
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(oxetan-3-yl)-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

329

Preparation of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: *(S)*-ethyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (300.0 mg, 0.604 mmol), 1*H*-indazole-5-boronic acid (117.3 mg, 0.725 mmol), potassium carbonate (250.3 mg, 1.811 mmol), and tetrakis(triphenylphosphine)palladium(0) (104.7 mg, 0.091 mmol) were taken 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 (6 mL) and degassed water (1.5 mL). The reaction mixture was heated at 95 °C for 6.5 h then cooled to room temperature. The reaction mixture was 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 $C_{29}H_{29}ClN_3O_3S$: 534.2 ($M+H^+$); Found: 533.8 ($M + H^+$).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(oxetan-3-yl)-2H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid and (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-(oxetan-3-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid: Prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,2-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid except starting from *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate instead of *(S)*-ethyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzo[*d*]thiazol-6-yl)acetate and 3-bromooxetane instead of iodomethane.

Example 178. Method BB: Preparation of (S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-isopropyl-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (330).



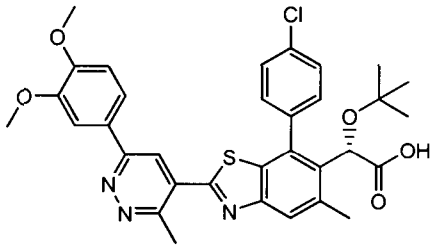
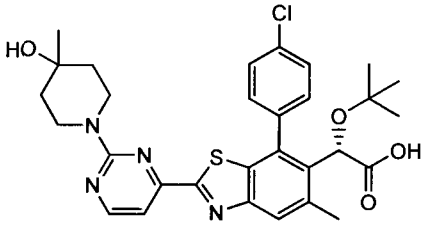
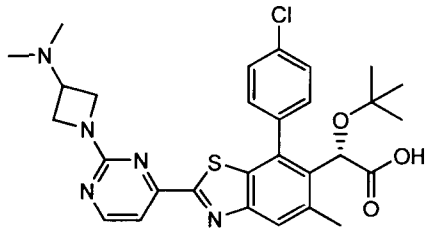
330

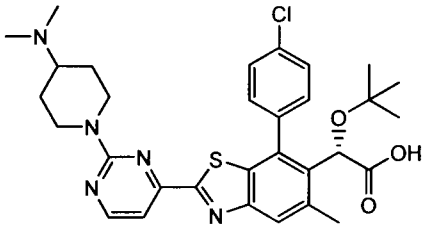
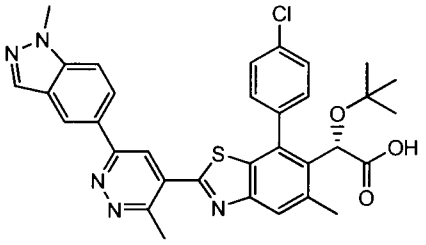
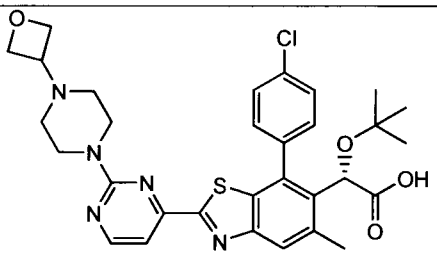
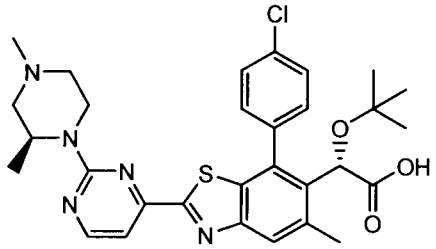
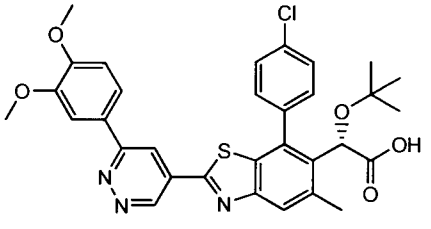
Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-isopropyl-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(3-isopropyl-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid was prepared in a similar manner as *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid except 1-(5-bromo-2-fluorophenyl)-2-methylpropan-1-ol was used instead of (5-bromo-2-fluorophenyl)(pyridin-3-yl)methanol. LCMS-ESI$^+$: calc'd for $C_{31}H_{33}ClN_3O_3S$: 562.2 (M+H$^+$); Found 562.3 (M + H$^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 8.03 (dd, J = 8.9, 1.6 Hz, 1H), 7.81 (s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.58 (dd, J = 9.4, 6.9 Hz, 4H), 5.26 (s, 1H), 4.01 (s, 3H), 3.45 (hept, J = 7.0 Hz, 1H), 2.61 (s, 3H), 1.46 (d, J = 7.0 Hz, 6H), 0.98 (s, 9H).

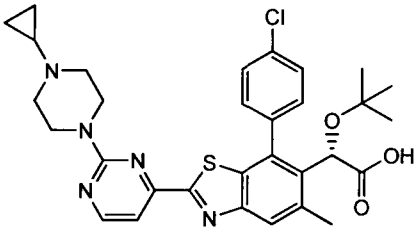
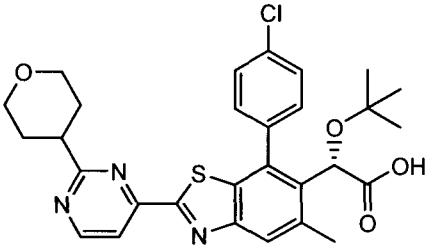
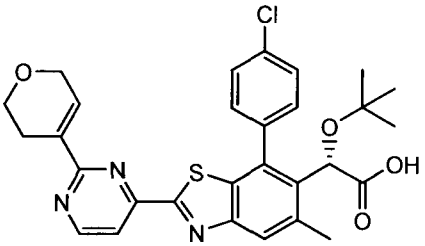
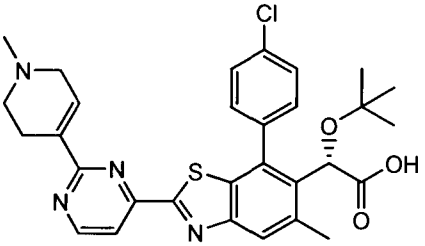
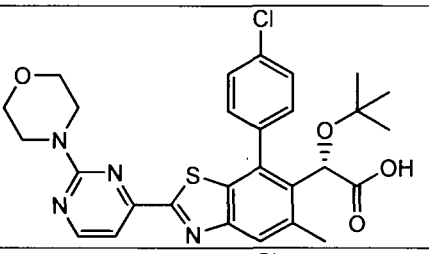
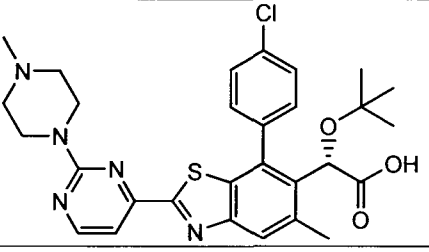
Example 179. Chemical synthesis and characterization data for compounds 331-463. The compounds were prepared by the general method noted in the table. Based on the general methods described above, the skilled artisan will be able to determine the appropriate reactants that will successfully produce the described compounds.

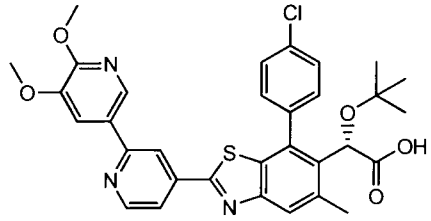
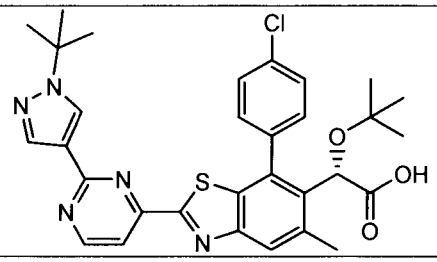
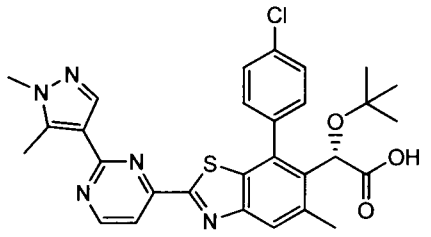
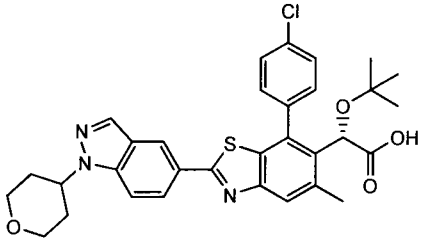
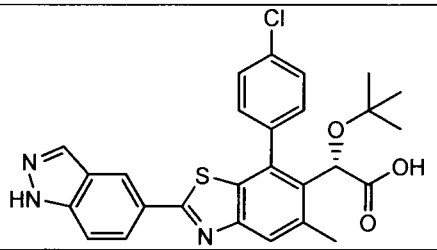
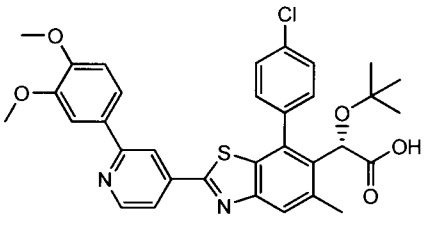
General methods

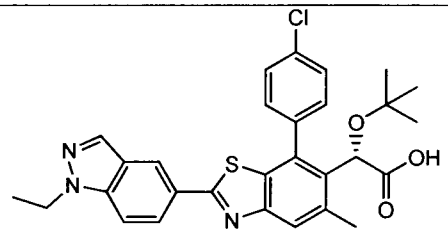
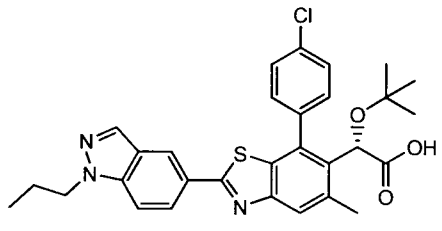
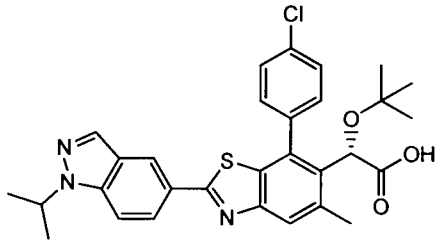
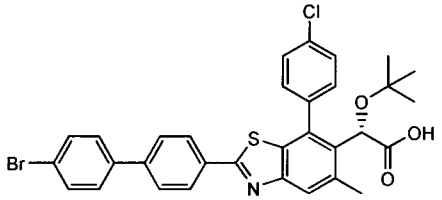
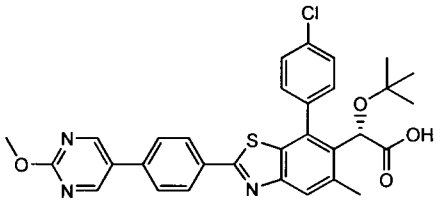
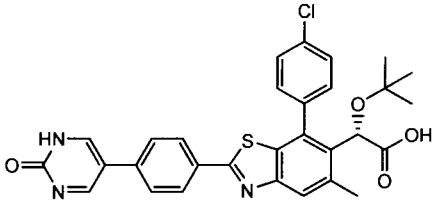
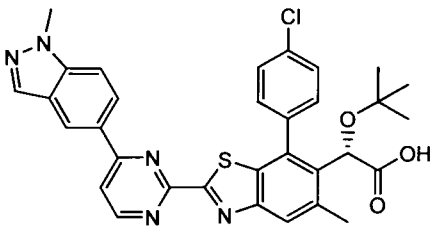
(Method C (example 15), Method F (example 18), Method H (example 20), Method J (example 22), Method O (example 46), Method P (example 47), Method V (example 50), Method W (example 51), Method Y (example 52), Method AA (example 54), Method AG (example 57), Method AJ (example 60), Method AK (example 61), Method AL (example 62), Method AM (example 63), Method AN (example 64), Method AO (example 65), Method AP (example 66), Method AQ (example 177), Method AR (example 67), Method AS (example 68), Method AT (example 69), Method AU (example 70), Method AV (example 71), Method AW (example 72), Method AX (example 73), Method AY (example 74), Method AZ (example 75), Method BA (example 76), Method BC (example 78), Method BE (example 80), Method BF (example 81), Method BG (example 82).

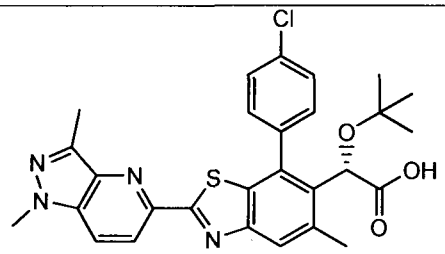
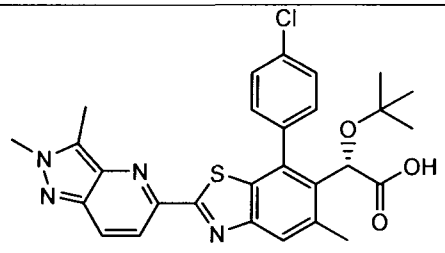
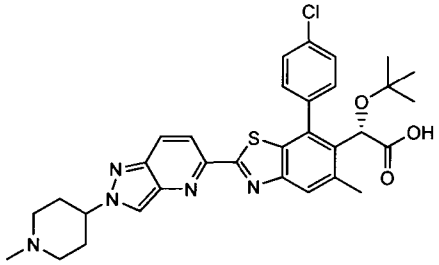
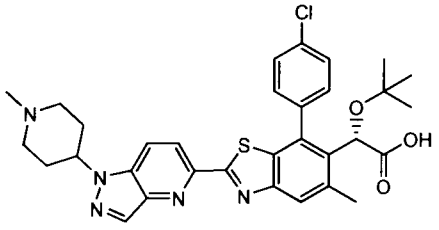
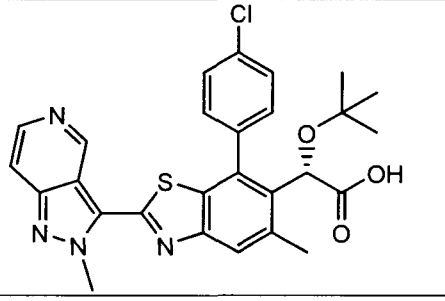
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
331		AR	618.14	618.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.03 – 7.95 (m, 1H), 7.94 (s, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.68 (dd, J = 8.4, 2.1 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.60 – 7.50 (m, 2H), 7.12 (d, J = 8.5 Hz, 1H), 5.15 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.04 (s, 3H), 2.69 (s, 3H), 0.94 (s, 9H).
332		AS	581.13	581.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, J = 5.1 Hz, 1H), 7.90 (s, 1H), 7.71 – 7.64 (m, 1H), 7.64 – 7.54 (m, 3H), 7.42 (d, J = 5.1 Hz, 1H), 5.26 (s, 1H), 4.32 – 4.19 (m, 2H), 3.61 – 3.49 (m, 2H), 2.62 (s, 3H), 1.72 – 1.52 (m, 4H), 1.25 (s, 3H), 0.97 (s, 9H).
333		AS	566.11	566.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.70 – 7.50 (m, 5H), 5.26 (s, 1H), 4.54 – 4.44 (m, 2H), 4.34 – 4.15 (m, 3H), 2.95 (s, 6H), 2.63 (s, 3H), 0.98 (s, 9H).

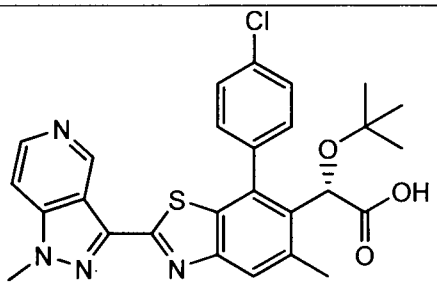
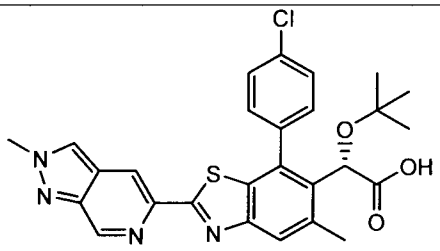
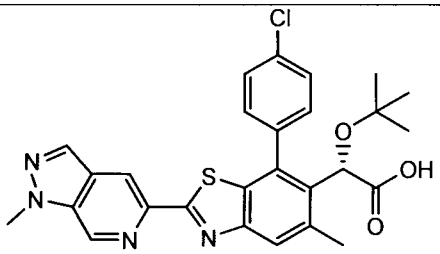
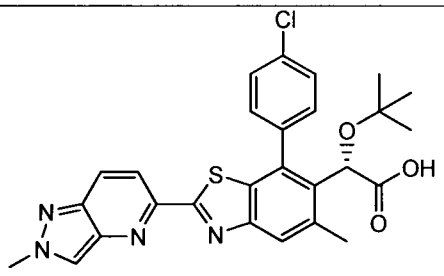
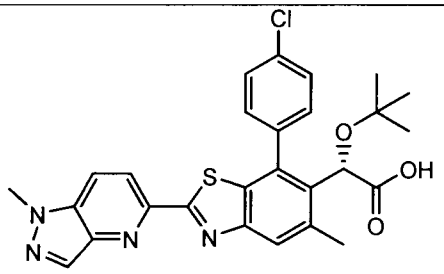
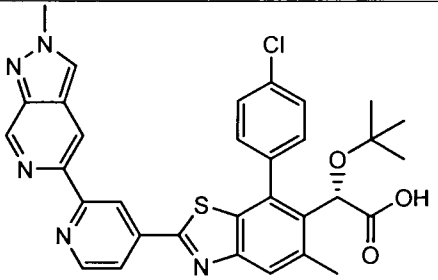
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
334		AS	594.17	593.8	^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (d, J = 5.0 Hz, 1H), 7.91 (s, 1H), 7.71 – 7.64 (m, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.48 (d, J = 5.0 Hz, 1H), 5.25 (s, 1H), 5.02 (br d, J = 13.9 Hz, 2H), 3.56 – 3.45 (m, 1H), 3.04 – 2.93 (m, 2H), 2.88 (s, 6H), 2.63 (s, 3H), 2.16 (br d, J = 10.6 Hz, 2H), 1.72 – 1.55 (m, 2H), 0.98 (s, 9H).
335		AR	612.14	611.9	^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 8.43 (s, 1H), 8.28 – 8.21 (m, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 7.93 – 7.86 (m, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.60 – 7.54 (m, 2H), 5.20 (s, 1H), 4.11 (s, 3H), 3.05 (s, 3H), 2.68 (s, 3H), 0.96 (s, 9H).
336		AS	608.15	608.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (d, J = 5.0 Hz, 1H), 7.92 (s, 1H), 7.70 – 7.64 (m, 1H), 7.63 – 7.52 (m, 4H), 5.25 (s, 1H), 4.93 – 4.88 (m, 2H), 4.83 – 4.77 (m, 2H), 4.57 – 3.46 (m, 5H), 3.22 (br s, 4H), 2.63 (s, 3H), 0.98 (s, 9H).
337		AS	580.14	580.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, J = 4.9 Hz, 1H), 7.92 (s, 1H), 7.71 – 7.63 (m, 1H), 7.63 – 7.53 (m, 4H), 5.33 – 5.26 (m, 1H), 5.25 (s, 1H), 4.95 – 4.89 (m, 1H), 3.65 – 3.45 (m, 2H), 3.43 – 3.33 (m, 1H), 3.29 – 3.23 (m, 1H), 3.17 – 3.03 (m, 1H), 2.96 (s, 3H), 2.63 (s, 3H), 1.37 (d, J = 7.1 Hz, 3H), 0.98 (s, 9H).
338		AR	604.12	604.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.67 (d, J = 1.9 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H), 7.97 (s, 1H), 7.89 – 7.82 (m, 2H), 7.75 (dd, J = 8.4, 2.0 Hz, 1H), 7.67 – 7.55 (m, 3H), 7.15 (d, J = 8.5 Hz, 1H), 5.22 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 2.67 (s, 3H), 0.96 (s, 9H).

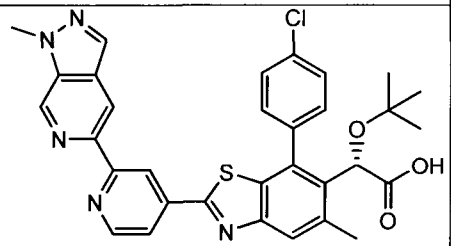
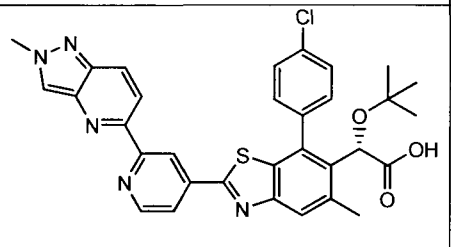
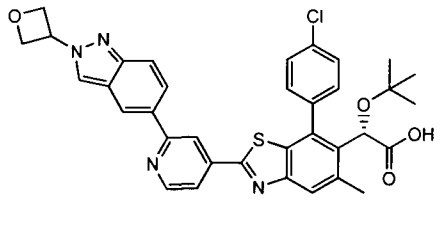
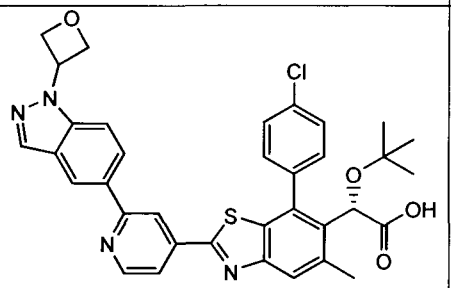
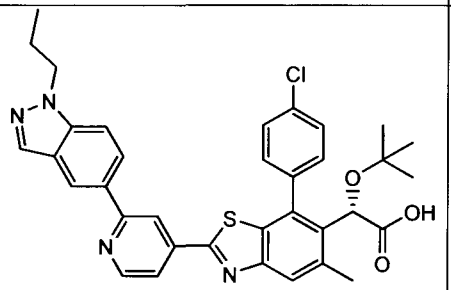
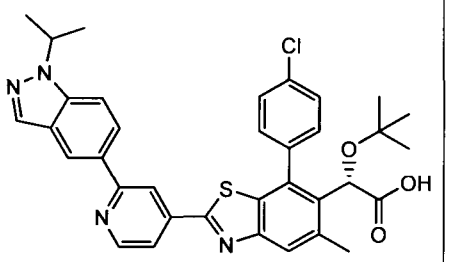
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
339		AS	592.15	592.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (d, J = 5.0 Hz, 1H), 7.92 (s, 1H), 7.72 – 7.64 (m, 1H), 7.64 – 7.51 (m, 4H), 5.25 (s, 1H), 4.11 (br s, 3H), 3.46 (m, 5H), 2.77 (br s, 1H), 2.63 (s, 3H), 0.98 (s, 13H).
340		AV	552.08	552.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.90 (d, J = 5.1 Hz, 1H), 8.12 (d, J = 5.2 Hz, 1H), 7.94 (s, 1H), 7.73 – 7.66 (m, 1H), 7.65 – 7.55 (m, 3H), 5.28 (s, 1H), 4.05 (dt, J = 11.5, 3.2 Hz, 2H), 3.66 – 3.53 (m, 2H), 3.24 – 3.11 (m, 1H), 2.63 (s, 3H), 2.05 – 1.90 (m, 4H), 0.98 (s, 9H).
341		AT	550.07	550.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.90 (d, J = 5.0 Hz, 1H), 8.08 (d, J = 5.3 Hz, 1H), 7.94 (s, 1H), 7.73 – 7.65 (m, 1H), 7.65 – 7.54 (m, 3H), 7.34 (s, 1H), 5.27 (s, 1H), 4.42 – 4.34 (m, 2H), 3.97 – 3.87 (m, 2H), 2.75 – 2.66 (m, 2H), 2.63 (s, 3H), 0.98 (s, 9H).
342		AT	563.11	563.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.97 (d, J = 5.1 Hz, 1H), 8.18 (d, J = 5.1 Hz, 1H), 7.96 (s, 1H), 7.73 – 7.65 (m, 1H), 7.65 – 7.53 (m, 3H), 7.31 (s, 1H), 5.26 (s, 1H), 4.16 (br s, 1H), 3.94 (br s, 1H), 3.75 (br s, 1H), 3.27 – 2.85 (m, 6H), 2.64 (s, 3H), 0.98 (s, 9H).
343		AS	553.07	553.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 5.0 Hz, 1H), 7.89 (s, 1H), 7.70 – 7.64 (m, 1H), 7.63 – 7.53 (m, 3H), 7.46 (d, J = 5.0 Hz, 1H), 5.25 (s, 1H), 3.84 – 3.69 (m, 8H), 2.62 (s, 3H), 0.97 (s, 9H).
344		AS	566.11	566.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (d, J = 5.0 Hz, 1H), 7.92 (s, 1H), 7.70 – 7.65 (m, 1H), 7.64 – 7.53 (m, 4H), 5.25 (s, 1H), 4.95 (br s, 2H), 3.58 (br s, 2H), 3.15 (br s, 4H), 2.95 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).

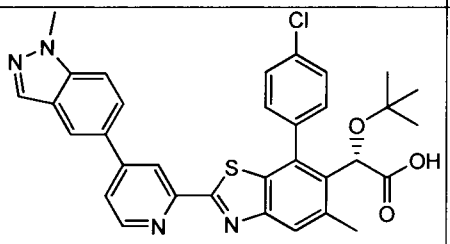
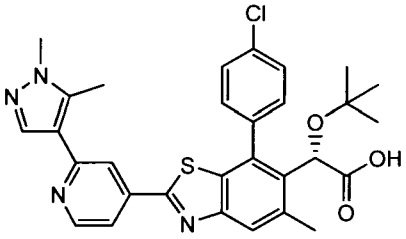
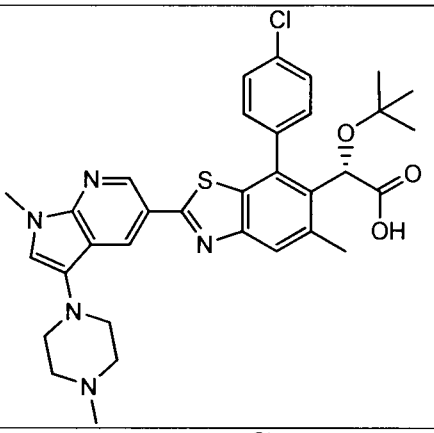
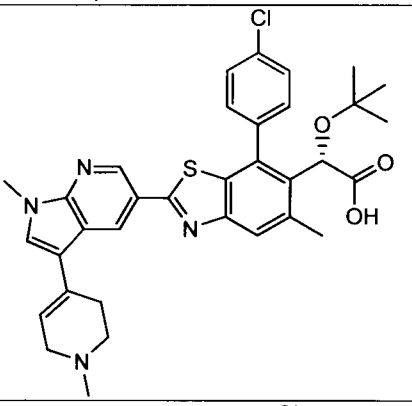
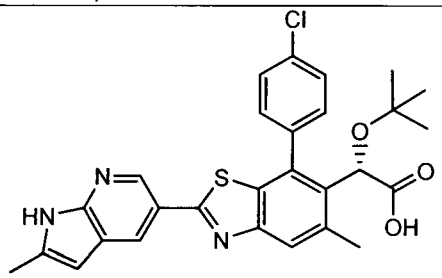
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
345		F	604.12	604.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (d, J = 5.3 Hz, 1H), 8.48 (s, 1H), 8.40 (d, J = 2.0 Hz, 1H), 7.97 (s, 1H), 7.95 (dd, J = 5.4, 1.5 Hz, 1H), 7.91 (d, J = 1.9 Hz, 1H), 7.74 – 7.67 (m, 1H), 7.65 – 7.56 (m, 3H), 5.28 (s, 1H), 4.03 (s, 3H), 3.97 (s, 3H), 2.65 (s, 3H), 0.98 (s, 9H).
346		AT	590.14	590.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.87 (d, J = 5.1 Hz, 1H), 8.42 (s, 1H), 8.18 (s, 1H), 8.04 (d, J = 5.2 Hz, 1H), 7.95 (s, 1H), 7.74 – 7.68 (m, 1H), 7.68 – 7.57 (m, 3H), 5.28 (s, 1H), 2.64 (s, 3H), 1.65 (s, 9H), 0.98 (s, 9H).
347		AT	562.08	561.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.89 (d, J = 5.1 Hz, 1H), 8.11 (s, 1H), 8.00 (d, J = 5.1 Hz, 1H), 7.94 (s, 1H), 7.73 – 7.68 (m, 1H), 7.65 – 7.57 (m, 3H), 5.28 (s, 1H), 3.85 (s, 3H), 2.75 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H).
348		AQ	590.13	590.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.45 – 8.43 (m, 1H), 8.17 (s, 1H), 8.12 (dd, J = 8.9, 1.7 Hz, 1H), 7.83 (s, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.64 – 7.56 (m, 3H), 5.26 (s, 1H), 4.94 – 4.86 (m, 1H), 4.12 (dd, J = 11.6, 4.5 Hz, 2H), 3.69 (td, J = 12.4, 2.1 Hz, 2H), 2.61 (s, 3H), 2.40 – 2.25 (m, 2H), 1.98 (dd, J = 12.6, 4.0 Hz, 2H), 0.98 (s, 9H).
349		J	506.02	506.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.18 (s, 1H), 8.14 – 8.08 (m, 1H), 7.83 (s, 1H), 7.68 (dd, J = 16.2, 8.8 Hz, 2H), 7.63 – 7.57 (m, 3H), 5.26 (s, 1H), 2.62 (s, 3H), 0.98 (s, 9H).
350		F	603.13	603.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.73 (d, J = 5.6 Hz, 1H), 8.54 (s, 1H), 8.05 (dd, J = 5.4, 1.6 Hz, 1H), 7.99 (s, 1H), 7.73 – 7.57 (m, 6H), 7.16 (d, J = 8.4 Hz, 1H), 5.29 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 2.65 (s, 3H), 0.99 (s, 9H).

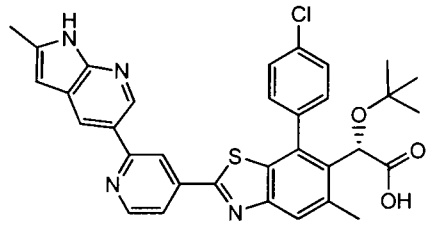
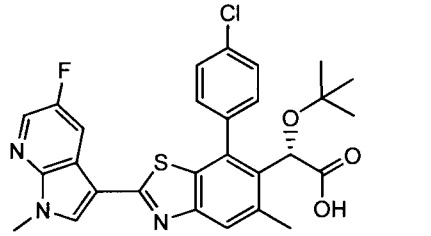
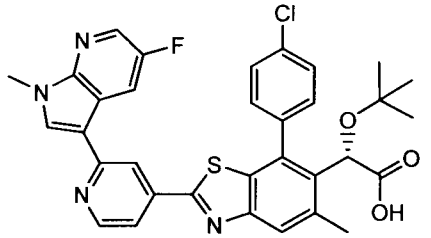
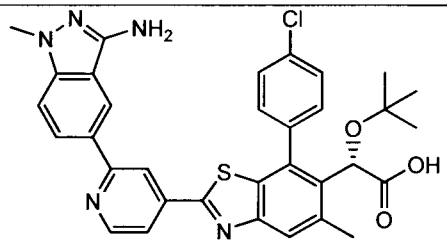
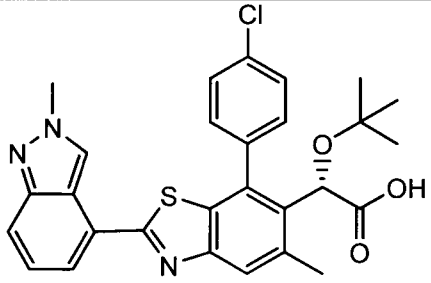
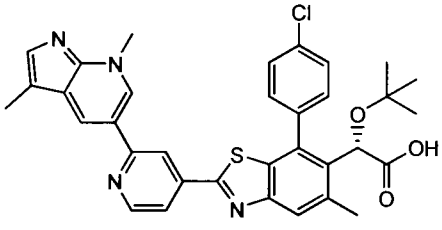
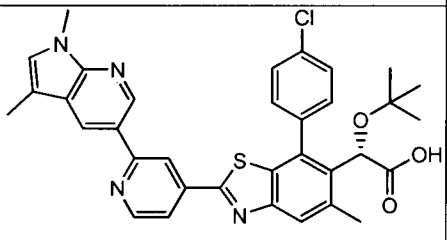
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
351		J	534.07	534	^{1}H NMR (400 MHz, CD_3OD) δ 8.43 – 8.41 (m, 1H), 8.14 (s, 1H), 8.11 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.81 (s, 1H), 7.72 – 7.67 (m, 2H), 7.59 (m, 3H), 5.25 (s, 1H), 4.50 (q, *J* = 7.2 Hz, 2H), 2.60 (s, 3H), 1.49 (t, *J* = 7.2 Hz, 3H), 0.98 (s, 9H).
352		J	548.1	548.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.46 – 8.44 (m, 1H), 8.15 (d, *J* = 0.9 Hz, 1H), 8.13 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.83 (s, 1H), 7.75 – 7.66 (m, 2H), 7.65 – 7.55 (m, 3H), 5.26 (s, 1H), 4.43 (t, *J* = 6.9 Hz, 2H), 2.61 (s, 3H), 2.07 – 1.83 (m, 2H), 0.98 (s, 9H), 0.91 (t, *J* = 7.4 Hz, 3H).
353		J	548.1	548.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (d, *J* = 1.3 Hz, 1H), 8.15 (s, 1H), 8.11 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.82 (d, *J* = 0.9 Hz, 1H), 7.76 – 7.66 (m, 2H), 7.64 – 7.56 (m, 3H), 5.26 (s, 1H), 5.01 (hept, *J* = 6.3 Hz, 1H), 2.61 (s, 3H), 1.58 (d, *J* = 6.7 Hz, 6H), 0.98 (s, 9H).
354		AU	620.98	621.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 – 8.05 (m, 2H), 7.83 (s, 1H), 7.79 – 7.72 (m, 2H), 7.73 – 7.65 (m, 1H), 7.65 – 7.54 (m, 7H), 5.26 (s, 1H), 2.61 (s, 3H), 0.97 (s, 9H).
355		AU	574.09	574	^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (s, 2H), 8.16 (d, *J* = 8.6 Hz, 2H), 7.89 – 7.78 (m, 3H), 7.73 – 7.66 (m, 1H), 7.63 – 7.57 (m, 3H), 5.26 (s, 1H), 4.07 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).
356		AU	560.06	560	^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (s, 2H), 8.14 (d, *J* = 8.2 Hz, 2H), 7.86 (s, 1H), 7.79 – 7.66 (m, 3H), 7.64 – 7.55 (m, 3H), 5.26 (s, 1H), 2.62 (s, 3H), 0.98 (s, 9H).
357		H	598.11	598.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.90 (d, *J* = 5.4 Hz, 1H), 8.79 (s, 1H), 8.41 (dd, *J* = 9.0, 1.7 Hz, 1H), 8.19 (d, *J* = 0.9 Hz, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 8.00 (s, 1H), 7.75 – 7.70 (m, 2H), 7.68 – 7.61 (m, 3H), 5.30 (s, 1H), 4.12 (s,

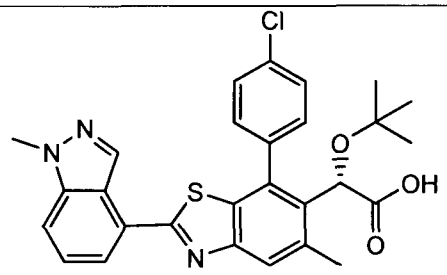
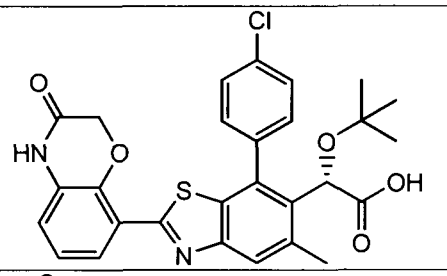
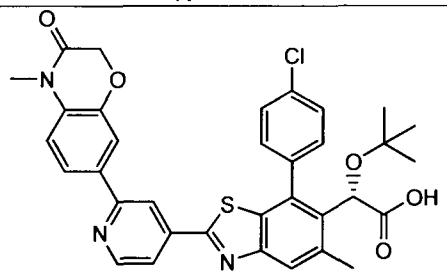
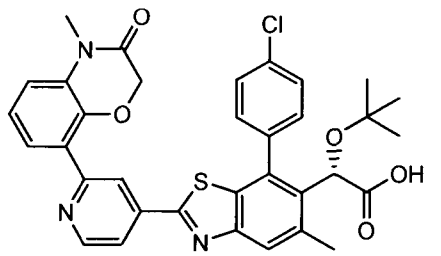
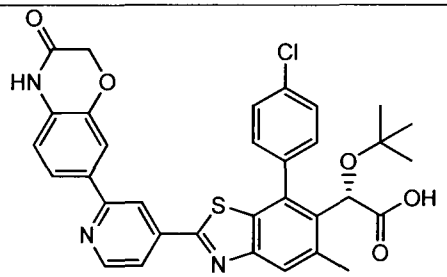
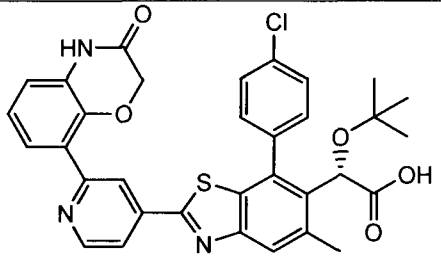
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
					3H), 2.65 (s, 3H), 0.99 (s, 9H).
358		F	535.15	535.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.55 (d, J = 2.4 Hz, 1H), 7.99 (s, 1H), 7.72-7.55 (m, 5H), 5.29 (s, 1H), 4.10(s, 3H), 2.64 (s, 6H), 0.98 (s, 9H).
359		F	535.15	535.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.63 (s, J = 2.2 Hz, 1H), 8.25 (d, J = 2.6 Hz, 1H), 7.94 (s, 1H), 7.72-7.61 (m, 4H), 5.27 (s, 1H), 4.18 (s, 3H), 2.72 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H).
360		F	604.16	604.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.26-8.24 (m, 1H), 8.14-8.12 (m, 2H), 7.70 (s, 1H), 7.61-7.59 (m, 1H), 7.50-7.47 (m, 3H), 5.17 (s, 1H), 9.63-4.91 (m, 1H), 3.65-3.62 (m, 2H), 3.24-3.22 (m, 2H), 2.89 (s, 3H), 2.50 (s, 3H), 2.47-2.41 (m, 2H), 2.24-2.21 (m, 2H), 0.87 (s, 9H).
361		F	604.16	604.4	^{1}H NMR (400 MHz, CD_3OD) δ:8.50 (s, 1H), 8.20-8.08 (s, 2H), 7.74 (s, 1H), 7.60-7.58 (s, 1H), 7.50-7.47 (m, 3H), 5.17 (s, 1H), 4.84-4.83 (m, 1H), 3.63-3.57 (m, 2H), 3.24-3.22 (m, 2H), 2.88 (s, 3H), 2.50 (s, 3H), 2.49-2.41 (m, 4H), 0.87 (s, 9H).
362		F	521.03	521.2	^{1}H NMR (400 MHz, CD_3OD) δ: 9.80 (s, 1H), 8.43 (d, J = 3 Hz, 1H), 7.95 (d, J = 3.4 Hz, 1H), 7.82 (s, 1H), 7.64-7.62 (m, 1H), 7.54-7.7.46 (m, 3H), 5.19 (s, 1H), 4.11 (s, 3H), 2.54 (s, 3H), 0.88 (s, 9H).

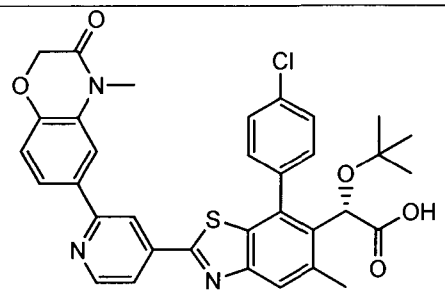
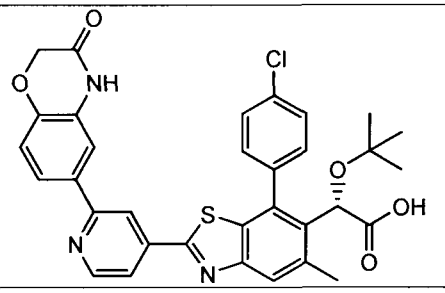
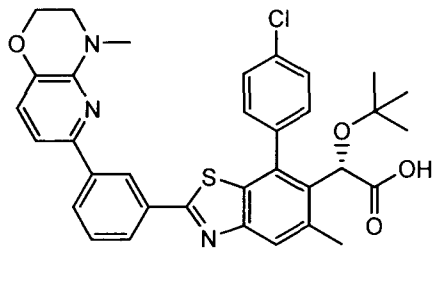
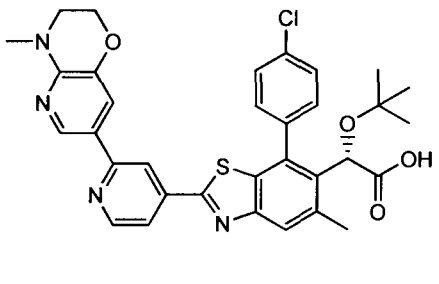
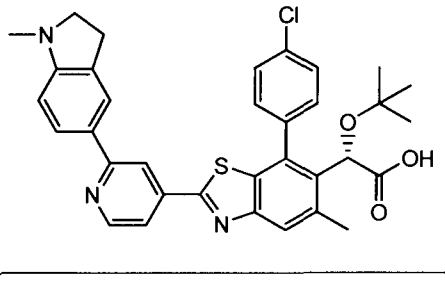
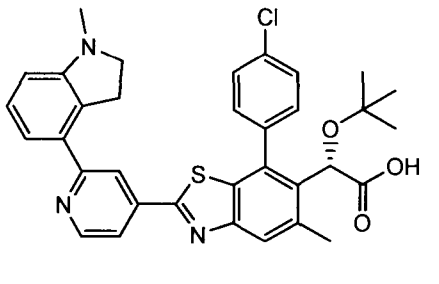
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
363		F	521.03	521.3	^{1}H NMR (400 MHz, CD_3OD) δ: 9.84 (s, 1H), 8.45 (d, J = 3.2 Hz, 1H), 7.99 (d, J = 3.6 Hz, 1H), 7.83 (s, 1H), 7.75-7.7.53 (m, 4H), 5.28 (s, 1H), 4.15 (s, 3H), 2.63 (s, 3H), 0.96 (s, 9H).
364		F	521.03	521.2	^{1}H NMR (400 MHz, CD_3OD) δ: 9.10 (s, 1H), 8.63 (s, 1H), 8.52 (s, 1H), 7.82 (s, 1H), 7.69 (d, J = 4.8 Hz, 1H), 7.60-7.58 (m, 3H), 5.27 (s, 1H), 4.32 (s, 3H), 2.61 (s, 3H), 0.97 (s, 9H).
365		F	521.03	521.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.88 (s, 1H), 8.50 (s, 1H), 8.12 (s, 1H), 7.67-7.49 (m, 5H), 5.17 (s, 1H), 4.08 (s, 3H), 2.51 (s, 3H), 0.88 (s, 9H).
366		F	521.03	521.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.34-8.32(m, 1H), 8.18-8.10 (m, 2H), 7.81 (s, 1H), 7.70-7.68 (m, 1H), 7.60-7.59 (m, 3H), 5.27 (s, 1H), 4.08 (s, 3H), 2.61 (s, 3H), 0.97 (s, 9H).
367		F	521.03	521.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.37(d, J = 4.4 Hz, 1H), 8.21-8.15 (m, 2H), 7.85 (s, 1H), 7.70-7.68 (m, 1H), 7.61-7.59 (m, 3H), 5.27 (s, 1H), 4.12 (s, 3H), 2.61 (s, 3H), 0.97 (s, 9H).
368		P	598.11	598.2	^{1}H NMR (400 MHz, CD_3OD) δ: 0.923 (S, 1H), 8.71-8.50 (m, 4H), 7./84 (s, 1H), 7.701 (s, 1H), 7.62-7.43 (m, 4J), 5.18 (s, 1H), 4.25 (s, 3H), 2.50 (s, 3H), 0.89 (s, 9H).

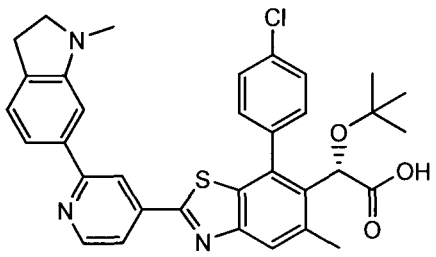
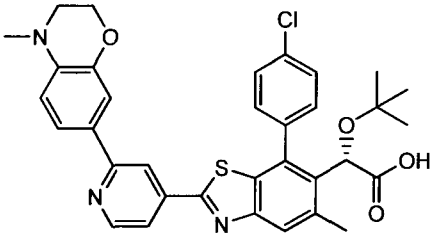
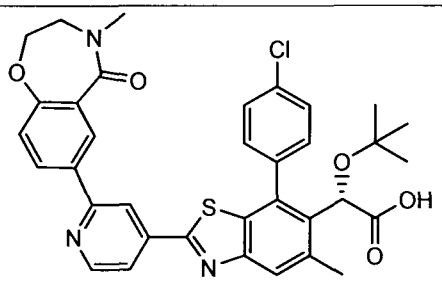
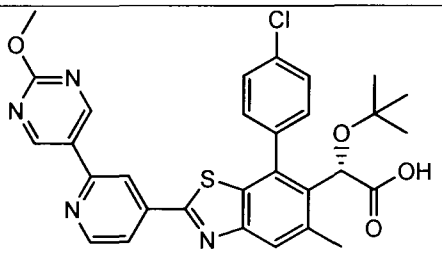
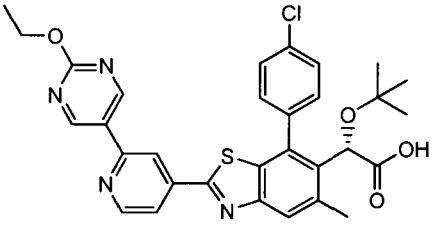
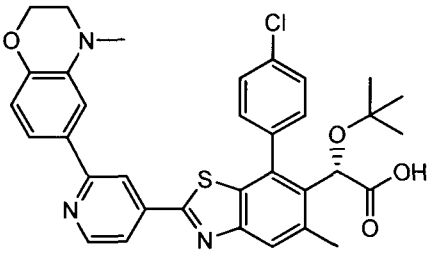
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
369		P	598.11	598.2	^{1}H NMR (400 MHz, CD_3OD) δ: 0.916 (s, 1H), 8.72-8.69 (m, 3H), 8.20 (s, 1H), 7.89-7.55 (m, 6H), 5.26 (s, 1H), 4.13 (s, 3H), 2.60 (s, 3H), 0.99 (s, 9H).
370		P	598.11	598.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.45 (s, 1H), 8.41 (d, J = 2.6 Hz, 1H), 8.21 (s, 1H), 8.02 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 4.6 Hz, 1H), 7.63-7.56 (m, 3H), 7.46-7.40 (m, 3H), 5.16 (s, 1H), 4.06 (s, 3H), 2.46 (s, 3H), 0.88 (s, 9H).
371		O	639.16	639.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.61 (d, J = 2.8 Hz, 1H), 8.42-8.31 (m, 3H), 7.88-7.82 (m, 3H), 7.72 (d, J = 2.8 Hz, 1H), 7.61-7.58 (m, 1H), 7.51-7.48 (m, 3H), 5.80-5.75 (m, 1H), 5.18 (s, 1H), 5.09-5.05 (m, 4H), 2.52 (s, 3H), 0.88 (s, 9H).
372		O	639.16	639.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.67 (d, J = 2.6 Hz, 1H), 8.49 (s, 1H), 8.39 (s, 1H), 8.21 (s, 1H), 8.01-7.98 (m, 2H), 7.87 (s, 1H), 7.71(d, J = 4.4 Hz, 1H), 7.62-7.60 (m, 1H), 7.52 (m, 2H), 5.96-5.92 (m, 1H), 5.19 (s, 1H), 5.16-5.06 (m, 4H), 2.55 (s, 3H), 0.89 (s, 9H).
373		F	625.18	625.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.77 (d, J = 2.6 Hz, 1H), 8.59 (s, 1H), 8.49 (s, 1H), 8.19 (s, 1H), 8.14-8.04 (m, 2H), 7.98 (s, 1H), 7.78-7.69 (m, 2H), 7.62-7.61 (m, 3H), 5.28 (s, 1H), 4.45 (t, J = 6.8 Hz, 2H), 2.65 (s, 3H), 1.99-1.64 (m, 2H), 0.98 (s, 9H), 0.925 (t. J = 7.4 Hz, 3H).
374		F	625.18	625.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.74 (d, J = 2.8 Hz, 1H), 8.52 (s, 1H), 8.46 (s, 1H), 8.17 (s, 1H), 8.11 (d, J= 4.2 Hz, 1H), 7.95-7.94 (m, 2H), 7.76-7.69 (m, 2H), 7.62-7.60 (m, 3H), 5.28 (s, 1H), 5.04-5.00 (m, 1H), 2.64 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 0.98 (s, 9H).

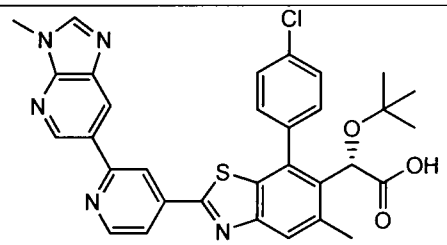
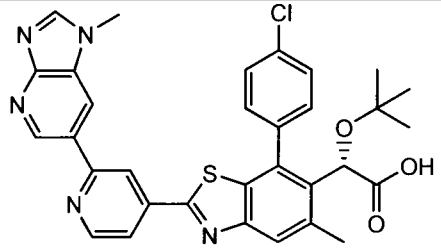
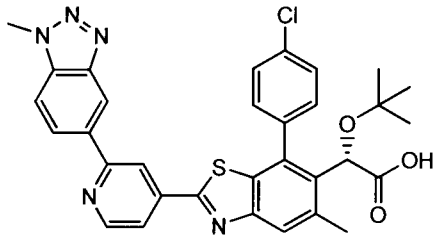
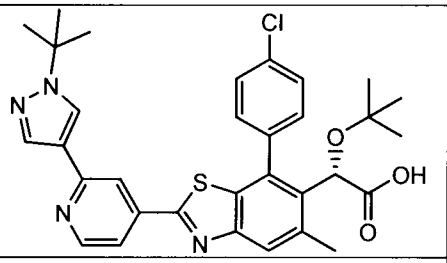
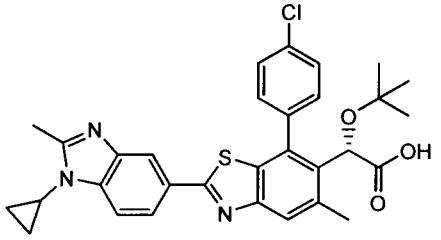
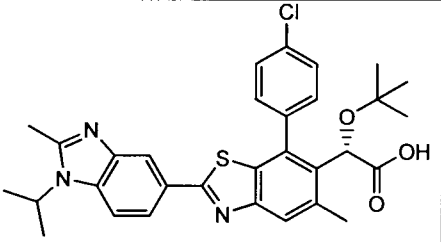
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
375		H	597.13	597.1	^{1}H NMR (400 MHz, CD_3OD) δ: 8.59 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.21 (s, 1H), 8.06 (s, 1H), 7.86-7.75 (m, 3H), 7.67-7.60 (m, 2H), 7.52-7.51 (m, 3H), 5.18 (s, 1H), 4.04 (3H), 2.53 (s, 3H), 0.88 (s, 9H).
376		C	561.09	561.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.69 (d, J = 2.8 Hz, 1H), 8.28 (s, 1H), 7.99-7.96 (m, 3H), 7.70-7.68 (m, 1H), 7.62-7.60 (m, 3H), 5.27 (s, 1H), 3.89 (s, 3H), 2.64 (s, 3H), 2.62 (s, 3H), 0.97 (s, 9H).
377		AN	618.23	618.39	^{1}H NMR (400 MHz, CD_3OD) δ 8.93 (d, J = 2 Hz, 1H), 8.60 (d, J = 1.6 Hz, 1H), 7.82 (s, 1H), 7.70-7.60(m, 4H), 7.15 (s, 1H), 5.25 (s, 1H), 3.88 (s, 3H), 3.71-3.48 (m, 6H), 3.13- 3.01 (m, 5H), 2.62 (s, 3H), 0.98 (s, 9H).
378		AN	615.22	615.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (d, J = 1.6 Hz, 1H), 8.84 (d, J = 1.6 Hz, 1H), 7.85-7.60 (m, 6H), 6.31 (s, 1H), 5.26 (s, 1H), 4.12-4.00 (m, 1H), 3.91 (s, 3H), 3.74 (s, 1H), 3.48-3.40 (m, 2H), 3.11 (s, 1H), 3.04 (s, 3H), 2.96 (s, 2H), 2.62 (s, 3H), 0.98 (s, 9H).
379		AN	520.04	520.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.77 (d, J = 1.6 Hz, 1H), 8.45 (d, J = 1.6 Hz, 1H), 7.83 (s, 1H), 7.70-7.58(m, 4H), 6.32 (s, 1H), 5.25 (s, 1H), 2.61 (s, 3H), 2.48 (s, 3H), 0.97 (s, 9H).

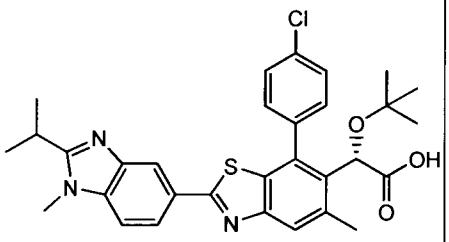
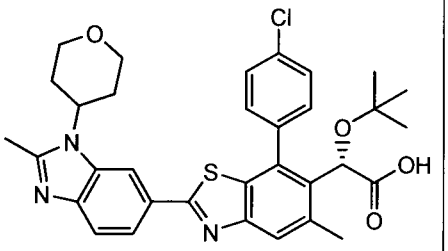
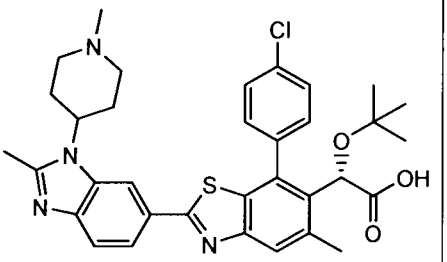
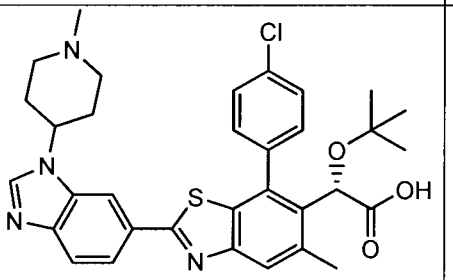
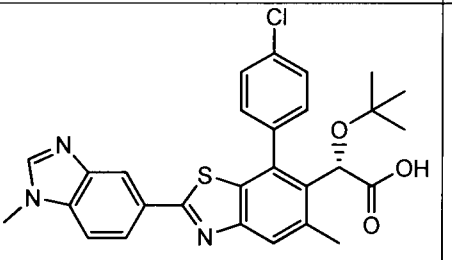
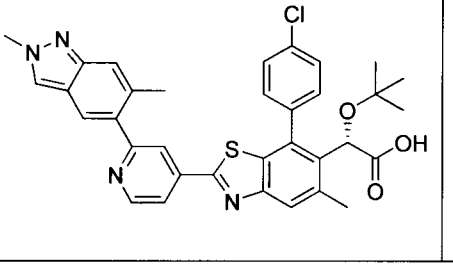
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
380		AO	597.13	597.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.79-8.76 (m, 2H), 8.50-8.48 (m, 2H), 7.97 (s, 1H), 7.91-7.62 (m, 5H), ,6.32 (s, 1H), 5.28 (s, 1H), 2.64 (s, 3H), 2.49(s, 3H), 0.98 (s, 9H).
381		AM	538.03	538.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.44-8.41 (m, 1H), 8.29 (d, J = 2 Hz, 1H), 8.19 (s, 1H), 7.80 (s, 1H), 7.69-7.57(m, 4H), 5.24 (s, 1H), 3.92 (s, 3H), 2.60 (s, 3H), 0.97 (s, 9H).
382		AL	615.12	615.2	^{1}H NMR (400 MHz, DMSO) δ 8.75-8.56 (m, 3H), 8.34-8.24 (m, 2H), 7.99 (s, 1H), 7.83-7.58 (m, 5H), 5.09 (s, 1H), 3.89 (s, 3H), 2.56 (s, 3H), 0.89 (s, 9H).
383		AO	612.14	612.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (d, J = 5.6 Hz, 1H),8.54 (s, 1H), 8.46 (s, 1H), 8.15-7.62 (m, 7H), 7.51 (d, J = 9.2 Hz, 1H), 5.28 (s, 1H), 3.86 (s, 3H), 2.65 (s, 3H), 0.98 (s, 9H).
384		AM	520.04	520.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.98 (s, 1H), 7.93 (s, 1H), 7.78-7.37 (m, 7H), 5.26 (s, 1H), 4.30 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).
385		AL	611.15	611.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (d, J = 2 Hz, 1H), 8.70-8.68 (m, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 0.8 Hz, 1H), 7.90-7.51 (m, 6H), 7.15 (s, 1H), 5.19 (s, 1H), 3.78 (s, 3H), 2.55 (s, 3H), 2.31 (d, J = 1.2 Hz, 3 H), 0.89 (s, 9H).
386		AL	611.15	611.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (d, J = 1.6 Hz, 1H), 8.77-8.70 (m, 2H), 8.58 (d, J = 1.2 Hz, 1H), 8.02-7.61 (m, 6H), 7.24 (d, J = 0.8 Hz, 1H), 5.28 (s, 1H), 3.86 (s, 3H), 2.64 (s, 3H), 2.39 (d, J = 0.8 Hz, 3 H), 0.98 (s, 9H).

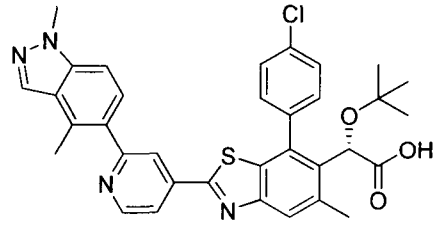
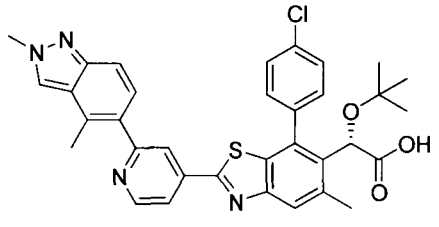
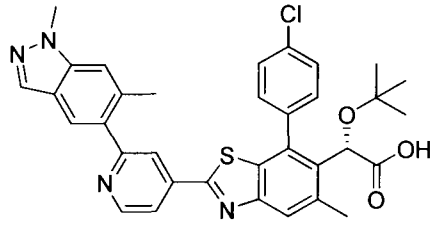
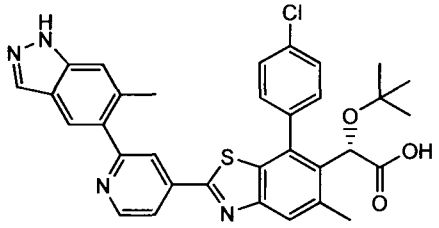
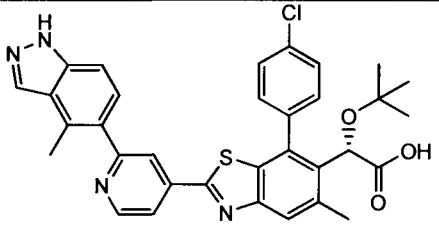
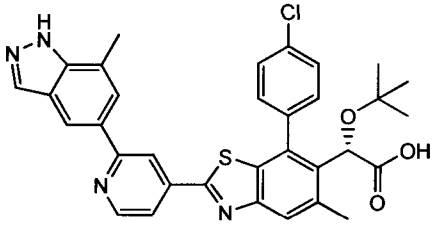
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
387		AM	520.04	520.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 7.85 (s, 1H), 7.66-7.39 (m, 7H), 5.17 (s, 1H), 4.04 (s, 3H), 2.54 (s, 3H), 0.88 (s, 9H).
388		J	537.03	537.2	^{1}H NMR (400 MHz, CD_3OD) δ: 7.75 (s, 1H), 7.67-7.65 (m, 1H), 7.57-7.54 (m, 5H), 7.96 (d, 1H), 5.23 (s, 1H), 4.62 (s, 2 H), 2.58 (s, 3H), 0.95 (s, 9H).
389		F	628.14	628.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.71 (d, 1H), 8.52 (s, 1 H), 8.08 (d, 1H), 7.91 (s, 1H), 7.80 (m, 1H), 7.77-7.68(m, 2H), 7.64-7.58 (m, 3H), 7.37 (d, 1H), 5.28 (s, 1H), 4.66 (s, 2 H), 3.40 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).
390		F	628.14	628.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.79 (d, 1H), 8.52 (s, 1 H), 8.08 (d, 1H), 7.88 (s, 1H), 7.68 (m, 1H), 7.62-7.58(m, 3H), 7.54-7.44 (m, 1H), 7.37-7.23 (m, 2H), 5..32 (s, 1H), 4.63 (s, 2 H), 3.37 (s, 3H), 2.62 (s, 3H), 1.02 (s, 9H).
391		F	614.11	614.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.69 (d, 1H), 8.43 (s, 1 H), 7.98 (d, 1H), 7.92 (s, 1H), 7.68 (m, 1H), 7.62-7.58(m, 5H), 7.05 (d, 1H), 5.27 (s, 1H), 4.64 (s, 2 H), 2.62 (s, 3H), 0.97 (s, 9H).
392		F	614.11	614.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.74 (d, 1H), 8.48 (s, 1 H), 8.06 (m, 1H), 7.85 (s, 1H), 7.66-7.44 (m, 1H), 7.57-7.51(m, 3H), 7.38-7.36 (m, 1H), 7.13-7.04 (m, 2H), 5..27 (s, 1H), 4.64 (s, 2 H), 2.59 (s, 3H), 0.96 (s, 9H).

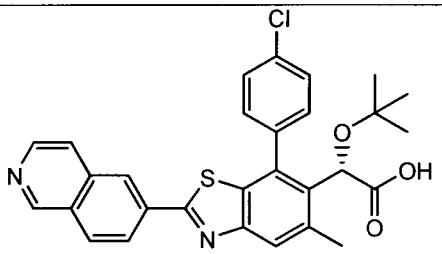
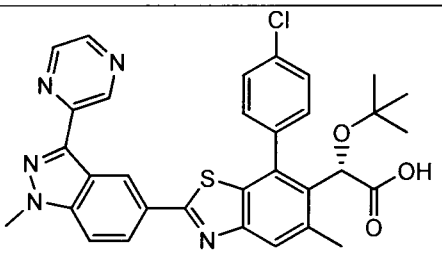
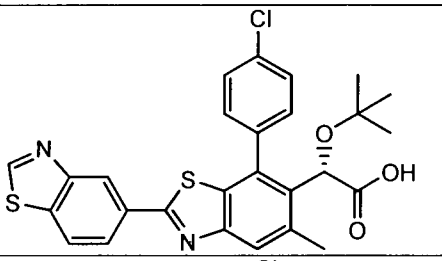
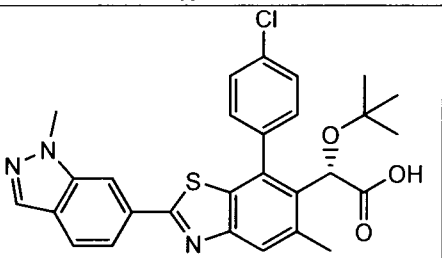
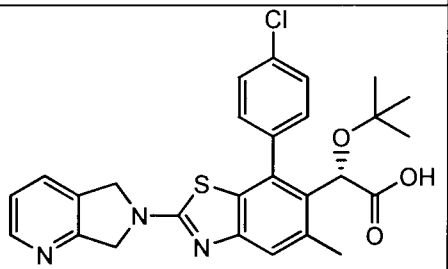
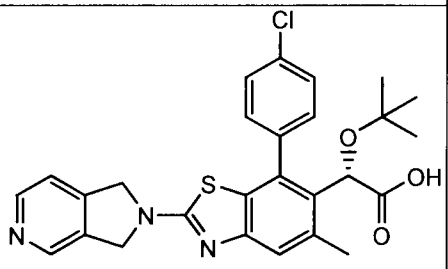
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
393		F	628.14	628.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.82 (d, 1H), 8.67 (s, 1 H), 8.27 (d, 1H), 8.02 (s, 1H), 7.81 (m, 1H), 7.73-7.71(m, 2H), 7.70-7.62 (m, 3H), 7.23 (m, 1H), 5.30 (s, 1H), 4.75 (s, 2 H), 3.49 (s, 3H), 2.67 (s, 3H), 1.008 (s, 9H).
394		F	614.11	614.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.70 (d, 1H), 8.40 (s, 1 H), 8.01 (m, 1H), 7.93 (s, 1H), 7.70-7.68 (m, 1H), 7.63-7.59 (m, 4H), 7.54-7.53(m, 1H), 7.09(d, 1H), 5.27 (s, 1H), 4.64(s, 2H), 2.63(s, 3H), 0.97 (s, 9H).
395		H	614.15	614.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.36 (m, 1H), 8.43 (s, 1 H), 7.98 (d, 1H), 7.86 (d, 1H), 7.80 (s, 1H), 7.68-7.65 (m, 1H), 7.56-7.50(m, 3H), 7.43 (d, 1H), 7.23(d, 1H), 5..27 (s, 1H), 4.54(dd, 2H), 3.40 (dd, 2 H), 2.97(s, 3H), 2.60 (s, 3H), 0.97 (s, 9H).
396		F	615.14	615.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.68 (d, 1H), 8.33 (s, 1 H), 8.27 (d, 1H), 7.98 (d, 1H), 7.89 (s, 1H), 7.88-7.84 (m, 1H), 7.69-7.67(m, 1H), 7.61-7.58(m, 3H), 5..27 (s, 1H), 4.36(dd, 2H), 3.75 (dd, 2 H), 3.30(s, 3H), 2.62 (s, 3H), 0.97 (s, 9H).
397		F	598.15	598.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.57 (d, 1H), 8.51 (s, 1 H), 8.05-8.04 (m, 2H), 7.82-7.72 (m, 3H), 7.68-7.66 (m, 3H), 6.64(d, 1H), 5.35 (s, 1H), 3.61-3.57(dd, 2H), 3.14-3.10 (dd, 2H), 2.94(s, 3H), 2.70 (s, 3H), 1.04(s, 9H).
398		F	598.15	598.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.77 (d, 1H), 8.35 (s, 1 H), 8.10-8.08 (m, 1H), 7.90 (s, 1H), 7.68-7.66 (m, 1H), 7.58-7.56(m, 3H), 7.40-7.38 (m, 1H), 7.27-7.25 (m, 1H), 7.02 (d, 1H), 5.26 (s, 1H), 3.56-3.53(dd, 2H), 3.31-3.27 (m, 2H), 2.96(s, 3H), 2.61(s, 3H), 0.96(s, 9H).

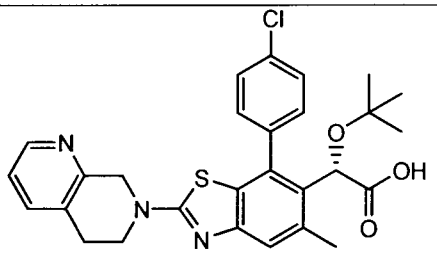
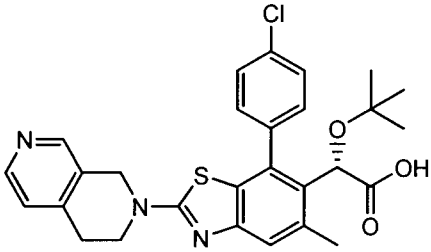
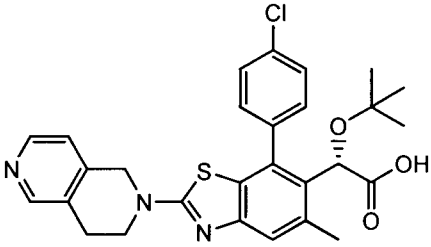
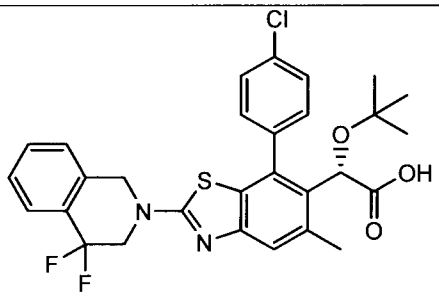
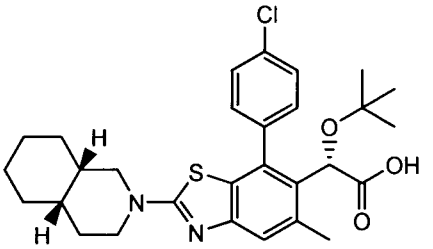
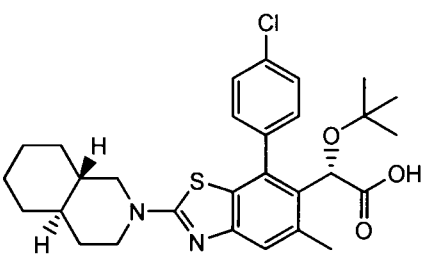
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
399		F	598.15	598.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.65 (d, 1H), 8.47 (s, 1 H), 8.07-8.06 (m, 1H), 7.88 (s, 1H), 7.68-7.66 (m, 1H), 7.60-7.53(m, 3H), 7.31-7.29 (m, 1H), 7.24-7.23 (m, 1H), 7.14 (s, 1H), 5.27 (s, 1H), 3.45-3.44(dd, 2H), 3.04-3.00 (m, 2H), 2.88(s, 3H), 2.60(s, 3H), 0.97(s, 9H).
400		F	614.15	614.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.38 (d, 1H), 8.24 (s, 1 H), 7.80-7.77 (m, 2H), 7.60-7.58 (m, 1H), 7.51-7.47(m, 3H), 7.38-7.36 (m, 1H), 7.22-7.21 (m, 1H), 6.66-6.64 (d, 1H), 5.18 (s, 1H), 4.14-4.12(dd, 2H), 3.28-3.26 (m, 2H), 2.88(s, 3H), 2.52(s, 3H), 0.88(s, 9H).
401		F	642.16	642.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.67(d, 1H), 8.36 (d, 2 H), 8.08-8.06 (m, 1H), 7.96-7.94(m, 1H), 7.84 (s, 1H), 7.64-7.63 (m, 1H), 7.55-7.53 (m, 3H), 7.12(d, 1H), 5.25 (s, 1H), 4.49-4.472(dd, 2H), 3.66-3.63 (dd, 2H), 3.20(s, 3H), 2.57(s, 3H), 0.96(s, 9H).
402		F	575.08	575.2	^{1}H NMR (400 MHz, CD_3OD) δ: 9.22 (s, 2H), 8.75-8.74 (d, 1 H), 8.42 (s, 1H), 7.89 (m, 2H), 7.68-7.67(m, 1H), 7.60-7.58 (m, 3H), 5.26 (s, 1H), 4.08(s, 3H), 2.61(s, 3H), 0.97(s, 9H).
403		F	589.1	589.2	^{1}H NMR (400 MHz, CD_3OD) δ: 9.22 (s, 2H), 8.77-8.76 (d, 1 H), 8.45 (s, 1H), 7.93-7.92 (m, 2H), 7.70-7.68 (m, 1H), 7.60-7.58 (m, 3H), 5.26 (s, 1H), 4.53 (m,2H), 2.61(s, 3H), 1.45(dd, 3H), 0.97(s, 9H).
404		F	614.15	614.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.48 (d, 1H), 8.30 (d, 1 H), 7.89-7.88 (m, 1H), 7.78 (s, 1H), 7.59-7.57(m, 1H), 7.50-7.46 (m, 3H), 7.13-7.12 (m, 1H), 7.09-7.06 (m, 1H),6.71(d, 1H), 5.18 (s, 1H), 4.21-4.19(dd, 2H), 3.18-3.16 (m, 2H), 2.86(s, 3H), 2.52(s, 3H), 0.88(s, 9H).

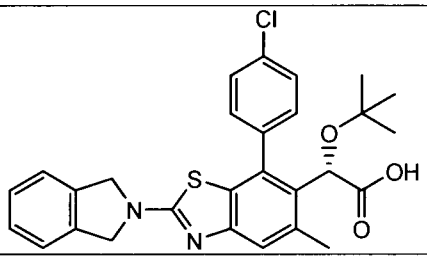
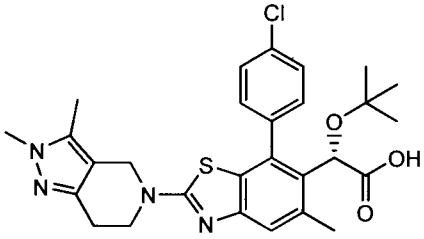
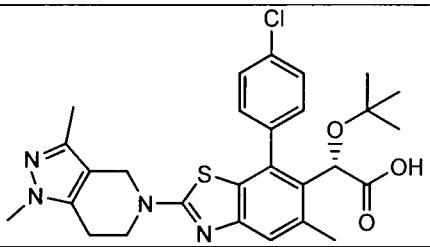
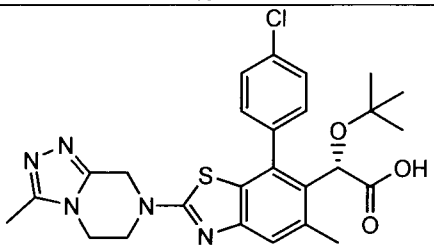
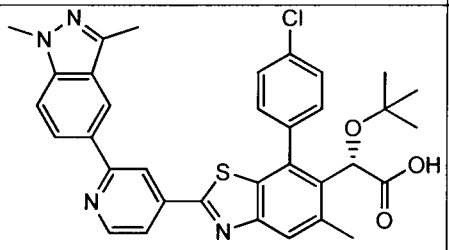
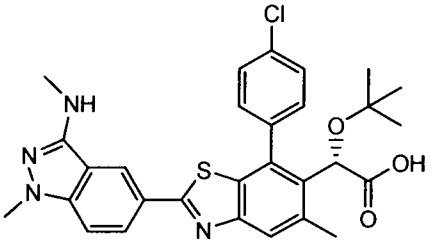
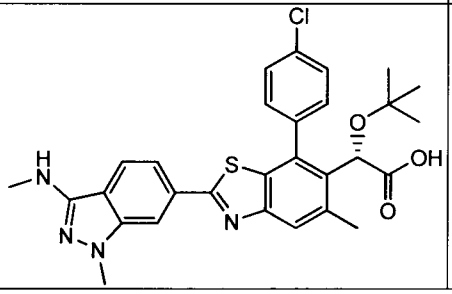
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
405		H	598.11	598.2	^{1}H NMR (400 MHz, CD_3OD) δ:9.00 (d, 1H), 8.63 (d, 1 H), 8.57 (s, 1H), 8.32-8.30(m, 2H), 7.78 (s, 1H), 7.72-7.69(m, 2H), 7.56-7.54 (m, 3H), 5.24 (s, 1H)), 3.88 (s, 3H), 2.58(s, 3H), 0.96(s, 9H).
406		H	598.11	598.2	^{1}H NMR (400 MHz, CD_3OD) δ:9.34 (s, 1H), 8.99 (d, 1 H), 8.82 (m, 2H), 8.59(s, 1H), 7.98-7.97 (m, 1H), 7.90 (s, 1H), 7.71-7.68(m, 1H), 7.61-7.59 (m, 3H), 5.27 (s, 1H)), 4.13 (s, 3H), 2.62(s, 3H), 0.98(s, 9H).
407		F	598.11	598.2	^{1}H NMR (400 MHz, CD_3OD) δ:8.80 (d, 1H), 8.67 (s, 1 H), 8.57 (s, 1H), 8.30-8.27(m, 1H), 7.80-7.99 (m, 1H), 7.95 (s, 1H), 7.91-7.89(m, 1H), 7.71-7.69 (m, 1H), 7.60-7.58(m, 3H), 5.27 (s, 1H)), 4.37 (s, 3H), 2.64(s, 3H), 0.98(s, 9H).
408		F	589.15	589.3	^{1}H NMR (400 MHz, CD_3OD) δ:8.62 (d, 1H), 8.57 (s, 1 H), 8.43 (s, 1H), 7.99(s, 1H), 7.98-7.97 (m, 2H), 7.71-7.68 (m, 1H), 7.62-7.609 (m, 3H), 5.27 (s, 1H)), 2.64 (s, 3H), 1.66(s, 9H), 0.98(s, 9H).
409		BG	560.17	560.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.39 (s, 1H), 8.22 (d, J = 12 Hz, 1H), 8.02 (d, J = 12 Hz, 1H), 7.87 (s, 1H), 7.68 (m, 1H), 7.60 (m, 3H), 5.26 (s, 1H), 3.58 (m, 1H), 2.93 (s, 3H), 2.62 (s, 3H), 1.43 (m, 2H), 1.27 (m, 2H), 0.97 (s, 9H).
410		BG	562.19	562.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.41 (s, 1H), 8.14-8.23 (m, 2H), 7.89 (s, 1H), 7.68 (m, 1H), 7.60 (m, 3H), 5.26 (s, 1H), 5.06 (m, 1H), 2.92 (s, 3H), 2.62 (s, 3H), 1.77 (d, J = 8 Hz, 6H), 0.98 (s, 9H).

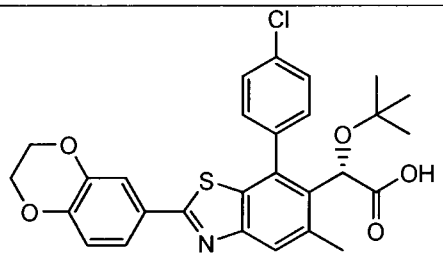
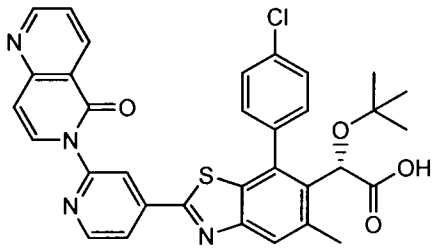
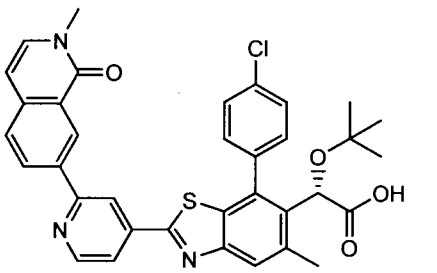
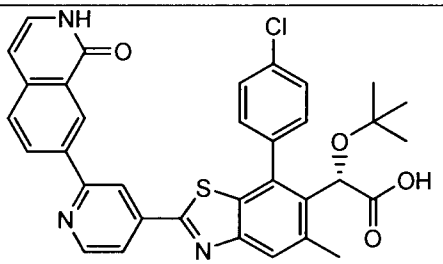
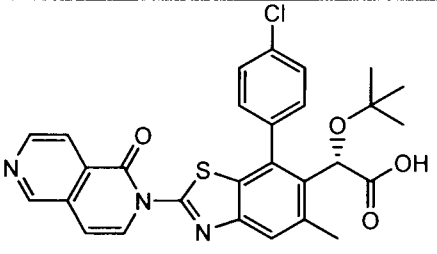
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
411		BG	562.19	562.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.41 (s, 1H), 8.26 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.89 (s, 1H), 7.69 (m, 1H), 7.61 (m, 3H), 5.26 (s, 1H), 4.08 (s, 3H), 3.70 (quint, J = 6.8 Hz, 1H), 2.62 (s, 3H), 1.55 (d, J = 6.8 Hz, 6H), 0.97 (s, 9H).
412		AP	604.16	604.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.64 (s, 1H), 8.15 (dd, J = 8.8, 1.2 Hz, 1H), 7.90 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.69 (m, 1H), 7.60 (m, 3H), 5.26 (s, 1H), 4.93 (m, 1H), 4.21 (dd, J = 11.2, 4.0 Hz, 2H), 3.71 (t, J = 11.2 Hz, 1H), 2.92 (s, 3H), 2.66 (m, 2H), 2.63 (s, 3H), 2.04 (br d, J = 8.4 Hz, 2H), 0.98 (s, 9H).
413		AP	617.2	617.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.48 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.68 (m, 1H), 7.60 (m, 3H), 5.25 (s, 1H), 4.99 (m, 1H), 3.79 (br m, 2H), 3.37 (m, 2H), 3.03 (s, 3H), 2.88 (s, 1H), 2.84 (m, 2H), 2.63 (s, 3H), 2.39 (br m, 2H), 0.98 (s, 9H).
414		AP	603.17	603.3	^{1}H NMR (400 MHz, CD_3OD) δ: 8.55 (s, 1H), 8.42 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.85 (m, 2H), 7.69 (m, 1H), 7.60 (m, 3H), 5.26 (s, 1H), 4.93 (m, 1H), 3.76 (m, 2H), 3.38 (m, 2H), 3.02 (m, 2H), 3.01 (s, 3H), 2.63 (s, 3H), 2.48 (m, 2H), 0.98 (s, 9H).
415		BG	520.04	520.1	^{1}H NMR (400 MHz, CD_3OD) δ: 9.20 (br s, 1H), 8.43 (s, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.85 (s, 1H), 7.67 (m, 1H), 7.58 (m, 3H), 5.26 (s, 1H), 4.10 (s, 3H), 2.62 (s, 3H), 0.97 (s, 9H).
416		BF	611.15	611.1	^{1}H NMR (400 MHz, CD_3OD) δ: 8.83 (d, J = 6.0 Hz, 1H), 8.40 (s, 1H), 8.31 (s, 1H), 8.27 (dd, J = 6.0, 2.0 Hz, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.69 (m, 1H), 7.60 (m, 4H), 5.28 (s, 1H), 4.24 (s, 3H), 2.63 (s, 3H), 2.42 (s, 3H), 0.97 (s, 9H).

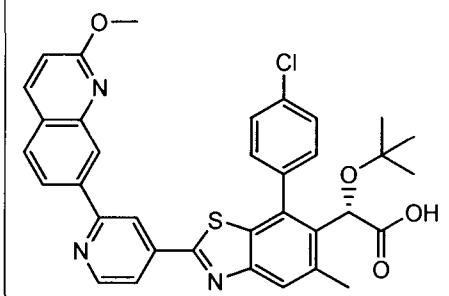
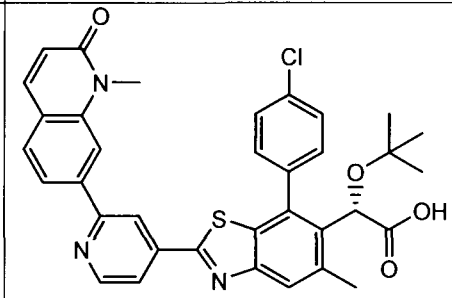
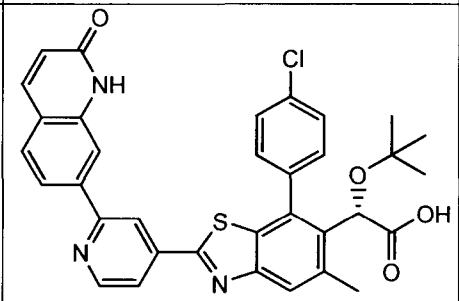
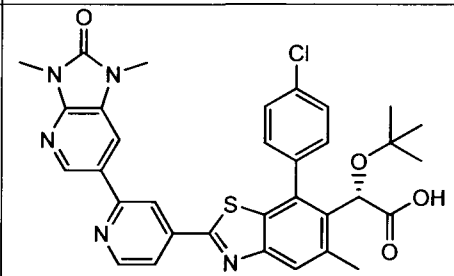
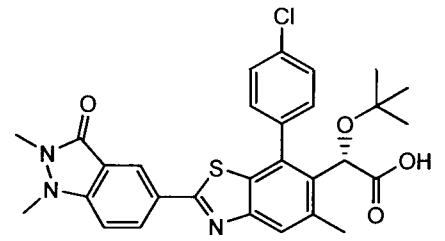
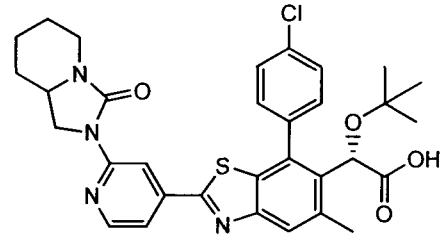
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
417		BF	611.15	611.1	^{1}H NMR (400 MHz, CD_3OD) δ: 8.84 (d, J = 5.6 Hz, 1H), 8.40 (s, 1H), 8.27 (dd, J = 5.6, 1.6 Hz, 1H), 8.23 (s, 1H), 7.99 (s, 1H), 7.69 (m, 1H), 7.55-7.61 (m, 5H), 5.28 (s, 1H), 4.12 (s, 3H), 2.66 (s, 3H), 2.64 (s, 3H), 0.97 (s, 9H).
418		BF	611.15	611.1	^{1}H NMR (400 MHz, CD_3OD) δ: 8.81 (d, J = 5.6 Hz, 1H), 8.44 (s, 1H), 8.31 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.98 (s, 1H), 7.69 (m, 1H), 7.60 (m, 4H), 7.43 (d, J = 8.8 Hz, 1H), 5.27 (s, 1H), 4.26 (s, 3H), 2.64 (s, 3H), 2.60 (s, 3H), 0.97 (s, 9H).
419		BF	611.15	611.1	^{1}H NMR (400 MHz, CD_3OD) δ: 8.84 (d, J = 5.6 Hz, 1H), 8.42 (s, 1H), 8.28 (d, J = 5.6 Hz, 1H), 8.07 (s, 1H), 7.99 (s, 1H), 7.91 (s, 1H), 7.69 (m, 1H), 7.60 (m, 4H), 5.28 (s, 1H), 4.10 (s, 3H), 2.64 (s, 3H), 2.50 (s, 3H), 0.97 (s, 9H).
420		F	597.13	597.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.83 (d, J = 5.6 Hz, 1H), 8.42 (s, 1H), 8.36 (dd, J = 5.6, 2.0 Hz, 1H), 8.12 (s, 1H), 7.99 (s, 1H), 7.93 (s, 1H), 7.69 (m, 1H), 7.56-7.61 (m, 4H), 5.27 (s, 1H), 2.63 (s, 3H), 2.47 (s, 3H), 0.97 (s, 9H).
421		F	597.13	597.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.87 (d, J = 6.0 Hz, 1H), 8.49 (s, 1H), 8.36 (dd, J = 6.0, 1.6 Hz, 1H), 8.30 (s, 1H), 8.02 (s, 1H), 7.69 (m, 1H), 7.53-7.61 (m, 5H), 5.28 (s, 1H), 2.69 (s, 3H), 2.64 (s, 3H), 0.97 (s, 9H).
422		F	597.13	597.2	^{1}H NMR (400 MHz, CD_3OD) δ: 8.76 (d, J = 5.6 Hz, 1H), 8.67 (s, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 8.00 (s, 1H), 7.83 (s, 1H), 7.69 (m, 1H), 7.61 (m, 3H), 5.28 (s, 1H), 2.68 (s, 3H), 2.65 (s, 3H), 0.98 (s, 9H).

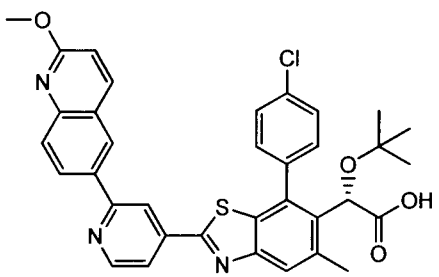
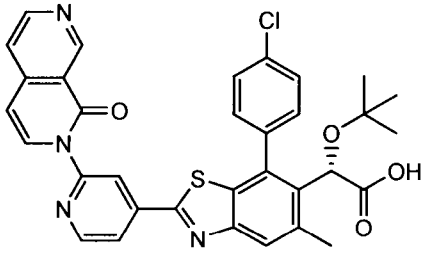
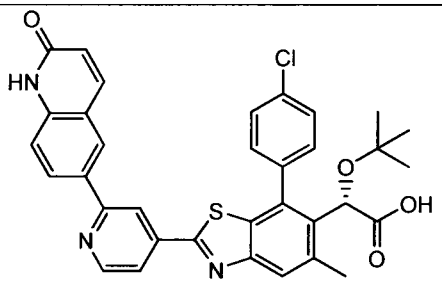
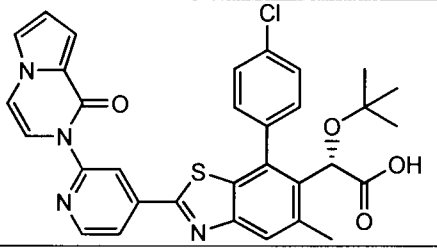
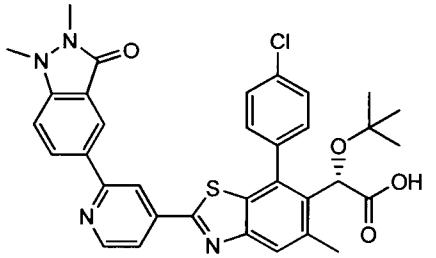
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
427		BA	517.04	517.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.61 (s, 1H), 8.79 (s, 1H), 8.59 (t, J = 7.0 Hz, 2H), 8.47 (d, J = 8.7 Hz, 1H), 8.32 (d, J = 6.3 Hz, 1H), 7.94 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.62 (s, 3H), 5.28 (s, 1H), 2.64 (s, 3H), 0.99 (s, 9H).
428		BC	598.11	598.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (s, 1H), 9.13 (s, 1H), 8.75 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.15 (d, J = 9.1 Hz, 1H), 7.83 (s, 1H), 7.70 (t, J = 8.1 Hz, 2H), 7.66 – 7.57 (m, 3H), 5.26 (s, 1H), 4.18 (s, 3H), 2.62 (s, 3H), 0.98 (s, 9H).
429		BA	523.07	523.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (s, 1H), 8.68 (d, J = 0.9 Hz, 1H), 8.16 (dt, J = 8.5, 5.0 Hz, 2H), 7.86 (s, 1H), 7.70 (dd, J = 6.2, 3.2 Hz, 1H), 7.60 (d, J = 2.2 Hz, 3H), 5.27 (s, 1H), 2.62 (s, 3H), 0.98 (s, 9H).
430		AZ	520.04	520.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 8.05 (d, J = 0.8 Hz, 1H), 7.93 – 7.76 (m, 3H), 7.69 (dd, J = 6.4, 3.1 Hz, 1H), 7.59 (t, J = 3.7 Hz, 3H), 5.27 (s, 1H), 4.12 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).
431		AX	508.03	508.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, J = 4.9 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.71 – 7.62 (m, 1H), 7.57 (app. d, J = 8.6 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.47 – 7.33 (m, 2H), 5.16 (s, 1H), 4.86 (s, 4H), 2.51 (s, 3H), 0.95 (s, 9H).
432		AX	508.03	508.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (s, 1H), 8.74 (d, J = 5.7 Hz, 1H), 7.95 (d, J = 5.7 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.62 – 7.48 (m, 3H), 7.42 (s, 1H), 5.17 (s, 1H), 5.13 – 4.98 (m, 4H), 2.53 (s, 3H), 0.97 (s, 9H).

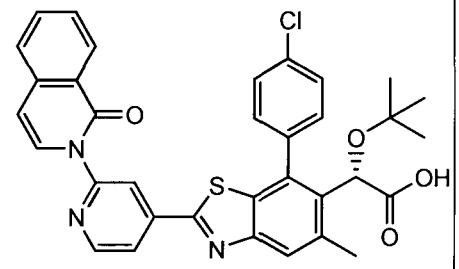
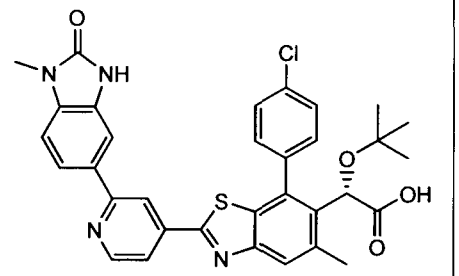
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
433		AX	522.06	522.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 5.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.71 – 7.59 (m, 1H), 7.60 – 7.43 (m, 4H), 7.38 (s, 1H), 5.16 (s, 1H), 4.93 (s, 2H), 3.91 (t, J = 5.9 Hz, 2H), 3.12 (t, J = 5.7 Hz, 2H), 2.52 (s, 3H), 0.95 (s, 9H).
434		AX	522.06	522.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 8.55 (d, J = 5.8 Hz, 1H), 7.77 (d, J = 5.8 Hz, 1H), 7.63 (dd, J = 8.4, 1.9 Hz, 1H), 7.59 – 7.45 (m, 3H), 7.37 (s, 1H), 5.15 (s, 1H), 4.95 (s, 2H), 3.92 (t, J = 5.9 Hz, 2H), 3.25 (t, J = 5.9 Hz, 2H), 2.51 (s, 3H), 0.95 (s, 9H).
435		AX	522.06	522.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (s, 1H), 8.60 (d, J = 5.9 Hz, 1H), 7.85 (d, J = 5.9 Hz, 1H), 7.63 (dd, J = 8.2, 2.1 Hz, 1H), 7.59 – 7.45 (m, 3H), 7.37 (s, 1H), 5.15 (s, 1H), 5.05 (s, 2H), 3.93 (t, J = 5.8 Hz, 2H), 3.17 (dd, J = 14.1, 8.3 Hz, 2H), 2.51 (s, 3H), 0.95 (s, 9H).
436		AX	557.05	557.1	^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 8.3, 6.4 Hz, 1H), 7.59 – 7.32 (m, 7H), 5.16 (s, 1H), 4.89 – 4.83 (m, 2H), 4.30 (td, J = 11.1, 2.6 Hz, 2H), , 2.52 (s, 3H), 0.95 (s, 9H).
437		AY	527.12	527.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.69 – 7.52 (m, 3H), 7.48 (dd, J = 8.4, 1.9 Hz, 1H), 7.30 (s, 1H), 5.15 (s, 1H), 4.11 – 3.94 (m, 1H), 3.94 – 3.79 (m, 1H), 3.02 – 2.82 (m, 1H), 2.52 (s, 3H), 1.92 – 1.53 (m, 5H), 1.53 – 1.20 (m, 5H), 1.06 (s, 2H), 0.95 (s, 3H).
438		AY	527.12	527.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.69 – 7.54 (m, 3H), 7.48 (dd, J = 9.8, 5.1 Hz, 1H), 7.30 (s, 1H), 5.15 (s, 1H), 3.92 (d, J = 14.3 Hz, 1H), 3.75 (d, J = 14.6 Hz, 1H), 3.63 – 3.36 (m, 2H), 2.53 (s, 3H), 2.11 – 1.83 (m, 3H), 1.78 – 1.24 (m, 9H), 0.95 (s, 9H).

Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
439		AY	507.04	507.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.71 – 7.47 (m, 4H), 7.47 – 7.32 (m, 5H), 5.17 (s, 1H), 5.03 – 4.87 (m, J = 22.4 Hz, 4H), 2.52 (s, 3H), 0.96 (s, 9H).
440		AX	539.09	539.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.69 – 7.45 (m, 4H), 7.35 (s, 1H), 5.15 (s, 1H), 4.61 (s, 2H), 3.93 (t, J = 5.7 Hz, 2H), 3.74 (s, 1H), 2.86 (t, J = 5.9 Hz, 2H), 2.52 (s, 3H), 2.25 (s, 3H), 0.95 (s, 9H).
441		AX	539.09	539.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.71 – 7.42 (m, 4H), 7.34 (s, 1H), 5.15 (s, 1H), 4.57 (s, 2H), 3.93 (t, J = 5.8 Hz, 2H), 3.69 (s, 3H), 2.87 (t, J = 5.7 Hz, 2H), 2.51 (s, 3H), 2.19 (s, 3H), 0.95 (s, 9H).
442		AX	526.05	526.3	^{1}H NMR (400 MHz, CD_3OD) δ 7.68 – 7.46 (m, J = 9.3, 2.7 Hz, 4H), 7.41 (s, 1H), 5.16 (s, 1H), 5.03 (s, 2H), 4.20 (t, J = 5.4 Hz, 2H), 4.11 (t, J = 5.3 Hz, 2H), 2.51 (s, 3H), 0.95 (s, 9H).
443		F	611.15	611.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (d, J = 5.6 Hz, 1H), 8.63 (s, 1H), 8.44 (s, 1H), 8.14 – 8.04 (m, 2H), 7.99 (s, 1H), 7.66 (dt, J = 18.8, 7.8 Hz, 5H), 5.28 (s, 1H), 4.04 (s, 3H), 2.65 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H).
444		AW	549.08	549.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 8.09 (d, J = 10.7 Hz, 1H), 7.79 (s, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.63-7.57 (m, J = 6.1 Hz, 3H), 7.40 (d, J = 8.8 Hz, 1H), 5.26 (s, 1H), 3.85 (s, 3H), 3.01 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).
445		AW	549.08	549.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (s, 1H), 7.82 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.61 – 7.55 (m, 3H), 5.25 (s, 1H), 3.83 (s, 3H), 3.01 (s, 3H), 2.60 (s, 3H), 0.95 (s, 9H).

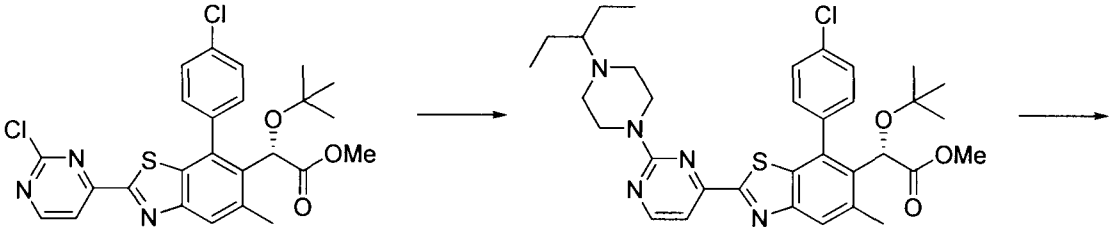
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
446		J	524.03	524.2	^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1H), 7.70-7.65 (m, 1H), 7.60-7.51 (m, 4H), 7.47 (dd, J = 8.2, 2.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 5.23 (s, 1H), 4.35-4.25 (m, 4H), 2.59 (s, 3H), 0.96 (s, 9H).
447		Y	611.11	611.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 4.4 Hz, 1H), 9.02 (d, J = 8.0 Hz, 1H), 8.70 (d, J = 5.2 Hz, 1H), 8.57 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 5.2 Hz, 1H), 7.94 (s, 1H), 7.72 – 7.67 (m, 2H), 7.55 – 7.47 (m, 3H), 6.13 (d, J = 8.4 Hz, 1H), 5.33 (s, 1H), 2.59 (s, 3H), 1.01 (s, 9H).
448		AG	624.15	624.4	^{1}H NMR (400 MHz, DMSO-d6) δ 9.00 (s, 1H), 8.85 (d, J = 5.2 Hz, 1H), 8.52 – 8.50 (m, 2H), 8.05 (s, 1H), 7.98 (d, J = 3.6 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.72 – 7.69 (m, 2H), 7.65 – 7.59 (m, 2H), 7.54 (d, J = 7.2 Hz, 1H), 6.68 (d, J = 7.2 Hz, 1H), 5.09 (s, 1H), 3.54 (s, 3H), 2.56 (s, 3H), 0.89 (s, 9H).
449		W	610.12	610.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 2H), 8.55 – 8.52 (m, 2H), 8.07 (s, 1H), 7.94 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.57 – 7.49 (m, 4H), 6.76 (d, J = 6.4 Hz, 1H), 5.34 (s, 1H), 2.60 (s, 3H), 1.01 (s, 9H).
450		AK	534.03	534.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 9.27 (d, J = 7.6 Hz, 1H), 8.93 (s, 1H), 7.89 (s, 1H), 7.79 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.58 – 7.50 (m, 3H), 6.93 (d, J = 7.6 Hz, 1H), 5.36 (s, 1H), 2.59 (s, 3H), 1.01 (s, 9H).

Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
451		AG	624.15	624.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 6.0 Hz, 1H), 8.72 (s, 1H), 8.52 (s, 1H), 8.24 (d, J = 6.0 Hz, 1H), 8.13 – 8.09 (m, 2H), 8.04 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.60 – 7.47 (m, 3H), 7.06 (d, J = 8.8 Hz, 1H), 5.37 (s, 1H), 4.16 (s, 3H), 2.64 (s, 3H), 1.03 (s, 9H).
452		AG	624.15	624.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, J = 5.6 Hz, 1H), 8.55 (s, 1H), 8.25 (s, 1H), 8.04 (d, J = 5.2 Hz, 1H), 8.01 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.81 – 7.73 (m, 3H), 7.58 – 7.49 (m, 3H), 6.90 (d, J = 9.6 Hz, 1H), 5.35 (s, 1H), 3.91 (s, 3H), 2.63 (s, 3H), 1.03 (s, 9H).
453		W	610.12	610.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.39 (s, 1H), 8.05 (s, 1H), 7.97 – 7.88 (m, 4H), 7.73 – 7.64 (m, 2H), 7.48 – 7.39 (m, 3H), 6.78 (d, J = 8.8 Hz, 1H), 5.27 (s, 1H), 2.54 (s, 3H), 0.94 (s, 9H).
454		W	628.14	628.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, J = 6.0 Hz, 1H), 8.66 (d, J = 13.6 Hz, 2H), 8.33 (s, 1H), 8.18 (d, J = 4.8 Hz, 1H), 8.03 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.57 – 7.47 (m, 3H), 5.35 (s, 1H), 3.58 (s, 3H), 3.56 (s, 3H), 2.62 (s, 3H), 1.01 (s, 9H).
455		AJ	550.07	550.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.8 Hz, 1H), 8.42 (s, 1H), 7.94 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.31 (d, J = 8.4 Hz, 1H), 5.34 (s, 1H), 3.57 (s, 3H), 3.47 (s, 3H), 2.58 (s, 3H), 1.01 (s, 9H).
456		Y	605.15	605.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, J = 4.4 Hz, 1H), 8.44 (d, J = 6.8 Hz, 1H), 7.97 (s, 1H), 7.88 (d, J = 6.4 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.56 – 7.44 (m, 3H), 5.33 (s, 1H), 4.51 – 4.45 (m, 1H), 4.04 (d, J = 13.2 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.81 – 3.76 (m, 1H), 2.93 – 2.87 (m,

Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
					1H), 2.60 (s, 3H), 2.06 (d, J = 12.8 Hz, 1H), 2.01 – 1.96 (m, 1H), 1.78 (d, J = 9.6 Hz, 1H), 1.55 – 1.38 (m, 3H), 1.01 (s, 9H).
457		W	624.15	624.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, J = 6.0 Hz, 1H), 8.69 (s, 1H), 8.62 (s, 1H), 8.22 – 7.20 (m, 3H), 8.09 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.52 – 7.49 (m, 1H), 6.05 (d, J = 9.2 Hz, 1H), 5.37 (s, 1H), 4.16 (s, 3H), 2.64 (s, 3H), 1.04 (s, 9H).
458		Y	611.11	611.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (br.s., 1H), 9.67 (s, 1H), 8.88 (d, J = 6.0 Hz, 1H), 8.69 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 5.2, 1.2 Hz, 1H), 7.93 (s, 1H), 7.81 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.55 – 7.47 (m, 3H), 6.77 (d, J = 8.0 Hz, 1H), 5.33 (s, 1H), 2.59 (s, 3H), 1.01 (s, 9H).
459		W	610.12	610.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 5.2 Hz, 1H), 8.37 (d, J = 13.2 Hz, 2H), 8.25 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 8.00 (s, 1H), 7.81 (d, J = 5.6 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.58 – 7.46 (m, 4H), 6.81 (d, J = 9.2 Hz, 1H), 5.35 (s, 1H), 2.63 (s, 3H), 1.03 (s, 9H).
460		Y	599.1	599.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.49 (s, 1H), 7.82 – 7.80 (m, 2H), 7.67 – 7.65 (m, 1H), 7.55 – 7.50 (m, 3H), 7.37 – 7.33 (m, 3H), 7.13 (d, J = 3.2 Hz, 1H), 6.60 – 6.58 (m, 1H), 5.25 (s, 1H), 2.58 (s, 3H), 0.96 (s, 9H).
461		AA	627.15	627.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (d, J = 5.2 Hz, 1H), 8.25 – 8.23 (m, 2H), 8.09 (dd, J = 8.4, 1.6 Hz, 1H), 7.82 (dd, J = 5.6, 1.6 Hz, 1H), 7.75 (s, 1H), 7.60 – 7.58 (m, 1H), 7.51 – 7.46 (m, 3H), 7.37 (d, J = 9.2 Hz, 1H), 5.18 (s, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 2.50 (s, 3H), 0.88 (s, 9H).

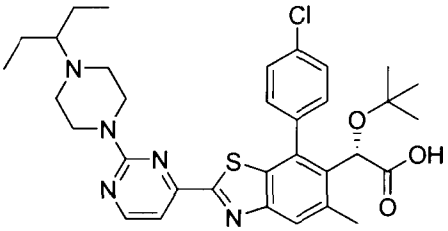
Cmpd #	Compound Structure	Method	Parent MW	LCMS -ESI+	1H NMR
462		Y	610.12	610.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (d, J = 5.6 Hz, 1H), 8.34 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 5.2 Hz, 1H), 7.72 (s, 1H), 7.64 – 7.56 (m, 3H), 7.51 (d, J = 7.6 Hz, 1H), 7.45 – 7.39 (m, 4H), 6.61 (d, J = 7.2 Hz, 1H), 5.15 (s, 1H), 2.48 (s, 3H), 0.86 (s, 9H).
463		V	613.13	613.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (d, J = 5.2 Hz, 1H), 8.50 (d, J = 0.8 Hz, 1H), 8.04 (dd, J = 5.6, 1.6 Hz, 1H), 7.96 (s, 1H), 7.78 (dd, J = 8.4, 1.6 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.65 – 7.60 (m, 3H), 7.27 (d, J = 8.4 Hz, 1H), 5.28 (s, 1H), 3.43 (s, 3H), 2.64 (s, 3H), 0.98 (s, 9H).

Example 180. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(pentan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid (464).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(pentan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(pentan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

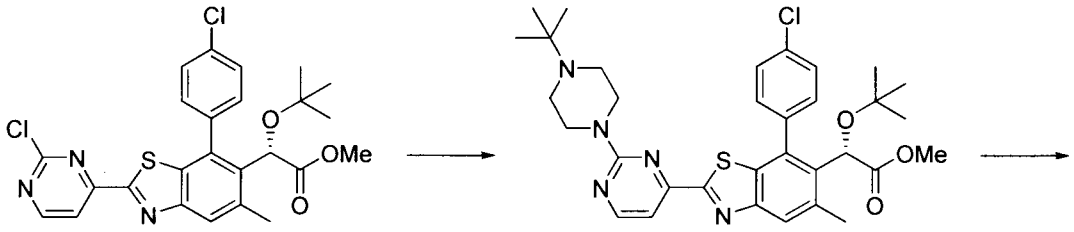
464

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(pentan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate: To (S)-methyl 2-tert-butoxy-2-

(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (40.0 mg, 0.077 mmol) was added 1-(3-propyl)-piperazine (60.5 mg, 0.387 mmol) in 1,4-dioxane (1 mL). The reaction mixture was stirred at room temperature for 20 min, then 40 °C for 1 h. Upon completion of the reaction, the reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{34}H_{43}ClN_5O_3S$ (M + H^+): 636.3; Found: 636.2 (M+H^+).

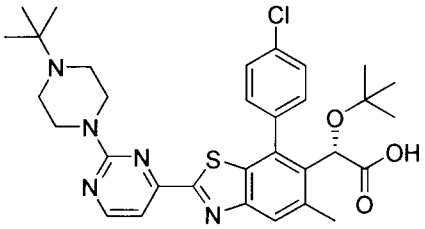
Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(pentan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid: To crude (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(pentan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate in THF (0.4 mL) and methanol (0.4 mL) was added NaOH (0.39 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{33}H_{41}ClN_5O_3S$ (M + H^+): 622.3; Found: 622.3 (M+H^+). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.62 (d, J = 5.0 Hz, 1H), 7.92 (s, 1H), 7.71 – 7.63 (m, 1H), 7.63 – 7.52 (m, 4H), 5.25 (s, 1H), 5.08 – 4.92 (m, 2H), 3.60 (s, 2H), 3.40 – 3.33 (m, 1H), 3.28 – 3.08 (m, 4H), 2.63 (s, 3H), 1.97 – 1.84 (m, 2H), 1.84 – 1.69 (m, 2H), 1.08 (t, J = 7.5 Hz, 6H), 0.98 (s, 9H).

Example 181. Preparation of (S)-2-tert-butoxy-2-(2-(2-(4-tert-butylpiperazin-1-yl)pyrimidin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (465).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-methyl 2-*tert*-butoxy-2-(2-(2-(4-*tert*-butylpiperazin-1-yl)pyrimidin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(2-(2-(4-*tert*-butylpiperazin-1-yl)pyrimidin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

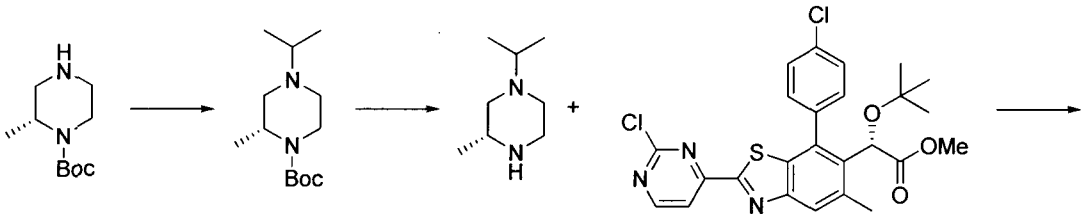
465

Preparation of (S)-methyl 2-tert-butoxy-2-(2-(2-(4-tert-butylpiperazin-1-yl)pyrimidin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate: A flask was charged with (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (40.0 mg, 0.077 mmol) and 1-*tert*-butylpiperazine (33.1 mg, 0.232 mmol). 1,4-Dioxane (1 mL) was added, and the reaction mixture was stirred at room temperature for 3 h. Upon completion of the reaction, the reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{33}H_{41}ClN_5O_3S$ (M + H^+): 622.3; Found: 622.2 (M+H^+).

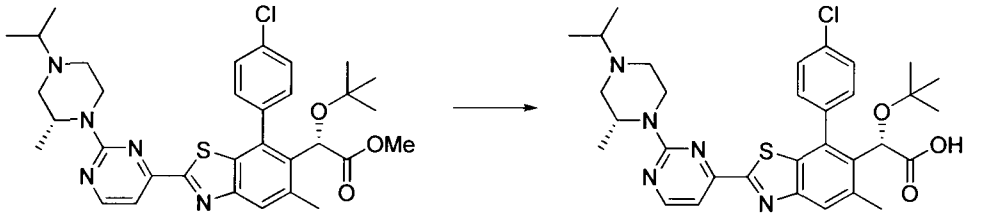
Preparation of (S)-2-tert-butoxy-2-(2-(2-(4-tert-butylpiperazin-1-yl)pyrimidin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: : To crude (S)-methyl 2-tert-butoxy-2-(2-(2-(4-tert-butylpiperazin-1-yl)pyrimidin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.4 mL) and methanol (0.4 mL) was added NaOH (0.39 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{39}ClN_5O_3S$ (M + H^+): 608.2; Found: 608.2 (M+H^+). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.62 (d, J = 5.0 Hz, 1H), 7.92 (s, 1H), 7.73 – 7.49 (m, 5H), 5.25 (s, 1H), 5.04 (d, J = 14.0 Hz, 2H), 3.72 (d, J = 10.8 Hz, 2H), 3.26 (d, J = 13.8 Hz, 2H), 3.21 – 3.08 (m,

2H), 2.63 (s, 3H), 1.45 (s, 9H), 0.98 (s, 9H).

Example 182. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (466).



(R)-1-Boc-2-methylpiperazine | (R)-1-Boc-2-methyl-4-isopropylpiperazine | (*R*)-1-isopropyl-3-methylpiperazine | (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*R*)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate | (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*R*)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

466

Preparation of (R)-1-Boc-2-methyl-4-isopropylpiperazine: To (R)-1-Boc-2-methylpiperazine (200.0 mg, 0.999 mmol) and sodium triacetoxyborohydride (444.5 mg, 2.097 mmol) in DMF (5 mL) was added acetone (116 mg, 0.147 mL, 1.997 mmol) and acetic acid (90.0 mg, 86 µL, 1.498 mmol). The reaction mixture was heated at 60 °C for 1 h. The reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organics were dried over sodium sulfate, filtered, concentrated, and used without further purification. LCMS-ESI$^+$: calc'd for $C_{13}H_{27}N_2O_2$ (M + H$^+$): 243.2; Found: 243.1 (M+H$^+$).

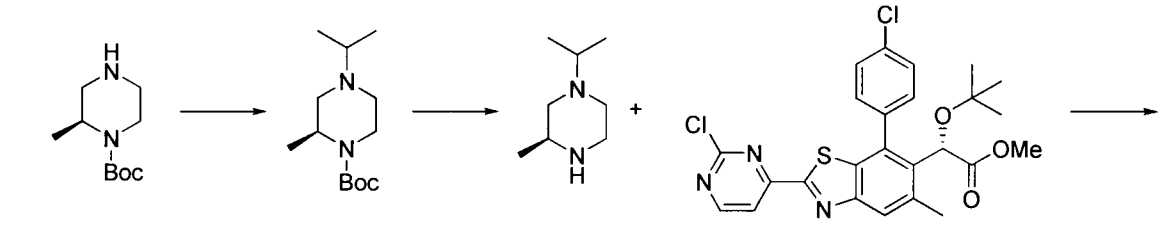
Preparation of (R)-1-isopropyl-3-methylpiperazine: To crude (R)-1-Boc-2-methyl-4-isopropylpiperazine in 1,4-dioxane (10 mL) was added HCl (5 mL of a 4M solution in 1,4-dioxane). The reaction mixture was stirred at room temperature for 28 h then concentrated. The resulting solid was suspended in diethyl ether, concentrated and dried on high vacuum for 1 d. The resulting solid was taken up in aq. 2N NaOH and the solution extracted three times with DCM. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to provide the free base of the product which was used without further purification. LCMS-

ESI$^+$: calc'd for $C_8H_{18}N_2$ (M + H$^+$): 143.1; Found: 143.7 (M+H$^+$).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (40.0 mg, 0.077 mmol) was added (R)-1-isopropyl-3-methylpiperazine (33.1 mg, 0.232 mmol) in 1,4-dioxane (1 mL) and triethylamine (15.7 mg, 22 μL, 0.155 mmol). The reaction mixture was stirred at 60 °C for 4 d, after which the reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{33}H_{41}ClN_5O_3S$ (M + H$^+$): 622.3; Found: 622.2 (M+H$^+$).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To crude (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.4 mL) and methanol (0.4 mL) was added NaOH (0.39 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{39}ClN_5O_3S$ (M + H$^+$): 608.2; Found: 608.3 (M+H$^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.63 (d, J = 4.9 Hz, 1H), 7.92 (s, 1H), 7.71 – 7.64 (m, 1H), 7.63 – 7.53 (m, 4H), 5.31 (br s, 1H), 5.25 (s, 1H), 4.95 (d, J = 15.0 Hz, 1H), 3.63 – 3.46 (m, 3H), 3.45 – 3.34 (m, 1H), 3.28 – 3.11 (m, 2H), 2.63 (s, 3H), 1.45 – 1.32 (m, 9H), 0.98 (s, 9H).

Example 183. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (467).

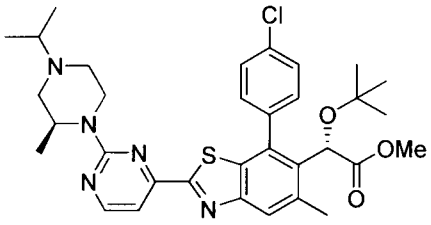


(S)-1-Boc-2-methylpiperazine

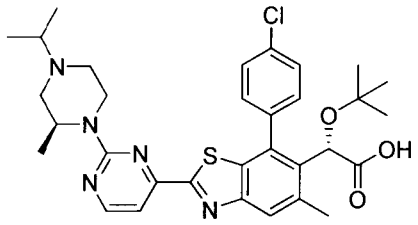
(S)-1-Boc-2-methyl-4-isopropylpiperazine

(S)-1-isopropyl-3-methylpiperazine

(S)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(S)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(S)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

467

Preparation of (S)-1-Boc-2-methyl-4-isopropylpiperazine: To (R)-1-Boc-2-methylpiperazine (200.0 mg, 0.999 mmol) and sodium triacetoxyborohydride (444.5 mg, 2.097 mmol) in DMF (5 mL) was added acetone (116 mg, 0.147 mL, 1.997 mmol) and acetic acid (90.0 mg, 86 μL, 1.498 mmol). The reaction mixture was heated at 60 °C for 1 h. The reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organics were dried over sodium sulfate, filtered, concentrated, and used without further purification. LCMS-ESI$^+$: calc'd for $C_{13}H_{27}N_2O_2$ ($M + H^+$): 243.2; Found: 243.2 ($M+H^+$).

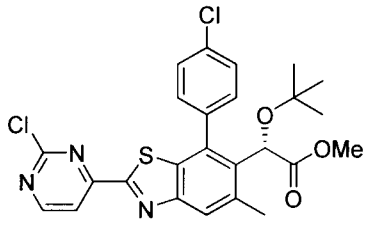
Preparation of (S)-1-isopropyl-3-methylpiperazine: To crude (S)-1-Boc-2-methyl-4-isopropylpiperazine in 1,4-dioxane (10 mL) was added HCl (5 mL of a 4M solution in 1,4-dioxane). The reaction mixture was stirred at room temperature for 28 h then concentrated. The resulting solid was suspended in diethyl ether, concentrated and dried on high vacuum for 1 d. The resulting solid was taken up in aq. 2N NaOH and the solution extracted three times with DCM. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to provide the free base of the product which was used without further purification. LCMS-ESI$^+$: calc'd for $C_8H_{18}N_2$ ($M + H^+$): 143.1; Found: 143.7 ($M+H^+$).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To (S)-methyl 2-

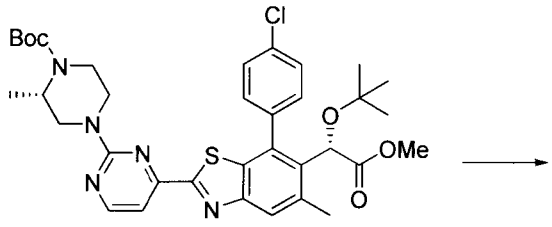
tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (40.0 mg, 0.077 mmol) was added (S)-1-isopropyl-3-methylpiperazine (33.1 mg, 0.232 mmol) in 1,4-dioxane (1 mL) and triethylamine (15.7 mg, 22 μL, 0.155 mmol). The reaction mixture was stirred at 60 °C for 4 d, after which the reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{33}H_{41}ClN_5O_3S$ (M + H^+): 622.3; Found: 622.2 (M+H^+).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To crude (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-4-isopropyl-2-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.4 mL) and methanol (0.4 mL) was added NaOH (0.39 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{39}ClN_5O_3S$ (M + H^+): 608.2; Found: 608.3 (M+H^+). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.63 (d, J = 5.0 Hz, 1H), 7.92 (s, 1H), 7.71 – 7.63 (m, 1H), 7.63 – 7.50 (m, 4H), 5.31 (br s, 1H), 5.25 (s, 1H), 4.95 (d, J = 14.6 Hz, 1H), 3.63 – 3.46 (m, 3H), 3.45 – 3.34 (m, 1H), 3.29 – 3.11 (m, 2H), 2.63 (s, 3H), 1.46 – 1.37 (m, 9H), 0.98 (s, 9H).

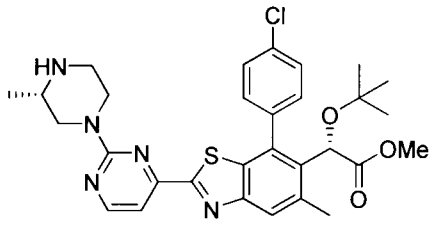
Example 184. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (468).



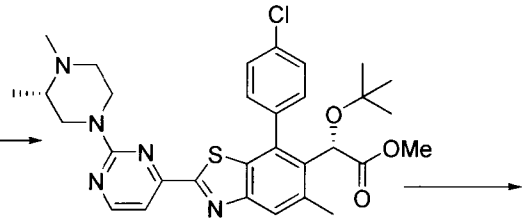
(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



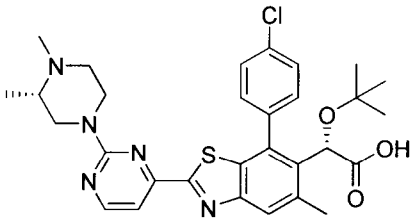
(*S*)-*tert*-butyl 4-(4-(6-((*S*)-1-*tert*-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((*S*)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*S*)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*S*)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

468

Preparation of (S)-tert-butyl 4-(4-(6-((S)-1-tert-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (80.0 mg, 0.155 mmol) and (S)-1-boc-2-methylpiperazine (93.1 mg, 0.465 mmol) in 1,4-dioxane (2 mL) was added triethylamine (156.8 mg, 0.19 mL, 1.549 mmol). The reaction mixture was stirred at 40 °C for 4 h, at room temperature overnight, then at 40 °C for an additional 7 h. The reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{35}H_{43}ClN_5O_5S$ (M + H^+): 680.3; Found: 680.0 (M+H^+).

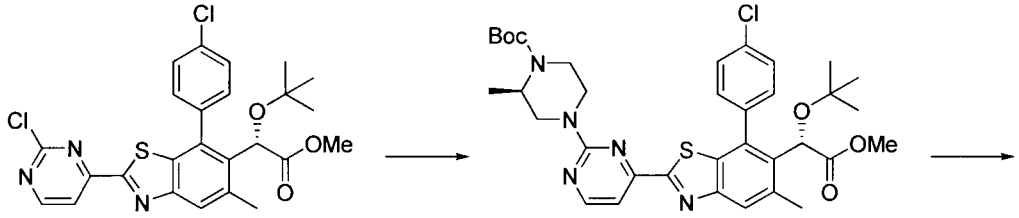
Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((S)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate: To crude (S)-tert-butyl 4-(4-

(6-((S)-1-tert-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate in 1,4-dioxane (1.25 mL) was added HCl (0.78 mL of a 4M solution in 1,4-dioxane). The reaction mixture was stirred at room temperature for 2.5 h then concentrated. The resulting solid was suspended in diethyl ether, concentrated and dried under high vacuum overnight. The resulting solid was taken up in water, basified with 2N NaOH, and extracted three times with DCM. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{30}H_{35}ClN_5O_3S$ (M + H^+): 580.2; Found: 580.2 (M+H^+).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To crude (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((S)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate (43.8 mg, 0.075 mmol) and sodium triacetoxyborohydride (80.1 mg, 0.377 mmol) in DMF (1 mL) was added acetic acid (22.7 mg, 21.6 μL, 0.377 mmol). The reaction mixture was heated to 60 °C, then 37% w/w aq. formaldehyde (9.1 mg, 21.6 μL, 0.302 mmol) was added dropwise over 1 min. The reaction mixture was heated at 60 °C for 2 h. Upon completion of the reaction, the reaction mixture was filtered through Celite (ethyl acetate eluent) and concentrated. Purification by flash column chromatography on silica gel using 100:5:1 EtOAc/MeOH/NH_4OH (0 to 100%) in EtOAc provided the product. LCMS-ESI$^+$ calc'd for $C_{31}H_{37}ClN_5O_3S$ (M + H^+): 594.2; Found: 593.6 (M+H^+).

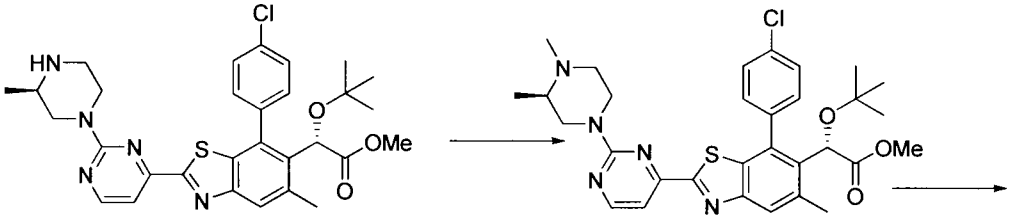
Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.3 mL) and methanol (0.3 mL) was added NaOH (0.30 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{30}H_{35}ClN_5O_3S$ (M + H^+): 580.2; Found: 580.1 (M+H^+). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.62 (d, J = 4.9 Hz, 1H), 7.92 (s, 1H), 7.72 – 7.64 (m, 1H), 7.65 – 7.58 (m, 3H), 7.58 – 7.53 (m, 1H), 5.25 (s, 1H), 5.01 – 4.73 (m, 2H), 3.61 (br s, 1H), 3.46 – 3.02 (m, 4H), 2.96 (s, 3H), 2.63 (s, 3H), 1.44 (br s, 3H), 0.97 (s, 9H).

Example 185. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (469).



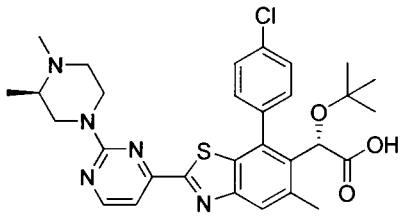
(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*R*)-*tert*-butyl 4-(4-(6-((*S*)-1-*tert*-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((*R*)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*R*)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*R*)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

469

Preparation of (R)-tert-butyl 4-(4-(6-((S)-1-tert-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (80.0 mg, 0.155 mmol) and (R)-1-boc-2-methylpiperazine (93.1 mg, 0.465 mmol) in 1,4-dioxane (2 mL) was added triethylamine (156.8 mg, 0.19 mL, 1.549 mmol). The reaction mixture was stirred at 40 °C for 4 h, at room temperature overnight, then at 40 °C for an additional 7 h. The reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{35}H_{43}ClN_5O_5S$ (M + H^+): 680.3; Found: 680.0 (M+H^+).

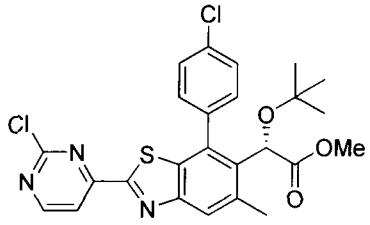
Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((R)-3-

methylpiperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate: To crude (R)-tert-butyl 4-(4-(6-((S)-1-tert-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate in 1,4-dioxane (1.25 mL) was added HCl (0.78 mL of a 4M solution in 1,4-dioxane). The reaction mixture was stirred at room temperature for 2.5 h then concentrated. The resulting solid was suspended in diethyl ether, concentrated and dried under high vacuum overnight. The resulting solid was taken up in water, basified with 2N NaOH, and extracted three times with DCM. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{30}H_{35}ClN_5O_3S$ (M + H^+): 580.2; Found: 580.2 (M+H^+).

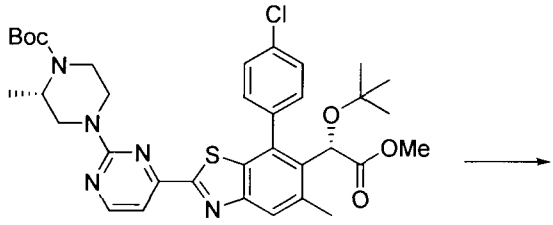
Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To crude (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((R)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate (45.8 mg, 0.079 mmol) and sodium triacetoxyborohydride (83.7 mg, 0.395 mmol) in DMF (1 mL) was added acetic acid (23.7 mg, 22.6 µL, 0.395 mmol). The reaction mixture was heated to 60 °C, then 37% w/w aq. formaldehyde (9.48 mg, 23.5 µL, 0.316 mmol) was added dropwise over 1 min. The reaction mixture was heated at 60 °C for 2 h. Upon completion of the reaction, the reaction mixture was filtered through Celite (ethyl acetate eluent) and concentrated. Purification by flash column chromatography on silica gel using 100:5:1 EtOAc/MeOH/NH_4OH (0 to 100%) in EtOAc provided the product. LCMS-ESI$^+$ calc'd for $C_{31}H_{37}ClN_5O_3S$ (M + H^+): 594.2; Found: 593.7 (M+H^+).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-3,4-dimethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.3 mL) and methanol (0.3 mL) was added NaOH (0.30 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{30}H_{35}ClN_5O_3S$ (M + H^+): 580.2; Found: 580.1 (M+H^+). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.62 (d, J = 4.8 Hz, 1H), 7.92 (s, 1H), 7.71 – 7.65 (m, 1H), 7.65 – 7.58 (m, 3H), 7.58 – 7.53 (m, 1H), 5.25 (s, 1H), 5.07 – 4.70(m, 2H), 3.61 (d, J = 13.4 Hz, 1H), 3.37 – 3.03 (m, 4H), 2.96 (s, 3H), 2.63 (s, 3H), 1.53 – 1.37 (m, 3H), 0.97 (s, 9H).

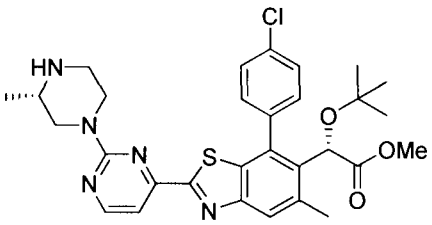
Example 186. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (470).



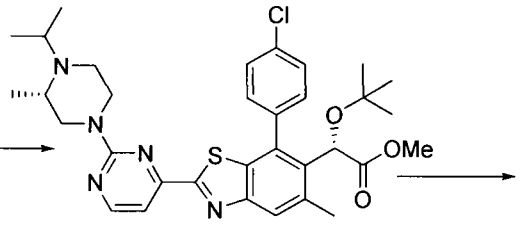
(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



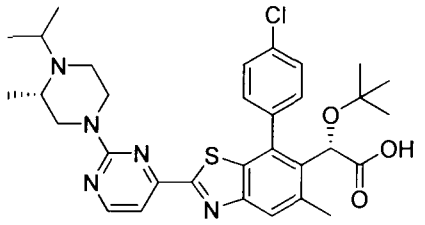
(*S*)-*tert*-butyl 4-(4-(6-((*S*)-1-*tert*-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((*S*)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*S*)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*S*)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

470

Preparation of (S)-tert-butyl 4-(4-(6-((S)-1-tert-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (80.0 mg, 0.155 mmol) and (S)-1-boc-2-methylpiperazine (93.1 mg, 0.465 mmol) in 1,4-dioxane (2 mL) was added triethylamine (156.8 mg, 0.19 mL, 1.549 mmol). The reaction mixture was stirred at 40 °C for 4 h, at room temperature overnight, then at 40 °C for an additional 7 h. The reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{35}H_{43}ClN_5O_5S$ (M + H^+): 680.3; Found: 680.0 (M+H^+).

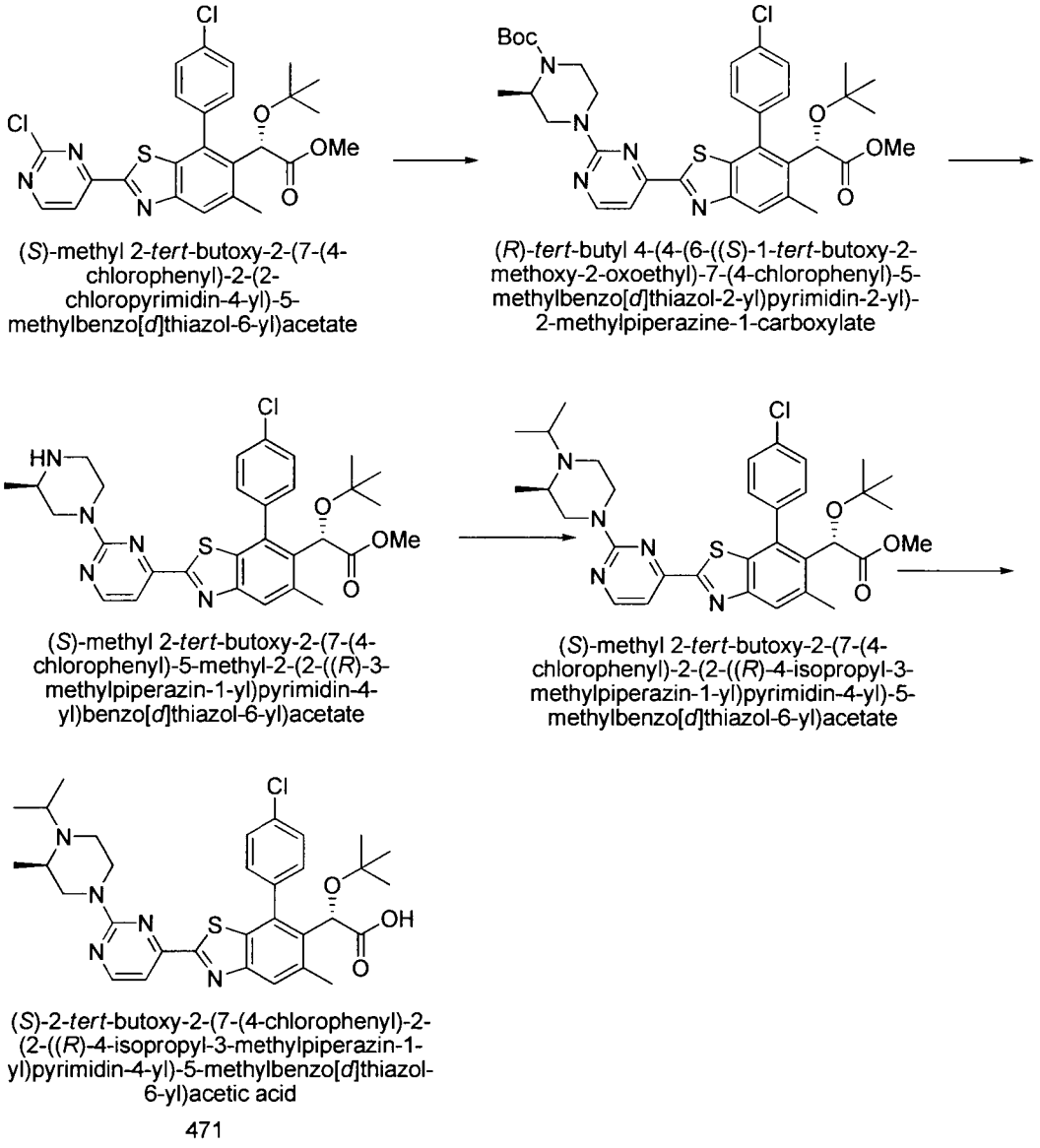
Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((S)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate: To crude (S)-tert-butyl 4-(4-(6-((S)-1-tert-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate in 1,4-dioxane (1.25 mL) was added HCl (0.78 mL of a 4M solution in 1,4-dioxane). The reaction mixture was stirred at room temperature for 2.5 h then concentrated. The resulting solid was suspended in diethyl ether, concentrated and dried under high vacuum overnight. The resulting solid was taken up in water, basified with 2N NaOH, and extracted three times with DCM. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{30}H_{35}ClN_5O_3S$ (M + H$^+$): 580.2; Found: 580.2 (M+H$^+$).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To crude (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((S)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate (43.8 mg, 0.075 mmol) and sodium triacetoxyborohydride (80.1 mg, 0.377 mmol) in DMF (1 mL) was added acetic acid (22.7 mg, 21.6 µL, 0.377 mmol) and acetone (17.6 mg, 22.2 µL, 0.302 mmol). The reaction mixture was heated at 60 °C for 6.5 h. Upon completion of the reaction, the reaction mixture was filtered through Celite (ethyl acetate eluent) and concentrated. Purification by flash column chromatography on silica gel using 100:5:1 EtOAc/MeOH/NH_4OH (0 to 100%) in EtOAc provided the product. LCMS-ESI$^+$ calc'd for $C_{33}H_{41}ClN_5O_3S$ (M + H$^+$): 622.3; Found: 622.2 (M+H$^+$).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.3 mL) and methanol (0.3 mL) was added NaOH (0.35 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{39}ClN_5O_3S$ (M + H$^+$): 608.2; Found: 608.2 (M+H$^+$). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.62 (d, J = 5.3 Hz, 1H), 7.92 (s, 1H), 7.70 – 7.65 (m, 1H), 7.64 – 7.58 (m, 3H), 7.58 – 7.53 (m, 1H), 5.25 (s, 1H), 5.03 – 4.75 (m, 2H), 4.11 – 3.93

(m, 1H), 3.70 – 3.05 (m, 5H), 2.63 (s, 3H), 1.48 – 1.39 (m, 6H), 1.34 – 1.23 (m, 3H), 0.98 (s, 9H).

Example 187. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (471).



Preparation of (R)-tert-butyl 4-(4-(6-((S)-1-tert-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (80.0 mg, 0.155 mmol) and (R)-1-boc-2-methylpiperazine (93.1 mg, 0.465 mmol) in 1,4-dioxane (2 mL) was added triethylamine (156.8 mg, 0.19 mL, 1.549 mmol). The reaction mixture was stirred at 40 °C for 4 h, at room temperature overnight, then at 40 °C for an additional 7 h. The reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for

$C_{35}H_{43}ClN_5O_5S$ (M + H^+): 680.3; Found: 680.0 (M+H^+).

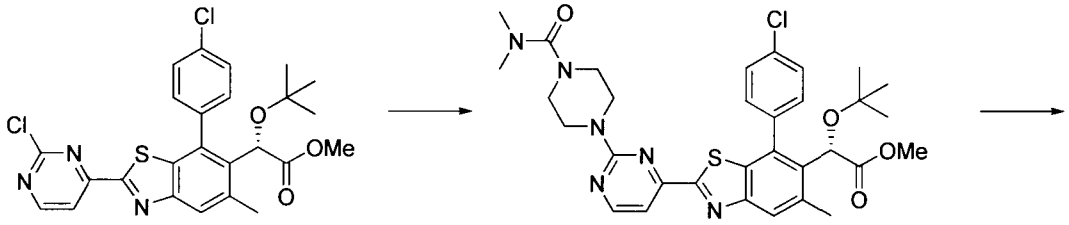
Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((R)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate: To crude (R)-tert-butyl 4-(4-(6-((S)-1-tert-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)pyrimidin-2-yl)-2-methylpiperazine-1-carboxylate in 1,4-dioxane (1.25 mL) was added HCl (0.78 mL of a 4M solution in 1,4-dioxane). The reaction mixture was stirred at room temperature for 2.5 h then concentrated. The resulting solid was suspended in diethyl ether, concentrated and dried under high vacuum overnight. The resulting solid was taken up in water, basified with 2N NaOH, and extracted three times with DCM. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{30}H_{35}ClN_5O_3S$ (M + H^+): 580.2; Found: 580.2 (M+H^+).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To crude (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-((R)-3-methylpiperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate (45.8 mg, 0.079 mmol) and sodium triacetoxyborohydride (83.7 mg, 0.395 mmol) in DMF (1 mL) was added acetic acid (23.7 mg, 22.6 μL, 0.395 mmol) and acetone (18.3 mg, 23.2 μL, 0.316 mmol). The reaction mixture was heated at 60 °C for 6.5 h. Upon completion of the reaction, the reaction mixture was filtered through Celite (ethyl acetate eluent) and concentrated. Purification by flash column chromatography on silica gel using 100:5:1 EtOAc/MeOH/NH_4OH (0 to 100%) in EtOAc provided the product. LCMS-ESI$^+$ calc'd for $C_{33}H_{41}ClN_5O_3S$ (M + H^+): 622.3; Found: 622.2 (M+H^+).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((R)-4-isopropyl-3-methylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.33 mL) and methanol (0.33 mL) was added NaOH (0.33 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{39}ClN_5O_3S$ (M + H^+): 608.2; Found: 608.2 (M+H^+). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.62 (d, J = 4.9 Hz, 1H), 7.92 (s, 1H), 7.70 – 7.65

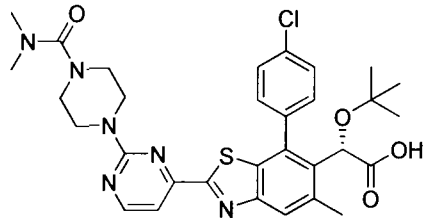
(m, 1H), 7.64 – 7.57 (m, 3H), 7.57 – 7.53 (m, 1H), 5.25 (s, 1H), 5.04 – 4.76 (m, 2H), 4.09 – 3.97 (m, 1H), 3.69 – 3.04 (m, 5H). 2.63 (s, 3H), 1.48 – 1.39 (m, 6H), 1.34 – 1.23 (m, 3H), 0.98 (s, 9H

Example 188. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-(dimethylcarbamoyl)piperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (472).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-(dimethylcarbamoyl)piperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-(dimethylcarbamoyl)piperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

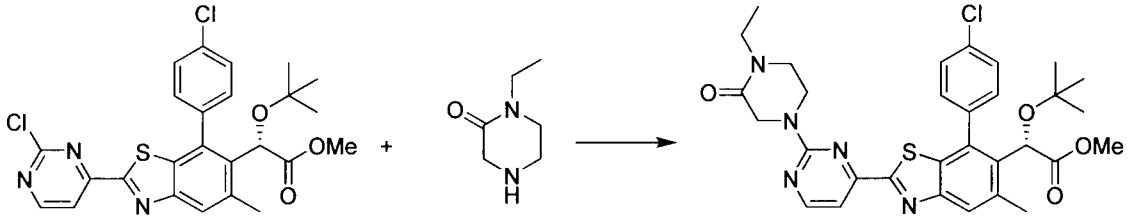
472

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-(dimethylcarbamoyl)piperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (30.0 mg, 0.058 mmol) was added piperazine-1-carboxylic acid dimethylamide (36.6 mg, 0.232 mmol) in 1,4-dioxane (1 mL). The reaction mixture was stirred at 40 °C for 4 h, then at room temperature overnight. The reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{32}H_{38}ClN_6O_4S$ (M + H^+): 637.2; Found: 637.2 (M+H^+).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-(dimethylcarbamoyl)piperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To crude (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-(dimethylcarbamoyl)piperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.3 mL) and methanol (0.3 mL) was added NaOH (0.29 mL of a 2N solution). The reaction mixture was heated at 40 °C for

4 h, then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{31}H_{36}ClN_6O_4S$ (M + H$^+$): 623.2; Found: 623.2 (M+H$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (br s, 1H), 8.60 (d, J = 4.9 Hz, 1H), 7.98 (s, 1H), 7.75 – 7.65 (m, 2H), 7.65 – 7.54 (m, 2H), 7.43 (d, J = 4.8 Hz, 1H), 5.07 (s, 1H), 3.81 – 3.69 (m, 4H), 3.22 – 3.13 (m, 4H), 2.77 (s, 6H), 2.55 (s, 3H), 0.88 (s, 9H).

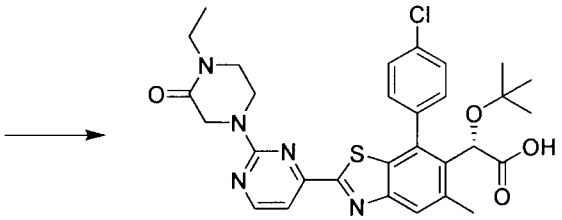
Example 189. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethyl-3-oxopiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid (473).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

1-ethylpiperazin-2-one

(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethyl-3-oxopiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



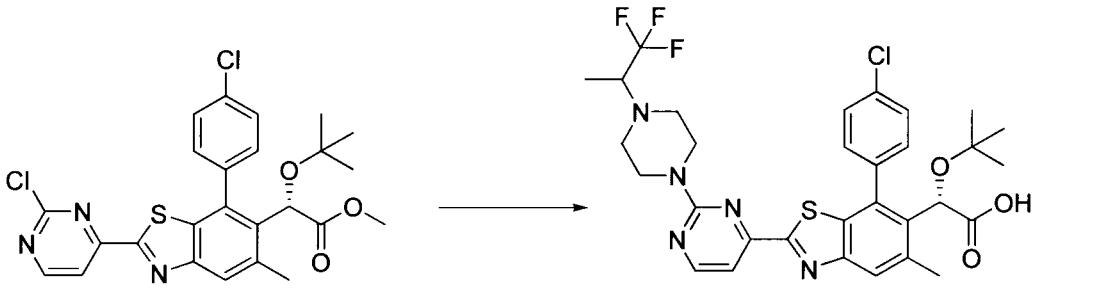
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethyl-3-oxopiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

473

Preparation of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethyl-3-oxopiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (15.0 mg, 0.029 mmol) in DMF (0.4 mL) was added 1-ethylpiperazin-2-one (7.4 mg, 0.058 mmol). The reaction mixture was heated at 100 °C overnight. Reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (silica gel, 0 to 100% ethyl acetate/hexanes) to give the product. LCMS-ESI$^+$: calc'd for $C_{31}H_{35}ClN_5O_4S$: 608.2 (M+H$^+$); found: 608.2 (M+H$^+$).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethyl-3-oxopiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid: To a solution of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethyl-3-oxopiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (4.1 mg, 0.007 mmol) in pyridine (0.4 mL) was added LiI (50 mg, excess). The reaction mixture was heated in a microwave at 170 °C for 90 min. The mixture was concentrated *in vacuo* and then purified by reverse phase HPLC, eluting by 0-100% acetonitrile in H_2O with 0.1% TFA to give the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (d, J = 5.0 Hz, 1H), 7.89 (s, 1H), 7.74 – 7.48 (m, 5H), 5.25 (s, 1H), 4.35 (s, 2H), 4.07 (t, J = 5.4 Hz, 2H), 3.55 – 3.43 (m, 4H), 2.62 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H), 0.97 (s, 9H); LCMS-ESI$^+$: calc'd for $C_{30}H_{33}ClN_5O_4S$: 594.2 ($M+H^+$); Found: 594.2($M+H^+$).

Example 190. Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid (474).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

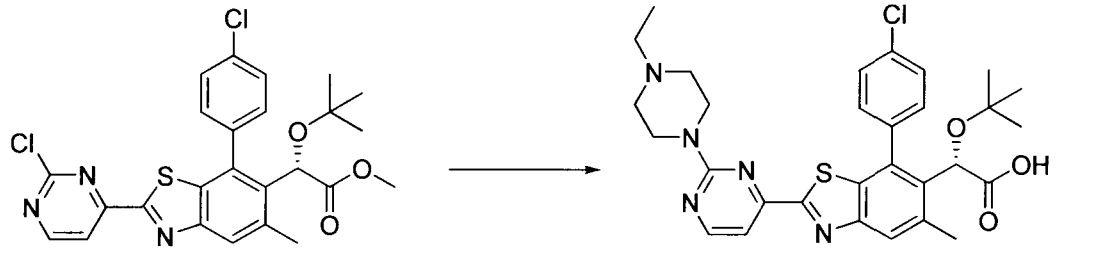
(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazin-1-yl)pyrimidin-4-yl) benzo[*d*]thiazol-6-yl)acetic acid

474

Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid: A vial was charged with a solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (10 mg), dioxane (500 μL), H_2O (200 μL), Et_3N (50 μL), and 1-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazine (30 mg). The reaction was heated to 60 °C for 1 h. Ethanol (absolute, 500 μL) and 5 M aq NaOH (500 μL) were added and the reaction was heated to 60 °C for 30 min. The reaction was cooled to 23 °C and directly purified by reverse phase HPLC (5-100% ACN/H_2O + 0.1% TFA) giving the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, J = 5.0 Hz, 1H), 7.89 (s, 1H), 7.70-7.51 (m, 5H), 7.43 (d, J = 4.9 Hz, 1H), 5.25 (s, 1H), 3.92 – 3.71 (m, 4H), 2.94 – 2.70 (m, 4H), 2.62 (s, 3H), 1.27 (d, J = 7.1 Hz, 3H), 0.97 (s, 9H).). LCMS-ESI$^+$: calc'd for $C_{31}H_{34}ClF_3N_5O_3S$

[M+H$^+$]: 648.2, 650.2; Found: 648.2, 650.2 (M+H$^+$).

Example 191. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (475).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

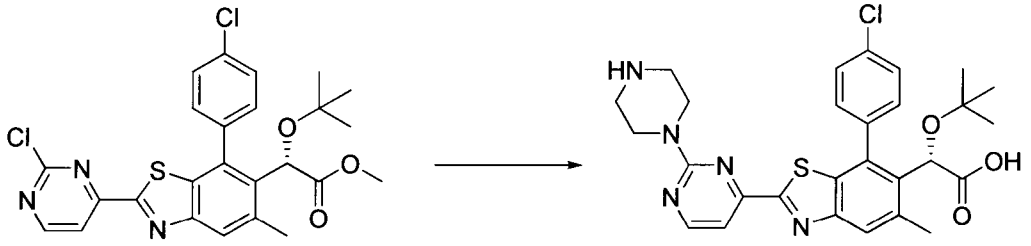
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

475

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-ethylpiperazin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A vial was charged with solid $LiAlH_4$ (100 mg). A solution of N-Acetylpiperazine (120 mg) in anhydrous Et_2O (4.0 mL) was added dropwise over 2 min at 23 °C. The vessel was placed under N_2 and stirred for 30 min. Water (100 μL) was added and the mixture was stirred for 3 min. 10 M aq NaOH (50 μL) was added and the mixture was stirred for 5 min. Finally, H_2O (300 μL) was added, the mixture was stirred for 15 min, and filtered. The filtrate was concentrated and vacuum dried (briefly, because product is volatile) giving N-ethylpiperazine, which was immediately used in the next reaction.

(S)-Methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (10 mg), dioxane (500 μL), and H_2O (200 μL) were added. The reaction was heated to 90 °C for 1 h. Ethanol (absolute, 500 μL) and 5 M aq NaOH (500 μL) were added and the reaction was heated to 90 °C for 30 min. The reaction was cooled to 23 °C and directly purified by reverse phase HPLC (5-100% ACN/H_2O + 0.1% TFA) giving the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (d, J = 5.0 Hz, 1H), 7.91 (s, 1H), 7.74 – 7.49 (m, 5H), 5.24 (s, 1H), 3.37 – 3.28 (m, 8H), 3.24 (q, J = 7.4 Hz, 2H), 2.62 (s, 3H), 1.38 (t, J = 7.3 Hz, 2H), 0.97 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{30}H_{35}ClN_5O_3S$ [M+H$^+$]: 580.2, 582.2 ; Found: 580.4, 582.2 (M+H$^+$).

Example 192. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid (476).



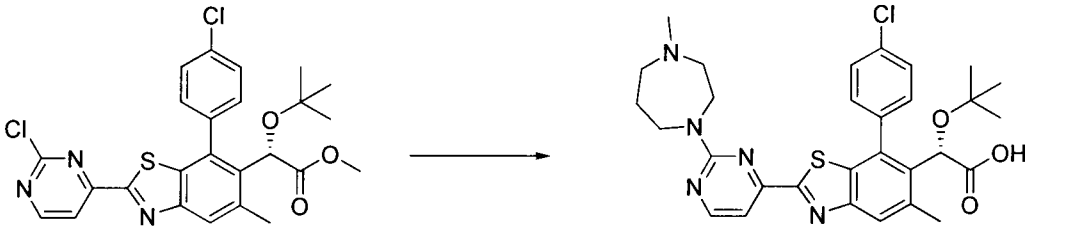
(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(piperazin-1-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

476

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid: A vial was charged with a solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (10 mg), dioxane (500 μL), H_2O (200 μL), Et_3N (50 μL), and piperazine (40 mg). The reaction was heated to 60 °C for 1 h. Ethanol (absolute, 500 μL) and 5 M aq NaOH (500 μL) were added. The reaction was heated to 60 °C for 30 min. The reaction was cooled to 23 °C and directly purified by reverse phase HPLC (5-100% ACN/H_2O + 0.1% TFA) giving the title compound. ^1H NMR (400 MHz, CD_3OD) δ 8.49 (d, J = 5.0 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.68 – 7.44 (m, 3H), 7.41 (d, J = 5.0 Hz, 1H), 5.08 (s, 1H), 3.92 – 3.69 (m, 4H), 2.85 (dd, J = 18.8, 13.9 Hz, 4H), 2.66 (s, 3H), 0.91 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{28}H_{31}ClN_5O_3S$ [M+H$^+$]: 552.2, 554.2; Found: 552.4, 552.2 (M+H$^+$).

Example 193. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid (477).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

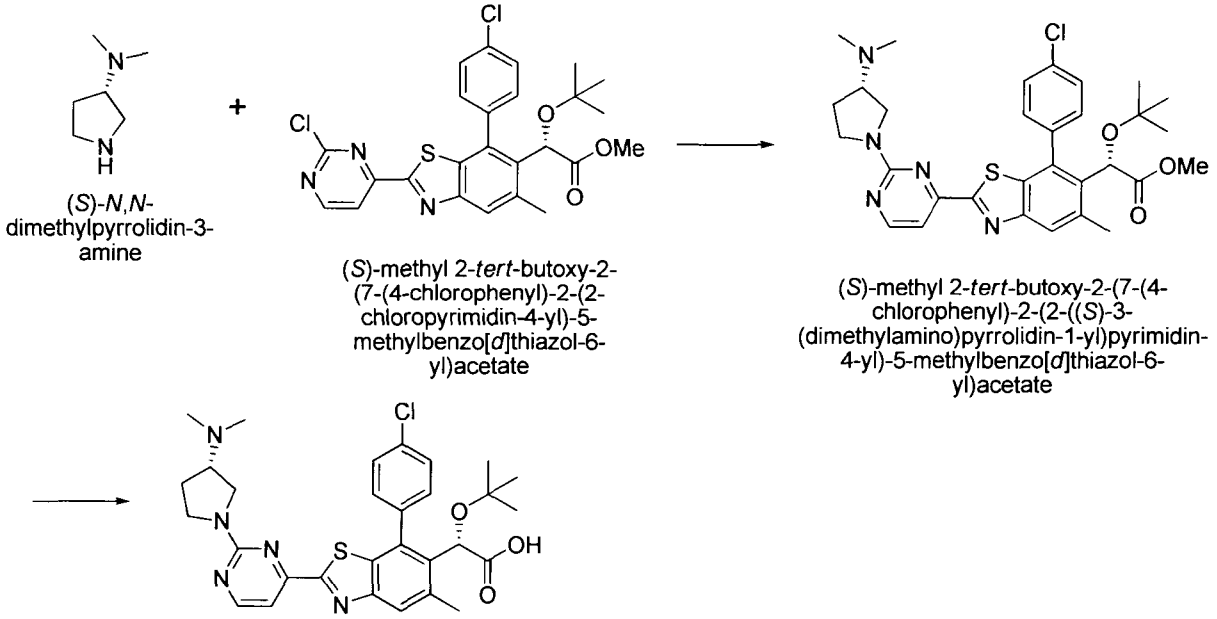
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

477

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid: A vial was charged with a solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (10 mg), dioxane (500 μL), H_2O (200 μL), Et_3N (50 μL),

and 1-methyl-1,4-diazepane (40 mg). The reaction was heated to 90 °C for 1 h. Ethanol (absolute, 500 μL) and 5 M aq NaOH (500 μL) were added. The reaction was heated to 90 °C for 30 min. The reaction was cooled to 23 °C and directly purified by reverse phase HPLC (5-100% ACN/H_2O + 0.1% TFA) giving the title compound. ^1H NMR (400 MHz, CD_3OD) δ 8.59 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.74 – 7.47 (m, 5H), 5.24 (s, 1H), 4.67 – 3.39 (m, 6H), 3.39-3.20 (m, 2H), 2.92 (s, 3H), 2.63 (s, 3H), 2.29-2.10 (m, 2H), 0.97 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{30}H_{35}ClN_5O_3S$ [M+H$^+$]: 580.2, 582.2; Found: 580.4, 582.2 (M+H$^+$).

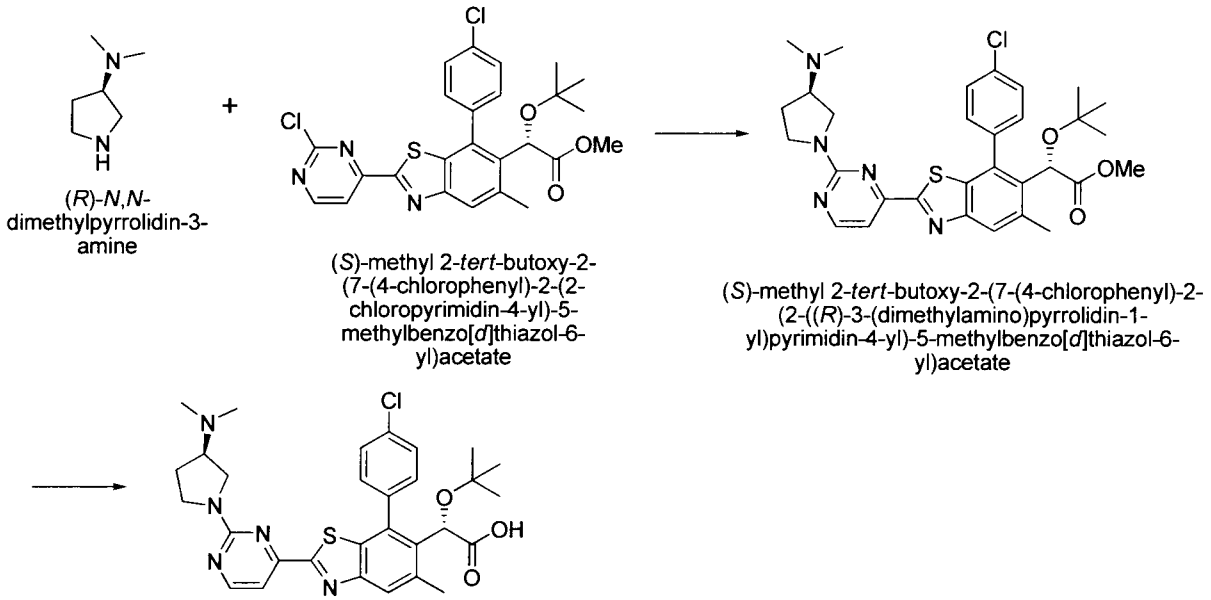
Example 194. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (478).



Preparation of (*S*)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (40 mg, 0.08 mmol) in dioxane (1 mL) was added (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine (89 mg, 0.78 mmol) at room temperature. The reaction mixture was allowed to stir for an additional 30 minutes and then concentrated *in vacuo* to provide the desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{37}ClN_5O_3S$: 594.2 (M+H$^+$); Found: 594.4 (M+H$^+$).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (*S*)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((S)-3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (46 mg, 0.08 mmol) in 1:5 THF/MeOH (1.2 mL) was added 2M aqueous NaOH (0.2 mL, 0.4 mmol) and stirred at 40 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 8.53 (d, J = 5.1 Hz, 1H), 7.90 (s, 1H), 7.67 (dd, J = 8.4, 2.0 Hz, 1H), 7.64 – 7.50 (m, 4H), 5.25 (s, 1H), 4.13 – 3.95 (m, 2H), 3.95 – 3.80 (m, 1H), 3.76 (dd, J = 11.4, 5.7 Hz, 1H), 3.60 (dt, J = 11.4, 7.9 Hz, 1H), 2.97 (s, 6H), 2.62 (s, 3H), 2.60 – 2.49 (m, 1H), 2.40 – 2.17 (m, 1H),z 0.97 (s, 9H); LCMS-ESI$^+$: calc'd for $C_{30}H_{35}ClN_5O_3S$: 580.2 ($M+H^+$); Found: 580.3 ($M+H^+$).

Example 195. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*R*)-3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (479).



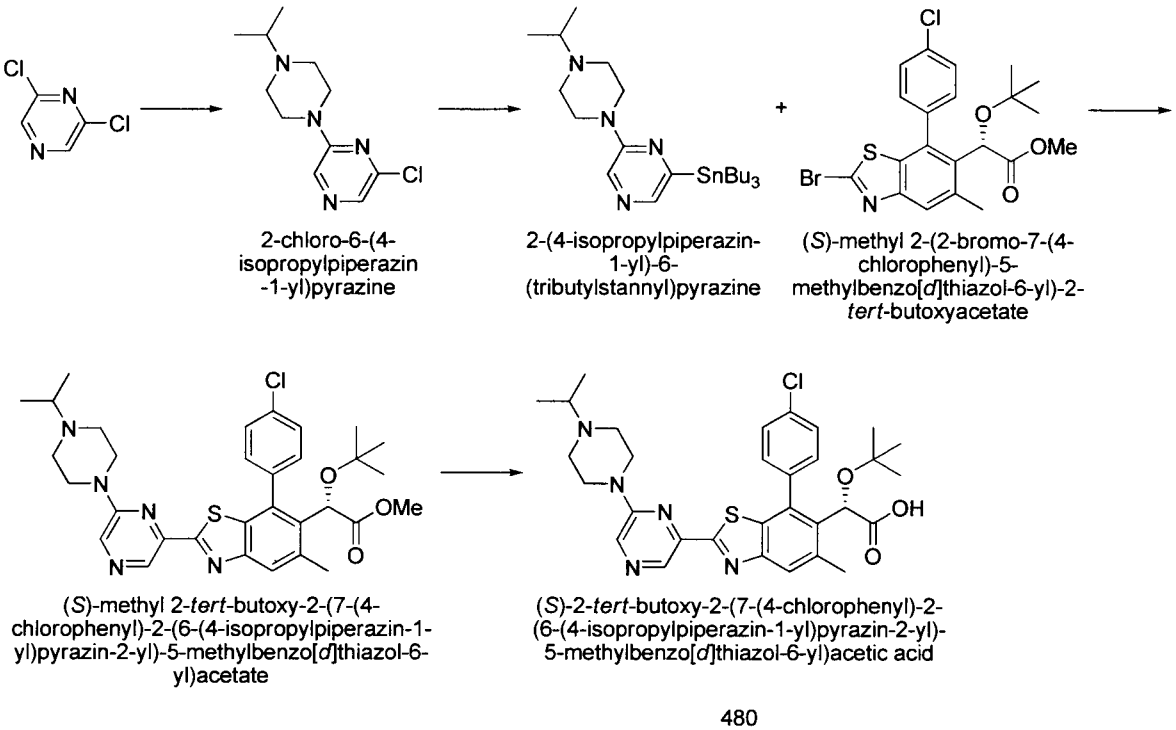
479

Preparation of (*S*)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*R*)-3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of (*S*)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-

methylbenzo[d]thiazol-6-yl)acetate (37 mg, 0.07 mmol) in dioxane (1 mL) was added (*R*)-*N*,*N*-dimethylpyrrolidin-3-amine (89 mg, 0.78 mmol) at room temperature. The reaction mixture was allowed to stir for an additional 30 minutes and then concentrated *in vacuo* to provide the desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{37}ClN_5O_3S$: 594.2 ($M+H^+$); Found: 594.4 ($M+H^+$).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*R*)-3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (*S*)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-((*R*)-3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (43 mg, 0.07 mmol) in 1:5 THF/MeOH (1.2 mL) was added 2M aqueous NaOH (0.2 mL, 0.4 mmol) and stirred at 40 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, *J* = 5.1 Hz, 1H), 7.89 (s, 1H), 7.67 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.64 – 7.47 (m, 4H), 5.25 (s, 1H), 4.12 – 3.97 (m, 2H), 3.97 – 3.80 (m, 1H), 3.75 (dd, *J* = 11.1, 5.5 Hz, 1H), 3.58 (dt, *J* = 11.4, 8.0 Hz, 1H), 2.97 (s, 6H), 2.62 (s, 3H), 2.59 – 2.46 (m, 1H), 2.36 – 2.21 (m, 1H), 0.97 (s, 9H).; LCMS-ESI$^+$: calc'd for $C_{30}H_{35}ClN_5O_3S$: 580.2 ($M+H^+$); Found: 580.3 ($M+H^+$).

Example 196. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(6-(4-isopropylpiperazin-1-yl)pyrazin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (480).



480

Preparation of 2-chloro-6-(4-isopropylpiperazin-1-yl)pyrazine: To 2,6-dichloropyrazine (250.0 mg, 1.678 mmol) in 1,4-dioxane (2 mL) was added 1-isopropylpiperazine (0.29 mL, 2.014 mmol) and triethylamine (0.70 mL, 5.034 mmol). The reaction mixture was stirred at room temperature for 1 day, filtered through Celite (1,4-dioxane eluent) then concentrated. Purification by flash column chromatography on silica gel using 100:5:1 EtOAc/MeOH/NH_4OH (0 to 100%) in EtOAc provided the product. LCMS-ESI$^+$ calc'd for $C_{11}H_{18}ClN_4$ (M + H^+): 241.1; Found: 241.2 (M+H^+).

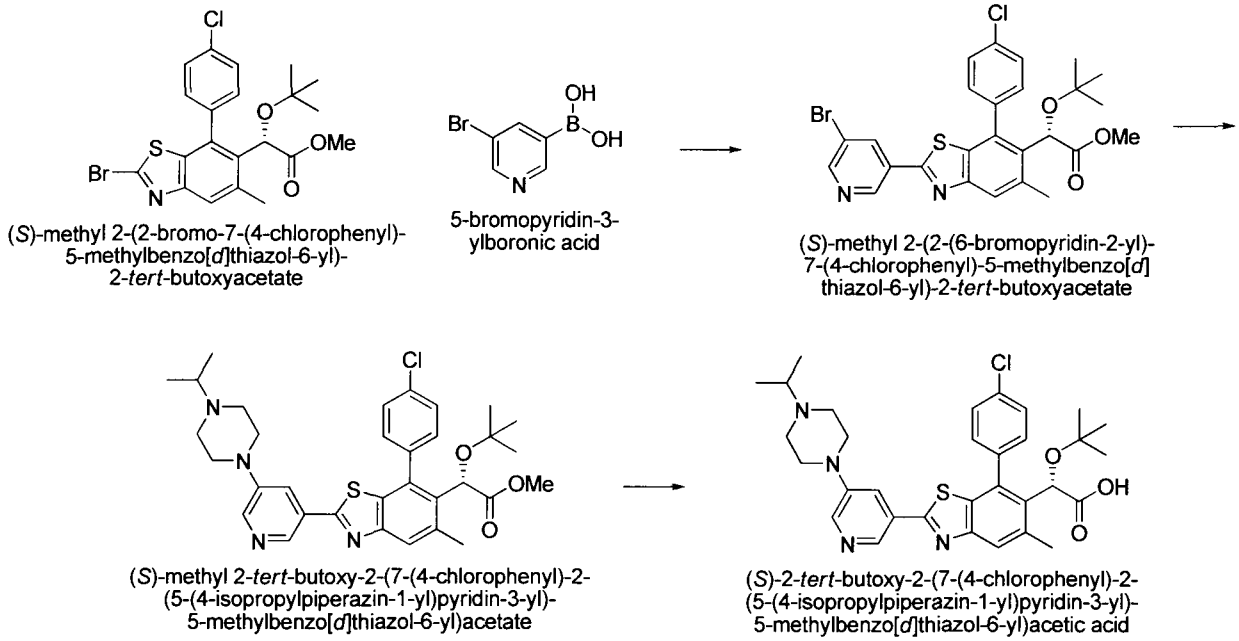
Preparation of 2-(4-isopropylpiperazin-1-yl)-6-(tributylstannyl)pyrazine: Tetrakis(triphenylphosphine)palladium(0) (120.0 mg, 0.104 mmol) and LiCl (132.1 mg, 3.115 mmol) were taken in a microwave vial and the vial vacuum pumped and flushed with argon three times. To this mixture was added 2-chloro-6-(4-isopropylpiperazin-1-yl)pyrazine (250.0 mg, 1.038 mmol) and hexabutylditin (903.7 mg, 0.79 mL, 1.558 mmol) in toluene (10 mL). The reaction mixture was heated at 140 °C for 1.5 h, filtered through Celite, and concentrated. Purification by flash column chromatography on silica gel using 79:20:1 DCM/MeOH/NH_3 (0 to 100%) in DCM provided the product. LCMS-ESI$^+$ calc'd for $C_{23}H_{44}N_4Sn$ (M + H^+): 497.3; Found: 496.6 (M+H^+).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(6-(4-isopropylpiperazin-1-yl)pyrazin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (60.0 mg, 0.124 mmol), tetrakis(triphenylphosphine)palladium(0) (21.5 mg, 0.019 mmol), lithium chloride (15.8 mg, 0.373 mmol), and copper(I) iodide (7.1 mg, 0.037 mmol) were taken in a microwave vial and the vial vacuum pumped and flushed with argon three times. To this mixture was added 2-(4-isopropylpiperazin-1-yl)-6-(tributylstannyl)pyrazine (73.9 mg, 0.149 mmol) in dioxane (1.5 mL), and the resulting mixture was stirred at 100 °C for 4.5 h. The reaction mixture was cooled, filtered through Celite (ethyl acetate eluent), and concentrated. Purification by flash column chromatography on silica gel using 79:20:1 DCM/MeOH/NH_3 (0 to 100%) in DCM provided the product. LCMS-ESI$^+$ calc'd for $C_{32}H_{39}ClN_5O_3S$ (M + H^+): 608.2; Found: 608.3 (M+H^+).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(6-(4-isopropylpiperazin-1-yl)pyrazin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(6-(4-isopropylpiperazin-1-yl)pyrazin-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (52.9 mg, 0.087 mmol) in THF (0.45 mL) and methanol (0.45 mL) was added NaOH

(0.44 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{31}H_{37}ClN_5O_3S$ (M + H^+): 594.2; Found: 594.4 (M+H^+). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.84 (s, 1H), 8.46 (s, 1H), 7.91 (s, 1H), 7.70 – 7.64 (m, 1H), 7.63 – 7.48 (m, 3H), 5.24 (s, 1H), 4.68 (br s, 2H), 3.76 – 3.50 (m, 3H), 3.26 (br s, 4H), 2.63 (s, 3H), 1.41 (d, J = 6.6 Hz, 6H), 0.98 (s, 9H).

Example 197. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5-(4-isopropylpiperazin-1-yl)pyridin-3-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (481).

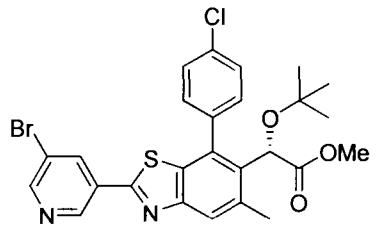


Preparation of (*S*)-methyl 2-(2-(6-bromopyridin-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate: To a solution of (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (121 mg, 0.25mmol) and 5-bromopyridin-3-ylboronic acid (61 mg, 0.30 mmol) in 1,4-dioxane (3 mL) was added potassium carbonate solution (0.50mL, 2 M aqueous) and tetrakis(triphenylphosphine)palladium (14 mg, 0.013 mmol). The reaction was stirred at 105 °C for 3 h. Diluted with brine and EtOAc. Layer separated and the organic layer was dried, filtered, concentrated *in vacuo* and purified by CombiFlash (EtOAc/Hex) to give desired product. LCMS-ESI$^+$: calc'd for $C_{26}H_{25}ClBrN_2O_3S$: 559.0 (M+H^+); Found: 559.1 (M+H^+).

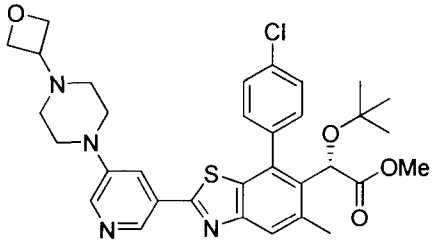
Preparation of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5-(4-isopropylpiperazin-1-yl)pyridin-3-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To a solution of (S)-methyl 2-(2-(6-bromopyridin-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (54 mg, 0.096 mmol) in 1,4-dioxane (1 mL) was added isopropylpiperazine (16 mg, 0.13 mmol), cesium carbonate (41 mg, 0.13 mmol), and Pd BrettPhos precatalyst (2 mg, 0.003 mmol). Reaction mixture was stirred at 110 °C in a sealed vial for 20 h and taken on crude. LCMS-ESI$^+$: calc'd for $C_{33}H_{40}ClN_4O_3S$: 607.2 ($M+H^+$); Found: 607.3 ($M+H^+$).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(5-(4-isopropylpiperazin-1-yl)pyridin-3-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: MeOH (2 mL) was added to the reaction mixture above followed by sodium hydroxide solution (0.20 mL, 2 M aqueous). The mixture was stirred at 60 °C for 4 h and was then filtered and purified using reverse phase HPLC, eluting by 2-100% acetonitrile in H_2O with 0.1% TFA to give the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.06 (br s, 1H), 7.89 (s, 1H), 7.67 (m, 1H), 7.59 (m, 3H), 5.26 (s, 1H), 4.11 (m, 2H), 3.62 (m, 4H), 3.20 (m, 3H), 2.62 (s, 3H), 1.43 (d, J = 7 Hz, 6 H), 0.97 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{32}H_{38}ClN_4O_3S$: 593.2 ($M+H^+$); Found: 593.3 ($M+H^+$).

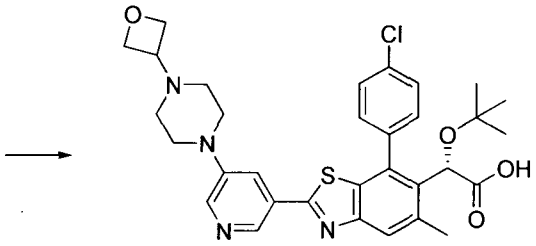
Example 198. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid (482).



(*S*)-methyl 2-(2-(6-bromopyridin-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)benzo[*d*]thiazol-6-yl)acetate



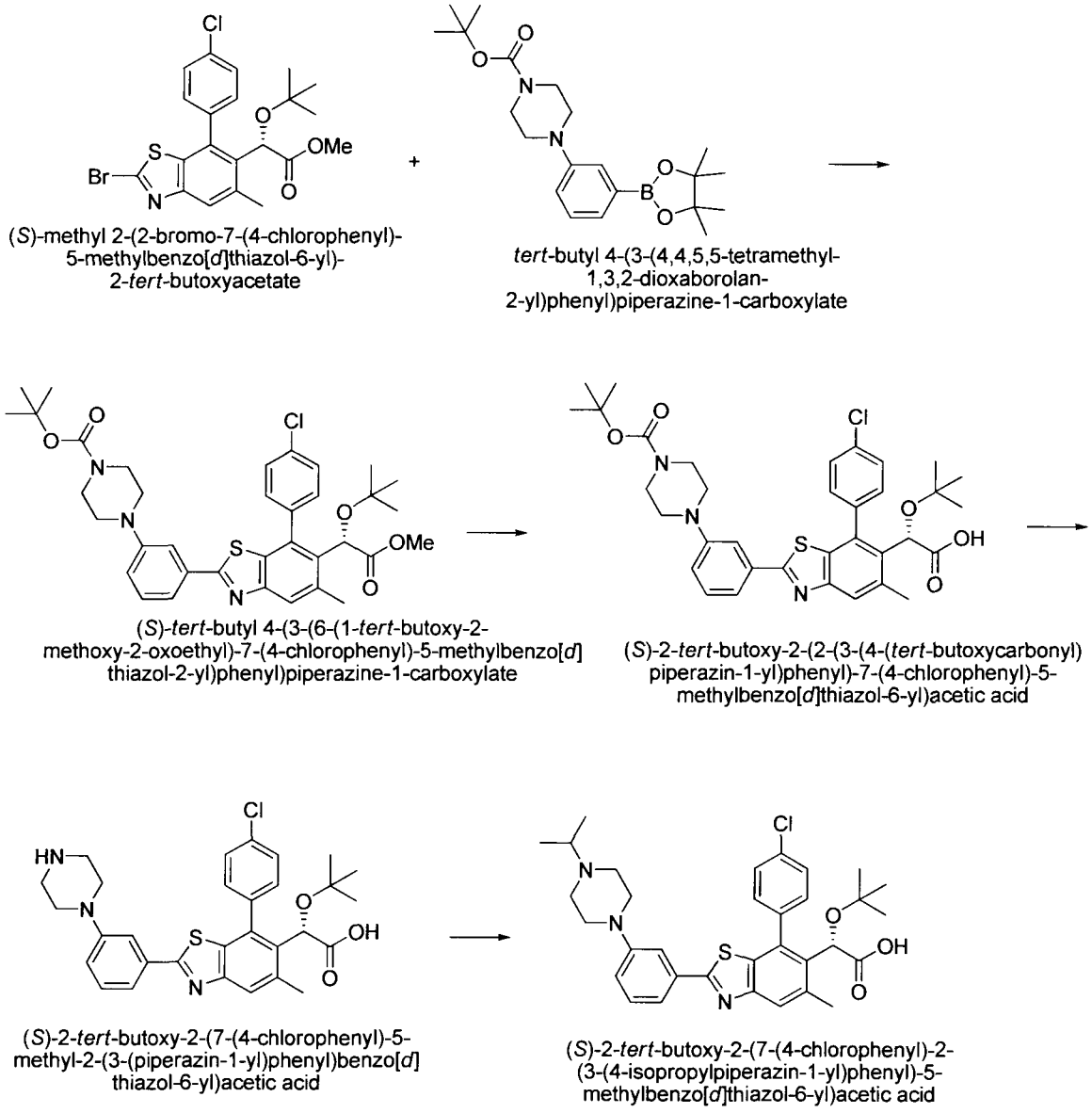
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)benzo[*d*]thiazol-6-yl)acetic acid

482

Preparation of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetate: To a solution of (S)-methyl 2-(2-(6-bromopyridin-2-yl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (54 mg, 0.096 mmol) in 1,4-dioxane (1 mL) was added 1-(oxetan-3-yl)piperazine (18 mg, 0.13 mmol), cesium carbonate (41 mg, 0.13 mmol), and Pd BrettPhos precatalyst (2 mg, 0.003 mmol). Reaction mixture was stirred at 110 °C in a sealed vial for 20 h and taken on crude. LCMS-ESI$^+$: calc'd for $C_{33}H_{38}ClN_4O_4S$: 621.2 ($M+H^+$); Found: 621.2 ($M+H^+$).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid: MeOH (2 mL) was added to the reaction mixture above followed by sodium hydroxide solution (0.20 mL, 2 M aqueous). The mixture was stirred at 60 °C for 4 h and was then filtered and purified using reverse phase HPLC, eluting by 2-100% acetonitrile in H_2O with 0.1% TFA to give the product. ^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.47 (s, 1H), 8.08 (s, 1H), 7.89 (s, 1H), 7.68 (m, 1H), 7.60 (m, 3H), 5.26 (s, 1H), 4.94 (m, 2H), 4.86 (m, 2H), 4.38 (m, 1H), 3.63 (m, 4H), 3.33 (m, 4H), 2.62 (s, 3H), 0.97 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{32}H_{36}ClN_4O_4S$: 607.2 ($M+H^+$); Found: 607.2 ($M+H^+$).

Example 199. Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(4-isopropylpiperazin-1-yl)phenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (483).



483

Preparation of (*S*)-*tert*-butyl 4-(3-(6-(1-*tert*-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)phenyl)piperazine-1-carboxylate: To a solution of (*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (193 mg, 0.40 mmol) and *tert*-butyl 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate (217 mg, 0.56 mmol) in 1,4-dioxane (3 mL) was added potassium carbonate solution (0.80 mL, 1.6 mmol, 2 M aqueous solution) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The reaction mixture was stirred at 105 °C for 3 h. The mixture was diluted with brine (5 mL) and EtOAc (5 mL). The layers were separated, and the organic layer was dried,

filtered, and concentrated *in vacuo* and used without further purification. LCMS-ESI$^+$: calc'd for $C_{36}H_{43}ClN_3O_5S$: 664.3 ($M+H^+$); Found: 664.3 ($M+H^+$).

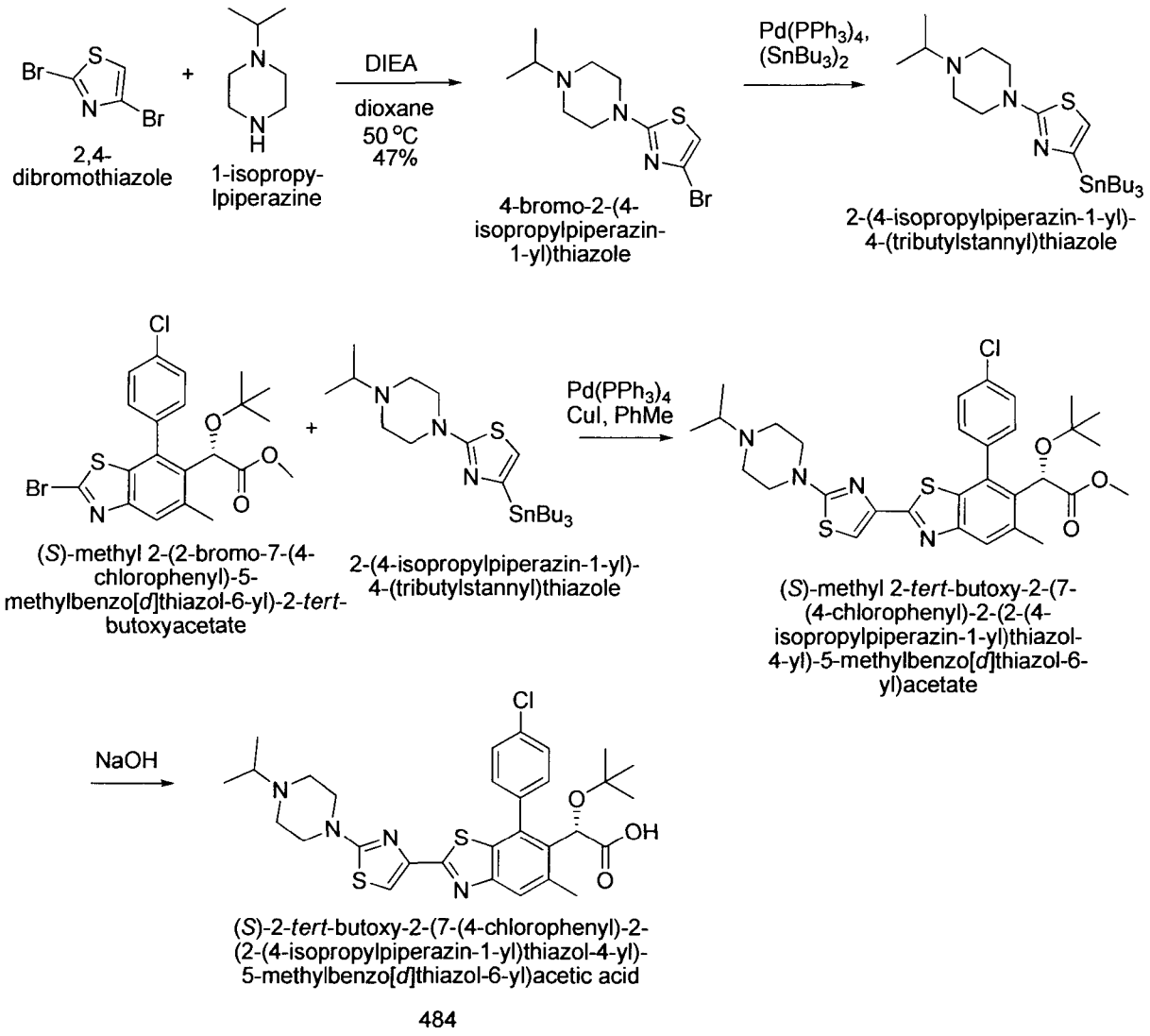
Preparation of (*S*)-2-*tert*-butoxy-2-(2-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (*S*)-*tert*-butyl 4-(3-(6-(1-*tert*-butoxy-2-methoxy-2-oxoethyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-2-yl)phenyl)piperazine-1-carboxylate (from above) in THF (4 mL) and methanol (4 mL) was added sodium hydroxide solution (1.0 mL, 2 mmol, 2 M aqueous solution). The mixture was stirred at 60 °C for 18 h. A saturated solution of NH_4Cl (20 mL) and EtOAc (15 mL) were added. The layers were separated, and the organic layer was dried, filtered, and concentrated *in vacuo* and used without further purification. LCMS-ESI$^+$: calc'd for $C_{35}H_{41}ClN_3O_5S$: 650.2 ($M+H^+$); Found: 650.2 ($M+H^+$).

.

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(3-(piperazin-1-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid: To a solution of (*S*)-2-*tert*-butoxy-2-(2-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (from above) in 1,4-dioxane (5 mL) was added 4M HCl in 1,4-dioxane (1 mL, 4 mmol). The reaction was stirred at rt for 6 h. A saturated solution of $NaHCO_3$ (10 mL) was added carefully. The layers were separated, and the organic layer was dried, filtered, and concentrated *in vacuo* and used without further purification. LCMS-ESI$^+$: calc'd for $C_{30}H_{33}ClN_3O_3S$: 550.2 ($M+H^+$); Found: 550.2 ($M+H^+$).

Preparation of (*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(4-isopropylpiperazin-1-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-(piperazin-1-yl)phenyl)benzo[d]thiazol-6-yl)acetic acid (30 mg, 0.055 mmol) in MeOH (1 mL) was added acetone (0.20 mL), acetic acid (0.08 mL), and sodium triacetoxyborohydride (58 mg, 0.27 mmol). Stirred at rt for 18 h then 60 °C for 3 h (reaction not to completion). H_2O added (1 mL) and purified using reverse phase HPLC, eluting by 2-100% acetonitrile in H_2O with 0.1% TFA to give the product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.68 (m, 2H), 7.58 (m, 3H), 7.43 (t, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 5.25 (s, 1H), 4.02 (m, 2H), 3.60 (m, 4H), 3.12 (m, 3H), 2.61 (s, 3H), 1.43 (d, J = 7 Hz, 6H), 0.97 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{33}H_{39}ClN_3O_3S$: 592.2 ($M+H^+$); Found: 592.3 ($M+H^+$).

Example 200. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)thiazol-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (484).



Preparation of 4-bromo-2-(4-isopropylpiperazin-1-yl)thiazole: In a 50 mL round bottom flask, 1-isopropylpiperazine (306 mg, 2.38 mmol) was dissolved in 4 mL dioxane. 2,4-Dibromothiazole (870 mg, 1.5 eq.) was added and the reaction was stirred at room temperature overnight. TLC and LC-MS showed desired product. DIEA (0.83 mL, 2 eq.) was added. The reaction was stirred at room temperature for 4 hours, then heated to 50 °C for 5 hours. Reaction was cooled and extracted using ethyl acetate/brine. The organic layer was concentrated and purified via combiflash to give desired compound. LCMS-ESI$^+$: calc'd for $C_{10}H_{17}BrN_3S$: 290.0 ($M+H^+$); Found: 290.2 ($M+H^+$).

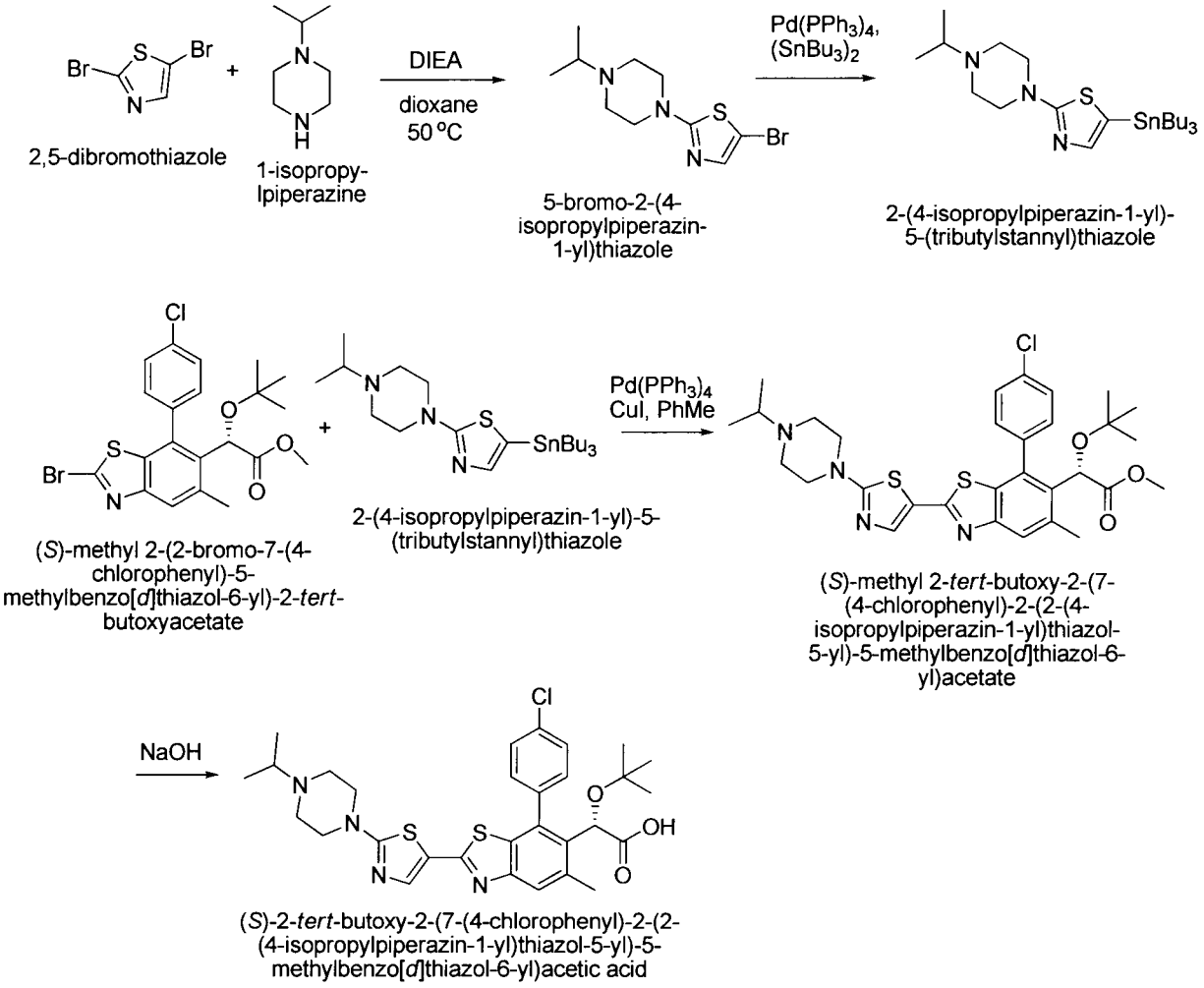
Preparation of 2-(4-isopropylpiperazin-1-yl)-4-(tributylstannyl)thiazole: A 5 mL microwave reaction tube was charged with 4-bromo-2-(4-isopropylpiperazin-1-yl)thiazole (61 mg, 0.21 mmol), $Pd(PPh_3)_4$ (37 mg, 15mol%), bis(tributyltin) (183 mg, 2 eq.) and toluene (1.5 mL). The reaction was heated to140 °C in oil bath for 1 hour. LC-MS of the reaction crude

show desired product. Reaction mixture was diluted with ethyl acetate and saturated NaF aqueous solution was added and stirred for 30 minutes. Extracted with ethyl acetate and the organic layer was concentrated and purified via Combiflash (0-100% Ethyl acetate in hexane) to desired compound. LCMS-ESI$^+$: calc'd for $C_{22}H_{44}N_4SSn$: 502.2 ($M+H^+$); Found: 502.2 ($M+H^+$).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)thiazol-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A 5 mL microwave reaction tube was charged with 2-(4-isopropylpiperazin-1-yl)-4-(tributylstannyl)thiazole (33 mg, 0,066 mmol), (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (40 mg, 1.2 eq.), $Pd(PPh_3)_4$ (15 mg, 15mol%), CuI (5 mg, 30mol%) and dioxane (1 mL). The reaction was heated to 110 °C in oil bath for 1 hour. Reaction mixture was diluted with ethyl acetate and saturated NaF aqueous solution was added and stirred for 30 minutes. Extracted with ethyl acetate and the organic layer was concentrated and purified via Combiflash (0-100% ethyl acetate in hexane) to give desired compound. LCMS-ESI$^+$: calc'd for $C_{31}H_{38}ClN_4O_3S_2$: 613.2 ($M+H^+$); Found: 613.4 ($M+H^+$).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)thiazol-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)thiazol-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (30 mg, 0.04 mmol) in 1:1 THF/MeOH (1.5 mL) was added 2M aqueous NaOH (0.2 mL, 0.4 mmol) and stirred at 40 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 7.67 (s, 1 H), 7.58 – 7.55 (m, 2H), 7.49 – 7.41 (m, 3H), 5.14 (s, 1H), 3.74 (m, 4H), 3.51-3.49 (m, 1 H), 3.33 (m, 4H), 2.50 (s, 3H), 1.30 (d, J = 6.65 Hz, 6H), 0.86 (s, 9H); LCMS-ESI$^+$: calc'd for $C_{30}H_{36}ClN_4O_3S_2$: 599.2 ($M+H^+$); Found: 599.4 ($M+H^+$).

Example 201. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)thiazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (485).



485

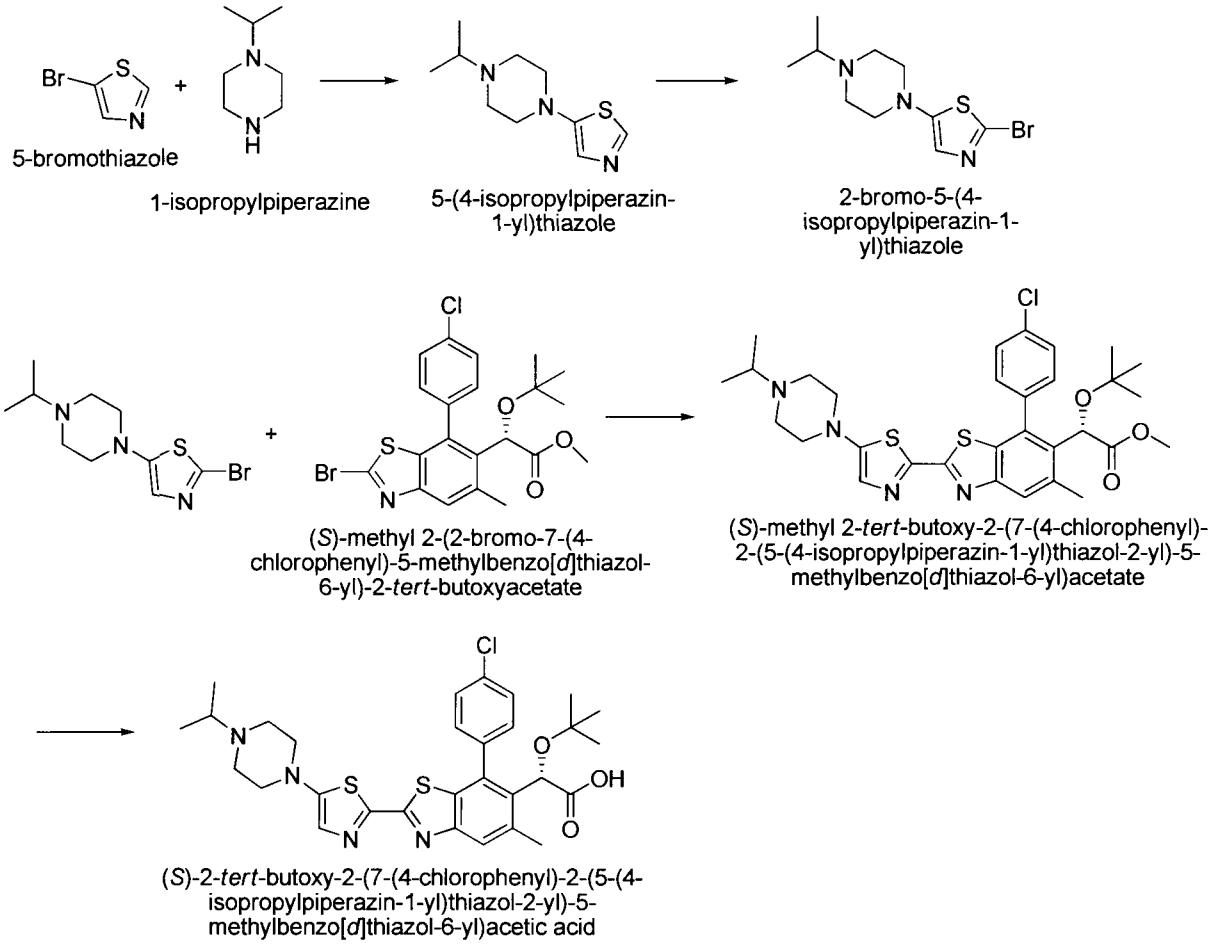
Preparation of 5-bromo-2-(4-isopropylpiperazin-1-yl)thiazole: In a 50 mL round bottom flask, 1-isopropylpiperazine (224 mg, 1.74 mmol) was dissolved in 4 mL dioxane. 2,5-Dibromothiazole (650 mg, 1.5 eq.) and DIEA (670 mg, 3 eq.) were added and the reaction was heated to 50 °C overnight. Reaction mixture was cooled and extracted using ethyl acetate / brine. The organic layer was concentrated and purified via combiflash to give desired compound. LCMS-ESI$^+$: calc'd for $C_{10}H_{17}BrN_3S$: 290.0 ($M+H^+$); Found: 290.2 ($M+H^+$).

Preparation of 2-(4-isopropylpiperazin-1-yl)-5-(tributylstannyl)thiazole: A 5 mL microwave reaction tube was charged with 5-bromo-2-(4-isopropylpiperazin-1-yl)thiazole (100 mg, 0.34 mmol), $Pd(PPh_3)_4$ (60 mg, 15mol%), Bis(tributyltin) (300 mg, 2 eq.) and toluene (1.5 mL). The reaction was heated to140 °C in oil bath for 1 hour. LC-MS of the reaction crude show desired product. Reaction mixture was diluted using ethyl acetate, saturated NaF aqueous solution was added and stirred for 30 minutes. Extracted with ethyl acetate and the organic layer was concentrated and purified via Combiflash (0-100% Ethyl acetate in hexane) to give desired compound. LCMS-ESI$^+$: calc'd for $C_{22}H_{44}N_4SSn$: 502.2 ($M+H^+$); Found: 502.2 ($M+H^+$).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)thiazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A 5 mL microwave reaction tube was charged with 2-(4-isopropylpiperazin-1-yl)-5-(tributylstannyl)thiazole (39 mg, 0,078 mmol), (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (40 mg, 1.1 eq.), $Pd(PPh_3)_4$ (15 mg, 15mol%), CuI (5 mg, 30mol%) and dioxane (1 mL). The reaction was heated to 110 °C in oil bath for 1 hour. Reaction mixture was diluted with ethyl acetate and saturated NaF aqueous solution was added and stirred for 30 minutes. Extracted with ethyl acetate and the organic layer was concentrated and purified via Combiflash (0-100% Ethyl acetate in hexane) to give desired compound. LCMS-ESI$^+$: calc'd for $C_{31}H_{38}ClN_4O_3S_2$: 613.2 ($M+H^+$); Found: 613.2 ($M+H^+$).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)thiazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(4-isopropylpiperazin-1-yl)thiazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (30 mg, 0.04 mmol) in 1:1 THF/MeOH (1.5 mL) was added 2M aqueous NaOH (0.2 mL, 0.4 mmol) and stirred at 40 °C overnight. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1 H), 7.66 – 7.64 (m, 2H), 7.57 – 7.50 (m, 3H), 5.21 (s, 1H), 3.65-3.57 (m, 1 H), 3.57 – 3.30 (m, 8H), 2.56 (s, 3H), 1.41 (d, J = 6.65 Hz, 6H), 0.95 (s, 9H); LCMS-ESI$^+$: calc'd for $C_{30}H_{36}ClN_4O_3S_2$: 599.2 ($M+H^+$); Found: 599.4 ($M+H^+$).

Example 202. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(5-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (486).



486

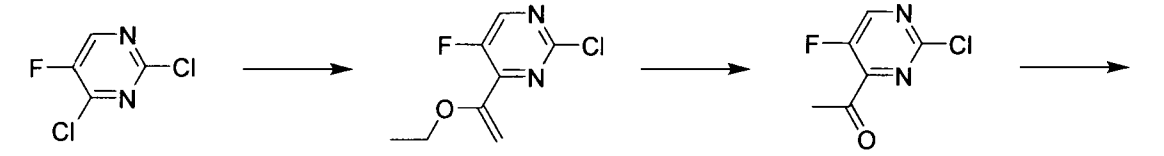
Preparation of 5-(4-isopropylpiperazin-1-yl)thiazole: To a 5 mL microwave reaction tube containing 5-bromothiazole (359 mg, 2.19 mmol), isopropylpiperazine (330 mg, 1.1 eq.), Bis(tri-t-butylphosphine)palladium (0) (22 mg, 15mol%), cetyltrimethylammonium bromide (15 mg, 30mol%), toluene (3 mL) was added one drop of 50% KOH aqueous solution. The reaction was heated to 110 °C for 4 hours. The reaction was cooled down and extracted using ethyl acetate/brine. The organic layers were concentrated and purified via Combiflash (0-20% MeOH/ Ethyl acetate) to give desired product. LCMS-ESI$^+$: calc'd for $C_{10}H_{18}N_3S$: 212.1 ($M+H^+$); Found: 212.1 ($M+H^+$).

Preparation of 2-bromo-5-(4-isopropylpiperazin-1-yl)thiazole: At -78 °C, n-butyl lithium (2.5 N in hexane, 0.27 mL, 2 eq.) was added to 5-(4-isopropylpiperazin-1-yl)thiazole (28 mg, 0.132 mmol) in 1 mL THF. CBr_4 (22 mg, 0.5 eq.) was added after 30 minutes. The reaction was stirred at -78 °C for 2 hours. The reaction was quenched by adding water. The reaction crude was extracted using EtOAc. The organic layers were concentrated and purified via Combiflash (0-20 % MeOH in EtOAc) to give desired product. LCMS-ESI$^+$: calc'd for $C_{10}H_{17}BrN_3S$: 290.0 ($M+H^+$); Found: 290.1 ($M+H^+$).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(5-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A 5 mL microwave reaction tube was charged with 2-bromo-5-(4-isopropylpiperazin-1-yl)thiazole (12 mg, 0.041 mmol), $Pd(PPh_3)_4$ (7 mg, 15mol%), CuI (4 mg, 30mol%) and $(SnBu_3)_2$ (48 mg, 2 eq.) and toluene (0.5 mL). The reaction was heated to 110 °C in oil bath. (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (20 mg, 1.1 eq.) in toluene (4 mL) was added slowly (over 1.5 hours). The reaction was heated at 110 °C in oil bath for 2 hours. The reaction crude was partitioned between ethyl acetate and brine. The organic layer were concentrated and purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA) to give desired product. LCMS-ESI$^+$: calc'd for $C_{31}H_{38}ClN_4O_3S_2$: 613.2 ($M+H^+$); Found: 613.2 ($M+H^+$).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(5-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To a solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(5-(4-isopropylpiperazin-1-yl)thiazol-2-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in 1:1 THF/MeOH (1.5 mL) was added 2M aqueous NaOH (0.2 mL, 0.4 mmol) and stirred at 40 °C for 2 days. The reaction mixture was cooled to room temperature, neutralized with AcOH, filtered, and then purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. ^1H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1 H), 7.67 – 7.65 (m, 2H), 7.60 – 7.50 (m, 3H), 5.23 (s, 1H), 3.65-3.60 (m, 1 H), 3.60 – 3.36 (m, 8H), 2.59 (s, 3H), 1.42 (d, J = 6.65 Hz, 6H), 0.95 (s, 9H); LCMS-ESI$^+$: calc'd for $C_{30}H_{36}ClN_4O_3S_2$: 599.2 ($M+H^+$); Found: 599.4 ($M+H^+$).

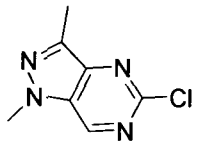
Example 203. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (487).



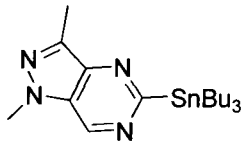
2,4-dichloro-5-fluoropyrimidine

2-chloro-4-(1-ethoxyvinyl)-5-fluoropyrimidine

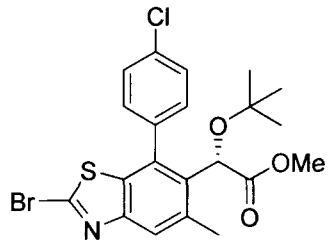
1-(2-chloro-5-fluoropyrimidin-4-yl)ethanone



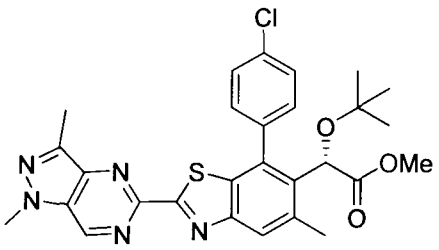
5-chloro-1,3-dimethyl-1*H*-pyrazolo[4,3-*d*]pyrimidine



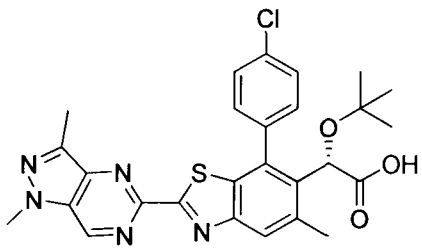
1,3-dimethyl-5-(tributylstannyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine



(*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

487

Preparation of 2-chloro-4-(1-ethoxyvinyl)-5-fluoropyrimidine: To a solution of 2,4-dichloro-5-fluoro-pyrimidine (5.2 g, 31.14 mmol) in DMF (60 mL) was added tributyl-(1-ethoxy-vinyl)-stannane (12.37 g, 361.2 mmol), followed by dichlorobis(triphenylphosphine) palladium(II) (0.438 g, 0.623 mmol). The mixture was heated at 75°C for 2 hours, cooled to rt and concentrated. The oily residue was dissolved in ethyl ether and a saturated solution of aqueous potassium fluoride was added and the mixture was stirred at room temperature for 18 hours. After dilution with EtOAc and filtration through Celite, the organic phase was washed with water, brine and concentrated. The crude material was purified by CombiFlash (0 to 10% EtOAc/Hex) to give desired product. LCMS-ESI$^+$: calc'd for $C_8H_9ClFN_2O$: 203.0 ($M+H^+$); Found: 203.1 ($M+H^+$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, J = 2.8 Hz, 1H), 5.30 (d, J = 3.1 Hz, 1H), 4.71 (d, J = 3.1 Hz, 1H), 3.96 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H).

Preparation of 1-(2-chloro-5-fluoropyrimidin-4-yl)ethanone: A mixture of 2-chloro-4-(1-ethoxyvinyl)-5-fluoropyrimidine (5.23 g, 25.81 mmol) in 3N HCl (100 mL) was stirred at rt for 6 h. Potassium hydroxide (50%) was added to give a cloudy mixture (pH was still less than 1) and extracted cloudy mixture with EtOAc. More potassium hydroxide (50%) was added and extracted with EtOAc. Again, more potassium hydroxide (50%) was added until pH = 7 and extracted with EtOAc. The combined organic layer dried ($MgSO_4$), filtered, concentrated and purified by CombiFlash (0 to 25% EtOAc/Hex) to give the desired product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2Hz, 1H), 2.71 (2, 3H); ^{19}F (376 MHz, CDCl3) δ -138.26.

Preparation of 5-chloro-1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidine: A solution of 1-(2-chloro-5-fluoropyrimidin-4-yl)ethanone (4.00 g, 22.91 mmol) and methylhydrazine (0.724 mL, 13.75 mmol) in ethylene glycol was heated at 120°C for 2 h. Reaction mixture was cooled to rt, diluted with H_2O and extracted with ethyl acetate (3x). The combined organic layer was washed with H_2O (2x), brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by CombiFlash (0 to 30% EtOAc/Hex) to give the title compound. LCMS-ESI$^+$: calc'd for $C_7H_8ClN_4$: 183.0 ($M+H^+$); Found: 183.0 ($M+H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 4.12 (s, 3H), 2.61 (s, 3H).

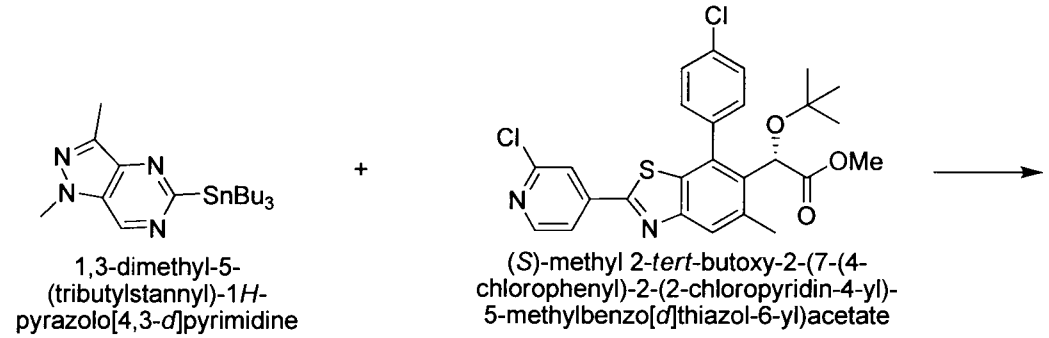
Preparation of 1,3-dimethyl-5-(tributylstannyl)-1H-pyrazolo[4,3-d]pyrimidine: 5-chloro-1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidine (0.193 g, 1.057 mmol) was dissolved in toluene (5 mL)and hexabutylditin (0.688 mL, 1.374 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.122 g, 0.106 mmol) were added. Reaction mixture was stirred at 170°C for 2 h to give a black mixture, cooled to rt, concentrated to ~2mL and purified by CombiFlash (0 to 30% EtOAc/Hex) to give title compound. LCMS-ESI$^+$: calc'd for $C_{19}H_{35}N_4Sn$: 439.2 ($M+H^+$); Found: 438.9 ($M+H^+$); ^1H NMR (400 MHz, Chloroform-d) δ 9.03 (s, 1H), 4.07 (s, 3H), 2.65 (s, 3H), 1.73 - 1.49 (m, 6H), 1.42 - 1.09 (m, 12H), 0.89 (q, J = 7.9, 7.3 Hz, 9H).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (0.055 g, 0.107 mmol), 1,3-dimethyl-5-(tributylstannyl)-1H-pyrazolo[4,3-d]pyrimidine (0.058 mg, 0.133 mmol), copper(I) iodide (6 mg, 0.032 mmol) and tetrakis(triphenylphosphine)palladium(0) (11 mg, 0.012 mmol) in dioxane (1 mL) was heated at 90°C for 16 hr. Reaction mixture was cooled to rt, filtered through a syringe filter and purified by CombiFlash (0 to 70% EtOAc/Hex) to give

title product. LCMS-ESI$^+$: calc'd for $C_{28}H_{29}ClN_5O_3S$: 550.2 (M+H$^+$); Found: 550.3 (M+H$^+$); ^{1}H NMR (400 MHz, Methanol-d4) δ 9.32 (s, 1H), 7.88 (s, 1H), 7.70 – 7.53 (m, 4H), 5.30 (s, 1H), 4.13 (s, 3H), 3.75 (s, 3H), 2.57 (s, 3H), 2.54 (s, 3H), 0.97 (s, 9H).

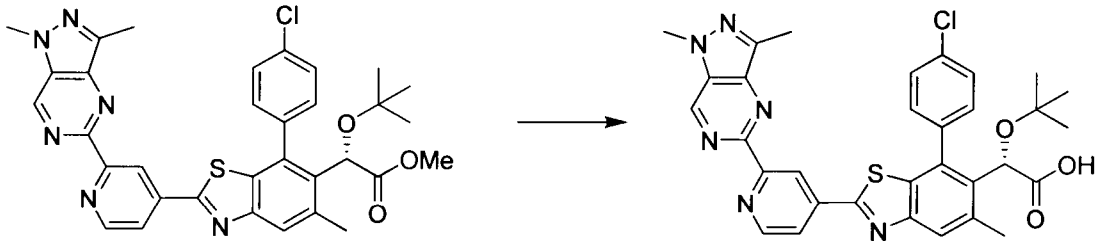
Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (38 mg, 0.07 mmol) and 5M sodium hydroxide (0.28 mL, 1.4 mmol) in THF (2 mL) and MeOH (0.5 mL) was stirred at 50 °C for 2h. Reaction mixture was cooled to rt, acetic acid (88 μL) and DMF (0.3 mL) were added and reaction mixture was concentrated to ~0.3 mL, filtered, purified by Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) and lyophilized to give desired product. LCMS-ESI$^+$: calc'd for $C_{27}H_{27}ClN_5O_3S$: 536.1 (M+H$^+$); Found: 536.2 (M+H$^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 9.29 (s, 1H), 7.92 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.62 (br s, 3H), 5.28 (s, 1H), 4.13 (s, 3H), 2.63 (s, 6H), 0.98 (s, 9H).

Example 204. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (488).



1,3-dimethyl-5-(tributylstannyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine

(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

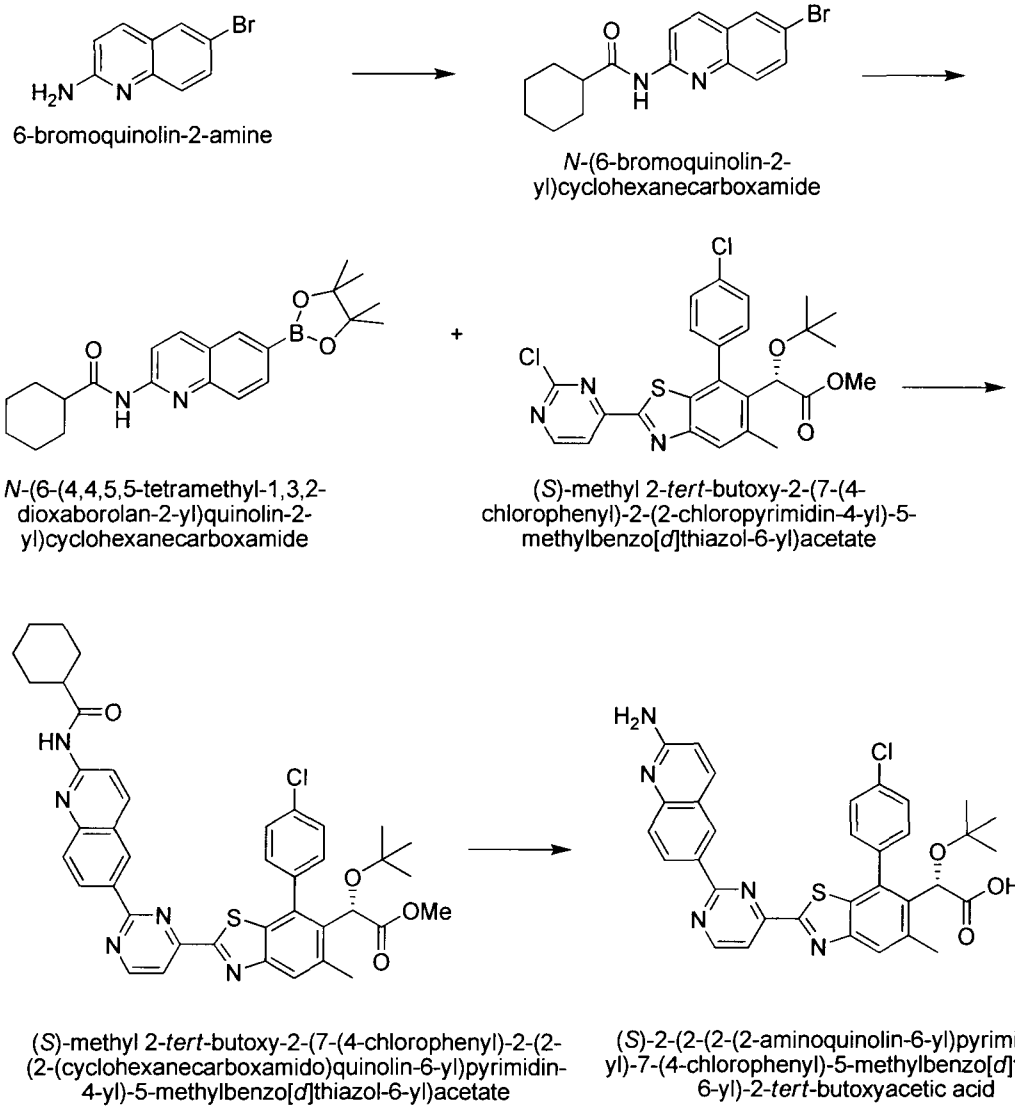
(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)pyridin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

488

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A mixture of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (0.055 g, 0.107 mmol), 1,3-dimethyl-5-(tributylstannyl)-1H-pyrazolo[4,3-d]pyrimidine (0.058 mg, 0.133 mmol), copper(I) iodide (6 mg, 0.032 mmol) and tetrakis(triphenylphosphine)palladium(0) (11 mg, 0.012 mmol) in dioxane was heated at 90°C for 16 hr. Reaction mixture was cooled to rt, filtered through a syringe filter and purified by CombiFlash (12 g, Gold, 10-100% EtOAc/Hex, then 15%MeOH/CH_2Cl_2 to elute product) to give impure product that was used in next step without further purification. LCMS-ESI$^+$: calc'd for $C_{33}H_{32}ClN_6O_3S$: 627.2 ($M+H^+$); Found: 627.2 ($M+H^+$).

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: A solution of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-(1,3-dimethyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)pyridin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (7.7 mg, 0.012 mmol) and 5M sodium hydroxide (20μL, 0.012 mmol) in THF (1 mL) and MeOH (0.2 mL) was stirred at 50 °C for 2h. Reaction mixture was cooled to rt, acetic acid (15 μL) and DMF (0.3 mL) were added and reaction mixture was concentrated to ~0.3 mL, filtered, purified by Gilson HPLC (Gemini, 5 to 100% ACN/H_2O + 0.1% TFA) and lyophilized to give desired product. LCMS-ESI$^+$: calc'd for $C_{32}H_{30}ClN_6O_3S$: 613.2 ($M+H^+$); Found: 613.2 ($M+H^+$); ^{1}H NMR (400 MHz, CD_3OD) δ 9.41 (s, 1H), 9.28 (s, 1H), 8.85 (s, 1H), 8.25 (s, 1H), 7.99 (s, 1H), 7.76 - 7.43 (m, 4H), 5.28 (s, 1H), 4.16 (s, 3H), 2.71 (s, 3H), 2.65 (s, 3H), 0.98 (s, 9H).

Example 205. Preparation of (*S*)-2-(2-(2-(2-aminoquinolin-6-yl)pyrimidin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid (489).



489

Preparation of *N*-(6-bromoquinolin-2-yl)cyclohexanecarboxamide: To a solution of 2-amino-6-bromoquinoline (250 mg, 1.121 mmol) in CH_2Cl_2 (7 mL) was added Et_3N (0.94 mL, 6.726 mmol) and DMAP (137 mg, 1.121 mmol) followed by cyclohexanecarbonyl chloride (0.46 mL, 3.362 mmol). The reaction mixture was stirred at rt for 20 min and then diluted with EtOAc, washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 40% ethyl acetate/hexanes) to give the product. LCMS-ESI$^+$: calc'd for $C_{16}H_{18}BrN_2O$: 333.0 ($M+H^+$); found: 333.1($M+H^+$).

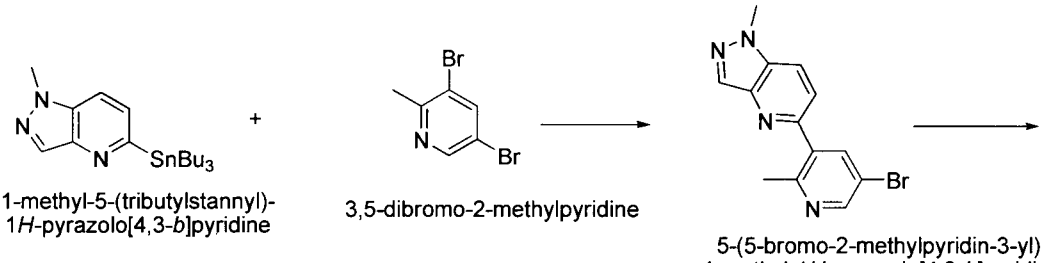
Preparation of *N*-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2-yl)cyclohexanecarboxamide: A solution of *N*-(6-bromoquinolin-2-yl)cyclohexanecarboxamide (100 mg, 0.300 mmol), bis(pinacolato)diboron (91 mg, 0.360 mmol) and potassium acetate (88 mg, 0.900 mmol) in dioxane (2.8 mL) was degassed for 5 min with N_2, then treated with $Pd(dppf)Cl_2 \cdot DCM$ (12 mg, 0.015 mmol). The resulting mixture was heated at 90 °C for 90 min.

After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 50% ethyl acetate/hexanes) to give the desired product. LCMS-ESI$^+$: calc'd for $C_{22}H_{30}BN_2O_3$: 381.2 ($M+H^+$); Found: 381.3 ($M+H^+$).

Preparation of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(cyclohexanecarboxamido)quinolin-6-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate: To a solution of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (20.0 mg, 0.038 mmol) and *N*-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2-yl)cyclohexanecarboxamide (17.2 mg, 0.045 mmol) in dioxane (0.4 mL) was added $Pd(PPh_3)_4$ (2.2 mg, 0.002 mmol) and 2N K_2CO_3 (79 μL, 0.158 mmol). The reaction was degassed for 5 minutes with N_2 and then heated at 90°C for 10 h. After cooling, the reaction mixture was diluted with EtOAc, extracted with H_2O, brine, dried over Na_2SO_4, filtered and concentrated and purified by flash column chromatography (silica gel, 0 to 50% ethyl acetate/hexanes) to give the product. LCMS-ESI$^+$: calc'd for $C_{41}H_{41}ClN_5O_4S$: 734.3 ($M+H^+$); found: 734.3 ($M+H^+$).

Preparation of (*S*)-2-(2-(2-(2-aminoquinolin-6-yl)pyrimidin-4-yl)-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetic acid: To a stirred solution of (*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(2-(cyclohexanecarboxamido)quinolin-6-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate (28.0 mg, 0.038 mmol) in THF (1.0 mL) and methanol (0.6 mL) was added 1N NaOH solution (0.6 mL, excess). The reaction mixture was stirred at 50 °C for 2h. The mixture was acidified with TFA and concentrated and purified by flash column chromatography (silica gel, 0 to 20% methanol/dichloromethane) to give the TFA salt of the product. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.12 (d, J = 5.1 Hz, 1H), 8.81 (d, J = 2.4 Hz, 1H), 8.64 – 8.55 (m, 1H), 8.34 (s, 1H), 8.17 (d, J = 5.1 Hz, 1H), 8.03 (s, 1H), 7.77 – 7.64 (m, 4H), 7.61 (dd, J = 8.6, 2.1 Hz, 1H), 6.96 (d, J = 9.2 Hz, 1H), 5.09 (s, 1H), 2.56 (s, 3H), 0.88 (s, 9H); LCMS-ESI$^+$: calc'd for $C_{33}H_{29}ClN_5O_3S$: 610.2 ($M+H^+$); found: 610.2 ($M+H^+$).

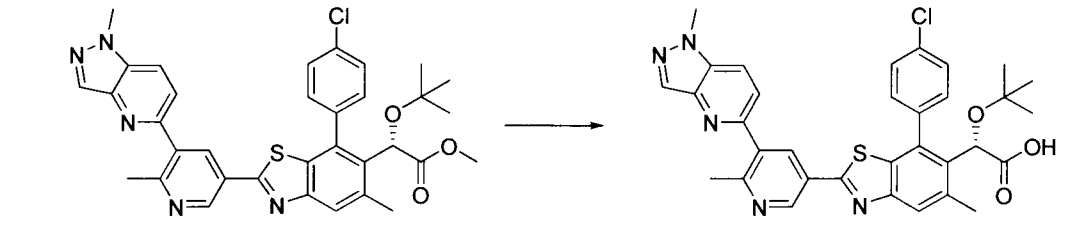
Example 206. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid (490).



1-methyl-5-(tributylstannyl)-1*H*-pyrazolo[4,3-*b*]pyridine

3,5-dibromo-2-methylpyridine

5-(5-bromo-2-methylpyridin-3-yl) -1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-5-yl)pyridin-3-yl)benzo[*d*]thiazol-6-yl)acetate

(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1*H*-pyrazolo[4,3-*b*]pyridin-5-yl) pyridin-3-yl)benzo[*d*]thiazol-6-yl)acetic acid

490

Preparation of 5-(5-bromo-2-methylpyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-b]pyridine: To a solution of 3,5-dibromo-2-methylpyridine (320 mg, 1.28 mmol) in dioxane (10 mL), was added 1-methyl-5-(tributylstannyl)-1H-pyrazolo[4,3-b]pyridine (540 mg, 1.28 mmol), CuI (73 mg, 0.38 mmol), LiCl (271 mg, 6.4 mmol) and $Pd(PPh_3)_4$ (147 mg, 0.12 mmol). The reaction mixture was heated at 100 °C for 2 h. The reaction was cooled down, washed by sat. $NaHCO_3$, extracted by EtOAc, dried over $MgSO_4$, filtered, concentrated down and purified by silica gel column, eluting by 0-100% EtOAc in hexanes give the product. LCMS-ESI$^+$: calc'd for $C_{13}H_{11}BrN_4$: 303.0 ($M+H^+$); Found: 303.2 ($M+H^+$).

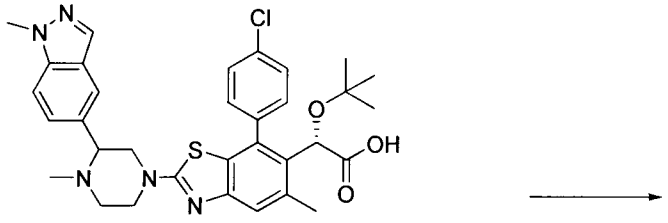
Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetate: To a solution of -(5-bromo-2-methylpyridin-3-yl)-1-methyl-1H-pyrazolo[4,3-b]pyridine (67 mg, 0.221 mmol) in dioxane (2 mL), was added bis(pinacolato)diboron (67 mg, 0.265 mmol), KOAc (86 mg, 0.884 mmol), $PdCl_2(dppf)$ (16 mg, 0.022 mmol). The reaction mixture was heated at 100 °C for 3 h. Then the reaction was cooled down and to the mixture was added *(S)*-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (106 mg, 0.221 mmol), $Pd(PPh_3)_4$ (12 mg, 0.011 mmol). The mixture was heated at 90 °C for 3 h. The reaction was cooled down, washed by sat. $NaHCO_3$, extracted by EtOAc, dried over $MgSO_4$, filtered, concentrated down and purified by silica gel column, eluting with 0-70% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_5O_3S$: 626.2 ($M+H^+$); Found:

626.2 ($M+H^+$).

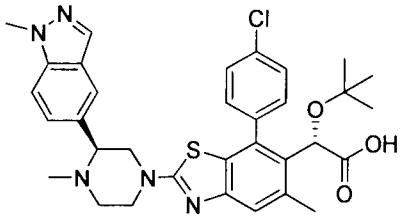
Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetic acid:

To a solution of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(6-methyl-5-(1-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)pyridin-3-yl)benzo[d]thiazol-6-yl)acetate (26 mg, 0.042 mmol) in THF (0.5 mL) and MeOH (0.5 mL) was added 2N NaOH (410 μL). The reaction mixture was heated at 60 °C for 3 h. The reaction mixture was concentrated down, the residue was dissolved in DMF and MeOH, filtered and purified by reverse phase HPLC, (10-100% ACN/H_2O +0.1% TFA) to give the product. ^1H NMR (400 MHz, CD_3OD) δ 9.11 (d, J = 0.8 Hz, 1H), 8.59 (d, J = 1.0 Hz, 1H), 8.22-8.18 (m, 2H), 7.81 (s, 1H), 7.69-7.62 (m, 2H), 7.53-7.51 (m, 3H), 5.23 (s, 1H), 4.15 (s, 3H), 2.67 (s, 3H), 2.57 (s, 1H), 0.95 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{33}H_{30}ClN_5O_3S$: 612.2 ($M+H^+$); Found: 612.1 ($M+H^+$).

Example 207. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((S)-4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (491) and (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((R)-4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (492).



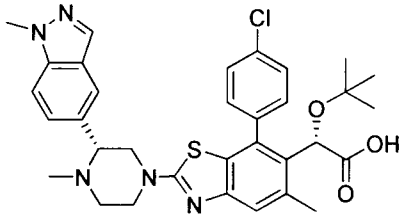
(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1*H*-indazol-5-yl)piperazin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((*S*)-4-methyl-3-(1-methyl-1*H*-indazol-5-yl)piperazin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid

491

+



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((*R*)-4-methyl-3-(1-methyl-1*H*-indazol-5-yl)piperazin-1-yl)benzo[*d*]thiazol-6-yl)acetic acid

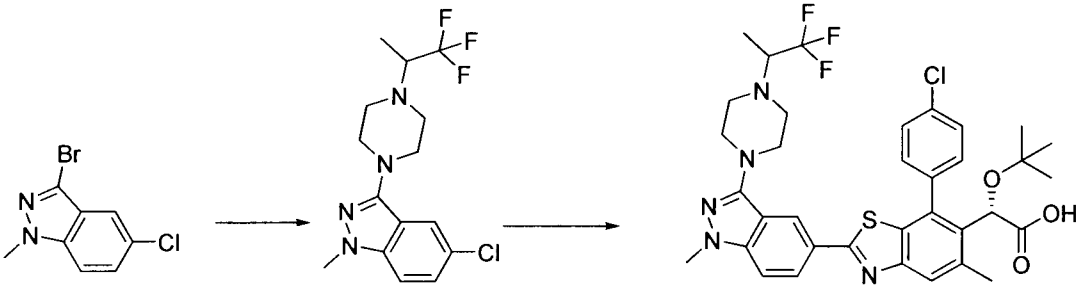
492

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((S)-4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid and (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-((R)-4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid: (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(4-methyl-3-(1-methyl-1H-indazol-5-yl)piperazin-1-yl)benzo[d]thiazol-6-yl)acetic acid (8 mg, a mixture of two diasteroisomers) was dissolved in heptane/isopropanol (1 mL, 70/30) and was purified by Chiralpac Chiral Column (AZ-H) with heptane/isopropanol (70/30). Two fractions were collected.

Less polar fraction: ^{1}H-NMR 400 MHz, (CD_3OD) δ 8.0 (s, 1 H), 7.8 (s, 1 H), 7.62-7.59 (m, 2 H), 7.58-7.46 (m, 4 H), 7.29 (s, 1 H), 5.12 (s, 1 H), 4.07 (s, 3 H), 4.0 (m, 2 H), 3.52-3.3 (m, 3 H), 3.2 (m, 1 H), 2.54 (m, 1 H), 2.48 (s, 3 H), 2.12 (s,3 H), 0.93 (s, 9 H); LCMS-ESI$^+$: calc'd for $C_{33}H_{36}ClN_5O_3S$: 618.2 ($M+H^+$); Found: 618.4 ($M+H^+$).

More polar fraction: ^{1}H-NMR 400 MHz, (CD_3OD) δ 7.99 (s, 1 H), 7.79 (s, 1 H), 7.64-7.45 (m, 6 H), 7.28 (s, 1 H), 5.12 (s, 1 H), 4.06 (s, 3 H), 3.98 (m, 2 H), 3.48 (m, 1 H), 3.30 (m, 2 H), 3.10 (m, 1 H), 2.50 (m, 1 H), 2.48 (s, 3 H), 2.10 (s, 3 H), 0.93 (s, 9 H); LCMS-ESI$^+$: calc'd for $C_{33}H_{36}ClN_5O_3S$: 618.2 ($M+H^+$); Found: 618.4 ($M+H^+$).

Example 208. Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazin-1-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (493).



3-bromo-5-chloro-1-methyl-1*H*-indazole

5-chloro-1-methyl-3-(4-((2R/2S)-1,1,1-trifluoropropan-2-yl) piperazin-1-yl)-1*H*-indazole

(2*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazin-1-yl)-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

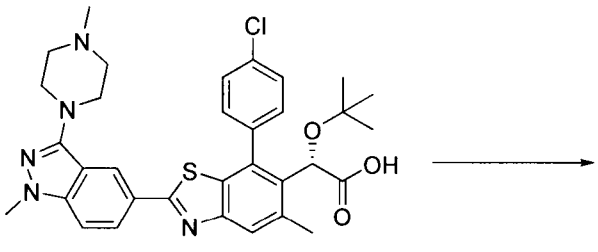
493

Preparation of 5-chloro-1-methyl-3-(4-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazin-1-yl)-1H-indazole: A solution of 3-bromo-5-chloro-1-methyl-1H-indazole (160 mg, 0.652 mmol), 1-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazine (119 mg, 0.652 mmol), and Dioxane (1.00 mL) was prepared. NaOtBu (94 mg, 0.978 mmol) and Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)][2-(2-aminoethyl)phenyl]Pd(II) (52 mg, 65

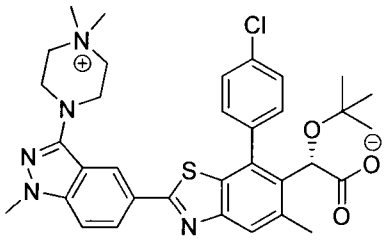
μmol) were charged and the vessel was sealed and heated to 100 °C overnight. Water (3 mL) was added and the reaction was filtered (0.45 micron). The filtrate was directly purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA) giving the title compound. LCMS-ESI$^+$: calc'd for $C_{15}H_{19}ClF_3N_4$: 347.2, 349.2 (M+H$^+$); Found: 347.1, 349.1 (M + H$^+$).

Preparation of (2S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazin-1-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid: A vial was charged with $Pd(OAc)_2$ (1.1 mg, trimeric), X-Phos ligand (4.5 mg), bis-pinacolatodiboron (29 mg), and KOAc (21 mg). The vessel was evacuated under vacuum and backfilled with argon. A solution of 5-chloro-1-methyl-3-(4-((2R/2S)-1,1,1-trifluoropropan-2-yl)piperazin-1-yl)-1H-indazole (50 mg) in dioxane (1.5 mL) was introduced. The reaction was stirred briefly at 23 °C, then heated to 110 °C. After 1.5 h, The reaction was cooled to 23 °C and charged with (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (35 mg), $KHCO_3$ (7 mg), $Pd(PPh_3)_4$ (2 mg), and 2 M aq K_2CO_3 (250 μL). The reaction was heated to 100 °C for 1 h. Ethanol (absolute, 0.5 mL) and 5 M aq NaOH (0.5 mL) were added. The reaction was heated at 100 °C for 30 min. The reaction was cooled to 23 °C and directly purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA) giving the title compound. ^{1}H NMR (400 MHz, CD_3OD): δ 8.44 (s, 1H), 7.99 (d, J = 9.4 Hz, 1H), 7.80 (s, 1H), 7.69 (d, J = 7.5 Hz, 2H), 7.65 – 7.54 (m, 5H), 7.48 (d, J = 9.0 Hz, 1H), 5.25 (s, 1H), 3.90 (s, 3H), 3.54 – 3.40 (m, 4H), 3.13 – 2.93 (m, 4H), 2.61 (s, 3H), 1.34 (d, J = 7.1 Hz, 3H), 0.97 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{35}H_{37}ClF_3N_5O_3S$ [M+H$^+$]: 700.2, 702.2 ; Found: 700.2, 702.2 (M + H$^+$).

Example 209. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(3-(4,4-dimethylpiperazin-1-ium-1-yl)-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (494).



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1*H*-indazol-5-yl)benzo[*d*]thiazol-6-yl)acetic acid

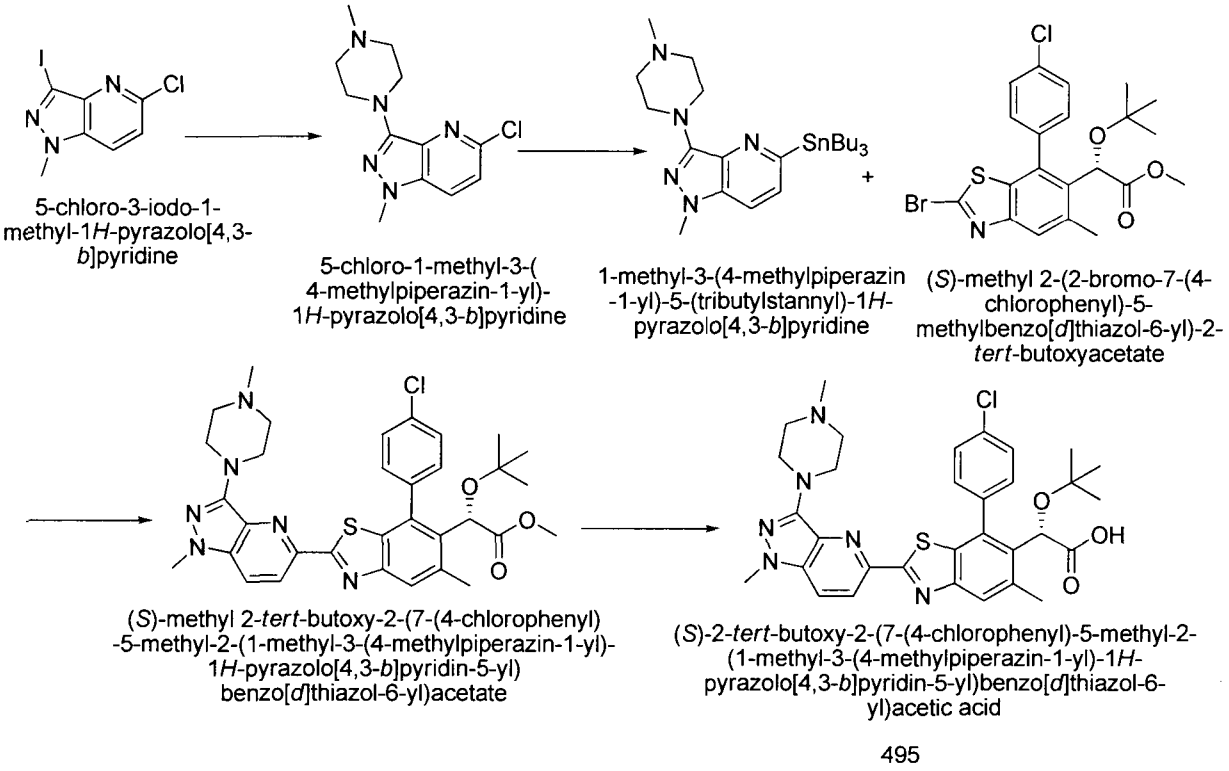


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(3-(4,4-dimethylpiperazin-1-ium-1-yl)-1-methyl-1*H*-indazol-5-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

494

Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(3-(4,4-dimethylpiperazin-1-ium-1-yl)-1-methyl-1H-indazol-5-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A vessel was charged with (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (15 mg), N,N-dimethylacetamide (500 μL), iodomethane (250 mg), and Cs_2CO_3 (50 mg). The vessel was sealed and warmed to 60 °C for 15 h. Ethanol (absolute, 0.5 mL) and 5M aq NaOH (0.5 mL) were added. Heating was continued at 60 °C. Then after 30 min, dioxane (0.5 mL) was added. Reaction was heated to 90 °C for 1 h. The reaction was cooled to 23 °C and directly purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA) giving the title compound. ^1H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.05 (d, J = 9.4 Hz, 1H), 7.80 (s, 1H), 7.69 (d, J = 9.5 Hz, 1H), 7.64 – 7.47 (m, 4H), 5.24 (s, 1H), 3.94 (s, 3H), 3.83 (d, J = 4.7 Hz, 4H), 3.75 – 3.67 (m, 4H), 2.69 (s, 6H), 2.61 (s, 3H), 0.96 (s, 9H).

Example 210. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-pyrazolo[4,3-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetic acid (495).



495

Preparation of 5-chloro-1-methyl-3-(4-methylpiperazin-1-yl)-1H-pyrazolo[4,3-b]pyridine: To a solution of 5-chloro-3-iodo-1-methyl-1H-pyrazolo[4,3-b]pyridine (104 mg, 0.354 mmol, containing the isomer 5-chloro-3-iodo-2-methyl-2H-pyrazolo[4,3-b]pyridine (360 mg, 1.22 mmol) was added 1-methylpiperazine (184 mg, 1.84 mmol), CuI (70 mg, 0.368 mmol), L-proline (84 mg, 0.736 mmol). The reaction mixture was heated at 100 °C for 4 h. The reaction was cooled, washed by sat. $NaHCO_3$, extracted with EtOAc, dried over $MgSO_4$, filtered, concentrated and purified by silica gel column, eluting by 0-100% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{12}H_{16}ClN_5$: 266.1 ($M+H^+$); Found: 266.2 ($M+H^+$).

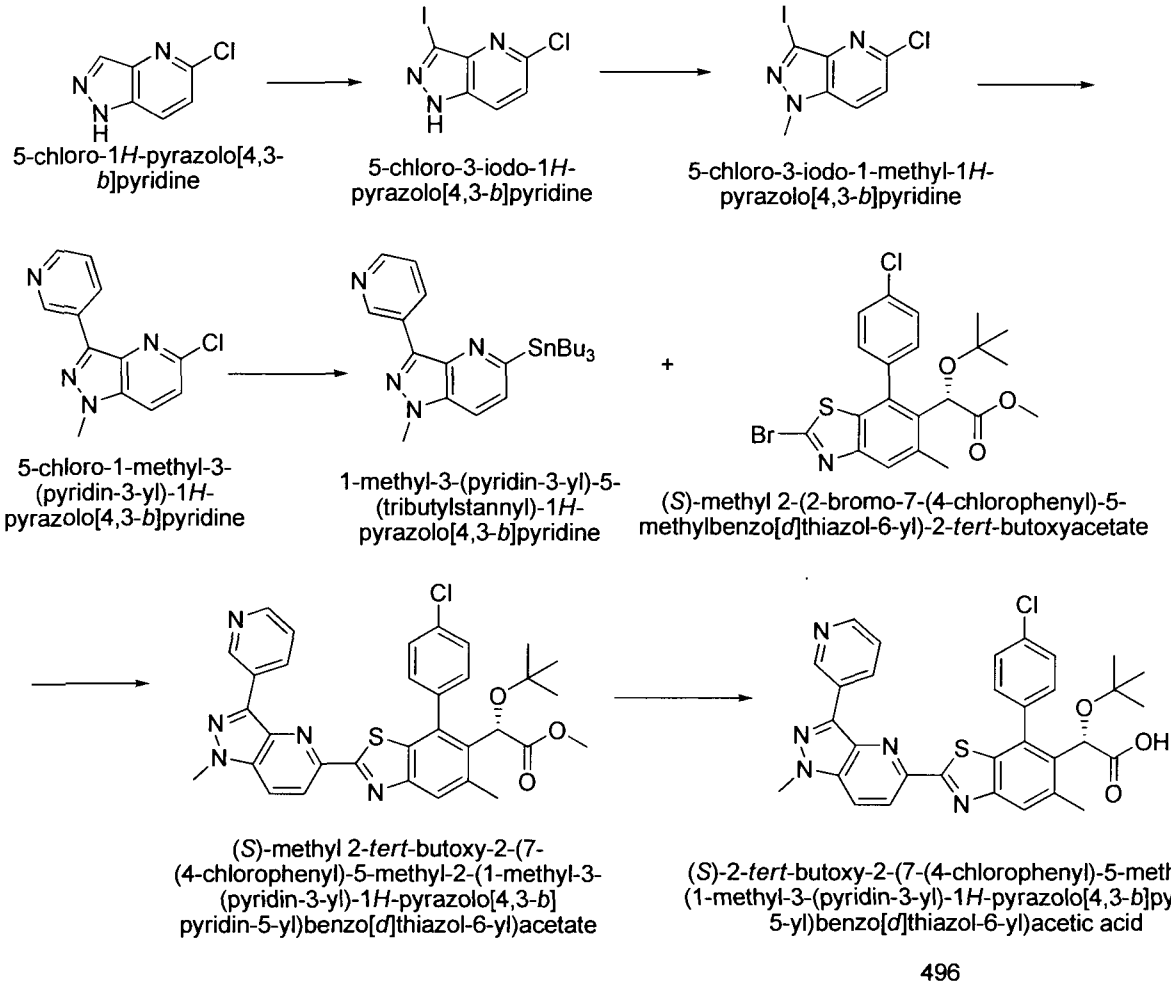
Preparation of 1-methyl-3-(4-methylpiperazin-1-yl)-5-(tributylstannyl)-1H-pyrazolo[4,3-b]pyridine: To a solution of 5-chloro-1-methyl-3-(4-methylpiperazin-1-yl)-1H-pyrazolo[4,3-b]pyridine (56 mg, 0.211 mmol) in toluene (12 mL), was added bis(tributyltin) (244 mg, 0.42 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol). The reaction mixture was heated at 170 °C for 1hr. The reaction mixture was cooled down, washed with H_2O, extracted by EtOAc, the organic phase was dried over $MgSO_4$, filtered, concentrated and purified by silica gel column to give the product. LCMS-ESI$^+$: calc'd for $C_{24}H_{43}N_5Sn$: 522.2 ($M+H^+$); Found: 522.1 ($M+H^+$).

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-pyrazolo[4,3-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-

butoxyacetate (22 mg, 0.046 mmol) in dioxane (2 mL), was added 1-methyl-3-(4-methylpiperazin-1-yl)-5-(tributylstannyl)-1H-pyrazolo[4,3-b]pyridine (20 mg, 0.038 mmol), CuI (7 mg, 0.038 mmol), LiCl (8 mg, 0.19 mmol) and $Pd(PPh_3)_4$ (4.4 mg, 0.004 mmol). The reaction mixture was heated at 100 °C for 2 h. The reaction was cooled, washed with sat. $NaHCO_3$, extracted with EtOAc, dried over $MgSO_4$, filtered, concentrated down and purified by silica gel column, first eluting by 0-100% EtOAc in hexanes, then eluting by 0-20% MeOH in dichloromethane to give the product. LCMS-ESI$^+$: calc'd for $C_{33}H_{37}ClN_6O_3S$: 633.2 ($M+H^+$); Found: 633.3 ($M+H^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-pyrazolo[4,3-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-(1-methyl-3-(4-methylpiperazin-1-yl)-1H-pyrazolo[4,3-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetate (11 mg, 0.017 mmol) in THF (0.5 mL) and MeOH (0.5 mL) was added 2N NaOH (174 μL). The reaction mixture was heated at 45 °C overnight. The reaction mixture was concentrated, the residue was dissolved in DMF and MeOH, filtered and purified by reverse phase HPLC (10-100% ACN/H_2O +0.1% TFA) to give the product. ^1H NMR (400 MHz, CD_3OD) δ 8.33 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 4.4 Hz, 1H), 7.85 (s, 1H), 7.70-7.57 (m, 4H), 5.22 (s, 1H), 4.75-4.74 (m, 2H), 3.92 (s, 3H), 3.61-3.59 (m, 2H), 3.36-3.34 (m, 4H), 2.94 (s, 3H), 2.61 (s, 3H), 0.96 (s, 9H). .LCMS-ESI$^+$: calc'd for $C_{32}H_{35}ClN_6O_3S$: 619.2 ($M+H^+$); Found: 619.3 ($M+H^+$).

Example 211. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-pyrazolo[4,3-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetic acid (496).



Preparation of 5-chloro-3-iodo-1H-pyrazolo[4,3-b]pyridine: To a solution of 5-chloro-1H-pyrazolo[4,3-b]pyridine (100mg, 0.65 mmol) in DMF (5 mL), was added KOH (91 mg, 1.63 mmol), I_2 (247 mg, 0.98 mmol) at 0 °C. The reaction mixture was stirred at 0 ° C for 5min and then stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and water. The organic phase was washed by sat. $NaHSO_3$, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column, eluting by 0-70% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_6H_3ClIN_3$: 279.9 ($M+H^+$); Found: 279.3 ($M+H^+$).

Preparation of 5-chloro-3-iodo-1-methyl-1H-pyrazolo[4,3-b]pyridine: To a solution of 5-chloro-3-iodo-1H-pyrazolo[4,3-b]pyridine (102 mg, 0.365 mmol) in DMF (3 mL), was added Cs_2CO_3 (237 mg, 0.73 mmol), MeI (35 µL, 0.55 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with EtOAc and water, the organic phase was dried over $MgSO_4$, filtered, concentrated and purified by silica gel column, eluting by 0-50% EtOAc in hexanes to give the product containing the isomer 5-chloro-3-iodo-

2-methyl-2H-pyrazolo[4,3-b]pyridine (in about 1.5:1 ratio). LCMS-ESI$^+$: calc'd for $C_7H_5ClIN_3$: 293.9 (M+H$^+$); Found: 294.1 (M+H$^+$).

Preparation of 5-chloro-1-methyl-3-(pyridin-3-yl)-1H-pyrazolo[4,3-b]pyridine: To a solution of 5-chloro-3-iodo-1-methyl-1H-pyrazolo[4,3-b]pyridine (104 mg, 0.354 mmol, containing the isomer 5-chloro-3-iodo-2-methyl-2H-pyrazolo[4,3-b]pyridine) was added pyridin-3-ylboronic acid (52 mg, 0.425 mmol). The reaction mixture was heated at 70 °C for 1hr. Then the temperature was raised to 90 °C and the reaction was stirred at 90 °C for 2 h. The reaction was cooled down, washed with sat. $NaHCO_3$, extracted with EtOAc, dried over $MgSO_4$, filtered, concentrated down and purified by silica gel column to give the product. LCMS-ESI$^+$: calc'd for $C_{12}H_9ClN_4$: 245.0 (M+H$^+$); Found: 245.3 (M+H$^+$).

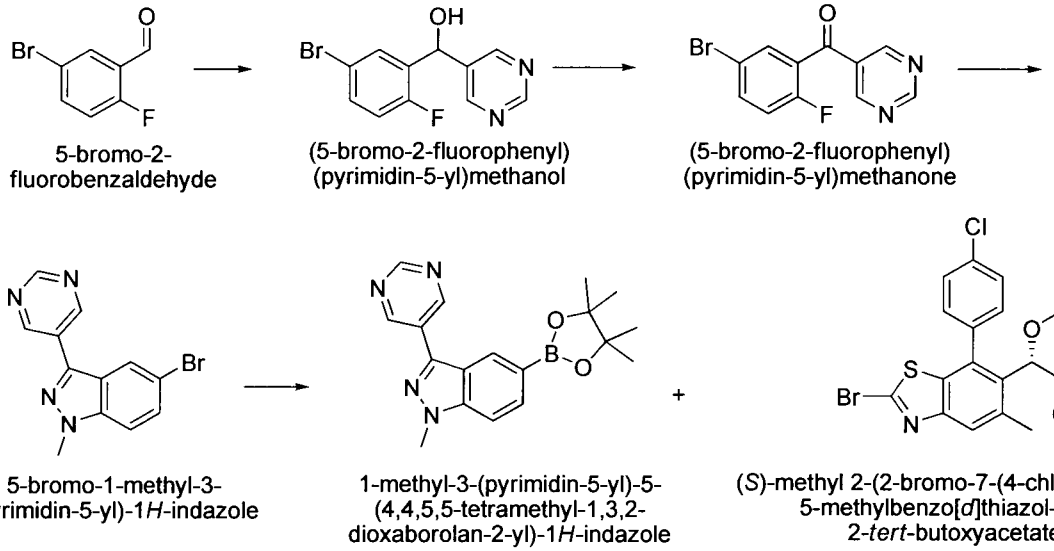
Preparation of 1-methyl-3-(pyridin-3-yl)-5-(tributylstannyl)-1H-pyrazolo[4,3-b]pyridine: To a solution of 5-chloro-1-methyl-3-(pyridin-3-yl)-1H-pyrazolo[4,3-b]pyridine (40 mg, 0.163 mmol) in toluene (5 mL), was added bis(tributyltin) (142 mg, 0.245 mmol) and $Pd(PPh_3)_4$ (19 mg, 0.016 mmol). The reaction mixture was heated at 170 °C for 1hr. The reaction mixture was cooled down, washed with H_2O, extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by silica gel column to give the product. LCMS-ESI$^+$: calc'd for $C_{24}H_{36}N_4Sn$: 501.2 (M+H$^+$); Found: 501.1 (M+H$^+$).

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-pyrazolo[4,3-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetate: To a solution of *(S)*-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-*tert*-butoxyacetate (8 mg, 0.018 mmol) in dioxane (2 mL), was added 1-methyl-3-(pyridin-3-yl)-5-(tributylstannyl)-1H-pyrazolo[4,3-b]pyridine (9 mg, 0.018 mmol),CuI (3.4 mg, 0.018 mmol), LiCl (3.8 mg, 0.09 mmol) and $Pd(PPh_3)_4$ (2 mg, 0.002 mmol). The reaction mixture was heated at 100 °C for 2 h. The reaction was cooled, washed with sat. $NaHCO_3$, extracted by EtOAc, dried over $MgSO_4$, filtered, concentrated down and purified by silica gel column, eluting with 0-100% EtOAc in hexanes to give the product. LCMS-ESI$^+$: calc'd for $C_{33}H_{30}ClN_5O_3S$: 612.2 (M+H$^+$); Found: 612.2 (M+H$^+$).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyridin-3-yl)-1H-pyrazolo[4,3-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-(1-methyl-3-(pyridin-3-yl)-1H-pyrazolo[4,3-b]pyridin-5-yl)benzo[d]thiazol-6-yl)acetate (6 mg, 0.01 mmol) in THF (0.5 mL)

and MeOH (0.5 mL) was added 2N NaOH (100 μL). The reaction mixture was heated at 45 °C overnight. The reaction mixture was concentrated, the residue was dissolved in DMF and MeOH, filtered and purified by reverse phase HPLC (10-100% ACN/H_2O +0.1% TFA) to give the product (3 mg). ^{1}H NMR (400 MHz, CD_3OD) δ 9.70 (bs, 1H), 8.97 (d, J = 3.8 Hz, 1H), 8.60 (bs, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.14 (d, J = 4.2 Hz, 1H), 7.84-7.56 (m, 6H), 5.24 (s, 1H), 4.13 (s, 3H), 2.63 (s, 3H), 0.98 (s, 9H). LCMS-ESI$^+$: calc'd for $C_{32}H_{28}ClN_5O_3S$: 598.2 ($M+H^+$); Found: 598.2 ($M+H^+$).

Example 212. Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyrimidin-5-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid (497).



497

Preparation of (5-bromo-2-fluorophenyl)(pyrimidin-5-yl)methanol: To an oven-dried flask was added anhydrous THF (40 mL) and 5-bromopyrimidine (6.36 g, 40 mmol). 2M isopropylmagnesium chloride in THF (22 mL) was then added dropwise over several minutes at 0 °C. The mixture was stirred at 0 °C for 30 minutes, and then 5-bromo-2-fluorobenzaldehyde (2.4 mL, 20 mmol) was added. After warming to room temperature, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, dried over

$MgSO_4$, and purified by column chromatography (gradient 0 to 60% EtOAc in hexanes) to afford the product. ^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.74 (s, 2H), 7.71 (dd, J = 6.4, 2.5 Hz, 1H), 7.43 (ddd, J = 8.7, 4.6, 2.6 Hz, 1H), 6.95 (dd, J = 9.5, 8.9 Hz, 1H), 6.15 (s, 1H).

Preparation of (5-bromo-2-fluorophenyl)(pyrimidin-5-yl)methanone: To a stirring solution of (5-bromo-2-fluorophenyl)(pyrimidin-5-yl)methanol (2.42 g, 8.55 mmol) in DCM (40 mL) was added Dess-Martin periodinane (4 g, 9.4 mmol) portion-wise over several minutes. The reaction was then quenched with saturated 1:1 $Na_2S_2O_3$/$NaHCO_3$ solution (80 mL) and stirred until gas evolution ceased. The aqueous layer was extracted with DCM, dried over $MgSO_4$, and purified by column chromatography (gradient 0 to 30% EtOAc in hexanes) to give the product. ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 9.09 (d, J = 1.6 Hz, 2H), 7.81 (dd, J = 6.0, 2.6 Hz, 1H), 7.74 (ddd, J = 8.8, 4.5, 2.6 Hz, 1H), 7.13 (t, J = 9.1 Hz, 1H).

Preparation of 5-bromo-1-methyl-3-(pyrimidin-5-yl)-1H-indazole: A heavy wall pressure flask was charged with (5-bromo-2-fluorophenyl)(pyrimidin-5-yl)methanone (2.08 g, 7.4 mmol) and dioxane (20 mL). Methylhydrazine (0.86 mL, 16.3 mmol) was then added, and the mixture was heated to 100 °C for 16 hours. The crude mixture was concentrated, and the residue suspended in DCM. After storing at -10 °C for 2 hours, the precipitated solids were filtered off to give the product. ^1H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 2H), 9.22 (s, 1H), 8.39 (d, J = 1.1 Hz, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.62 (dd, J = 8.9, 1.7 Hz, 1H), 4.15 (s, 3H).

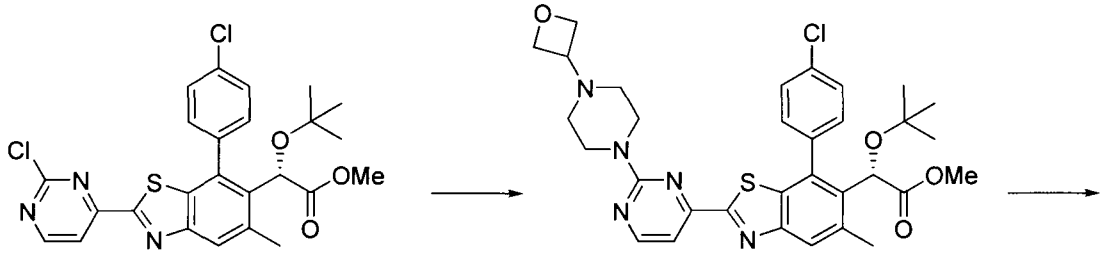
Preparation of 1-methyl-3-(pyrimidin-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole: To a vial flushed with argon was added 5-bromo-1-methyl-3-(pyrimidin-5-yl)-1H-indazole (376 mg, 1.3 mmol), $PdCl_2$(dppf)·DCM (107 mg, 0.13 mmol), bis(pinacolato)diboron (363 mg, 1.43 mmol), and KOAc (383 mg, 3.9 mmol). Anhydrous dioxane (7 mL) was added, and the mixture was heated to 90 °C for 3 hours. After cooling to room temperature, the crude reaction was filtered over a plug of Celite, concentrated, and the crude product used directly without further purification. LCMS-ESI$^+$: calc'd for $C_{18}H_{22}BN_4O_2$: 337.2 ($M+H^+$); Found: 337.3 ($M+H^+$).

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyrimidin-5-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate: To a vial flushed with argon was added (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (110 mg, 0.23 mmol), 1-methyl-3-(pyridin-3-

yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (92 mg, 0.27 mmol), $Pd(PPh_3)_4$ (26 mg, 23 μmol), and K_2CO_3 (95 mg, 0.68 mmol). De-gassed dioxane (2 mL) and water (0.5 mL) were then added, and the reaction was heated to 100 °C for 1 h. After cooling to room temperature, the reaction was filtered over a plug of Celite, concentrated, and purified by column chromatography (gradient 0 to 50% EtOAc in hexanes) to give the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 2H), 9.27 (s, 1H), 8.56 (s, 1H), 8.22 (dd, *J* = 8.9, 1.3 Hz, 1H), 7.88 (s, 1H), 7.59 – 7.45 (m, 5H), 5.22 (s, 1H), 4.19 (s, 3H), 3.75 (s, 3H), 2.60 (s, 3H), 0.99 (s, 9H).

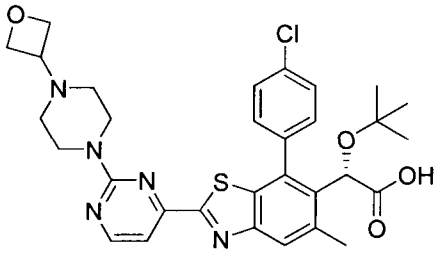
Preparation of (S)-2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyrimidin-5-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetic acid: To a vial was dissolved (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(1-methyl-3-(pyrimidin-5-yl)-1H-indazol-5-yl)benzo[d]thiazol-6-yl)acetate (130 mg, 0.212 mmol) in THF (3 mL) and MeOH (1.5 mL). 1M NaOH (1.5 mL) was added, and the mixture was heated to 50 °C for 3 hours. The reaction was cooled to room temperature, and filtered (0.45 micron teflon syringe filter). The filtrate was was purified by reverse phase column chromatography (5-100% ACN/H_2O + 0.1% TFA). Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{32}H_{29}ClN_5O_3S$: 598.1 ($M+H^+$); Found: 598.2 ($M+H^+$). ^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (s, 2H), 9.14 (s, 1H), 8.57 (s, 1H), 8.01 (d, *J* = 8.9 Hz, 1H), 7.77 (s, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.58 (d, *J* = 6.0 Hz, 3H), 5.25 (s, 1H), 4.13 (s, 3H), 2.61 (s, 3H), 0.98 (s, 9H).

Example 213. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid (336).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

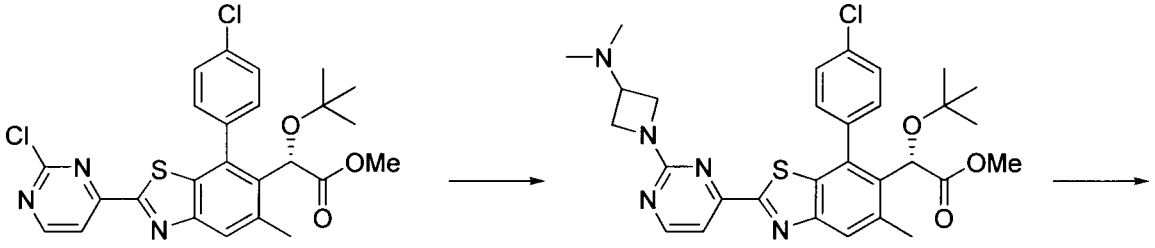
336

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate: To *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (49.0 mg, 0.095 mmol) was added 1-(oxetan-3-yl)piperazine (27.0 mg, 0.190 mmol) in 1,4-dioxane (1 mL). The reaction mixture was stirred at room temperature for 6 h. Upon completion of the reaction, the reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{32}H_{37}ClN_5O_4S$ (M + H^+): 622.2; Found: 622.2 (M+H^+).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetic acid: To crude *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidin-4-yl)benzo[d]thiazol-6-yl)acetate in THF (0.5 mL) and methanol (0.5 mL) was added NaOH (0.47 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{31}H_{35}ClN_5O_4S$ (M + H^+): 608.2; Found: 608.2 (M+H^+). ^{1}H

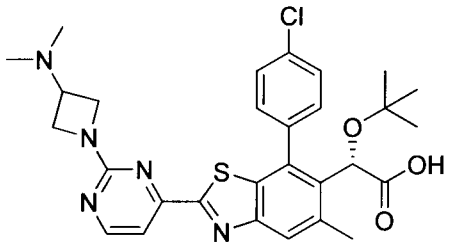
NMR (400 MHz, Methanol-d_4) δ 8.62 (d, J = 5.0 Hz, 1H), 7.92 (s, 1H), 7.70 – 7.64 (m, 1H), 7.63 – 7.52 (m, 4H), 5.25 (s, 1H), 4.93 – 4.88 (m, 2H), 4.83 – 4.77 (m, 2H), 4.57 – 3.46 (m, 5H), 3.22 (br s, 4H), 2.63 (s, 3H), 0.98 (s, 9H).

Example 214. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-(dimethylamino)azetidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid (333).



(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-(dimethylamino)azetidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate



(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-(dimethylamino)azetidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetic acid

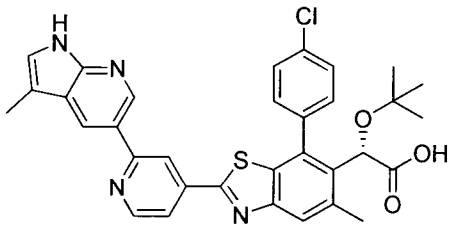
333

Preparation of *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-(dimethylamino)azetidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: To *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate (30.0 mg, 0.058 mmol) and 3-(dimethylamino)azetidine dihydrochloride (30.2 mg, 0.174 mmol) in 1.4-dioxane (1 mL) was added triethylamine (58.8 mg, 81.0 μL, 0.581 mmol). The reaction mixture was heated at 50 °C for 1 h. Upon completion of the reaction, the reaction mixture was filtered through Celite (ethyl acetate eluent), concentrated, and used without further purification. LCMS-ESI$^+$ calc'd for $C_{30}H_{35}ClN_5O_3S$ (M + H^+): 580.2; Found: 580.1 (M+H^+).

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-(dimethylamino)azetidin-

1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetic acid: To crude *(S)*-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-(3-(dimethylamino)azetidin-1-yl)pyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate in THF (0.5 mL) and methanol (0.5 mL) was added NaOH (0.29 mL of a 2N solution). The reaction mixture was heated at 30 °C overnight, then cooled, filtered, and purified by reverse phase HPLC, eluting with 5-100% acetonitrile in water with 0.1% TFA. Fractions containing the product were pooled and lyophilized to provide the TFA salt of the product. LCMS-ESI$^+$: calc'd for $C_{29}H_{33}ClN_5O_3S$ (M + H^+): 566.2; Found: 566.1 (M+H^+). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.59 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.70 – 7.50 (m, 5H), 5.26 (s, 1H), 4.54 – 4.44 (m, 2H), 4.34 – 4.15 (m, 3H), 2.95 (s, 6H), 2.63 (s, 3H), 0.98 (s, 9H).

Example 215. Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (498).

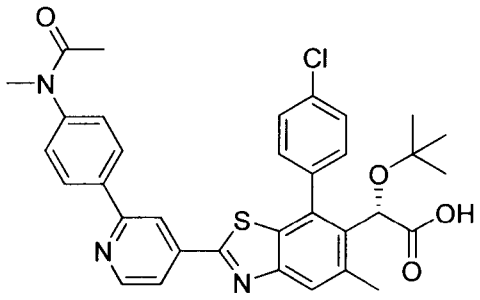


(*S*)-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridin-4-yl)benzo[*d*]thiazol-6-yl)acetic acid

498

Preparation of *(S)*-2-*tert*-butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: *(S)*-2-*tert*-Butoxy-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid can be prepared from the ethyl ester ((S)-ethyl 2-(tert-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(3-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetate) by the following the hydrolysis step described in method H. LCMS-ESI$^+$: calc'd for $C_{33}H_{29}ClN_4O_3S$: 597.2 (M+H^+); found: 597.2 (M+H^+).^{1}H NMR (400 MHz, CD_3OD): δ 8.99 (s, 1H), 8.96 (s, 1H), 8.82 (d, J = 5.6 Hz, 1H), 8.66 (s, 1H), 8.06-8.03 (m, 1H), 7.98 (s, 1H), 7.73-7.65 (m, 1H), 7.65 – 7.60 (m, 3H), 7.37 (s, 1H), 5.28 (s, 1H), 2.65 (s, 3H), 2.45 (s, 3H), 0.98 (s, 9H).

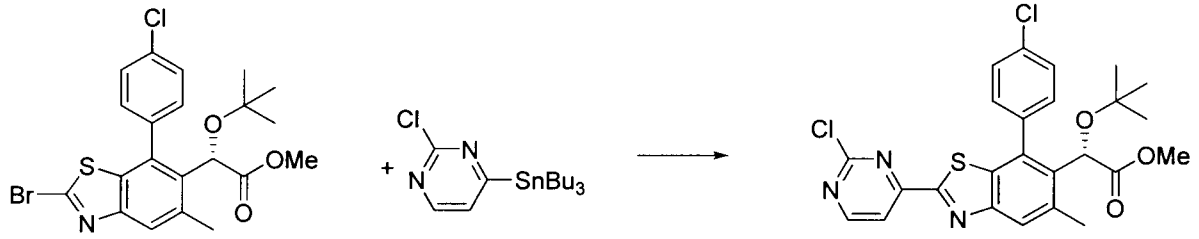
Example 216. Preparation of (*S*)-2-(tert-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(N-methylacetamido)phenyl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid (499).



499

Preparation of (*S*)-2-(tert-butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(N-methylacetamido)phenyl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid: (*S*)-2-(tert-Butoxy)-2-(7-(4-chlorophenyl)-5-methyl-2-(2-(4-(N-methylacetamido)phenyl)pyridin-4-yl)benzo[d]thiazol-6-yl)acetic acid was prepared following the procedure of method W . LCMS-ESI$^+$: calc'd for $C_{34}H_{32}ClN_3O_4S$: 614.15 ($M+H^+$); found: 614.2 ($M+H^+$). ^1H NMR (400 MHz, CD_3OD) δ 8.66 (d, J = 4.8 Hz, 1H), 8.41 (s, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 5.2 Hz, 1H), 7.81 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.51 – 7.48 (m, 3H), 7.40 (d, J = 8.0 Hz, 2H), 5.18 (s, 1H), 3.21 (s, 3H), 2.52 (s, 3H), 1.87 (s, 3H), 0.88 (s, 9H).

Example 217. Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate.



(*S*)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[*d*]thiazol-6-yl)-2-*tert*-butoxyacetate

2-chloro-4-(tributylstannyl) pyrimidine

(*S*)-methyl 2-*tert*-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[*d*]thiazol-6-yl)acetate

Preparation of (S)-methyl 2-tert-butoxy-2-(7-(4-chlorophenyl)-2-(2-chloropyrimidin-4-yl)-5-methylbenzo[d]thiazol-6-yl)acetate: A microwave vial was charged with (S)-methyl 2-(2-bromo-7-(4-chlorophenyl)-5-methylbenzo[d]thiazol-6-yl)-2-tert-butoxyacetate (496.3 mg, 1.03 mmol), tetrakis(triphenylphosphine)palladium(0) (178.2 mg, 0.15 mmol), lithium chloride (43.6 mg, 1.03 mmol), and copper(I) iodide (58.7 mg, 0.31 mmol) and the vial was evacuated and backfilled with argon (3x). To this mixture was added 2-chloro-4-(tributyl)stannyl pyrimidine (456.3 mg, 1.13 mmol) in 1,4-dioxane (10 mL). The reaction mixture was heated at 90 °C

overnight, then 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 $C_{25}H_{23}Cl_2N_3O_3S$ (M + H^+): 516.1; Found: 516.2 (M+H^+).

Example 218.

The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I or I' ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
Compound X=	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
Compound X=	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
Compound X=	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection 1 (1 mg/ml)	mg/ml
Compound X= (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
Compound X= (free acid form)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(vi) Aerosol	mg/can
Compound X=	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

All references, including publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred 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 use of the terms "a" and "an" and "the" and similar references in the context of this disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., such as, preferred, preferably) provided herein, is intended merely to further illustrate the content of the disclosure and does not pose a limitation on the scope of the claims. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the present disclosure.

Alternative embodiments of the claimed disclosure are described herein, including the best mode known to the inventors for practicing the claimed invention. Of these, variations of the disclosed embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing disclosure. The inventors expect skilled artisans to employ such variations as appropriate (e.g., altering or combining features or embodiments), and the inventors intend for the invention to be practiced otherwise than as specifically described herein.

Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any

combination of the above described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

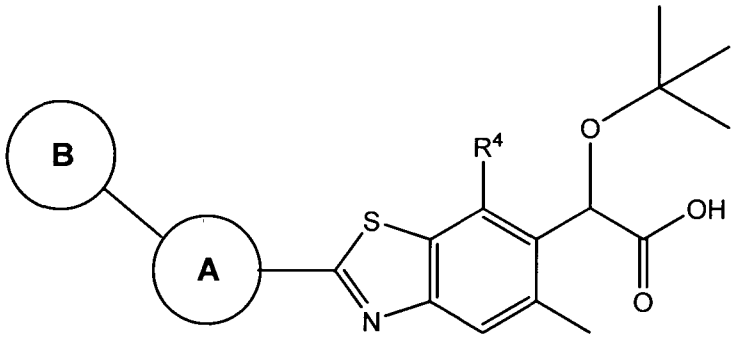
The use of individual numerical values is stated as approximations as though the values were preceded by the word "about" or "approximately." Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about" or "approximately." In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms "about" and "approximately" when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the disclosed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered include the criticality of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to limit how the use of the words "about" or "approximately" will serve to broaden a particular numerical value or range. Thus, as a general matter, "about" or "approximately" broaden the numerical value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term "about" or "approximately." Thus, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.

It is to be understood that any ranges, ratios and ranges of ratios that can be formed by, or derived from, any of the data disclosed herein represent further embodiments of the present disclosure and are included as part of the disclosure as though they were explicitly set forth. This includes ranges that can be formed that do or do not include a finite upper and/or lower boundary. Accordingly, a person of ordinary skill in the art most closely related to a particular range, ratio or range of ratios will appreciate that such values are unambiguously derivable from the data presented herein.

CLAIMS

What is claimed is:

1. A compound of formula I':



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, $(C_1$-$C_6)$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;

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, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$alkenyl, $(C_2$-$C_3)$alkynyl, $(C_1$-$C_3)$haloalkyl, $(C_3$-$C_7)$carbocycle, 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 and heterocycle of Z^{1a} is optionally substituted with one or more halogen or $(C_1$-$C_6)$alkyl;

each Z^{1b} is independently selected from halo, CN, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$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, wherein any $(C_3$-$C_7)$carbocycle and heterocycle of Z^{1b} is optionally substituted with one or more halogen or $(C_1$-$C_6)$alkyl; and

R_a, R_b, R_c and R_d are each independently H or $(C_1\text{-}C_6)$alkyl;

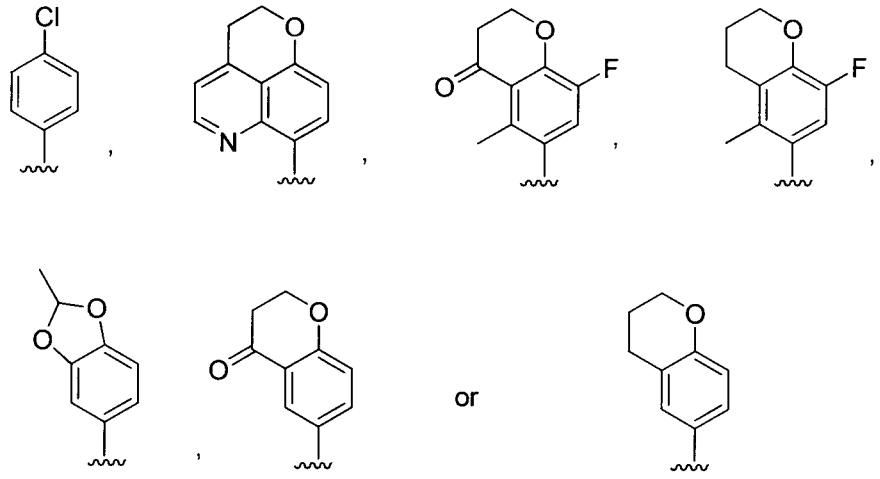
or a salt thereof.

2. The compound of claim 1 wherein the configuration of the $-OC(CH_3)_3$ group as shown in formula I' is the (*S*) stereochemistry.

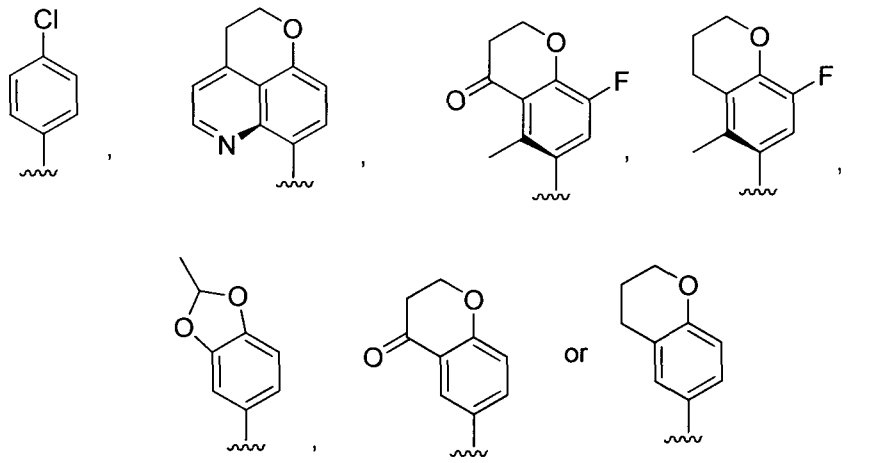
3. The compound of claim 1 or claim 2 wherein R^4 is selected from aryl, heterocycle and heteroaryl, wherein any aryl, heterocycle and heteroaryl of R^4 is optionally substituted with one or more halo or $(C_1\text{-}C_6)$alkyl.

4. The compound claim 1 or claim 2 wherein 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.

5. The compound of claim 1 or claim 2 wherein R^4 is:



6. The compound of claim 1 or claim 2 wherein R^4 is:



7. The compound of any one of claims 1-6 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 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 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.

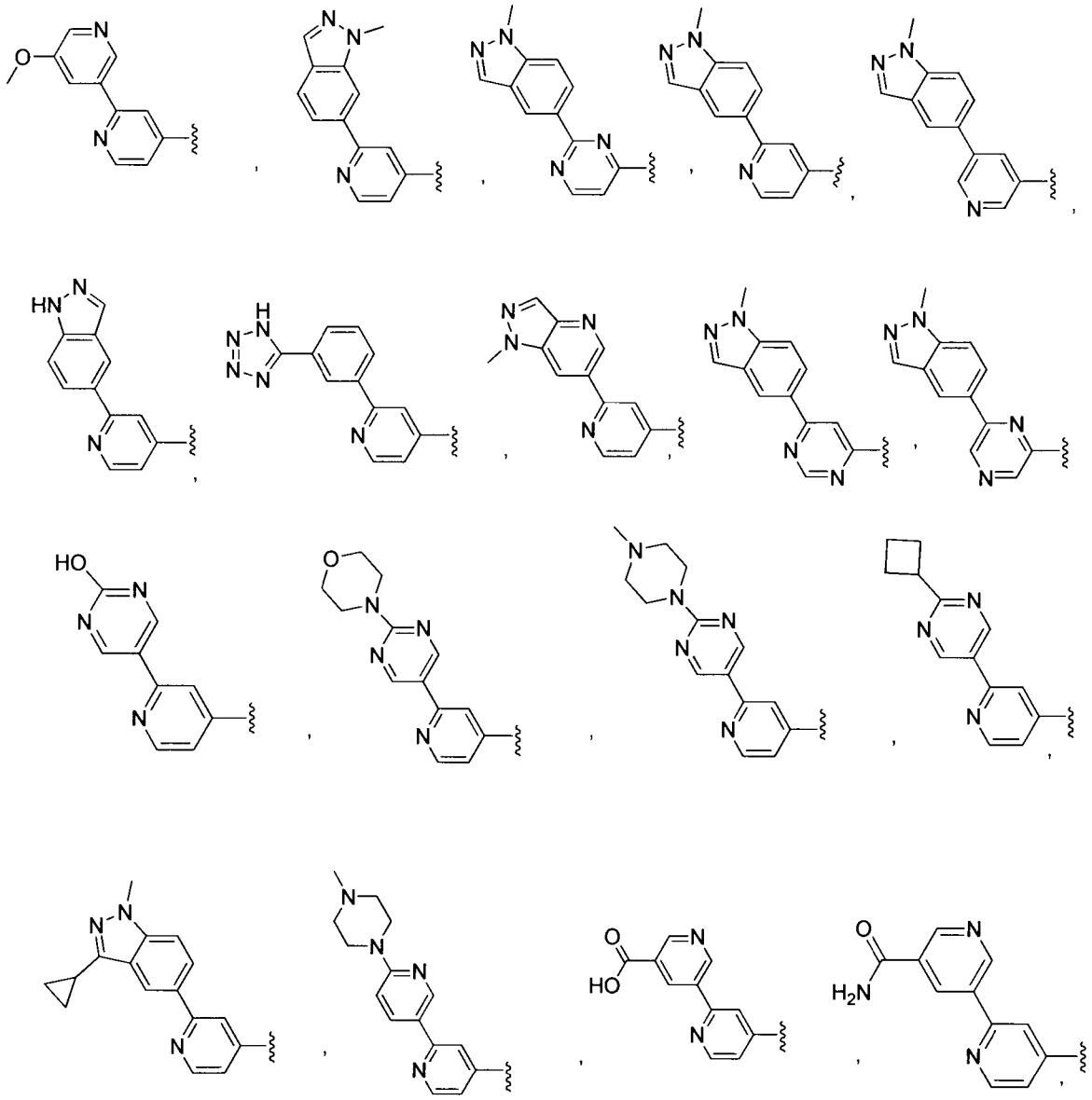
10. The compound of any one of claims 1-6 wherein A is pyridinyl, pyrimidinyl or pyrazinyl and B is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of B is optionally substituted with one or more Z^{1b} groups.

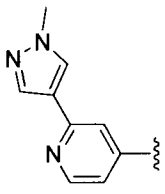
11. The compound of any one of claims 1-6 wherein A and B together form a bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle, wherein bicyclic aryl, bicyclic heteroaryl or bicyclic heterocycle is optionally substituted with one or more Z^{1b} groups.

12. The compound of any one of claims 1-6 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 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 wherein A-B is selected from:

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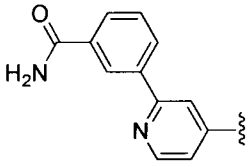
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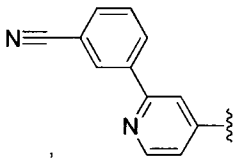
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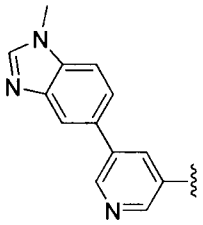
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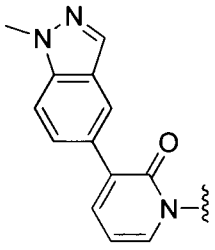
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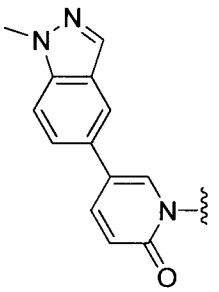
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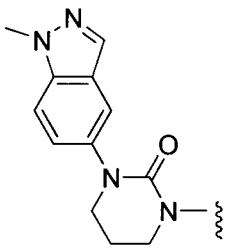
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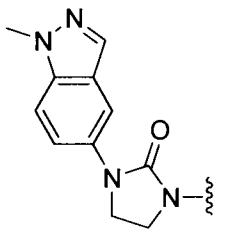
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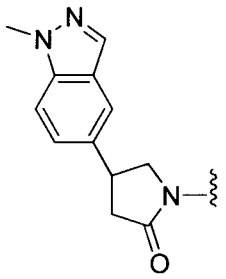
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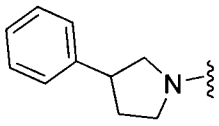
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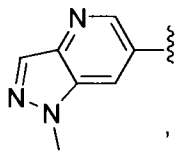
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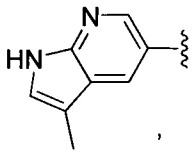
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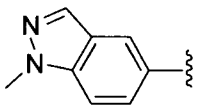
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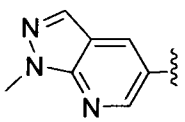
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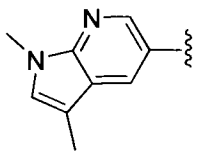
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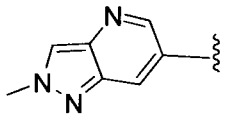
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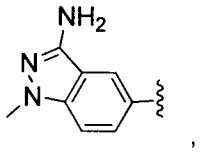
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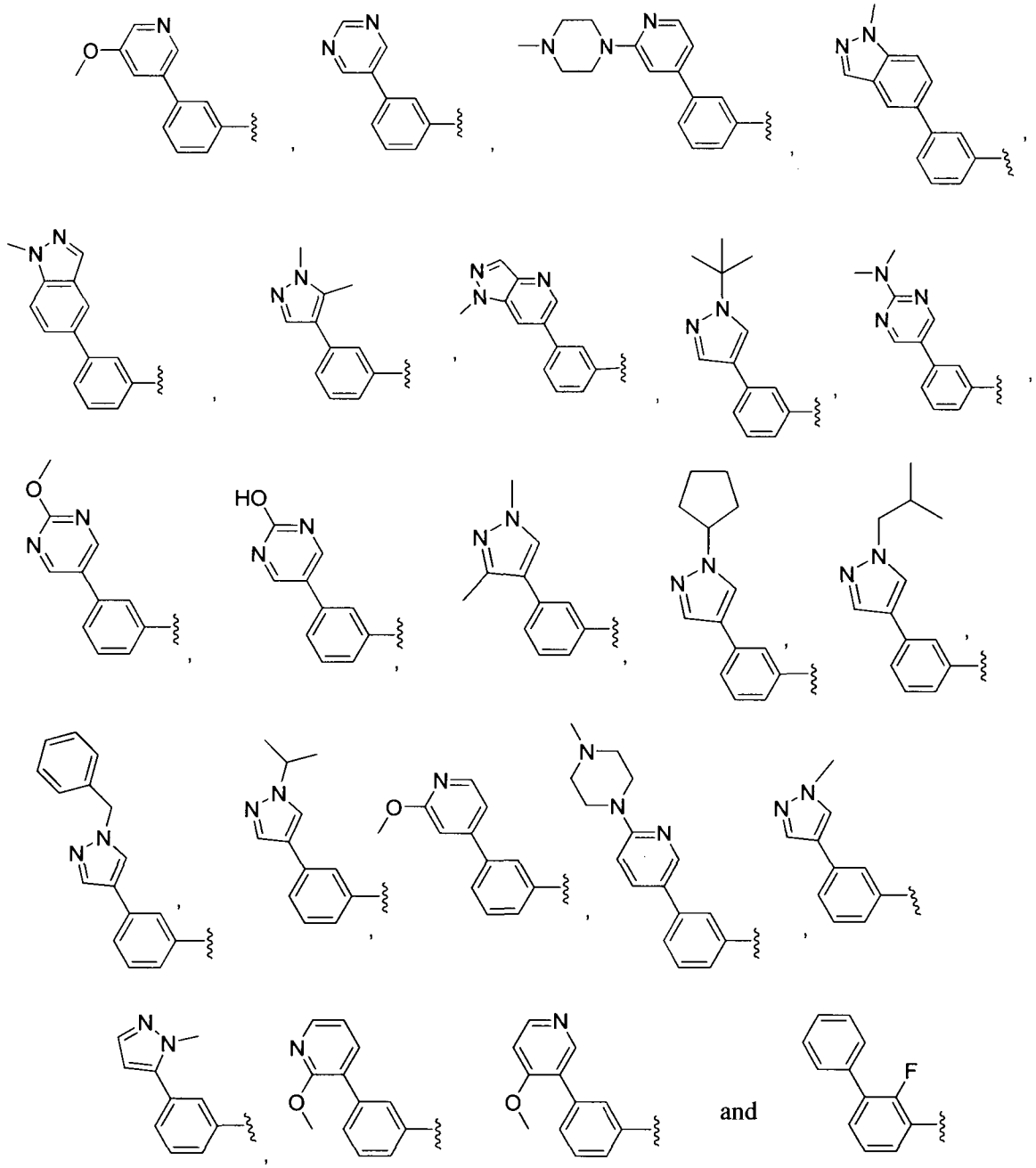
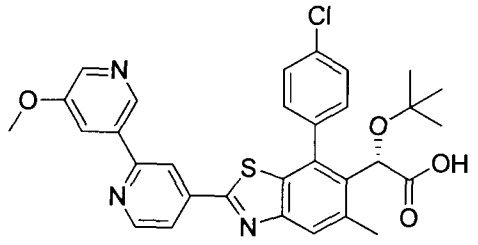


and

15. The compound of claim 1 wherein the salt is a pharmaceutically acceptable salt.

16. The compound of claim 1 which is selected from:



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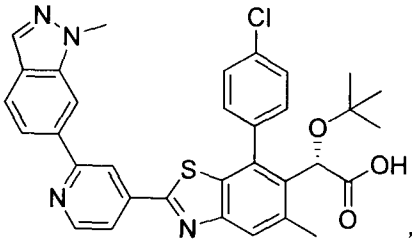

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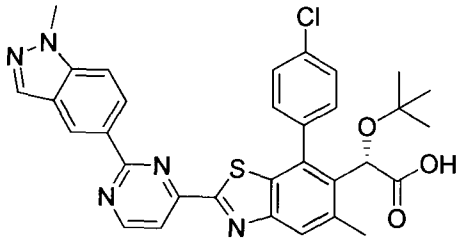

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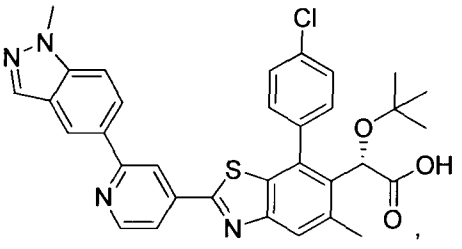

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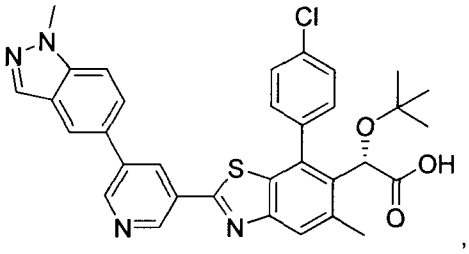

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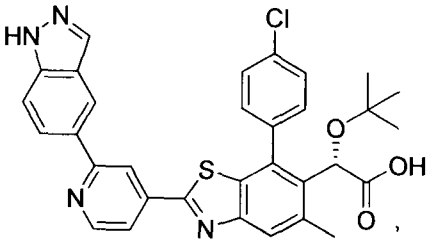

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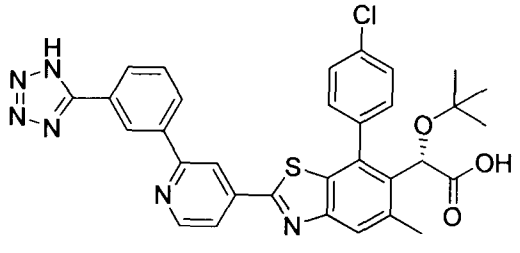

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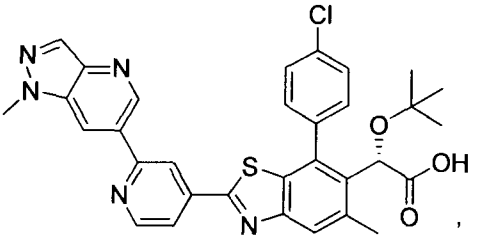

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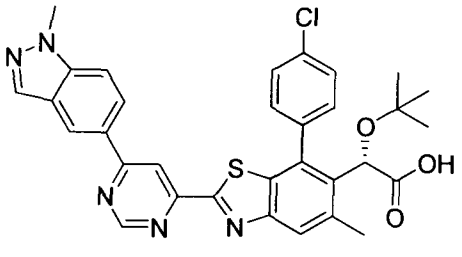

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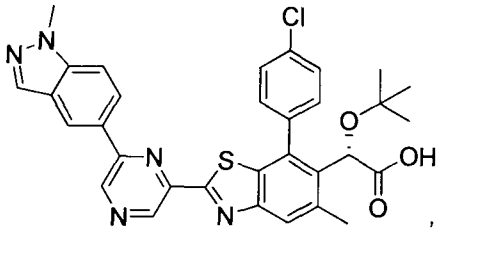

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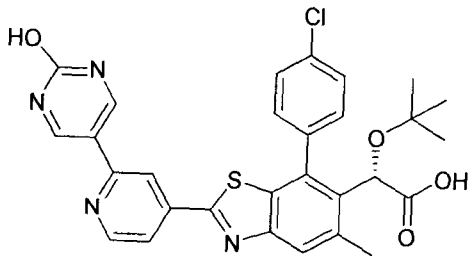

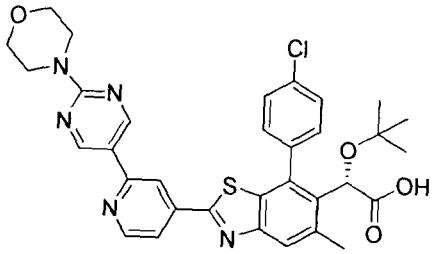

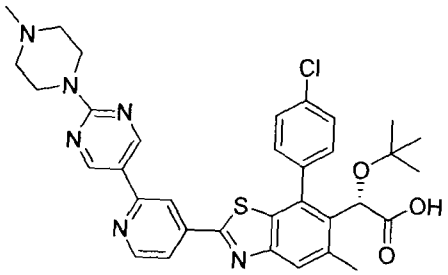

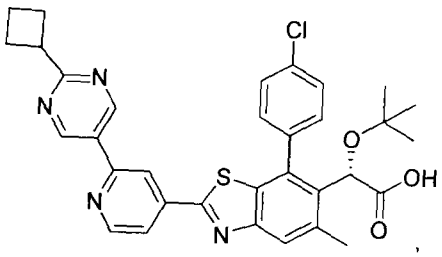

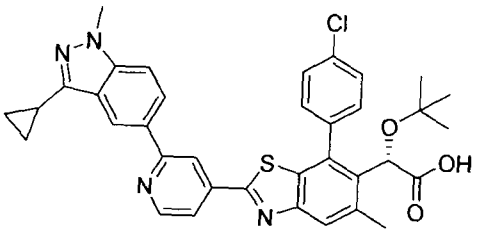

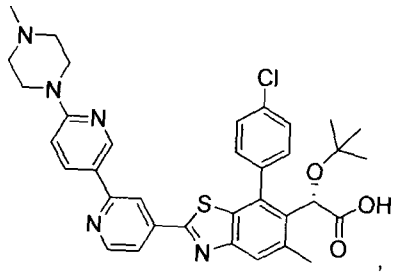

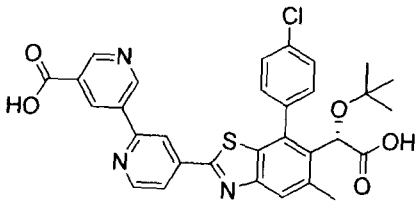

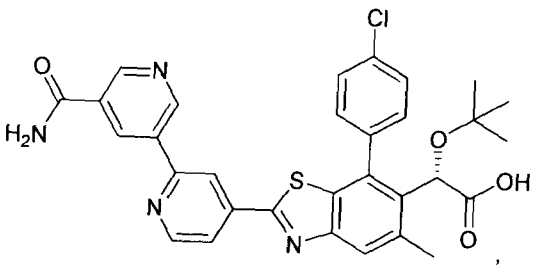

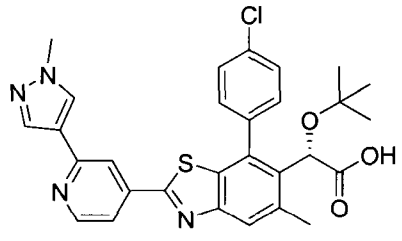

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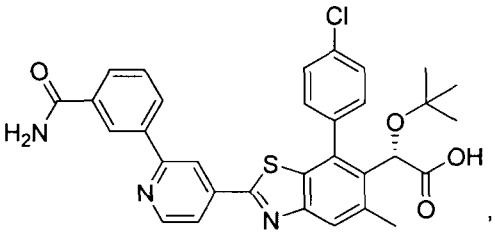

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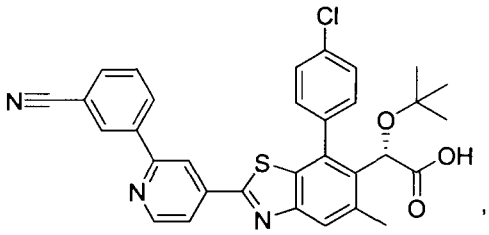

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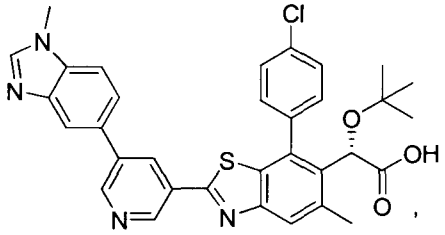

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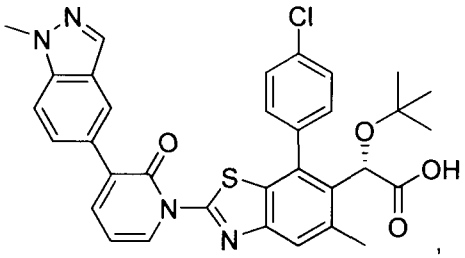

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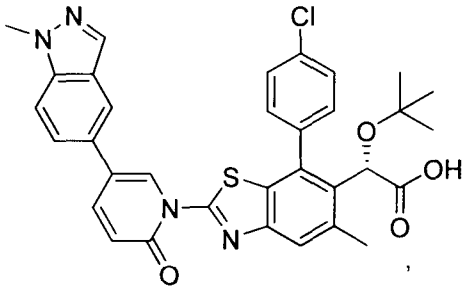

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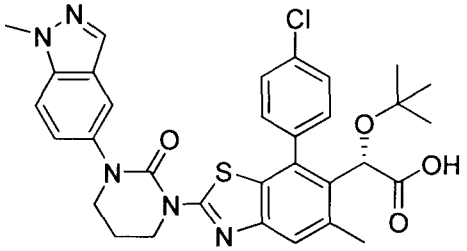

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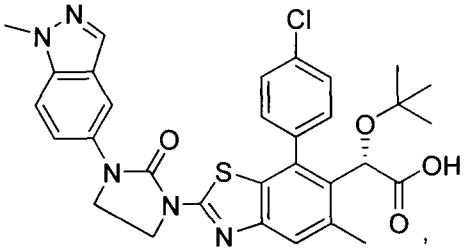

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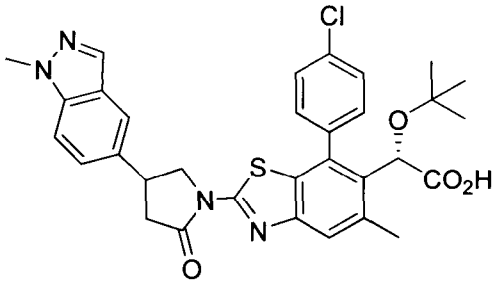

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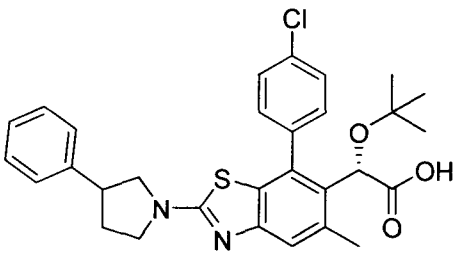

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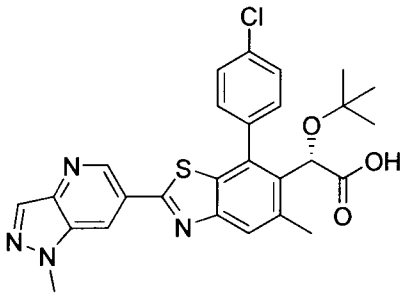

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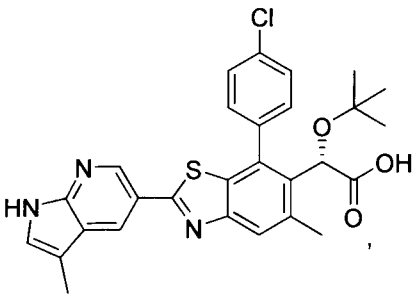

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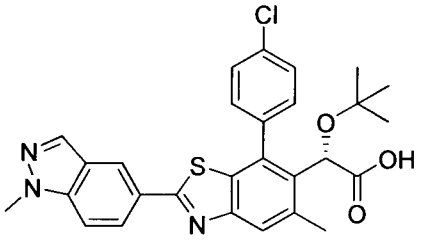

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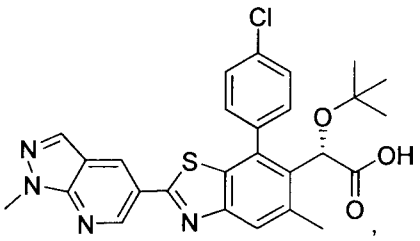

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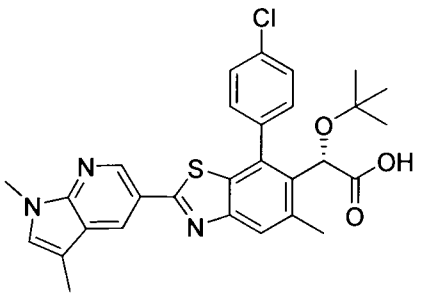

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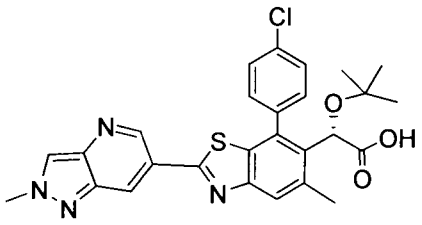

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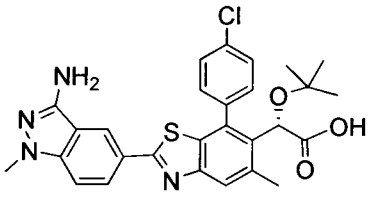

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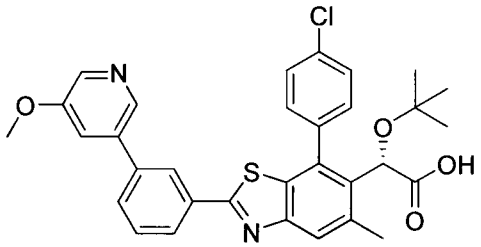

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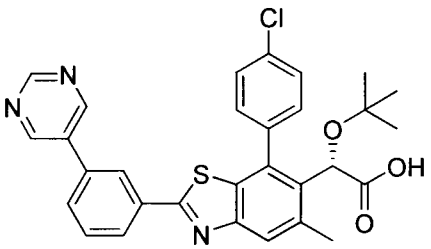

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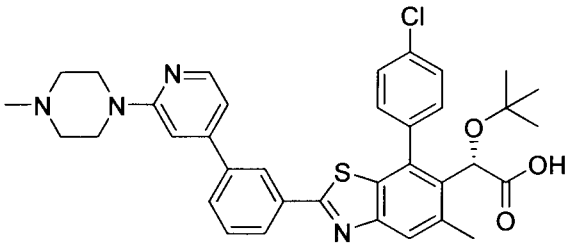

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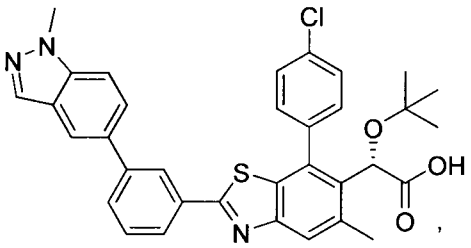

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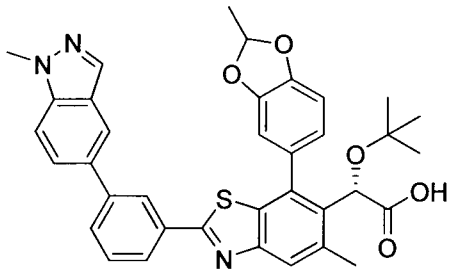

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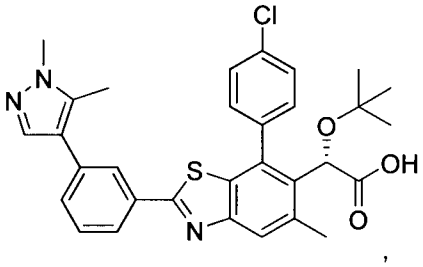

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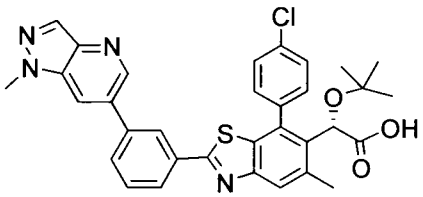

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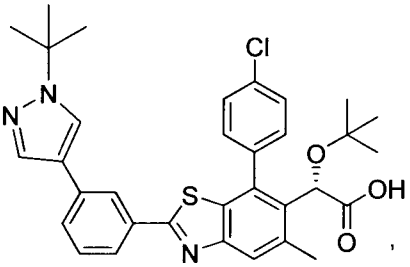

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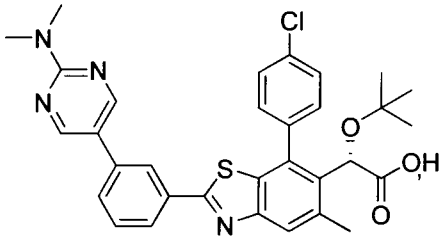

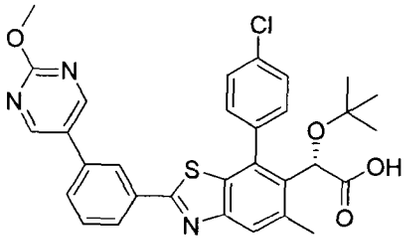

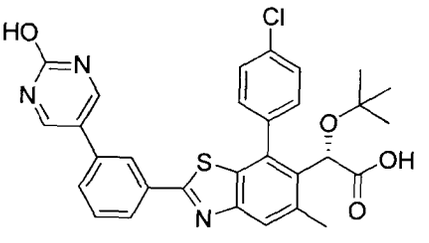

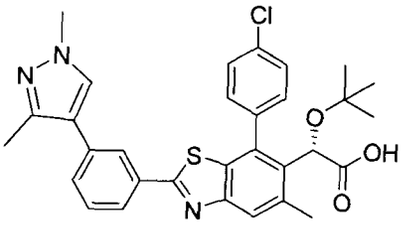

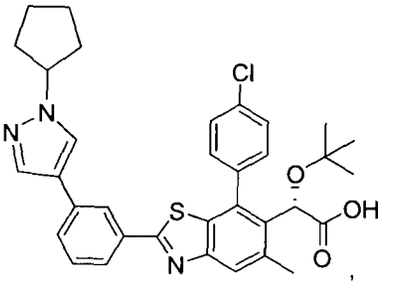

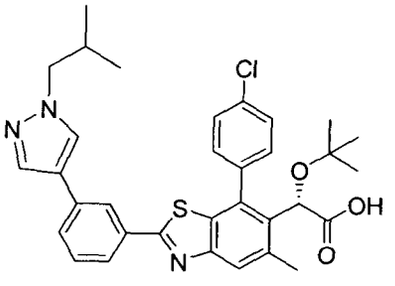

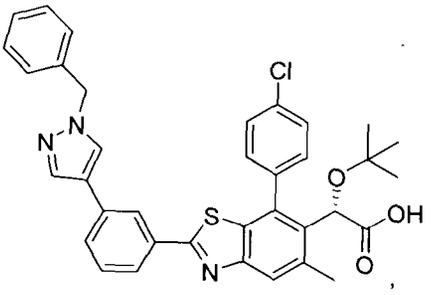

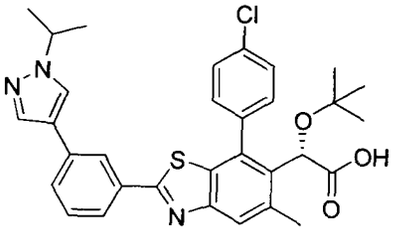

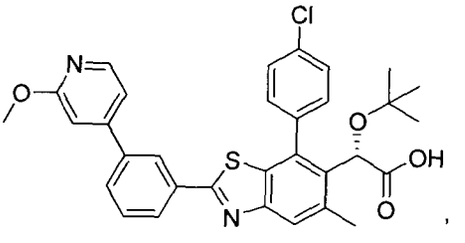

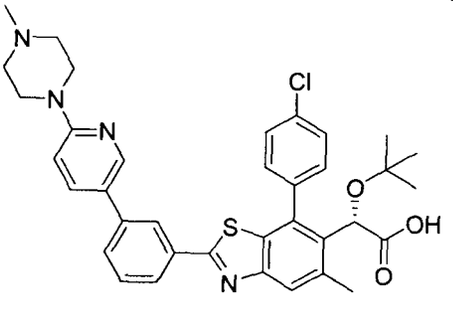

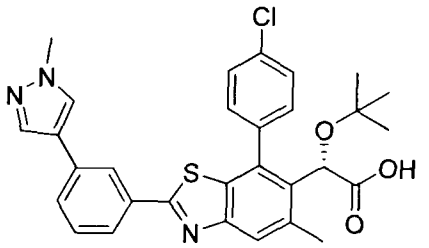

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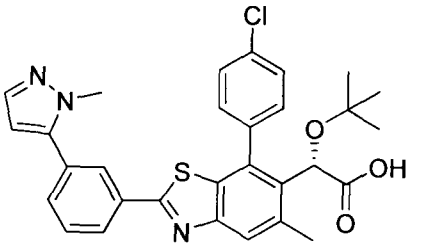

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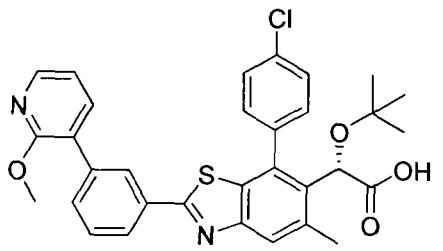

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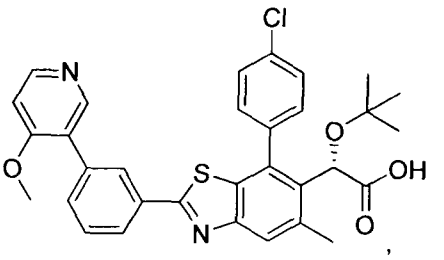

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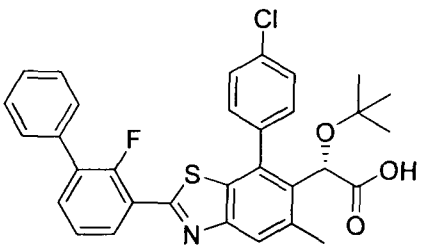

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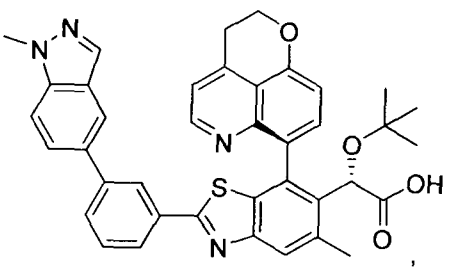

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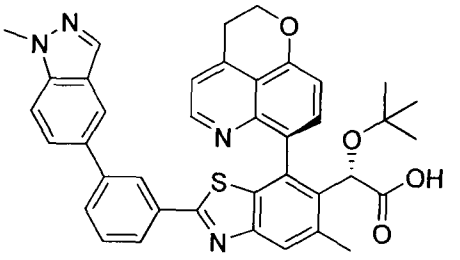

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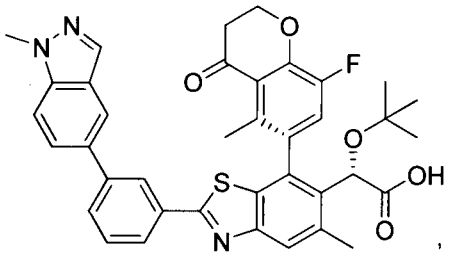
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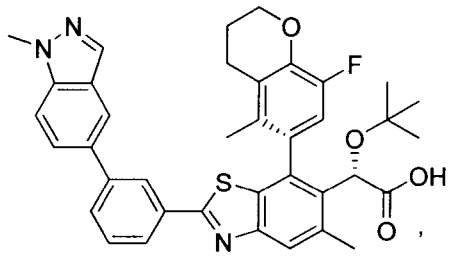
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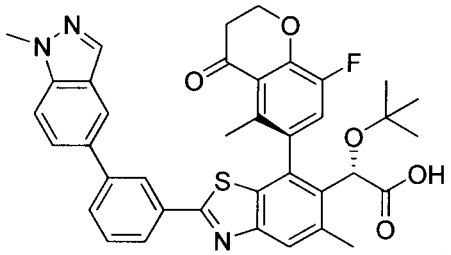
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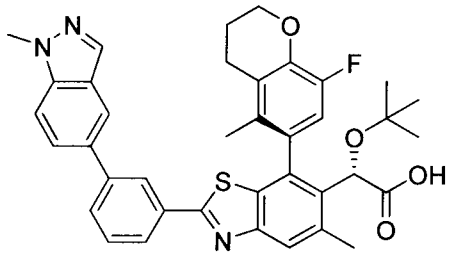
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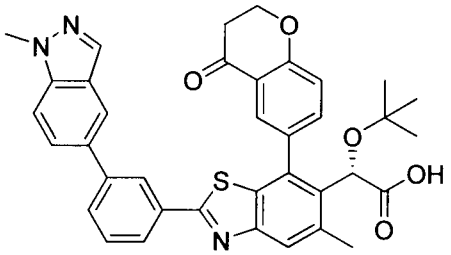
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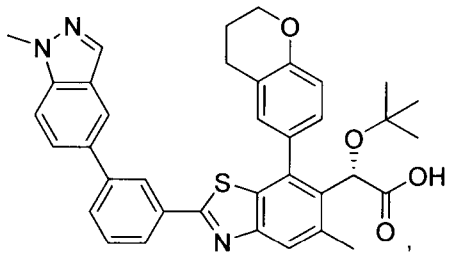
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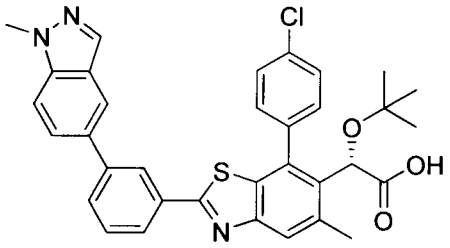
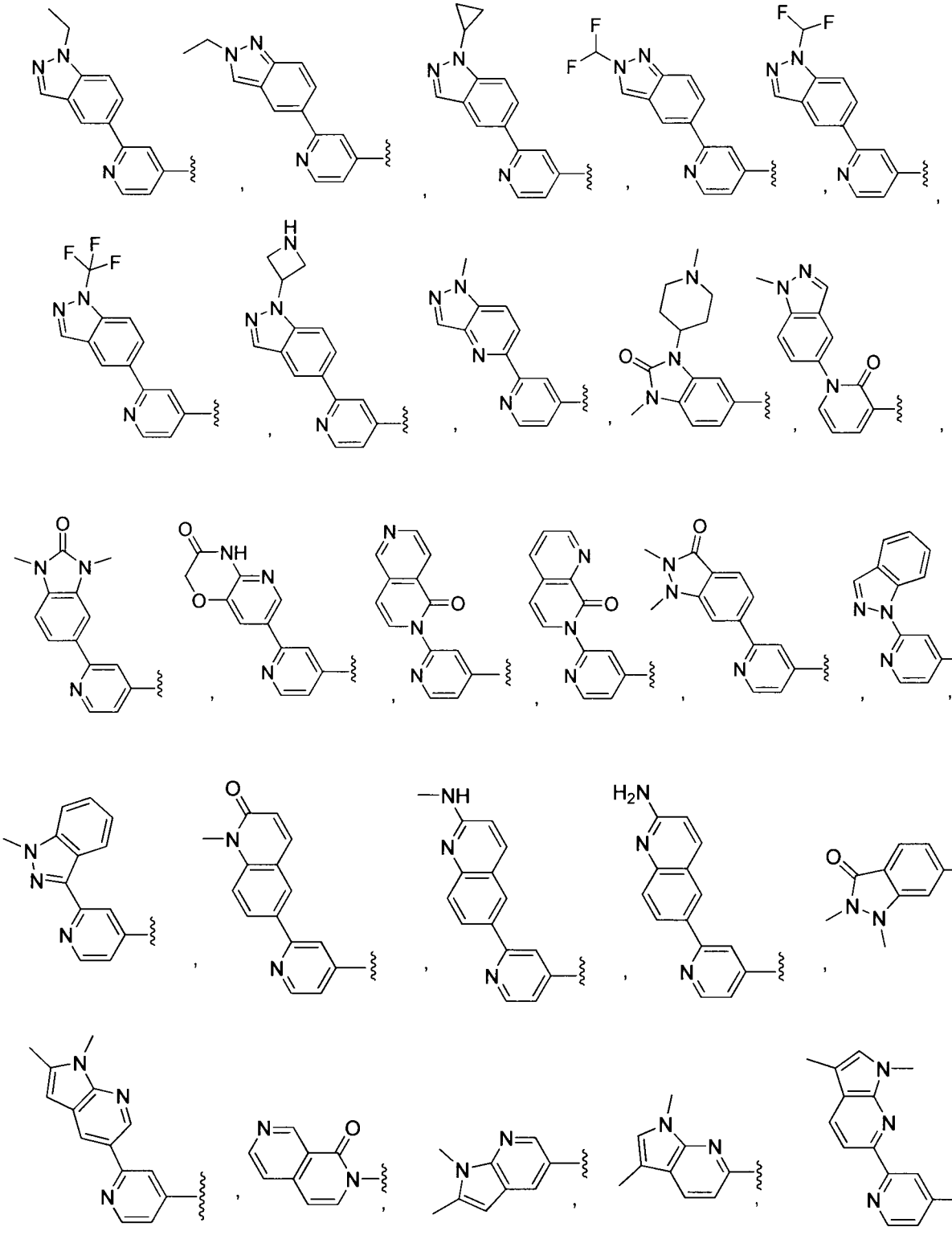
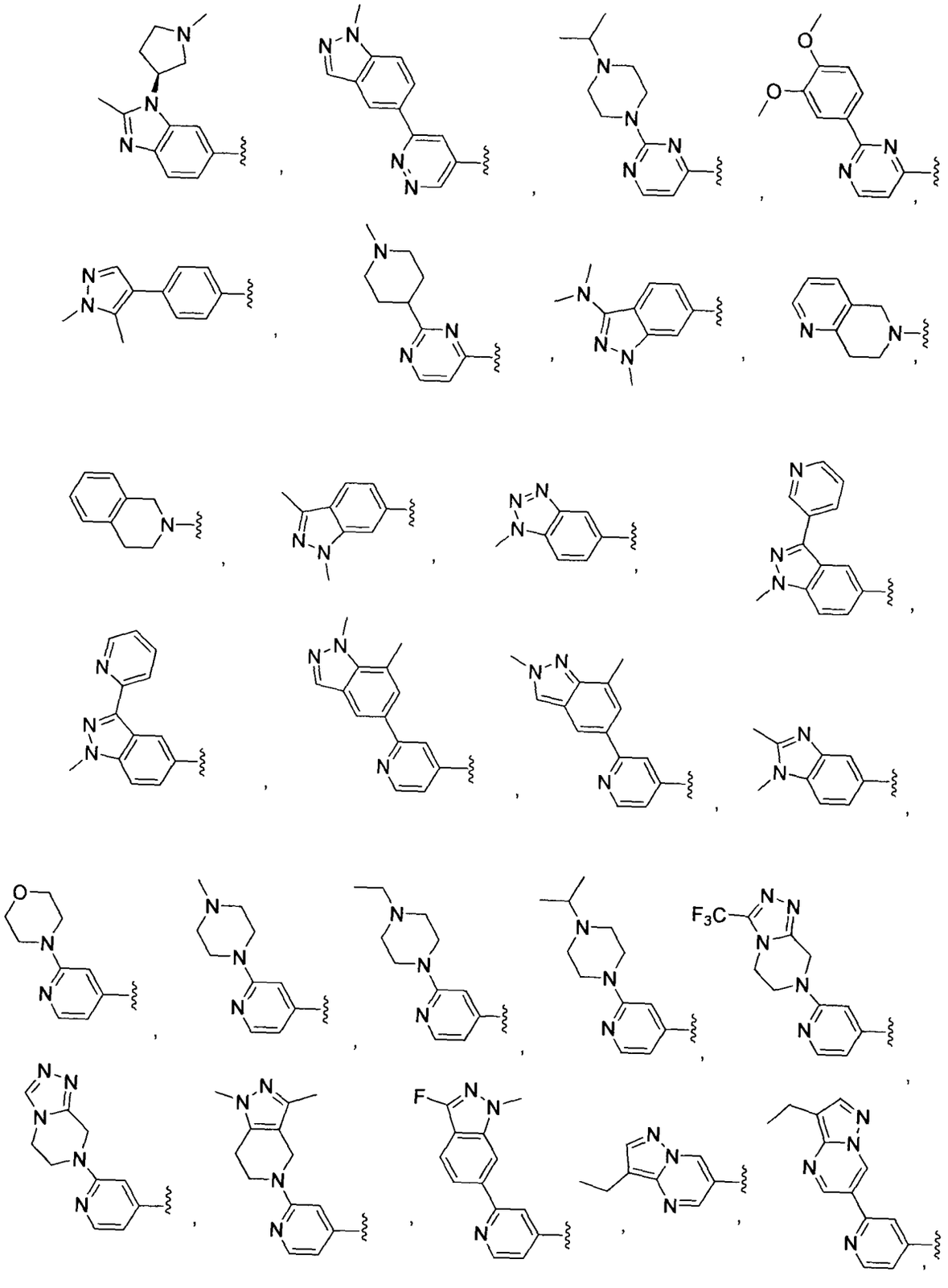
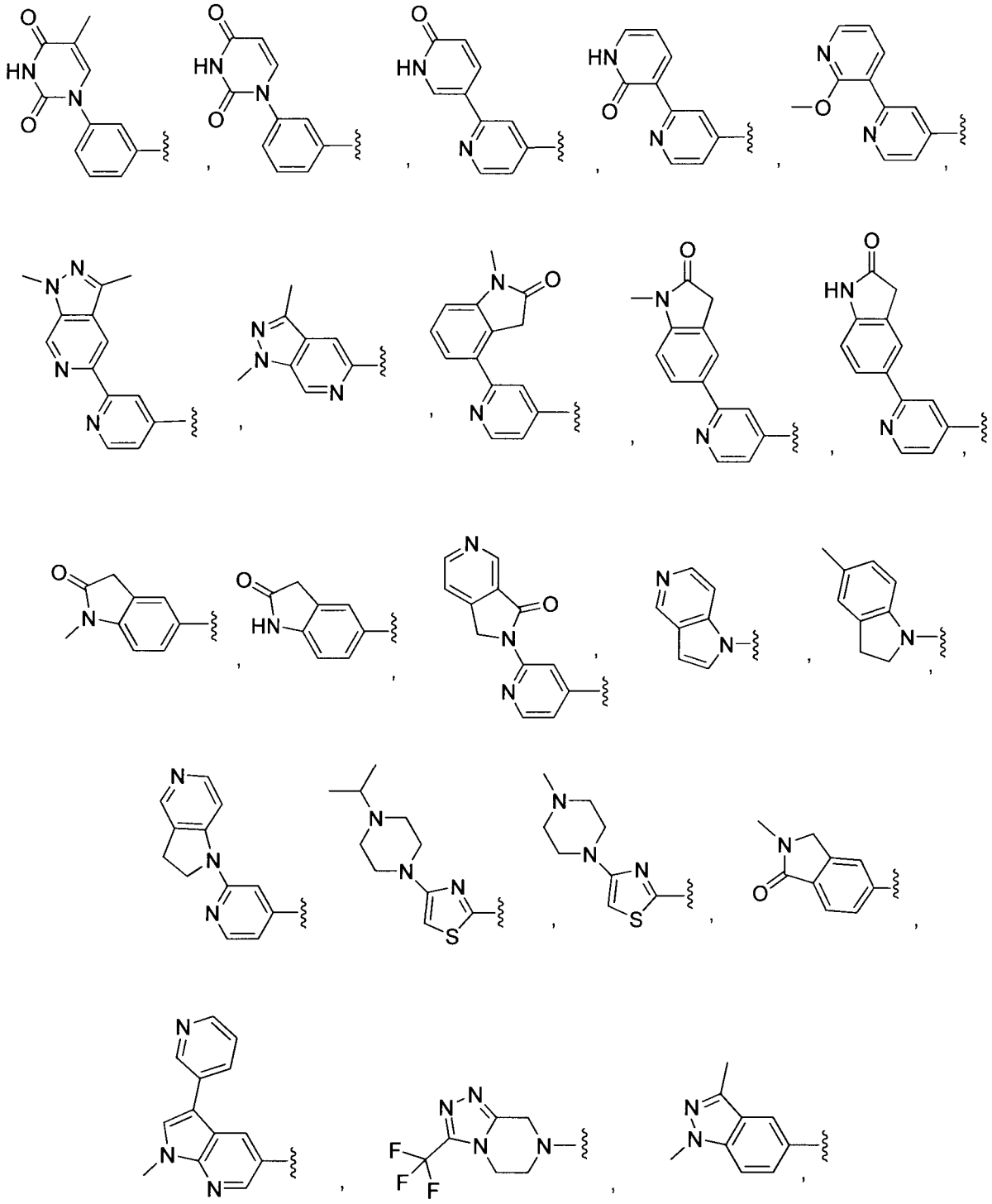


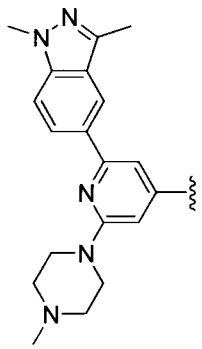
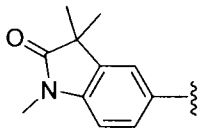
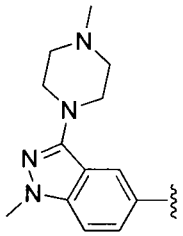
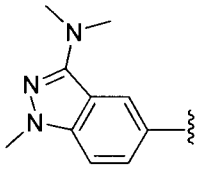
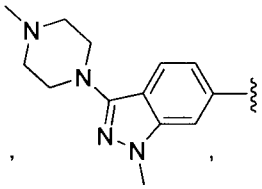
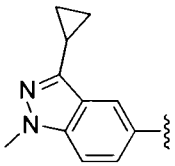
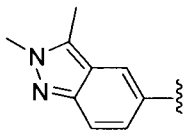
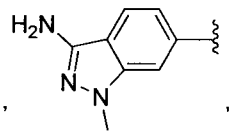
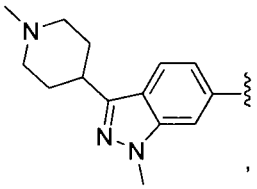
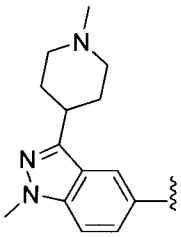
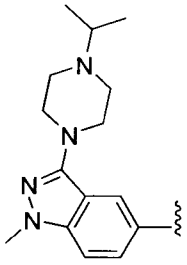
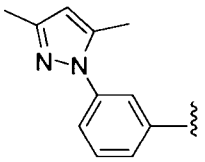
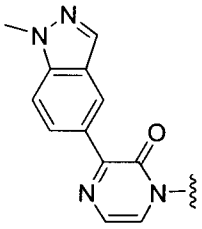
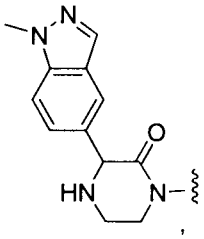
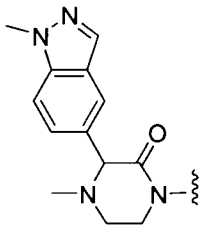
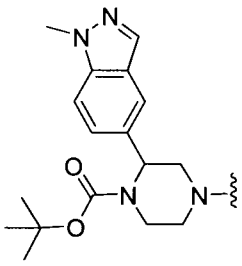
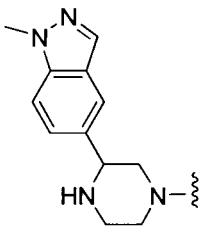
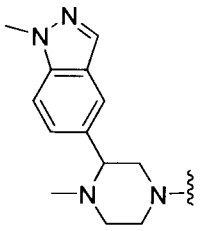
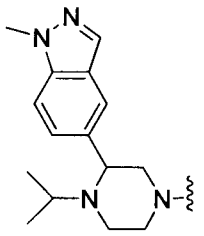
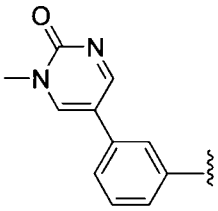
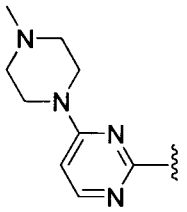
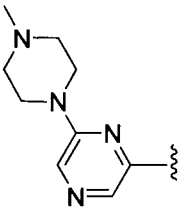
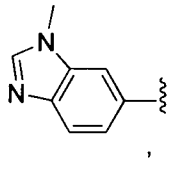
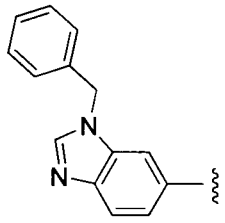
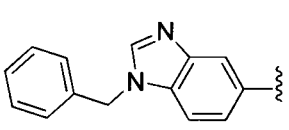
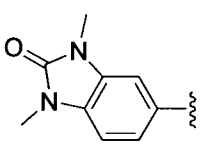
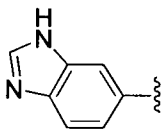
and pharmaceutically acceptable salts thereof.

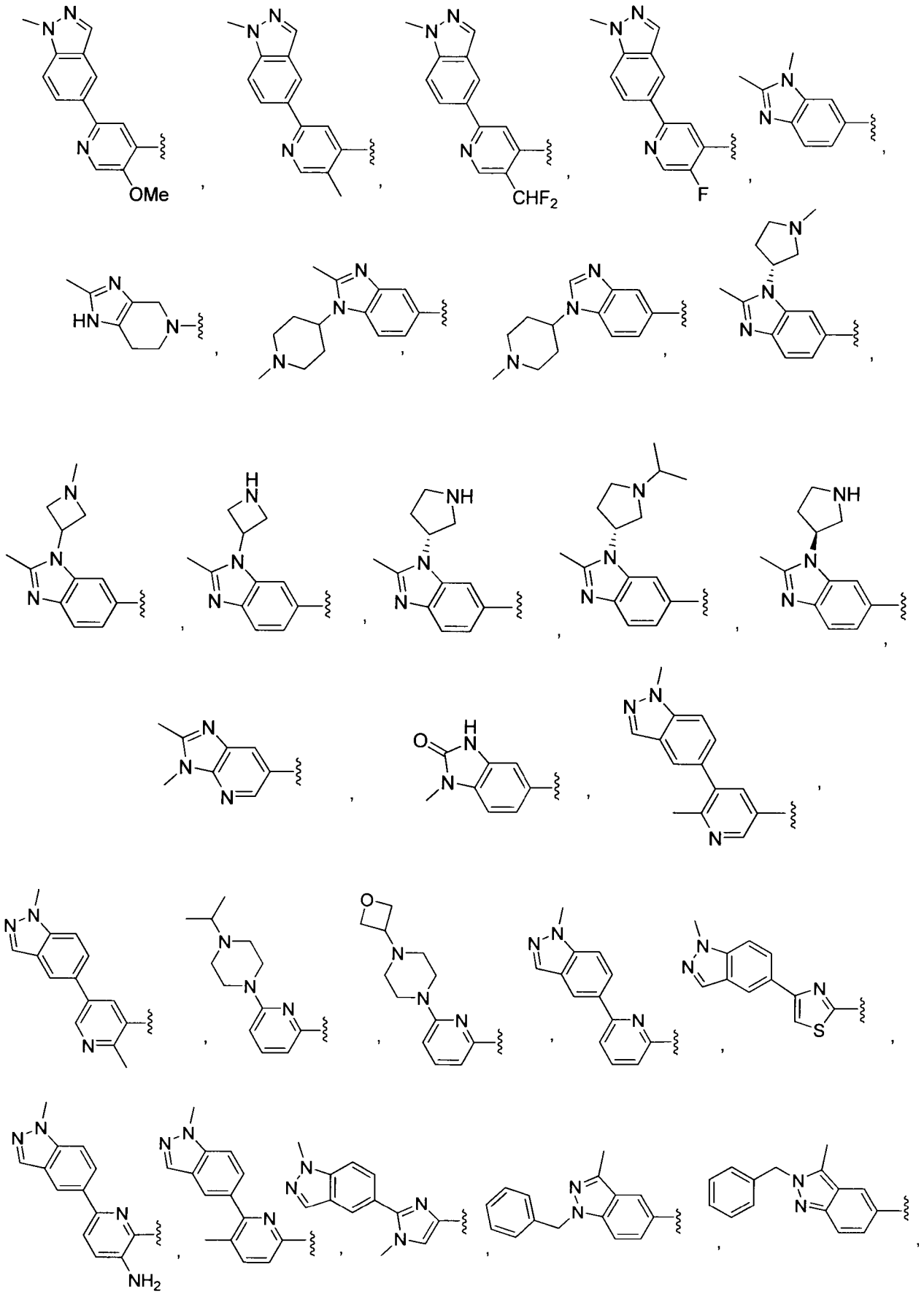
17. The compound of any one of claims 1-6 wherein A-B is selected from:

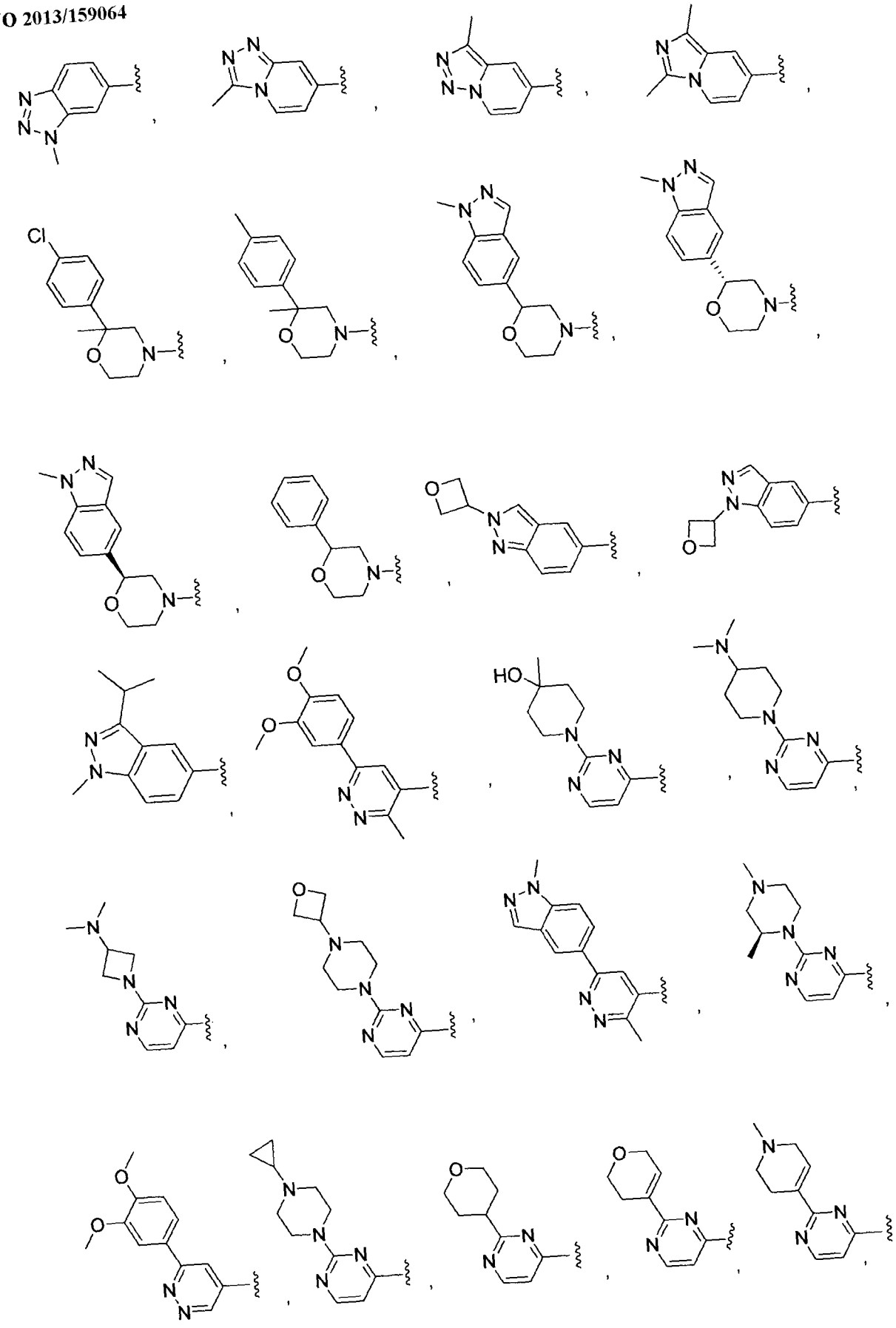


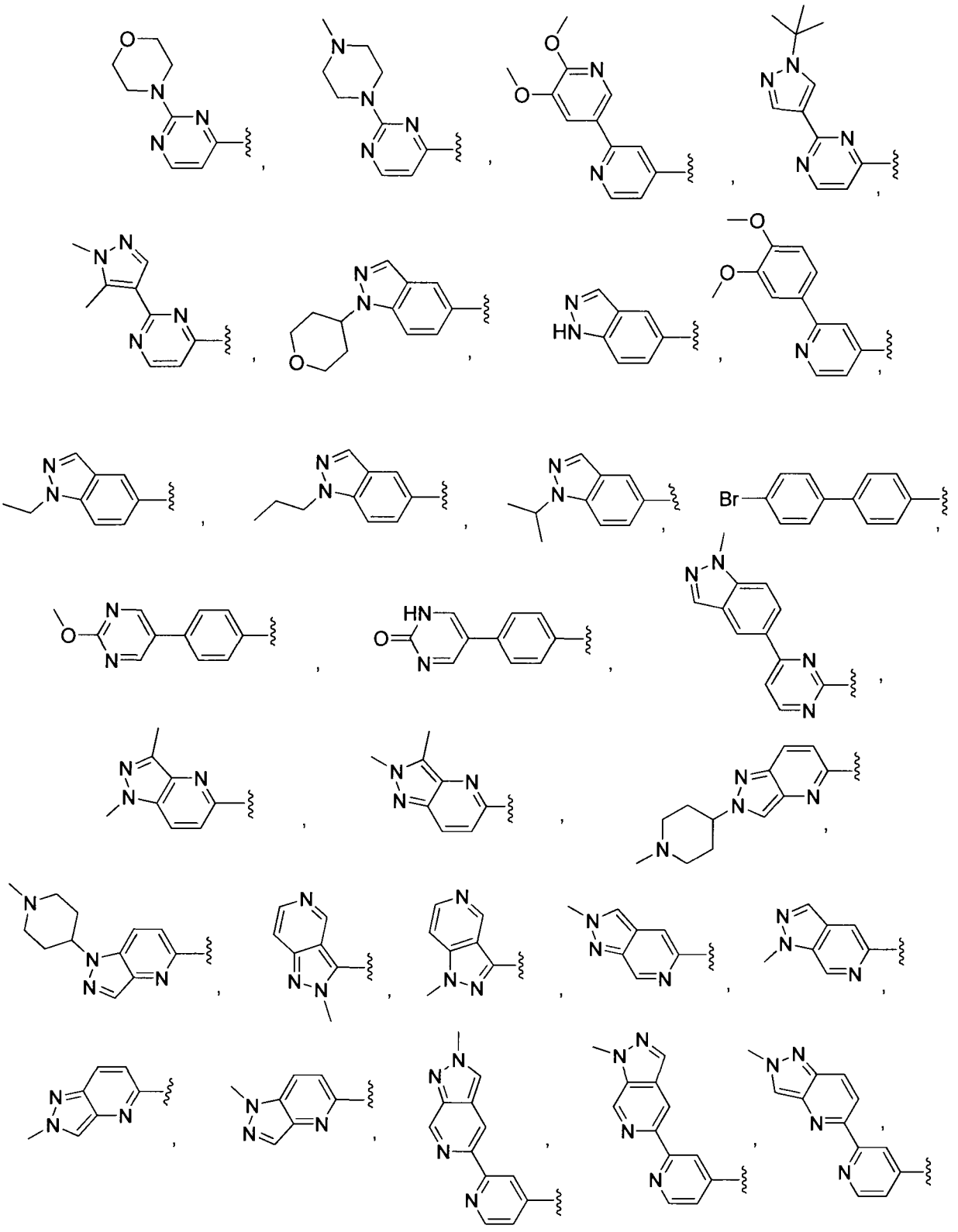


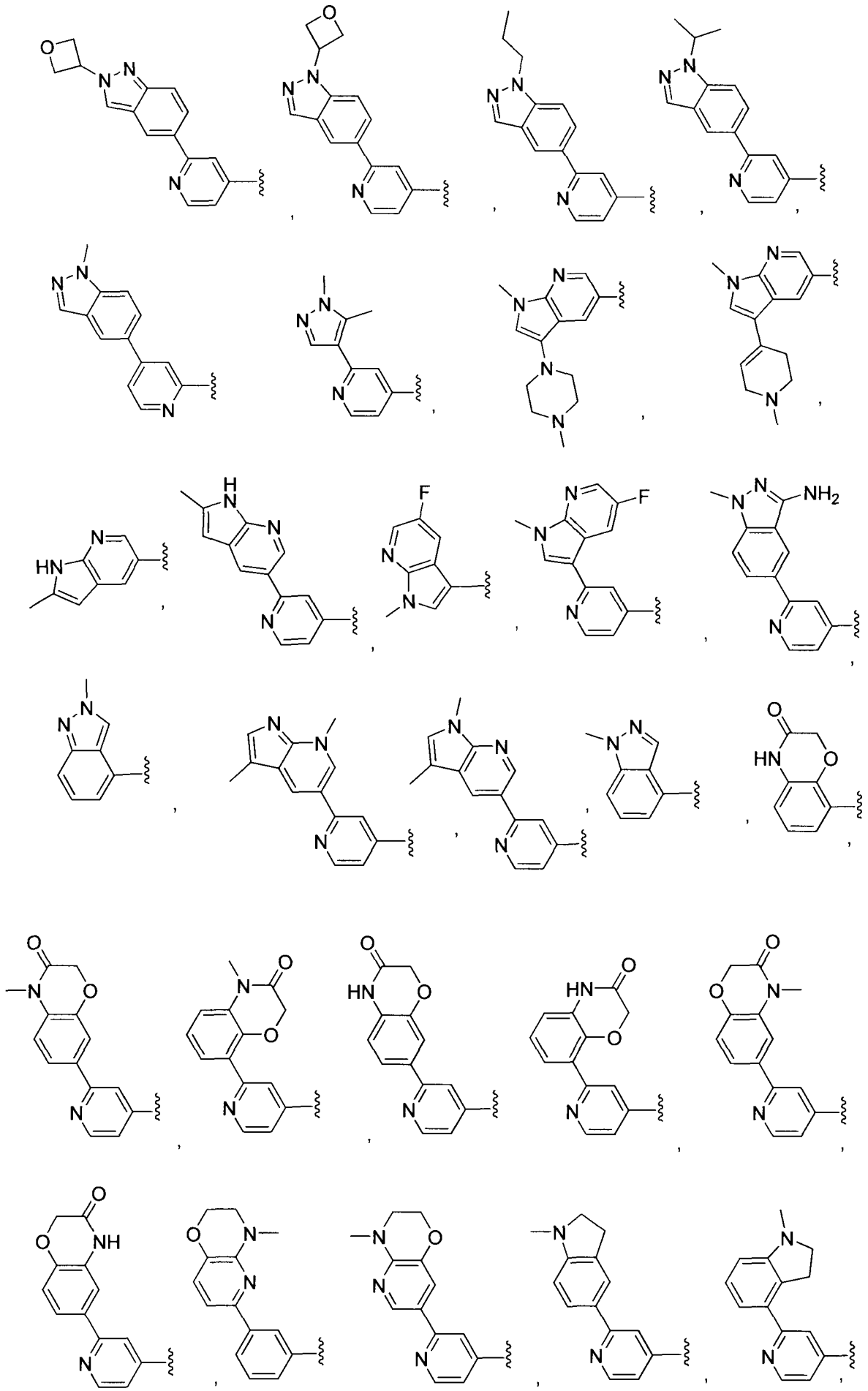


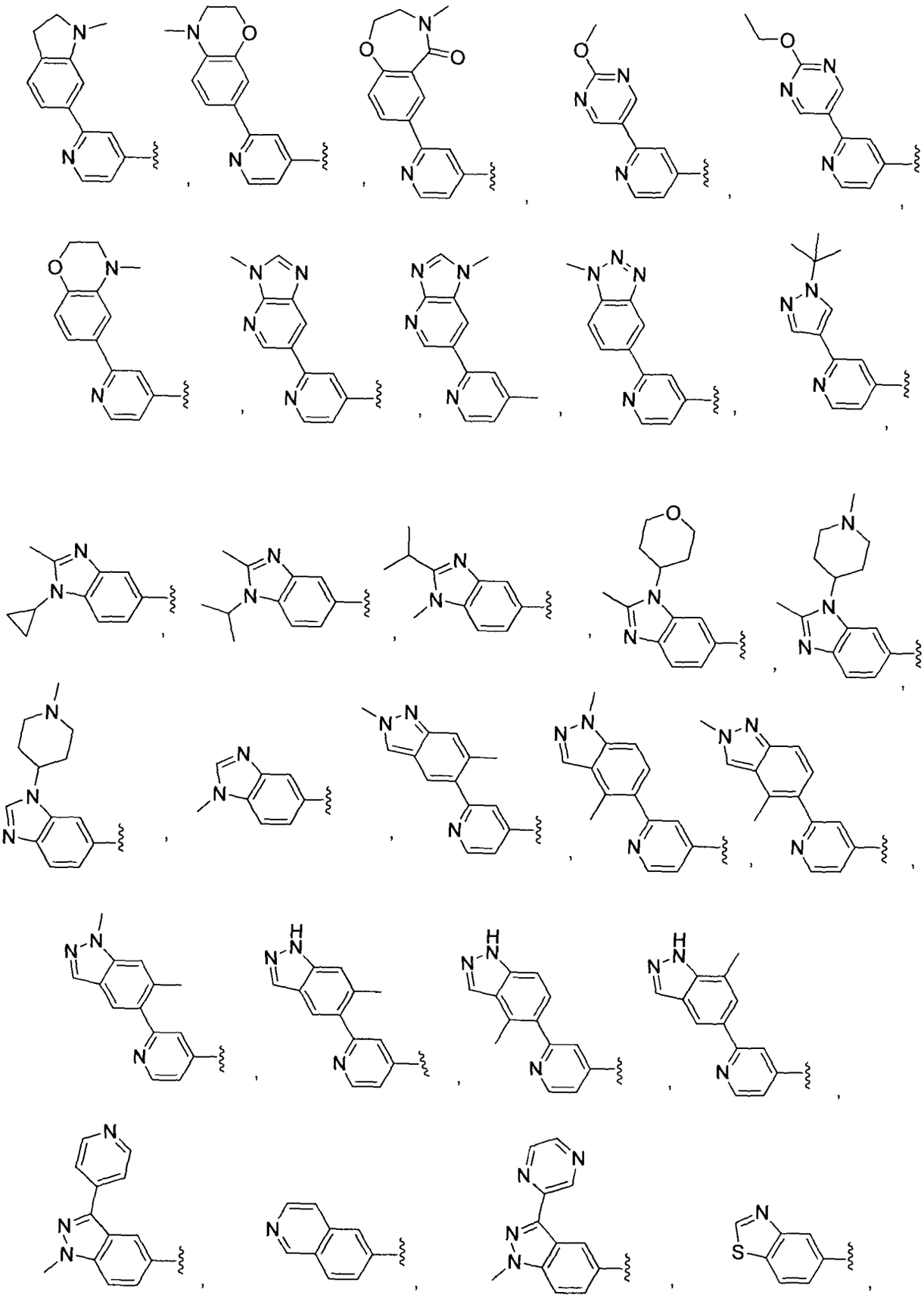




























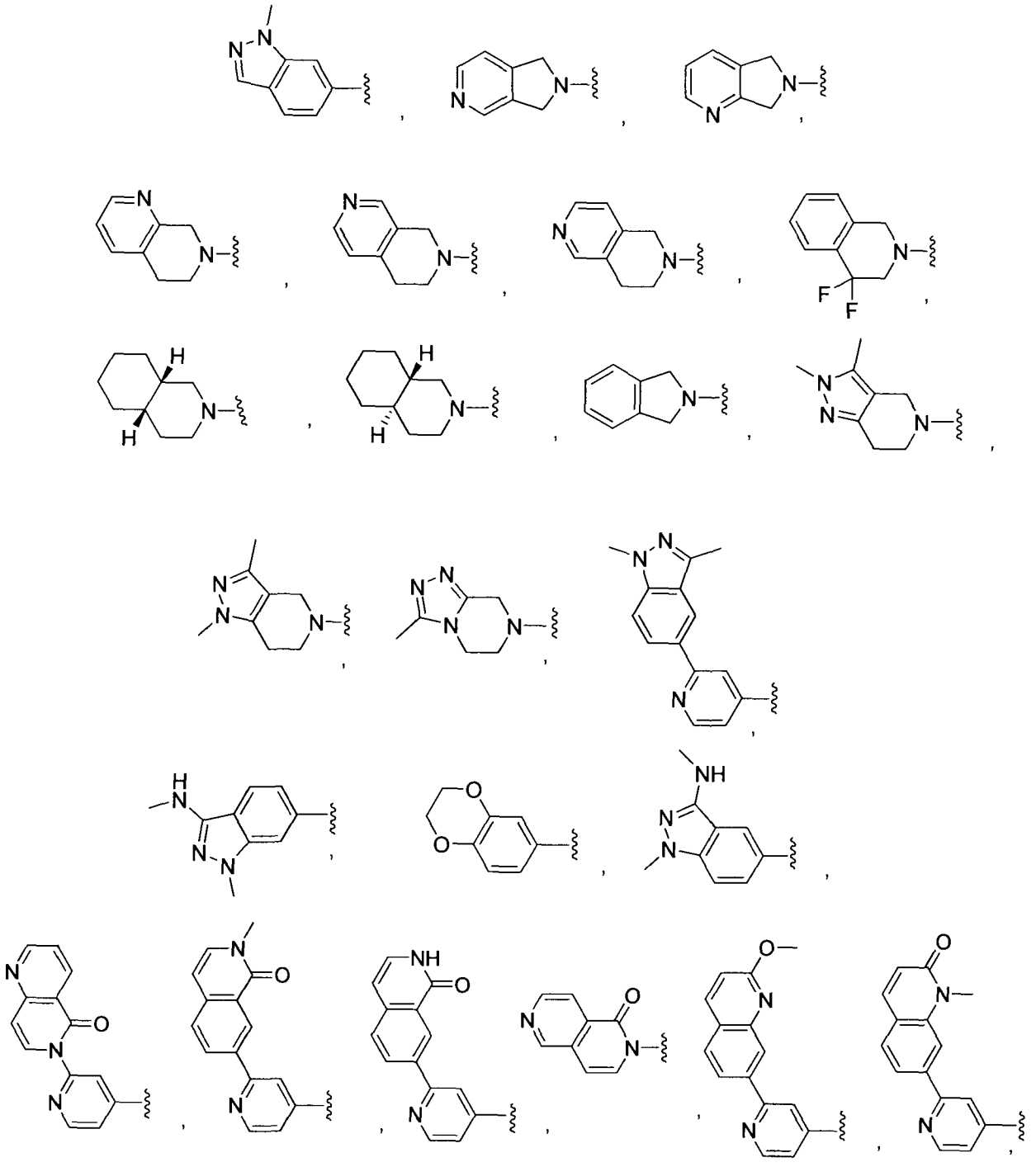


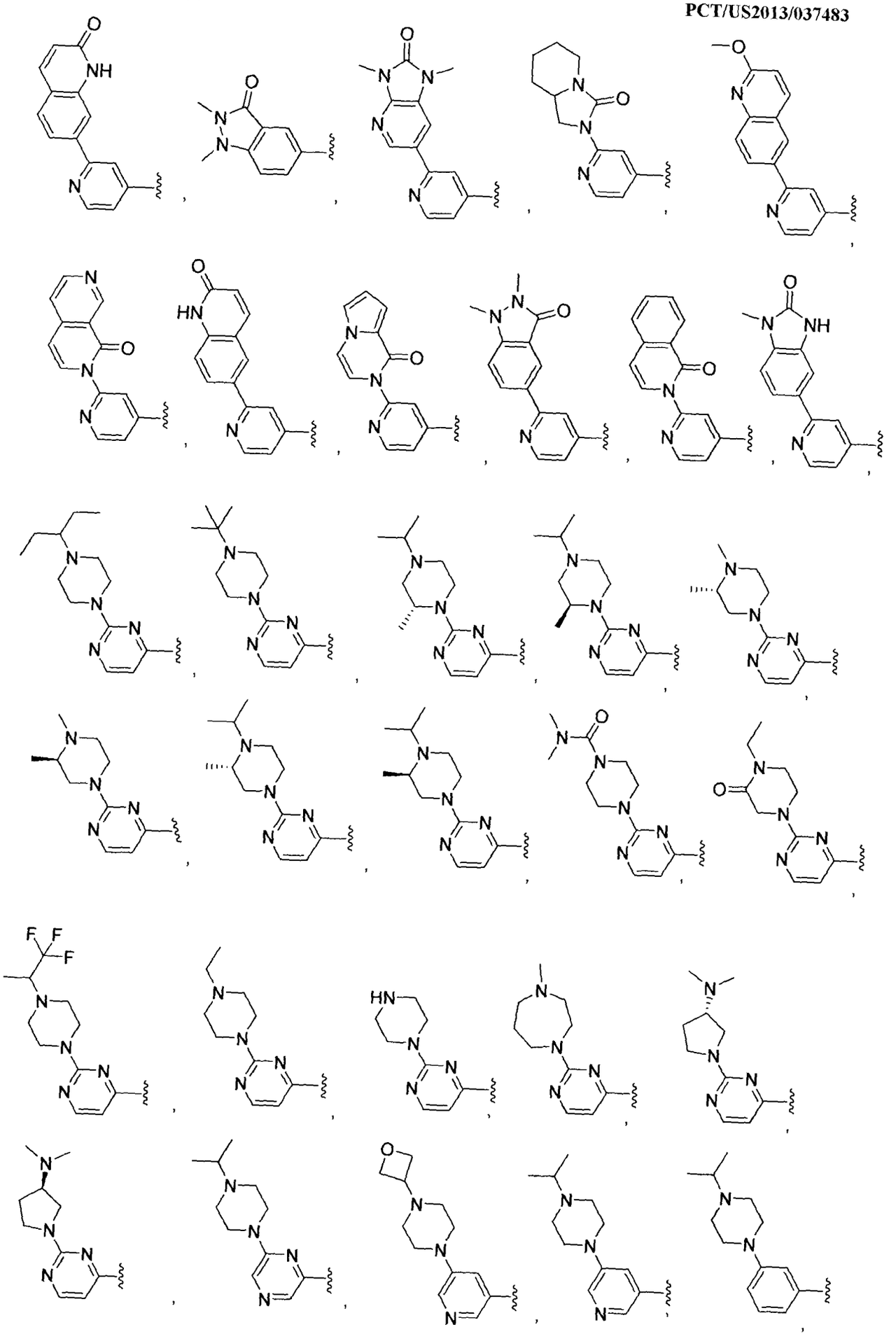


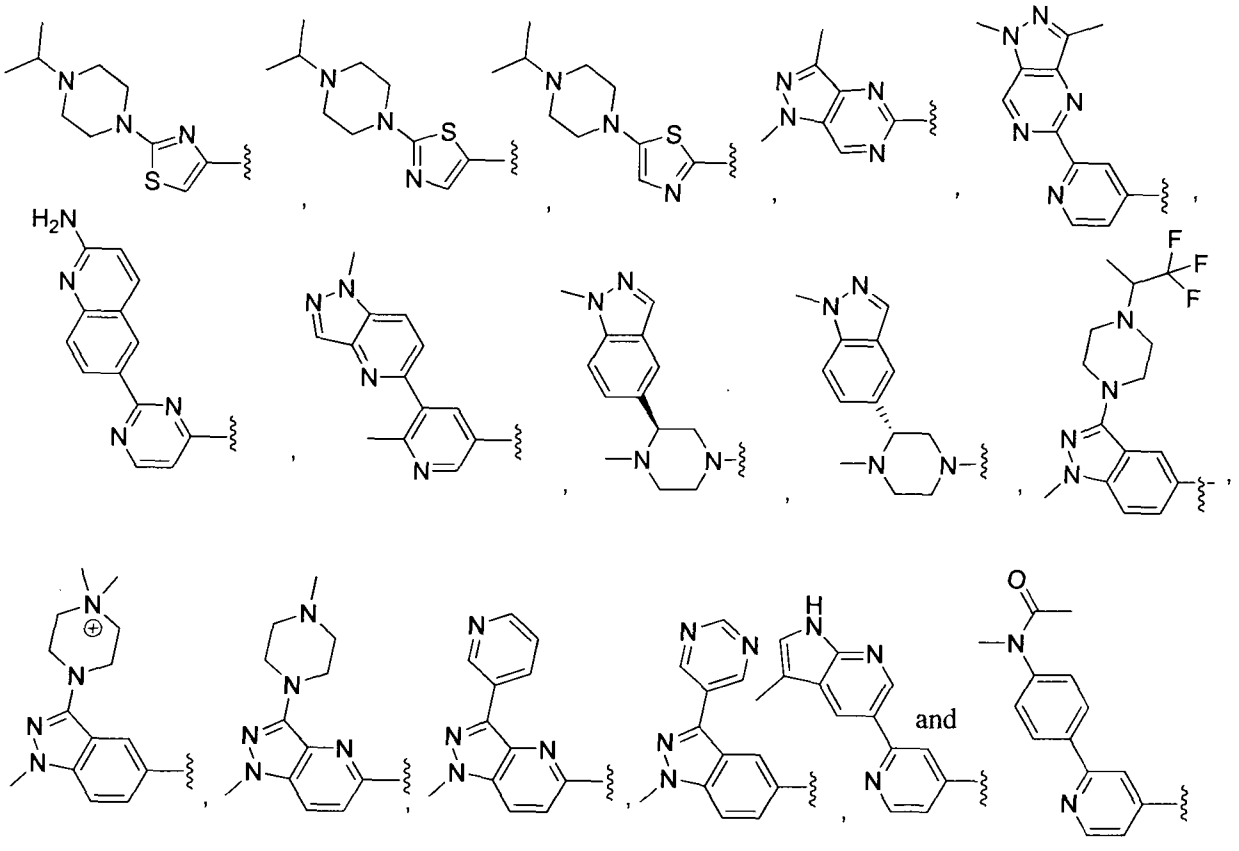




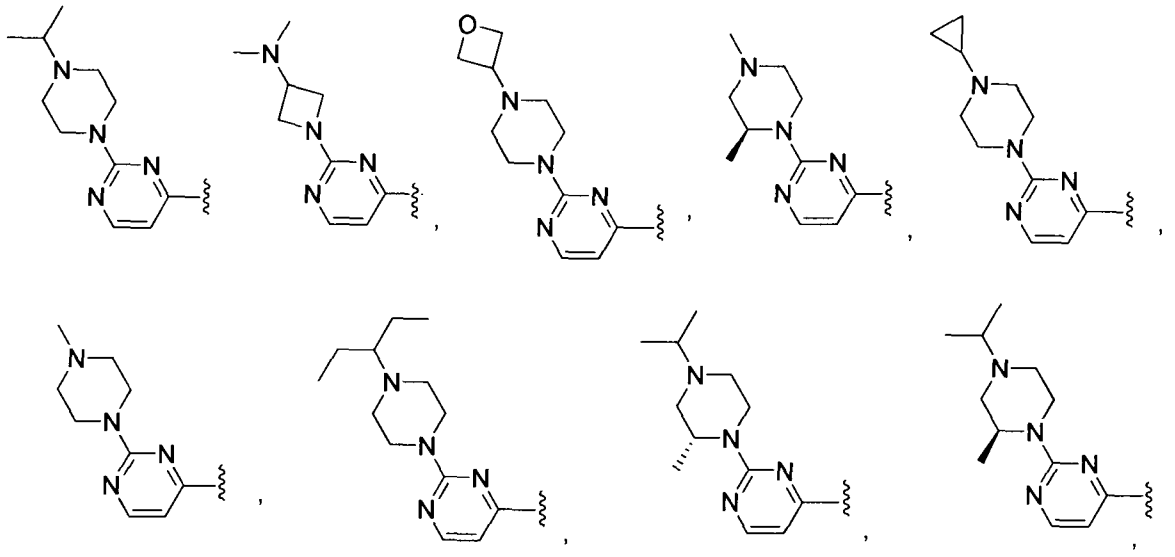


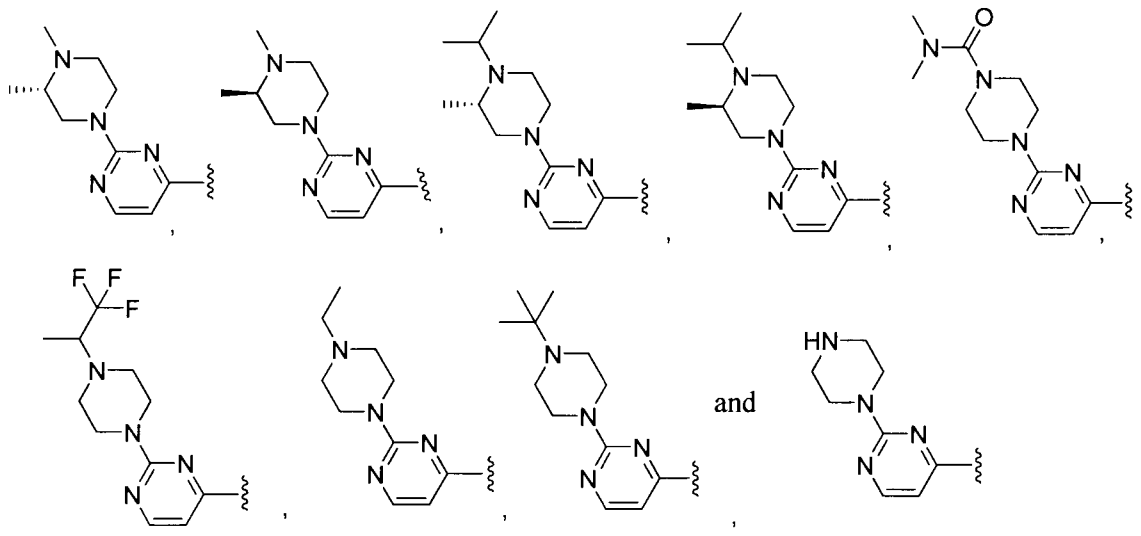




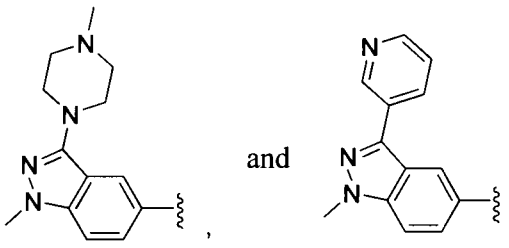


18. The compound of any one of claims 1-6 wherein A-B is selected from:

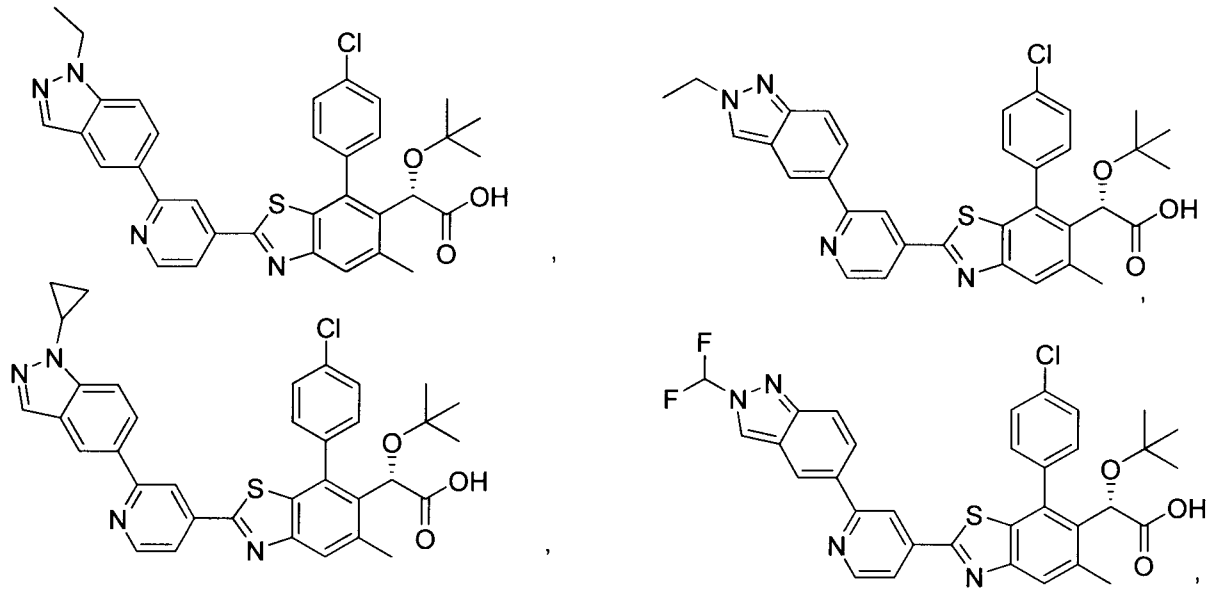


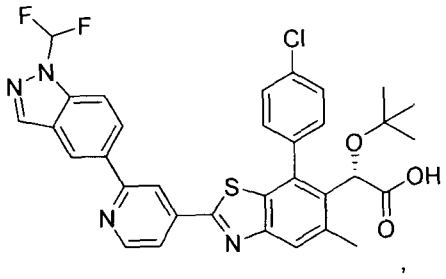


19. The compound of any one of claims 1-6 wherein A-B is selected from:



20. The compound of claim 1 which is selected from:





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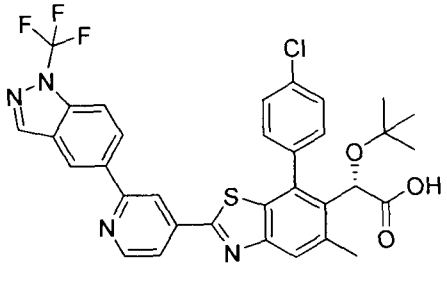

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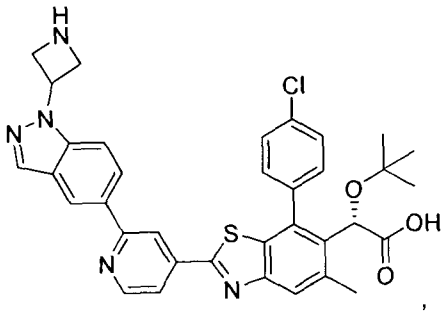

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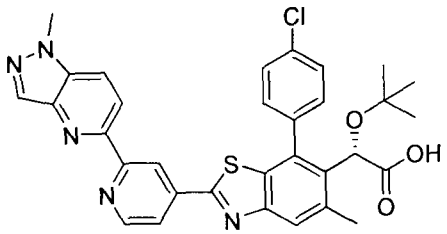

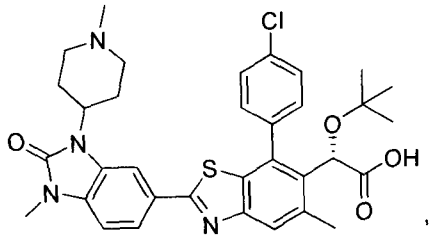

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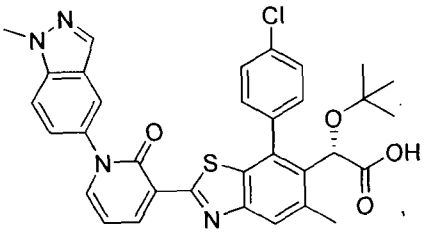

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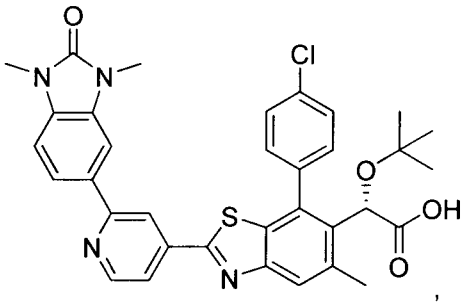

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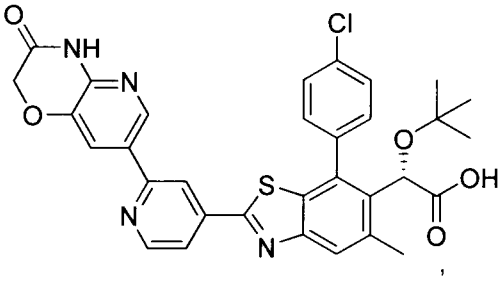

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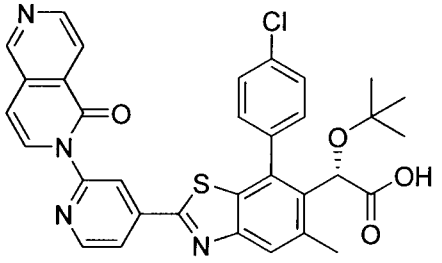

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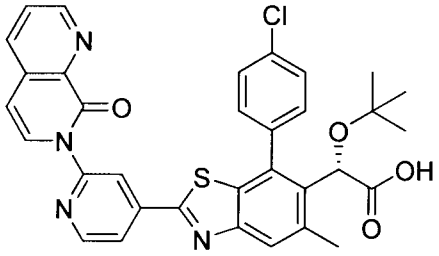

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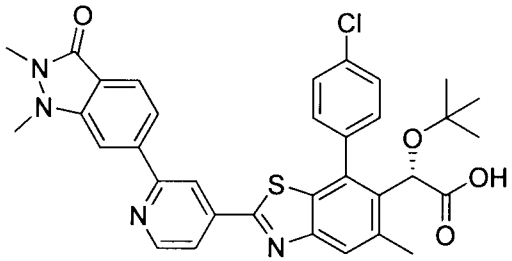

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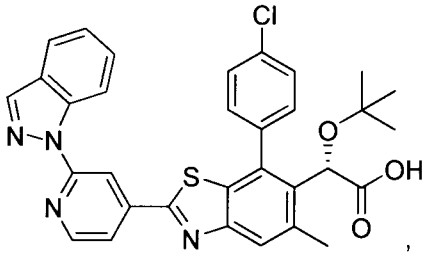

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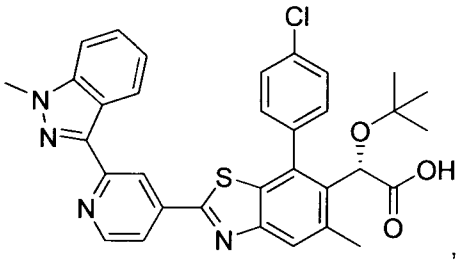

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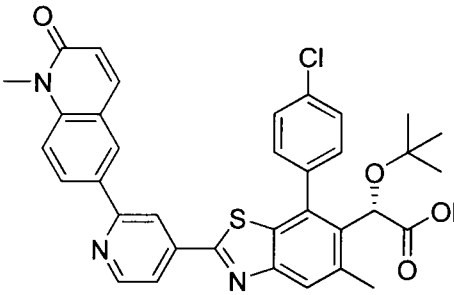

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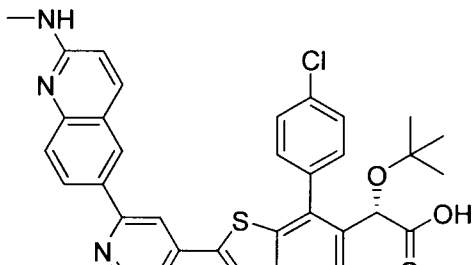

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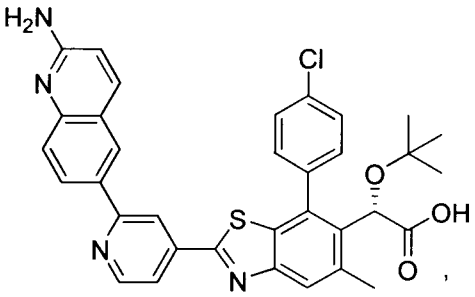

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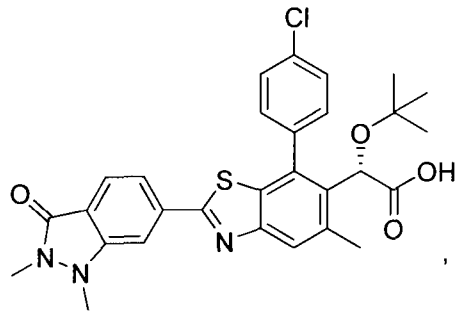

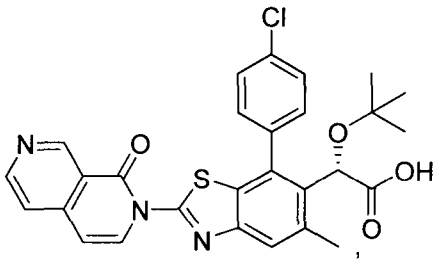

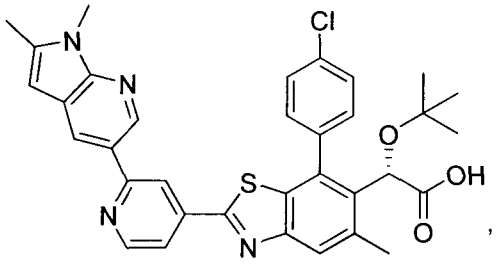

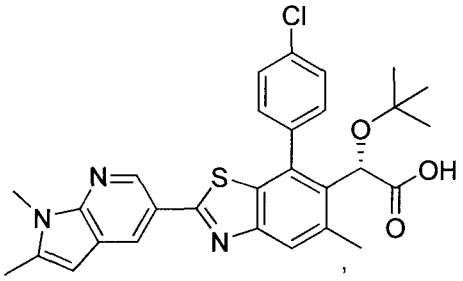

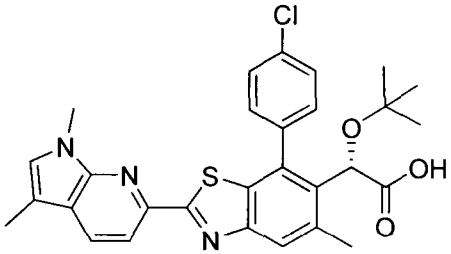

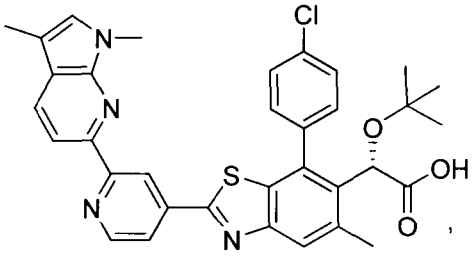

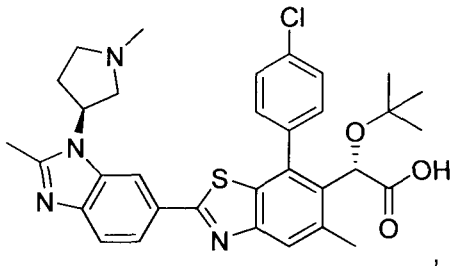

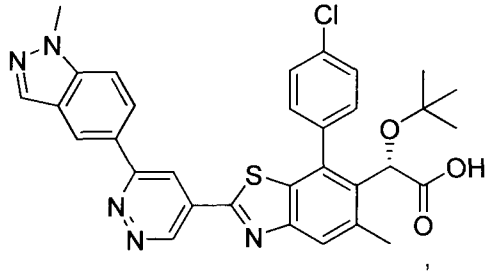

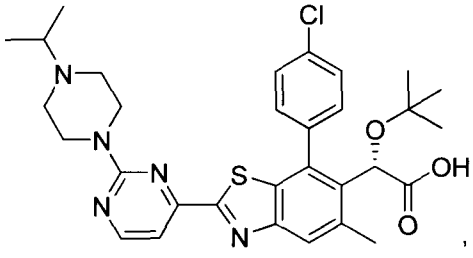

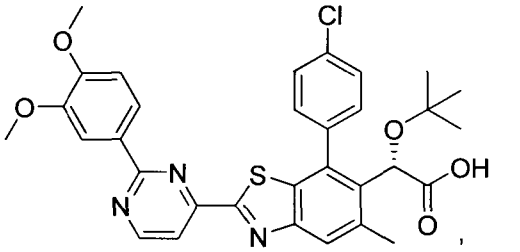

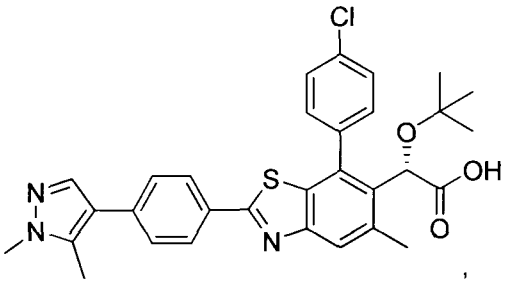

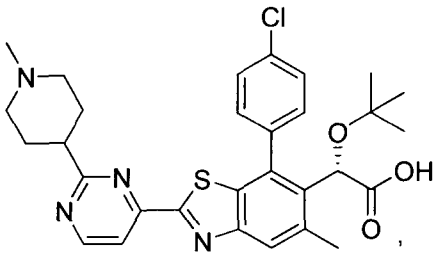

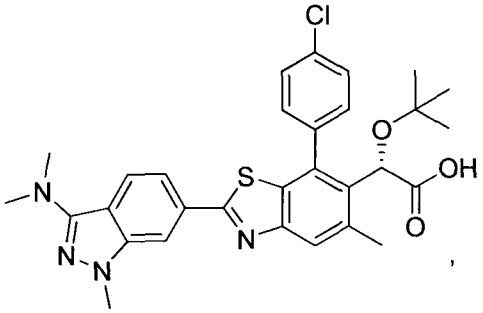

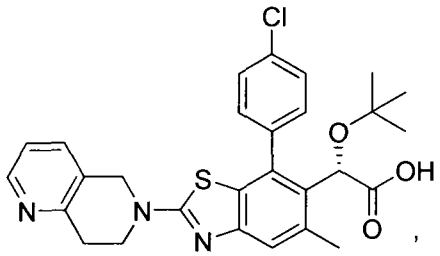

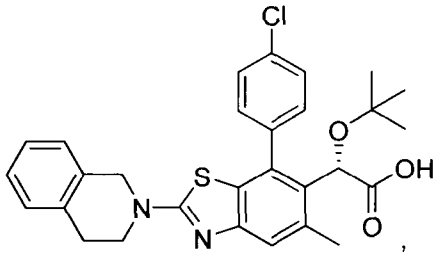

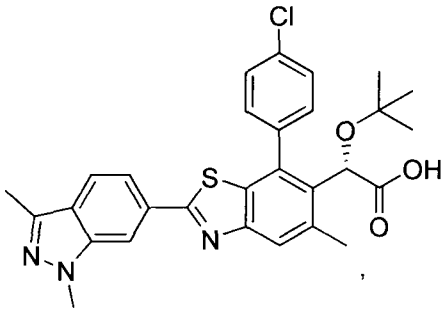

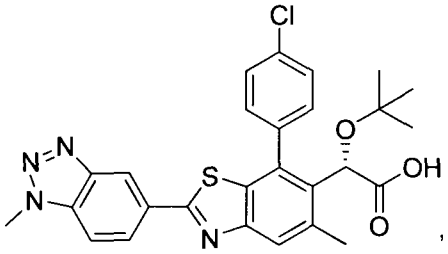

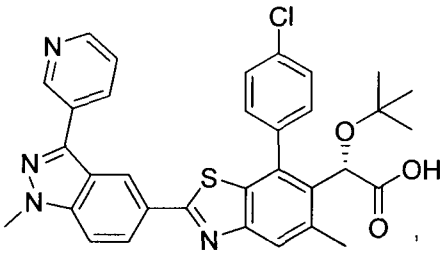

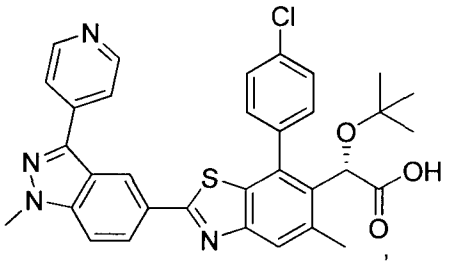

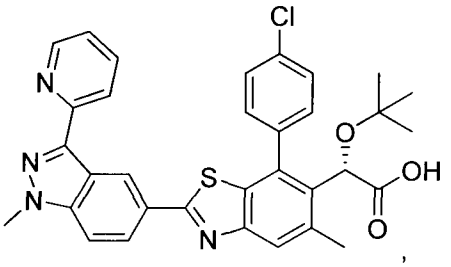

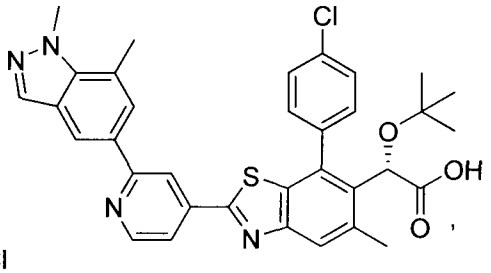

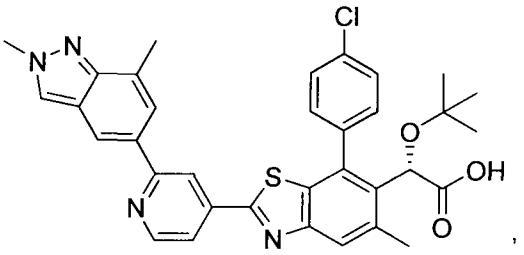

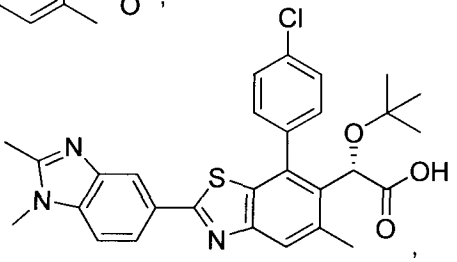

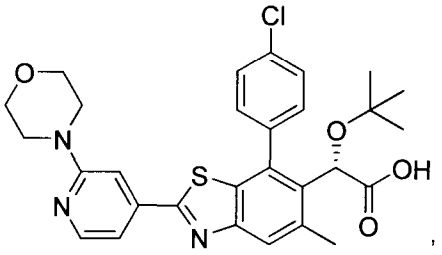

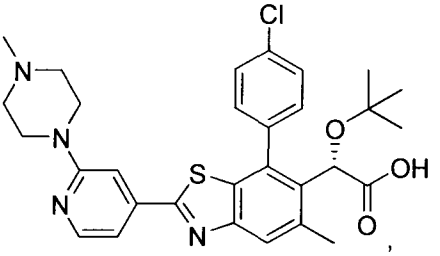

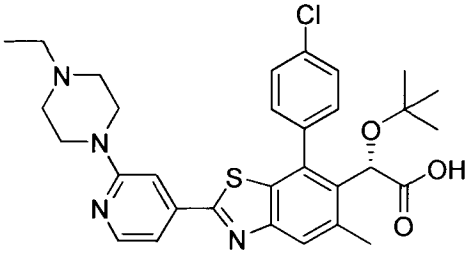

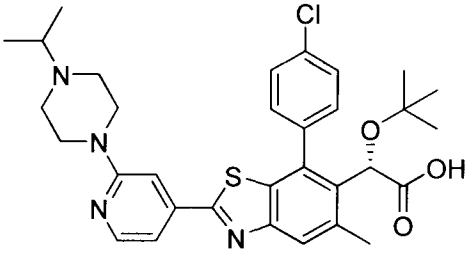

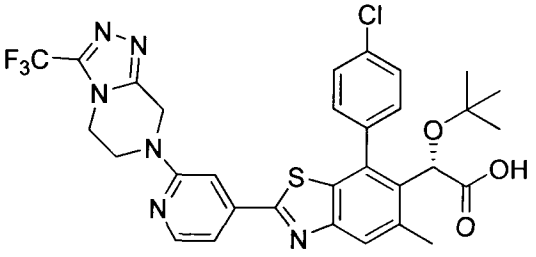

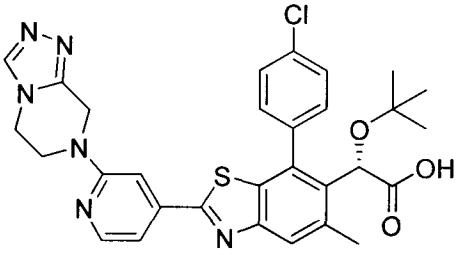

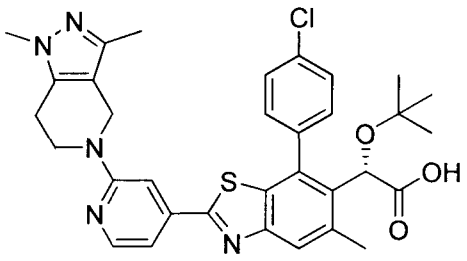

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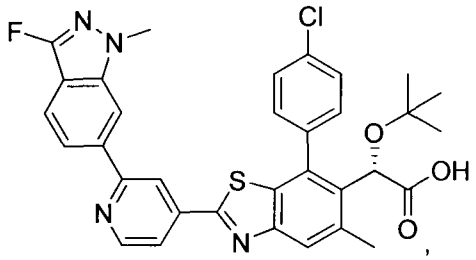

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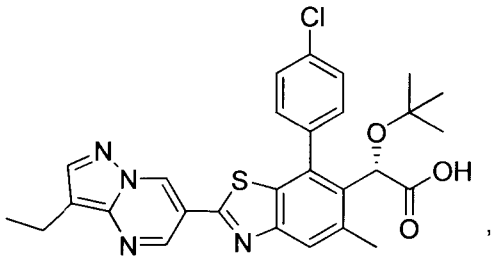

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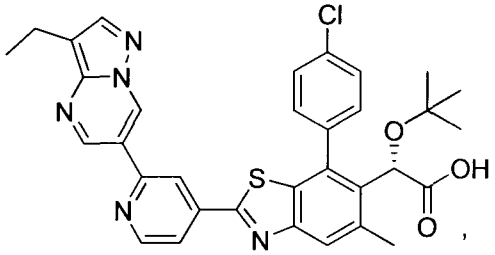

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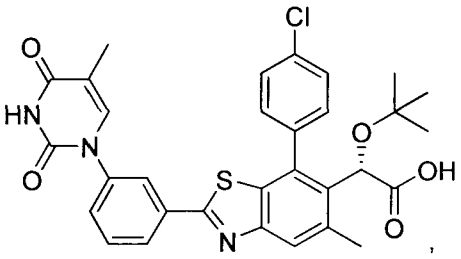

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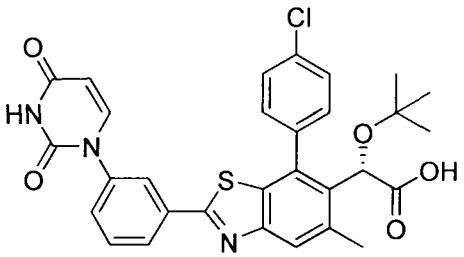

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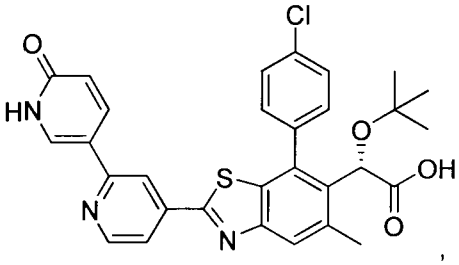

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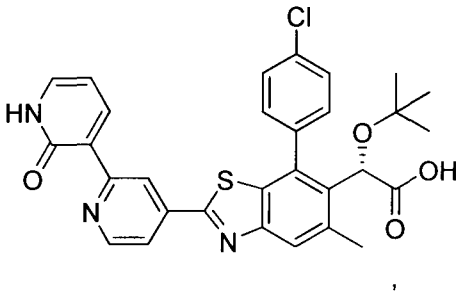

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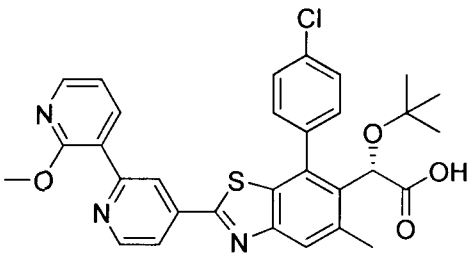

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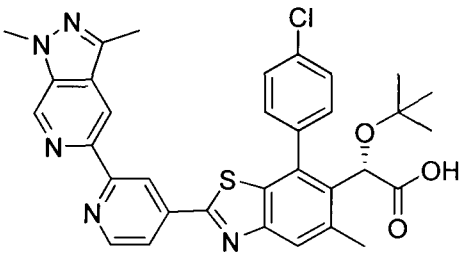

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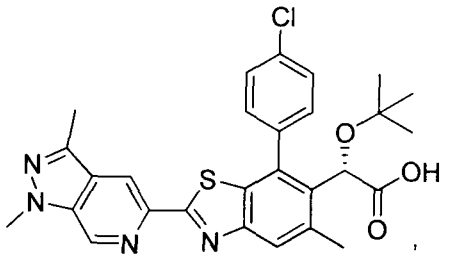

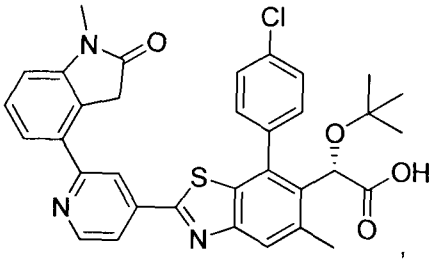

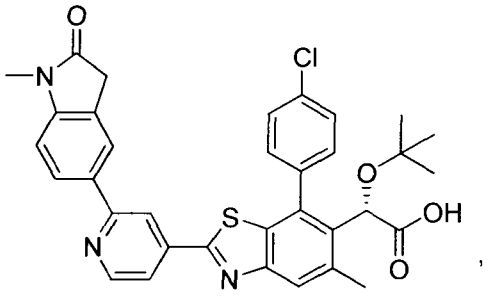

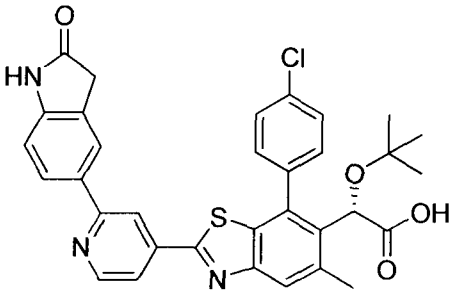

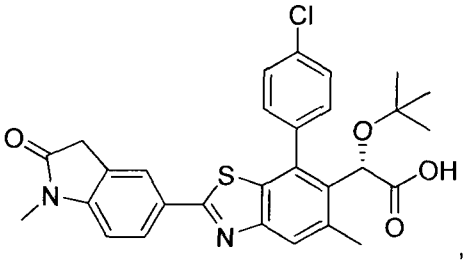

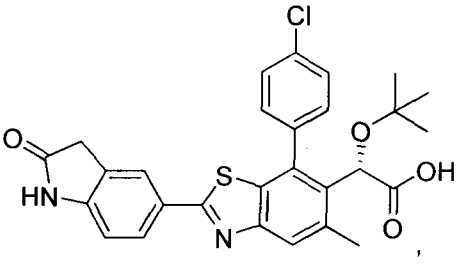

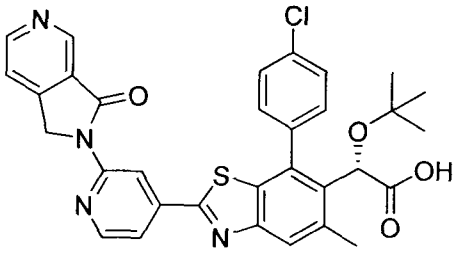

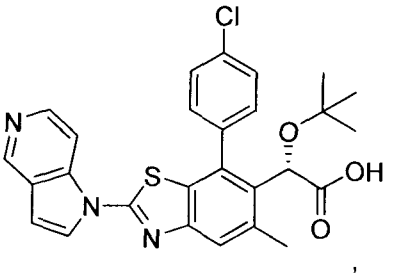

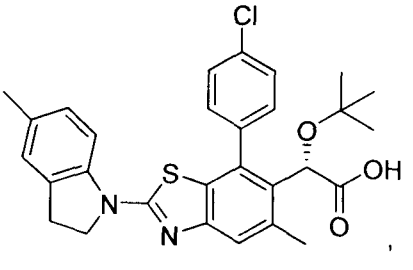

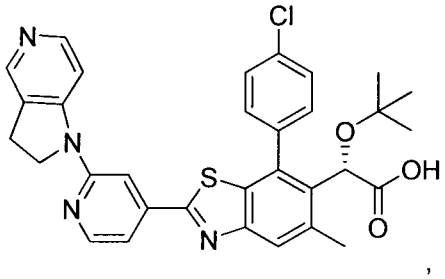

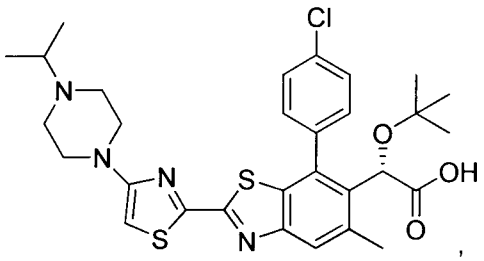

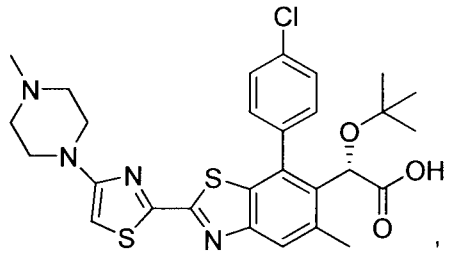

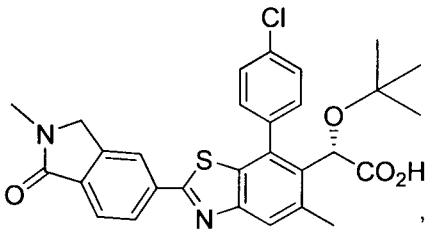

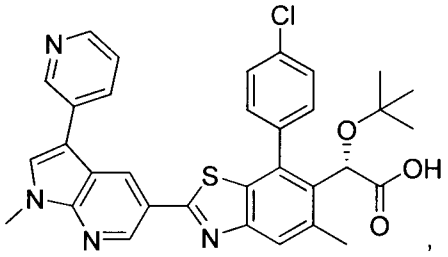

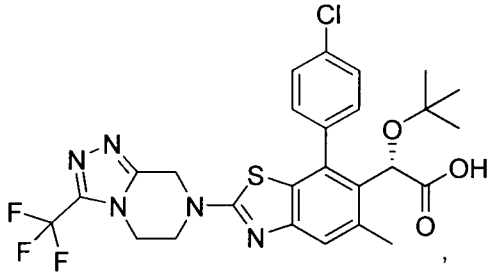

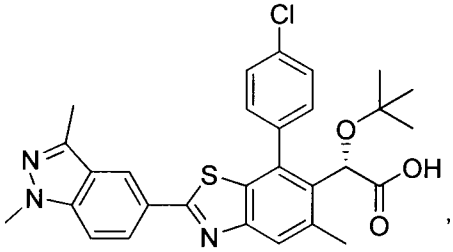

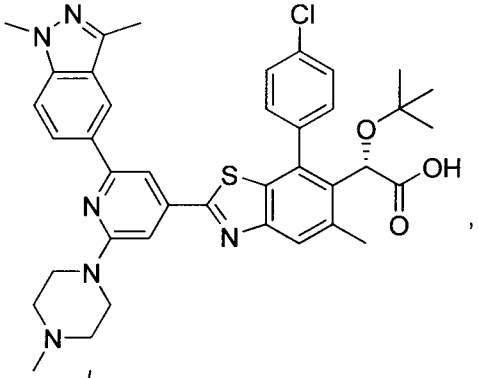

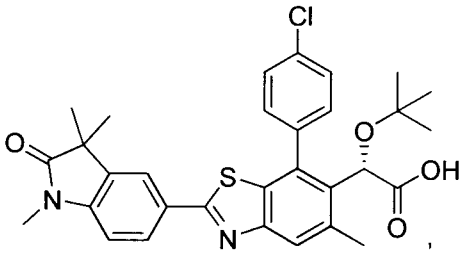

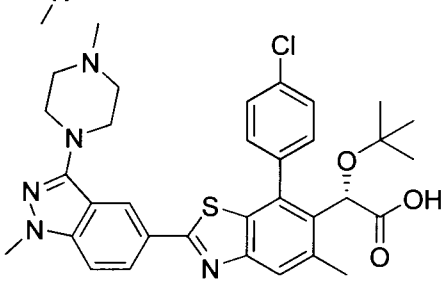

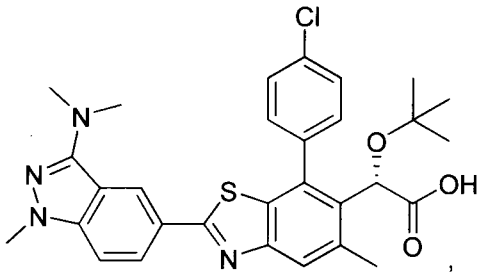

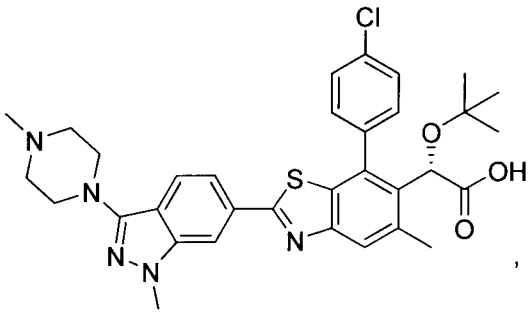

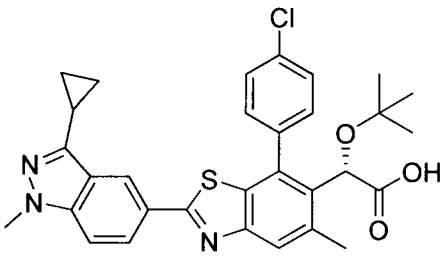

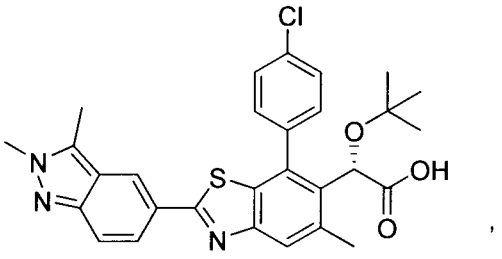

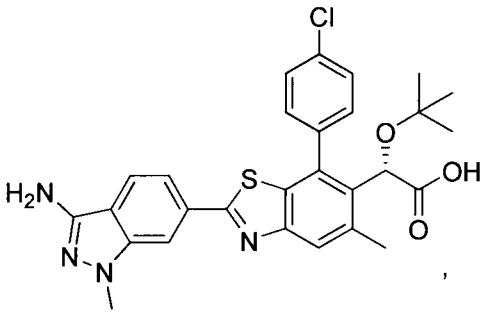

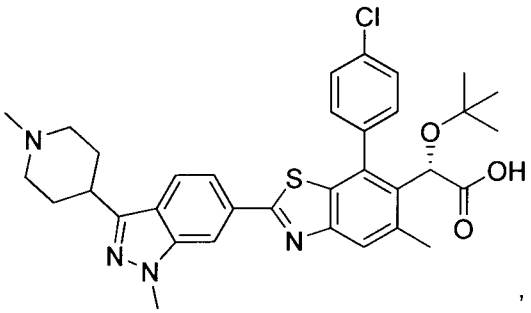

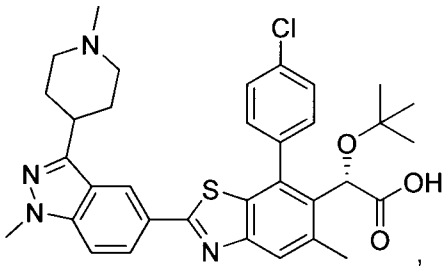

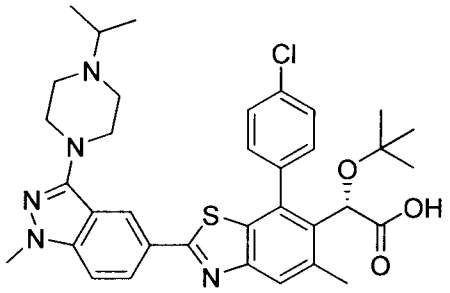

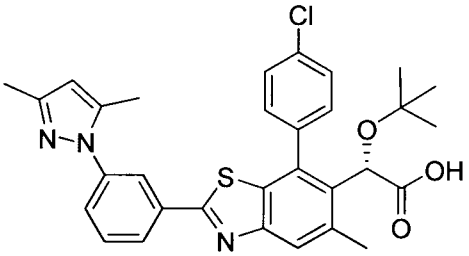

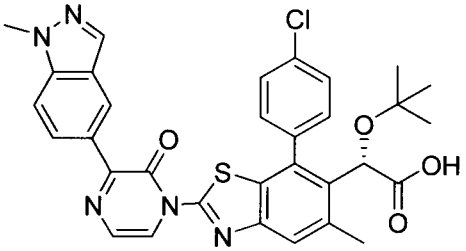

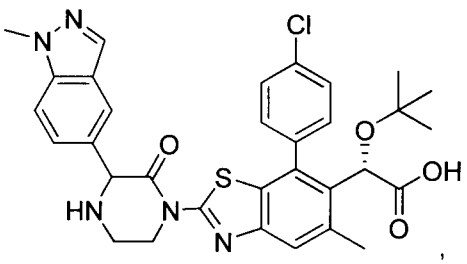

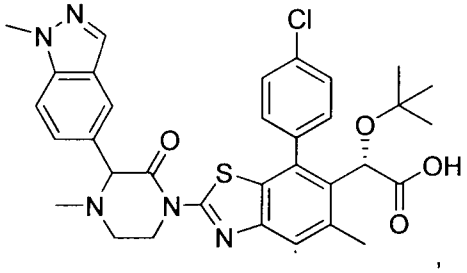

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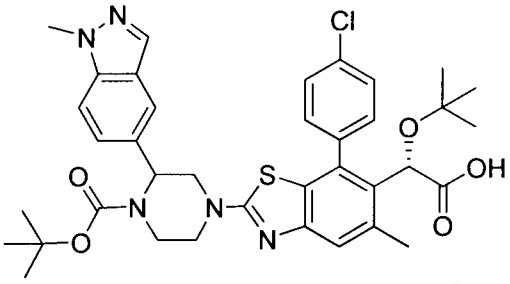

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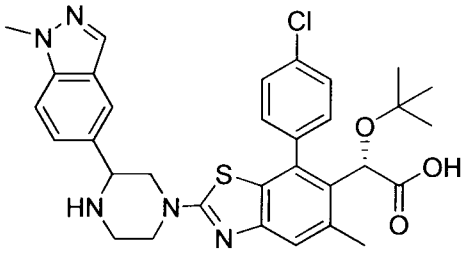

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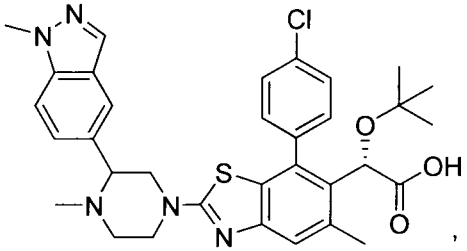

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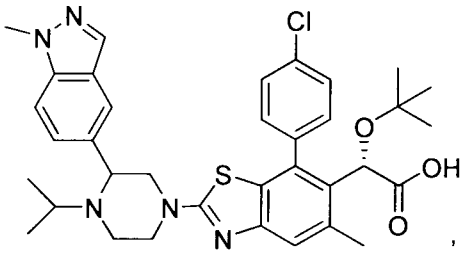

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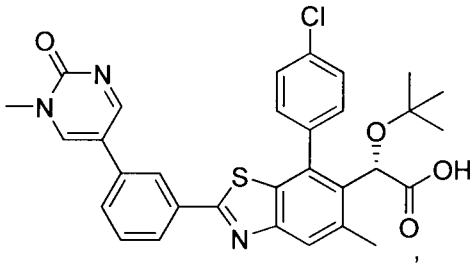

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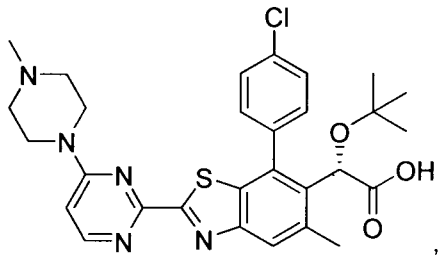

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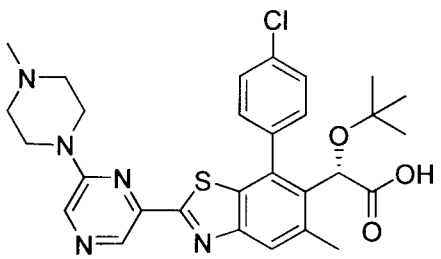

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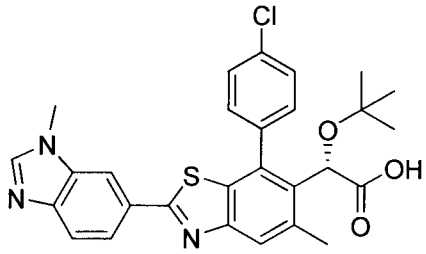

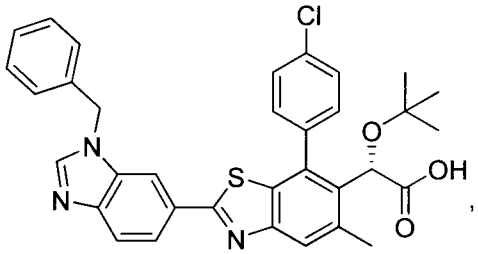

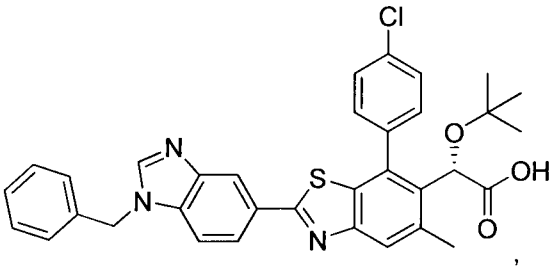

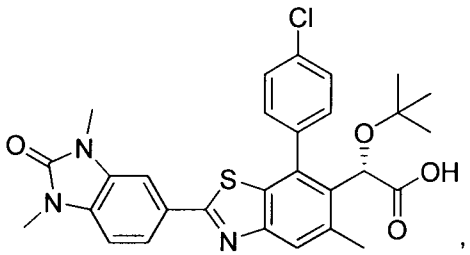

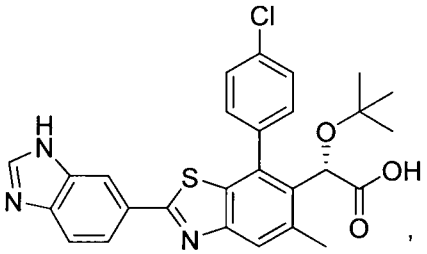

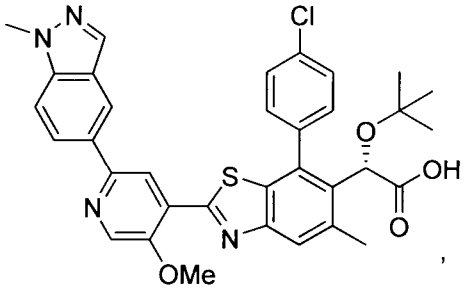

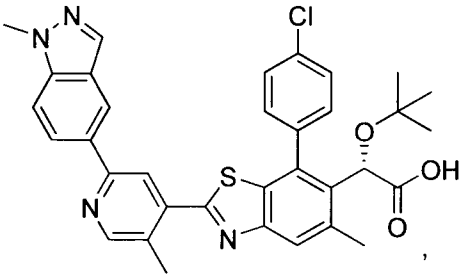

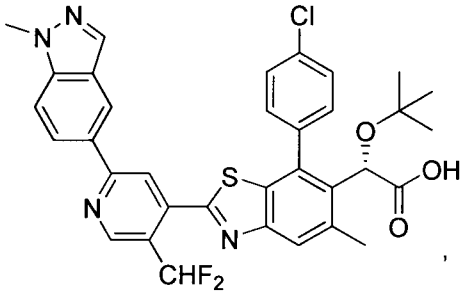

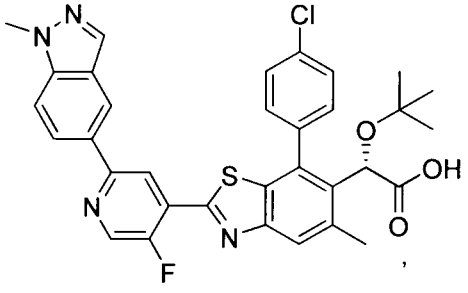

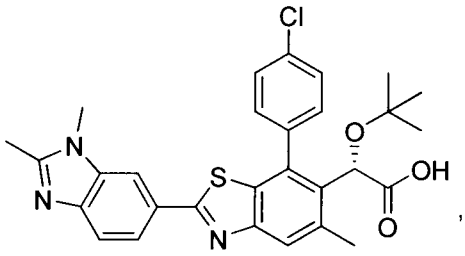

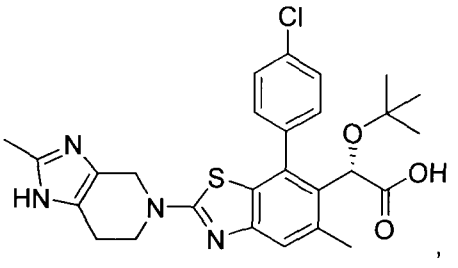

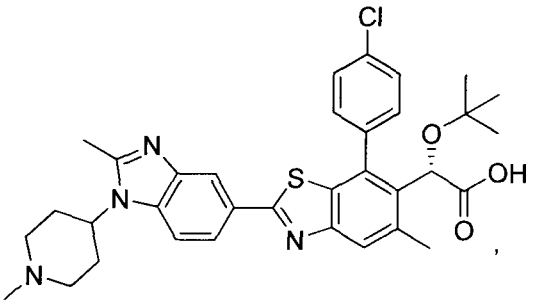

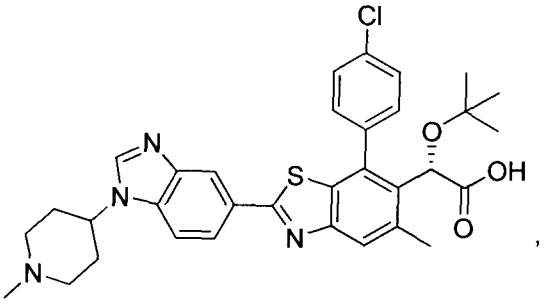

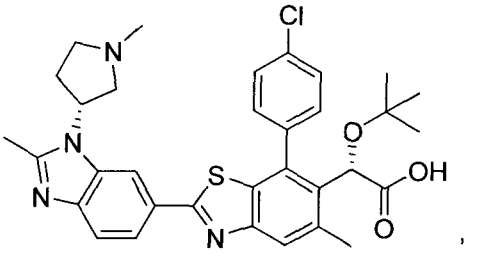

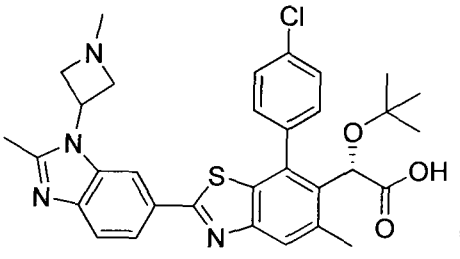

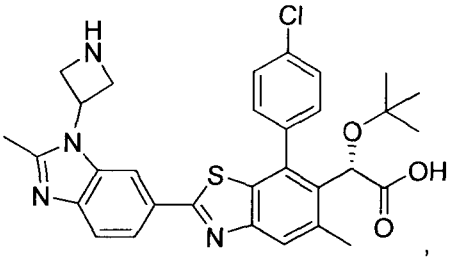

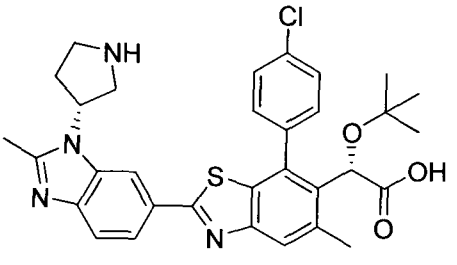

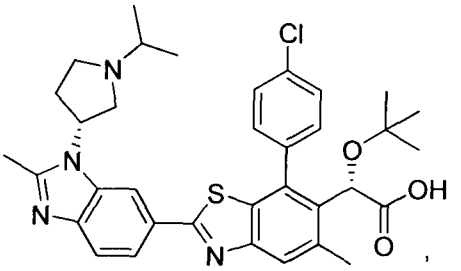

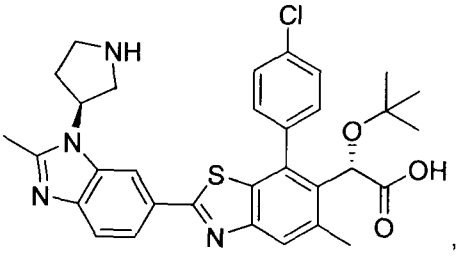

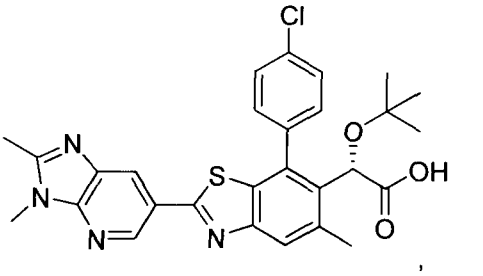

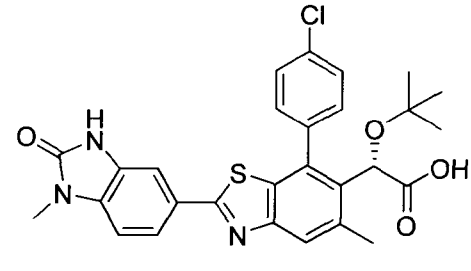

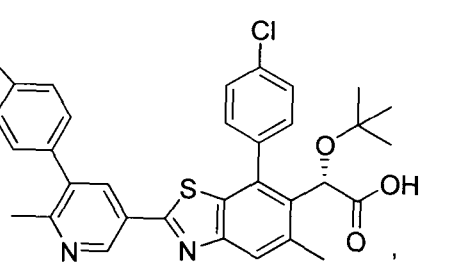

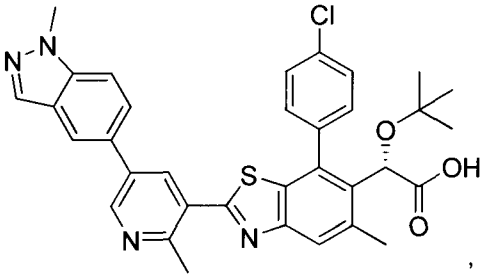

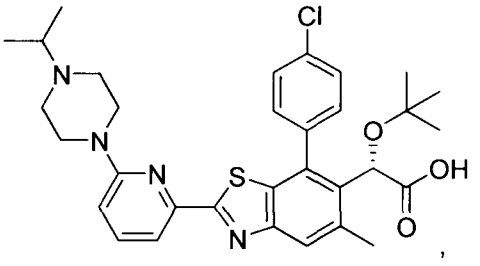

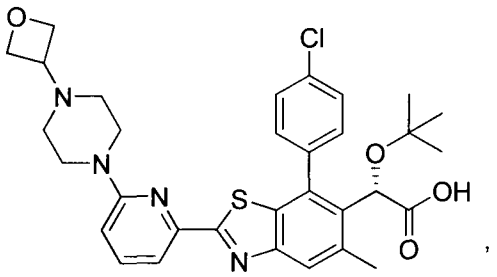

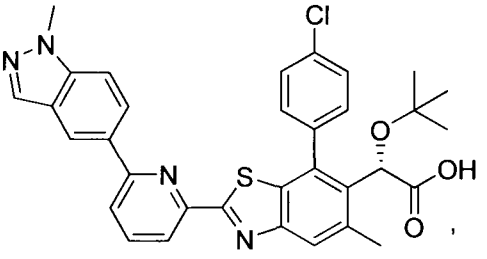

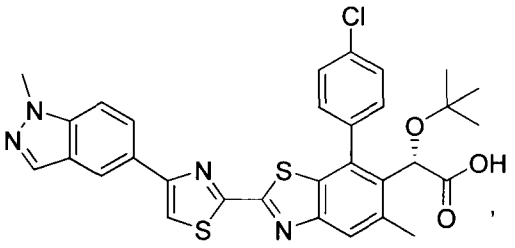

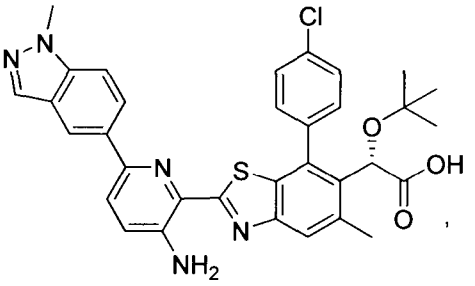

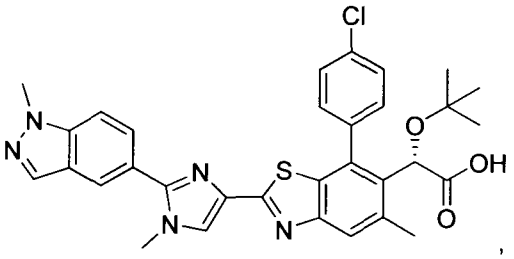

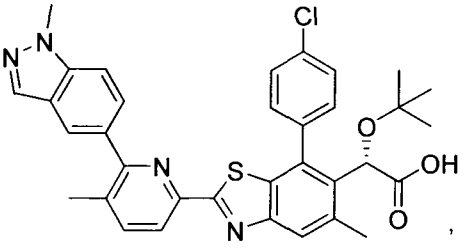

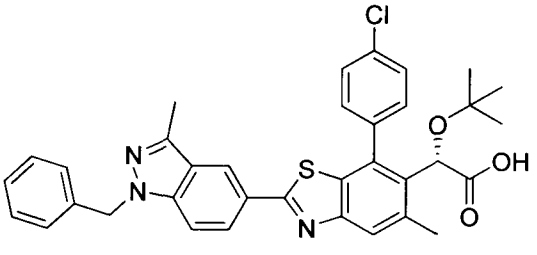

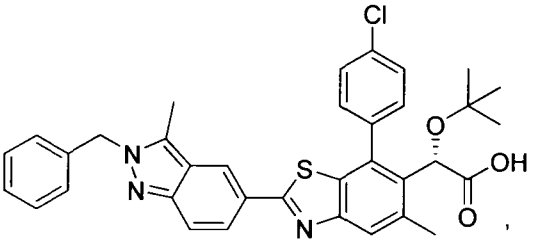

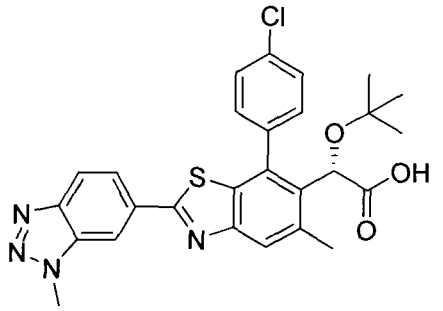

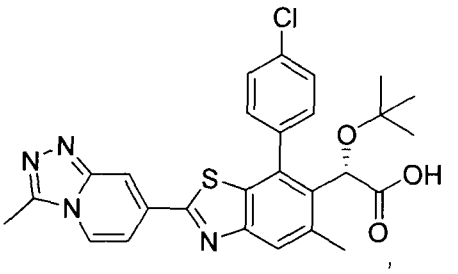

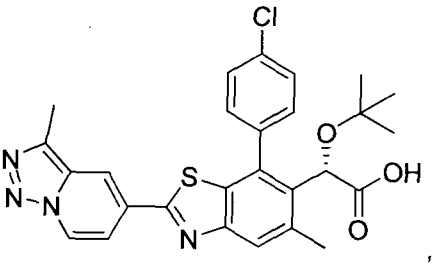

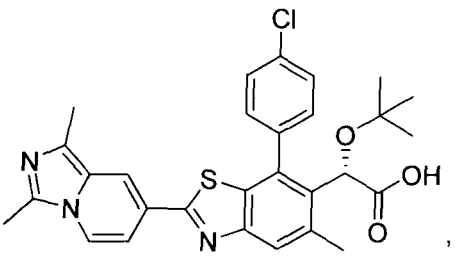

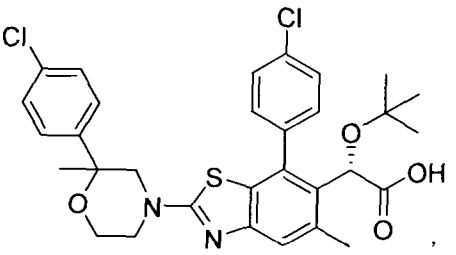

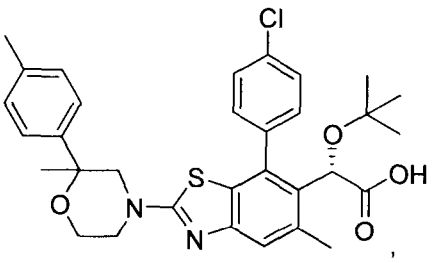

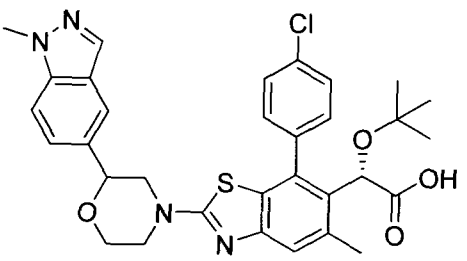

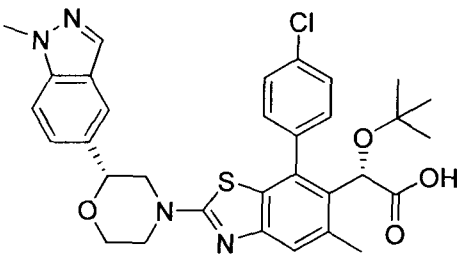

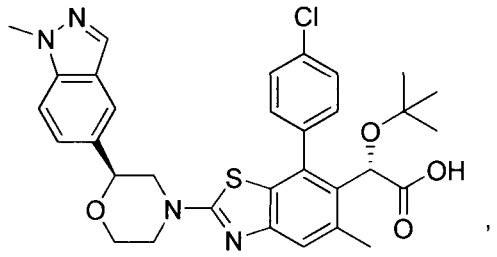

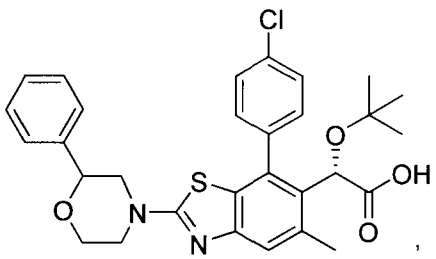

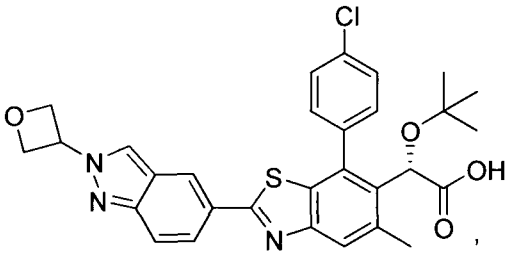

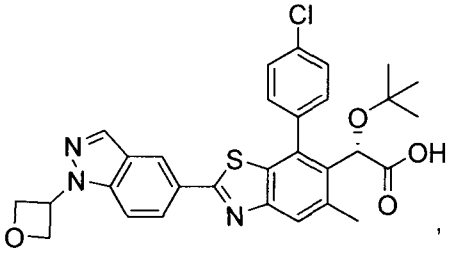

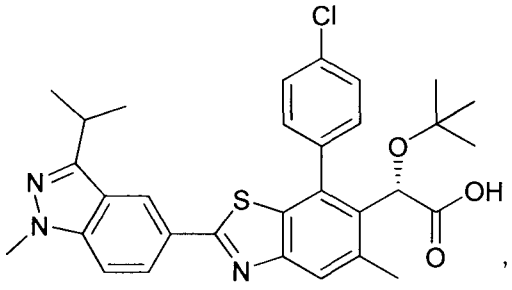

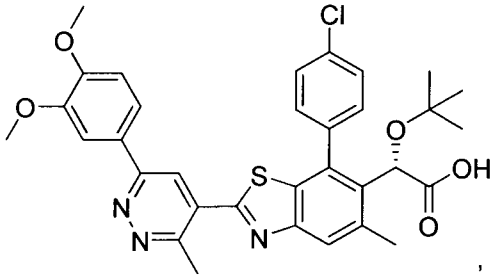

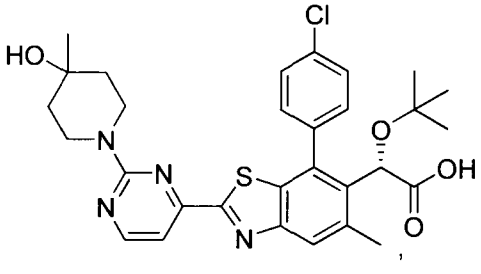

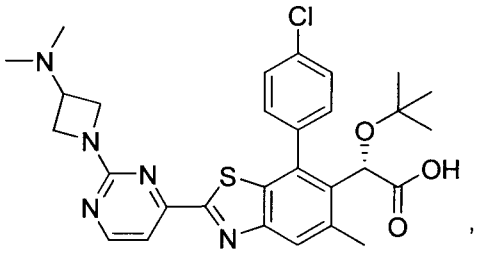

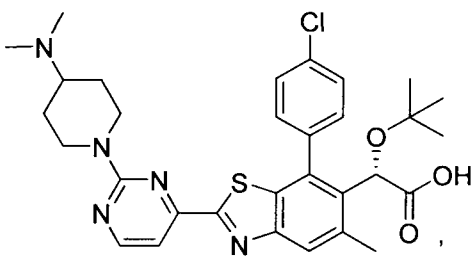

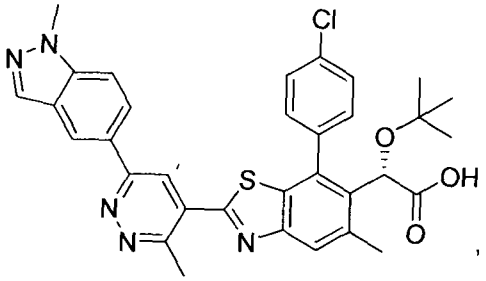

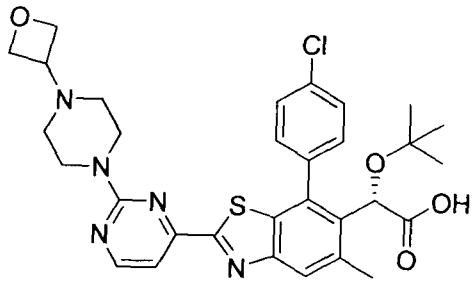

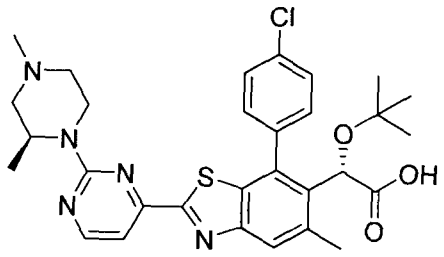

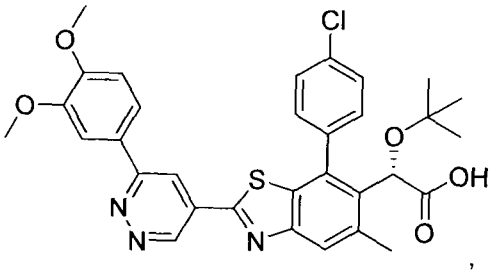

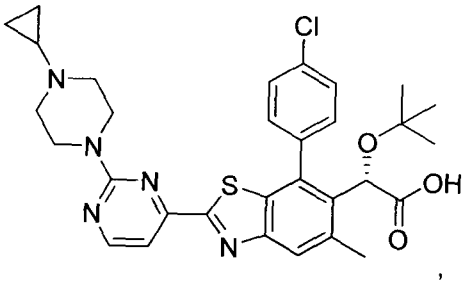

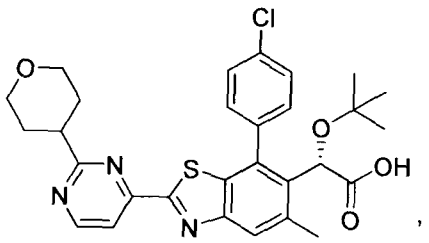

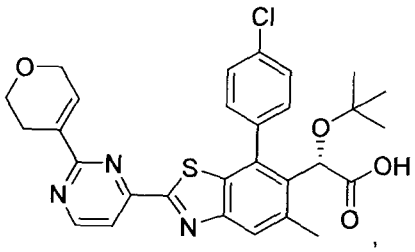

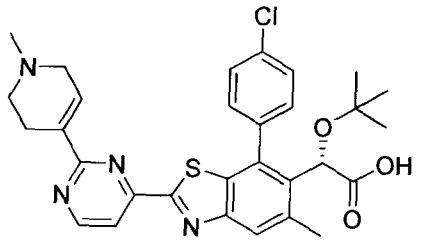

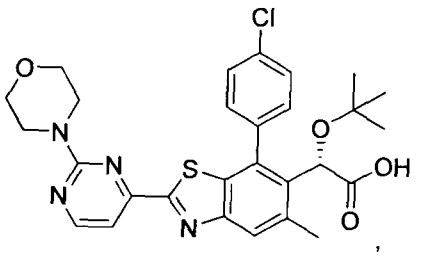

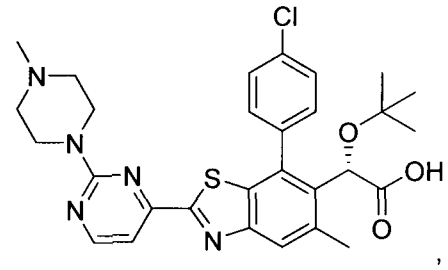

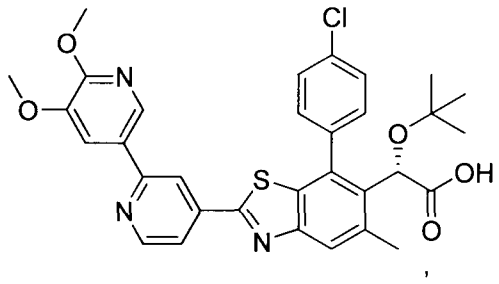

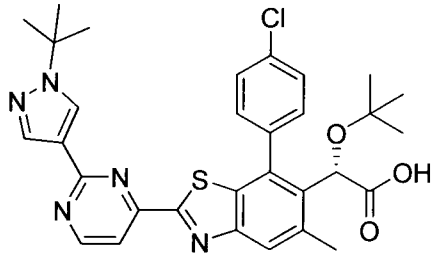

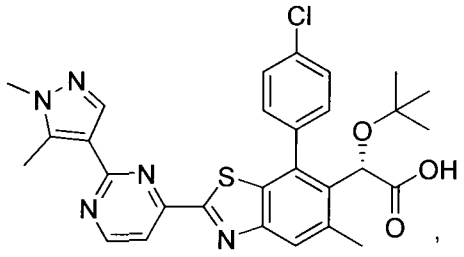

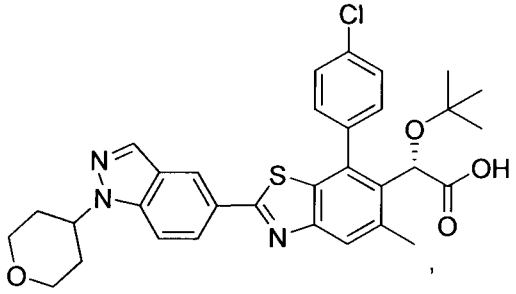

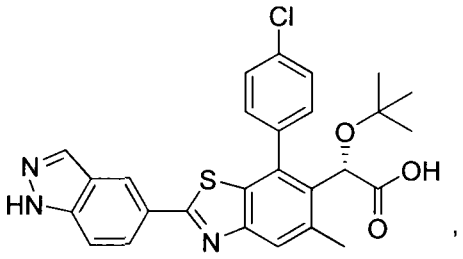

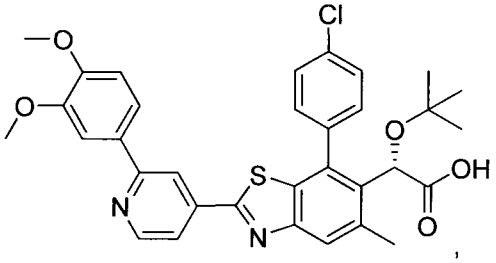

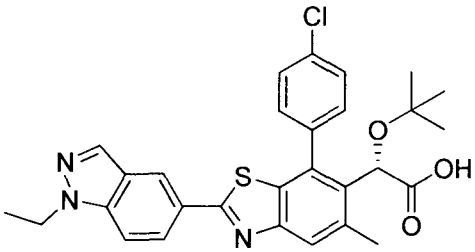

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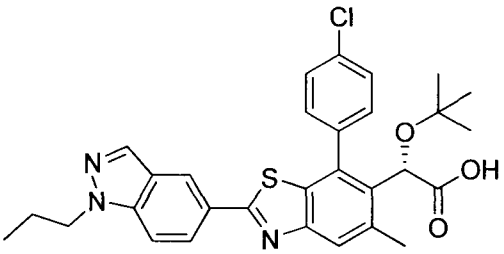

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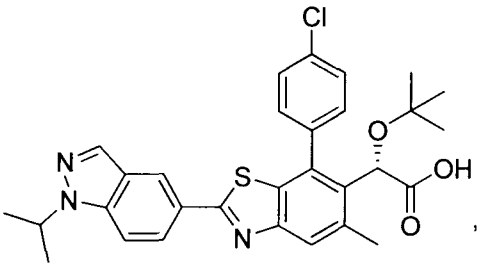

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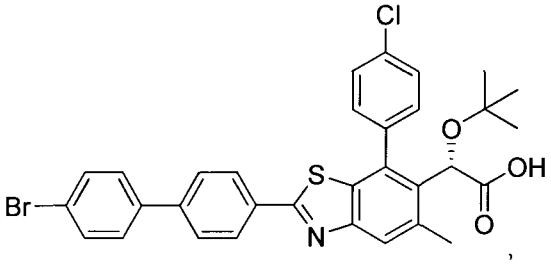

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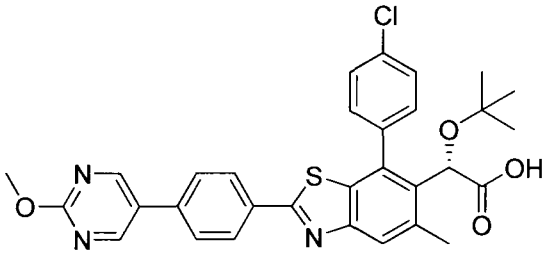

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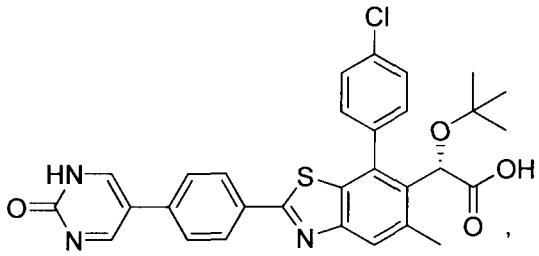

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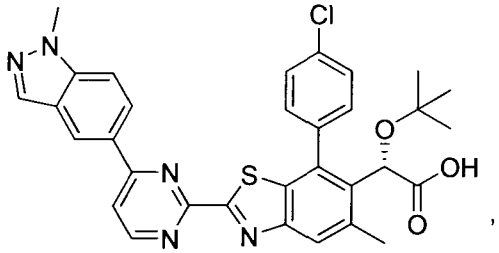

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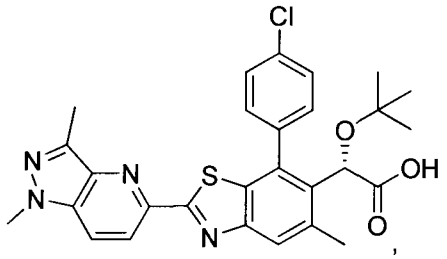

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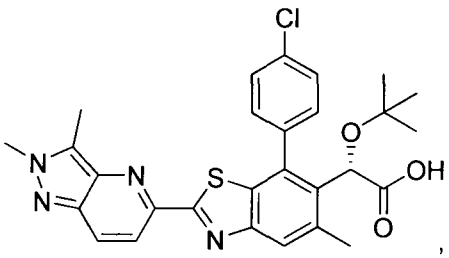

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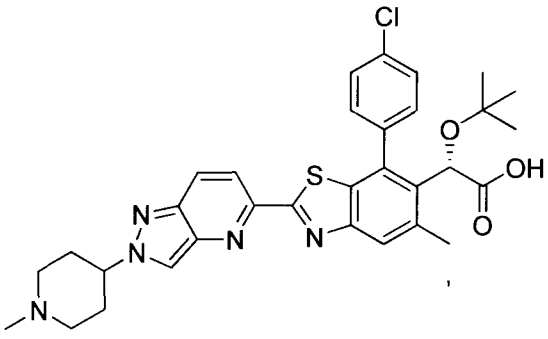

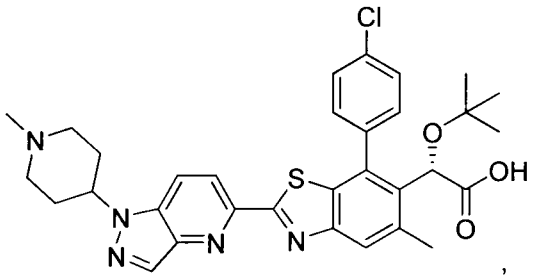

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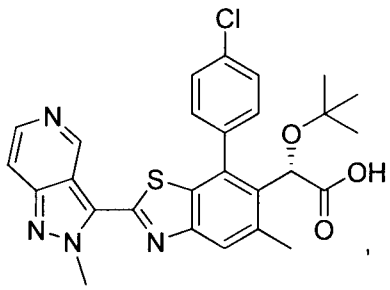

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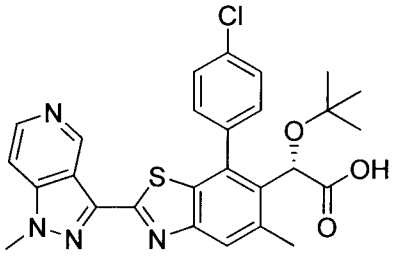

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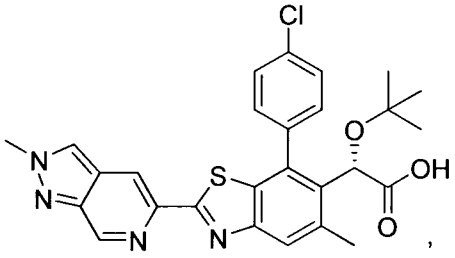

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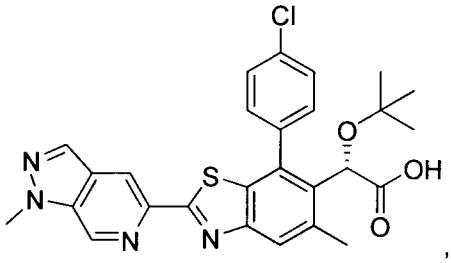

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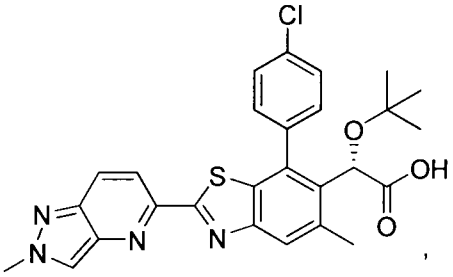

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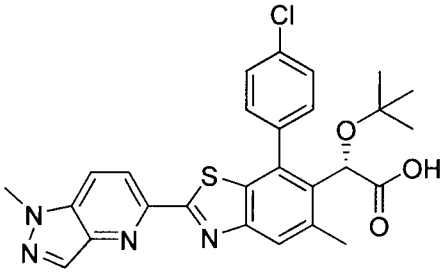

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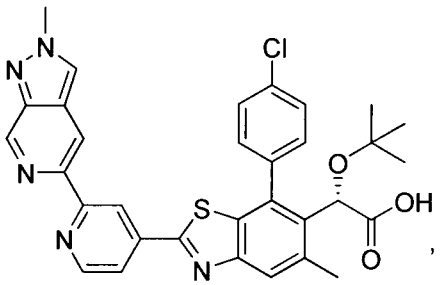

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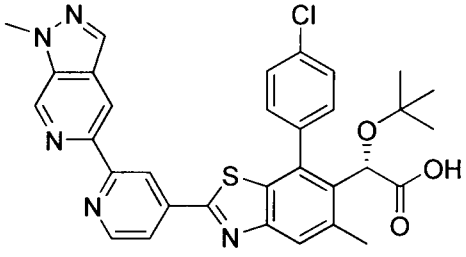

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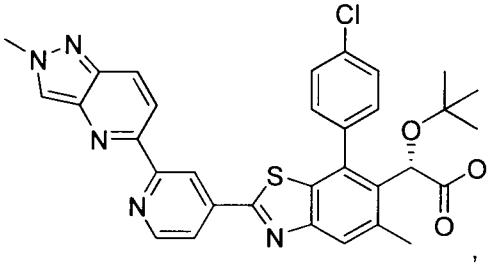

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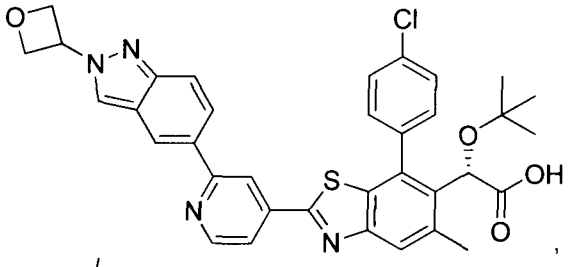

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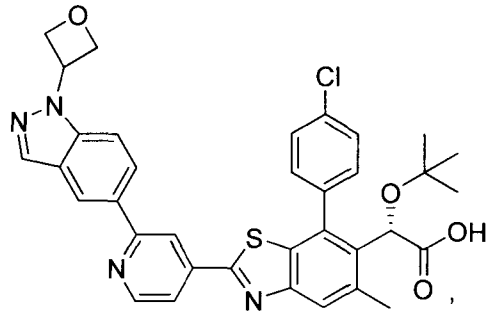

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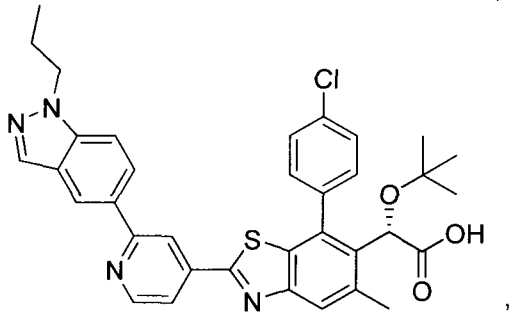

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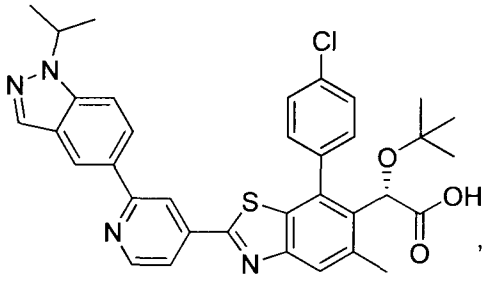

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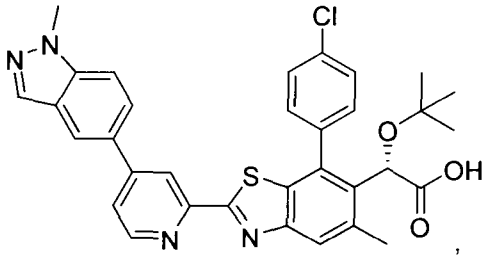

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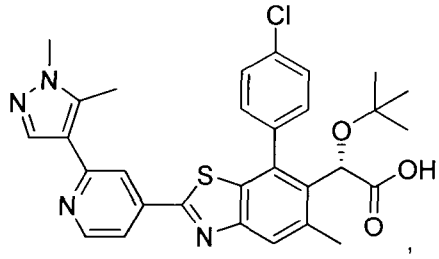

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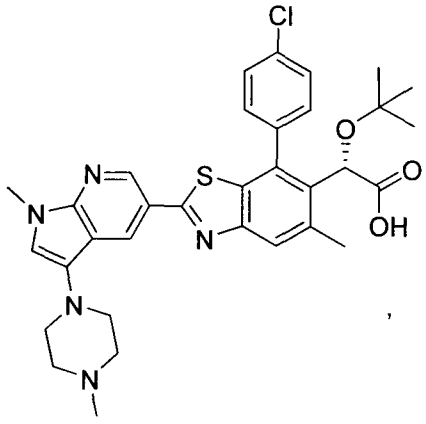

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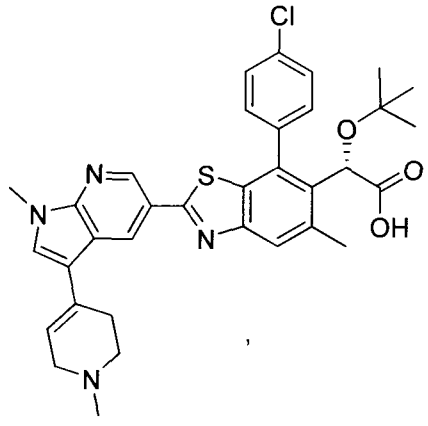

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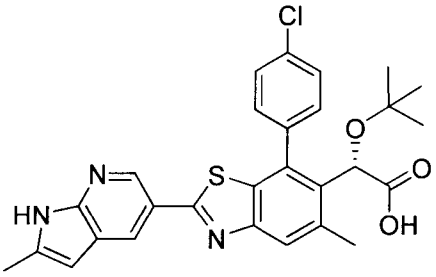

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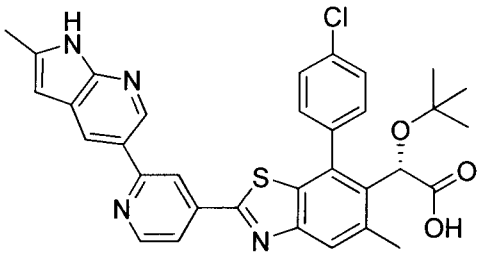

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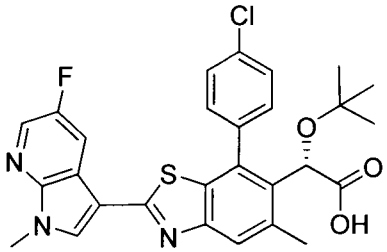

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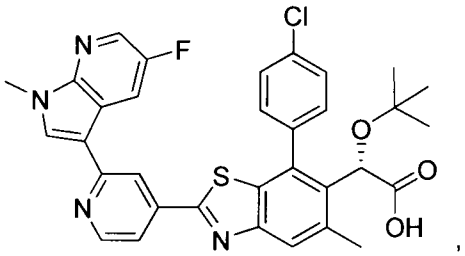

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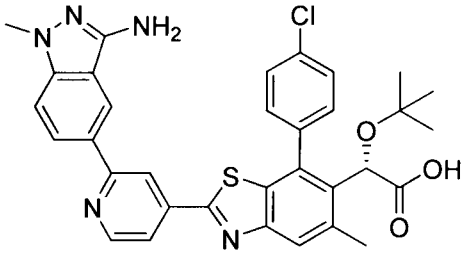

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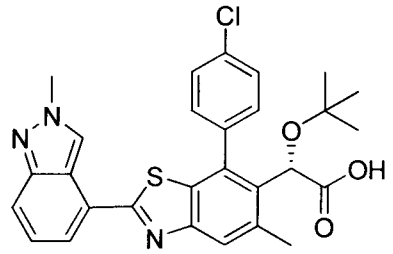

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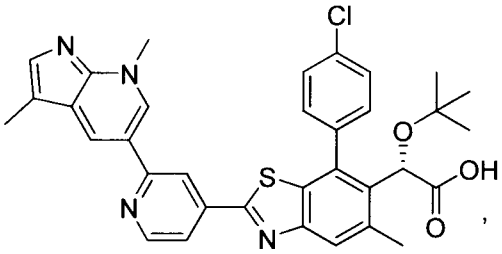

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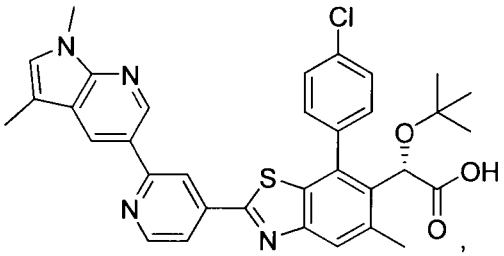

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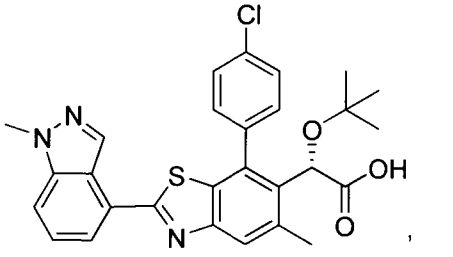

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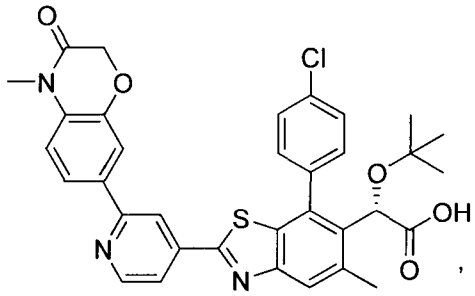

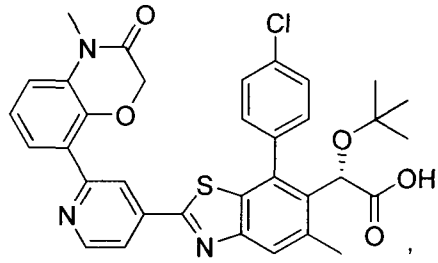

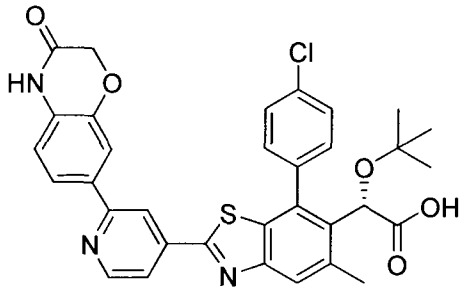

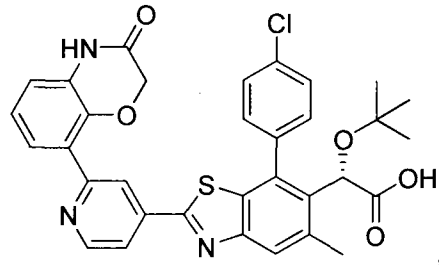

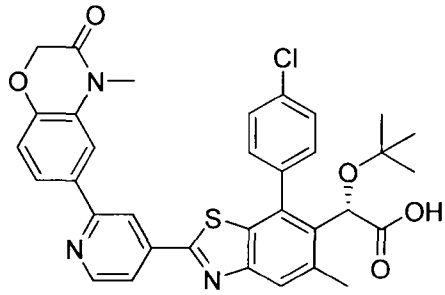

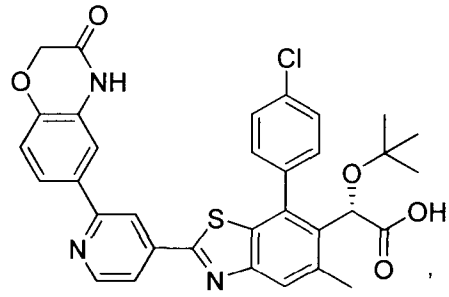

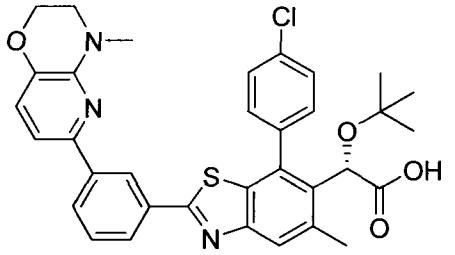

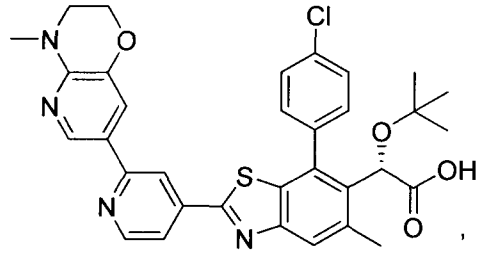

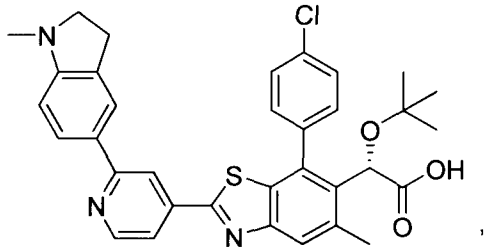

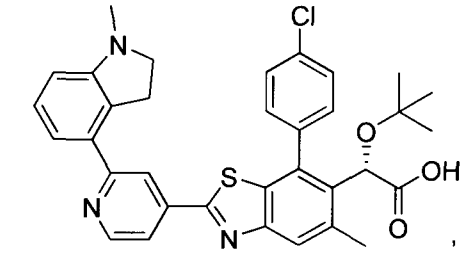

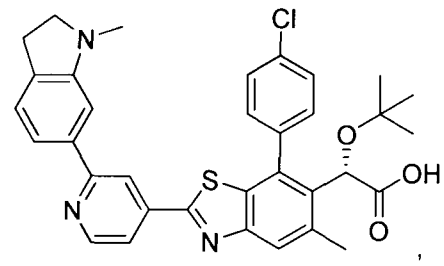

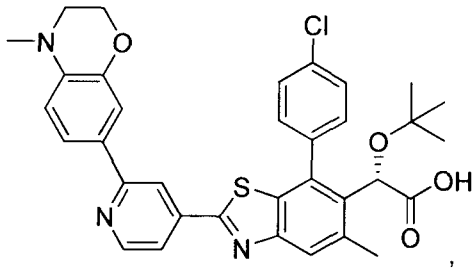

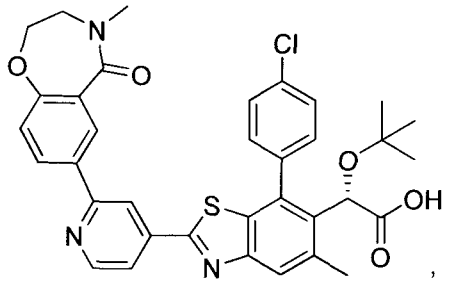

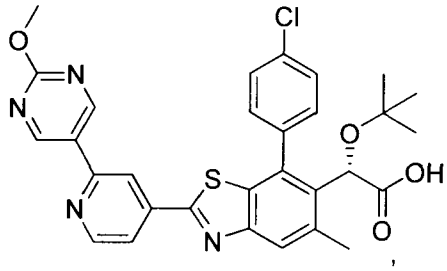

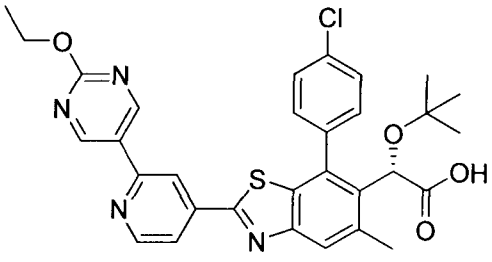

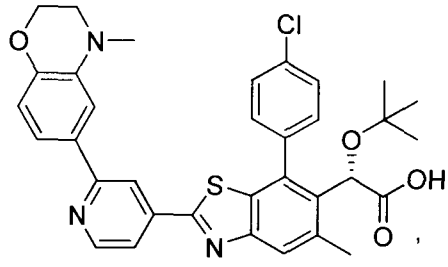

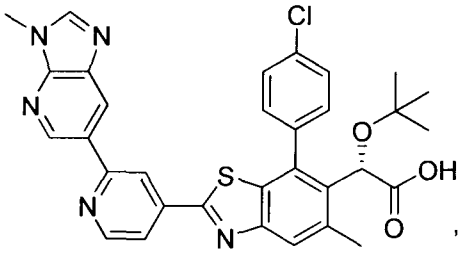

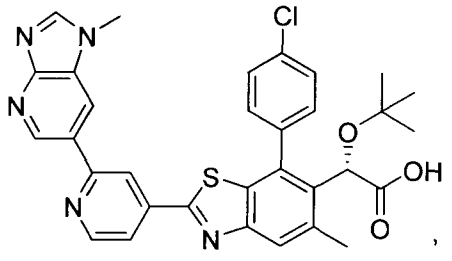

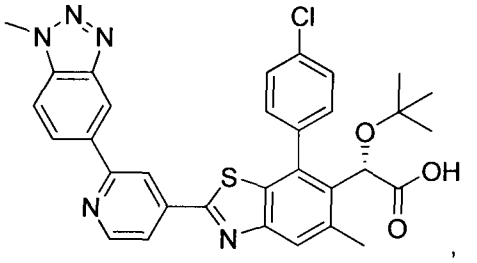

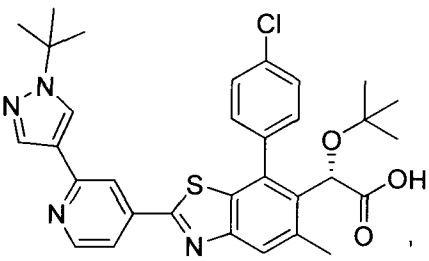

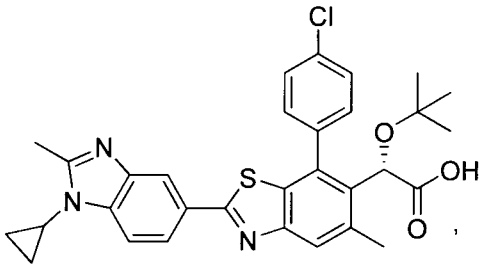

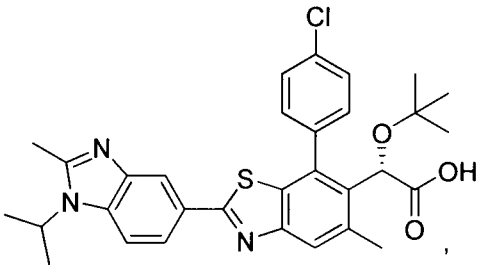

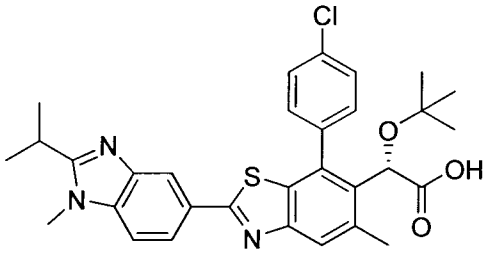

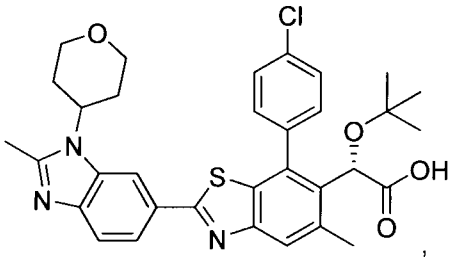

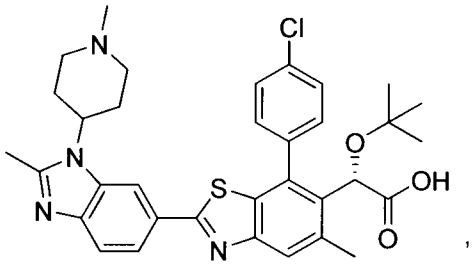

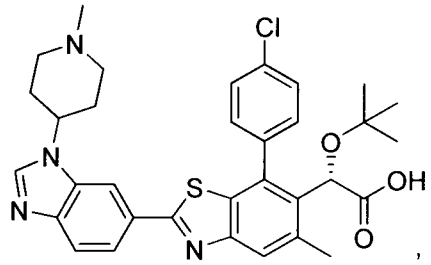

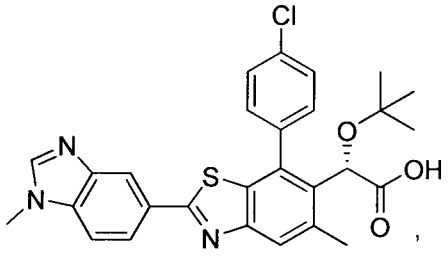

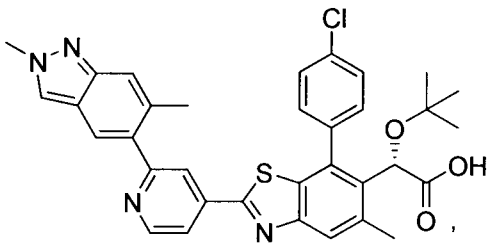

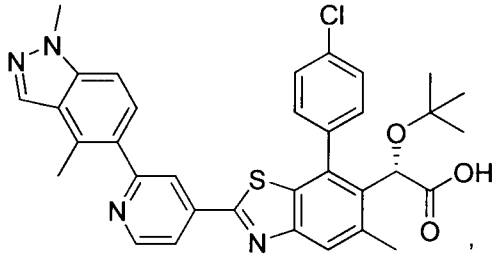

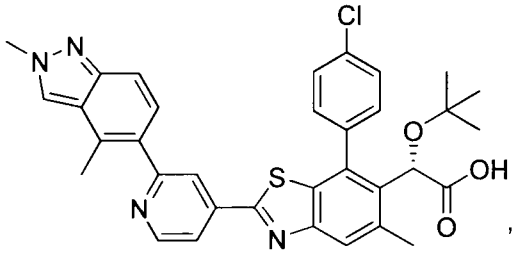

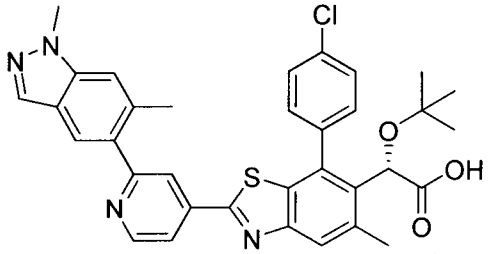

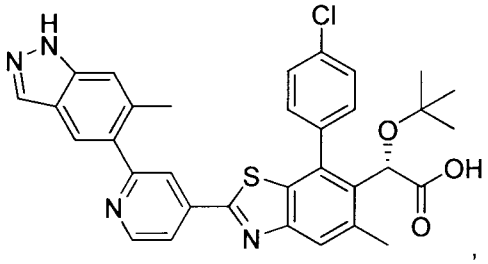

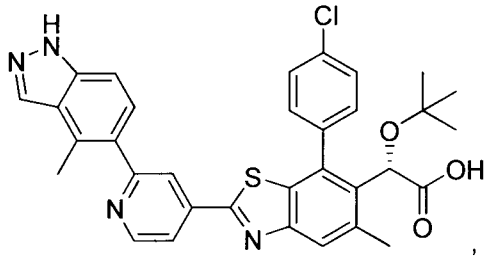

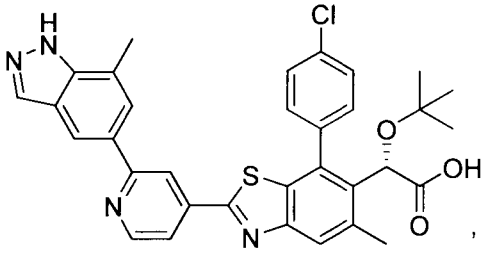

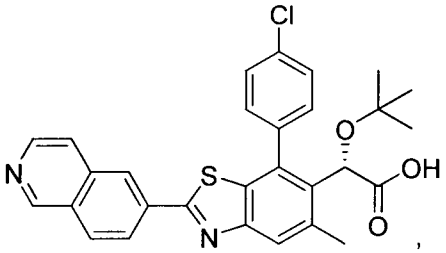

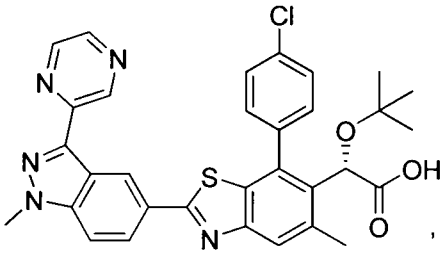

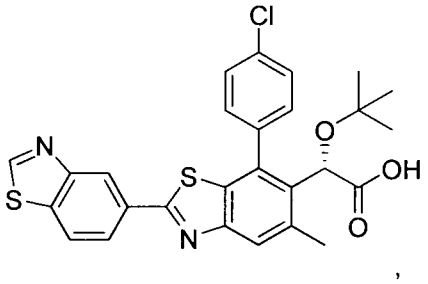

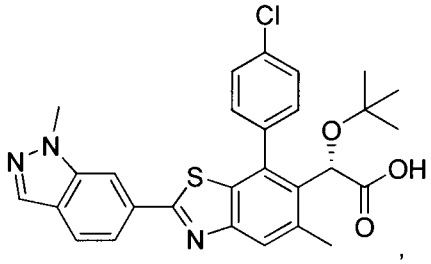

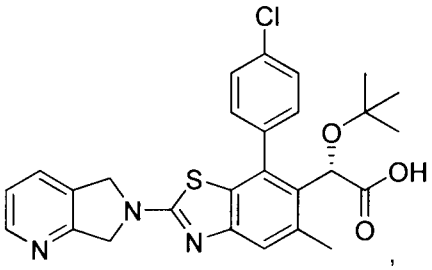

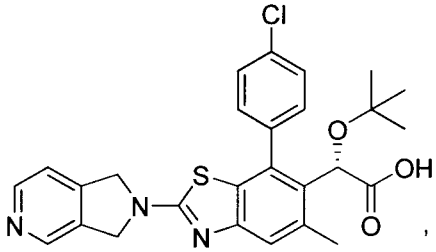

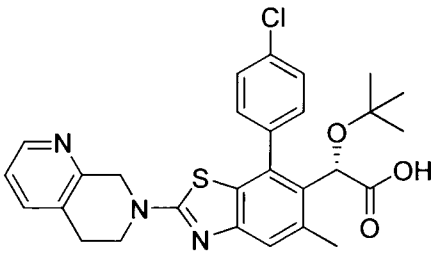

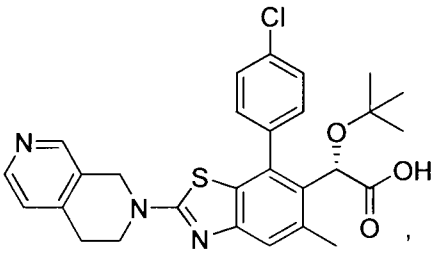

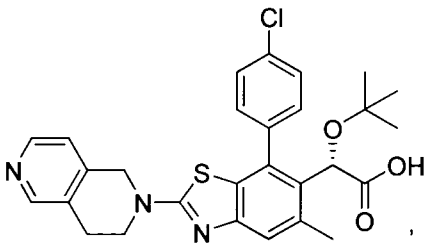

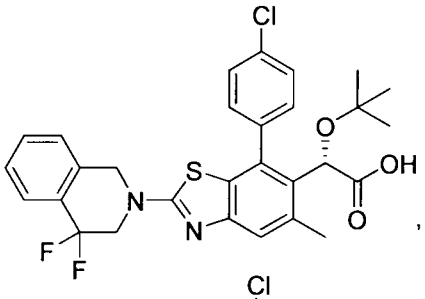

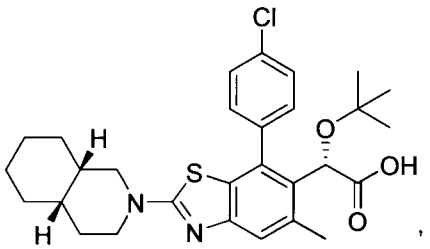

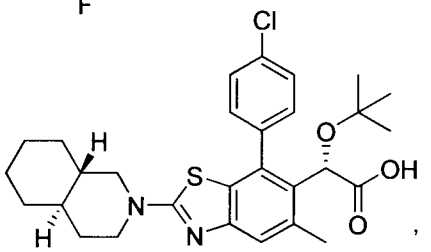

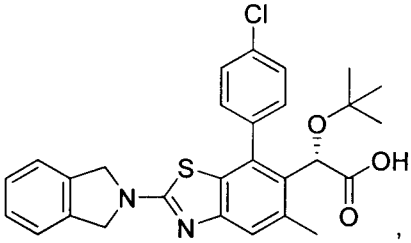

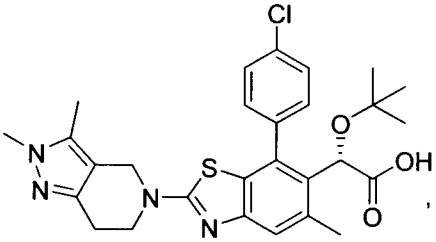

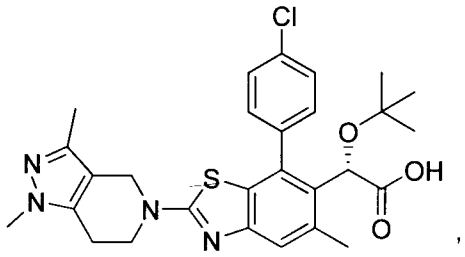

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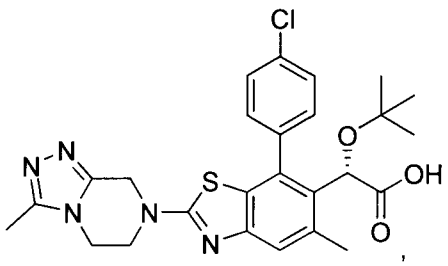

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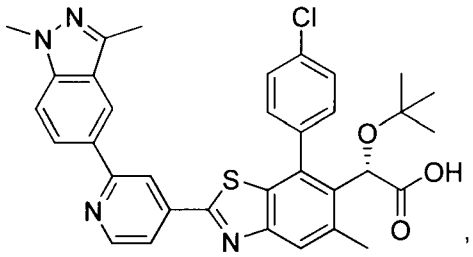

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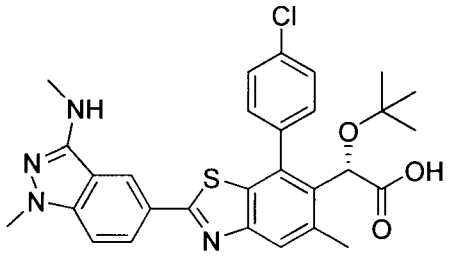

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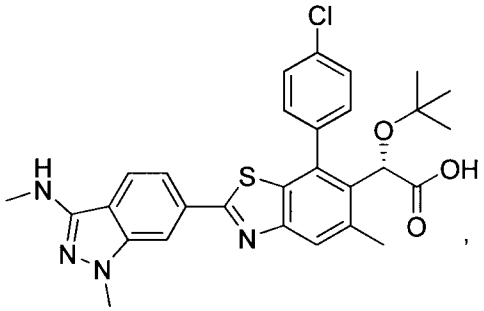

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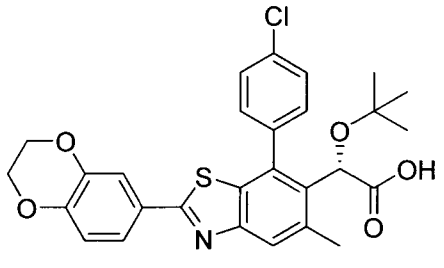

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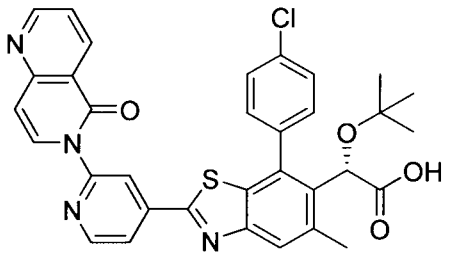

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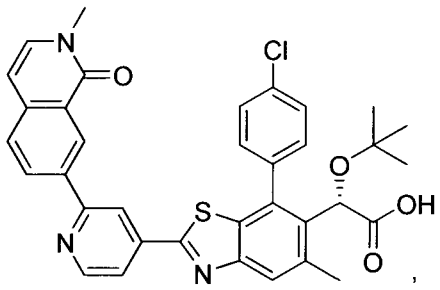

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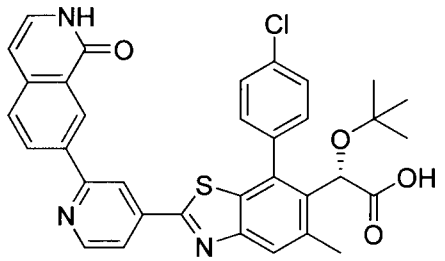

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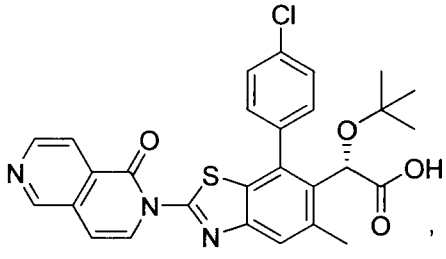

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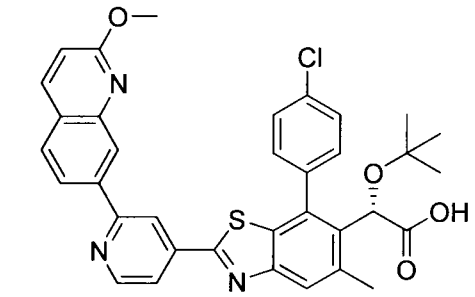

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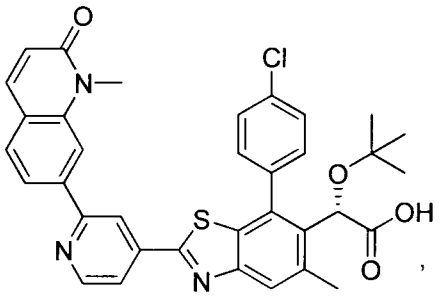

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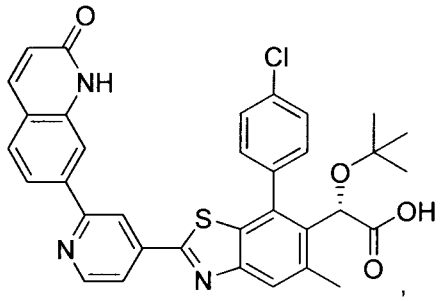

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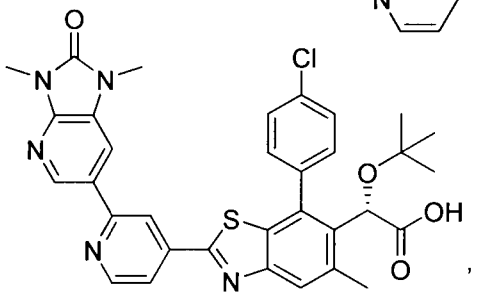

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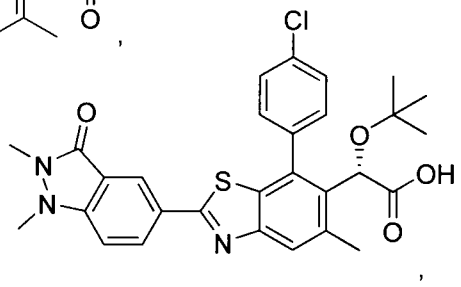

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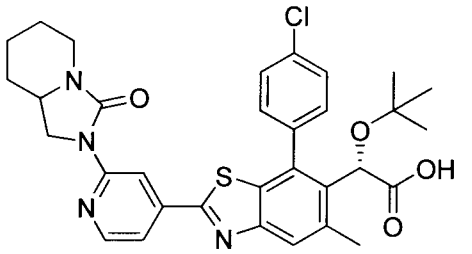

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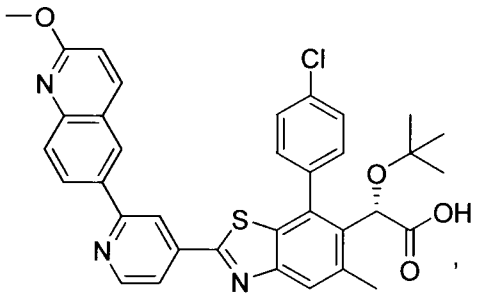

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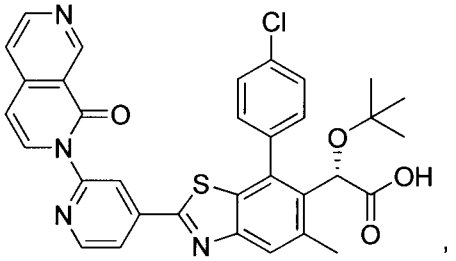

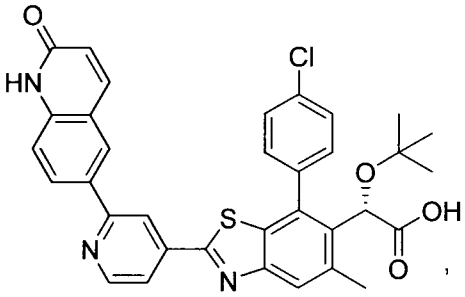

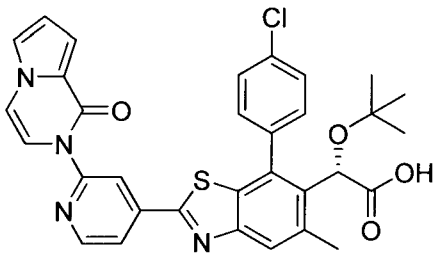

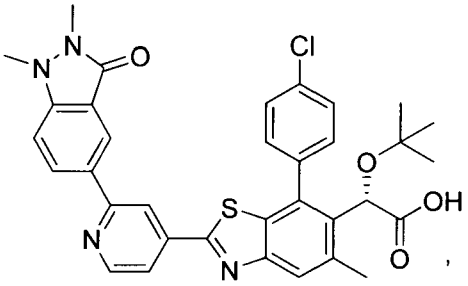

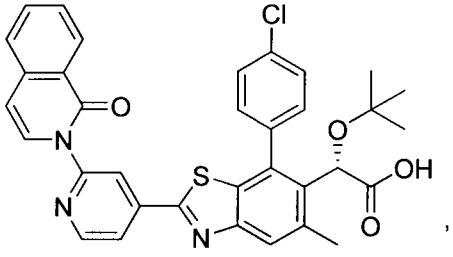

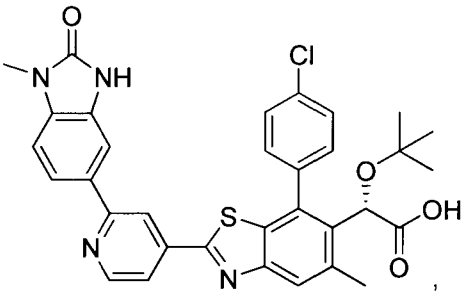

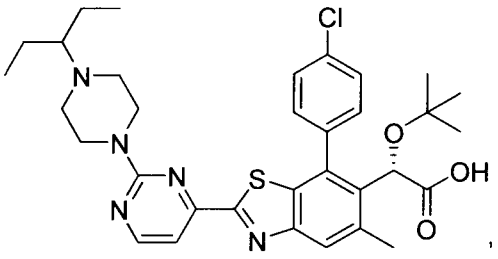

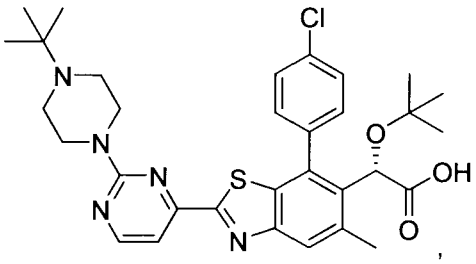

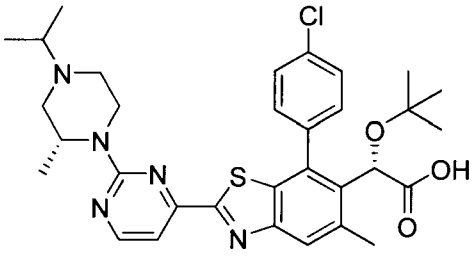

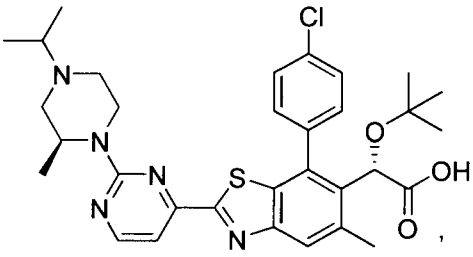

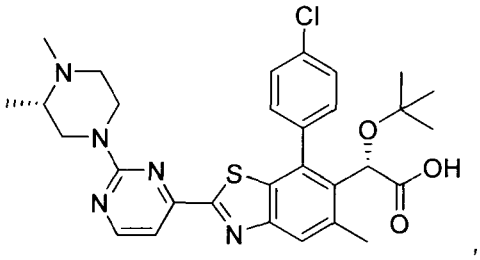

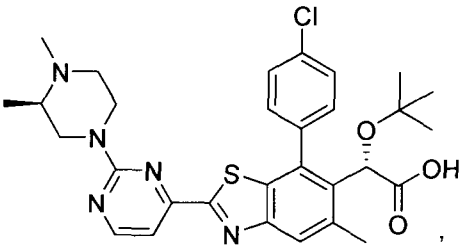

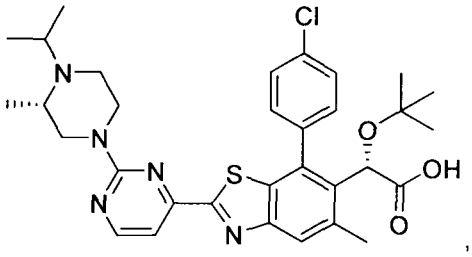

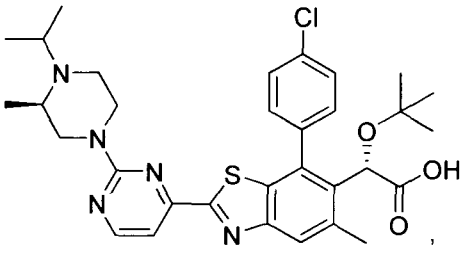

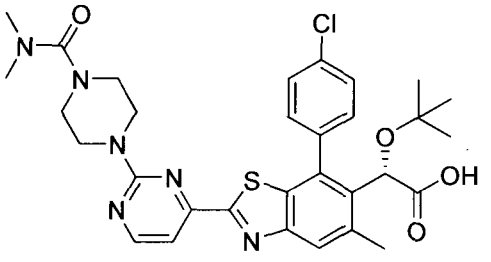

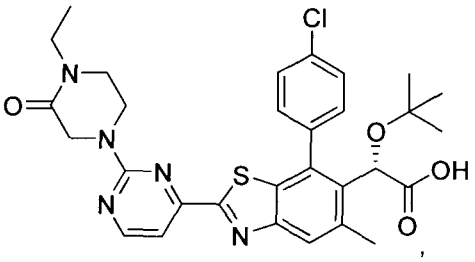

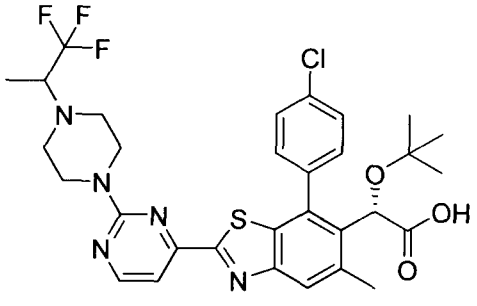

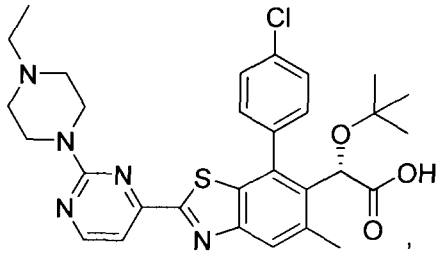

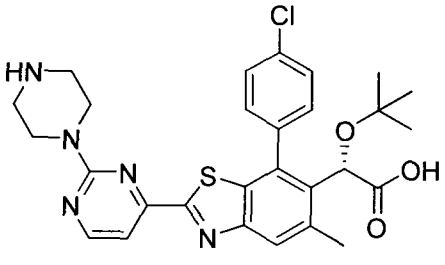

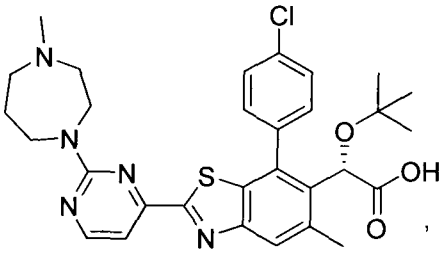

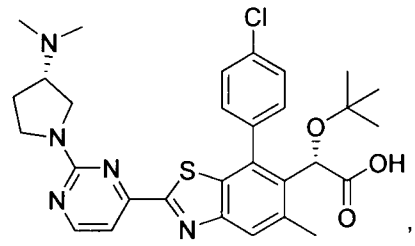

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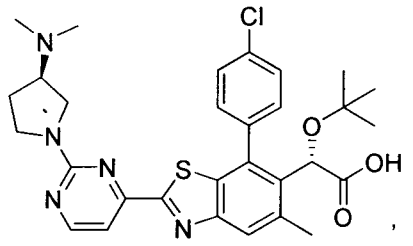

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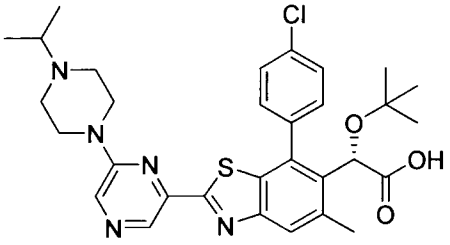

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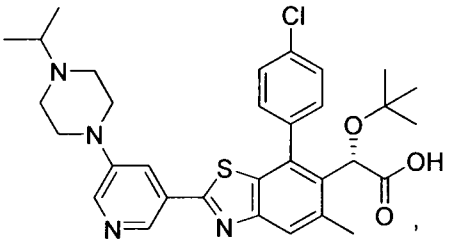

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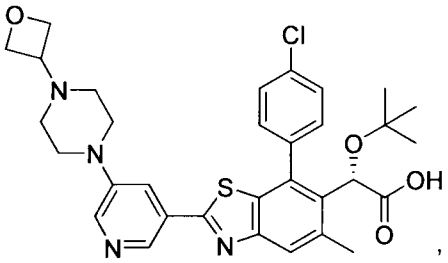

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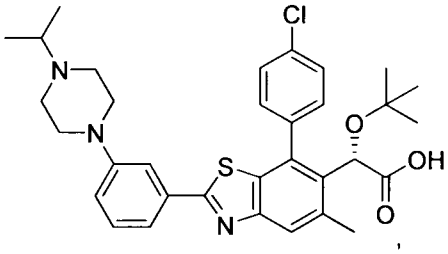

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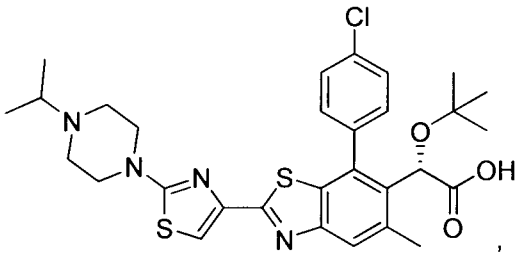

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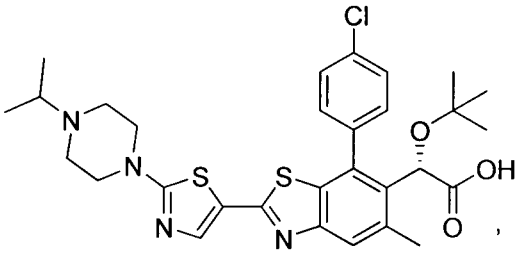

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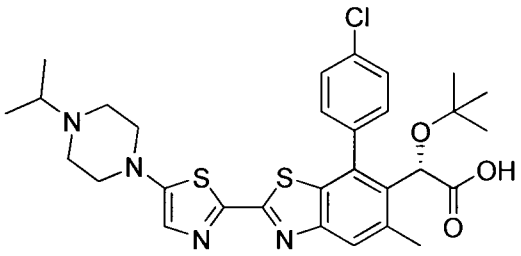

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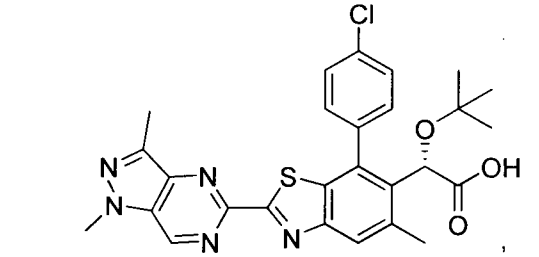

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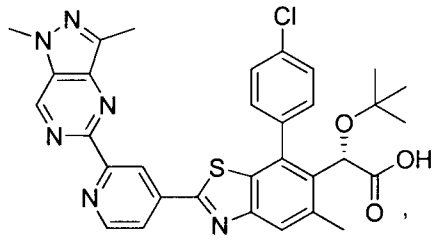

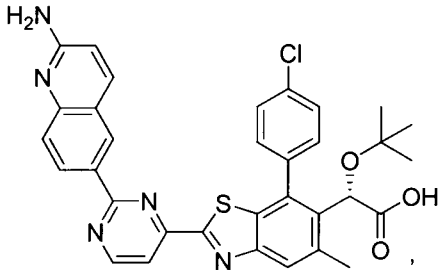

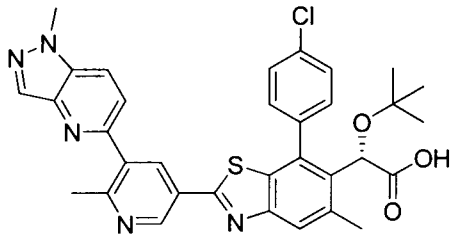

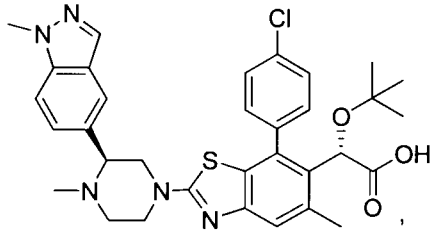

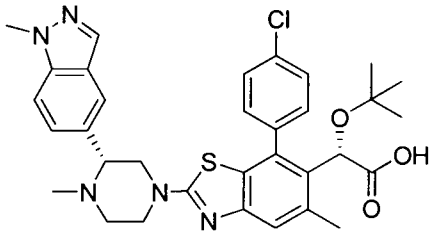

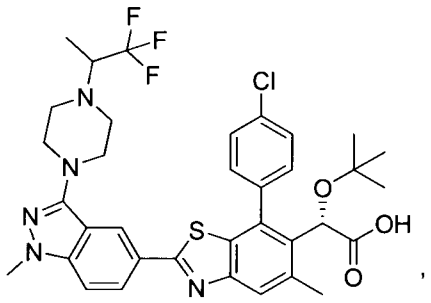

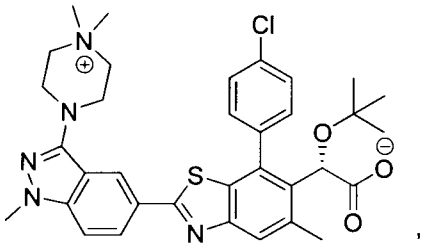

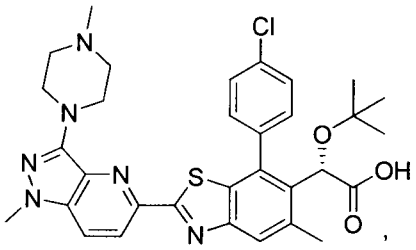

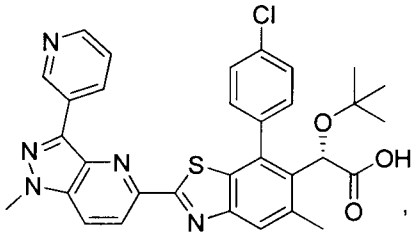

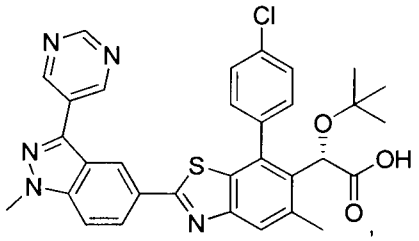

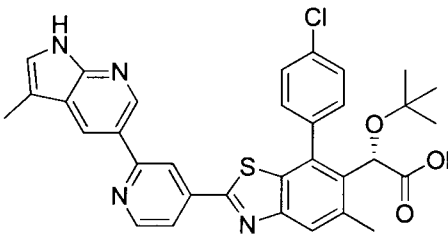

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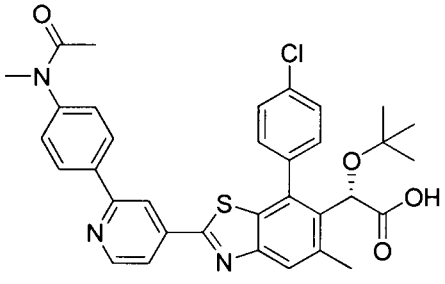
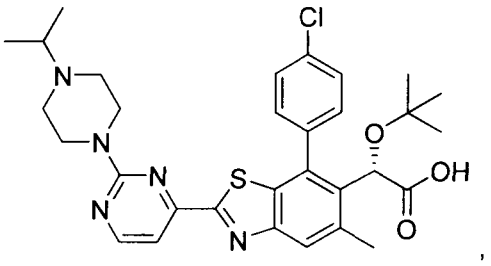
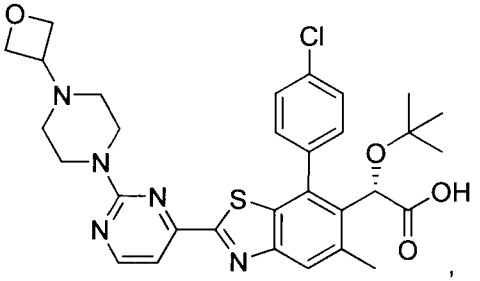
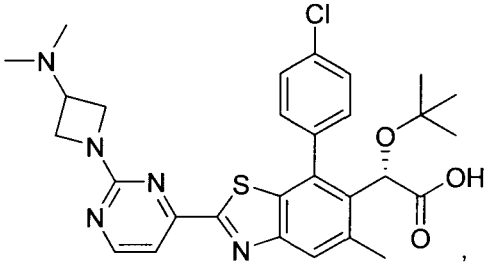


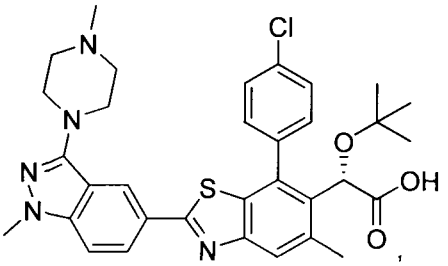
and pharmaceutically acceptable salts thereof.

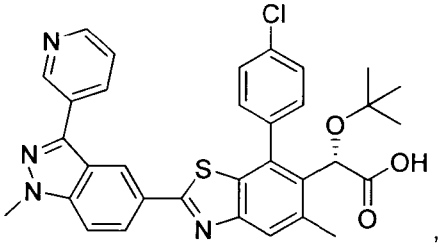
21. The compound of claim 1 which is selected from:

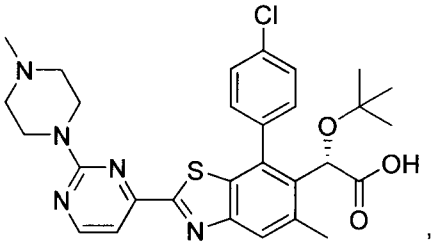


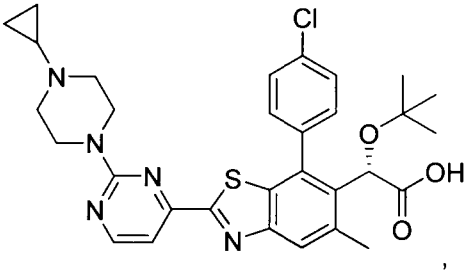


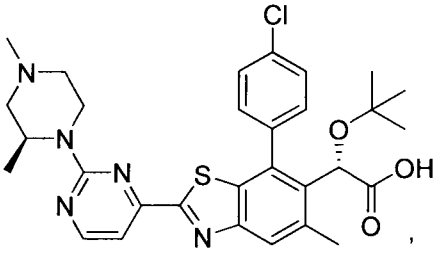


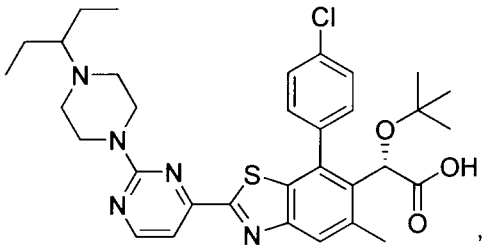


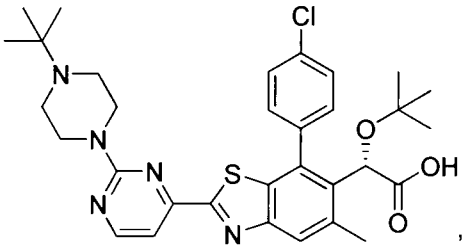


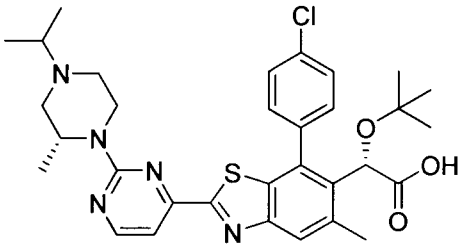


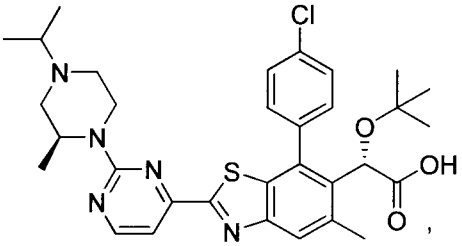


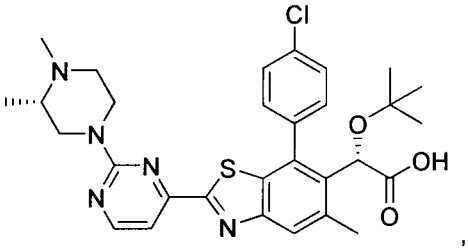


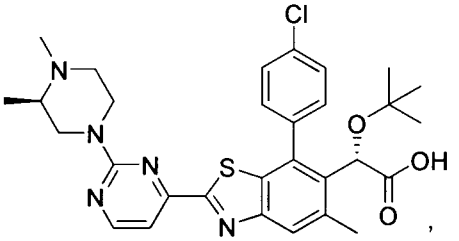


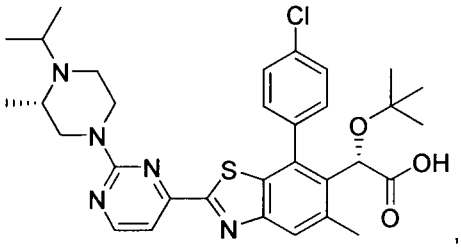


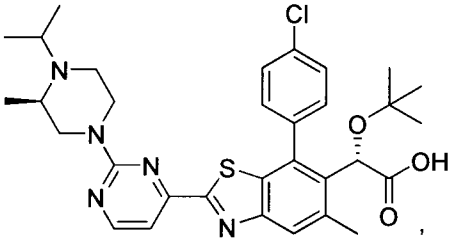


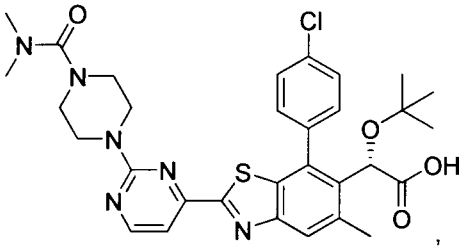


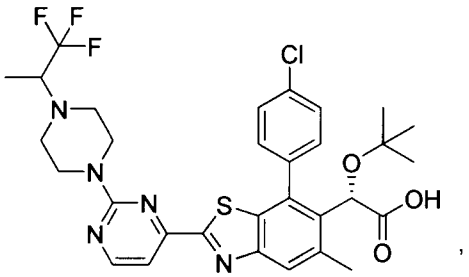












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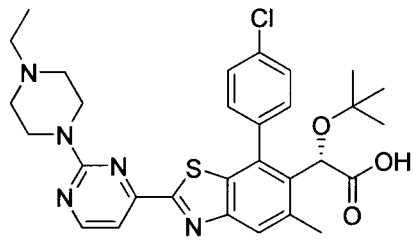

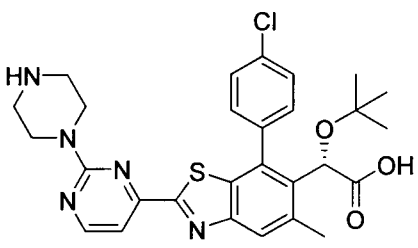

and pharmaceutically acceptable salts thereof.

22. A pharmaceutical composition comprising a compound of formula I' as described in any one of claims 1-21, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

23. A method of treating an HIV infection in a mammal comprising administering a compound of formula I' as described in any one of claims 1-21, or a pharmaceutically acceptable salt thereof, to the mammal.

24. A method for treating an HIV infection in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I' as described in any one of claims 1-21, 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 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.

25. A compound of formula I' as described in any of claims 1-21, or a pharmaceutically acceptable salt thereof for use in medical therapy.

26. The use of a compound of formula I' as described in any one of claims 1-21, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating an HIV infection in a mammal.

27. A compound of formula I' as described in any one of claims 1-21, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection.

28. A compound or method as described herein.