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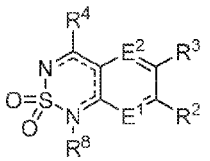
(54) Title: KRAS G12C INHIBITORS FOR THE TREATMENT OF CANCER



(I)

(57) Abstract: Provided herein are KRAS G12C inhibitors of the general formula (I) and pharmaceutical compositions comprising the same. These inhibitors are useful for treating a number of disorders, including pancreatic, colorectal, and lung cancers.

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KRAS G12C INHIBITORS AND METHODS OF USING THE SAME

FIELD OF THE INVENTION

[0001] The present invention relates to compounds that inhibit the KRAS G12C protein; methods of treating diseases or conditions, such as cancer, using the compounds; and pharmaceutical compositions containing the compounds.

BACKGROUND

[0001] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

[0002] KRAS gene mutations are common in pancreatic cancer, lung adenocarcinoma, colorectal cancer, gall bladder cancer, thyroid cancer, and bile duct cancer. KRAS mutations are also observed in about 25% of patients with NSCLC, and some studies have indicated that KRAS mutations are a negative prognostic factor in patients with NSCLC. Recently, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations have been found to confer resistance to epidermal growth factor receptor (EGFR) targeted therapies in colorectal cancer; accordingly, the mutational status of KRAS can provide important information prior to the prescription of TKI therapy. Taken together, there is a need for new medical treatments for patients with pancreatic cancer, lung adenocarcinoma, or colorectal cancer, especially those who have been diagnosed to have such cancers characterized by a KRAS mutation, and including those who have progressed after chemotherapy.

[0002a] It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

[0003] The compounds disclosed herein can be in the form of a pharmaceutically acceptable salt. The compounds provided can be formulated into a pharmaceutical formulation comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

[0004] Also provided is a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with a compound or composition disclosed herein. Further provided is a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of a compound or composition disclosed herein. In some embodiments, the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

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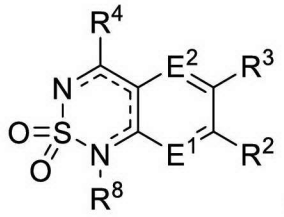
SUMMARY

[0004a] In a first aspect, the present invention provides a compound having a structure of formula (I)



(I)

wherein

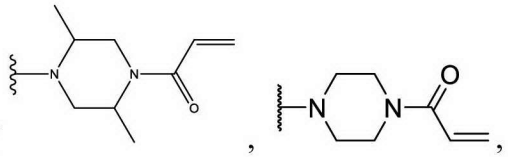
E^1 and E^2 are each independently N or CR^1;

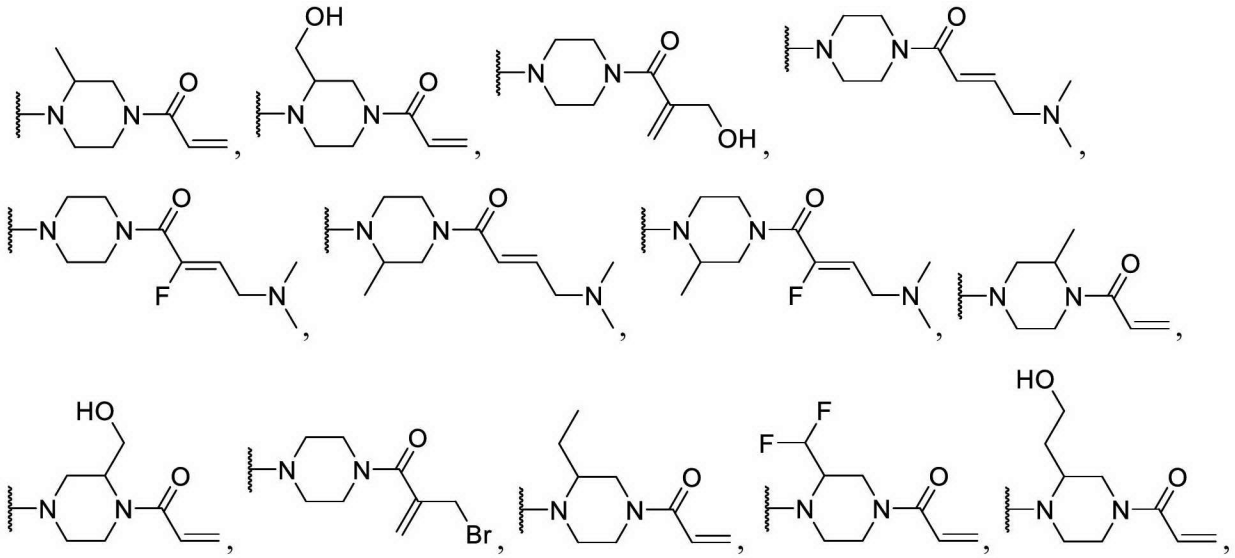
--- is a single or double bond as necessary to give every atom its normal valence;

R^1 is independently H, hydroxy, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N(C_{1-4}alkyl)$_2$, cyano, or halo;

R^2 is substituted aryl;

R^3 is halo, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -OC_{1-6}alkyl, C_{3-6}cycloalkyl, -C_{2-14}heterocycloalkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, aryl, or heteroaryl;

R^4 is selected from the group consisting of 



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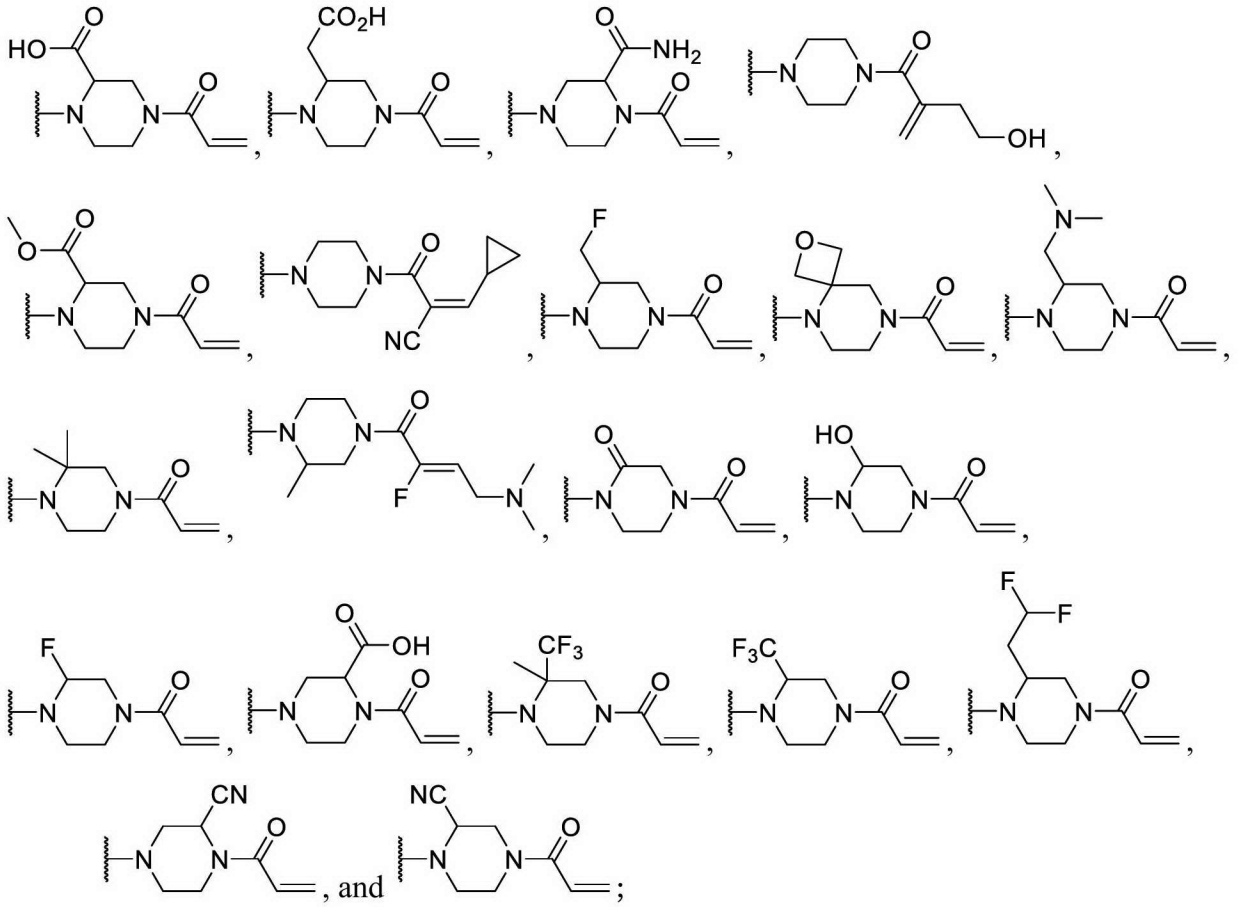

R^8 is -C_{6-14}aryl or -C_{3-14}heteroaryl;

wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups of any of the R^2, R^3 and R^8 substituents have 1, 2, 3, or 4 heteroatoms independently selected from O, N, or S, wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, and the -OC_{1-6}alkyl of any of the R^1, R^2, R^3 and R^8 substituents are unsubstituted or substituted by 1, 2, or 3 R^9 substituents independently selected from OH, -OC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, halo, -O-haloC_{1-6}alkyl, -CN, -NR^aR^b, -OSO_2R^a, -SO_2R^a, -(=O), -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, -O-$SiR^aR^bR^c$, -$SiR^aR^bR^c$, -O-(3- to 10-membered heterocycloalkyl), a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N, or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O

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group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group of any of the R^1, R^2, R^3, R^8, and R^9 substituents can be unsubstituted or substituted with 1, 2, 3, or 4 R^{10} substituents independently selected from OH, halo, $-NR^cR^d$, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-C_{1-6}$alkyl-OH, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, $-C_{1-6}$haloalkyl, -O-haloC_{1-6}alkyl, $-SO_2R^c$, -CN, $-C(=O)NR^cR^d$, $-C(=O)R^c$, $-OC(=O)R^a$, $-C(=O)OR^c$, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups of R^{10} have 1, 2, 3, or 4 heteroatoms independently selected from O, N, or S, wherein the cycloalkyl, spirocycloalkyl, and spiroheterocycloalkyl groups of R^{10} or the heterocycloalkyl group of R^{10} may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

wherein each R^a, R^b, R^c, and R^d is independently hydrogen, OH, $-C_{1-6}$alkyl, phenyl, $-C_{1-6}$alkyl–C(=O)OH, $-C_{1-6}$alkyl–C(=O)-O-C_{1-6}alkyl, $-C_{1-6}$alkyl–3- to 12-membered cycloalkyl, $-C_{1-6}$alkyl–3- to 12-membered heterocycloalkyl, $-C_{1-6}$alkyl–6- to 12-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl group, heterocycloalkyl group of R^a, R^b, R^c, and R^d or the heterocycloalkyl group of the $-C_{1-6}$alkyl–heterocycloalkyl group of R^a, R^b, R^c, and R^d has from 1, 2, 3, or 4 heteroatoms independently selected from O, N, or S, wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the $-C_{1-6}$alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may include a double bond, and further wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the $-C_{1-6}$alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may contain a C=O group; and

the alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl groups of R^a, R^b, R^c, and R^d or the heterocycloalkyl groups of the $-C_{1-6}$alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with from 1, 2, 3, or 4 R^{12} substituents,wherein each R^{12} is independently selected from H, OH, halo, $-C_{1-6}$alkyl, $N(CH_3)_2$, $-C_{1-6}$haloalkyl, $C(=O)CH_3$, $-C(=O)OCH_3$, or $-C_{1-6}$alkyl-O-C_{1-6}alkyl; or

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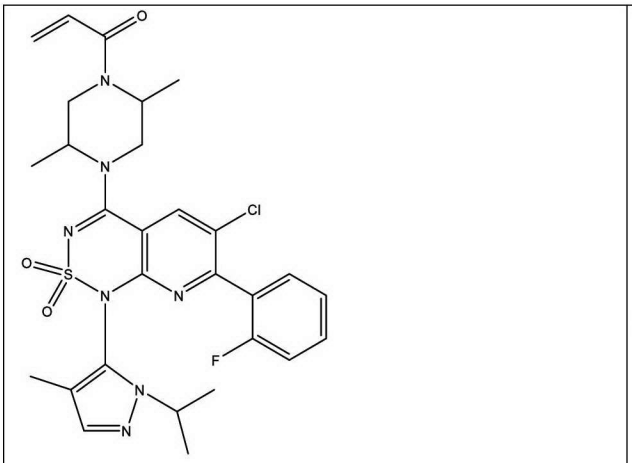
a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

[0004b] In a second aspect, the present invention provides a compound selected from the group consisting of: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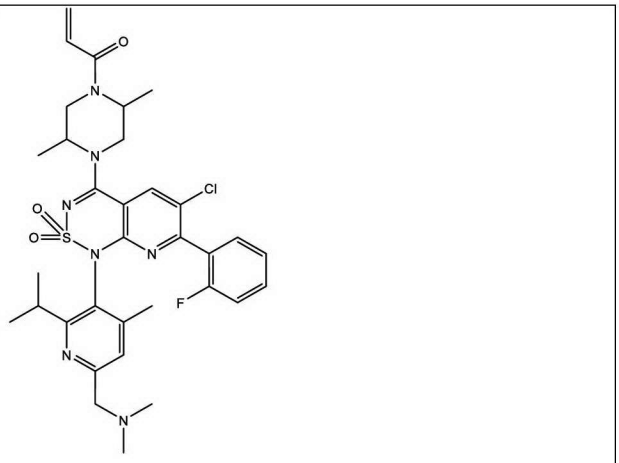
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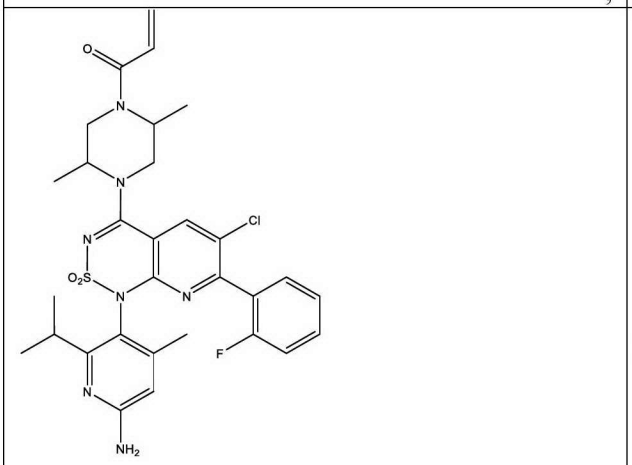
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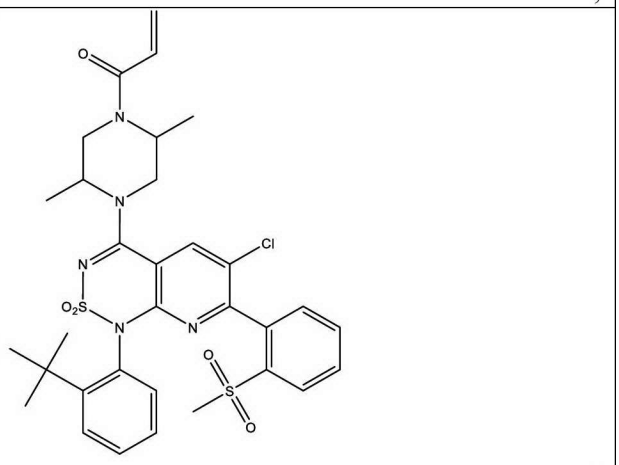
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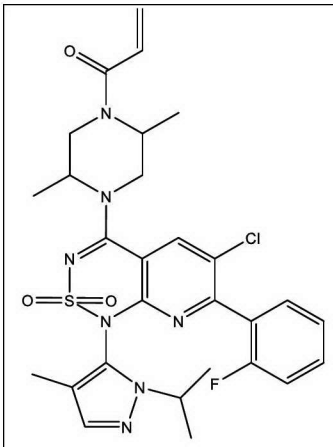
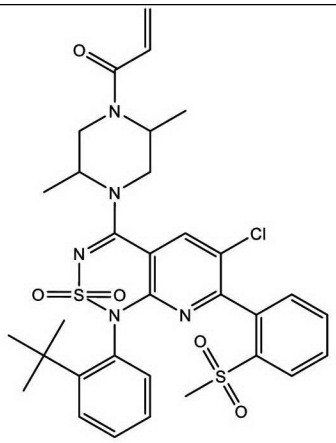
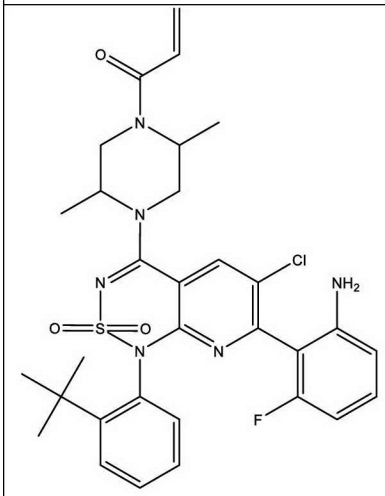
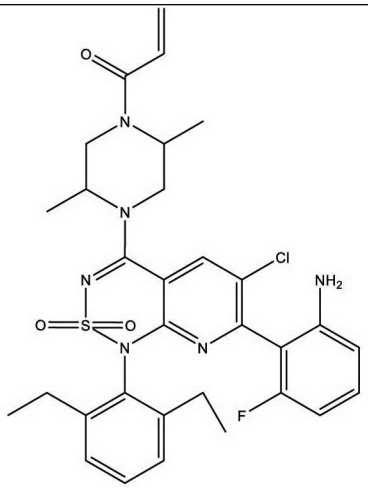
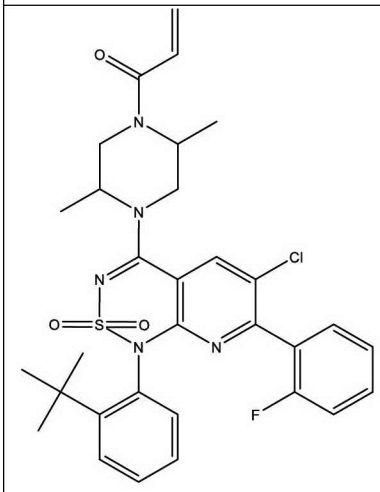
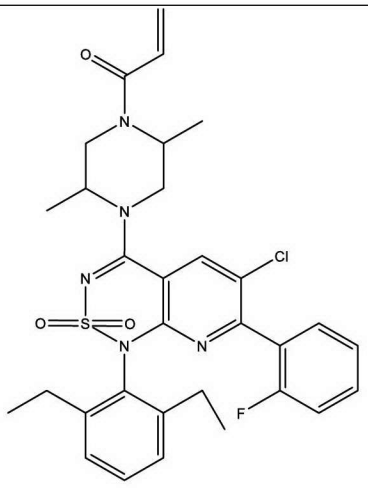
 ;	 ;
 ;	 ;
 ;	 ;

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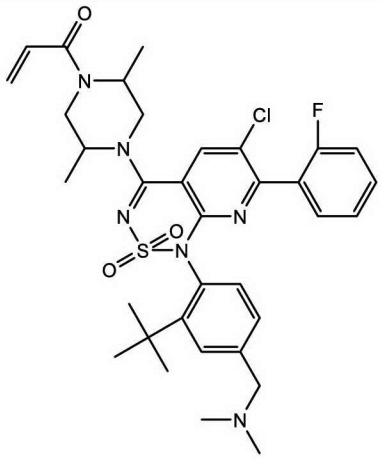
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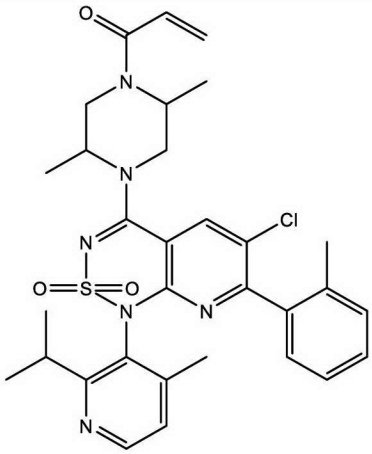
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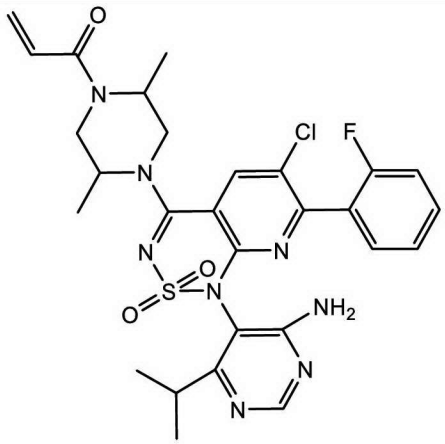
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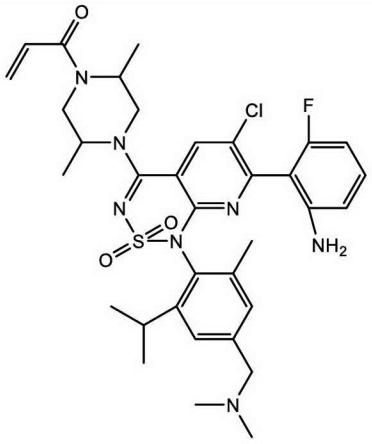
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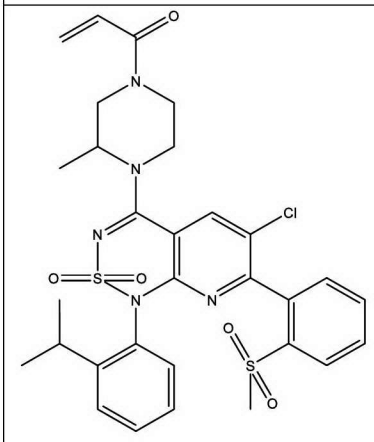
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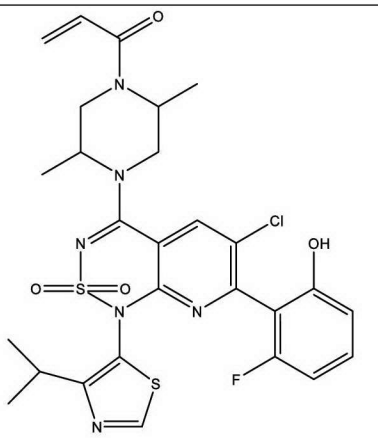
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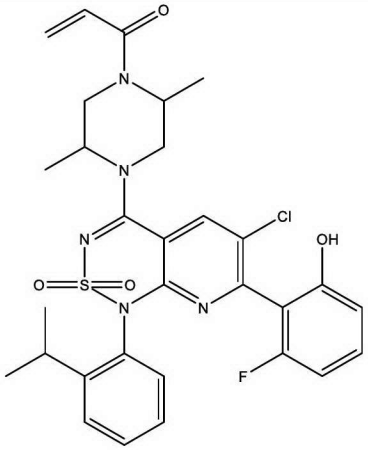

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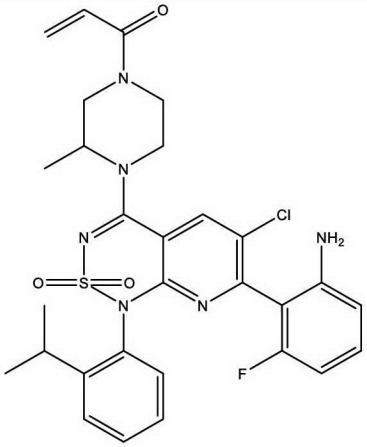

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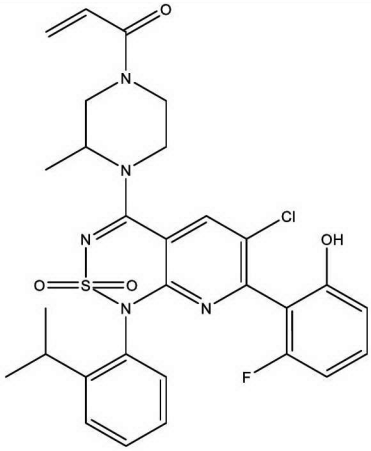

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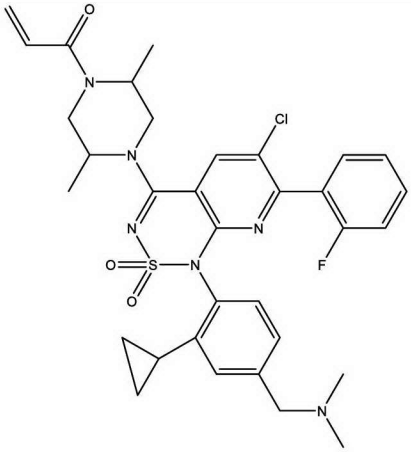

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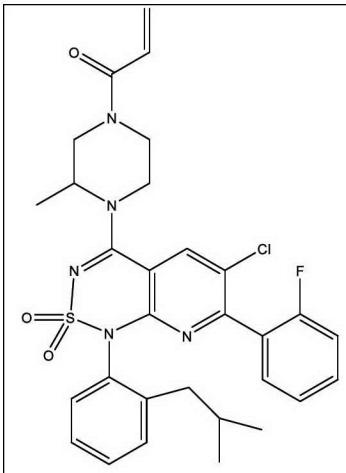
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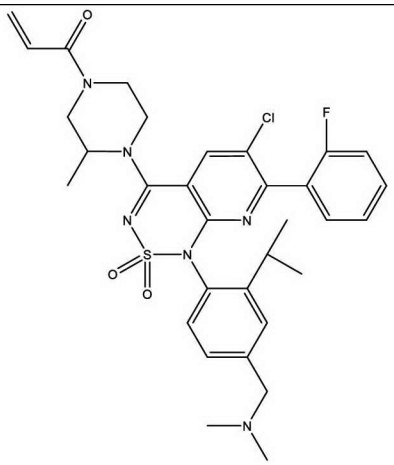
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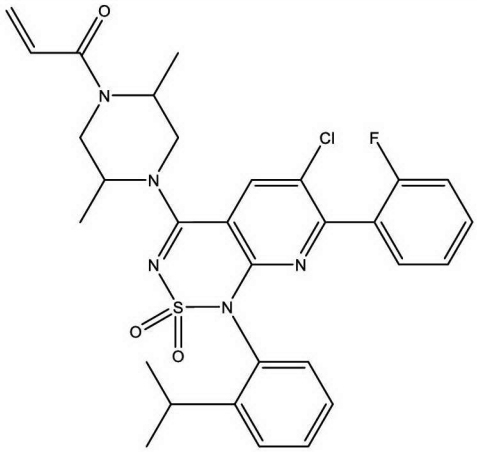
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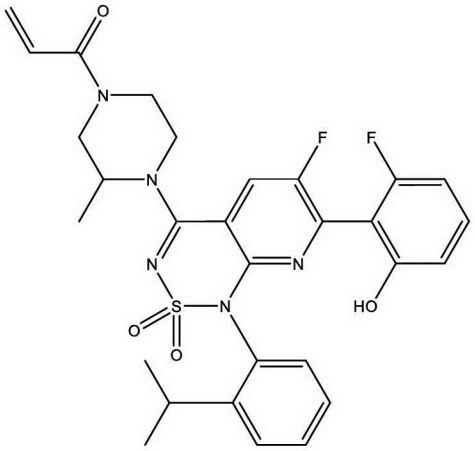
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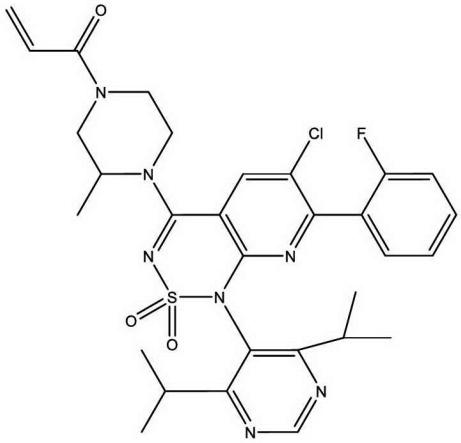
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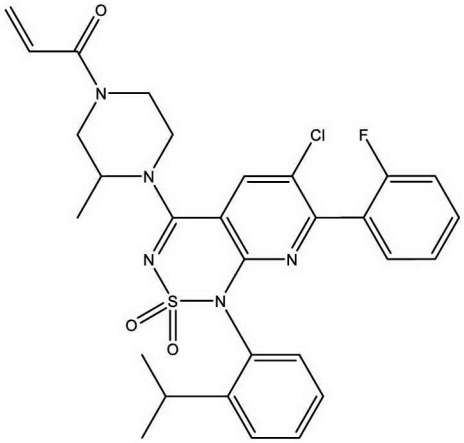
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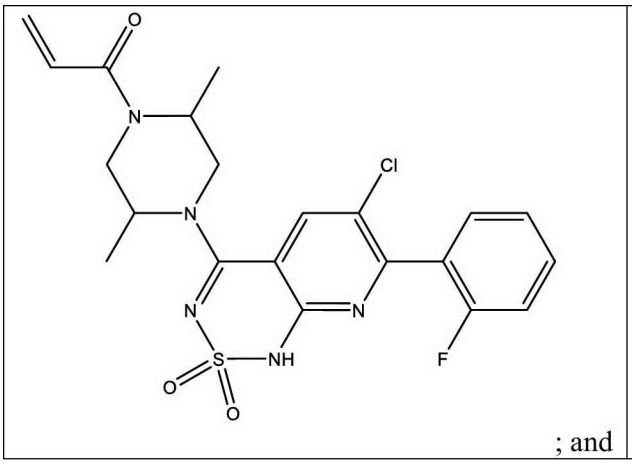
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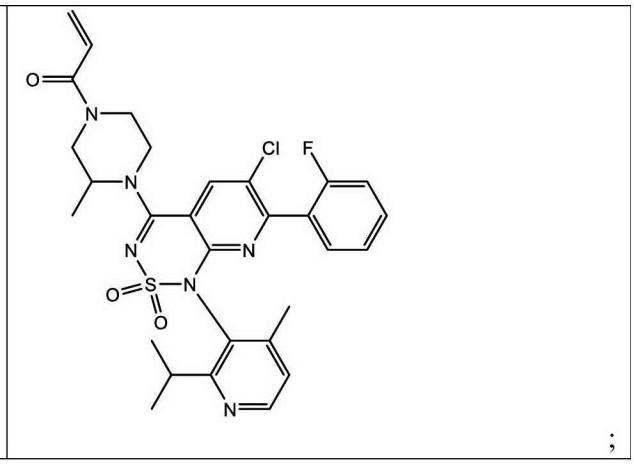
;

or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

[0004c] In a third aspect, the present invention provides a pharmaceutical composition comprising the compound of the first or second aspect and a pharmaceutically acceptable excipient.

[0004d] In a fourth aspect, the present invention provides a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of the first or second aspect or the composition of the third aspect.

[0004e] In a fifth aspect, the present invention provides an in vitro method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of the first or second aspect or the composition of the third aspect.

[0004f] In a sixth aspect, the present invention provides a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound of the first or second aspect or the composition of the third aspect, wherein the cancer is mediated by a KRAS G12C mutation.

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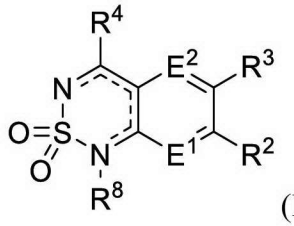
[0004g] In a seventh aspect, the present invention provides use the compound of the first or second aspect or the composition of the third aspect in the manufacture of a medicament for treating cancer, wherein the cancer is mediated by a KRAS G12C mutation.

[0005] Described herein is a compound having a structure of formula (I)



(I)

wherein

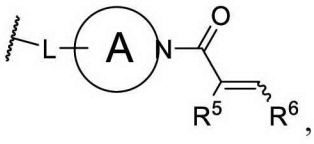
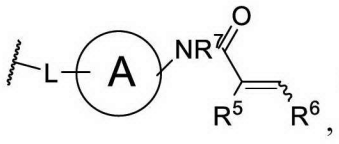
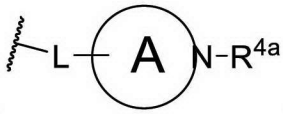
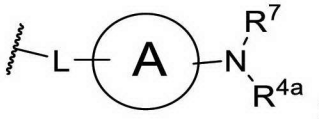
E^1 and E^2 are each independently N or CR^1;

--- is a single or double bond as necessary to give every atom its normal valence;

R^1 is independently H, hydroxy, -$C_{1–6}$alkyl, -$C_{1–6}$haloalkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N(C_{1-4}alkyl)$_2$, cyano, or halo;

R^2 is halo, -$C_{1–6}$alkyl, -$C_{1–6}$haloalkyl, -OR^{2a}, -N(R^{2a})$_2$, -$C_{2–6}$alkenyl, -$C_{2–6}$alkynyl, -$C_{0–3}$alkylene-$C_{3–14}$cycloalkyl, -$C_{0–3}$alkylene-$C_{2–14}$heterocycloalkyl, aryl, heteroaryl, -$C_{0–3}$alkylene-C_{6-14}aryl, or -$C_{0–3}$alkylene-$C_{2–14}$heteroaryl, and each R^{2a} is independently H, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{3-14}cycloalkyl, -C_{2-14}heterocycloalkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, aryl, or heteroaryl, or two R^{2a} substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

R^3 is halo, -$C_{1–6}$alkyl, -$C_{1–6}$haloalkyl, -$C_{1–6}$alkoxy, $C_{3–6}$cycloalkyl, -C_{2-14}heterocycloalkyl, -$C_{2–6}$alkenyl, -$C_{2–6}$alkynyl, aryl, or heteroaryl;

R^4 is  ,  ,  , or  ;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

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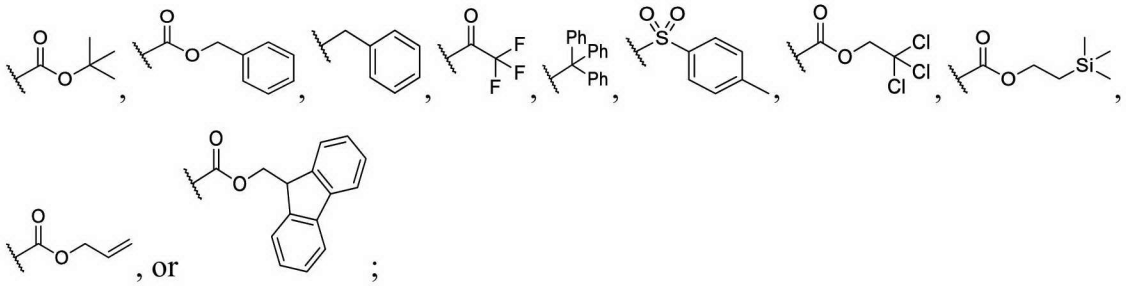
L is a bond, -C_{1-6}alkylene, -O-C_{0-6}alkylene, -S-C_{0-6}alkylene, or -NH-C_{0-6}alkylene, and for -C_{2-6}alkylene, -O-C_{2-6}alkylene, -S-C_{2-6}alkylene, and NH-C_{2-6} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^{4a} is H, C_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6}alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6} haloalkyl, cycloalklyl, heterocycloalkyl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14} heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{6-14}aryl, or selected from



, or ;

R^5 and R^6 are each independently H, halo, -C_{1-6}alkyl, -C_{2-6}alkynyl, -C_{1-6} alkylene-O-C_{1-4}alkyl, -C_{1-6}alkylene-OH, -C_{1-6}haloalkyl, -C_{1-6}alkyleneamine, -C_{0-6} alkylene-amide, -C_{0-3}alkylene-C(O)OH, -C_{0-3}alkylene-C(O)OC_{1-4}alkyl, -C_{1-6} alkylene-O-aryl, -C_{0-3}alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_{0-3}alkylene-C_{3-14}cycloalkyl, -C_{0-3}alkylene-C_{2-14}heterocycloalkyl, -C_{0-3}alkylene-C_{6-14}aryl, -C_{0-3}alkylene-C_{2-14}heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring;

R^7 is H or C_{1-6}alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring;

R^8 is H, -C_{1-6}alkyl,-C_{0-3}alkylene-C_{6-14}aryl, -C_{0-3}alkylene-C_{3-14}heteroaryl, -C_{0-3} alkylene-C_{3-14}cycloalkyl, -C_{0-3}alkylene-C_{2-14}heterocycloalkyl, -C_{1-6}alkoxy, -O-C_{0-3} alkylene-C_{6-14}aryl, -O-C_{0-3}alkylene-C_{3-14}heteroaryl, -O-C_{0-3} alkylene-C_{3-14}cycloalkyl, -O-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, -NH-C_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, -NH-C_{0-3}alkylene-C_{6-14}aryl, -NH-C_{0-3}alkylene-C_{2-14}heteroaryl, -NH-C_{0-3}alkylene-C_{3-14}cycloalkyl, -NH-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, halo, cyano, or C_{1-6}alkylene-amine;

wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups of any of the R^2, R^{2a}, R^3, R^4, R^{4a}, R^5, R^6, R^7, and R^8 substituents have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

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wherein the -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl and the -OC_{1-6}alkyl of any of the R^1, R^2, R^{2a}, R^3, R^4, R^{4a}, L, R^5, R^6, R^7, and R^8 substituents is unsubstituted or substituted by 1, 2 or 3 R^9 substituents independently selected from OH, -OC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, halo, -O-haloC_{1-6}alkyl, -CN, -NR^aR^b, -$(NR^aR^bR^c)_n$, -OSO_2R^a, -SO_2R^a, -$(CH_2CH_2O)_nCH_3$, -(=O), -C(=O), -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, -O-$SiR^aR^bR^c$, -$SiR^aR^bR^c$, -O-(3- to 10-membered heterocycloakyl), a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group of any of the R^1, R^2, R^{2a}, R^3, R^4, R^{4a}, R^5, R^6, R^7, R^8 and R^9 substituents can be unsubstituted or substituted with 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c , a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups of R^{10} have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, and spiroheterocycloalkyl groups of R^{10} or the heterocycloalkyl group of R^{10} may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

wherein each R^a, R^b, R^c and R^d is independently hydrogen, OH, -C_{1-6}alkyl, -$(CH_2CH_2O)_nCH_3$, -$NR^{11}R^{11}$, -C_{1-6}alkyl-$NR^{11}R^{11}$, phenyl, -C_{1-6}alkyl–C(=O)OH , -C_{1-6}alkyl–C(=O)-O-C_{1-6}alkyl, -C_{1-6}alkyl–3- to 12-membered cycloalkyl, -C_{1-6}alkyl–3- to 12-membered heterocycloalkyl, -C_{1-6}alkyl–6- to 12-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl group, heterocycloalkyl

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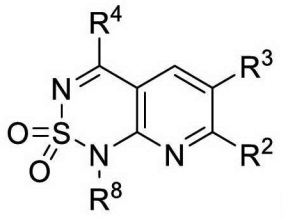
group of R^a, R^b, R^c, and R^d or the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl group of R^a, R^b, R^c, and R^d has from 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may include a double bond, and further wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may contain a C=O group; and

the alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl groups of R^a, R^b, R^c, and R^d or the heterocycloalkyl groups of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with from 1, 2, 3, or 4 R^{12} substituents,wherein each R^{12} is independently selected from H, OH, halo, -C_{1-6}alkyl, $N(CH_3)_2$, -C_{1-6}haloalkyl, $C(=O)CH_3$, -$C(=O)OCH_3$, or -C_{1-6}alkyl-O-C_{1-6}alkyl; or

a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

[0006] In another aspect of the present invention, the present invention comprises a compound having a structure of formula (Ia)



(Ia); or

a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

[0007] One aspect of the present invention provides various compounds, stereoisomers, atropisomers, pharmaceutically acceptable salts, pharmaceutically acceptable salts of the stereoisomers, and pharmaceutically acceptable salts of the atropisomers as described in the embodiments set forth below.

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[0008] Another aspect of the present invention provides a pharmaceutical composition that includes the compound of any of the embodiments or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

[0009] Another aspect of the present invention provides a method of treating cancer. Such methods include: administering to a patient in need thereof a therapeutically effective amount of the compound of any of the embodiments or a pharmaceutically acceptable salt thereof. In some such methods, the cancer is a hematologic malignancy. In some such methods, the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous leukemia. In some other such methods, the cancer is multiple myeloma. In some other such methods, the cancer is acute myelogenous leukemia. In some other such methods, the cancer is non-Hodgkin's lymphoma. In another aspect, the method further includes administering to a patient in need thereof a therapeutically effective amount of an additional pharmaceutically active compound. For example, in some such methods the additional pharmaceutically active compound is carfilzomib. In others, the additional pharmaceutically active compound is venetoclax. In still other such methods, the additional pharmaceutically active compound is cytarabine. In still other such methods, the additional pharmaceutically active compound is daratumumab. In still other such methods, the additional pharmaceutically active compound is an MCl-1 inhibitor. In still other such methods, the MCl-1 inhibitor is AMG-176. In still other such methods, the additional pharmaceutically active compound is an IMiD.

[0010] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0011] Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the Claims.

DETAILED DESCRIPTION

Definitions

Abbreviations: The following abbreviations may be used herein:

AcOH	acetic acid
aq or aq.	aqueous
BOC or Boc	*tert*-butyloxycarbonyl
DCM	dichloromethane
DIPEA or Hunig's Base	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
Dppf, DPPF or dppf	1,1'-bis(diphenylphosphino)ferrocene
eq or eq. or equiv.	equivalent
ESI or ES	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram(s)
h or hr	hour(s)
HPLC	high pressure liquid chromatography
iPr	isopropyl
iPr_2NEt or DIPEA	*N*-ethyl diisopropylamine (Hünig's base)
KHMDS	potassium hexamethyldisilazide
KOAc	potassium acetate
LC MS, LCMS, LC-MS or LC/MS	liquid chromatography mass spectroscopy
LHMDS or LiHMDS	lithium hexamethyldisilazide
m/z	mass divided by charge
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligrams
min	minutes
mL	milliliters
MS	mass spectra
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance

$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2 \cdot DCM$, $Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
PR or PG or Prot. group	protecting group
rbf	round-bottom flask
RP-HPLC	reverse phase high pressure liquid chromatography
RT or rt or r.t.	room temperature
sat. or sat'd	saturated
SFC	supercritical fluid chromatography
TBAF	tetra-*n*-butylammonium fluoride
TEA or Et_3N	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
UV	ultraviolet

[0011a] Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

[0012] The use of the terms "a," "an," "the," and similar referents in the context of describing the invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein merely are 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. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended to better illustrate the invention and is not a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0013] As used herein, the term "alkyl" refers to straight chained and branched C1-C_8 hydrocarbon groups, including but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, and 2-ethybutyl. The term C_{m-n} means the alkyl group has "m" to "n" carbon

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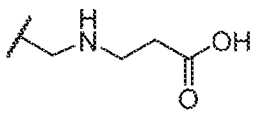
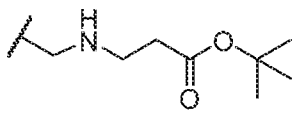
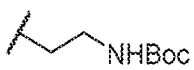
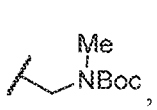
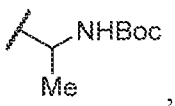
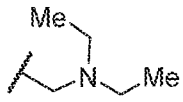
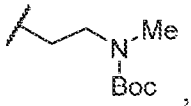
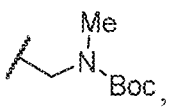
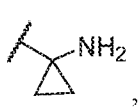
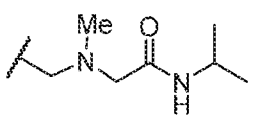
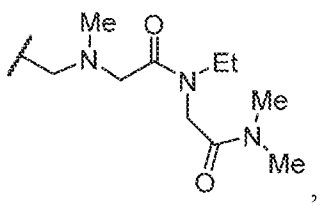
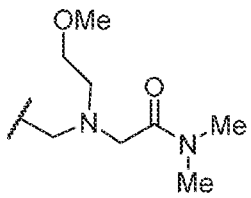
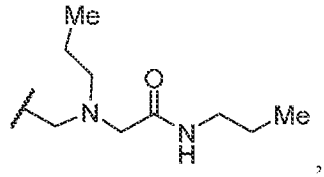
atoms. The term "alkylene" refers to an alkyl group having a substituent. An alkyl (e.g., methyl), or alkylene (e.g., -CH_2-), group can be substituted with one or more, and typically one to three, of independently selected, for example, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, nitro, cyano, alkylamino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -NC, amino, -CO_2H, -CO_2C_1-

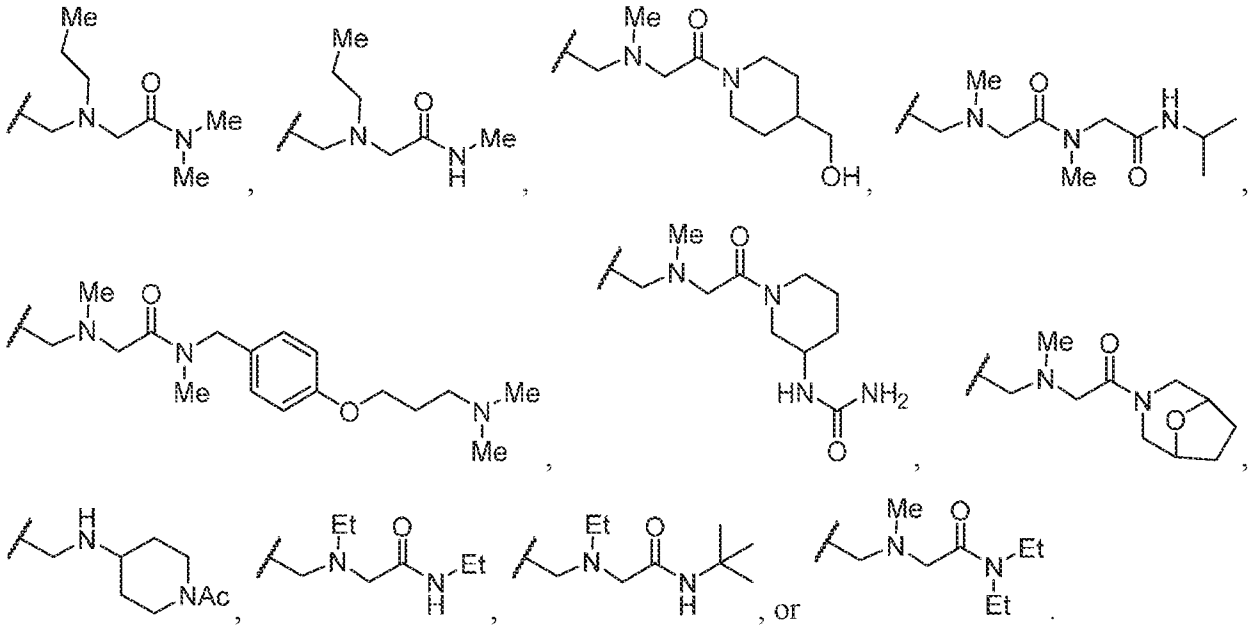
C_6alkyl, -OCOC_1-C_6alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_5-C_{10}aryl, and C_5-C_{10} heteroaryl. The term "haloalkyl" specifically refers to an alkyl group wherein at least one, e.g., one to six, or all of the hydrogens of the alkyl group are substituted with halo atoms.

[0014] The terms "alkenyl" and "alkynyl" indicate an alkyl group that further includes a double bond or a triple bond, respectively.

[0015] As used herein, the term "halo" refers to fluoro, chloro, bromo, and iodo. The term "alkoxy" is defined as -OR, wherein R is alkyl.

[0016] As used herein, the term "amino" or "amine" interchangeably refers to a -NR_2 group, wherein each R is, e.g., H or a substituent. In some embodiments, the amino group is further substituted to form an ammonium ion, e.g., NR_3^+. Ammonium moieties are specifically included in the definition of "amino" or "amine." Substituents can be, for example, an alkyl, alkoxy, cycloalkyl, heterocycloalkyl, amide, or carboxylate. An R group may be further substituted, for example, with one or more, e.g., one to four, groups selected from halo, cyano, alkenyl, alkynyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, urea, carbonyl, carboxylate, amine, and amide. An "amide" or "amido" group interchangeably refers to a group similar to an amine or amino group but further including a C(O), e.g., -$C(O)NR_2$. Some contemplated amino or amido groups (some with optional alkylene groups, e.g., alkylene-amino, or alkylene-amido) include CH_2NH_2, $CH(CH_3)NH_2$, $CH(CH_3)_2NH_2$, $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, CH_2NHCH_3, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $CH_2C(O)NH$phenyl, $CH_2NHC(O)CH_3$, $CH_2NHCH_2CH_2OH$, $CH_2NHCH_2CO_2H$, $CH_2NH(CH_3)CH_2CO_2CH_3$,$CH_2NHCH_2CH_2OCH_3$, $CH_2NH(CH_3)CH_2CH_2OCH_3$, $CH_2NH(CH_3)CH_2C(O)N(CH_3)_2$, $CH_2NH(CH_3)CH_2C(O)NHCH_3$, CH_2CH_2CCH, CH_2NMe_2, $CH_2NH(CH_3)CH_2CH_2OH$, $CH_2NH(CH_3)CH_2CH_2F$, $CH_2N^+(CH_3)_3$, $CH_2NHCH_2CHF_2$, $CH_2NHCH_2CH_3$,



[0017] As used herein, the term "aryl" refers to a C_{6-14} monocyclic or polycyclic aromatic group, preferably a C_{6-10} monocyclic or bicyclic aromatic group, or C_{10-14} polycyclic aromatic group. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, azulenyl, anthryl, phenanthryl, pyrenyl, biphenyl, and terphenyl. Aryl also refers to C_{10-14} bicyclic and tricyclic carbon rings, where one ring is aromatic and the others are saturated, partially unsaturated, or aromatic, for example, dihydronaphthyl, indenyl, indanyl, or tetrahydronaphthyl (tetralinyl). Unless otherwise indicated, an aryl group can be unsubstituted or substituted with one or more, and in particular one to four, groups independently selected from, for example, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-CF_3$, $-OCF_3$, $-NO_2$, -CN, -NC, -OH, alkoxy, amino, $-CO_2H$, $-CO_2C_1$-C_6alkyl, $-OCOC_1$-C_6alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_5-C_{10}aryl, and C_5-C_{10} heteroaryl.

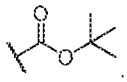
[0018] As used herein, the term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic carbocyclic ring, where the polycyclic ring can be fused, bridged, or spiro. The carbocyclic ring can have 3 to 10 carbon ring atoms. Contemplated carbocyclic rings include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl.

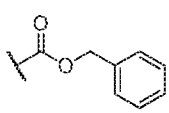
[0019] As used herein, the term "heterocycloalkyl" means a monocyclic or polycyclic (e.g., bicyclic), saturated or partially unsaturated, ring system containing 3 or more (e.g., 3 to 12, 4 to 10, 4 to 8, or 5 to 7) total atoms, of which one to five (e.g., 1, 2, 3, 4, or 5) of the atoms are independently selected from nitrogen, oxygen, and sulfur. Nonlimiting examples of

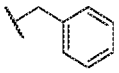
heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, dihydropyrrolyl, morpholinyl, thiomorpholinyl, dihydropyridinyl, oxacycloheptyl, dioxacycloheptyl, thiacycloheptyl, and diazacycloheptyl.

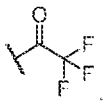
[0020] Unless otherwise indicated, a cycloalkyl or heterocycloalkyl group can be unsubstituted or substituted with one or more, and in particular one to four, groups. Some contemplated substituents include halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OCF_3$, $-NO_2$, -CN, -NC, -OH, alkoxy, amino, $-CO_2H$, $-CO_2C_1$-C_6alkyl, $-OCOC_1$-C_8alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_5-C_{10}aryl, and C_5-C_{10} heteroaryl.

[0021] As used herein, the term "heteroaryl" refers to a monocyclic or polycyclic ring system (for example, bicyclic) containing one to three aromatic rings and containing one to four (e.g., 1, 2, 3, or 4) heteroatoms selected from nitrogen, oxygen, and sulfur in an aromatic ring. In certain embodiments, the heteroaryl group has from 5 to 20, from 5 to 15, from 5 to 10 ring, or from 5 to 7 atoms. Heteroaryl also refers to C_{10-14} bicyclic and tricyclic rings, where one ring is aromatic and the others are saturated, partially unsaturated, or aromatic. Examples of heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, triazolyl, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzothiophenyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quiazolinyl, thiadiazolopyrimidyl, and thienopyridyl. Unless otherwise indicated, a heteroaryl group can be unsubstituted or substituted with one or more, and in particular one to four or one or two, substituents. Contemplated substituents include halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OCF_3$, $-NO_2$, -CN, -NC, -OH, alkoxy, amino, $-CO_2H$, $-CO_2C_1$-C_6alkyl, $-OCOC_1$-C_6alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, C_5-C_{10}aryl, and C_5-C_{10} heteroaryl.

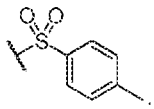
[0022] As used herein, the term Boc refers to the structure  .

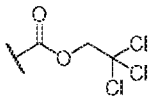
[0023] As used herein, the term Cbz refers to the structure  .

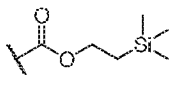
[0024] As used herein, the term Bn refers to the structure  .

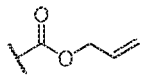
[0025] As used herein, the term trifluoroacetamide refers to the structure  .

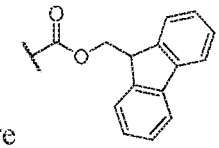
[0026] As used herein, the term trityl refers to the structure  .

[0027] As used herein, the term tosyl refers to the structure  .

[0028] As used herein, the term Troc refers to the structure  .

[0029] As used herein, the term Teoc refers to the structure  .

[0030] As used herein, the term Alloc refers to the structure  .

[0031] As used herein, the term Fmoc refers to the structure  .

COMPOUNDS OF THE DISCLOSURE

[0032] The compounds disclosed herein include all pharmaceutically acceptable isotopically-labeled compounds wherein one or more atoms of the compounds disclosed herein are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabelled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of the disclosure, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive

isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

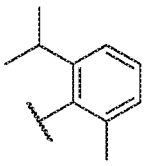
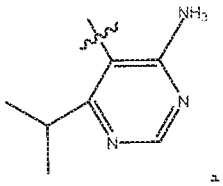
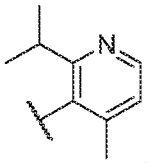
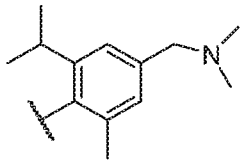
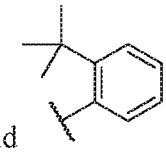
[0033] Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence are preferred in some circumstances.

[0034] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of structure (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Preparations and Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0035] Isotopically-labeled compounds as disclosed herein can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying examples and schemes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0036] Certain of the compounds as disclosed herein may exist as stereoisomers (i.e., isomers that differ only in the spatial arrangement of atoms) including optical isomers and conformational isomers (or conformers). The compounds disclosed herein include all stereoisomers, both as pure individual stereoisomer preparations and enriched preparations of each, and both the racemic mixtures of such stereoisomers as well as the individual diastereomers and enantiomers that may be separated according to methods that are known to those skilled in the art. Additionally, the compounds disclosed herein include all tautomeric forms of the compounds.

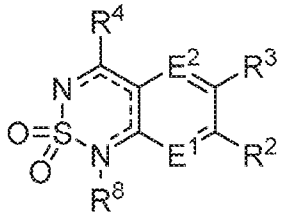
[0037] Certain of the compounds disclosed herein may exist as atropisomers, which are conformational stereoisomers that occur when rotation about a single bond in the molecule is prevented, or greatly slowed, as a result of steric interactions with other parts of the molecule. The compounds disclosed herein include all atropisomers, both as pure individual atropisomer preparations, enriched preparations of each, or a non-specific mixture of each. Where the rotational barrier about the single bond is high enough, and interconversion between conformations is slow enough, separation and isolation of the isomeric species may be permitted. For example,

groups such as, but not limited to, the following R^8 groups  ,  ,  ,  , and  may exhibit restricted rotation.

EMBODIMENTS

Embodiment 1

[0038] In one embodiment of the present invention, the present invention comprises a compound having formula (I)



(I)

wherein

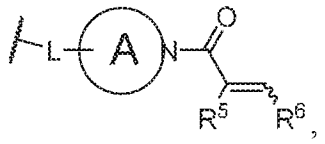
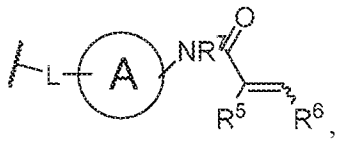
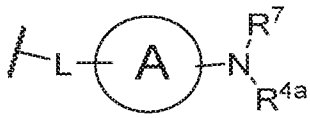
E^1 and E^2 are each independently N or CR^1;

=== is a single or double bond as necessary to give every atom its normal valence;

R^1 is independently H, hydroxy, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N(C_{1-4}alkyl)$_2$, cyano, or halo;

R^2 is halo, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -OR^{2a}, -$N(R^{2a})_2$, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{0-3}alkylene-C_{3-14}cycloalkyl, -C_{0-3}alkylene-C_{2-14}heterocycloalkyl, aryl, heteroaryl, -C_{0-3}alkylene-C_{6-14}aryl, or -C_{0-3}alkylene-C_{2-14}heteroaryl, and each R^{2a} is independently H, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{3-14}cycloalkyl, -C_{2-14}heterocycloalkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, aryl, or heteroaryl, or two R^{2a} substituents, together with the nitrogen atom to which they are attached, form a 3-7-membered ring;

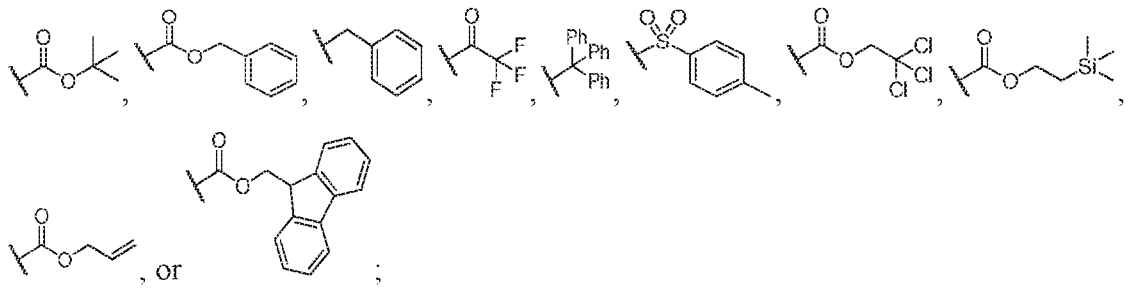
R^3 is halo, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{1-6}alkoxy, C_{3-6}cycloalkyl, -C_{2-14}heterocycloalkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, aryl, or heteroaryl;

R^4 is  ,  ,  , or  ;

ring A is a monocyclic 4–7 membered ring or a bicyclic, bridged, fused, or spiro 6–11 membered ring;

L is a bond, -C_{1-6}alkylene, -O-C_{0-6}alkylene, -S-C_{0-6}alkylene, or -NH-C_{0-6}alkylene, and for -C_{2-6}alkylene, -O-C_{2-6}alkylene, -S-C_{2-6}alkylene, and NH-C_{2-6} alkylene, one carbon atom of the alkylene group can optionally be replaced with O, S, or NH;

R^{4a} is H, C_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6}alkylene-O-C_{1-4}alkyl, C_{1-6}alkylene-OH, C_{1-6} haloalkyl, cycloalklyl, heterocycloalkyl, C_{0-3}alkylene-C_{3-14}cycloalkyl, C_{0-3}alkylene-C_{2-14} heterocycloalkyl, aryl, heteroaryl, C_{0-3}alkylene-C_{6-14}aryl, or selected from



R^5 and R^6 are each independently H, halo, -C_{1-6}alkyl, -C_{2-6}alkynyl, -C_{1-6} alkylene-O-C_{1-4}alkyl, -C_{1-6}alkylene-OH, -C_{1-6}haloalkyl, -C_{1-6}alkyleneamine, -C_{0-6} alkylene-amide, -C_{0-3}alkylene-C(O)OH, -C_{0-3}alkylene-C(O)OC_{1-4}alkyl, -C_{1-6} alkylene-O-aryl, -C_{0-3}alkylene-C(O)C_{1-4}alkylene-OH, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_{0-3}alkylene-C_{3-14}cycloalkyl, -C_{0-3}alkylene-C_{2-14}heterocycloalkyl, -C_{0-3}alkylene-C_{6-14}aryl, -C_{0-3}alkylene-C_{2-14}heteroaryl, or cyano, or R^5 and R^6, together with the atoms to which they are attached, form a 4–6 membered ring;

R^7 is H or C_{1-6}alkyl, or R^7 and R^5, together with the atoms to which they are attached, form a 4–6 membered ring;

R^8 is H, -C_{1-6}alkyl,-C_{0-3}alkylene-C_{6-14}aryl, -C_{0-3}alkylene-C_{3-14}heteroaryl, -C_{0-3} alkylene-C_{3-14}cycloalkyl, -C_{0-3}alkylene-C_{2-14}heterocycloalkyl, -C_{1-6}alkoxy, -O-C_{0-3} alkylene-C_{6-14}aryl, -

O-C_{0-3}alkylene-C_{3-14}heteroaryl, -O-C_{0-3} alkylene-C_{3-14}cycloalkyl, -O-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, -NH-C_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, -NH-C_{0-3}alkylene-C_{6-14}aryl, -NH-C_{0-3}alkylene-C_{2-14}heteroaryl, -NH-C_{0-3}alkylene-C_{3-14}cycloalkyl, -NH-C_{0-3} alkylene-C_{2-14}heterocycloalkyl, halo, cyano, or C_{1-6}alkylene-amine;

wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups of any of the R^2, R^{2a}, R^3, R^4, R^{4a}, R^5, R^6, R^7, and R^8 substituents have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl and the -OC_{1-6}alkyl of any of the R^1, R^2, R^{2a}, R^3, R^4, R^{4a}, L, R^5, R^6, R^7, and R^8 substituents is unsubstituted or substituted by 1, 2 or 3 R^9 substituents independently selected from OH, -OC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, halo, -O-haloC_{1-6}alkyl, -CN, -NR^aR^b, -$(NR^aR^bR^c)_n$, -OSO_2R^a, -SO_2R^a, -$(CH_2CH_2O)_nCH_3$, -(=O), -C(=O), -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, -O-$SiR^aR^bR^c$, -$SiR^aR^bR^c$, -O-(3- to 10-membered heterocycloakyl), a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group of any of the R^1, R^2, R^{2a}, R^3, R^4, R^{4a}, R^5, R^6, R^7, R^8 and R^9 substituents can be unsubstituted or substituted with 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c , a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups of R^{10} have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the

cycloalkyl, spirocycloalkyl, and spiroheterocycloalkyl groups of R^{10} or the heterocycloalkyl group of R^{10} may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

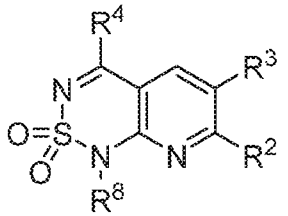
wherein each R^a, R^b, R^c and R^d is independently hydrogen, OH, -C_{1-6}alkyl, -$(CH_2CH_2O)_nCH_3$, -$NR^{11}R^{11}$, -C_{1-6}alkyl-$NR^{11}R^{11}$, phenyl, -C_{1-6}alkyl–C(=O)OH , -C_{1-6}alkyl–C(=O)-O-C_{1-6}alkyl, -C_{1-6}alkyl–3- to 12-membered cycloalkyl, -C_{1-6}alkyl–3- to 12-membered heterocycloalkyl, -C_{1-6}alkyl–6- to 12-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl group, heterocycloalkyl group of R^a, R^b, R^c, and R^d or the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl group of R^a, R^b, R^c, and R^d has from 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may include a double bond, and further wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may contain a C=O group; and

the alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl groups of R^a, R^b, R^c, and R^d or the heterocycloalkyl groups of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with from 1, 2, 3, or 4 R^{12} substituents,wherein each R^{12} is independently selected from H, OH, halo, -C_{1-6}alkyl, $N(CH_3)_2$, -C_{1-6}haloalkyl, $C(=O)CH_3$, -$C(=O)OCH_3$, or -C_{1-6}alkyl-O-C_{1-6}alkyl; or

a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

Embodiment 2

[0039] In another embodiment of the present invention, the present invention comprises a compound having a structure of formula (Ia)



(Ia); or

[0040] a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

Embodiment 3

[0041] In another embodiment of the present invention, R^1 is H.

Embodiment 4

[0042] In another embodiment of the present invention, R^2 is an unsubstituted or substituted aryl.

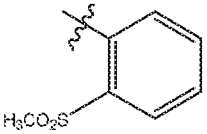
Embodiment 5

[0043] In another embodiment of the present invention, R^2 is a substituted aryl.

Embodiment 6

[0044] In another embodiment of the present invention, R^2 is a fluorinated phenyl.

Embodiment 7

[0045] In another embodiment of the present invention, R^2 is 

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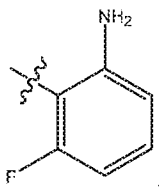
Embodiment 8

[0046] In another embodiment of the present invention, R^2 is 

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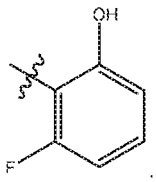
Embodiment 9

[0047] In another embodiment of the present invention, R^2 is 

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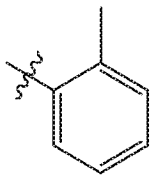
Embodiment 10

[0048] In another embodiment of the present invention, R^2 is  .

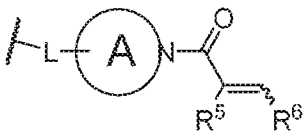
Embodiment 11

[0049] In another embodiment of the present invention, R^3 is halo.

Embodiment 12

[0050] In another embodiment of the present invention, R^3 is Cl.

Embodiment 13

[0051] In another embodiment of the present invention, R^4 is  .

Embodiment 14

[0052] In another embodiment of the present invention, L is a bond.

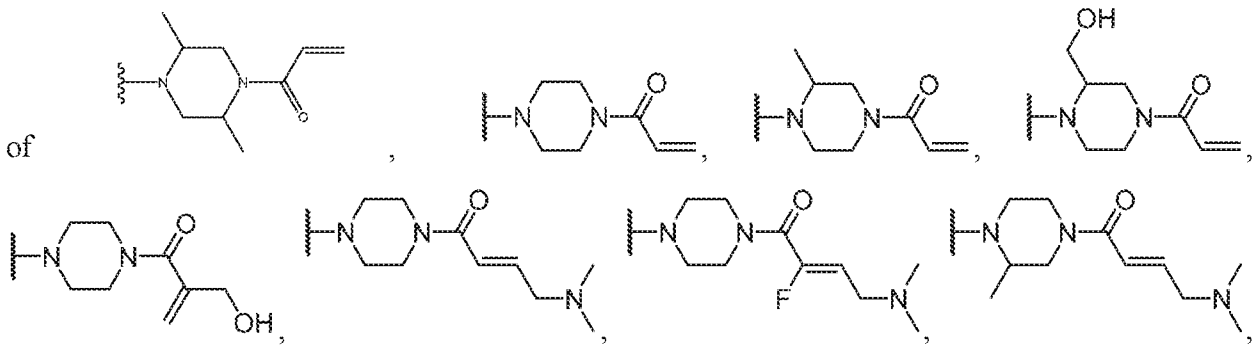
Embodiment 15

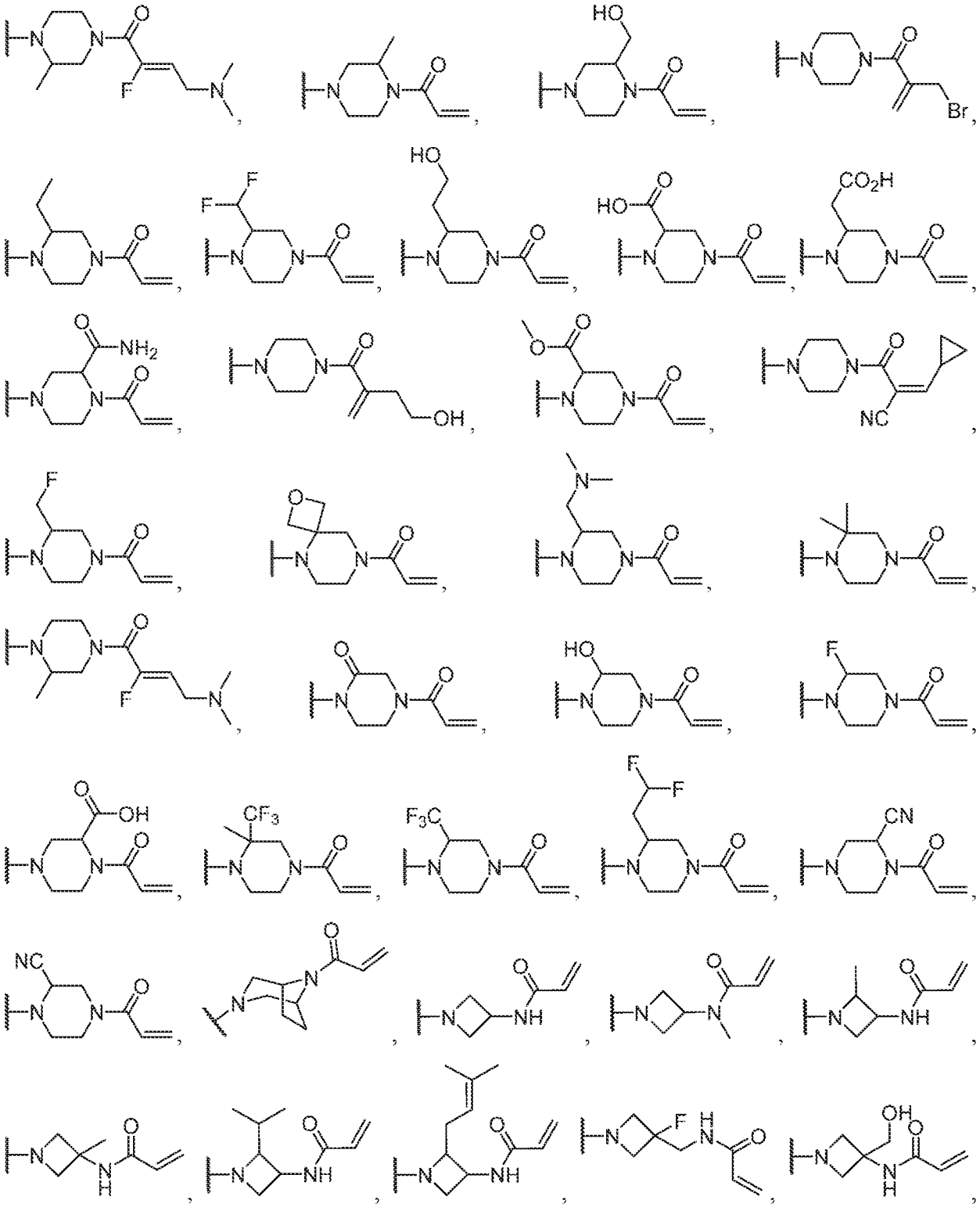
[0053] In another embodiment of the present invention, ring A is a monocyclic 4–7 membered ring.

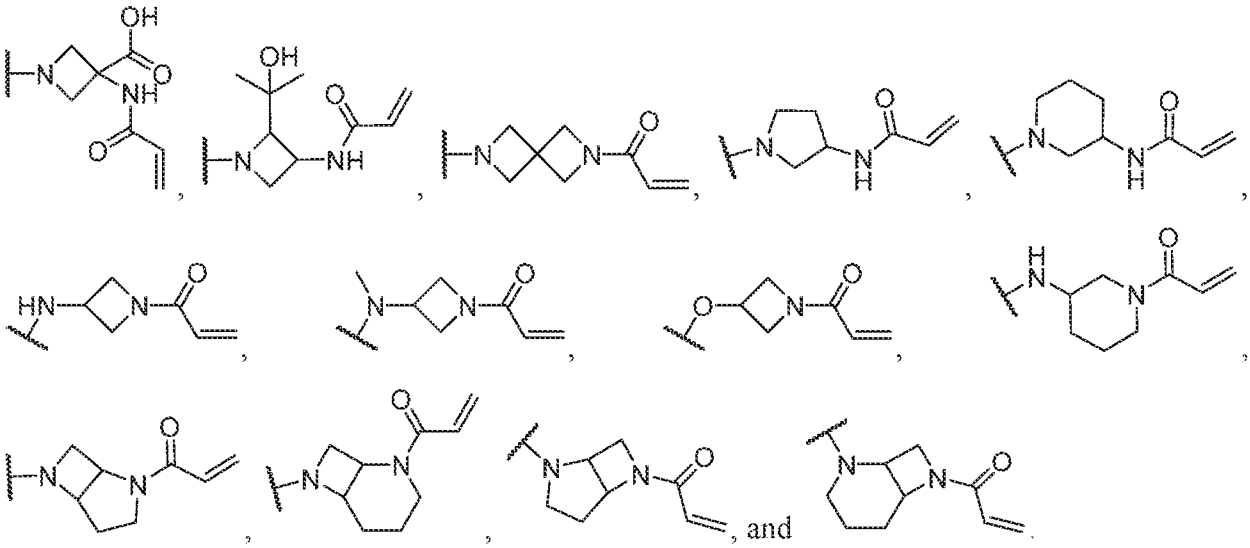
Embodiment 16

[0054] In another embodiment of the present invention, A is an unsubstituted or substituted heterocycle.

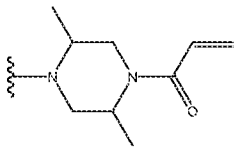
Embodiment 17

[0055] In another embodiment of the present invention, R^4 is selected from the group consisting of  .

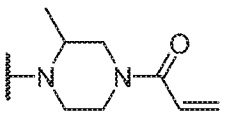




Embodiment 18

[0056] In another embodiment of the present invention, R^4 is  .

Embodiment 19

[0057] In another embodiment of the present invention, R^4 is  .

Embodiment 20

[0058] In another embodiment of the present invention, R^8 is H, -C_{1-6}alkyl,-C_{0-3}alkylene-C_{6-14}aryl, or -C_{0-3}alkylene-C_{3-14}heteroaryl.

Embodiment 21

[0059] In another embodiment of the present invention, R^8 is H.

Embodiment 22

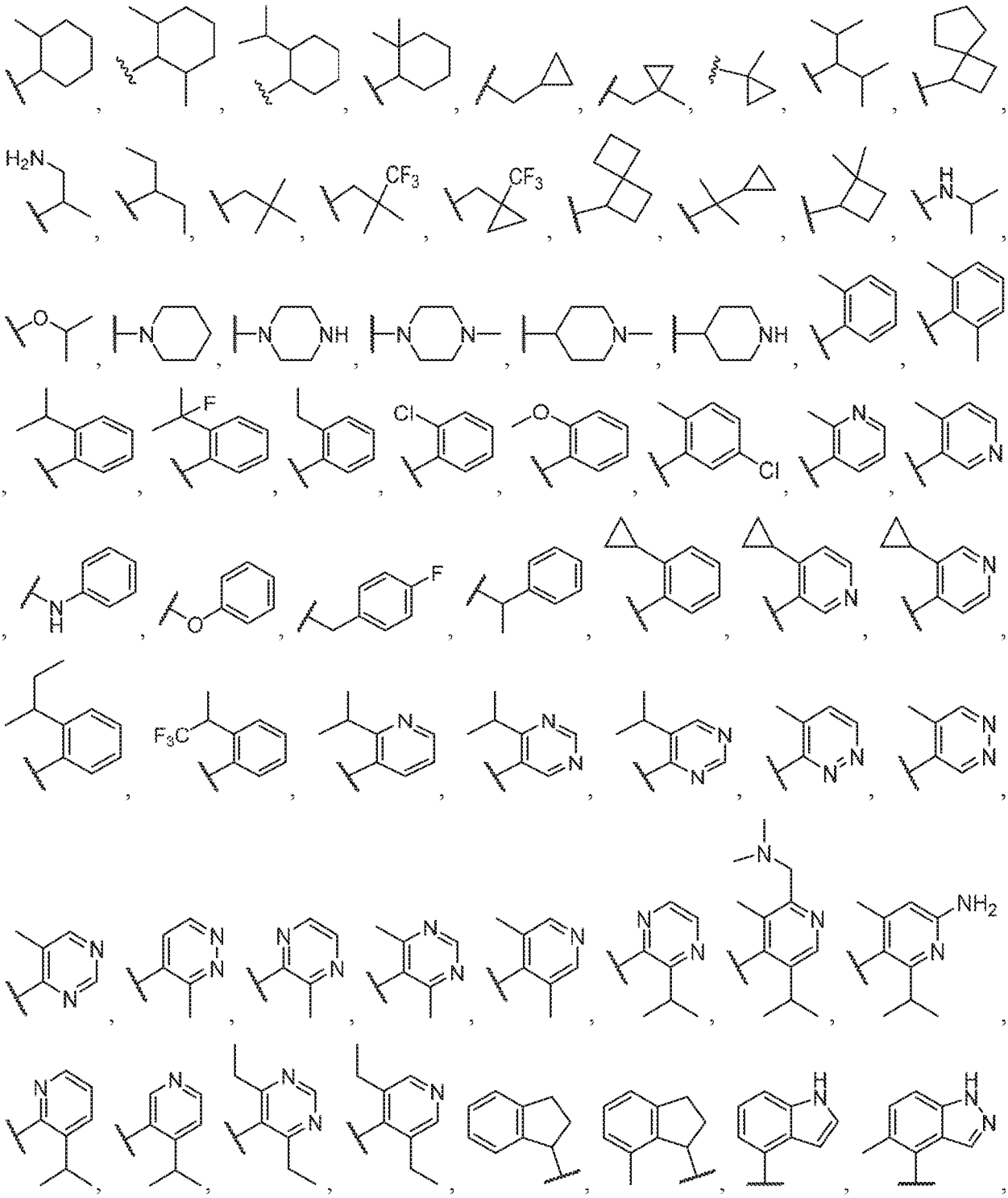
[0060] In another embodiment of the present invention, R^8 is -C_{6-14}aryl.

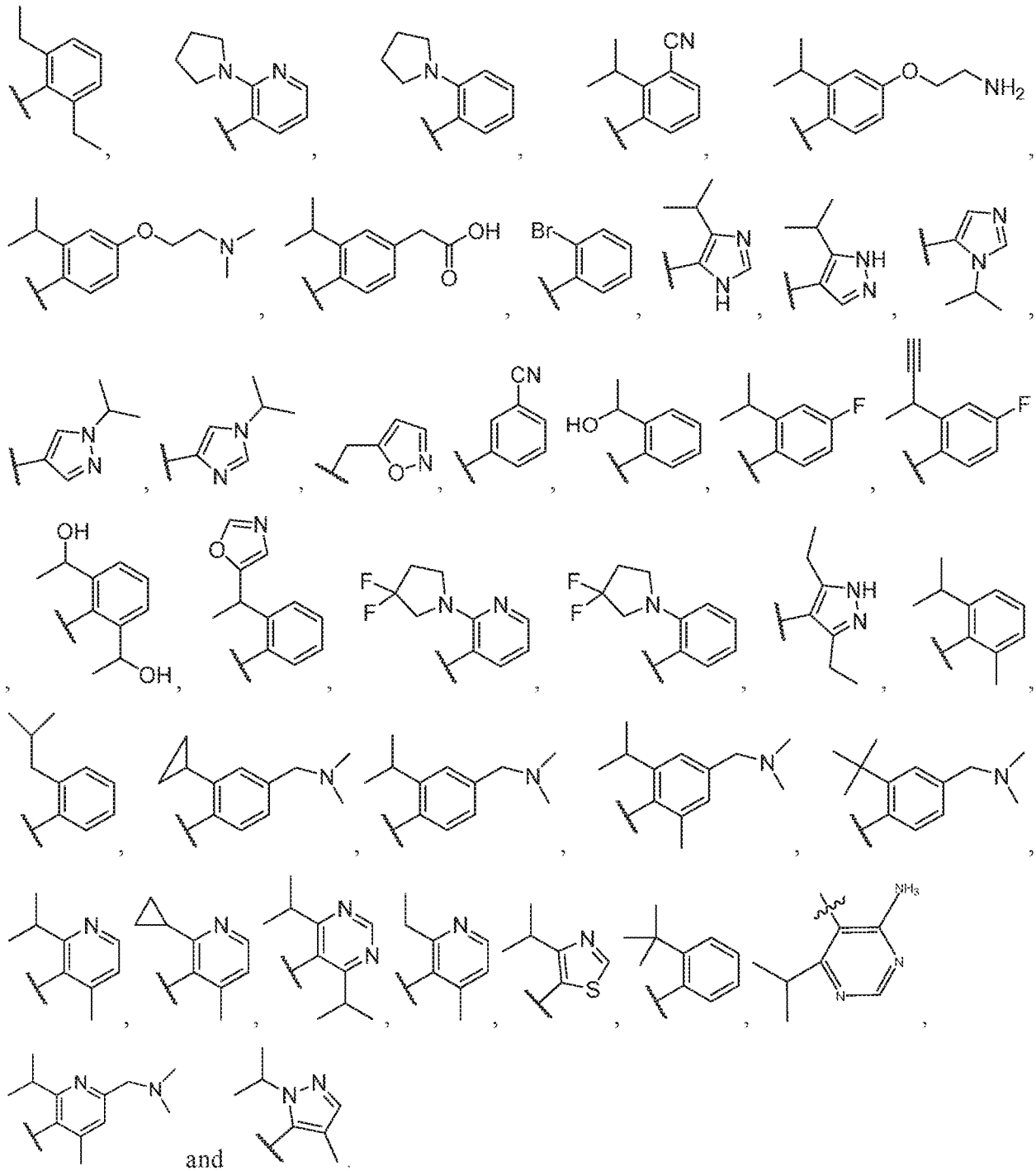
Embodiment 23

[0061] In another embodiment of the present invention, R^8 is -C_{3-14}heteroaryl.

Embodiment 24

[0062] In another embodiment of the present invention, R^8 is selected from the group consisting of *i*-Pr, *t*-Bu, phenyl, benzyl, OCH_3, Cl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

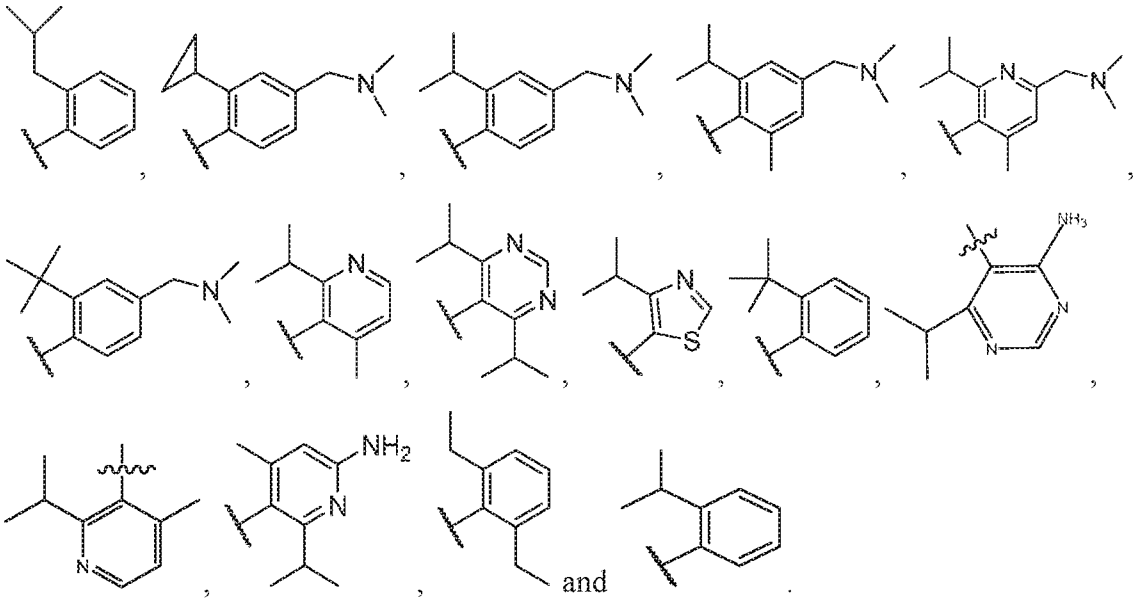




and

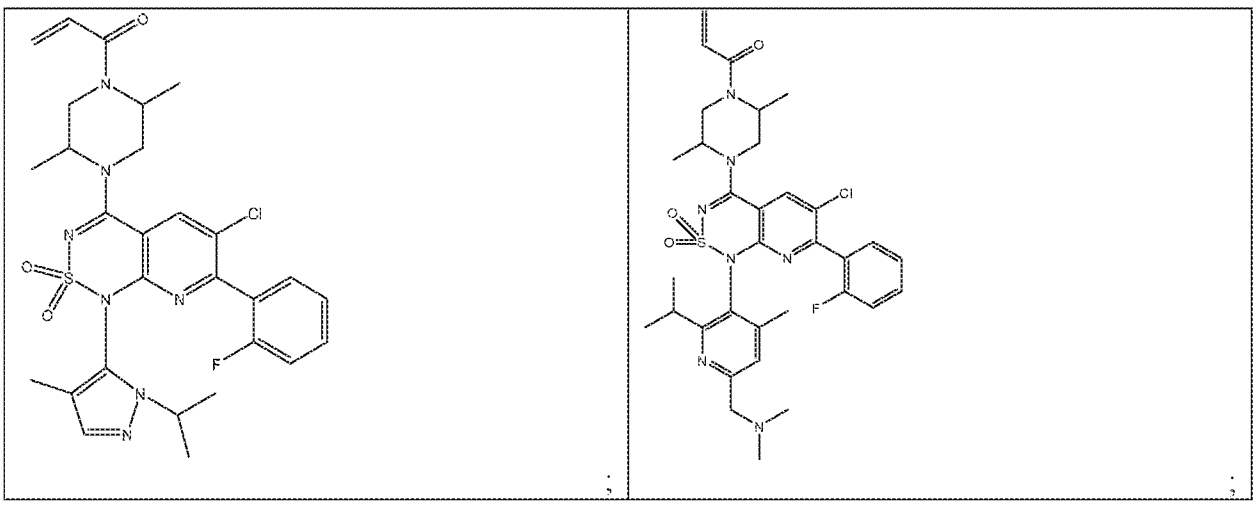
Embodiment 25

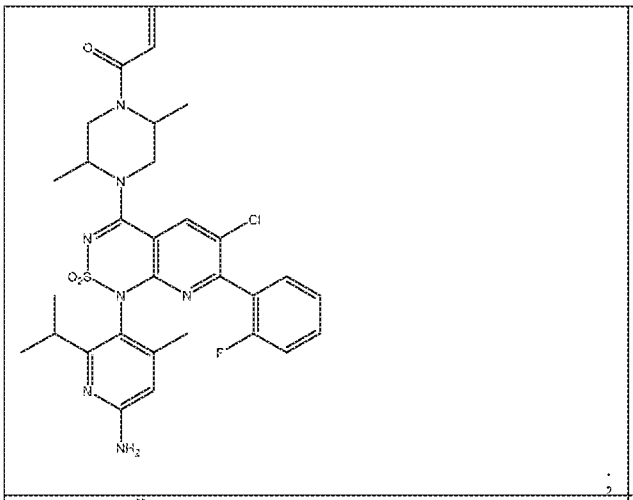
[0063] In another embodiment of the present invention, R^8 is selected from the group consisting of

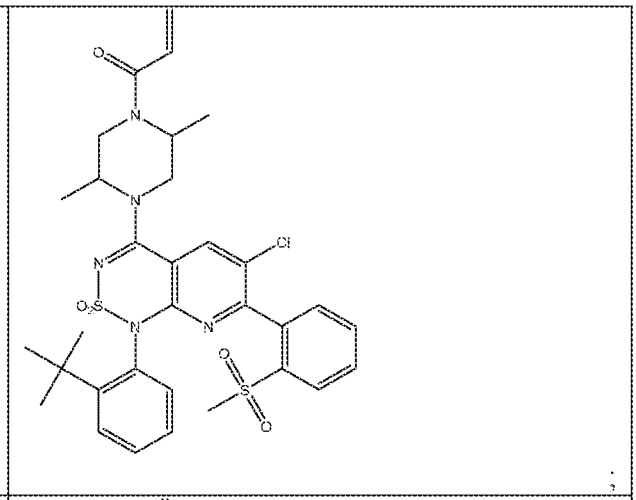


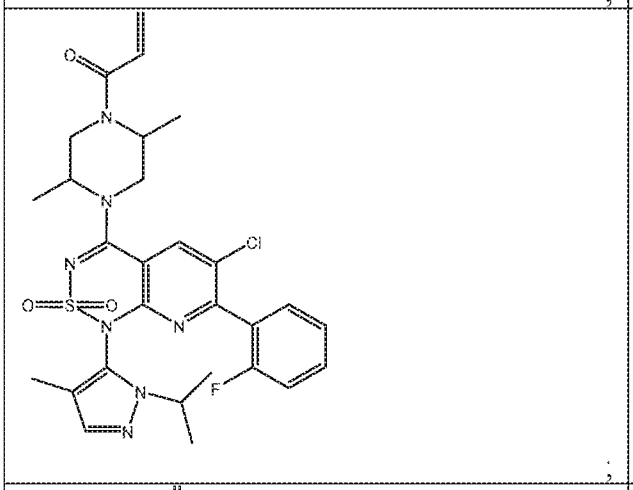
Embodiment 26

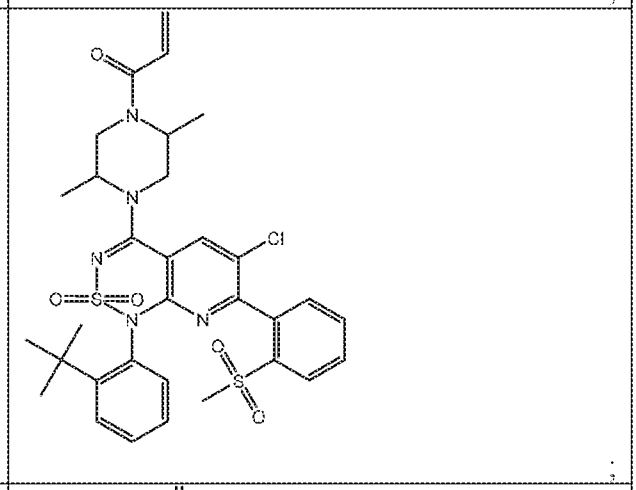
[0064] In another embodiment of the present invention, the present invention comprises a compound having a structure selected from the formula

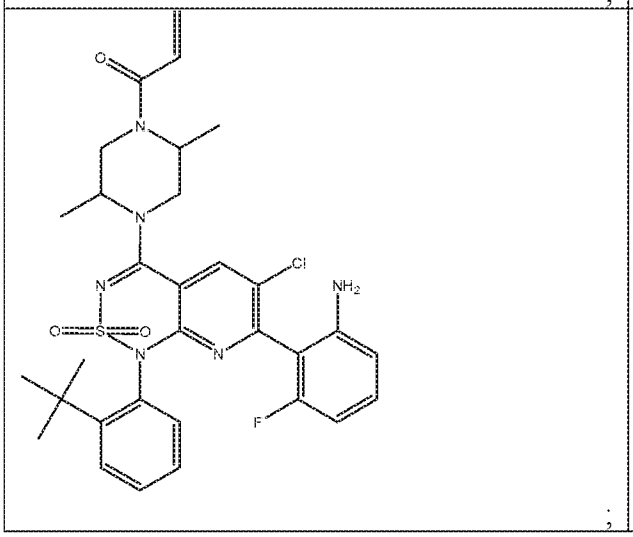


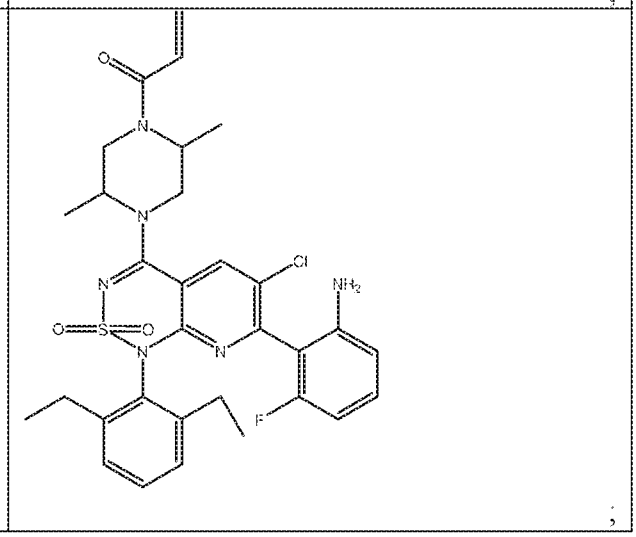


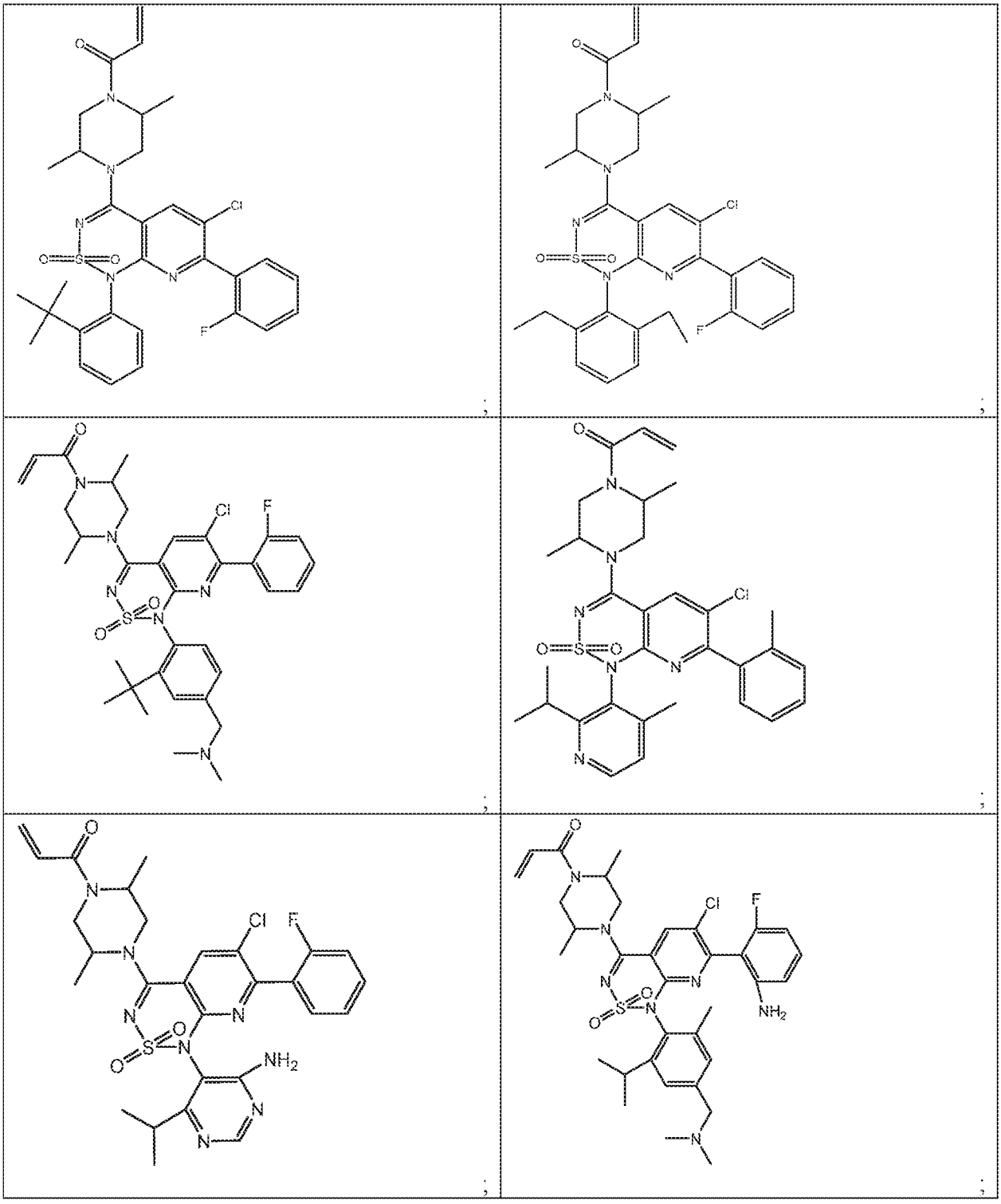


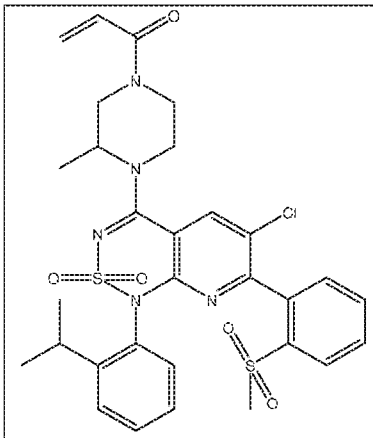












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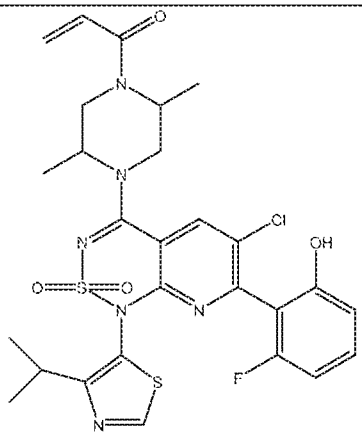

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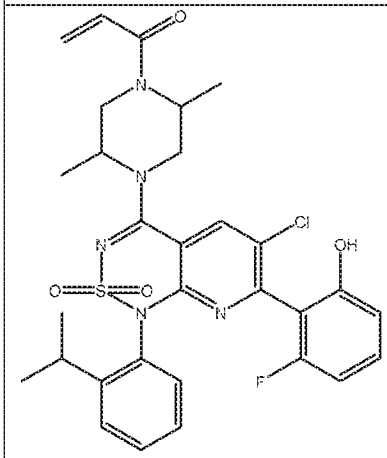

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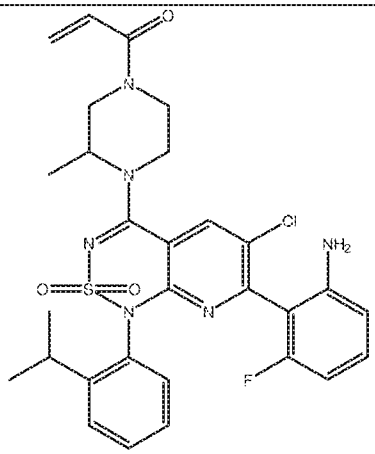

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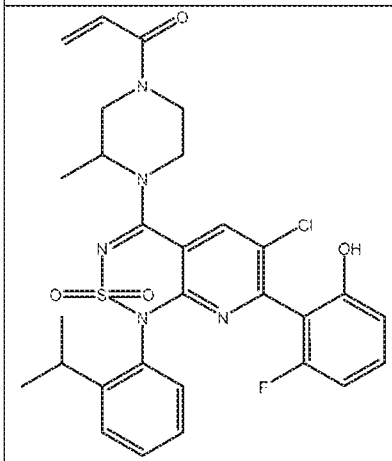

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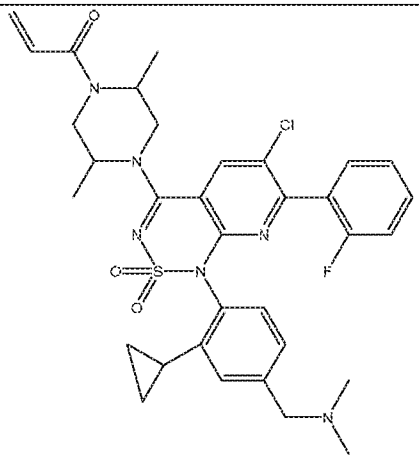

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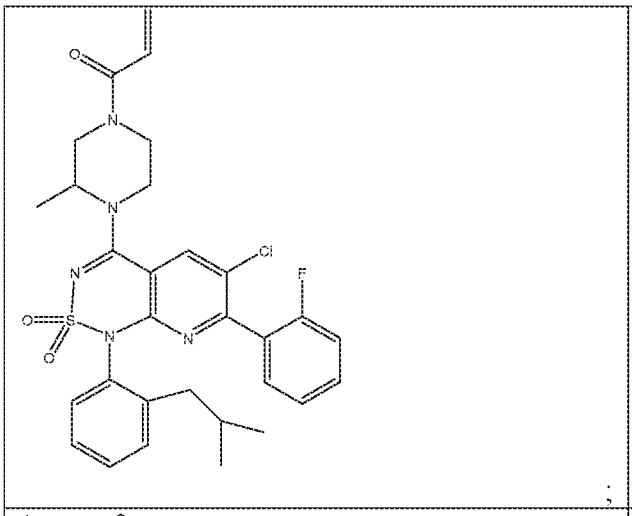
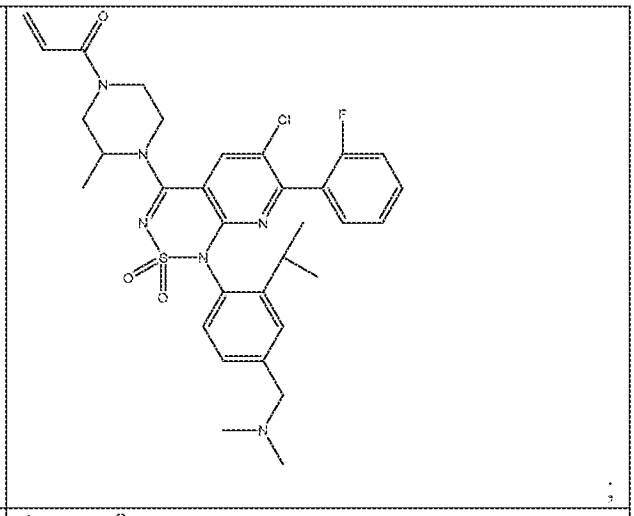
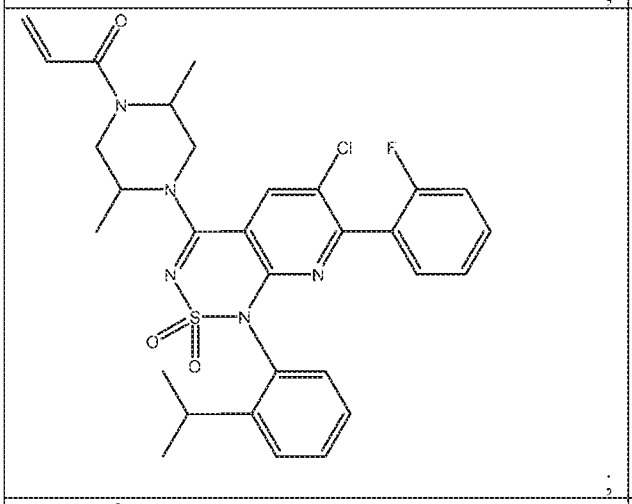
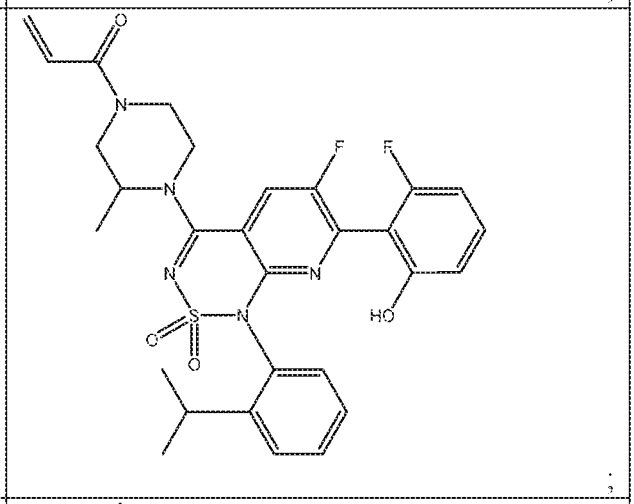
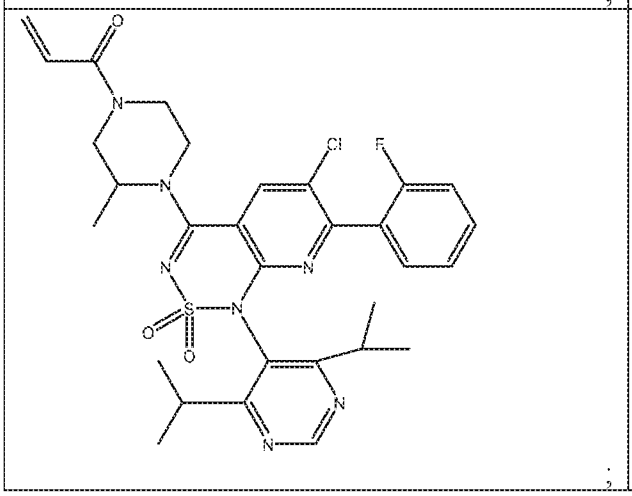
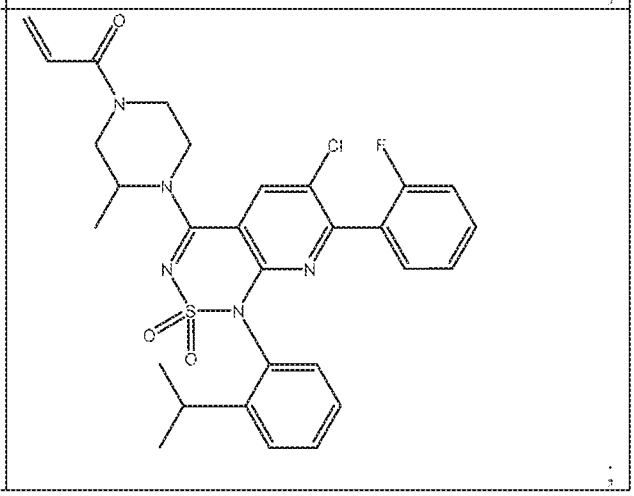


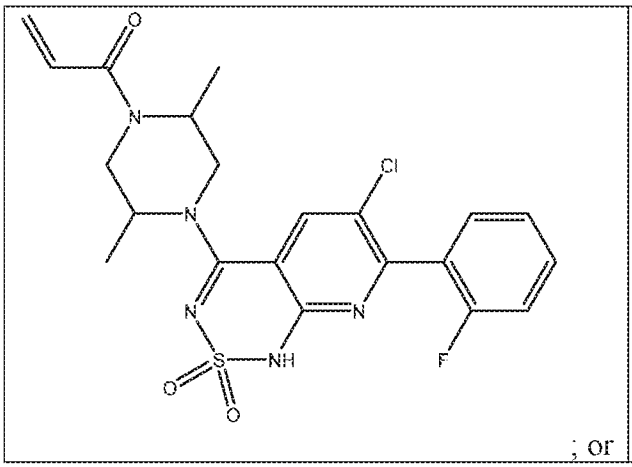


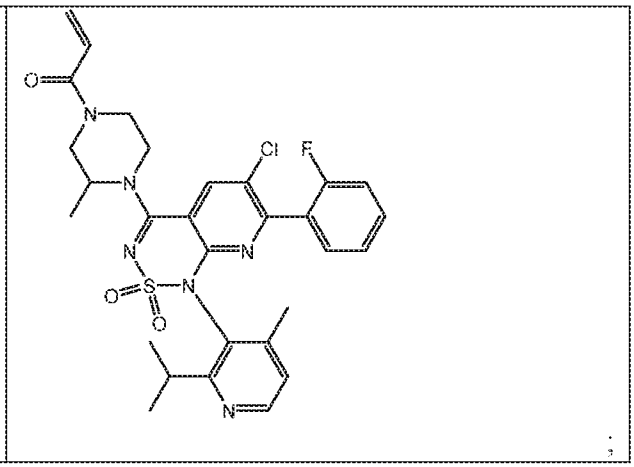









; or


;

[0065] or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

Embodiment 27

[0066] In another embodiment of the present invention, the present invention comprises the compound of any one of embodiments 1-26 in the form of a pharmaceutically acceptable salt.

Embodiment 28

[0067] In another embodiment of the present invention, the present invention comprises a pharmaceutical formulation comprising the compound of any one of the embodiments 1-27 and a pharmaceutically acceptable excipient.

Embodiment 29

[0068] In another embodiment of the present invention, the present invention comprises a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of the embodiments 1-28.

Embodiment 30

[0069] In another embodiment of the present invention, the present invention comprises a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound or formulation of any one of the embodiments 1-29.

Embodiment 31

[0070] In another embodiment of the present invention, the present invention comprises a method of the embodiment 30, wherein the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

Embodiment 32

[0071] In another embodiment of the present invention, the cancer is lung cancer.

Embodiment 33

[0072] In another embodiment of the present invention, the cancer is non-small cell lung cancer.

Embodiment 34

[0073] In another embodiment of the present invention, the cancer is pancreatic cancer.

Embodiment 35

[0074] In another embodiment of the present invention, the cancer is colorectal cancer.

Embodiment 36

[0075] In another embodiment of the present invention, the present invention comprises administering to the patient in need thereof a therapeutically effective amount of an additional pharmaceutically active compound.

Embodiment 37

[0076] In another embodiment of the present invention, the additional pharmaceutically active compound is an anti-PD-1 antibody.

Embodiment 38

[0077] In another embodiment of the present invention, the additional pharmaceutically active compound is nivolumab.

Embodiment 39

[0078] In another embodiment of the present invention, the additional pharmaceutically active compound is pembrolizumab.

Embodiment 40

[0079] In another embodiment of the present invention, the additional pharmaceutically active compound is AMG 404.

Embodiment 41

[0080] In another embodiment of the present invention, the additional pharmaceutically active compound is a MEK inhibitor.

Embodiment 42

[0081] In another embodiment of the present invention, the additional pharmaceutically active compound is daratumumab.

Embodiment 43

[0082] In another embodiment of the present invention, the additional pharmaceutically active compound is an IMiD.

Embodiment 44

[0083] In another embodiment of the present invention, the present invention comprises the use of a compound or formulation according to any one of the embodiments 1-42 for treating cancer in a subject.

Embodiment 45

[0084] In another embodiment of the present invention, the present invention comprises a compound or formulation according to any one of the embodiments 1-42 in the preparation of a medicament for treating cancer.

Embodiment 46

[0085] In another embodiment of the present invention, the cancer is a solid tumor.

Pharmaceutical compositions, dosing, and routes of administration

[0086] Also provided herein are pharmaceutical compositions that includes a compound as disclosed herein, together with a pharmaceutically acceptable excipient, such as, for example, a diluent or carrier. Compounds and pharmaceutical compositions suitable for use in the present invention include those wherein the compound can be administered in an effective amount to achieve its intended purpose. Administration of the compound described in more detail below.

[0087] Suitable pharmaceutical formulations can be determined by the skilled artisan depending on the route of administration and the desired dosage. *See, e.g.*, Remington's Pharmaceutical Sciences, 1435-712 (18th ed., Mack Publishing Co, Easton, Pennsylvania, 1990). Formulations may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the administered agents. Depending on the route of administration, a suitable dose may be calculated according to body weight, body surface areas or organ size. Further refinement of the calculations necessary to determine the appropriate treatment dose is routinely made by those of ordinary skill in the art without undue experimentation, especially in light of the dosage information and assays disclosed herein as well as the pharmacokinetic data obtainable through animal or human clinical trials.

[0088] The phrases "pharmaceutically acceptable" or "pharmacologically acceptable" refer to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, "pharmaceutically acceptable" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such excipients for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the therapeutic compositions, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions. In exemplary embodiments, the formulation may comprise corn syrup solids, high-oleic safflower oil, coconut oil, soy oil, L-leucine, calcium phosphate tribasic, L-tyrosine, L-proline, L-lysine acetate, DATEM (an emulsifier), L-glutamine, L-valine, potassium phosphate dibasic, L-isoleucine, L-arginine, L-alanine, glycine, L-asparagine monohydrate, L-serine, potassium citrate, L-threonine, sodium citrate, magnesium chloride, L-histidine, L-methionine, ascorbic acid, calcium carbonate, L-glutamic acid, L-cystine dihydrochloride, L-tryptophan, L-aspartic acid, choline chloride, taurine, m-inositol, ferrous sulfate, ascorbyl palmitate, zinc sulfate, L-carnitine, alpha-tocopheryl acetate, sodium chloride, niacinamide, mixed tocopherols, calcium pantothenate, cupric sulfate, thiamine chloride hydrochloride, vitamin A palmitate, manganese sulfate, riboflavin, pyridoxine hydrochloride, folic acid, beta-carotene, potassium iodide, phylloquinone, biotin, sodium selenate, chromium chloride, sodium molybdate, vitamin D3 and cyanocobalamin.

[0089] The compound can be present in a pharmaceutical composition as a pharmaceutically acceptable salt. As used herein, "pharmaceutically acceptable salts" include, for example base addition salts and acid addition salts.

[0090] Pharmaceutically acceptable base addition salts may be formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Pharmaceutically acceptable salts of compounds may also be prepared with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations. Carbonates or hydrogen carbonates are also possible. Examples of metals used as cations are sodium, potassium, magnesium, ammonium, calcium, or ferric, and the like. Examples of suitable amines include isopropylamine, trimethylamine, histidine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine.

[0091] Pharmaceutically acceptable acid addition salts include inorganic or organic acid salts. Examples of suitable acid salts include the hydrochlorides, formates, acetates, citrates, salicylates, nitrates, phosphates. Other suitable pharmaceutically acceptable salts are well known to those skilled in the art and include, for example, formic, acetic, citric, oxalic, tartaric, or mandelic acids, hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid; with organic carboxylic, sulfonic, sulfo or phospho acids or N-substituted sulfamic acids, for example acetic acid, trifluoroacetic acid (TFA), propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, lactic acid, oxalic acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid; and with amino acids, such as the 20 alpha amino acids involved in the synthesis of proteins in nature, for example glutamic acid or aspartic acid, and also with phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane 1,2-disulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, naphthalene 2-sulfonic acid, naphthalene 1,5-disulfonic acid, 2- or 3-phosphoglycerate, glucose 6-phosphate, N-cyclohexylsulfamic acid (with the formation of cyclamates), or with other acid organic compounds, such as ascorbic acid.

[0092] Pharmaceutical compositions containing the compounds disclosed herein can be manufactured in a conventional manner, e.g., by conventional mixing, dissolving, granulating,

dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen.

[0093] For oral administration, suitable compositions can be formulated readily by combining a compound disclosed herein with pharmaceutically acceptable excipients such as carriers well known in the art. Such excipients and carriers enable the present compounds to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a compound as disclosed herein with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added. Pharmaceutically acceptable ingredients are well known for the various types of formulation and may be for example binders (e.g., natural or synthetic polymers), lubricants, surfactants, sweetening and flavoring agents, coating materials, preservatives, dyes, thickeners, adjuvants, antimicrobial agents, antioxidants and carriers for the various formulation types.

[0094] When a therapeutically effective amount of a compound disclosed herein is administered orally, the composition typically is in the form of a solid (e.g., tablet, capsule, pill, powder, or troche) or a liquid formulation (e.g., aqueous suspension, solution, elixir, or syrup).

[0095] When administered in tablet form, the composition can additionally contain a functional solid and/or solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder can contain about 1 to about 95% compound, and preferably from about 15 to about 90% compound.

[0096] When administered in liquid or suspension form, a functional liquid and/or a liquid carrier such as water, petroleum, or oils of animal or plant origin can be added. The liquid form of the composition can further contain physiological saline solution, sugar alcohol solutions, dextrose or other saccharide solutions, or glycols. When administered in liquid or suspension form, the composition can contain about 0.5 to about 90% by weight of a compound disclosed herein, and preferably about 1 to about 50% of a compound disclosed herein. In one embodiment contemplated, the liquid carrier is non-aqueous or substantially non-aqueous. For administration in liquid form, the composition may be supplied as a rapidly-dissolving solid formulation for dissolution or suspension immediately prior to administration.

[0097] When a therapeutically effective amount of a compound disclosed herein is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, in addition to a compound disclosed herein, an isotonic vehicle. Such compositions may be prepared for administration as solutions of free base or pharmacologically acceptable salts in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions also can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can optionally contain a preservative to prevent the growth of microorganisms.

[0098] Injectable compositions can include sterile aqueous solutions, suspensions, or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions, suspensions, or dispersions. In all embodiments the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must resist the contaminating action of microorganisms, such as bacteria and fungi, by optional inclusion of a preservative. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. In one embodiment contemplated, the carrier is non-aqueous or substantially non-aqueous. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size of the compound in the embodiment of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many embodiments, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0099] Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating

the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the embodiment of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00100] Slow release or sustained release formulations may also be prepared in order to achieve a controlled release of the active compound in contact with the body fluids in the GI tract, and to provide a substantially constant and effective level of the active compound in the blood plasma. For example, release can be controlled by one or more of dissolution, diffusion, and ion-exchange. In addition, the slow release approach may enhance absorption via saturable or limiting pathways within the GI tract. For example, the compound may be embedded for this purpose in a polymer matrix of a biological degradable polymer, a water-soluble polymer or a mixture of both, and optionally suitable surfactants. Embedding can mean in this context the incorporation of micro-particles in a matrix of polymers. Controlled release formulations are also obtained through encapsulation of dispersed micro-particles or emulsified micro-droplets via known dispersion or emulsion coating technologies.

[0100] For administration by inhalation, compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant. In the embodiment of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0101] The compounds disclosed herein can be formulated for parenteral administration by injection (e.g., by bolus injection or continuous infusion). Formulations for injection can be presented in unit dosage form (e.g., in ampules or in multidose containers), with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

[0102] Pharmaceutical formulations for parenteral administration include aqueous solutions of the compounds in water-soluble form. Additionally, suspensions of the compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include

fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle (e.g., sterile pyrogen-free water) before use.

[0103] Compounds disclosed herein also can be formulated in rectal compositions, such as suppositories or retention enemas (e.g., containing conventional suppository bases). In addition to the formulations described previously, the compounds also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (e.g., subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0104] In particular, a compound disclosed herein can be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. A compound also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which can contain other substances, for example, salts, or sugar alcohols, such as mannitol, or glucose, to make the solution isotonic with blood.

[0105] For veterinary use, a compound disclosed herein is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

[0106] In some embodiments, all the necessary components for the treatment of KRAS-related disorder using a compound as disclosed herein either alone or in combination with another agent or intervention traditionally used for the treatment of such disease may be packaged into a kit. Specifically, the present invention provides a kit for use in the therapeutic intervention of the disease comprising a packaged set of medicaments that include the compound disclosed herein as well as buffers and other components for preparing deliverable forms of said medicaments, and/or

devices for delivering such medicaments, and/or any agents that are used in combination therapy with the compound disclosed herein, and/or instructions for the treatment of the disease packaged with the medicaments. The instructions may be fixed in any tangible medium, such as printed paper, or a computer readable magnetic or optical medium, or instructions to reference a remote computer data source such as a world wide web page accessible via the internet.

[0107] A "therapeutically effective amount" means an amount effective to treat or to prevent development of, or to alleviate the existing symptoms of, the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Generally, a "therapeutically effective dose" refers to that amount of the compound that results in achieving the desired effect. For example, in one preferred embodiment, a therapeutically effective amount of a compound disclosed herein decreases KRAS activity by at least 5%, compared to control, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%.

[0108] The amount of compound administered can be dependent on the subject being treated, on the subject's age, health, sex, and weight, the kind of concurrent treatment (if any), severity of the affliction, the nature of the effect desired, the manner and frequency of treatment, and the judgment of the prescribing physician. The frequency of dosing also can be dependent on pharmacodynamic effects on arterial oxygen pressures. However, the most preferred dosage can be tailored to the individual subject, as is understood and determinable by one of skill in the art, without undue experimentation. This typically involves adjustment of a standard dose (e.g., reduction of the dose if the patient has a low body weight).

[0109] While individual needs vary, determination of optimal ranges of effective amounts of the compound is within the skill of the art. For administration to a human in the curative or prophylactic treatment of the conditions and disorders identified herein, for example, typical dosages of the compounds of the present invention can be about 0.05 mg/kg/day to about 50 mg/kg/day, for example at least 0.05 mg/kg, at least 0.08 mg/kg, at least 0.1 mg/kg, at least 0.2 mg/kg, at least 0.3 mg/kg, at least 0.4 mg/kg, or at least 0.5 mg/kg, and preferably 50 mg/kg or less, 40 mg/kg or less, 30 mg/kg or less, 20 mg/kg or less, or 10 mg/kg or less, which can be about 2.5 mg/day (0.5 mg/kg x 5kg) to about 5000 mg/day (50mg/kg x 100kg), for example. For example, dosages of the compounds can be about 0.1 mg/kg/day to about 50 mg/kg/day, about

0.05 mg/kg/day to about 10 mg/kg/day, about 0.05 mg/kg/day to about 5 mg/kg/day, about 0.05 mg/kg/day to about 3 mg/kg/day, about 0.07 mg/kg/day to about 3 mg/kg/day, about 0.09 mg/kg/day to about 3 mg/kg/day, about 0.05 mg/kg/day to about 0.1 mg/kg/day, about 0.1 mg/kg/day to about 1 mg/kg/day, about 1 mg/kg/day to about 10 mg/kg/day, about 1 mg/kg/day to about 5 mg/kg/day, about 1 mg/kg/day to about 3 mg/kg/day, about 3 mg/day to about 500 mg/day, about 5 mg/day to about 250 mg/day, about 10 mg/day to about 100 mg/day, about 3 mg/day to about 10 mg/day, or about 100 mg/day to about 250 mg/day. Such doses may be administered in a single dose or it may be divided into multiple doses.

Methods of using KRAS G12C inhibitors

[0110] The present disclosure provides a method of inhibiting RAS-mediated cell signaling comprising contacting a cell with an effective amount of one or more compounds disclosed herein. Inhibition of RAS-mediated signal transduction can be assessed and demonstrated by a wide variety of ways known in the art. Non-limiting examples include a showing of (a) a decrease in GTPase activity of RAS; (b) a decrease in GTP binding affinity or an increase in GDP binding affinity; (c) an increase in K off of GTP or a decrease in K off of GDP; (d) a decrease in the levels of signaling transduction molecules downstream in the RAS pathway, such as a decrease in pMEK, pERK, or pAKT levels; and/or (e) a decrease in binding of RAS complex to downstream signaling molecules including but not limited to Raf. Kits and commercially available assays can be utilized for determining one or more of the above.

[0111] The disclosure also provides methods of using the compounds or pharmaceutical compositions of the present disclosure to treat disease conditions, including but not limited to conditions implicated by G12C KRAS, HRAS or NRAS mutation (e.g., cancer).

[0112] In some embodiments, a method for treatment of cancer is provided, the method comprising administering an effective amount of any of the foregoing pharmaceutical compositions comprising a compound as disclosed herein to a subject in need thereof. In some embodiments, the cancer is mediated by a KRAS, HRAS or NRAS G12C mutation. In various embodiments, the cancer is pancreatic cancer, colorectal cancer or lung cancer. In some embodiments, the cancer is gall bladder cancer, thyroid cancer, and bile duct cancer.

[0113] In some embodiments the disclosure provides method of treating a disorder in a subject in need thereof, wherein the said method comprises determining if the subject has a KRAS, HRAS or NRAS G12C mutation and if the subject is determined to have the KRAS, HRAS or NRAS

G12C mutation, then administering to the subject a therapeutically effective dose of at least one compound as disclosed herein or a pharmaceutically acceptable salt thereof.

[0114] The disclosed compounds inhibit anchorage-independent cell growth and therefore have the potential to inhibit tumor metastasis. Accordingly, another embodiment the disclosure provides a method for inhibiting tumor metastasis, the method comprising administering an effective amount a compound disclosed herein.

[0115] KRAS, HRAS or NRAS G12C mutations have also been identified in hematological malignancies (e.g., cancers that affect blood, bone marrow and/or lymph nodes). Accordingly, certain embodiments are directed to administration of a disclosed compounds (e.g., in the form of a pharmaceutical composition) to a patient in need of treatment of a hematological malignancy. Such malignancies include, but are not limited to leukemias and lymphomas. For example, the presently disclosed compounds can be used for treatment of diseases such as Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Chronic myelogenous leukemia (CML), Acute monocytic leukemia (AMoL) and/ or other leukemias. In other embodiments, the compounds are useful for treatment of lymphomas such as all subtypes of Hodgkins lymphoma or non-Hodgkins lymphoma. In various embodiments, the compounds are useful for treatment of plasma cell malignancies such as multiple myeloma, mantle cell lymphoma, and Waldenstrom's macroglubunemia.

[0116] Determining whether a tumor or cancer comprises a G12C KRAS, HRAS or NRAS mutation can be undertaken by assessing the nucleotide sequence encoding the KRAS, HRAS or NRAS protein, by assessing the amino acid sequence of the KRAS, HRAS or NRAS protein, or by assessing the characteristics of a putative KRAS, HRAS or NRAS mutant protein. The sequence of wild-type human KRAS, HRAS or NRAS is known in the art, (e.g. Accession No. NP203524).

[0117] Methods for detecting a mutation in a KRAS, HRAS or NRAS nucleotide sequence are known by those of skill in the art. These methods include, but are not limited to, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays, polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) assays, real-time PCR assays, PCR sequencing, mutant allele-specific PCR amplification (MASA) assays, direct sequencing, primer extension reactions, electrophoresis, oligonucleotide ligation assays, hybridization assays, TaqMan assays, SNP genotyping assays, high resolution melting assays and microarray analyses. In some embodiments, samples are evaluated for G12C KRAS, HRAS or NRAS mutations by

real-time PCR. In real-time PCR, fluorescent probes specific for the KRAS, HRAS or NRAS G12C mutation are used. When a mutation is present, the probe binds and fluorescence is detected. In some embodiments, the KRAS, HRAS or NRAS G12C mutation is identified using a direct sequencing method of specific regions (e.g., exon 2 and/or exon 3) in the KRAS, HRAS or NRAS gene. This technique will identify all possible mutations in the region sequenced.

[0118] Methods for detecting a mutation in a KRAS, HRAS or NRAS protein are known by those of skill in the art. These methods include, but are not limited to, detection of a KRAS, HRAS or NRAS mutant using a binding agent (e.g., an antibody) specific for the mutant protein, protein electrophoresis and Western blotting, and direct peptide sequencing.

[0119] Methods for determining whether a tumor or cancer comprises a G12C KRAS, HRAS or NRAS mutation can use a variety of samples. In some embodiments, the sample is taken from a subject having a tumor or cancer. In some embodiments, the sample is a fresh tumor/cancer sample. In some embodiments, the sample is a frozen tumor/cancer sample. In some embodiments, the sample is a formalin-fixed paraffin-embedded sample. In some embodiments, the sample is a circulating tumor cell (CTC) sample. In some embodiments, the sample is processed to a cell lysate. In some embodiments, the sample is processed to DNA or RNA.

[0120] The disclosure also relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof. In some embodiments, said method relates to the treatment of a subject who suffers from a cancer such as acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS-related cancers (e.g. Lymphoma and Kaposi's Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myleoproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer,

gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or viral-induced cancer. In some embodiments, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

[0121] In some embodiments, the methods for treatment are directed to treating lung cancers, the methods comprise administering an effective amount of any of the above described compound (or a pharmaceutical composition comprising the same) to a subject in need thereof. In certain embodiments the lung cancer is a non- small cell lung carcinoma (NSCLC), for example adenocarcinoma, squamous-cell lung carcinoma or large-cell lung carcinoma. In some embodiments, the lung cancer is a small cell lung carcinoma. Other lung cancers treatable with the disclosed compounds include, but are not limited to, glandular tumors, carcinoid tumors and undifferentiated carcinomas.

[0122] The disclosure further provides methods of modulating a G12C Mutant KRAS, HRAS or NRAS protein activity by contacting the protein with an effective amount of a compound of the disclosure. Modulation can be inhibiting or activating protein activity. In some embodiments, the disclosure provides methods of inhibiting protein activity by contacting the G12C Mutant KRAS, HRAS or NRAS protein with an effective amount of a compound of the disclosure in solution. In some embodiments, the disclosure provides methods of inhibiting the G12C Mutant KRAS, HRAS or NRAS protein activity by contacting a cell, tissue, or organ that expresses the protein of interest. In some embodiments, the disclosure provides methods of inhibiting protein activity in subject including but not limited to rodents and mammal (e.g., human) by administering into the subject an effective amount of a compound of the disclosure. In some embodiments, the percentage modulation exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%. In some embodiments, the percentage of inhibiting exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

[0123] In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a cell by contacting said cell with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said cell. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a tissue by contacting said tissue with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said tissue. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in an organism by contacting said organism with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said organism. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in an animal by contacting said animal with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said animal. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a mammal by contacting said mammal with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said mammal. In some embodiments, the disclosure provides methods of inhibiting KRAS, HRAS or NRAS G12C activity in a human by contacting said human with an amount of a compound of the disclosure sufficient to inhibit the activity of KRAS, HRAS or NRAS G12C in said human. The present

disclosure provides methods of treating a disease mediated by KRAS, HRAS or NRAS G12C activity in a subject in need of such treatment.

Combination Therapy:

[0124] The present disclosure also provides methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound of the present disclosure, or a pharmaceutically acceptable salt thereof. In one aspect, such therapy includes but is not limited to the combination of one or more compounds of the disclosure with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect.

[0125] Many chemotherapeutics are presently known in the art and can be used in combination with the compounds of the disclosure. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti- hormones, angiogenesis inhibitors, and anti-androgens. Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec® (Imatinib Mesylate), Kyprolis® (carfilzomib), Velcade® (bortezomib), Casodex (bicalutamide), Iressa® (gefitinib), Venclexta™ (venetoclax) and Adriamycin™, (docorubicin) as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (Cytoxan™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, chlorocyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, Casodex™, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo- L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins,

mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel and docetaxel; retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0126] Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, (Nolvadex™), raloxifene, aromatase inhibiting 4(5)- imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO).

[0127] Where desired, the compounds or pharmaceutical composition of the present disclosure can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 17-N-Allylamino-17-

demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell-cycle nonspecific antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitrucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126 or Zosuquidar.

[0128] This disclosure further relates to a method for using the compounds or pharmaceutical compositions provided herein, in combination with radiation therapy for inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the disclosure in this combination therapy can be determined as described herein.

[0129] Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (e.g. At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm- 153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner of the present disclosure include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of

radionuclide(s), e.g., a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

[0130] The compounds or pharmaceutical compositions of the disclosure can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, antiproliferative agents, glycolysis inhibitors, or autophagy inhibitors.

[0131] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound of the disclosure and pharmaceutical compositions described herein. Anti-angiogenesis agents include, for example, rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include alecoxib, valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 WO 96/27583 European Patent Publication EP0818442, European Patent Publication EP1004578 , WO 98/07697, WO 98/03516, WO 98/34918, WO 98/34915, WO 98/33768, WO 98/30566, European Patent Publication 606046, European Patent Publication 931 788, WO 90/05719, WO 99/52910, WO 99/52889, WO 99/29667, WO1999007675, European Patent Publication EP1786785, European Patent Publication No. EP1181017, United States Publication No. US20090012085, United States Publication US5863 949, United States Publication US5861 510, and European Patent Publication EP0780386, all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (i. e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP- 8, MMP-10, MMP-11, MMP-12, andMMP-13). Some specific examples of MMP inhibitors useful in the disclosure are AG-3340, RO 32-3555, and RS 13-0830.

[0132] The present compounds may also be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate,

DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-$_{n3}$, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburiembodiment, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical),

granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

[0133] The compounds of the invention may further be used with VEGFR inhibitors. Other compounds described in the following patents and patent applications can be used in combination therapy: US 6,258,812, US 2003/0105091, WO 01/37820, US 6,235,764, WO 01/32651, US 6,630,500, US 6,515,004, US 6,713,485, US 5,521,184, US 5,770,599, US 5,747,498, WO 02/68406, WO 02/66470, WO 02/55501, WO 04/05279, WO 04/07481, WO 04/07458, WO 04/09784, WO 02/59110, WO 99/45009, WO 00/59509, WO 99/61422, US 5,990,141, WO 00/12089, and WO 00/02871.

[0134] In some embodiments, the combination comprises a composition of the present invention in combination with at least one anti-angiogenic agent. Agents are inclusive of, but not limited to, *in vitro* synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth.

[0135] Exemplary anti-angiogenic agents include ERBITUX™ (IMC-C225), KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF, or soluble VEGF receptors or a ligand binding region thereof) such as AVASTIN™ or VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto), EGFR inhibitory agents (e.g., antibodies or antigen

binding regions that specifically bind thereto) such as Vectibix (panitumumab), IRESSA™ (gefitinib), TARCEVA™ (erlotinib), anti-Ang1 and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie2 kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). The pharmaceutical compositions of the present invention can also include one or more agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor "c-met".

[0136] Other anti-angiogenic agents include Campath, IL-8, B-FGF, Tek antagonists (Ceretti et al., U.S. Publication No. 2003/0162712; U.S. Patent No. 6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see, Wiley, U.S. Patent No. 6,727,225), ADAM distintegrin domain to antagonize the binding of integrin to its ligands (Fanslow et al., U.S. Publication No. 2002/0042368), specifically binding anti-eph receptor and/or anti-ephrin antibodies or antigen binding regions (U.S. Patent Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto).

[0137] Additional anti-angiogenic/anti-tumor agents include: SD-7784 (Pfizer, USA); cilengitide.(Merck KGaA, Germany, EPO 770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US 5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol, (EntreMed, USA); TLC ELL-12, (Elan, Ireland); anecortave acetate, (Alcon, USA); alpha-D148 Mab, (Amgen, USA); CEP-7055,(Cephalon, USA); anti-Vn Mab, (Crucell, Netherlands) DAC:antiangiogenic, (ConjuChem, Canada); Angiocidin, (InKine Pharmaceutical, USA); KM-2550, (Kyowa Hakko, Japan); SU-0879, (Pfizer, USA); CGP-79787, (Novartis, Switzerland, EP 970070); ARGENT technology, (Ariad, USA); YIGSR-Stealth, (Johnson & Johnson, USA); fibrinogen-E fragment, (BioActa, UK); angiogenesis inhibitor, (Trigen, UK); TBC-1635, (Encysive Pharmaceuticals, USA); SC-236, (Pfizer, USA); ABT-567, (Abbott, USA);

Metastatin, (EntreMed, USA); angiogenesis inhibitor, (Tripep, Sweden); maspin, (Sosei, Japan); 2-methoxyestradiol, (Oncology Sciences Corporation, USA); ER-68203-00, (IVAX, USA); Benefin, (Lane Labs, USA); Tz-93, (Tsumura, Japan); TAN-1120, (Takeda, Japan); FR-111142, (Fujisawa, Japan, JP 02233610); platelet factor 4, (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist, (Borean, Denmark); bevacizumab (pINN), (Genentech, USA); angiogenesis inhibitors, (SUGEN, USA); XL 784, (Exelixis, USA); XL 647, (Exelixis, USA); MAb, alpha5beta3 integrin, second generation, (Applied Molecular Evolution, USA and MedImmune, USA); gene therapy, retinopathy, (Oxford BioMedica, UK); enzastaurin hydrochloride (USAN), (Lilly, USA); CEP 7055, (Cephalon, USA and Sanofi-Synthelabo, France); BC 1, (Genoa Institute of Cancer Research, Italy); angiogenesis inhibitor, (Alchemia, Australia); VEGF antagonist, (Regeneron, USA); rBPI 21 and BPI-derived antiangiogenic, (XOMA, USA); PI 88, (Progen, Australia); cilengitide (pINN), (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); cetuximab (INN), (Aventis, France); AVE 8062, (Ajinomoto, Japan); AS 1404, (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin, (Boston Childrens Hospital, USA); ATN 161, (Attenuon, USA); ANGIOSTATIN, (Boston Childrens Hospital, USA); 2-methoxyestradiol, (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and Research Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, USA); OXI 4503, (OXiGENE, USA); o-guanidines, (Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aeterna, Canada); vaccine, angiogenesis, (EntreMed, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-1alfa inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea);

GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol, (EntreMed, USA); anginex, (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510, (Abbott, USA); AAL 993, (Novartis, Switzerland); VEGI, (ProteomTech, USA); tumor necrosis factor-alpha inhibitors, (National Institute on Aging, USA); SU 11248, (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16, (Yantai Rongchang, China); S-3APG , (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR, (ImClone Systems, USA); MAb, alpha5 beta1, (Protein Design, USA); KDR kinase inhibitor, (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116, (South Florida University, USA and Yale University, USA); CS 706, (Sankyo, Japan); combretastatin A4 prodrug, (Arizona State University, USA); chondroitinase AC, (IBEX, Canada); BAY RES 2690, (Bayer, Germany); AGM 1470, (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925, (Agouron, USA); Tetrathiomolybdate, (University of Michigan, USA); GCS 100, (Wayne State University, USA) CV 247, (Ivy Medical, UK); CKD 732, (Chong Kun Dang, South Korea); MAb, vascular endothelium growth factor, (Xenova, UK); irsogladine (INN), (Nippon Shinyaku, Japan); RG 13577, (Aventis, France); WX 360, (Wilex, Germany); squalamine (pINN), (Genaera, USA); RPI 4610, (Sirna, USA); cancer therapy, (Marinova, Australia); heparanase inhibitors, (InSight, Israel); KL 3106, (Kolon, South Korea); Honokiol, (Emory University, USA); ZK CDK, (Schering AG, Germany); ZK Angio, (Schering AG, Germany); ZK 229561, (Novartis, Switzerland, and Schering AG, Germany); XMP 300, (XOMA, USA); VGA 1102, (Taisho, Japan); VEGF receptor modulators, (Pharmacopeia, USA); VE-cadherin-2 antagonists , (ImClone Systems, USA); Vasostatin, (National Institutes of Health, USA);vaccine, Flk-1, (ImClone Systems, USA); TZ 93, (Tsumura, Japan); TumStatin, (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1), (Merck & Co, USA); Tie-2 ligands, (Regeneron, USA); and, thrombospondin 1 inhibitor, (Allegheny Health, Education and Research Foundation, USA).

[0138] Autophagy inhibitors include, but are not limited to chloroquine, 3- methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4- imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that

inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy), may also be used.

[0139] Additional pharmaceutically active compounds/agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of the present invention include: epoetin alfa; darbepoetin alfa; panitumumab; pegfilgrastim; palifermin; filgrastim; denosumab; ancestim; AMG 102; AMG 176; AMG 386; AMG 479; AMG 655; AMG 745; AMG 951; and AMG 706, or a pharmaceutically acceptable salt thereof.

[0140] In certain embodiments, a composition provided herein is conjointly administered with a chemotherapeutic agent. Suitable chemotherapeutic agents may include, natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (e.g., etoposide and teniposide), antibiotics (e.g., dactinomycin (actinomycin D), daunorubicin, doxorubicin, and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin), mitomycin, enzymes (e.g., L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine), antiplatelet agents, antiproliferative/antimitotic alkylating agents such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide and analogs, melphalan, and chlorambucil), ethylenimines and methylmelamines (e.g., hexaamethylmelaamine and thiotepa), CDK inhibitors (e.g., seliciclib, UCN-01, P1446A-05, PD-0332991, dinaciclib, P27-00, AT-7519, RGB286638, and SCH727965), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine (BCNU) and analogs, and streptozocin), trazenes-dacarbazinine (DTIC), antiproliferative/antimitotic antimetabolites such as folic acid analogs (e.g., methotrexate), pyrimidine analogs (e.g., fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (e.g., mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine), aromatase inhibitors (e.g., anastrozole, exemestane, and letrozole), and platinum coordination complexes (e.g., cisplatin and carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide, histone deacetylase (HDAC) inhibitors (e.g., trichostatin, sodium butyrate, apicidan, suberoyl anilide hydroamic acid, vorinostat, LBH 589, romidepsin, ACY-1215, and panobinostat), mTor inhibitors (e.g., temsirolimus, everolimus, ridaforolimus, and sirolimus), KSP(Eg5) inhibitors (e.g., Array 520), DNA binding agents (e.g., Zalypsis), PI3K delta inhibitor (e.g., GS-1101 and TGR-1202), PI3K delta and gamma inhibitor (e.g., CAL-130), multi-kinase inhibitor (e.g., TG02 and sorafenib), hormones (e.g., estrogen) and hormone agonists such as leutinizing hormone releasing

hormone (LHRH) agonists (e.g., goserelin, leuprolide and triptorelin), BAFF-neutralizing antibody (e.g., LY2127399), IKK inhibitors, p38MAPK inhibitors, anti-IL-6 (e.g., CNTO328), telomerase inhibitors (e.g., GRN 163L), aurora kinase inhibitors (e.g., MLN8237), cell surface monoclonal antibodies (e.g., anti-CD38 (HUMAX-CD38), anti-CS1 (e.g., elotuzumab), HSP90 inhibitors (e.g., 17 AAG and KOS 953), P13K / Akt inhibitors (e.g., perifosine), Akt inhibitor (e.g., GSK-2141795), PKC inhibitors (e.g., enzastaurin), FTIs (e.g., Zarnestra™), anti-CD138 (e.g., BT062), Torc1/2 specific kinase inhibitor (e.g., INK128), kinase inhibitor (e.g., GS-1101), ER/UPR targeting agent (e.g., MKC-3946), cFMS inhibitor (e.g., ARRY-382), JAK1/2 inhibitor (e.g., CYT387), PARP inhibitor (e.g., olaparib and veliparib (ABT-888)), BCL-2 antagonist. Other chemotherapeutic agents may include mechlorethamine, camptothecin, ifosfamide, tamoxifen, raloxifene, gemcitabine, navelbine, sorafenib, or any analog or derivative variant of the foregoing.

[0141] The compounds of the present invention may also be used in combination with radiation therapy, hormone therapy, surgery and immunotherapy, which therapies are well known to those skilled in the art.

[0142] In certain embodiments, a pharmaceutical composition provided herein is conjointly administered with a steroid. Suitable steroids may include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difuprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and salts and/or derivatives thereof.In a particular embodiment, the compounds of the present invention can also be used in combination with additional pharmaceutically active agents that treat nausea. Examples

of agents that can be used to treat nausea include: dronabinol; granisetron; metoclopramide; ondansetron; and prochlorperazine; or a pharmaceutically acceptable salt thereof.

[0143] The compounds of the present invention may also be used in combination with an additional pharmaceutically active compound that disrupts or inhibits RAS-RAF-ERK or PI3K-AKT-TOR signaling pathways. In other such combinations, the additional pharmaceutically active compound is a PD-1 and PD-L1 antagonist. The compounds or pharmaceutical compositions of the disclosure can also be used in combination with an amount of one or more substances selected from EGFR inhibitors, MEK inhibitors, PI3K inhibitors, AKT inhibitors, TOR inhibitors, Mcl-1 inhibitors, BCL-2 inhibitors, SHP2 inhibitors, proteasome inhibitors, and immune therapies, including monoclonal antibodies, immunomodulatory imides (IMiDs), anti-PD-1, anti-PDL-1, anti-CTLA4, anti-LAG1, and anti-OX40 agents, GITR agonists, CAR-T cells, and BiTEs.

[0144] EGFR inhibitors include, but are not limited to, small molecule antagonists, antibody inhibitors, or specific antisense nucleotide or siRNA. Useful antibody inhibitors of EGFR include cetuximab (Erbitux), panitumumab (Vectibix), zalutumumab, nimotuzumab, and matuzumab. Small molecule antagonists of EGFR include gefitinib, erlotinib (Tarceva), and most recently, lapatinib (TykerB). See e.g., Yan L, et. al., *Pharmacogenetics and Pharmacogenomics In Oncology Therapeutic Antibody Development*, BioTechniques 2005; 39(4): 565-8, and Paez J G, et. al., *EGFR Mutations In Lung Cancer Correlation With Clinical Response To Gefitinib Therapy*, Science 2004; 304(5676): 1497-500.

[0145] Non-limiting examples of small molecule EGFR inhibitors include any of the EGFR inhibitors described in the following patent publications, and all pharmaceutically acceptable salts and solvates of said EGFR inhibitors: European Patent Application EP 520722, published Dec. 30, 1992; European Patent Application EP 566226, published Oct. 20, 1993; PCT International Publication WO 96/33980, published Oct. 31, 1996; U.S. Pat. No. 5,747,498, issued May 5, 1998; PCT International Publication WO 96/30347, published Oct. 3, 1996; European Patent Application EP 787772, published Aug. 6, 1997; PCT International Publication WO 97/30034, published Aug. 21, 1997; PCT International Publication WO 97/30044, published Aug. 21, 1997; PCT International Publication WO 97/38994, published Oct. 23, 1997; PCT International Publication WO 97/49688, published Dec. 31, 1997; European Patent Application EP 837063, published Apr. 22, 1998; PCT International Publication WO 98/02434, published Jan. 22, 1998; PCT International Publication WO 97/38983, published Oct. 23, 1997; PCT International Publication WO 95/19774,

published Jul. 27, 1995; PCT International Publication WO 95/19970, published Jul. 27, 1995; PCT International Publication WO 97/13771, published Apr. 17, 1997; PCT International Publication WO 98/02437, published Jan. 22, 1998; PCT International Publication WO 98/02438, published Jan. 22, 1998; PCT International Publication WO 97/32881, published Sep. 12, 1997; German Application DE 19629652, published Jan. 29, 1998; PCT International Publication WO 98/33798, published Aug. 6, 1998; PCT International Publication WO 97/32880, published Sep. 12, 1997; PCT International Publication WO 97/32880 published Sep. 12, 1997; European Patent Application EP 682027, published Nov. 15, 1995; PCT International Publication WO 97/02266, published Jan. 23, 197; PCT International Publication WO 97/27199, published Jul. 31, 1997; PCT International Publication WO 98/07726, published Feb. 26, 1998; PCT International Publication WO 97/34895, published Sep. 25, 1997; PCT International Publication WO 96/31510', published Oct. 10, 1996; PCT International Publication WO 98/14449, published Apr. 9, 1998; PCT International Publication WO 98/14450, published Apr. 9, 1998; PCT International Publication WO 98/14451, published Apr. 9, 1998; PCT International Publication WO 95/09847, published Apr. 13, 1995; PCT International Publication WO 97/19065, published May 29, 1997; PCT International Publication WO 98/17662, published Apr. 30, 1998; U.S. Pat. No. 5,789,427, issued Aug. 4, 1998; U.S. Pat. No. 5,650,415, issued Jul. 22, 1997; U.S. Pat. No. 5,656,643, issued Aug. 12, 1997; PCT International Publication WO 99/35146, published Jul. 15, 1999; PCT International Publication WO 99/35132, published Jul. 15, 1999; PCT International Publication WO 99/07701, published Feb. 18, 1999; and PCT International Publication WO 92/20642 published Nov. 26, 1992. Additional non-limiting examples of small molecule EGFR inhibitors include any of the EGFR inhibitors described in Traxler, P., 1998, Exp. Opin. Ther. Patents 8(12):1599-1625.

[0146] Antibody-based EGFR inhibitors include any anti-EGFR antibody or antibody fragment that can partially or completely block EGFR activation by its natural ligand. Non-limiting examples of antibody-based EGFR inhibitors include those described in Modjtahedi, H., et al., 1993, Br. J. Cancer 67:247-253; Teramoto, T., et al., 1996, Cancer 77:639-645; Goldstein et al., 1995, Clin. Cancer Res. 1:1311-1318; Huang, S. M., et al., 1999, Cancer Res. 15:59(8):1935-40; and Yang, X., et al., 1999, Cancer Res. 59:1236-1243. Thus, the EGFR inhibitor can be monoclonal antibody Mab E7.6.3 (Yang, 1999 supra), or Mab C225 (ATCC Accession No. HB-8508), or an antibody or antibody fragment having the binding specificity thereof.

[0147] MEK inhibitors include, but are not limited to, tremetinib (Mekinist®), CI-1040, AZD6244, PD318088, PD98059, PD334581, RDEA119, ARRY-142886, ARRY-438162, and PD-325901.

[0148] PI3K inhibitors include, but are not limited to, wortmannin, 17-hydroxywortmannin analogs described in WO 06/044453, 4-[2-(1H-Indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036,082 and WO 09/055,730), 2-Methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-c]quinolin-1-yl]phenyl]propionitrile (also known as BEZ 235 or NVP-BEZ 235, and described in PCT Publication No. WO 06/122806), (S)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6-yl)methyl)piperazin-1-yl)-2-hydroxypropan-1-one (described in PCT Publication No. WO 2008/070740), LY294002 (2-(4-Morpholinyl)-8-phenyl-4H-1-benzopyran-4-one available from Axon Medchem), PI 103 hydrochloride (3-[4-(4-morpholinylpyrido-[3′,2′:4,5]furo[3,2-d]pyrimidin-2-yl]phenol hydrochloride available from Axon Medchem), PIK 75 (N′-[(1E)-(6-bromoimidazo[1,2-a]pyridin-3-yl)methylene]-N,2-dimethyl-5-nitrobenzenesulfono-hydrazide hydrochloride available from Axon Medchem), PIK 90 (N-(7,8-dimethoxy-2,3-dihydro-imidazo[1,2-c]quinazolin-5-yl)-nicotinamide available from Axon Medchem), GDC-0941 bismesylate (2-(1H-Indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine bismesylate available from Axon Medchem), AS-252424 (5-[1-[5-(4-Fluoro-2-hydroxy-phenyl)-furan-2-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione available from Axon Medchem), and TGX-221 (7-Methyl-2-(4-morpholinyl)-9-[1-(phenylamino)ethyl]-4H-pyrido-[1,2-a]pyrimidin-4-one available from Axon Medchem), XL-765, and XL-147. Other PI3K inhibitors include demethoxyviridin, perifosine, CAL101, PX-866, BEZ235, SF1126, INK1117, IPI-145, BKM120, XL147, XL765, Palomid 529, GSK1059615, ZSTK474, PWT33597, IC87114, TG100-115, CAL263, PI-103, GNE-477, CUDC-907, and AEZS-136.

[0149] AKT inhibitors include, but are not limited to, Akt-1-1 (inhibits Akt1) (Barnett et al. (2005) *Biochem. J.*, 385 (Pt. 2), 399-408); Akt-1-1,2 (inhibits Ak1 and 2) (Barnett et al. (2005) *Biochem. J.* 385 (Pt. 2), 399-408); API-59CJ-Ome (e.g., Jin et al. (2004) *Br. J. Cancer* 91, 1808-12); 1-H-imidazo[4,5-c]pyridinyl compounds (e.g., WO05011700); indole-3-carbinol and derivatives thereof (e.g., U.S. Pat. No. 6,656,963; Sarkar and Li (2004) *J Nutr.* 134(12 Suppl), 3493S-3498S); perifosine (e.g., interferes with Akt membrane localization; Dasmahapatra et al.

(2004) *Clin. Cancer Res.* 10(15), 5242-52, 2004); phosphatidylinositol ether lipid analogues (e.g., Gills and Dennis (2004) *Expert. Opin. Investig. Drugs* 13, 787-97); and triciribine (TCN or API-2 or NCI identifier: NSC 154020; Yang et al. (2004) *Cancer Res.* 64, 4394-9).

[0150] TOR inhibitors include, but are not limited to, AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30 and Torin 1. Other TOR inhibitors in FKBP12 enhancer; rapamycins and derivatives thereof, including: CCI-779 (temsirolimus), RAD001 (Everolimus; WO 9409010) and AP23573; rapalogs, e.g. as disclosed in WO 98/02441 and WO 01/14387, e.g. AP23573, AP23464, or AP23841; 40-(2-hydroxyethyl)rapamycin, 40-[3-hydroxy(hydroxymethyl)methylpropanoate]-rapamycin (also called CC1779), 40-epi-(tetrazolyt)-rapamycin (also called ABT578), 32-deoxorapamycin, 16-pentynyloxy-32(S)-dihydrorapanycin, and other derivatives disclosed in WO 05005434; derivatives disclosed in U.S. Pat. No. 5,258,389, WO 94/090101, WO 92/05179, U.S. Pat. No. 5,118,677, U.S. Pat. No. 5,118,678, U.S. Pat. No. 5,100,883, U.S. Pat. No. 5,151,413, U.S. Pat. No. 5,120,842, WO 93/111130, WO 94/02136, WO 94/02485, WO 95/14023, WO 94/02136, WO 95/16691, WO 96/41807, WO 96/41807 and U.S. Pat. No. 5,256,790; phosphorus-containing rapamycin derivatives (e.g., WO 05016252); 4H-1-benzopyran-4-one derivatives (e.g., U.S. Provisional Application No. 60/528,340).

[0151] MCl-1 inhibitors include, but are not limited to, AMG-176, MIK665, and S63845. The myeloid cell leukemia-1 (MCL-1) protein is one of the key anti-apoptotic members of the B-cell lymphoma-2 (BCL-2) protein family. Over-expression of MCL-1 has been closely related to tumor progression as well as to resistance, not only to traditional chemotherapies but also to targeted therapeutics including BCL-2 inhibitors such as ABT-263.

[0152] SHP inhibitors include, but are not limited to, SHP099.

[0153] Proteasome inhibitors include, but are not limited to, Kyprolis®(carfilzomib), Velcade®(bortezomib), and oprozomib.

[0154] Immune therapies include, but are not limited to, anti-PD-1 agents, anti-PDL-1 agents, anti-CTLA-4 agents, anti-LAG1 agents, and anti-OX40 agents.

[0155] Monoclonal antibodies include, but are not limited to, Darzalex® (daratumumab), Herceptin® (trastuzumab), Avastin® (bevacizumab), Rituxan® (rituximab), Lucentis® (ranibizumab), and Eylea® (aflibercept).

[0156] Immunomodulatory imide drugs (IMiDs) are a class of immunomodulatory drugs (drugs that adjust immune responses) containing an imide group. The IMiD class includes thalidomide and its analogues (lenalidomide, pomalidomide, and apremilast).

[0157] Exemplary anti-PD-1 antibodies and methods for their use are described by Goldberg et al., *Blood* 110(1):186-192 (2007), Thompson et al., *Clin. Cancer Res.* 13(6):1757-1761 (2007), and Korman et al., International Application No. PCT/JP2006/309606 (publication no. WO 2006/121168 A1), each of which are expressly incorporated by reference herein, include: nivolumab, pembrolizumab, AMG 404, Yervoy™ (ipilimumab) or Tremelimumab (to CTLA-4), galiximab (to B7.1), BMS-936558 (to PD-1), MK-3475 (to PD-1), AMP224 (to B7DC), BMS-936559 (to B7-H1), MPDL3280A (to B7-H1), MEDI-570 (to ICOS), AMG557 (to B7H2), MGA271 (to B7H3), IMP321 (to LAG-3), BMS-663513 (to CD137), PF-05082566 (to CD137), CDX-1127 (to CD27), anti-OX40 (Providence Health Services), huMAbOX40L (to OX40L), Atacicept (to TACI), CP-870893 (to CD40), Lucatumumab (to CD40), Dacetuzumab (to CD40), Muromonab-CD3 (to CD3), Ipilumumab (to CTLA-4). Immune therapies also include genetically engineered T-cells (e.g., CAR-T cells) and bispecific antibodies (e.g., BiTEs).

[0158] GITR agonists include, but are not limited to, GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies), such as, a GITR fusion protein described in U.S. Pat. No. 6,111,090box.c, European Patent No.: 090505B1, U.S. Pat. No. 8,586,023, PCT Publication Nos.: WO 2010/003118 and 2011/090754, or an anti-GITR antibody described, e.g., in U.S. Pat. No. 7,025,962, European Patent No.: 1947183B1, U.S. Pat. No. 7,812,135, U.S. Pat. No. 8,388,967, U.S. Pat. No. 8,591,886, European Patent No.: EP 1866339, PCT Publication No.: WO 2011/028683, PCT Publication No.: WO 2013/039954, PCT Publication No.: WO2005/007190, PCT Publication No.: WO 2007/133822, PCT Publication No.: WO2005/055808, PCT Publication No.: WO 99/40196, PCT Publication No.: WO 2001/03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/115451, U.S. Pat. No. 7,618,632, and PCT Publication No.: WO 2011/051726.

[0159] The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the one or more compounds of the disclosure will be co-administered with other agents as described above. When used in combination therapy, the compounds described herein are administered with the second agent simultaneously or separately. This administration in

combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the disclosure and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present disclosure can be administered just followed by and any of the agents described above, or vice versa. In some embodiments of the separate administration protocol, a compound of the disclosure and any of the agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

[0160] As one aspect of the present invention contemplates the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present invention, and a second pharmaceutical compound. The kit comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes, and bags. In some embodiments, the kit comprises directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing health care professional.

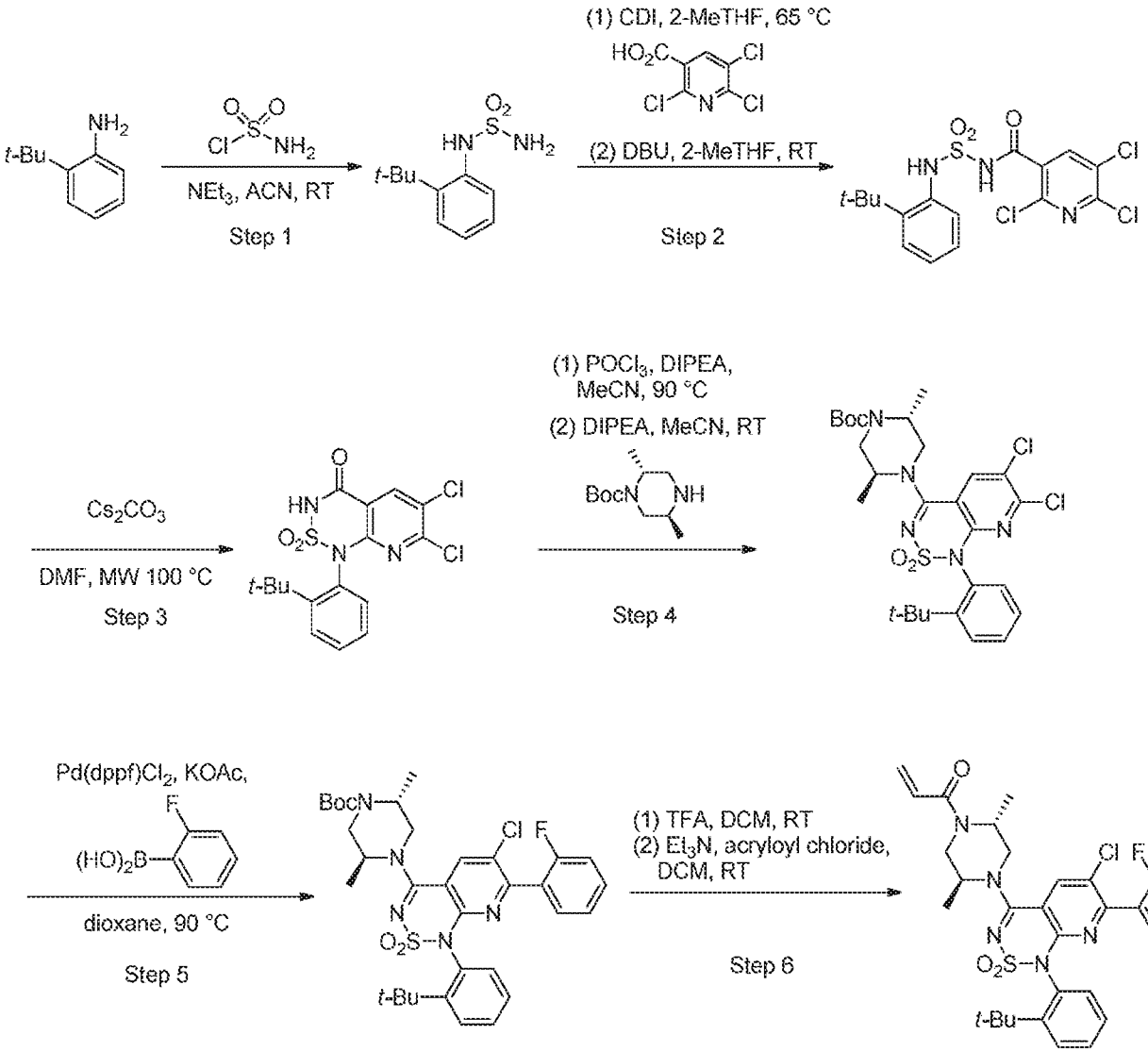
SYNTHESIS OF DISCLOSED COMPOUNDS

[0161] Compounds as disclosed herein can be synthesized via a number of specific methods. The examples which outline specific synthetic routes, and the generic schemes below are meant to provide guidance to the ordinarily skilled synthetic chemist, who will readily appreciate that the solvent, concentration, reagent, protecting group, order of synthetic steps, time, temperature, and the like can be modified as necessary, well within the skill and judgment of the ordinarily skilled artisan.

SECTION 1 – GENERAL PROCEDURES

Method 1

[0162] Example 1-1: 1-((2*R*,5*S*)-4-(6-Chloro-7-(2-fluorophenyl)-1-(2-(2-methyl-2-propanyl)phenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one.



[0163] Step 1: *N*-[2-(1,1-Dimethylethyl)phenyl]-sulfamide. To a mixture of sulfamoyl chloride (2.8 g, 24 mmol, Combi-Blocks, San Diego, CA, USA) in acetonitrile (10 mL) at 0 °C was added a solution of 2-(1,1-dimethylethyl)benzenamine (3.13 ml, 20.1 mmol) and triethylamine (2.8 mL, 20 mmol) in acetonitrile (10 mL). The reaction was stirred for 5 min and then was partitioned between brine (100 mL) and EtOAc (100 mL). The organic layer was separated, dried

over $MgSO_4$, and adsorbed onto silica gel. The crude product was purified by silica gel chromatography (eluent: 0–40% EtOAc-EtOH (3:1)/heptane) to provide *N*-[2-(1,1-dimethylethyl)phenyl]-sulfamide (3.5 g, 15 mmol, 75% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.96 (s, 1H), 7.58 (dd, J = 7.2, 2.2 Hz, 1H), 7.37 (d, J = 6.7 Hz, 1H), 7.11-7.24 (m, 2H), 6.91 (s, 2H), 1.38 (s, 9H); *m/z* (ESI, +ve ion): 229.1 $(M+H)^+$.

[0164] Step 2: *N*-(*N*-(2-(*tert*-Butyl)phenyl)sulfamoyl)-2,5,6-trichloronicotinamide. A solution of 2,5,6-trichloronicotinic acid (0.50 g, 2.2 mmol), CDI (0.37 g, 2.2 mmol), and 2-methyltetrahydrofuran (22 mL) was heated to 70 °C for 3 h then cooled to rt. *N*-[2-(1,1-dimethylethyl)phenyl]-sulfamide (0.48 g, 2.1 mmol) was added in a single portion, followed by 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.33 mL, 2.2 mmol). The reaction was stirred at rt for 1 h then was partitioned between 1:1 sat. ammonium chloride to brine (100 mL) and EtOAc (100 mL). The organic layer was separated, dried over $MgSO_4$, and adsorbed onto silica gel. The crude product was purified by silica gel chromatography (eluent: 0–40% EtOAc-EtOH (3:1)/heptane) to provide *N*-(*N*-(2-(*tert*-butyl)phenyl)sulfamoyl)-2,5,6-trichloronicotinamide (0.50 g, 1.1 mmol, 52% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 - 8.20 (m, 1 H), 7.47 (br d, J = 6.4 Hz, 1 H), 7.42 - 7.32 (m, 1 H), 7.25 - 7.14 (m, 2 H), 7.09 (m, 1 H), 7.01 - 6.85 (m, 1 H), 1.41 (s, 9H); *m/z* (ESI, +ve ion): 436.8 $(M+H)^+$.

[0165] Step 3: 1-(2-(*tert*-Butyl)phenyl)-6,7-dichloro-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-(3*H*)-one 2,2-dioxide. To a solution of *N*-(*N*-(2-(*tert*-butyl)phenyl)sulfamoyl)-2,5,6-trichloronicotinamide (0.50 g, 1.1 mmol) in *N*, *N*-dimethylformamide (1 mL) was added cesium carbonate (1.9 g, 5.7 mmol). The heterogenous mixture was heated to 100 °C for 40 min via microwave irradiation, then partitioned between EtOAc (50 mL) and brine (50 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo to provide 1-(2-(*tert*-butyl)phenyl)-6,7-dichloro-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide (0.45 g, 1.1 mmol, 98% yield) as a foamy solid, which was used without further purification. *m/z* (ESI, +ve ion): 400.0 $(M+H)^+$.

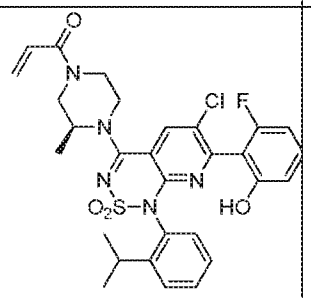
[0166] Step 4: *tert*-Butyl (2*R*,5*S*)-4-(1-(2-(tert-butyl)phenyl)-6,7-dichloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. Phosphorous oxychloride (0.14 mL, 1.5 mmol) was added dropwise to a solution of 1-(2-(*tert*-butyl)phenyl)-6,7-dichloro-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide (0.45 g, 1.1 mmol) and DIPEA (0.28 mL, 1.6 mmol) in acetonitrile (1.1 mL). This mixture was heated to 90 °C for 1 h,

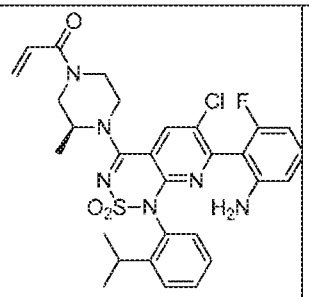
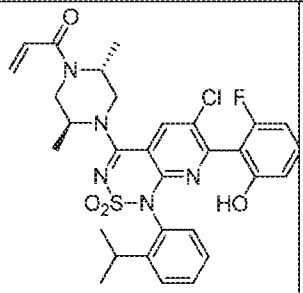
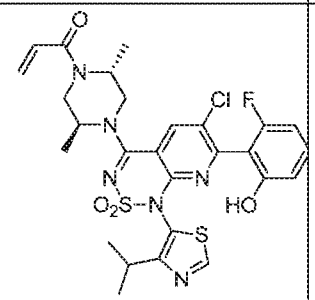
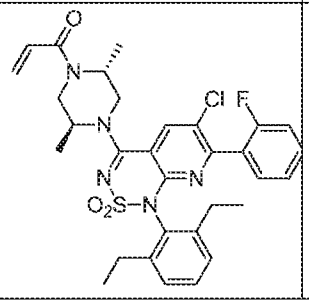
then the reaction mixture was cooled to 0 °C. DIPEA (0.59 mL, 3.4 mmol) was added followed by (2*R*,6*S*)-*tert*-butyl 2,6-dimethylpiperazine-1-carboxylate (0.25 g, 1.2 mmol, eNovation Chemicals LLC, Bridgewater, NJ, USA). This homogenous solution was warmed to rt and stirred for 18 h. The mixture was poured into cold (0 °C) sat. $NaHCO_3$ (50 mL), and stirred vigorously for 10 min. EtOAc (50 mL) was added, and the organic layer was separated. The aqueous layer was back-extracted with EtOAc (2x), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (eluent: 0–40% EtOAc-EtOH (3:1)/heptane) to provide *tert*-butyl (2*R*,5*S*)-4-(1-(2-(*tert*-butyl)phenyl)-6,7-dichloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.34 g, 0.57 mmol, 51% yield) as a white solid. ^{1}H NMR showed a mix of atropisomers (400 MHz, $CDCl_3$) δ 7.92 - 7.75 (m, 1 H), 7.65 - 7.56 (m, 1 H), 7.52 - 7.28 (m, 3 H), 4.64 (br s, 1 H), 4.51 - 4.26 (m, 1 H), 3.97 - 3.44 (m, 3 H), 3.35 - 3.00 (m, 1 H), 1.49 (s, 9 H), 1.45 - 1.31 (m, 6 H), 1.28 (d, J = 1.0 Hz, 9 H); *m/z* (ESI, +ve ion): 540.0 $(M-t\text{Bu}+H)^+$.

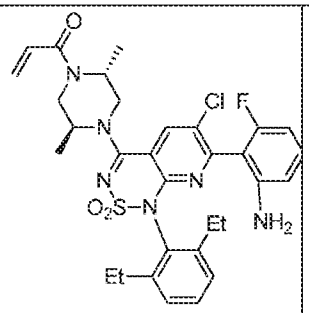
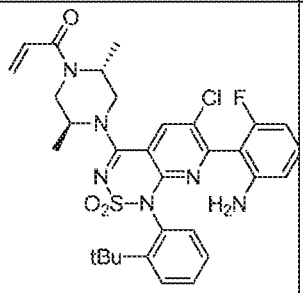
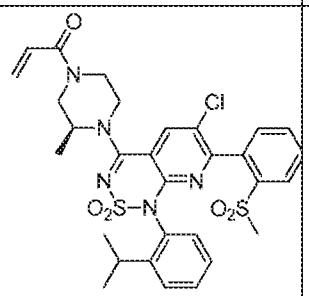
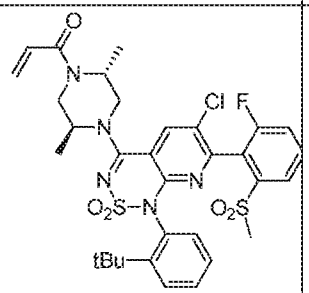
[0167] Step 5: *tert*-Butyl (2*R*,5*S*)-4-(1-(2-(tert-butyl)phenyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. A re-sealable vial was charged with *tert*-butyl (2*R*,5*S*)-4-(1-(2-(*tert*-butyl)phenyl)-6,7-dichloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.17 g, 0.29 mmol), (2-fluorophenyl)boranediol (48 mg, 0.34 mmol, Combi-Blocks, San Diego, CA, USA), dichloro[1,1'bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (21 mg, 0.030 mmol, Strem, Newburyport, MA, USA), and potassium acetate (140 mg, 1.4 mmol). The vial was evacuated and backfilled with N_2 (3x) followed by addition of 1,4-dioxane (2.3 mL) and water (0.57 mL). The mixture was stirred at 90 °C for 2 h, then was cooled to rt. The crude product was purified by silica gel chromatography (eluent: 20% EtOAc-EtOH (3:1)/heptane) to provide *tert*-butyl (2*R*,5*S*)-4-(1-(2-(*tert*-butyl)phenyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.15 g, 0.23 mmol, 80% yield) as a yellow solid. ^{1}H NMR showed a mix of atropisomers (400 MHz, $CDCl_3$) δ 7.93 - 7.73 (m, 1 H), 7.54 - 7.41 (m, 3 H), 7.41 - 7.25 (m, 2 H), 7.25 (s, 1 H), 7.18 - 7.03 (m, 2 H), 4.72 - 4.14 (m, 2 H), 3.82 (br s, 1 H), 3.76 - 3.49 (m, 2 H), 3.36 - 2.89 (m, 1 H), 1.47 (s, 9 H), 1.43 - 1.26 (m, 6 H), 1.28 - 1.20 (m, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –111.70 (s, 1F), –111.73 (s, 1F); *m/z* (ESI, +ve ion): 656.0 $(M+H)^+$.

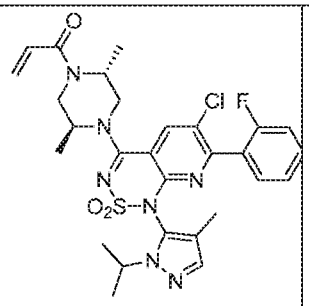
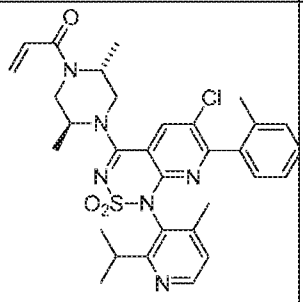
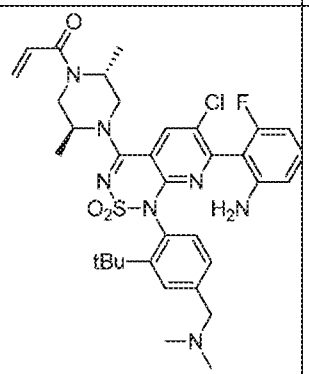
[0168] Step 6: 1-((2*R*,5*S*)-4-(1-(2-(*tert*-Butyl)phenyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one. To a solution of *tert*-butyl (2*R*,5*S*)-4-(1-(2-(*tert*-butyl)phenyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.15 g, 0.23 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.34 mL, 4.6 mmol). The reaction mixture was stirred at rt for 1 h and then was concentrated in vacuo. The crude residue was redissolved in dichloromethane (1 mL). Triethylamine (0.16 mL, 1.1 mmol) was added, followed by dropwise addition of acryloyl chloride (1.1 M in DCM, 0.31 mL, 0.34 mmol). The homogenous solution was stirred at rt for 30 min and then partitioned between EtOAc (20 mL) and sat. $NaHCO_3$ (20 mL). The organic layer was separated, washed with $NaHCO_3$ (2x), and brine (1x), then dried over $MgSO_4$. The crude mixture was adsorbed onto silica gel and purified by silica gel chromatography (eluent: 0–60% EtOAc-EtOH (3:1)/heptane) to provide 1-((2*R*,5*S*)-4-(1-(2-(*tert*-butyl)phenyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one (0.10 g, 0.17 mmol, 74% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1 H), 7.92 (s, 1 H), 7.99 - 7.88 (m, 1 H), 7.55 (dd, *J* = 1.3, 8.0 Hz, 1 H), 7.48 - 7.28 (m, 3 H), 7.20 - 7.07 (m, 2 H), 6.74 - 6.32 (m, 2 H), 5.85 - 5.78 (m, 1 H), 4.66 - 4.13 (m, 3 H), 3.82 - 3.47 (m, 2 H), 3.07 (br d, *J* = 11.4 Hz, 1 H), 1.66 - 1.46 (m, 6 H), 1.28 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –111.65 (s, 1F); *m/z* (ESI, +ve ion): 610.0 $(M+H)^+$.

[0169] Table 1: Compounds 1-2 to 1-13 were prepared following the procedure described in Method 1, Steps 1-6, above as follows:

Ex. #	Chemical Structure	Name	Reagents
1-2		1-((3*S*)-4-(6-chloro-7-(2-fluoro-6-hydroxyphenyl)-2,2-dioxido-1-(2-(2-propanyl)phenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 2-isopropylaniline **Step 3**: LiH/THF 70 °C **Step 4-2**: (S)-*tert*-butyl 3-methylpiperazine-1-carboxylate (CNH Technologies, Inc., Woburn, MA, USA) **Step 5**: (2-fluoro-6-hydroxyphenyl)boronic acid (Combi-blocks Inc., San Diego, CA, USA)

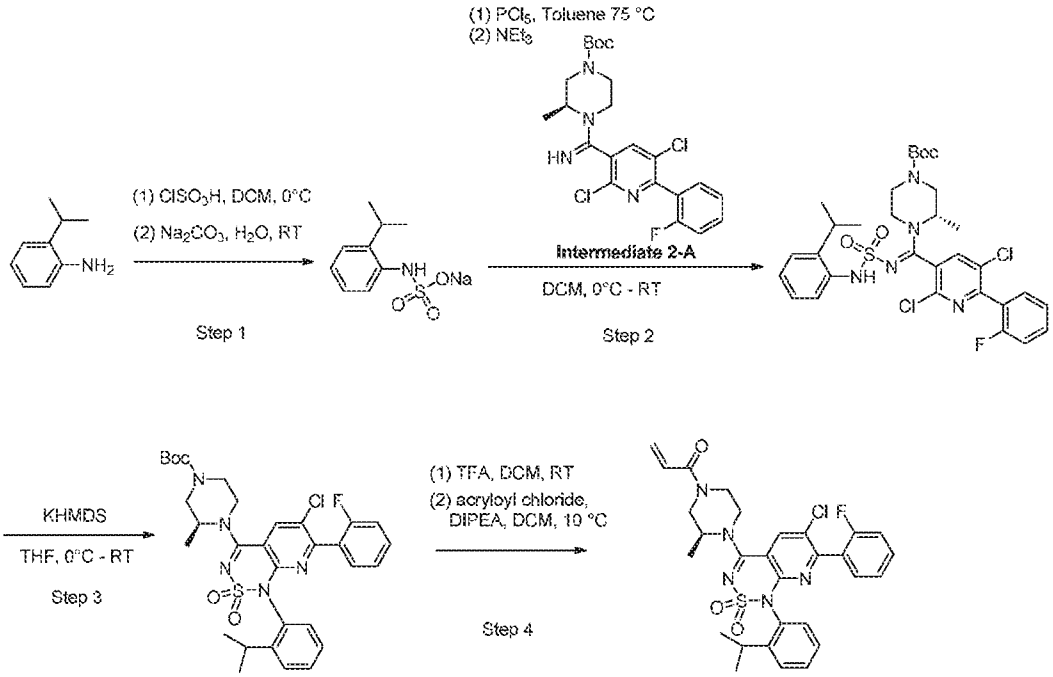
1-3		1-((3*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-2,2-dioxido-1-(2-(2-propanyl)phenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 2-isopropylaniline **Step 3**: LiH/THF 70 °C **Step 4-2**: (S)-*tert*-butyl 3-methylpiperazine-1-carboxylate (CNH Technologies, Inc., Woburn, MA, USA) **Step 5**: (2-amino-6-fluorophenyl)boronic acid pinacol ester (CombiPhos Catalysts Inc., Princeton, NJ, USA), $Pd(PPh_3)_4$, K_2CO_3
1-4		1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluoro-6-hydroxyphenyl)-2,2-dioxido-1-(2-(2-propanyl)phenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 2-isopropylaniline **Step 3**: LiH/THF 70 °C **Step 5**: (2-fluoro-6-hydroxyphenyl)boronic acid (Combi-blocks Inc., San Diego, CA, USA)
1-5		1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluoro-6-hydroxyphenyl)-2,2-dioxido-1-(4-(2-propanyl)-1,3-thiazol-5-yl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 4-isopropylthiazol-5-amine (Enamine, Monmouth Jct., NJ, USA) **Step 3**: LiH/THF 70 °C **Step 5**: (2-fluoro-6-hydroxyphenyl)boronic acid (Combi-blocks Inc., San Diego, CA, USA)
1-6		1-((2*R*,5*S*)-4-(6-chloro-1-(2,6-diethylphenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 2,6-diethylanaline **Step 5**: (2-amino-6-fluorophenyl)boronic acid pinacol ester (Combi-Phos Catalysis Inc., Princeton, NJ, USA)

1-7		1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(2,6-diethylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 2,6-diethylanaline **Step 5**: (2-amino-6-fluorophenyl)boronic acid pinacol ester (Combi-Phos Catalysis Inc., Princeton, NJ, USA)
1-8		1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-1-(2-(*tert*-butyl)phenyl)-6-chloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one	**Step 1**: 2-(1,1-dimethylethyl)benzenamine (Combi-Blocks, San Diego, CA, USA) **Step 5**: (2-amino-6-fluorophenyl)boronic acid pinacol ester (Combi-Phos Catalysis Inc., Princeton, NJ, USA)
1-9		1-((3*S*)-4-(6-chloro-7-(2-(methylsulfonyl)phenyl)-2,2-dioxido-1-(2-(2-propanyl)phenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 2-isopropylaniline **Step 3**: LiH/THF 70 °C **Step 4-2**: (S)-*tert*-butyl 3-methylpiperazine-1-carboxylate (CNH Technologies, Inc., Woburn, MA, USA) **Step 5**: (2-(methylsulfonyl)phenyl)boronic acid (Combi-blocks Inc., San Diego, CA, USA)
1-10		1-((2*R*,5*S*)-4-(6-chloro-1-(2-(2-methyl-2-propanyl)phenyl)-7-(2-(methylsulfonyl)phenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 2-(1,1-dimethylethyl)benzenamine (Combi-Blocks, San Diego, CA, USA) **Step 5**: (2-methylsulfonylphenyl)boronic acid (Combi-blocks Inc., San Diego, CA, USA)

1-11		1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(4-methyl-1-(2-propanyl)-1*H*-pyrazol-5-yl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 1-isopropyl-4-methyl-1*H*-pyrazol-5-amine (Enamine Ltd., Monmouth, NJ, USA)
1-12		1-((2*R*,5*S*)-4-(6-chloro-7-(2-methylphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**Step 1**: 2-isopropyl-4-methylpyridin-3-amine **(Intermediate 1-A)** **Step 5**: *o*-tolylboronic acid
1-13		1-((2*R*,5*S*)-4-(6-chloro-1-(4-((dimethylamino)methyl)-2-(2-methyl-2-propanyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**Step 1:** 2-(*tert*-butyl)-4-((dimethylamino)methyl)aniline **(Intermediate 1-B)** **Step 5**: (2-amino-6-fluorophenyl)boronic acid pinacol ester (CombiPhos Catalysts Inc., Princeton, NJ, USA), $Pd(PPh_3)_4$, K_2CO_3

Method 2

[0170] Example 2-1: (*S*)-1-(4-(6-Chloro-7-(2-fluorophenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one.



[0171] Step 1: Sodium (2-isopropylphenyl)sulfamate. A solution of chlorosulfonic acid (2.0 mL, 30 mmol) in DCM (15 mL) was added dropwise over 30 min to a solution of 2-(methylethyl)phenylamine (13 mL, 90 mmol) in DCM (100 mL) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to rt and was stirred for an additional 2 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in an aqueous solution of sodium carbonate (100 mL, 0.45 M). The resulting mixture was extracted twice with DCM. The aqueous phase was concentrated in vacuo. The residue was suspended in refluxing ethanol (60 mL) and the hot suspension was filtered. The filtrate was concentrated under reduced pressure to give sodium (2-isopropylphenyl)sulfamate as a white solid (6.2 g, 26 mmol, 87% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.46 (dd, J = 8.2, 1.1 Hz, 1 H), 7.07 (dd, J = 7.7, 1.2 Hz, 1 H), 6.98 (t, J = 7.3 Hz, 1 H), 6.77 (t, J = 7.5 Hz, 1 H), 6.34 (s, 1H), 3.06 (spt, J = 6.8 Hz, 1 H), 1.12 (d, J = 6.8 Hz, 6 H).

[0172] Alternative work up for Step 1: After the reaction was complete, the reaction was filtered and the resulting solid was washed with DCM to afford the corresponding sulfamic acid. Both the sodium sulfamate and the sulfamic acid can be used in the next step.

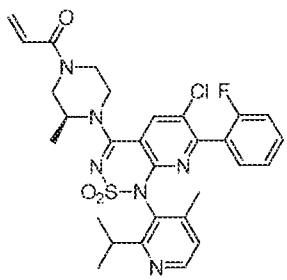
[0173] Step 2: *tert*-Butyl (*S*,*Z*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)((*N*-(2-isopropylphenyl)sulfamoyl)imino)methyl)-3-methylpiperazine-1-carboxylate. Sodium (2-isopropylphenyl)sulfamate (220 mg, 0.50 mmol) was suspended in toluene (2 mL) and phosphorus pentachloride (100 mg, 0.50 mmol) was added. The reaction mixture was heated to 75 °C for 1 h then was cooled to rt and filtered. The filtrate was concentrated in vacuo. The light-yellow oil was taken up in DCM (0.70 mL) and added to a solution of *tert*-butyl (*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(imino)methyl)-3-methylpiperazine-1-carboxylate (Intermediate 2-A, 230 mg, 0.50 mmol) and triethylamine (0.70 mL, 5.0 mmol) in DCM (0.70 mL) at 0 °C. The reaction was warmed to rt and stirred overnight. The reaction mixture was diluted with water and EtOAc and the aq. phase was neutralized with 1 N aq. HCl. The organic phase was separated and dried over $MgSO_4$. The residue was adsorbed onto silica gel and purified by silica gel chromatography (eluent: 10–50% EtOAc/heptane) to provide *tert*-butyl (*S*,*Z*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)((*N*-(2-isopropylphenyl)sulfamoyl)imino)methyl)-3-methylpiperazine-1-carboxylate (200 mg, 0.30 mmol, 60%) as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 - 1.10 (m, 6 H), 1.24 - 1.32 (m, 3 H), 1.42 (br d, J = 2.3 Hz, 9 H), 2.78 - 3.29 (m, 4 H), 3.38 - 4.18 (m, 4 H), 4.52 - 4.98 (m, 1 H), 6.83 - 7.08 (m, 1 H), 7.17 - 7.31 (m, 3 H), 7.32 - 7.42 (m, 3 H), 7.42 - 7.49 (m, 1 H), 7.56 - 7.64 (m, 1 H), 8.73 - 8.80 (m, 1 H); *m/z* (ESI, +ve ion): 664.0 $(M+H)^+$.

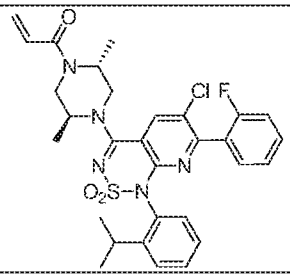
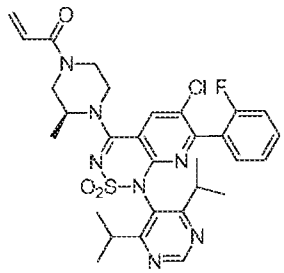
[0174] Step 3: *tert*-Butyl (*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate. A solution of KHMDS (1.0 M in THF, 0.27 mL, 0.27 mmol) was added dropwise to a solution of *tert*-butyl (*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)((*N*-(2-isopropylphenyl) sulfamoyl) imino)methyl)-3-methylpiperazine-1-carboxylate (140 mg, 0.21 mmol) in THF (4.5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 12 h. The reaction mixture was diluted with sat. ammonium chloride and EtOAc. The aqueous layer was extracted twice with EtOAc and the combined organic layers were dried over $MgSO_4$. The filtrate was adsorbed onto silica gel and purified by silica gel chromatography (eluent: 10–50% EtOAc/heptane) to provide *tert*-butyl (*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(2-isopropylphenyl)-

2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate (64 mg, 0.10 mmol, 48% yield) as a white solid. *m/z* (ESI, +ve ion): 628.0 $(M+H)^+$.

[0175] Step 4: (*S*)-1-(4-(6-Chloro-7-(2-fluorophenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one. TFA (0.24 mL, 3.1 mmol) was added to a solution of *tert*-butyl (*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate (64 mg, 0.10 mmol) in DCM (2.0 mL) at rt. The reaction mixture was allowed to stir for 30 min and subsequently concentrated in vacuo. The residue was dissolved in DCM (1.0 mL), the solution was cooled to 10 °C and DIPEA (0.090 mL, 0.51 mmol) was added followed by acryloyl chloride (8.3 µl, 0.10 mmol). After 5 min, the reaction was diluted with DCM (10 mL), sat. $NaHCO_3$ (5.0 mL) and brine (2.0 mL). The organic phase was separated and dried over $MgSO_4$. The solution was filtered and the crude material was absorbed onto silica gel and purified by silica gel chromatography (eluent: 10–100% EtOAc/heptane) to provide (*S*)-1-(4-(6-chloro-7-(2-fluorophenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one (44 mg, 0.076 mmol, 74% yield) as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.98 - 1.08 (m, 3 H), 1.12 - 1.18 (m, 3 H), 1.22 - 1.36 (m, 3 H), 1.31 - 1.36 (m, 1 H), 2.98 - 3.09 (m, 1 H), 3.14 - 3.20 (m, 1 H), 3.56 - 4.76 (m, 5 H), 5.72 - 5.86 (m, 1 H), 6.14 - 6.29 (m, 1 H), 6.75 - 6.94 (m, 1 H),7.22 - 7.48 (m, 7 H), 7.49 - 7.56 (m, 1 H), 8.45 - 8.61 (m, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm –113.5 (s, 1F); *m/z* (ESI, +ve ion): 581.9 $(M+H)^+$.

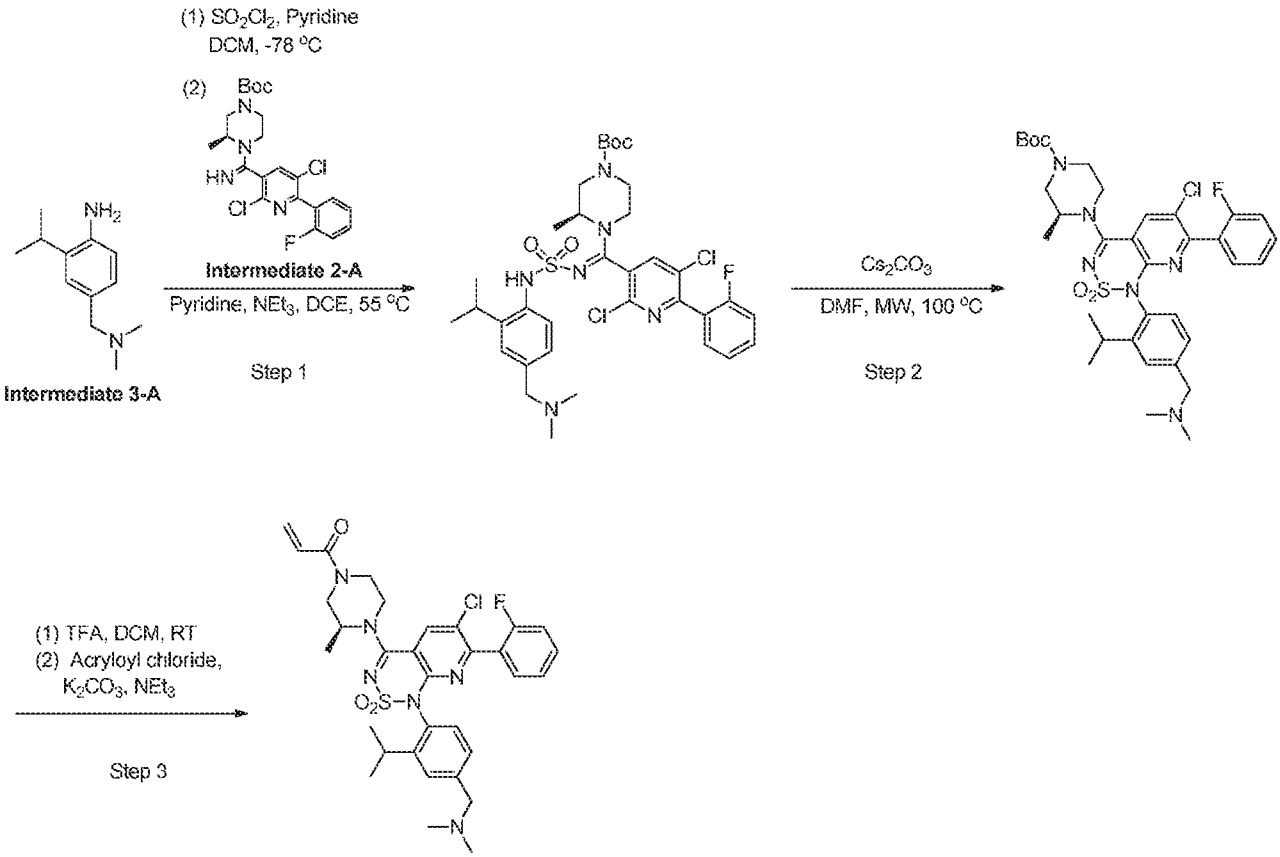
[0176] Table 2: Compounds 2-2 to 2-4 were prepared following the procedure described in Method 3, Steps 1-3, above as follows:

Ex. #	Chemical Structure	Name	Reagents
2-2		(*S*)-1-(4-(6-chloro-7-(2-fluorophenyl)-1-(2-isopropyl-4-methylpyridin-3-yl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one	**Step 1:** 2-isopropyl-4-methylpyridin-3-amine (**Intermediate 1-A**). Alternative work up used.

2-3		1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one	**Step 2:** (2*R*,5*S*)-*tert*-butyl 4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(imino)methyl)-2,5-dimethylpiperazine-1-carboxylate (**Intermediate 2-B**)
2-4		(*S*)-1-(4-(6-chloro-1-(4,6-diisopropylpyrimidin-5-yl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one	**Step 1:** 4,6-diisopropylpyrimidin-5-amine (**Intermediate 2-C**). Alternative work up used.

Method 3

[0177] Example 3-1: 1-((3*S*)-4-(6-Chloro-1-(4-((dimethylamino)methyl)-2-(2-propanyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methyl-1-piperazinyl)-2-propen-1-one



[0178] Step 1: *tert*-Butyl (*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)((*N*-(4-((dimethylamino)methyl)-2-isopropylphenyl)sulfamoyl)imino)methyl)-3-methylpiperazine-1-carboxylate. To a solution of 4-((dimethylamino)methyl)-2-isopropylaniline (Intermediate 3-A, 0.50 g, 2.6 mmol) and pyridine (0.22 mL, 2.6 mmol) in DCM (5.0 mL) at –78 °C under N_2 was added sulfuryl chloride (1.0 M in DCM, 2.6 mL, 2.6 mmol). After addition, the reaction was stirred at 0 °C for 3.5 h. Additional portions of sulfuryl chloride (1.0 M in DCM, 2.6 mL, 2.6 mmol) and pyridine (0.11 mL, 1.3 mmol) were added. The reaction was stirred at 0 °C for 5 min before adding a solution of *tert*-butyl (*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(imino)methyl)-3-methylpiperazine-1-carboxylate (Intermediate 2-A, 1.2 g, 2.6 mmol), pyridine (0.22 mL, 2.6 mmol), and triethylamine (1.8 mL, 13 mmol) in DCE (5.0 mL). The resulting mixture was stirred

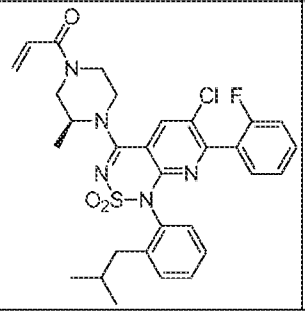
at 55 °C for 16 h. The mixture was diluted with sat. $NaHCO_3$ (30 mL) and extracted with EtOAc (2 x 80 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–15% 2.0 M NH_3 in MeOH/DCM) to provide *tert*-butyl (*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)((*N*-(4-((dimethylamino)methyl)-2-isopropylphenyl)sulfamoyl)imino)methyl)-3-methylpiperazine-1-carboxylate (170 mg, 9% yield) as a yellow solid. *m/z* (ESI, +ve ion): 721.0 $(M+H)^+$.

[0179] Step 2: *tert*-Butyl (*S*)-4-(6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylphenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate. To a solution of *tert*-butyl (*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)((N-(4-((dimethylamino)methyl)-2-isopropylphenyl)sulfamoyl)imino)methyl)-3-methylpiperazine-1-carboxylate (160 mg, 0.22 mmol) in DMF (4.0 mL) was added cesium carbonate (360 mg, 1.1 mmol). The reaction was heated to 100 °C via microwave irradiation for 1 h. The reaction was diluted with sat. $NaHCO_3$ (20 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–20% 2.0M NH_3 in MeOH/DCM) to provide *tert*-butyl (*S*)-4-(6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylphenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate (89 mg, 59% yield) as a yellow oil. *m/z* (ESI, +ve ion): 684.8 $(M+H)^+$.

[0180] Step 3: (*S*)-1-(4-(6-Chloro-1-(4-((dimethylamino)methyl)-2-isopropylphenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one. To a solution of *tert*-butyl (*S*)-4-(6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylphenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate (89 mg, 0.13 mmol) in DCM (1.0 mL) was added trifluoroacetic acid (0.19 mL, 2.6 mmol). After the addition, the reaction was stirred at rt for 1 h then concentrated in vacuo. The crude residue was dissolved in DCM (2.0 mL) and cooled to 0 °C. Potassium carbonate (0.38 g, 2.6 mmol) and triethylamine (0.18 mL, 1.3 mmol) were added, followed by a solution of acryloyl chloride (11 µl, 0.13 mmol) in DCM (0.20 mL). The reaction was stirred at 0 °C for 20 min. The reaction was quenched with sat. $NaHCO_3$ (5.0 mL) and extracted with EtOAc (2 x 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–10% 2.0 M NH_3 in MeOH/DCM)

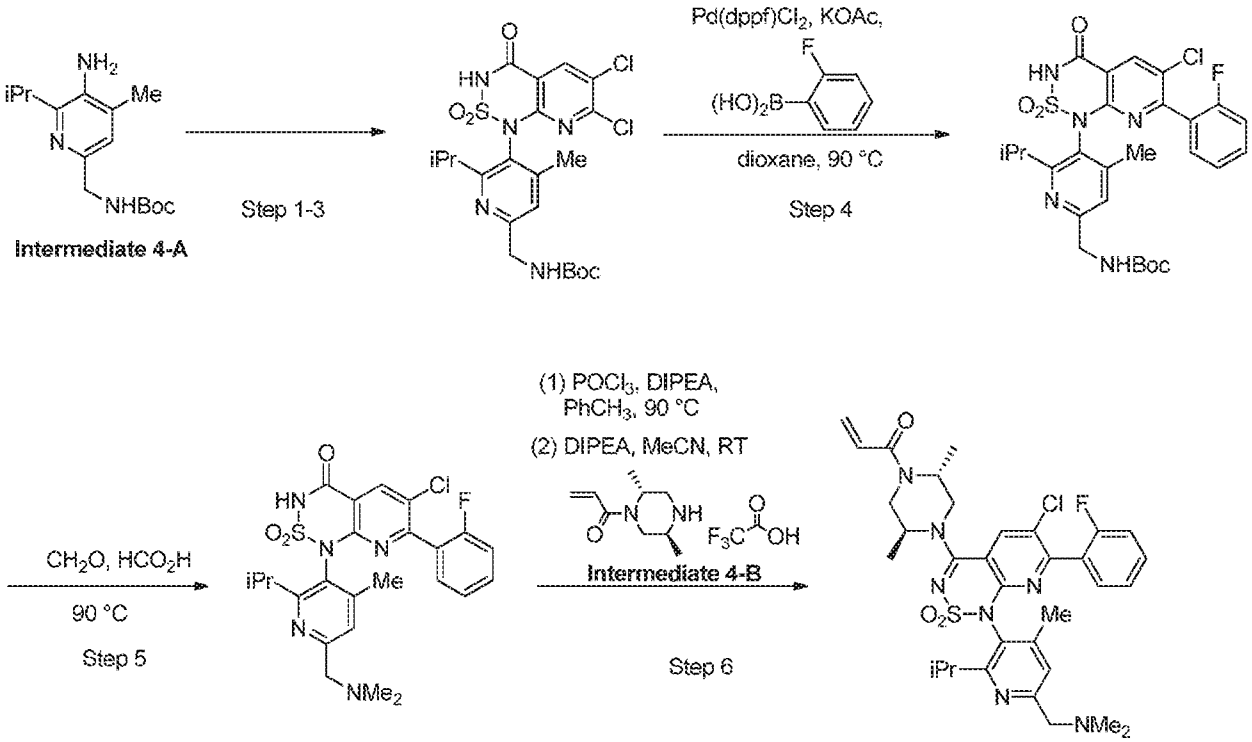
to provide (*S*)-1-(4-(6-chloro-1-(4-((dimethylamino)methyl)-2-isopropylphenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one (32 mg, 39% yield) as a light-yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.45 - 8.58 (m, 1 H), 7.48 - 7.58 (m, 1 H), 7.14 - 7.38 (m, 6 H), 6.74 - 6.92 (m, 1 H), 6.20 (br d, J = 17.8 Hz, 1 H), 5.74 - 5.79 (m, 1H), 4.54 - 4.81 (m, 1 H), 3.95 - 4.49 (m, 3 H), 3.44 - 3.88 (m, 2 H), 3.39 (s, 2 H), 3.28 (br s, 1 H), 2.97 - 3.08 (m, 1 H), 2.14 (s, 6 H), 1.21 - 1.37 (m, 3 H), 1.15 (d, J = 6.8 Hz, 3 H), 1.02 (dd, J = 10.1, 6.9 Hz, 3 H); ^{19}F NMR (DMSO-d_6): δ –113.30 (s, 1F); *m/z* (ESI, +ve ion): 638.8 $(M+H)^+$.

[0181] Table 3: Compound 3-2 was prepared following the procedure described in Method 3, Steps 1-3, above as follows:

Ex. #	Chemical Structure	Name	Reagents
3-2		1-((3*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(2-(2-methylpropyl)phenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methyl-1-piperazinyl)-2-propen-1-one	**Step 1:** 2-isobutylaniline (Enamine Ltd., Monmouth, NJ, USA)

SECTION 2 – INDIVIDUAL EXAMPLES

[0182] Example 4: 1-((2*R*,5*S*)-4-(6-Chloro-1-(6-((dimethylamino)methyl)-4-methyl-2-(2-propanyl)-3-pyridinyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one



[0183] Steps 1-3: *tert*-Butyl ((5-(6,7-dichloro-2,2-dioxido-4-oxo-3,4-dihydro-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-1-yl)-6-isopropyl-4-methylpyridin-2-yl)methyl)carbamate. The title compound was prepared using the procedure described in Method 1, Steps 1-3 with the following modification: Step 1 was performed with *tert*-butyl ((5-amino-6-isopropyl-4-methylpyridin-2-yl)methyl)carbamate (Intermediate 4-A). *m/z* (ESI, +ve ion): 530.2 $(M+H)^+$.

[0184] Step 4: *tert*-Butyl ((5-(6-chloro-7-(2-fluorophenyl)-2,2-dioxido-4-oxo-3,4-dihydro-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-1-yl)-6-isopropyl-4-methylpyridin-2-yl)methyl) carbamate. A vial was charged with *tert*-butyl ((5-(6,7-dichloro-2,2-dioxido-4-oxo-3,4-dihydro-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-1-yl)-6-isopropyl-4-methylpyridin-2-yl)methyl)carbamate (0.94 g, 1.8 mmol), (2-fluorophenyl)boranediol (0.37 g, 2.7 mmol, Combi-Blocks, San Diego, CA, USA), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.13 g, 0.18 mmol), and potassium acetate (0.87 g, 8.8 mmol). The vial was evacuated and

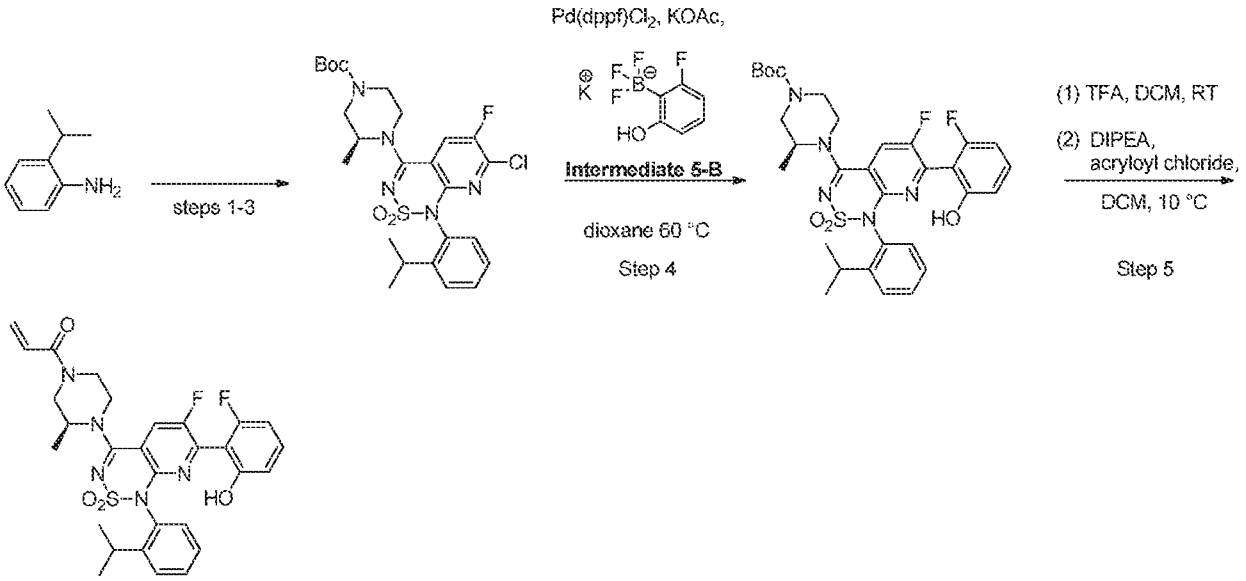
backfilled with N_2 (3x). 1,4-dioxane (14 mL) and water (3.5 mL) were added. The homogenous solution was stirred at 90 °C for 1 h, cooled to rt, and adsorbed onto silica gel. The crude product was purified by silica gel chromatography (eluent: 0–10% (90:9:1 DCM:MeOH:NH_4OH)/ DCM) to provide *tert*-butyl ((5-(6-chloro-7-(2-fluorophenyl)-2,2-dioxido-4-oxo-3,4-dihydro-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-1-yl)-6-isopropyl-4-methylpyridin-2-yl)methyl)carbamate (0.65 g, 1.1 mmol, 62% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1 H), 7.57 - 7.35 (m, 1 H), 7.30 - 7.15 (m, 3 H), 6.94 (br s, 2 H), 4.16 (br d, J = 5.8 Hz, 2 H), 3.25 - 3.06 (m, 1 H), 2.15 - 2.06 (m, 3 H), 1.49 - 1.34 (m, 9 H), 1.21 - 1.07 (m, 6 H), 0.83 (br d, J = 6.6 Hz, 3 H); ^{19}F NMR (376 MHz, DMSO-d_6): δ –115.00 (s, 1F); *m/z* (ESI, +ve ion) 590.2 $(M+H)^+$.

[0185] Step 5: 6-Chloro-1-(6-((dimethylamino)methyl)-2-isopropyl-4-methylpyridin-3-yl)-7-(2-fluorophenyl)-1*H*-pyrido[2,3-c][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide. A solution of *tert*-butyl ((5-(6-chloro-7-(2-fluorophenyl)-2,2-dioxido-4-oxo-3,4-dihydro-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-1-yl)-6-isopropyl-4-methylpyridin-2-yl)methyl)carbamate (0.55 g, 0.93 mmol), formaldehyde (34 wt %, 0.82 mL, 9.3 mmol), and formic acid (0.87 mL, 23.2 mmol) was heated to 90 °C for 1 h. The crude mixture was adsorbed onto silica gel and purified by silica gel chromatography (eluent: 90:9:1 DCM:MeOH:NH_4OH) to provide 6-chloro-1-(6-((dimethylamino)methyl)-2-isopropyl-4-methylpyridin-3-yl)-7-(2-fluorophenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide (0.16 g, 0.30 mmol, 33% yield) as a tan solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.34 (s, 1 H), 7.45 (m, 1 H), 7.19 - 7.30 (m, 4 H), 4.26 (br s, 2 H), 3.29 - 3.32 (m, 1 H), 2.76 (m, 6 H), 2.08 (s, 3 H), 1.21 (d, J = 6.6 Hz, 3 H), 0.89 ppm (d, J = 6.6 Hz, 3 H); *m/z* (ESI, +ve ion): 518.2 $(M+H)^+$.

[0186] Step 6: 1-((2*R*,5*S*)-4-(6-Chloro-1-(6-((dimethylamino)methyl)-2-isopropyl-4-methylpyridin-3-yl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one. To a solution of 6-chloro-1-(6-((dimethylamino)methyl)-2-isopropyl-4-methylpyridin-3-yl)-7-(2-fluorophenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide (0.16 g, 0.30 mmol) and DIPEA (0.53 mL, 3.0 mmol) in toluene (1.5 mL) was added phosphorous oxychloride (0.14 mL, 1.5 mmol) dropwise. The mixture was heated to 70 °C for 10 min. The reaction mixture was cooled to 0 °C and a solution of 1-((2*R*,5*S*)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one TFA salt (Intermediate 4-B, 0.40 g, 0.60 mmol) and DIPEA (0.21 mL, 1.2 mmol) in acetonitrile (1.5 mL) was added in one portion. The reaction mixture was warmed to rt and stirred for 1 h. The mixture was poured into cold sat.

$NaHCO_3$ solution and stirred vigorously for 10 min, then extracted with EtOAc and the aqueous phase was extracted with additional EtOAc (2x). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by silica gel chromatography (eluent: 10–20% MeOH/DCM) to afford 1-((2*R*,5*S*)-4-(6-chloro-1-(6-((dimethylamino)methyl)-2-isopropyl-4-methylpyridin-3-yl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one (0.09 g, 0.07 mmol, 23% yield) as a yellow solid. ^{1}H NMR indicated atropisomers (400 MHz, $CDCl_3$): □ 8.04 - 7.96 (m, 1 H), 7.55 - 7.40 (m, 1 H), 7.38 - 7.31 (m, 1 H), 7.26 - 7.12 (m, 3 H), 6.68 - 6.52 (m, 1 H), 6.48 - 6.37 (m, 1 H), 5.83 (br dd, J = 3.2, 10.1 Hz, 1 H), 5.11 - 4.27 (m, 3 H), 4.09 - 3.36 (m, 3 H), 3.02 (m, 1 H), 2.48 - 2.28 (m, 6 H), 1.53 - 1.44 (m, 3 H), 1.37 - 1.20 (m, 6 H); *m/z* (ESI, +ve ion) 668.2 $(M+H)^+$.

[0187] Example 5: 1-((3*S*)-4-(6-Fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one.



[0188] Steps 1-3: *tert*-Butyl (*S*)-4-(7-chloro-6-fluoro-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate. The title compound was prepared using the procedure described in Method 2, steps 1-3 with the following modification: Step 2 was performed with *tert*-butyl (*S*)-4-((2,6-dichloro-5-fluoropyridin-3-

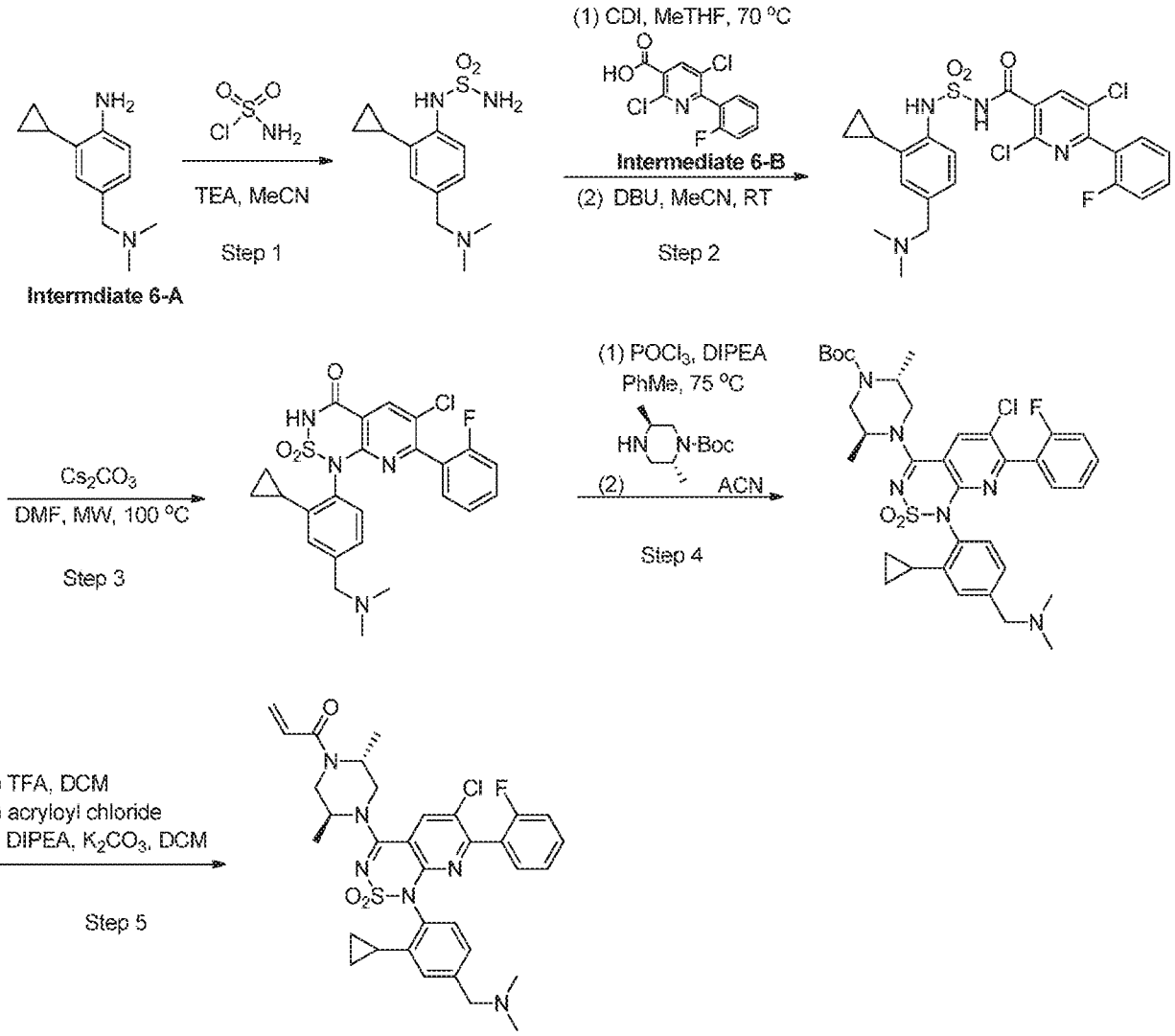
yl)(imino)methyl)-3-methylpiperazine-1-carboxylate (Intermediate 5-A). *m/z* (ESI, +ve ion): 495.6 $(M–H_2C=C(CH_3)_2)^+$.

[0189] Step 4: *tert*-Butyl (3*S*)-4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate. A vial was charged with *tert*-butyl (*S*)-4-(7-chloro-6-fluoro-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate (52 mg, 0.090 mmol), potassium trifluoro(2-fluoro-6-hydroxyphenyl)borate (Intermediate 5-B, 27 mg, 0.12 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (6.9 mg, 9.4 μmol), and potassium acetate (37 mg, 0.38 mmol). The vial was evacuated and backfilled with N_2. 1,4-Dioxane (280 μL) and water (94 μL) were added to the vial and the reaction mixture was heated to 60 °C for 2 h and for one additional hour at 80 °C. The reaction mixture was cooled to rt, diluted with EtOAc, and absorbed onto silica gel. Purification by silica gel chromatography (eluent: 5–50% EtOAc/heptane) provided *tert*-butyl (3*S*)-4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate (27 mg, 0.043 mmol, 46 % yield) as a light-yellow solid. *m/z* (ESI, +ve ion): 428.1 $(M+H)^+$.

[0190] Step 5: 1-((3*S*)-4-(6-Fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one. TFA (0.10 mL, 1.3 mmol) was added to a solution of *tert*-butyl (3*S*)-4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazine-1-carboxylate (27 mg, 0.040 mmol) in DCM (2.0 mL) at rt. After 2 h, the reaction mixture was concentrated in vacuo. The crude material was dissolved in toluene (2.0 mL) and the solvent was removed in vacuo. The residue was taken up in DCM (2.0 mL) and the solution as was cooled to 10 °C, followed by addition of DIPEA (0.020 mL, 0.090 mmol) and acryloyl chloride (1.1 M in DCM, 0.040 mL, 0.040 mmol). After 10 min, the reaction mixture was diluted with DCM, sat. $NaHCO_3$ (5.0 mL) and brine. The organic phase was separated and dried over $MgSO_4$. The crude material was purified by silica gel chromatography (eluent: 10–100% EtOAc/heptane) to provide 1-((3*S*)-4-(6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(2-isopropylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one (19 mg, 0.030 mmol, 76% yield) as a light-yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 - 1.34 (m, 9 H), 2.92 - 3.09 (m, 1 H), 3.51 - 3.80 (m, 2 H), 3.95 -

4.24 (m, 2 H), 4.26 - 4.36 (m, 1 H), 4.38 - 4.54 (m, 1 H), 4.56 - 4.74 (m, 1 H), 5.67 - 5.87 (m, 1 H), 6.10 - 6.30 (m, 1 H), 6.66 - 6.78 (m, 2 H), 6.78 - 6.94 (m, 1 H), 7.22 - 7.34 (m, 3 H), 7.37 - 7.49 (m, 2 H), 8.22 - 8.50 (m, 1 H), 10.12 - 10.38 (m, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm –115.1 (m, 1F), –127.7 (m, 1 F); *m/z* (ESI, +ve ion): 582.0 $(M+H)^+$.

[0191] Example 6: 1-((2*R*,5*S*)-4-(6-Chloro-1-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one



[0192] Step 1: *N*-(2-Cyclopropyl-4-((dimethylamino)methyl)phenyl)sulfuric diamide. To a solution of sulfamoyl chloride (2.7 g, 23 mmol) in acetonitrile (50 mL) at 0 °C under N_2 was added a solution of 2-cyclopropyl-4-((dimethylamino)methyl)aniline (**Intermediate 6-A** , 3.7 g, 19

mmol) in acetonitrile (25 mL) dropwise, followed by triethylamine (13 mL, 96 mmol) dropwise. The mixture was stirred at 0 °C for 5 min and at rt for 16 h. The residue was purified by silica gel chromatography (eluent: 0–15% 2.0 M NH_3 in MeOH/DCM) to provide *N*-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)sulfuric diamide (4.5 g, 86% yield) as a light-yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm 8.32 (br s, 1H), 7.31 (d, J = 8.1 Hz, 1 H), 7.05 (br d, J = 8.5 Hz, 1 H), 6.77 - 6.92 (m, 3 H), 3.31 - 3.40 (m, 2 H), 2.08 - 2.24 (m, 7 H), 0.92 (dd, J = 8.5, 1.9 Hz, 2 H), 0.52 - 0.61 (m, 2 H); *m/z* (ESI, +ve ion): 270.0 $(M+H)^+$.

[0193] Step 2: 2,5-Dichloro-*N*-(*N*-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)sulfamoyl)-6-(2-fluorophenyl)nicotinamide. A solution of 2,5-dichloro-6-(2-fluorophenyl)nicotinic acid (Intermediate 6-B, 2.6 g, 8.9 mmol) and 1,1'-carbonyldiimidazole (1.4 g, 8.9 mmol) in 2-methyltetrahydrofuran (26 mL) was heated to 70 °C and stirred for 2 h. The reaction was cooled to rt and a solution of *N*-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)sulfuric diamide (2.0 g, 7.4 mmol) in acetonitrile (30 mL) and 2-methyltetrahydrofuran (20 mL) was added, followed by 1,8-diazabicyclo-[5.4.0]undec-7-ene (1.3 mL, 8.9 mmol). The reaction mixture was stirred at rt for 40 min. The mixture was concentrated in vacuo and the crude material was purified by silica gel chromatography (eluent: 0–15% 2.0 M NH_3 in MeOH/DCM) to provide 2,5-dichloro-*N*-(*N*-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)sulfamoyl)-6-(2-fluorophenyl)nicotinamide (3.4 g, 84% yield) as a light-yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm 8.00 (s, 1 H), 7.88 (s, 1 H), 7.53 - 7.60 (m, 2 H), 7.48 (td, J = 7.6, 1.7 Hz, 1 H), 7.30 - 7.39 (m, 2 H), 7.13 (br d, J = 8.1 Hz, 1 H), 7.05 (br s, 1 H), 3.22 - 3.30 (m, 2 H), 2.51 (br s, 6 H), 1.93 - 2.03 (m, 1 H), 0.87 - 1.01 (m, 2H), 0.53 - 0.63 (m, 2H); *m/z* (ESI, +ve ion): 537.0 $(M+H)^+$.

[0194] Step 3: 6-Chloro-1-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)-7-(2-fluorophenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide. A solution of 2,5-dichloro-*N*-(*N*-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)sulfamoyl)-6-(2-fluorophenyl)nicotinamide (3.4 g, 6.3 mmol) in DMF (80 mL) was divided into 4 microwave vials. To each vial was added cesium carbonate (2.6 g, 7.8 mmol). The reactions were heated to 100 °C via microwave irradiation for 2 h. Additional portions of cesium carbonate (2.6 g, 7.8 mmol) were added to each reaction and heated to 100°C for an additional 2 h via microwave irradiation. The reactions were combined and partitioned between EtOAc (700 mL), H_2O (30 mL), and sat. Na_2CO_3 (300 mL). The aqueous phase was extracted with additional EtOAc (1 x 400 mL). The organic

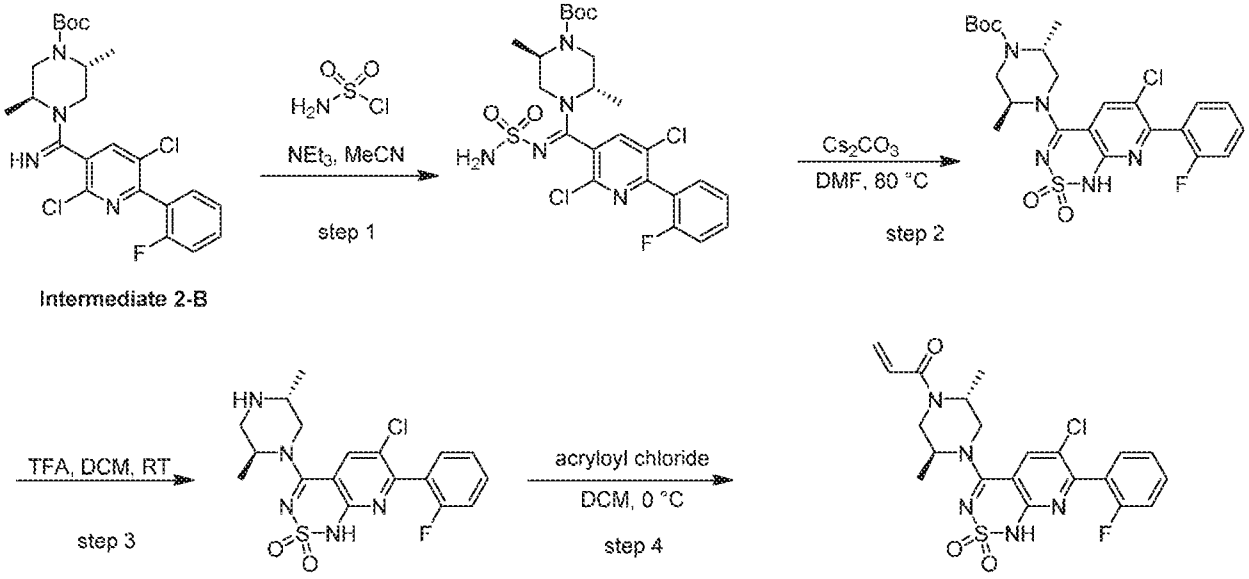
phases were combined, washed with sat. Na_2CO_3 (3 x 300 mL), and dried over Na_2SO_4. The residue was purified by silica gel chromatography (eluent: 0–25% 2.0 M NH_3 in MeOH/DCM) to provide 6-chloro-1-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)-7-(2-fluorophenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide (2.5 g, 80% yield) as light-yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm 9.43 (br s, 1 H), 8.28 (s, 1 H), 7.37 - 7.50 (m, 2 H), 7.18 - 7.30 (m, 4 H), 7.04 (s, 1 H), 4.01 - 4.19 (m, 2 H), 2.65 (br s, 6 H), 1.77 - 1.89 (m, 1 H), 0.65 - 0.83 (m, 3 H), 0.29 - 0.40 (m, 1 H); *m/z* (ESI, +ve ion): 501.0 $(M+H)^+$.

[0195] Step 4: *tert*-Butyl (2*R*,5*S*)-4-(6-chloro-1-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. To a solution of 6-chloro-1-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)-7-(2-fluorophenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide (2.5 g, 5.0 mmol) in toluene (100 mL) was added DIPEA (8.7 mL, 50 mmol). The mixture was cooled to 0 °C and phosphorus oxychloride (2.3 mL, 25 mmol) was added dropwise. After addition, the mixture was stirred at 75 °C for 10 min then cooled to rt. A solution of (2*R*,5*S*)-*tert*-butyl 2,5-dimethylpiperazine-1-carboxylate (2.1 g, 9.9 mmol, eNovation Chemicals LLC, Bridgewater, NJ, USA) in acetonitrile (40 mL) was added. The resulting mixture was stirred at rt for 1 h. Sat. $NaHCO_3$ (100 mL) and EtOAc (200 mL) were added and the mixture was stirred for 5 min. The organic phase was collected and aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–25% 2.0 M NH_3 in MeOH/DCM) to provide *tert*-butyl (2*R*,5*S*)-4-(6-chloro-1-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (3.5 g, 100% yield) as a yellow solid. *m/z* (ESI, +ve ion): 697.1 $(M+H)^+$.

[0196] Step 5: 1-((2*R*,5*S*)-4-(6-Chloro-1-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one. To a solution of *tert*-butyl (2*R*,5*S*)-4-(6-chloro-1-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (3.5 g, 5.0 mmol) in DCM (15 mL) was added TFA (7.4 mL, 100 mmol). The resulting mixture was stirred at rt for 30 min, then concentrated in vacuo and the resulting residue was

dissolved in DCM (45 mL). The reaction was cooled to 0 °C and potassium carbonate (10 g, 75 mmol) was added followed by DIPEA (8.7 mL, 50 mmol). The reaction was stirred at 0 °C for 5 min before adding a solution of acryloyl chloride (0.40 mL, 5.0 mmol) in DCM (5.0 mL) dropwise. After stirring for 5 mins, the reaction was diluted with water (30 mL) and sat. $NaHCO_3$ (50 mL). The reaction mixture was stirred at rt for 2 min and the organic layer was collected. The aqueous layer was extracted with EtOAc (1 x 50 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–15% 2.0 M NH_3 in MeOH/DCM) to provide 1-((2*R*,5*S*)-4-(6-chloro-1-(2-cyclopropyl-4-((dimethylamino)methyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one (1.6 g, 50% yield) as a light-yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm 8.28-8.69 (m, 1H), 7.49 - 7.60 (m, 1 H), 7.08 - 7.44 (m, 5 H), 6.95 (d, J = 1.2 Hz, 1 H), 6.68 - 6.87 (m, 1 H), 6.18 (br d, J = 16.6 Hz, 1H), 5.75 (dt, J = 10.4, 2.3 Hz, 1 H), 4.36 - 4.89 (m, 2 H), 3.99 - 4.27 (m, 1 H), 3.50 - 3.98 (m, 3 H), 3.35 (s, 2 H), 2.12 (s, 6 H), 1.64 - 1.89 (m, 1 H), 0.90 - 1.49 (m, 6 H), 0.22 - 0.80 (m, 4 H); ^{19}F NMR (DMSO-d_6) δ ppm –113.41 - –112.74 (m, 1F); *m/z* (ESI, +ve ion): 651.0 $(M+H)^+$.

[0197] Example 7: 1-((2*R*,5*S*)-4-(6-Chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one



[0198] Step 1: *tert*-Butyl (2*R*,5*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(sulfamoylimino)methyl)-2,5-dimethylpiperazine-1-carboxylate. To a solution of sulfamoyl chloride (230 mg, 2.0 mmol) in acetonitrile (5.0 mL) at 0 °C was added a solution of *tert*-butyl (2*R*,5*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(imino)methyl)-2,5-dimethylpiperazine-1-carboxylate (Intermediate 2-B, 0.80 g, 1.7 mmol) in acetonitrile (4.0 mL), followed by triethylamine (1.2 mL, 8.3 mmol). The resulting suspension was stirred at 0 °C for 30 min, then warmed to rt and stirred for 16 h. The reaction was quenched with water (5.0 mL) and diluted with EtOAc (55 mL) and brine (50 mL). The organic phase was collected, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–5% 2.0 M NH_3 in MeOH/DCM) to provide *tert*-butyl (2*R*,5*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(sulfamoylimino)methyl)-2,5-dimethylpiperazine-1-carboxylate (510 mg, 0.91 mmol, 55% yield) as a yellow solid. *m/z* (ESI, +ve ion): 560.2 $(M+H)^+$.

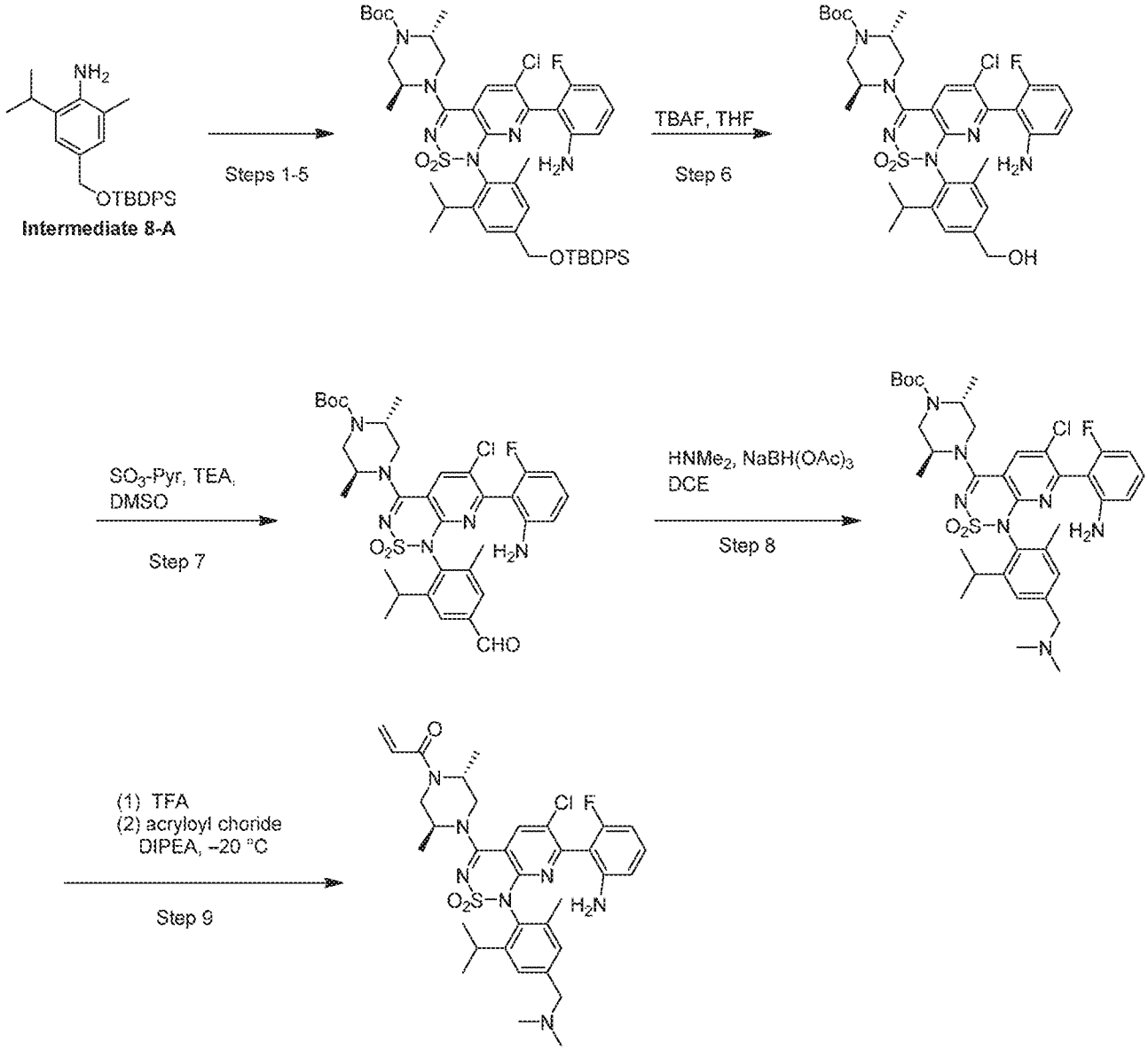
[0199] Step 2: *tert*-Butyl (2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. A mixture of *tert*-butyl (2*R*,5*S*)-4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(sulfamoylimino)methyl)-2,5-dimethylpiperazine-1-carboxylate (510 mg, 0.91 mmol) and cesium carbonate (0.89 g, 2.7 mmol) in DMF (0.91 mL) was stirred at 80 °C for 20 min. The reaction was cooled to rt and partitioned between water (5.0 mL), 1 M LiCl solution (20 mL), and EtOAc (25 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (1 x 25 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to afford crude *tert*-butyl (2*R*,5S)-4-(6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate as a bright-yellow foam which was carried forward in the next step without purification. *m/z* (ESI, +ve ion): 546.0 $(M+Na)^+$.

[0200] Step 3: 6-Chloro-4-((2*S*,5*R*)-2,5-dimethylpiperazin-1-yl)-7-(2-fluorophenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide. A solution of crude *tert*-butyl (2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.10 g, 0.20 mmol) in DCM (0.60 mL) was treated with TFA (0.30 mL, 4.0 mmol). The reaction was stirred for 30 min then loaded onto a Varian Mega Bond Elut SCX column. The column was washed with 2.0 M NH_3 in MeOH solution (5 column volumes) to elute the free-based product. The eluent was concentrated under reduced pressure to afford crude 6-chloro-4-((2*S*,5*R*)-

2,5-dimethylpiperazin-1-yl)-7-(2-fluorophenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide that was used directly in the next reaction. *m/z* (ESI, +ve ion): 424.1 $(M+H)^+$.

[0201] Step 4: 1-((2*R*,5*S*)-4-(6-Chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one. Crude 6-chloro-4-((2*S*,5*R*)-2,5-dimethylpiperazin-1-yl)-7-(2-fluorophenyl)-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide (0.080 g, 0.19 mmol) was suspended in DCM (5.0 mL) and then cooled to 0 °C. Acryloyl chloride (0.26 M in DCM, 0.74 mL, 0.19 mmol,) was added dropwise. After 90 min, additional acryloyl chloride was added (0.26 M in DCM, 0.20 mL, 0.050 mmol). The reaction was quenched with sat. aqueous ammonium chloride (10 mL) and diluted with water (50 mL) and DCM (60 mL). The organic phase was collected and the aqueous phase was extracted with DCM (2 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to afford 1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one (53 mg, 0. 11 mmol, 58% yield) as a bright-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 – 1.22 (m, 3 H), 1.23 – 1.31 (m, 3 H), 3.38 – 4.85 (m, 6 H), 5.69 – 5.80 (m, 1 H), 6.17 (dd, J = 16.7, 2.2 Hz, 1 H), 6.70 – 6.89 (m, 1 H), 7.33 – 7.46 (m, 2 H), 7.53 – 7.67 (m, 2 H), 8.34 (s, 1 H), 12.29 (br s, 1 H); ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -113.69 (s, 1 F); *m/z* (ESI, +ve ion) 478.1 $(M+ H)^+$.

[0202] Example 8: 1-((2*R*,5*S*)-4-(7-(2-Amino-6-fluorophenyl)-6-chloro-1-(4-((dimethylamino)methyl)-2-methyl-6-(2-propanyl)phenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one.



[0203] Steps 1–5: (2*R*,5*S*)-*tert*-Butyl 4-(7-(2-amino-6-fluorophenyl)-1-(4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-isopropyl-6-methylphenyl)-6-chloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. The title compound was prepared using the procedure described in Method 1, Steps 1–5 with the following modifications: Step 1 was performed with 4-(((*tert*-butyl diphenylsilyl)oxy)methyl)-2-isopropyl-6-methylaniline (Intermediate 8-A) and step 5 was performed with (2-amino-6-

fluorophenyl)boronic acid pinacol ester (CombiPhos Catalysts Inc., Princeton, NJ, USA), $Pd(PPh_3)_4$, and K_2CO_3. *m/z* (ESI, +ve ion) 938.4 $(M+H)^+$.

[0204] Step 6: (2*R*,5*S*)-*tert*-Butyl 4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-(hydroxymethyl)-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. To a solution of *tert*-butyl (2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-1-(4-(((*tert*-butyl diphenylsilyl)oxy)methyl)-2-isopropyl-6-methylphenyl)-6-chloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.44 g, 0.46 mmol) in THF (9.0 mL) was added TBAF (1.0 M in THF, 0.60 mL, 0.60 mmol) dropwise at rt. The reaction was stirred at rt overnight, then partitioned between EtOAc and water. The organic phase was separated and washed sequentially with water and brine then dried over $MgSO_4$ and concentrated in vacuo. The material was purified by silica gel chromatography (eluent: 10–100% 3:1 EtOAc-EtOH (3:1)/heptane) to provide *tert*-butyl (2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-(hydroxymethyl)-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.27 g, 0.39 mmol, 83% yield) as a white solid. *m/z*: (ESI, +ve ion) 700.4 $(M+H)^+$.

[0205] Step 7: (2*R*,5*S*)-*tert*-Butyl 4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-formyl-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. To a solution of pyridine-sulfur trioxide complex (0.18 g, 1.2 mmol) in DCM (2.5 mL) and DMSO (2.5 mL) was added triethylamine (0.33 mL, 2.3 mmol). After 5 min a solution of *tert*-butyl (2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-(hydroxymethyl)-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.27 g, 0.39 mmol) in DCM (2.5 mL) was added. The reaction was stirred at rt for 30 min then partitioned between DCM and water. The aqueous phase was extracted with additional DCM and the combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The material was purified by silica gel chromatography (eluent: 20–100% EtOAc/heptane followed by 20% MeOH/DCM) to provide *tert*-butyl (2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-formyl-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.27 g, 0.38 mmol, 99% yield). *m/z* (ESI, +ve ion) 698.4 $(M+H)^+$.

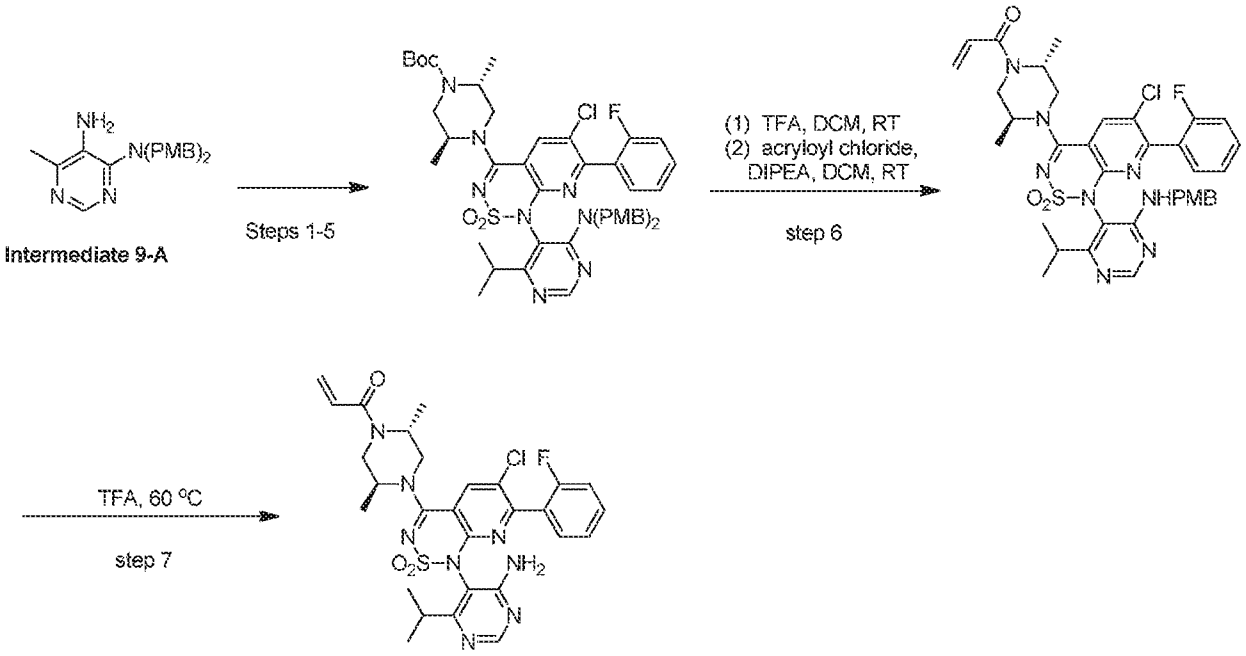
[0206] Step 8: (2*R*,5*S*)-*tert*-Butyl 4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-

***c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate.** To a solution of *tert*-butyl (2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-formyl-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.090 g, 0.13 mmol) in DCE (1.6 mL) was added dimethylamine (2.0 M in THF, 0.12 mL, 0.24 mmol) followed by sodium triacetoxyborohydride (0.030 g, 0.15 mmol). After stirring at rt for 4 h, additional portions of dimethylamine solution (0.030 mL) and sodium triacetoxyborohydride (8.0 mg) were added and the reaction stirred at rt overnight. The reaction was partitioned between water and EtOAc. The organic phase was separated and washed sequentially with sat. sodium bicarbonate solution and brine then dried over $MgSO_4$. The material was purified by silica gel chromatography (eluent: 0–10% (2.0 M NH_3 in MeOH)/DCM) to provide (2*R*,5*S*)-*tert*-butyl 4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (75 mg, 100 mmol, 78% yield). *m/z* (ESI, +ve ion) 727.6 $(M+H)^+$.

[0207] Step 9: 1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one. To a solution of *tert*-butyl (2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.22 g, 0.30 mmol) in DCM (6.0 mL) was added TFA (0.90 mL, 12 mmol). The reaction was stirred at rt for 2 h then concentrated in vacuo and the resulting residue was partitioned between EtOAc and 2.0 M aq. sodium carbonate solution. The organic phase was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was taken up in DCM (6.0 mL) and cooled to –20 °C in a salt water-ice bath. DIPEA (0.060 mL, 0.33 mmol) was added followed by dropwise addition of acryloyl chloride (1.1 M in DCM, 0.24 mL, 0.27 mmol). After 10 min the reaction was quenched with methanol and concentrated in vacuo. The material was purified by silica gel chromatography (eluent: 0–20% (2.0 M NH_3 in MeOH)/DCM) to provide 1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-((dimethylamino)methyl)-2-isopropyl-6-methylphenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one (0.07 g, 0.10 mmol, 34% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.97 - 8.04 (m, 1 H), 7.06 - 7.21 (m, 3 H), 6.34 - 6.68 (m, 4 H), 5.75 - 5.85 (m, 1 H), 4.54 - 5.09 (m, 2 H), 4.29 - 4.45 (m, 1 H), 4.05 -

4.19 (m, 1 H), 3.63 - 3.99 (m, 4 H), 3.37 - 3.58 (m, 2 H), 2.75 - 3.11 (m, 1 H), 2.06 - 2.36 (m, 9 H), 1.22 - 1.48 (m, 12 H). *m/z* (ESI, +ve ion) 681.6 $(M+H)^+$.

[0208] Example 9: 1-((2*R*,5*S*)-4-(1-(4-Amino-6-(2-propanyl)-5-pyrimidinyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one



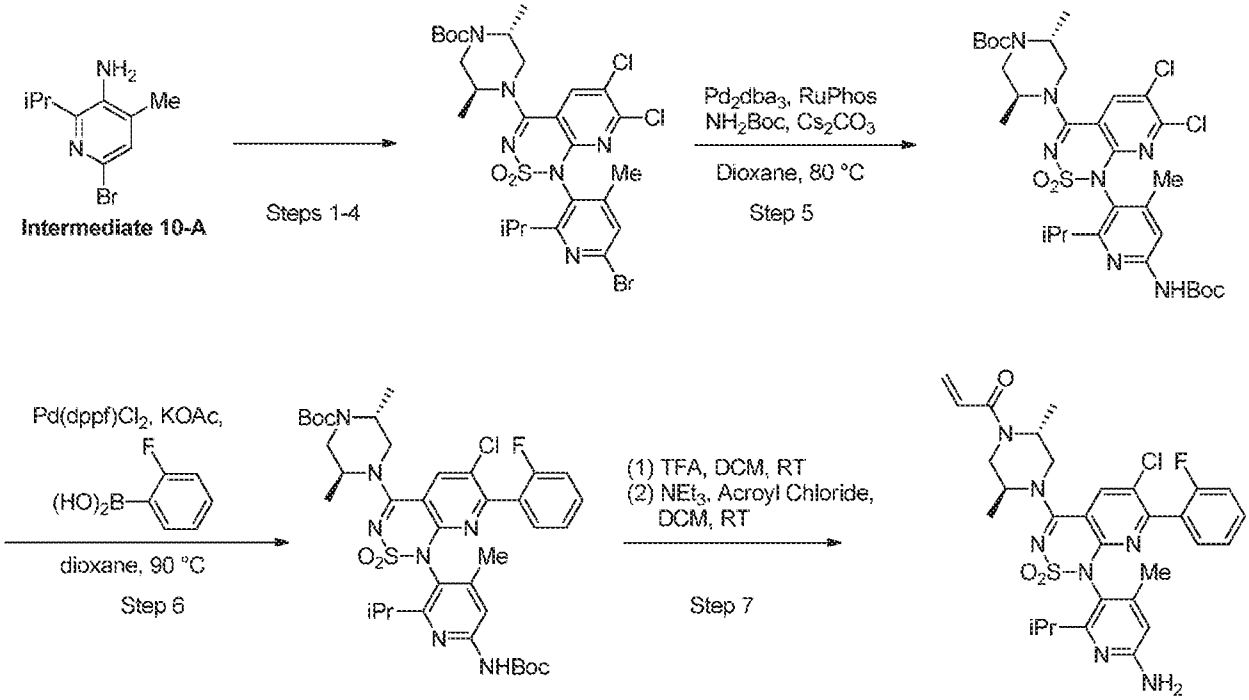
[0209] Steps 1–5: (2*R*,5*S*)-*tert*-Butyl 4-(1-(4-(bis(4-methoxybenzyl)amino)-6-isopropylpyrimidin-5-yl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. The title compound was prepared using the procedure described in Method 1, Steps 1–5 with the following modification: Step 1 was performed with 6-isopropyl-N^4,N^4-bis(4-methoxybenzyl)pyrimidine-4,5-diamine (Intermediate 9-A). *m/z* (ESI, +ve ion) 898.4 $(M+H)^+$.

[0210] Step 6: 1-((2*R*,5*S*)-4-(6-Chloro-7-(2-fluorophenyl)-1-(4-isopropyl-6-((4-methoxybenzyl)amino)pyrimidin-5-yl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one. To a solution of *tert*-butyl (2*R*,5*S*)-4-(1-(4-(bis(4-methoxybenzyl)amino)-6-isopropylpyrimidin-5-yl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.46 g, 0.51 mmol) in DCM (10 mL) was added TFA (1.5 mL, 20 mmol). The reaction was stirred at rt for 1 h then concentrated in vacuo. The residue was taken up in DCM (10 mL) before adding DIPEA (0.45

mL, 2.6 mmol) followed by dropwise addition of acryloyl chloride (1.1 M in DCM, 0.42 mL, 0.46 mmol). After 5 minutes the reaction was partitioned between EtOAc and 2.0 M aq. sodium carbonate solution. The organic phase was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting material was used without further purification assuming theoretical yield. *m/z* (ESI, +ve ion) 732.4 $(M+H)^+$.

[0211] Step 7: 1-((2*R*,5*S*)-4-(1-(4-Amino-6-isopropylpyrimidin-5-yl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one. To a solution of 1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(4-isopropyl-6-((4-methoxybenzyl)amino)pyrimidin-5-yl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one (0.37 g, 0.51 mmol) in TFA (3.9 mL, 51 mmol) was added trifluoromethane sulfonic acid (0.05 mL, 0.51 mmol). The reaction was stirred at 60 °C for 10 min then cooled to r.t. and concentrated in vacuo. The crude material was partitioned between EtOAc and 2.0 M aq. sodium carbonate. The organic phase was separated, washed with brine, and dried over $MgSO_4$. The crude product was purified by silica gel chromatography (eluent: 10–100% EtOAc-EtOH (3:1)/heptane) to afford 1-((2*R*,5*S*)-4-(1-(4-amino-6-isopropylpyrimidin-5-yl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one (0.20 g, 0.33 mmol, 64% yield) as a pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.39 - 8.52 (m, 1 H), 8.32 (d, J = 3.1 Hz, 1 H), 7.53 - 7.62 (m, 1 H), 7.41 - 7.50 (m, 1 H), 7.31 - 7.40 (m, 2 H), 6.50 - 6.92 (m, 2 H), 6.47 - 7.00 (m, 1 H), 6.20 (dt, J = 16.7, 2.6 Hz, 1 H), 5.71 - 5.82 (m, 1 H), 5.65 - 5.66 (m, 1 H), 4.45 - 4.88 (m, 2 H), 3.62 - 4.21 (m, 4 H), 2.77 - 2.93 (m, 1 H), 1.31 - 1.45 (m, 3 H), 1.19 - 1.26 (m, 3 H), 1.08 (dd, J = 6.6, 2.9 Hz, 3 H), 0.94 (dd, J = 12.9, 6.8 Hz, 3 H). *m/z* (ESI, +ve ion) 612.6 $(M+H)^+$.

[0212] Example 10: 1-((2*R*,5*S*)-4-(1-(6-Amino-4-methyl-2-(2-propanyl)-3-pyridinyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one



[0213] Steps 1–4: *tert*-Butyl (2*R*,5*S*)-4-(1-(6-bromo-2-isopropyl-4-methylpyridin-3-yl)-6,7-dichloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. The title compound was prepared using the procedure described in Method 1, Steps 1–4 with the following modification: Step 1 performed with 6-bromo-2-isopropyl-4-methylpyridin-3-amine (Intermediate 10-A). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.92 (br s, 1 H), 7.20 - 7.37 (m, 1 H), 4.26 - 4.79 (m, 2 H), 3.33 - 3.99 (m, 3 H), 2.68 - 3.03 (m, 2 H), 2.08 - 2.32 (m, 3 H), 1.50 (br s, 9 H), 1.43 (m, 3 H), 1.27 (m, 6 H), 1.21 (m, 3 H); *m/z* (ESI, +ve ion) 675.0 $(M+H)^+$.

[0214] Step 5: *tert*-Butyl (2*R*,5*S*)-4-(1-(6-((*tert*-butoxycarbonyl)amino)-2-isopropyl-4-methylpyridin-3-yl)-6,7-dichloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. A flask was charged with *tert*-butyl (2*R*,5*S*)-4-(1-(6-bromo-2-isopropyl-4-methylpyridin-3-yl)-6,7-dichloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.30 g, 0.44 mmol), cesium carbonate (0.22 g, 0.67 mmol), 1,1-dimethylethyl carbamate (0.06 g, 0.51 mmol), palladium(0) bis(dibenzylideneacetone) (0.050 g, 0.090 mmol, Strem Chemicals, Newburyport, MA, USA), and 2-dicyclohexylphosphino-

2',6'-di-i-propoxy-1,1'-biphenyl (0.04 g, 0.09 mmol, Strem Chemicals, Newburyport, MA, USA). The reaction vessel was evacuated and backfilled with N_2 (3x), then 1,4-dioxane (1.1 mL) was added and the mixture was heated to 80 °C for 2 h. The mixture was cooled to rt, filtered through a short pad of silica gel using EtOAc, and concentrated in vacuo. The crude product was purified by silica gel chromatography (eluent: 30–50% EtOAc-EtOH (3:1)/heptane) to provide *tert*-butyl (2*R*,5*S*)-4-(1-(6-((*tert*-butoxycarbonyl)amino)-2-isopropyl-4-methylpyridin-3-yl)-6,7-dichloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.22 g, 0.31 mmol, 71% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.88 (br s, 1 H), 7.28 - 7.40 (m, 1 H), 4.18 - 4.77 (m, 3 H), 3.27 - 3.99 (m, 3 H), 2.81 - 3.02 (m, 1 H), 2.09 - 2.32 (m, 3 H), 1.50 (s, 9 H), 1.44 - 1.48 (m, 9 H), 1.43 (s, 3 H), 1.36 - 1.42 (m, 3 H), 1.23 (m, 3 H). *m/z* (ESI, +ve ion): 712.3 $(M+H)^+$.

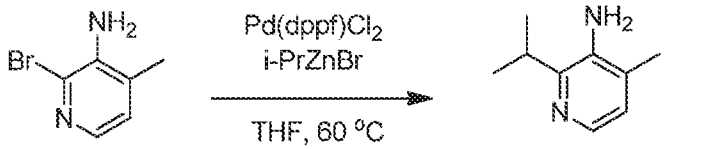
[0215] Step 6: *tert*-Butyl (2*R*,5*S*)-4-(1-(6-((*tert*-butoxycarbonyl)amino)-2-isopropyl-4-methylpyridin-3-yl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate. The title compound was prepared using the procedure described in Method 1, Step 5, to provide *tert*-butyl (2*R*,5*S*)-4-(1-(6-((*tert*-butoxycarbonyl)amino)-2-isopropyl-4-methylpyridin-3-yl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.24 g, 0.31 mmol, 98% yield) as a yellow oil. *m/z* (ESI, +ve ion) 772.3 $(M+H)^+$.

[0216] Step 7: 1-((2*R*,5*S*)-4-(1-(6-Amino-2-isopropyl-4-methylpyridin-3-yl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one. To a solution of *tert*-butyl (2*R*,5*S*)-4-(1-(6-((*tert*-butoxycarbonyl)amino)-2-isopropyl-4-methylpyridin-3-yl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazine-1-carboxylate (0.22 g, 0.29 mmol) in DCM (1.4 mL) was added TFA (0.43 mL, 5.8 mmol). After stirring at rt for 1 h the reaction mixture was concentrated in vacuo. The residue was redissolved in DCM (1.4 mL) and triethylamine (0.41 mL, 2.9 mmol) and cooled to 0 °C, followed by dropwise addition of acryloyl chloride (1.1 M in DCM, 0.26 mL, 0.29 mmol). The reaction was stirred at rt for 30 min then was partitioned between EtOAc (25 mL) and sat. $NaHCO_3$ (25 mL). The organic phase was separated and washed with sat. $NaHCO_3$ (2 x) and brine (1 x), then dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (eluent: 0–100% EtOAc-EtOH (3:1)/heptane) followed by SFC purification (OD-H column (21 x 250 mm, 5 μm), (20% MeOH) in supercritical

CO_2), to provide 1-((2*R*,5*S*)-4-(1-(6-amino-2-isopropyl-4-methylpyridin-3-yl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one (0.025 g, 0.020 mmol, 7% yield) (mixture of isomers) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.97 (d, *J* = 5.6 Hz, 1 H), 7.55 - 7.43 (m, 1 H), 7.41 - 7.30 (m, 1 H), 7.26 - 7.14 (m, 2 H), 6.68 - 6.51 (m, 1 H), 6.47 - 6.36 (m, 1 H), 6.33 (br s, 1 H), 5.87 - 5.80 (m, 1 H), 5.14 - 4.64 (m, 2H), 4.57 - 4.33 (m, 1H), 4.07 - 3.65 (m, 2H), 2.98 - 2.85 (m, 1 H), 2.36 - 2.15 (m, 3 H), 1.50 - 1.42 (m, 3 H), 1.42 - 1.32 (m, 3 H), 1.32 - 1.22 (m, 6 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -112.32 (s, 1F). *m/z* (ESI, +ve ion): 626.2 $(M+H)^+$.

SECTION 3 – INTERMEDIATES

[0217] Intermediate 1-A: 2-Isopropyl-4-methylpyridin-3-amine

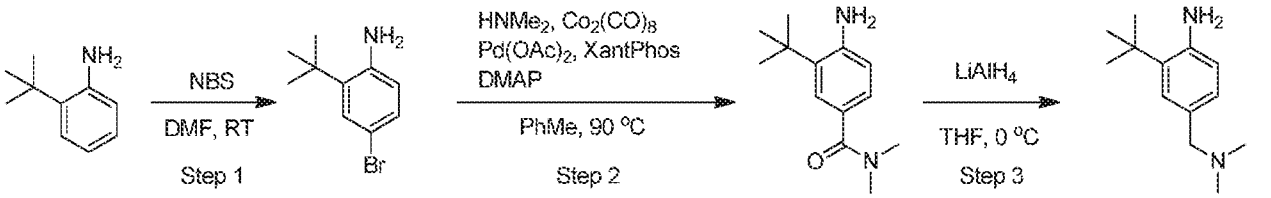


Intermediate 1-A

Step 1

[0218] **Step 1: 2-Isopropyl-4-methylpyridin-3-amine.** To a slurry of 3-amino-2-bromo-4-picoline (360 mg, 1.9 mmol, Combi-Blocks, San Diego, CA, USA) in THF (4.0 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (79 mg, 0.10 mmol). The mixture was deoxygenated with argon for 2 min and then 2-propylzinc bromide (0.50 M in THF, 5.4 mL, 2.7 mmol) was added. The resulting solution was heated at 60 °C for 17 h, then the reaction cooled to rt. The reaction was quenched with water (10 mL) and 1 N NaOH solution (20 mL) and then was extracted with EtOAc (2 x). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–15% MeOH/DCM) to provide 2-isopropyl-4-methylpyridin-3-amine (**Intermediate 1-A**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.66 (d, *J* = 4.6 Hz, 1 H), 6.78 (d, *J* = 4.8 Hz, 1 H), 4.72 (br s, 2 H), 3.14 - 3.25 (m, 1 H), 2.08 (s, 3 H), 1.14 (d, *J* = 6.8 Hz, 6 H); *m/z* (ESI, +ve ion): 151.1 $(M+H)^+$.

[0219] Intermediate 1-B: 2-(*tert*-Butyl)-4-((dimethylamino)methyl)aniline



Intermediate 1-B

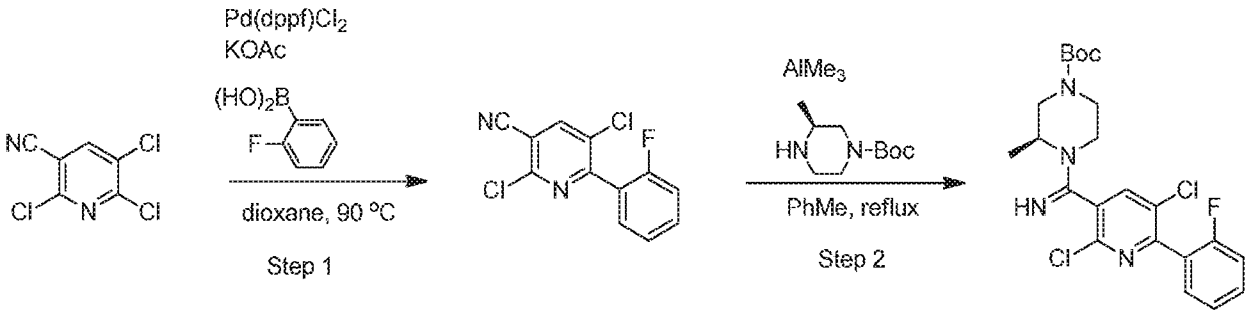
[0220] Step 1: 4-Bromo-2-(*tert*-butyl)aniline. To a solution of 2-*tert*-butylaniline (10 mL, 67 mmol) in DMF (130 mL) was added *N*-bromosuccinimide (6.9 g, 80 mmol). The reaction was stirred at rt for 2 h and then partitioned between water and EtOAc. The aqueous phase was washed with additional EtOAc and the organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 10–100% EtOAc/heptane) to provide 4-bromo-2-(*tert*-butyl)aniline (12 g, 53 mmol, 79% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.10 (d, J = 2.5 Hz, 1 H), 7.03 (dd, J = 8.5, 2.3 Hz, 1 H), 6.61 (d, J = 8.5 Hz, 1 H), 4.97 (s, 2 H), 1.31 (s, 9 H). *m/z* (ESI, +ve ion): 229.8 $(M+H)^+$.

[0221] Step 2: 4-Amino-3-(*tert*-butyl)-*N*,*N*-dimethylbenzamide. To a solution of 9,9-dimethyl-4,5-bis(bis[3,5-dimethyl-4-methoxyphenyl]phosphino)xanthene (1.0 g, 1.8 mmol, Strem Chemicals, Newburyport, MA, USA), palladium(II) acetate (0.20 g, 0.88 mmol), DMAP (4.3 g, 35 mmol), and 4-bromo-2-(*tert*-butyl)aniline (4.0 g, 18 mmol) in toluene (58 mL) was added dimethylamine (2.0 M in THF, 18 mL, 35 mmol). Cobalt carbonyl (0.43 g, 2.2 mmol, Strem Chemicals, Newburyport, MA, USA) was added in one portion. The reaction was heated at 90 °C for 3 h, then partitioned between water and EtOAc. The organic layer was washed sequentially with 1:1 sat. ammonium chloride/water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 20–100% EtOAc/heptane) to provide 4-amino-3-(*tert*-butyl)-*N*,*N*-dimethylbenzamide (2.1 g, 9.6 mmol, 55% yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.18 (d, J = 1.9 Hz, 1 H), 7.02 (dd, J = 8.1, 1.9 Hz, 1 H), 6.63 (d, J = 8.3 Hz, 1 H), 5.18 (s, 2 H), 2.95 (s, 6 H), 1.34 (s, 9 H). *m/z* (ESI, +ve ion): 221.0 $(M+H)^+$.

[0222] Step 3: 2-(*tert*-Butyl)-4-((dimethylamino)methyl)aniline. To a 0 °C solution of 4-amino-3-(*tert*-butyl)-*N*,*N*-dimethylbenzamide (3.0 g, 14 mmol) in THF (50 mL) was added lithium

aluminum hydride (1.0 M in THF, 25 mL, 25 mmol) dropwise via cannula. The reaction was warmed to rt and stirred for 2 h, then cooled to 0 °C before carefully adding water (20 mL) and 5 N NaOH (20 mL) followed by an additional portion of water (60 mL). The reaction was warmed to rt and diluted with EtOAc. The mixture was filtered over Celite® and the filter cake was washed with EtOAc. The layers of the biphasic filtrate were separated and the organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–20% (2.0 M NH_3 in MeOH)/DCM) to provide 2-(*tert*-butyl)-4-((dimethylamino)methyl)aniline (**Intermediate 1-B**, 1.8 g, 8.6 mmol, 63% yield) as a brown liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.96 (d, J = 1.9 Hz, 1 H), 6.79 (dd, J = 8.1, 1.9 Hz, 1 H), 6.58 (d, J = 8.1 Hz, 1 H), 4.64 (br s, 2 H), 3.20 (s, 2 H), 2.09 (s, 6 H), 1.33 (s, 8 H), 1.31 - 1.34 (m, 1 H); *m/z* (ESI, +ve ion): 162.2 $(M+H)^+$.

[0223] Intermediate 2-A: (*S*)-*tert*-Butyl 4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(imino)methyl)-3-methylpiperazine-1-carboxylate

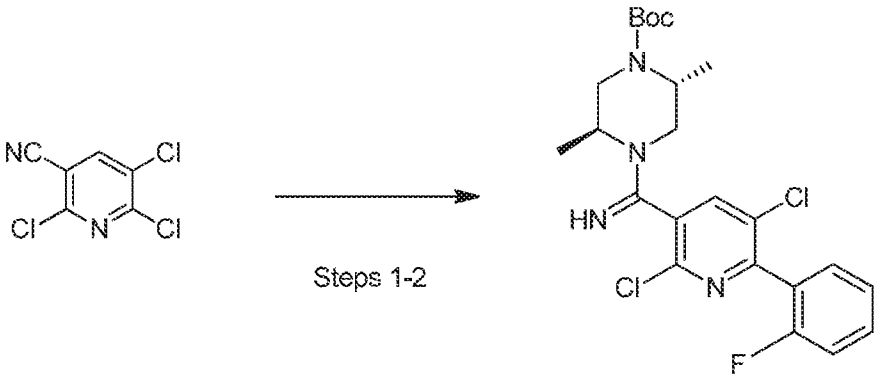


[0224] Step 1: 2,5-Dichloro-6-(2-fluorophenyl)nicotinonitrile. A suspension of 2,5,6-trichloronicotinonitrile (4.5 g, 22 mmol), 2-fluorophenylboronic acid (3.3 g, 24 mmol, Combi-Blocks, San Diego, CA, USA), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II), complex with DCM (0.18 g, 0.22 mmol), potassium acetate (6.4 g, 65 mmol) in 1,4-dioxane (50 mL) was sparged with argon for 5 min then heated at 90 °C for 50 min. The reaction was partitioned between EtOAc (150 mL) and 5% $NaHCO_3$ (50 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (eluent: 0–10% MTBE/heptane) to provide 2,5-dichloro-6-(2-fluorophenyl) (3.5 g, 13 mmol, 60% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.09 (s, 1H),

7.44 - 7.56 (m, 2 H), 7.27 - 7.33 (m, 1 H), 7.19 (dd, J = 9.3, 19.7 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm –111.88 (s, 1F); *m/z* (ESI, +ve ion): 267.0 $(M+H)^+$.

[0225] Step 2: (*S*)-*tert*-Butyl 4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(imino)methyl)-3-methylpiperazine-1-carboxylate. To a stirring solution of 2,5-dichloro-6-(2-fluorophenyl)nicotinonitrile (1.0 g, 3.7 mmol) and (*S*)-4-Boc-2-methylpiperazine (1.7 g, 8.2 mmol) in toluene (10 mL) at 20 °C was added trimethylaluminum (2.0 M in toluene, 4.1 mL, 8.2 mmol) while maintaining an internal temp below 30 °C. After 15 min, the reaction was heated to reflux for 2 h. The reaction was cooled to 25 °C then the mixture was added dropwise to a suspension of silica gel (10 g) in EtOAc (40 mL). The mixture was concentrated in vacuo and purified by silica gel chromatography (eluent: 0–100% EtOAc/heptane) to provide (*S*)-*tert*-butyl 4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(imino)methyl)-3-methylpiperazine-1-carboxylate (**Intermediate 2-A**, 0.83 g, 1. 8 mmol, 47% yield) as an orange foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.72 (s, 1 H), 7.45 - 7.52 (m, 2 H), 7.27 - 7.31 (m, 1 H), 7.14 - 7.22 (m, 1 H), 3.80 - 4.25 (m, 3 H), 2.75 - 3.50 (m, 4 H), 1.48 (s, 9 H), 1.27 (d, J = 7.1 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm –112.76 (s, 1 F); *m/z* (ESI, +ve ion): 467.1 $(M+H)^+$.

[0226] Intermediate 2-B: (2*R*,5*S*)-*tert*-Butyl 4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(imino)methyl)-2,5-dimethylpiperazine-1-carboxylate

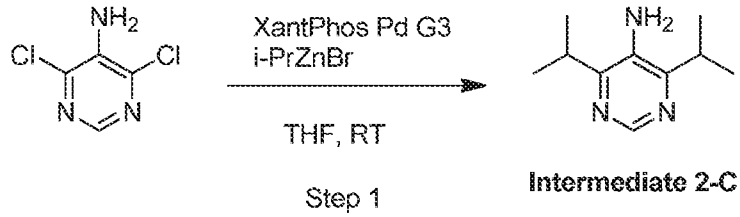


Intermediate 2-B

[0227] Steps 1–2: (2*R*,5*S*)-*tert*-Butyl 4-((2,5-dichloro-6-(2-fluorophenyl)pyridin-3-yl)(imino)methyl)-2,5-dimethylpiperazine-1-carboxylate. The title compound was prepared using the procedure described for the synthesis of Intermediate 2-A with the following modification: Step 2 was performed with (2*R*,5*S*)-*tert*-butyl 2,5-dimethylpiperazine-1-carboxylate

(eNovation Chemicals LLC, Bridgewater, NJ, USA). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 - 9.01 (m, 1 H), 8.24 - 8.52 (m, 1 H), 7.51 - 7.66 (m, 2 H), 7.41 (m, 2 H), 4.30 - 4.86 (m, 1 H), 4.09 - 4.26 (m, 1 H), 3.28 - 3.87 (m, 3 H), 2.91 - 3.28 (m, 1 H), 1.42 (br s, 9 H), 1.12 - 1.32 (m, 6 H). *m/z* (ESI, +ve ion): 481.2 $(M+H)^+$.

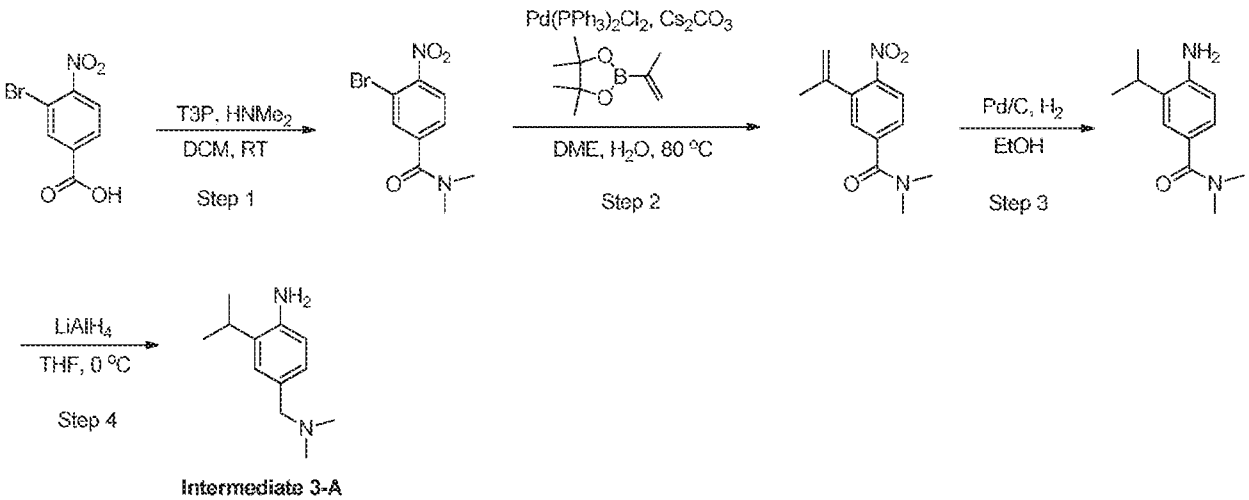
[0228] Intermediate 2-C: 4,6-Diisopropylpyrimidin-5-amine



Intermediate 2-C

[0229] Step 1: 4,6-Diisopropylpyrimidin-5-amine. A solution of 4,6-dichloro-5-aminopyrimidine (3.0 g, 18 mmol, Combi-Blocks Inc., San Diego, CA, USA) in THF (18 mL) was deoxygenated by bubbling argon into the mixture for 5 min. 2-Isopropylzinc bromide (0.5 M in THF, 91 mL, 46 mmol) was added via syringe followed by XantPhos Pd G3 (430 mg, 0.46 mmol, Sigma-Aldrich, St. Louis, MO, USA). The resulting mixture was stirred at rt for 16 h then filtered through a pad of Celite®. The filter cake was rinsed with EtOAc and the filtrate was concentrated in vacuo to afford 4,6-diisopropylpyrimidin-5-amine (3.5 g, **Intermediate 2-C**). This material was used without further purification. *m/z* (ESI, +ve ion): 180.2 $(M+H)^+$.

[0230] Intermediate 3-A: 4-((Dimethylamino)methyl)-2-isopropylaniline



Intermediate 3-A

[0231] Step 1: 3-Bromo-*N*,*N*-dimethyl-4-nitrobenzamide. To a 0 °C solution of 3-bromo-4-nitrobenzoic acid (2.9 g, 12 mmol) in DCM (80 mL) was added 1-propanephosphonic acid cyclic anhydride (50 wt % in EtOAc, 28 mL, 47 mmol). The resulting mixture was stirred at 0 °C for 2 min, then dimethylamine (2.0 M in THF, 12 mL, 24 mmol) was added. The resulting mixture was stirred at rt for 24 min. Additional portions of 1-propanephosphonic acid cyclic anhydride (50 wt % in EtOAc, 28 mL, 47 mmol) and dimethylamine (2.0 M in THF, 5.9 mL, 12 mmol) were added and the mixture was stirred at rt for 1 hour. The mixture was quenched with sat. $NaHCO_3$ then extracted with EtOAc (2 x 200 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–100% EtOAc/heptane) to provide 3-bromo-*N*,*N*-dimethyl-4-nitrobenzamide (3.2 g, 99% yield) as a yellow oil. *m/z* (ESI, +ve ion): 272.9 $(M+H)^+$.

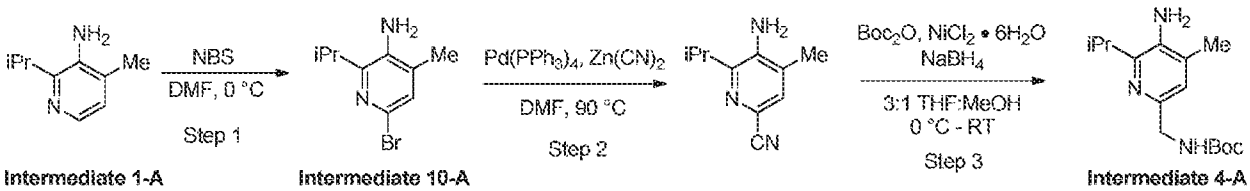
[0232] Step 2: *N*,*N*-Dimethyl-4-nitro-3-(prop-1-en-2-yl)benzamide. To a solution of 3-bromo-*N*,*N*-dimethyl-4-nitrobenzamide (3.2 g, 12 mmol) in DME (60 mL) and water (12 mL) was added (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isopropene (5.8 mL, 35 mmol), cesium carbonate (11 g, 35 mmol), and *trans*-dichlorobis(triphenyl-phosphine)palladium (II) (0.81 g, 1.2 mmol, Strem Chemicals, Newburyport, MA, USA). The resulting mixture was purged with N_2 for 5 min then stirred at 80 °C for 45 min. The mixture was diluted with water (40 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0%–100% EtOAc/heptane) to provide *N*,*N*-dimethyl-4-nitro-3-(prop-1-en-2-yl)benzamide as a yellow oil, which was used without further purification assuming theoretical yield. *m/z* (ESI, +ve ion): 234.9 $(M+H)^+$.

[0233] Step 3: 4-Amino-3-isopropyl-*N*,*N*-dimethylbenzamide. To a solution of *N*,*N*-dimethyl-4-nitro-3-(prop-1-en-2-yl)benzamide (2.7 g, 12 mmol) in EtOH (50 mL) was added palladium, 10% on activated carbon (1.23 g, 1.2 mmol). The resulting mixture was stirred under H_2 (40 psi) for 48 h then filtered through a pad of Celite®. The filter cake was washed with EtOAc (2 x 150 mL) and the combined filtrates were concentrated in vacuo to provide 4-amino-3-isopropyl-*N*,*N*-dimethylbenzamide (2.4 g, 100% yield) as a yellow solid. *m/z* (ESI, +ve ion): 207.1 $(M+H)^+$.

[0234] Step 4: 4-((Dimethylamino)methyl)-2-isopropylaniline. To a 0 °C solution of 4-amino-3-isopropyl-*N*,*N*-dimethylbenzamide (2.3 g, 11 mmol) in THF (50 mL) was added lithium

aluminum hydride (1.0M in THF, 34 mL, 34 mmol) dropwise. The reaction was warmed to rt and stirred for 1 h, then heated to 80 °C for 20 min. The reaction was cooled to 0 °C, then quenched with H_2O (40 mL) and NaOH (50% in water, 50 mL). The mixture was diluted with THF (50 mL) and stirred at rt for 1 h. The mixture was extracted with EtOAc (5 x 150 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0–20% (2.0 M NH_3 in MeOH)/DCM) to provide 4-((dimethylamino)methyl)-2-isopropylaniline (**Intermediate 3-A**, 1.7 g, 8.74 mmol, 77% yield) as a yellow liquid. ^{1}H NMR ($CDCl_3$) δ ppm 7.06 (d, *J* = 1.5 Hz, 1 H), 6.95 (dd, *J* = 8.1, 1.7 Hz, 1 H), 6.64 (d, *J* = 7.9 Hz, 1 H), 3.48 - 3.78 (m, 2 H), 3.38 (br s, 2 H), 2.90 (dt, *J* = 13.6, 6.8 Hz, 1 H), 2.25 (s, 6 H), 1.26 (d, *J* = 6.8 Hz, 6 H); m/z (ESI, +ve ion): 193.1 $(M+H)^+$.

[0235] Intermediate 4-A: *tert*-Butyl ((5-amino-6-isopropyl-4-methylpyridin-2-yl)methyl)carbamate



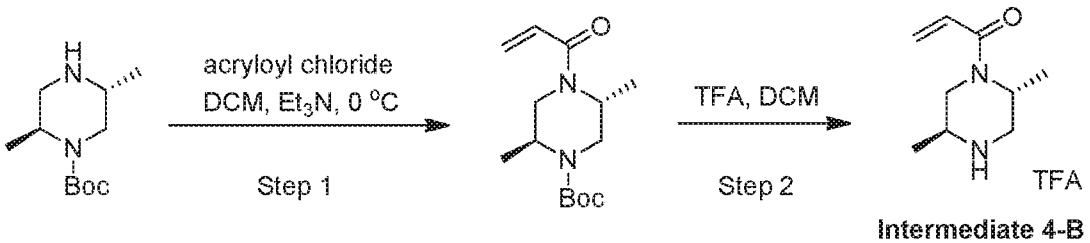
[0236] Step 1: 6-Bromo-2-isopropyl-4-methylpyridin-3-amine. To a solution of 2-isopropyl-4-methylpyridin-3-amine (**Intermediate 1-A**, 3.0 g, 20.0 mmol) in DMF (67 ml) at 0°C was added *N*-bromosuccinimide (3.7 g, 21.0 mmol). The reaction mixture was stirred at 0°C for 30 min then quenched with 0.5 M NaOH (20 mL) and partitioned between EtOAc (150 mL) and 1.0 M LiCl (150 mL). The organic layer was separated and the aqueous was extracted with EtOAc (2x). The combined organic phases were adsorbed onto silica gel and purified by silica gel chromatography (eluent: 0-100% EtOAc-EtOH (3:1)/heptane), to provide 6-bromo-2-isopropyl-4-methylpyridin-3-amine (**Intermediate 10-A**, 3.7 g, 16.2 mmol, 81 % yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 1H), 3.58 (br s, 2H), 2.96 (td, J=6.74, 13.48 Hz, 1H), 2.13 (s, 3H), 1.28 (d, J=6.63 Hz, 6H); *m/z* (ESI, +ve ion): 229.1 $(M+H)^+$.

[0237] Step 2: 5-Amino-6-isopropyl-4-methylpicolinonitrile. A flask was charged with 6-bromo-2-isopropyl-4-methylpyridin-3-amine (**Intermediate 10-A**, 2.0 g, 8.7 mmol), tetrakis(triphenylphosphine)palladium (0) (0.5 g, 0.44 mmol), and dicyanozinc (1.3 g, 10.9 mmol). The flask was evacuated and backfilled with N_2 (3x), then DMF (8.7 ml) was added and the

reaction mixture was heated to 90°C for 2 h. The reaction mixture was partitioned between EtOAc (150 mL) and brine (150 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2x). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by silica gel chromatography (eluent: 0-40% EtOAc-EtOH (3:1)/heptane) to provide 5-amino-6-isopropyl-4-methylpicolinonitrile (1.3 g, 7.1 mmol, 82 % yield) as a yellow solid. ^{1}H NMR (400MHz, CDCl3) δ = 7.25 (s, 1H), 4.12 (br s, 2H), 3.05 - 2.92 (m, 1H), 2.18 (s, 3H), 1.29 (d, *J*=6.6 Hz, 6H); *m/z* (ESI, +ve ion): 176.3 $(M+H)^+$.

[0238] Step 3: *tert*-Butyl ((5-amino-6-isopropyl-4-methylpyridin-2-yl)methyl)carbamate. To a solution of 5-amino-6-isopropyl-4-methylpicolinonitrile (4.8 g, 27 mmol), nickel (II) chloride hexahydrate (1.6 g, 27 mmol), di-*tert*-butyl dicarbonate (6.36 ml, 27 mmol) in methanol (34 ml) and tetrahydrofuran (100 ml), at 0°C was added sodium borohydride (3.1 g, 82 mmol) in portions. The reaction mixture was warmed to rt and stirred for 1 h before cooling to 0 °C and quenching with water. The reaction mixture was diluted with EtOAc (100 mL) and sat. $NaHCO_3$ (100 mL). The solution was filtered through Celite®, and the organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo to provide *tert*-butyl ((5-amino-6-isopropyl-4-methylpyridin-2-yl)methyl)carbamate (**Intermediate 4-A**, 7.66 g, 27.4 mmol, 100 % yield), which was used without further purification. ^{1}H NMR (400 MHz, CDCl3) δ = 6.78 (s, 1H), 5.61 (br s, 1H), 4.27 (d, *J*=4.4 Hz, 2H), 3.54 (bs, 2H), 3.02 (td, *J*=6.7, 13.5 Hz, 1H), 2.15 (s, 3H), 1.47 (d, *J*=1.7 Hz, 9H), 1.29 (d, *J*=6.8 Hz, 6H). *m/z* (ESI, +ve ion): 280.3 $(M+H)^+$.

[0239] Intermediate 4-B: 1-((2*R*,5*S*)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one



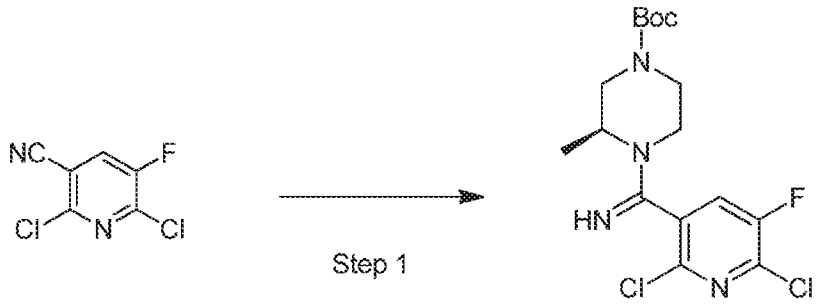
Intermediate 4-B

[0240] Step 1: (2*S*,5*R*)-*tert*-Butyl 4-acryloyl-2,5-dimethylpiperazine-1-carboxylate. To a solution of (2*S*,5*R*)-1-Boc-2,5-dimethylpiperazine (3.5 g, 16.33 mmol, AstaTech, Inc. Bristol, PA, USA) and triethylamine (4.59 ml, 32.7 mmol) in DCM (35 mL) at 0 °C was added acryloyl chloride (1.46 ml, 17.96 mmol) over 5 min. Water (10 ml) was added and the mixture was warmed to rt and stirred for 10 min. The organic phase was collected, washed sequentially with 2.0 N HCl (40

ml), water, and brine. The reaction mixture was dried over $MgSO_4$ and concentrated in vacuo to afford crude *tert*-butyl (2*S*,5*R*)-4-acryloyl-2,5-dimethylpiperazine-1-carboxylate (4.4 g, 16.4 mmol, 100 % yield) as yellow oil. *m/z* (ESI, +ve ion): 213.3 $(M - t\text{Bu} + H)^+$.

[0241] Step 2: 1-((2*R*,5*S*)-2,5-Dimethylpiperazin-1-yl)prop-2-en-1-one 2,2,2-trifluoroacetate. To a solution of crude *tert*-butyl (2*S*,5*R*)-4-acryloyl-2,5-dimethylpiperazine-1-carboxylate (4.4 g, 16.4 mmol) in DCM (40 ml) was added TFA (12.6 ml, 163 mmol and the mixture was stirred at rt for 4 h. The mixture was concentrated and dried in vacuo to afford 1-((2*R*,5*S*)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one 2,2,2-trifluoroacetate (~9 g) as an oil. Analysis of the material by qNMR using benzyl benzoate as internal standard showed 40.2 wt% purity. The material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.03 (br s, 1H), 8.95 (br s, 1H), 6.77 (dd, J=10.6, 16.8 Hz, 1H), 6.16 (dd, J=2.3, 16.8 Hz, 1H), 5.74 (dd, J=2.3, 10.6 Hz, 1H), 4.69 - 4.56 (m, 1H), 4.09 - 3.94 (m, 1H), 3.70 - 3.57 (m, 1H), 3.45 - 3.19 (m, 2H), 2.98 - 3.09 (m, 1H), 1.25 (d, J=6.8 Hz, 3H), 1.20 (d, J=6.8 Hz, 3H). *m/z* (ESI, +ve ion): 169.3 $(M+H)^+$.

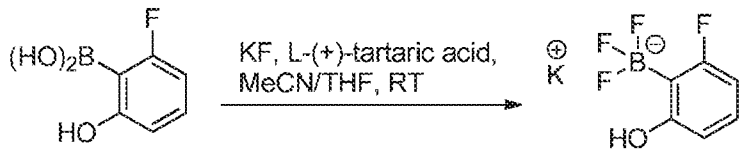
[0242] Intermediate 5-A: *tert*-Butyl (*S*)-4-((2,6-dichloro-5-fluoropyridin-3-yl)(imino)methyl)-3-methylpiperazine-1-carboxylate



Intermediate 5-A

[0243] Step 1: *tert*-Butyl (*S*)-4-((2,6-dichloro-5-fluoropyridin-3-yl)(imino)methyl)-3-methylpiperazine-1-carboxylate. The title compound was prepared using the procedure described for the synthesis of **Intermediate 2-B**, step 2 with the following modification: Step 2 was performed with 2,6-dichloro-5-fluoronicotinonitrile (Combi Blocks, San Diego, CA, USA).. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J*=6.8 Hz, 1H), 4.00-4.20 (m, 1H), 3.89 (br s, 1H), 3.22 (br s, 1H), 3.12 (br s, 1H), 2.75-3.01 (m, 1H), 1.47 (s, 9H), 1.38 (br d, *J*=7.9 Hz, 1H), 1.13-1.33 (m, 9H), 1.04 (br dd, *J*=13.6, 6.9 Hz, 1H), 0.83-0.94 ppm (m, 3H). *m/z* (ESI, +ve ion): 391.0 $(M+H)^+$

[0244] Intermediate 5-B: 2-Fluoro-6-hydroxyphenyl)potassium trifluoroborate

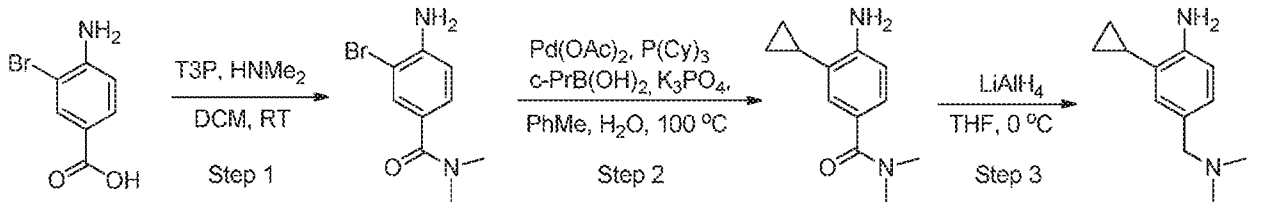


Step 1

Intermediate 5-B

[0245] Step 1: 2-Fluoro-6-hydroxyphenyl)potassium trifluoroborate. A solution of potassium fluoride (44.7 g, 770 mmol) in water (75 mL) was added to a suspension of (2-fluoro-6-hydroxyphenyl)boronic acid (30 g, 192 mmol, Combi-Blocks, San Diego, CA, USA) in acetonitrile (750 mL). The mixture was stirred for 2 min and then a solution of L-(+)-tartaric acid (72.2 g, 481 mmol) in THF (375 mL) was added over a 10 min period via addition funnel. The mixture was stirred vigorously with a mechanical stirrer for 1 h, and the resulting suspension was filtered, and the filtered solids were washed with a small amount of THF. The solids were discarded and the filtrate was partially concentrated until solids started to precipitate out of solution. The mixture was then cooled to -20 °C and stirred for 16 h. The reaction was slowly warmed and 2-propanol (20 mL) was added. The resulting suspension was filtered and the filtered solids were washed with 2-propanol. The filtrate was again partially concentrated until a suspension formed and then was cooled to -20 °C and stirred for an additional 20 min. The resulting suspension was diluted with 2-propanol and filtered, and the filtered solids were washed with 2-propanol. The two batches of solids were combined to provide 2-fluoro-6-hydroxyphenyl)potassium trifluoroborate (**Intermediate 5-B**). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.07 (q, J = 14.7 Hz, 1 H) 6.93 (q, J = 7.5 Hz, 1 H) 6.30-6.38 (m, 2 H).

[0246] Intermediate 6-A: 2-Cyclopropyl-4-((dimethylamino)methyl)aniline



Intermediate 6-A

[0247] Step 1: 4-Amino-3-bromo-*N*,*N*-dimethylbenzamide. To a solution of 4-amino-3-bromobenzoic acid (5.0 g, 23 mmol) in DCM (50 mL) was added dimethylamine (2.0 M in THF,

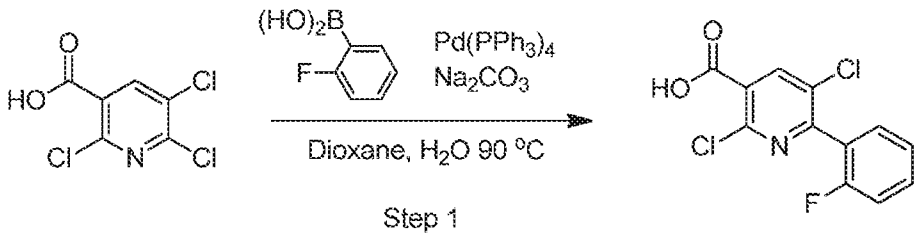
35 mL, 69 mmol). The mixture was cooled to 0 °C and 1-propanephosphonic acid cyclic anhydride (50 wt % in EtOAc, 42 mL, 69.4 mmol) was added dropwise. After addition, the mixture was stirred at rt for 16 h. The mixture was quenched with sat. $NaHCO_3$ solution then extracted with EtOAc (2 x 150 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0%-100% EtOAc/heptane) to provide 4-amino-3-bromo-*N,N*-dimethylbenzamide (5.28 g, 94 % yield) as a light yellow oil. ^1H NMR (400 MHz , $CDCl_3$) δ: 7.57 (d, J=1.0 Hz, 1H), 7.24 (dd, J=8.4, 1.1 Hz, 1H), 6.75 (d, J=8.1 Hz, 1H), 3.06 (s, 6H). *m/z* (ESI, +ve ion): 242.9 $(M+H)^+$.

[0248] Step 2: 4-Amino-3-cyclopropyl-*N,N*-dimethylbenzamide. To a solution of 4-amino-3-bromo-*N,N*-dimethylbenzamide (5.28 g, 21.72 mmol) in toluene (90 mL) and water (9.00 mL) was added cyclopropylboronic acid (4.20 g, 48.9 mmol), palladium (II) acetate (0.55 g, 2.44 mmol), tricyclohexylphosphine (0.69 g, 2.44 mmol), and potassium phosphate (15.6 g, 73.3 mmol). The resulting mixture was purged with N_2 for 5 mins then stirred at 100 °C for 45 min. Additional portions of tricyclohexylphosphine (0.69 g, 2.44 mmol), palladium (II) acetate (0.55 g, 2.44 mmol), cyclopropylboronic acid (4.20 g, 48.9 mmol) were added and the mixture was stirred at 100 °C for 16 h. The mixture was cooled to rt and diluted with water (200 mL). The mixture was extracted with EtOAc (2 x 300 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0%-10% 2M NH_3 in MeOH in DCM) to provide 4-amino-3-cyclopropyl-N,N-dimethylbenzamide (2.5 g, 50.1 % yield) as light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.19 (d, J=1.0 Hz, 1H), 7.15 (dd, J=8.1, 1.7 Hz, 1H), 6.64 (d, J=8.1 Hz, 1H), 3.94-4.32 (m, 2H), 3.05 (s, 6H), 1.63-1.69 (m, 1H), 0.88-0.95 (m, 2H), 0.59-0.64 (m, 2H). *m/z* (ESI, +ve ion): 205.1 $(M+H)^+$.

[0249] Step 3: 2-Cyclopropyl-4-((dimethylamino)methyl)aniline. To a solution of 4-amino-3-cyclopropyl-*N,N*-dimethylbenzamide (2.5 g, 12.2 mmol) in tetrahydrofuran (50 mL) under N_2 was added lithium aluminum hydride (1.0 M in THF, 24.5 mL, 24.5 mmol) dropwise. The mixture was stirred at rt for 20 min then heated to 75 °C for 15 min. The mixture was cooled to 0 °C before adding water (50 mL) followed by NaOH solution (50% in water, 50 mL). The mixture was warmed to rt and stirred for 1 h. The mixture was filtered through Celite® and the filter cake was washed with EtOAc (2 x 100 mL). The biphasic filtrate was mixed and the organic phase was collected. The aqueous phase was extracted with EtOAc (1 x 200 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel

chromatography (eluent: 0%-30% 2.0M NH_3 in MeOH in DCM) to provide 2-cyclopropyl-4-((dimethylamino)methyl)aniline (**Intermediate 6-A**, 1.72 g, 9.04 mmol, 74 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.95-7.01 (m, 2H), 6.64 (d, J=7.7 Hz, 1H), 3.78-4.08 (m, 2H), 3.39 (br s, 2H), 2.18-2.35 (m, 6H), 1.63-1.70 (m, 1H), 0.86-0.93 (m, 2H), 0.57-0.66 (m, 2H). m/z (ESI, +ve ion): 191.0 $(M+H)^+$

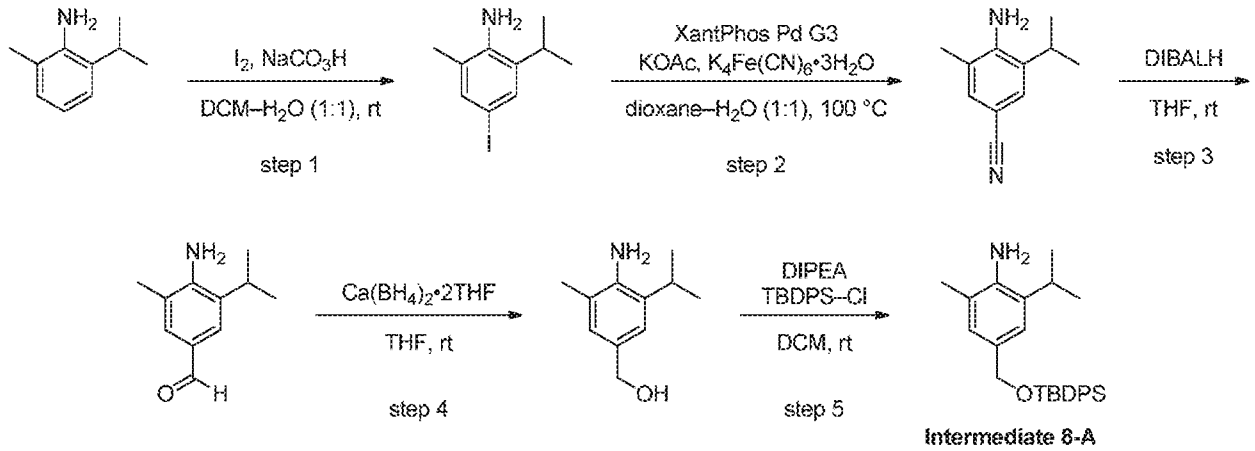
[0250] Intermediate 6-B: 2,5-Dichloro-6-(2-fluorophenyl)nicotinic acid



Intermediate 6-B

[0251] Step 1: 2,5-dichloro-6-(2-fluorophenyl)nicotinic acid. A mixture of 2,5,6-trichloronicotinic acid (1.03 g, 4.54 mmol, Combi-Blocks, San Diego, CA, USA), palladium tetrakis (0.131 g, 0.114 mmol), (2-fluorophenyl)boronic acid (0.70 g, 5.0 mmol, TCI America, Portland, OR, USA), and sodium carbonate (2.0 M in water, 6.82 mL, 13.6 mmol) in 1,4-dioxane (11 mL) was sparged with nitrogen and heated to 80 °C for 1 h then 90 °C for 5 h. The reaction mixture was diluted with EtOAc (150 mL), washed with 1.0 N aqueous citric acid (2 × 100 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to give 2,5-dichloro-6-(2-fluorophenyl)nicotinic acid (**Intermediate 6-B**, 1.27 g, 4.43 mmol, 97% yield) as an amber oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 14.13 (br s, 1 H) 8.49 (s, 1 H) 7.55 - 7.64 (m, 2 H) 7.38 - 7.44 (m, 2 H). *m/z* (ESI, +ve ion): 285.8 $(M+H)^+$.

[0252] Intermediate 8-A: 4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-isopropyl-6-methylaniline



[0253] Step 1: 4-Iodo-2-isopropyl-6-methylaniline. To a suspension of 2-isopropyl-6-methylaniline (3.2 mL, 20 mmol, Advanced Chemblocks Inc, Burlingame, CA, USA), and sodium bicarbonate (3.4 g, 40 mmol) in DCM (20 mL) and water (20 mL) was added iodine (5.4 g, 21 mmol) in three portions. After 90 min, the reaction was quenched by adding 1.0 N sodium thiosulfate (30 mL). The mixture was diluted with DCM (30 mL) and water (10 mL). The organic phase was collected and the aqueous layer was extracted with DCM (1 × 100 mL). The combined organic phases were washed with brine (300 mL), dried over $MgSO_4$ and concentrated in vacuo to afford a dark purple oil. The mixture was purified by silica gel chromatography (eluent: 0–30% EtOAc/heptane) to afford 4-iodo-2-isopropyl-6-methylaniline as a red-purple oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.11 (d, J = 6.8 Hz, 6 H), 2.04 (s, 3 H), 2.97 (sept, J = 6.8 Hz, 1 H), 4.73 (s, 2 H), 7.08 – 7.10 (s, 1 H), 7.10 – 7.13 (m, 1 H). *m/z* (ESI, +ve ion): 275.9 $(M+H)^+$.

[0254] Step 2: 4-Amino-3-isopropyl-5-methylbenzonitrile. A nitrogen-sparged suspension of 4-iodo-2-isopropyl-6-methylaniline (2.2 g, 7.9 mmol), XantPhos Pd G3 (170 mg, 0.20 mmol), potassium acetate (580 mg, 5.9 mmol), and potassium hexacyanoferrate(II) trihydrate (5.0 g, 12 mmol) in 1,4-dioxane (20 mL) and water (20 mL) was vigorously stirred at 100 °C for 4 h. The reaction mixture was diluted with water (200 mL) and EtOAc (150 mL). The layers were partitioned and the aqueous layer was further extracted with EtOAc (2 × 70 mL). The combined organic phases were dried over $MgSO_4$and concentrated in vacuo to afford a brown oil. The crude material was purified by silica gel chromatography (eluent: 0–40% EtOAc/heptane) to afford 4-

amino-3-isopropyl-5-methylbenzonitrile as an amber oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 – 1.18 (m, 6 H), 2.08 (s, 3 H), 3.02 (sept, J = 6.6 Hz, 1 H), 5.59 (br s, 2 H), 7.20 (br s, 1 H), 7.22 (br s, 1 H). *m/z* (ESI, +ve ion): 175.1 $(M+H)^+$.

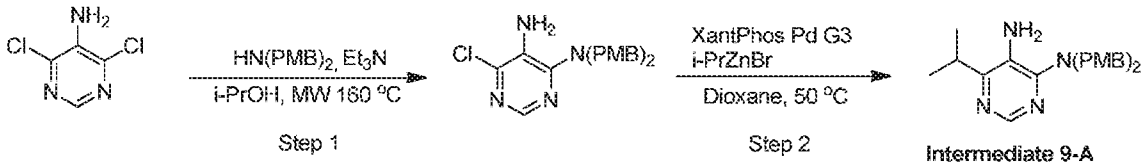
[0255] Step 3: 4-Amino-3-isopropyl-5-methylbenzaldehyde. Diisobutylaluminum hydride (1.0 M in toluene, 17 mL, 17 mmol) was added dropwise to a room temperature solution of 4-amino-3-isopropyl-5-methylbenzonitrile (1.2 g, 6.9 mmol) in THF (34 mL). After 20 min, the reaction mixture was cooled to 0 °C in an ice-water bath and quenched by adding 1.0 M aqueous Rochelle salt solution (35 mL). After stirring for 45 min, the reaction was diluted with EtOAc. The organic phase was collected and the aqueous phase was extracted with EtOAc (1 × 70 mL). The combined organic phases were washed with brine (300 mL), dried over $MgSO_4$, filtered through Celite®, and concentrated in vacuo. The crude material was purified by silica gel chromatography (eluent: 0–15% EtOAc/heptane) to afford 4-amino-3-isopropyl-5-methylbenzaldehyde as a thick yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (d, J = 6.6 Hz, 6 H), 2.14 (s, 3 H), 3.06 (sept, J = 6.6 Hz, 1 H), 5.75 (s, 2 H), 7.35 (s, 1 H), 7.44 (s, 1 H), 9.59 (s, 1 H). *m/z* (ESI, +ve ion)178.1 $(M+H)^+$.

[0256] Step 4: (4-Amino-3-isopropyl-5-methylphenyl)methanol. To a stirred solution of 4-amino-3-isopropyl-5-methylbenzaldehyde (970 mg, 5.5 mmol) in THF (8.0 mL) was added calcium borohydride bis(tetrahydrofuran) (1.8 g, 8.2 mmol). After stirring 2 h at rt, the reaction was slowly quenched by adding sat. NH_4Cl (30 mL) and diluted with EtOAc (20 mL). The layers were partitioned and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude (4-amino-3-isopropyl-5-methylphenyl)methanol which was carried forward without further purification. *m/z* (ESI, +ve ion): 180.2 $(M+H)^+$.

[0257] Step 5: 4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-isopropyl-6-methylaniline. To a solution of crude (4-amino-3-isopropyl-5-methylphenyl)methanol (710 mg, 4.0 mmol) in DCM (10 mL) was added DIPEA (1.4 mL, 8.2 mmol) and *tert*-butyl(chloro)diphenylsilane (1.7 mL, 6.6 mmol). After maintaining the solution at room temperature for 4 h, the mixture was concentrated under reduced pressure and then purified by silica gel chromatography (eluent: 0–40% EtOAc/heptane) to afford 4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-isopropyl-6-methylaniline (**Intermediate 8-A**). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.01 (s, 9 H), 1.11 (d, J = 6.8 Hz, 6 H), 2.05 (s, 3 H), 3.00 (sept, J = 6.7 Hz, 1 H), 4.48 (s, 2 H), 4.59 (s, 2 H), 6.71 (s, 1 H), 6.86 (d, J

= 1.2 Hz, 1 H), 7.38 – 7.49 (m, 6 H), 7.63 (dd, J = 7.8, 1.6 Hz, 4 H). *m/z* (ESI, +ve ion): 418.1 (M+H)+.

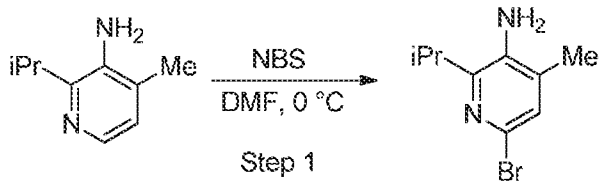
[0258] Intermediate 9-A: 6-Isopropyl-N^4,N^4-bis(4-methoxybenzyl)pyrimidine-4,5-diamine



[0259] Step 1: 6-Chloro-N^4,N^4-bis(4-methoxybenzyl)pyrimidine-4,5-diamine. To a solution of bis(4-methoxybenzyl)-amine (2.67 g, 10.37 mmol), and 4,6-dichloropyrimidin-5-amine (1.7 g, 10.37 mmol) in isopropanol (10.37 mL) was added triethylamine (2.89 mL, 20.7 mmol). The reaction was heated to 160 °C via microwave irradiation for 1 h. The reaction was cooled to rt and partitioned between EtOAc and water. The organic phase was separated, washed with water (2x) and brine, then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: 0-50% EtOAc/Heptane) to provide 6-chloro-N^4,N^4-bis(4-methoxybenzyl)pyrimidine-4,5-diamine (2.36 g, 6.13 mmol, 59.2 % yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.89 (s, 1 H) 7.12 (d, *J*=8.50 Hz, 4 H) 6.82 - 6.87 (m, 4 H) 5.19 (s, 2 H) 4.41 (s, 4 H) 3.72 (s, 6 H) 2.31 (s, 2 H). *m/z* (ESI, +ve ion): 384.8 $(M+H)^+$.

[0260] Step 2: 6-Isopropyl-N^4,N^4-bis(4-methoxybenzyl)pyrimidine-4,5-diamine. A flask was charged with 6-chloro-N^4,N^4-bis(4-methoxybenzyl)pyrimidine-4,5-diamine (2.36 g, 6.13 mmol), and XantPhos Pd 3 G dichloromethane adduct (0.32 g, 0.31 mmol, Strem Chemicals, Newburyport, MA, USA). The flask was sealed and evacuated / backfilled with N_2 (3x). 1,4-dioxane (6.13 mL) was added followed by 2-propylzinc bromide (0.5 M in THF, 24.5 mL, 12.3 mmol). The reaction was stirred in a pre-heated 50 °C oil bath for 16 h. The reaction mixture was partitioned between EtOAc and 50% sat. ammonium chloride solution. The organic phase was collected, washed with brine, and dried over $MgSO_4$. The crude residue was purified by silica gel chromatography (eluent: 10-90% EtOAc/heptane) to provide 6-isopropyl-N^4,N^4-bis(4-methoxybenzyl)pyrimidine-4,5-diamine (**Intermediate 9-A**, 2.36 g, 6.01 mmol, 98 % yield) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.06 (s, 1 H) 7.13 (d, *J*=8.50 Hz, 4 H) 6.83 (d, *J*=8.50 Hz, 4 H) 4.74 (s, 2 H) 4.28 (s, 4 H) 3.72 (s, 6 H) 3.18 - 3.30 (m, 1 H) 1.16 (d, *J*=6.63 Hz, 6 H). *m/z* (ESI, +ve ion): 392.8 $(M+H)^+$.

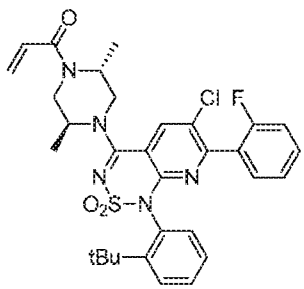
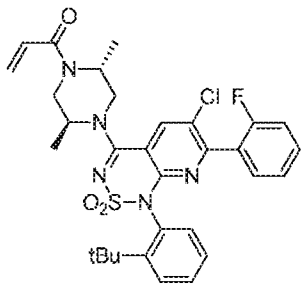
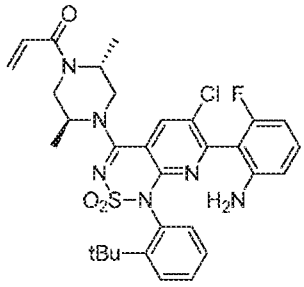
[0261] Intermediate 10-A: 6-bromo-2-isopropyl-4-methylpyridin-3-amine

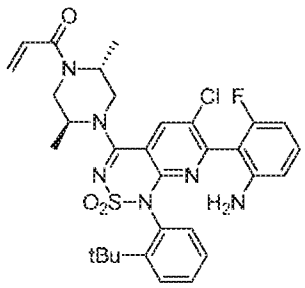
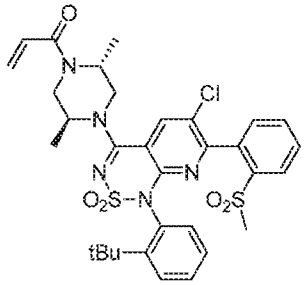
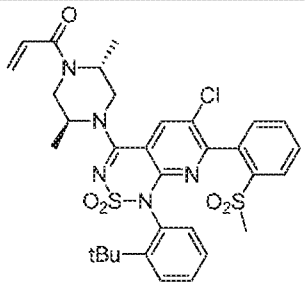
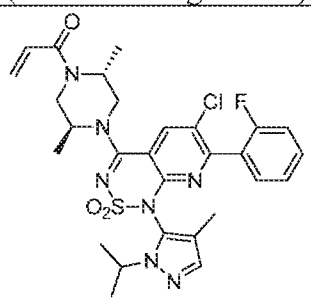
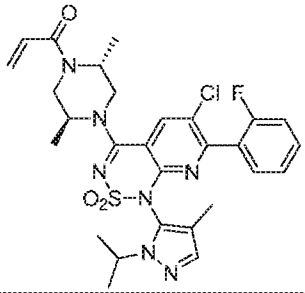


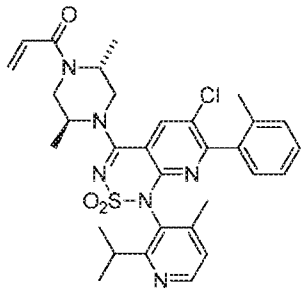
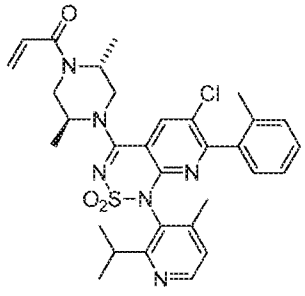
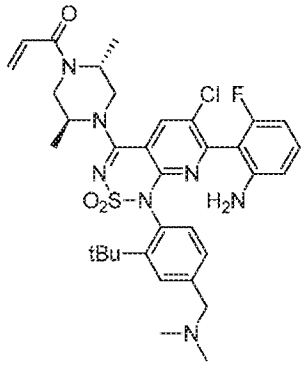
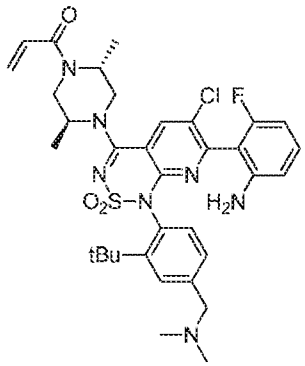
Intermediate 1-A **Intermediate 10-A**

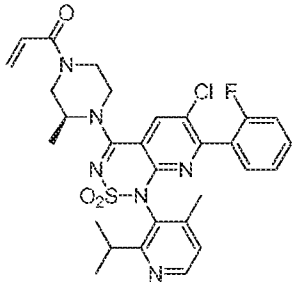
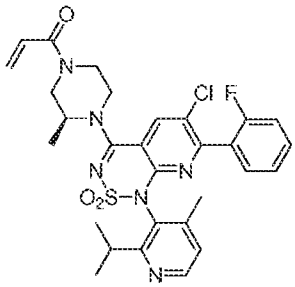
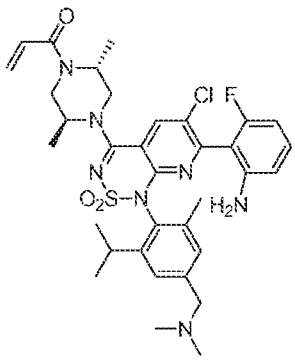
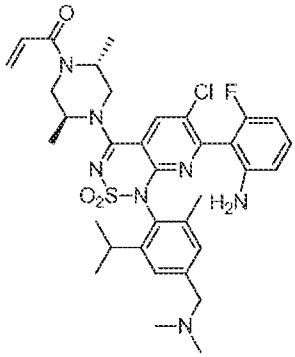
[0262] Step 1: 6-bromo-2-isopropyl-4-methylpyridin-3-amine. The title compound was prepared as described in the synthesis for **Intermediate 4-A**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 3.58 (br s, 2H), 2.96 (td, J=6.74, 13.48 Hz, 1H), 2.13 (s, 3H), 1.28 (d, J=6.63 Hz, 6H). *m/z* (ESI, +ve ion): 231.1 $(M+H)^+$.

Table 4: Separated Compounds, Including Atropisiomers

Ex. #	Chemical Structure	Name	Racemic SM/separation conditions
1-1-1	 (First eluting isomer)	1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(2-(2-methyl-2-propanyl)phenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**1-1/ SFC** (Chiralcel OD-H (5 µm, 21x250 mm) F=80 mL/min, 20% methanol, 80% carbon dioxide, 120 bar)
1-1-2	 (second eluting isomer)	1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(2-(2-methyl-2-propanyl)phenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**1-1/ SFC** (Chiralcel OD-H (5 µm, 21x250 mm) F=80 mL, 20% methanol, 80% carbon dioxide, 120 bar)
1-8-1		1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-1-(2-(*tert*-butyl)phenyl)-6-chloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one	**1-8/ SFC** (Chiralcel OX-H (5 µm, 4.6x250 mm) F= 80mL/min, 35% methanol, 65% carbon dioxide, 120 bar)

	(First eluting isomer)		
1-8-2	 (second eluting isomer)	1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-1-(2-(*tert*-butyl)phenyl)-6-chloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one	**1-8/ SFC** (Chiralcel OX-H (5 µm, 4.6x250 mm) F=80 mL/min, 35% methanol, 65% carbon dioxide, Back pressure= 120 bar)
1-10-1	 (first eluting isomer)	1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-1-(2-(*tert*-butyl)phenyl)-6-chloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one	**1-10/ SFC** (Chiralcel OD (5 µm, 21x250 mm) F=80 mL/min, 12% methanol, 88% carbon dioxide, 100 bar)
1-10-2	 (second eluting isomer)	1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-1-(2-(*tert*-butyl)phenyl)-6-chloro-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one	**1-10/ SFC** (Chiralcel OD (5 µm, 21x250 mm) F=80 mL/min, 12% methanol, 88% carbon dioxide, 100 bar)
1-11-1	 (first eluting isomer)	1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(4-methyl-1-(2-propanyl)-1*H*-pyrazol-5-yl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**1-11/SFC** (Chiralpak IC (5 µm, 21x250 mm) F=80 mL/min, 50% Methanol with 0.2% NEt_3, 50% carbon dioxide, 90 bar)
1-11-2		1-((2*R*,5*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(4-methyl-1-(2-propanyl)-1*H*-pyrazol-5-yl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-	**1-11/SFC** (Chiralpak IC (5 µm, 21x250 mm) F=80 mL/min, 50% Methanol with 0.2% NEt_3, 50% carbon dioxide, 90 bar)

	(second eluting isomer)	piperazinyl)-2-propen-1-one	
1-12-1	 (first eluting isomer)	1-((2*R*,5*S*)-4-(6-chloro-7-(2-methylphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**1-12 / SFC** (Chiralpak IC (5 µm, 21x250 mm) F=80 mL/min, 35% Methanol, 65% carbon dioxide
1-12-2	 (second eluting isomer)	1-((2*R*,5*S*)-4-(6-chloro-7-(2-methylphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**1-12/ SFC** (Chiralpak IC (5 µm, 21x250 mm) F=80 mL/min, 35% Methanol, 65% carbon dioxide
1-13-1	 (first eluting isomer)	1-((2*R*,5*S*)-4-(6-chloro-1-(4-((dimethylamino)methyl)-2-(2-methyl-2-propanyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**1-13 / SFC** (Chiralcel OJ-H (5 µm, 21x250 mm) F=80 mL/min, 15% Methanol with 0.2% Net_3, 85% carbon dioxide, 90 bar)
1-13-2	 (second eluting isomer)	1-((2*R*,5*S*)-4-(6-chloro-1-(4-((dimethylamino)methyl)-2-(2-methyl-2-propanyl)phenyl)-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**1-13 / SFC** (Chiralcel OJ-H (5 µm, 21x250 mm) F=80 mL/min, 15% Methanol with 0.2% Net_3, 85% carbon, 90 bar)

2-2-1	 (first eluting isomer)	1-((3*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methyl-1-piperazinyl)-2-propen-1-one	**2-2 / SFC** (Chiralpak IC (5 µm, 150x21 mm), F = 60 mL/min, 50% methanol with 50% carbon dioxide, 102 bar)
2-2-2	 (second eluting isomer)	1-((3*S*)-4-(6-chloro-7-(2-fluorophenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-3-methyl-1-piperazinyl)-2-propen-1-one	**2-2 / SFC** (Chiralpak IC (5 µm, 150x21 mm), F = 60 mL/min, 50% methanol with 50% carbon dioxide, 102 bar)
8-1	 (first eluting isomer)	1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-((dimethylamino)methyl)-2-methyl-6-(2-propanyl)phenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**8 / SFC** (Chiralpak AZ-H (5 µm, 21x250 mm) F=80 mL/min, 20% Ethanol with 0.4% triethylamine, 80% carbon dioxide)
8-2	 (second eluting isomer)	1-((2*R*,5*S*)-4-(7-(2-amino-6-fluorophenyl)-6-chloro-1-(4-((dimethylamino)methyl)-2-methyl-6-(2-propanyl)phenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**8 / SFC** (Chiralpak AZ-H (5 µm, 21x250 mm) F=80 mL/min, 20% Ethanol with 0.4% triethylamine, 80% carbon dioxide)

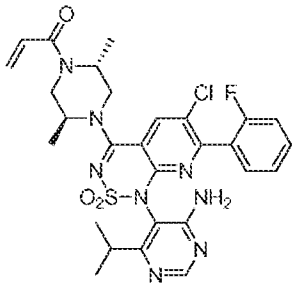
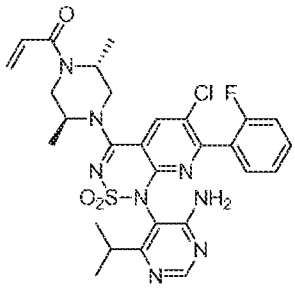
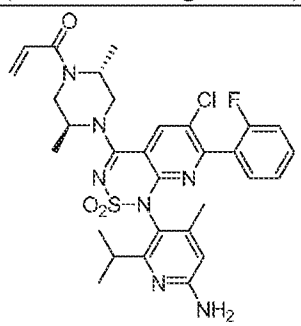
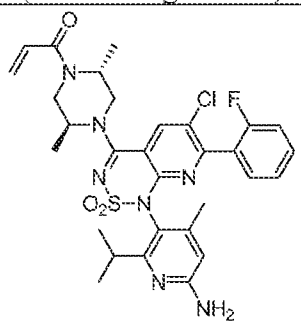
9-1	 (first eluting isomer)	1-((2*R*,5*S*)-4-(1-(4-amino-6-(2-propanyl)-5-pyrimidinyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**9 / SFC** (Chiralcel OX-H (5 µm, 21x250 mm) F=80 mL/min, 30% Methanol, 70% carbon dioxide)
9-2	 (second eluting isomer)	1-((2*R*,5*S*)-4-(1-(4-amino-6-(2-propanyl)-5-pyrimidinyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**9 / SFC** (Chiralcel OX-H (5 µm, 21x250 mm) F=80 mL/min, 30% Methanol, 70% carbon dioxide)
10-1	 (first eluting isomer)	1-((2*R*,5*S*)-4-(1-(6-amino-4-methyl-2-(2-propanyl)-3-pyridinyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**10/SFC** (Chiralcel OD-H (5 µm, 21x250 mm) two in series, F=80 mL/min, 20% Methanol with 80% carbon dioxide, 100 bar)
10-2	 (second eluting isomer)	1-((2*R*,5*S*)-4-(1-(6-amino-4-methyl-2-(2-propanyl)-3-pyridinyl)-6-chloro-7-(2-fluorophenyl)-2,2-dioxido-1*H*-pyrido[2,3-*c*][1,2,6]thiadiazin-4-yl)-2,5-dimethyl-1-piperazinyl)-2-propen-1-one	**10 / SFC** (Chiralcel OD-H (5 µm, 21x250 mm) two in series, F=80 mL/min, 20% Methanol with 80% carbon dioxide, 100 bar)

Table 5: Analytical Data

Ex. #	LRMS: (ESI + ve ion) *m/z*	NMR
1-1	610.0	^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 - 7.73 (m, 1H), 7.58 - 7.50 (m, 1H), 7.48 - 7.28 (m, 4H), 7.24

		- 7.20 (m, 1H), 7.18 - 7.05 (m, 2H), 6.67 - 6.46 (m, 1H), 6.44 - 6.32 (m, 1H), 5.83 - 5.75 (m, 1H), 5.22 - 4.76 (m, 1H), 4.64 - 4.01 (m, 2H), 3.59 (s, 2H), 1.69 - 1.56 (m, 1H), 1.52 – 1.30-1.46 (m, 6H), 1.30 - 1.23 (m, 9H); ^{19}F NMR (376 MHz, CDCl3) δ = -109.99 - -113.90 (m, 1F)
1-1-1	610.0	^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1H), 7.92 (s, 1H), 7.99 - 7.88 (m, 1H), 7.55 (dd, J=1.3, 8.0 Hz, 1H), 7.48 - 7.28 (m, 3H), 7.20 - 7.07 (m, 2H), 6.74 - 6.32 (m, 2H), 5.85 - 5.78 (m, 1H), 5.17 (br d, J=3.9 Hz, 1H), 4.66 - 4.13 (m, 3H), 3.82 - 3.47 (m, 2H), 1.66 - 1.46 (m, 6H), 1.28 (d, J=2.9 Hz, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -111.65 (s, 1F)
1-1-2	610.0	^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 - 7.82 (m, 1H), 7.57 - 7.46 (m, 2H), 7.45 - 7.28 (m, 4H), 7.20 - 7.04 (m, 2H), 6.65 - 6.49 (m, 1H), 6.45 - 6.34 (m, 1H), 5.80 (br d, J=10.4 Hz, 1H), 5.34 - 4.75 (m, 2H), 4.45 - 3.53 (m, 4H), 1.44-1.66 (br s, 6H), 1.28 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -111.53 (s, 1F)
1-2	597.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.08 - 10.30 (m, 1 H) 8.44 - 8.55 (m, 1 H) 7.37 - 7.50 (m, 2 H) 7.20 - 7.33 (m, 3 H) 6.77 - 6.94 (m, 1 H) 6.62 - 6.76 (m, 2 H) 6.14 - 6.26 (m, 1 H) 5.77 - 5.80 (m, 1 H) 4.56 - 4.74 (m, 1 H) 3.87 - 4.51 (m, 4 H) 3.46 - 3.82 (m, 2 H) 2.90 - 3.09 (m, 1 H) 1.34 (br d, J=6.22 Hz, 3 H) 1.14 (br d, J=6.84 Hz, 3 H) 1.01 (br t, J=6.74 Hz, 3 H)
1-3	596.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.36 - 8.54 (m, 1 H) 7.35 - 7.72 (m, 2 H) 7.20 - 7.33 (m, 2 H) 7.04 - 7.13 (m, 1 H) 6.79 - 6.94 (m, 1 H) 6.47 (br d, J=8.09 Hz, 1

		H) 6.35 (t, J=8.81 Hz, 1 H) 6.21 (br d, J=16.79 Hz, 1 H) 5.76 - 5.80 (m, 1 H) 5.10 - 5.34 (m, 2 H) 4.57 - 4.84 (m, 1 H) 4.15 - 4.49 (m, 2 H) 4.00 - 4.11 (m, 1 H) 3.50 - 3.85 (m, 2 H) 3.08 - 3.23 (m, 1 H) 2.97 - 3.08 (m, 1 H) 1.27 - 1.40 (m, 3 H) 1.15 (d, J=6.84 Hz, 3 H) 0.96 - 1.08 (m, 3 H)
1-4	611.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 - 10.33 (m, 1 H) 8.38 - 8.63 (m, 1 H) 7.36 - 7.50 (m, 2 H) 7.13 - 7.35 (m, 3 H) 6.61 - 6.87 (m, 3 H) 6.19 (br d, *J*=18.04 Hz, 1 H) 5.76 (ddd, *J*=10.21, 5.75, 1.87 Hz, 1 H) 4.37 - 4.87 (m, 2 H) 3.51 - 4.23 (m, 4 H) 2.80 - 3.05 (m, 1 H) 1.20 - 1.42 (m, 6 H) 1.12 (br dd, *J*=13.37, 6.95 Hz, 3 H) 0.92 - 1.05 (m, 3 H)
1-5	619.2	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.12 - 10.38 (m, 1 H) 9.10 (s, 1 H) 8.36 - 8.62 (m, 1 H) 7.26 - 7.36 (m, 1 H) 6.66 - 6.88 (m, 3 H) 6.19 (dd, *J*=16.79, 2.07 Hz, 1 H) 5.71 - 5.81 (m, 1 H) 4.41 - 4.90 (m, 2 H) 3.60 - 4.25 (m, 4 H) 2.85 - 3.08 (m, 1 H) 1.36 (br s, 3 H) 1.08 - 1.30 (m, 9 H)
1-6	610.3	^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, J=4.8 Hz, 1H), 7.43 - 7.28 (m, 3H), 7.20 - 7.04 (m, 4H), 6.64 - 6.44 (m, 1H), 6.42 - 6.30 (m, 1H), 5.82 - 5.71 (m, 1H), 5.06 - 4.28 (m, 2H), 4.06 - 3.28 (m, 4H), 2.71 - 2.51 (m, 3H), 2.51 - 2.38 (m, 1H), 1.47 - 1.32 (m, 6H), 1.21 - 1.13 (m, 3H), 1.07 (q, J=7.7 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -111.81 (s, 1F)
1-7	625.6	^{1}H NMR (400 MHz, , $CDCl_3$) δ = 7.97 (br s, 1H), 7.36 - 7.28 (m, 1H), 7.22 - 7.05 (m, 4H), 6.48 - 6.32 (m, 3H), 5.81 - 5.70 (m, 1H), 5.13 - 4.24 (m, 2H), 4.26 - 4.15 (m, 1H), 3.99 - 3.58 (m, 3H), 2.83

		- 2.59 (m, 1H), 2.54 - 2.21 (m, 3H), 1.41 (br d, J=6.8 Hz, 3H), 1.27 - 1.12 (m, 6H), 1.12 - 0.99 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -110.98 (s, 1F)
1-8-1	625.1	^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (br s, 1H), 7.57 (br d, J=8.1 Hz, 1H), 7.35-7.49 (m, 2H), 7.28-7.30 (m, 1H), 7.25 (s, 1H), 7.05-7.12 (m, 1H), 6.31-6.57 (m, 4H), 5.77 (m, 1H), 4.81-5.17 (m, 1H), 4.26 (m, 2H), 4.03 (br s, 1H), 3.90 (m, 1H), 3.41-3.83 (m, 2H), 1.40 (br s, 3H), 1.25 (s, 9H), 1.09-1.19 ppm (m, 3H); ^{19}F NMR ((376 MHz, $CDCl_3$): δ = -109.97 (s, 1F)
1-8-2	625.1	^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88-8.01 (m, 1H), 7.57 (d, J=7.7 Hz, 1H), 7.35-7.45 (m, 2H), 7.28-7.30 (m, 1H), 7.25 (s, 1H), 7.06-7.13 (m, 1H), 6.28-6.70 (m, 4H), 5.15 (br s, 1H), 4.14-4.74 (m, 3H), 3.43-4.04 (m, 2H), 3.04 (br s, 2H), 1.57-1.71 (m, 3H), 1.48 (m, 3H), 1.25 (s, 9H); ^{19}F NMR ((376 MHz, $CDCl_3$): δ = -110.18 ppm (s, 1F)
1-9	641.4	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.42 - 8.76 (m, 1 H) 7.89 - 8.04 (m, 1 H) 7.66 - 7.87 (m, 2 H) 7.20 - 7.57 (m, 4 H) 7.16 - 7.58 (m, 1 H) 6.77 - 6.94 (m, 1 H) 6.22 (br d, *J*=16.17 Hz, 1 H) 5.69 - 5.84 (m, 1 H) 3.33 - 4.92 (m, 7 H) 2.80 - 2.99 (m, 1 H) 2.53 - 2.75 (m, 3 H) 1.14 - 1.28 (m, 3 H) 0.99 - 1.13 (m, 3 H) 0.81 - 0.90 (m, 3 H)
1-10	670.1	^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 - 7.85 (m, 2H), 7.74 - 7.58 (m, 2H), 7.53 - 7.28 (m, 4H), 7.23 - 7.13 (m, 1H), 6.66 - 6.44 (m, 1H), 6.44 - 6.33 (m, 1H), 5.84 - 5.75 (m, 1H), 5.20 - 4.81 (m, 1H), 4.58 - 3.42 (m, 5H), 2.47 - 2.31

		(m, 3H), 1.62 - 1.37 (m, 3H), 1.33 (s, 9H), 1.30 - 1.18 (m, 3H)
1-10-1	670.1	^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 - 7.99 (m, 1H), 7.95 (br d, J=8.5 Hz, 1H), 7.75 - 7.58 (m, 2H), 7.55 - 7.48 (m, 2H), 7.41 - 7.26 (m, 2H), 7.20 - 7.14 (m, 1H), 6.67 - 6.45 (m, 1H), 6.43 - 6.33 (m, 1H), 5.80 (br t, J=9.4 Hz, 1H), 5.15 (br s, 1H), 4.79 - 3.97 (m, 3H), 3.78 - 3.40 (m, 2H), 2.35 (s, 3H), 1.68-1.56 (m, 6H), 1.33 (s, 9H)
1-10-2	670.1	^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 - 7.93 (m, 1H), 7.92 - 7.82 (m, 1H), 7.73 - 7.56 (m, 2H), 7.54 - 7.42 (m, 2H), 7.39 - 7.28 (m, 2H), 7.21 - 7.12 (m, 1H), 6.62 - 6.47 (m, 1H), 6.43 - 6.32 (m, 1H), 5.78 (br d, J=10.4 Hz, 1H), 4.95 (br s, 1H), 4.48 - 3.53 (m, 5H), 2.42 (s, 3H), 1.33 (s, 9H), 1.31 - 1.16 (m, 6H)
1-11	600.2	^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (s, 1H), 7.44-7.54 (m, 2H), 7.31-7.43 (m, 1H), 7.23-7.26 (m, 1H), 7.17 (t, J=9.1 Hz, 1H), 6.47-6.67 (m, 1H), 6.42 (br s, 1H), 5.83 (br d, J=10.0 Hz, 1H), 4.76-5.11 (m, 1H), 4.28-4.58 (m, 2H), 3.61-4.01 (m, 4H), 1.86-2.05 (m, 3H), 1.39-1.57 (m, 12H); ^{19}F NMR ((376MHz, CDCl3): δ = -112.10 ppm (s, 1F)
1-11-1	600.2	^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (s, 1H), 7.43-7.53 (m, 2H), 7.28-7.42 (m, 1H), 7.24 (d, J=7.5 Hz, 1H), 7.17-7.20 (m, 1H), 6.50-6.66 (m, 1H), 6.36-6.46 (m, 1H), 5.82 (br dd, J=9.7, 4.6 Hz, 1H), 4.31-5.14 (m, 3H), 3.31-4.22 (m, 4H), 1.95-2.05 (m, 3H), 1.24-1.51 ppm (m, 12H); ^{19}F NMR ((376 MHz, $CDCl_3$): δ = -112.08 ppm (s, 1F)

1-11-2	600.2	^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (s, 1H), 7.45-7.53 (m, 2H), 7.29-7.43 (m, 1H), 7.14-7.26 (m, 2H), 6.51-6.67 (m, 1H), 6.37-6.47 (m, 1H), 5.80-5.87 (m, 1H), 4.29-5.14 (m, 3H), 3.39-4.17 (m, 4H), 1.91 (br s, 3H), 1.25-1.54 (m, 12H); ^{19}F NMR ((376MHz, CDCl3): δ = -112.10 ppm (s, 1F)
1-12	606.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.54 - 8.68 (m, 1 H) 8.43 (dd, J=4.77, 2.69 Hz, 1 H) 7.31 - 7.39 (m, 1 H) 7.16 - 7.30 (m, 4 H) 6.75 - 6.89 (m, 1 H) 6.19 (br d, J=16.59 Hz, 1 H) 5.76 (ddd, J=10.26, 5.29, 2.28 Hz, 1 H) 4.38 - 4.84 (m, 2 H) 3.65 - 4.05 (m, 4 H) 2.91 - 3.22 (m, 1 H) 2.08 - 2.33 (m, 3 H) 1.97 - 2.01 (m, 3 H) 1.36 (br t, J=7.46 Hz, 3 H) 1.08 - 1.23 (m, 6 H) 0.80 - 0.91 (m, 3 H)
1-12-1	606.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (s, 1 H) 8.42 (d, J=4.77 Hz, 1 H) 7.31 - 7.39 (m, 1 H) 7.20 - 7.30 (m, 4 H) 6.73 - 6.88 (m, 1 H) 6.19 (br d, J=16.38 Hz, 1 H) 5.71 - 5.82 (m, 1 H) 4.40 - 4.80 (m, 2 H) 3.43 - 4.11 (m, 4 H) 3.09 - 3.17 (m, 1 H) 2.11 (br s, 3 H) 1.98 (s, 3 H) 1.36 (br t, J=7.46 Hz, 3 H) 1.08 - 1.25 (m, 6 H) 0.99 (br d, J=6.43 Hz, 3 H)
1-12-2	606.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.64 (d, J=4.35 Hz, 1 H) 8.42 (d, J=4.77 Hz, 1 H) 7.32 - 7.38 (m, 1 H) 7.17 - 7.30 (m, 4 H) 6.76 - 6.87 (m, 1 H) 6.19 (br d, J=16.38 Hz, 1 H) 5.76 (ddd, J=10.21, 5.34, 1.87 Hz, 1 H) 4.40 - 4.84 (m, 2 H) 3.45 - 4.15 (m, 4 H) 2.95 (dt, J=13.16, 6.48 Hz, 1 H) 2.28 (s, 3 H) 1.99 (s, 3 H) 1.30 - 1.42 (m, 3 H) 1.04 - 1.24 (m, 6 H) 0.84 (br d, J=6.22 Hz, 3 H)
1-13	666.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.21 - 8.76 (m, 1 H) 7.52 (td,

		J=5.96, 1.55 Hz, 1 H) 7.46 (br d, *J*=4.15 Hz, 1 H) 7.19 - 7.37 (m, 4 H) 7.15 - 7.39 (m, 1 H) 6.66 - 6.92 (m, 1 H) 6.11 - 6.27 (m, 1 H) 5.76 - 5.80 (m, 1 H) 4.49 - 4.96 (m, 2 H) 4.04 - 4.41 (m, 2 H) 3.67 - 3.95 (m, 2 H) 3.45 (br d, *J*=0.83 Hz, 2 H) 2.18 (s, 6 H) 1.35 - 1.56 (m, 3 H) 1.23 (d, *J*=8.71 Hz, 12 H)
1-13-1	667.2	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.25 (d, J=8.91 Hz, 1 H) 7.49 - 7.58 (m, 1 H) 7.45 (s, 1 H) 7.21 - 7.38 (m, 5 H) 6.69 - 6.91 (m, 1 H) 6.12 - 6.25 (m, 1 H) 5.71 - 5.82 (m, 1 H) 4.08 - 4.97 (m, 4 H) 3.48 - 3.90 (m, 2 H) 3.36 - 3.46 (m, 2 H) 2.07 - 2.22 (m, 6 H) 1.48 (br d, J=2.49 Hz, 3 H) 1.16 - 1.36 (m, 12 H)
1-13-2	667.2	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.46 - 8.76 (m, 1 H) 7.49 - 7.56 (m, 1 H) 7.44 (s, 1 H) 7.18 - 7.38 (m, 5 H) 6.69 - 6.87 (m, 1 H) 6.12 - 6.24 (m, 1 H) 5.70 - 5.81 (m, 1 H) 3.91 - 4.94 (m, 4 H) 3.52 - 3.88 (m, 2 H) 3.41 (s, 2 H) 2.15 (s, 6 H) 0.86 - 1.45 (m, 15 H)
2-1	581.9	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.98 - 1.08 (m, 3 H) 1.12 - 1.18 (m, 3 H) 1.22 - 1.36 (m, 3 H) 1.31 - 1.36 (m, 1 H) 2.98 - 3.09 (m, 1 H) 3.14 - 3.20 (m, 1 H) 3.56 - 4.76 (m, 5 H) 5.72 - 5.86 (m, 1 H) 6.14 - 6.29 (m, 1 H) 6.75 - 6.94 (m, 1 H) 7.22 - 7.48 (m, 7 H) 7.49 - 7.56 (m, 1 H) 8.45 - 8.61 (m, 1 H). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -113.5
2-2	596.9	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 (dd, *J* = 13.3, 6.6 Hz, 3 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 1.30 (br s, 3 H), 2.18 (d, *J* = 8.7 Hz, 3 H), 2.93 - 3.26 (m, 2 H), 3.50 - 4.82 (m, 6 H), 5.77 (dd, *J* = 10.5, 2.2 Hz, 1 H), 6.20 (br d, *J* = 16.0 Hz, 1 H), 6.74 - 6.93 (m, 1 H),

		7.23 (dd, *J* = 4.8, 2.7 Hz, 1 H), 7.27 - 7.36 (m, 2 H), 7.37 - 7.47 (m, 1 H), 7.50 - 7.61 (m, 1 H), 8.43 (d, *J* = 4.8 Hz, 1 H), 8.61 (br d, *J* = 7.1 Hz, 1 H); ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -113.69 (s, 1 F), -113.61 (s, 1 F)
2-2-1	596.9	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (d, *J* = 6.6 Hz, 3 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 1.29 (br d, *J* = 6.4 Hz, 3 H), 2.17 (s, 3 H), 2.92 - 3.05 (m, 0.5 H), 3.10 (sept, *J* = 6.6 Hz, 1 H), 3.16 - 3.25 (m, 0.5 H), 3.35 - 4.88 (m, 6 H), 5.71 - 5.82 (m, 1 H), 6.20 (br d, *J* = 17.2 Hz, 1 H), 6.75 - 6.92 (m, 1 H), 7.23 (d, *J* = 4.8 Hz, 1 H), 7.26 - 7.35 (m, 2 H), 7.39 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.50 - 7.60 (m, 1 H), 8.43 (d, *J* = 4.8 Hz, 1 H), 8.62 (s, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -113.60 (s, 1 F)
2-2-2	597.1	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 (d, *J* = 6.6 Hz, 3 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 1.30 (br d, *J* = 5.0 Hz, 3 H), 2.19 (s, 3 H), 3.01 - 3.12 (m, 1.5 H), 3.15 - 3.26 (m, 0.5 H), 3.37 - 4.82 (m, 6 H), 5.71 - 5.82 (m, 1 H), 6.20 (br d, *J* = 16.8 Hz, 1 H), 6.73 - 6.95 (m, 1 H), 7.24 (d, *J* = 4.8 Hz, 1 H), 7.27 - 7.36 (m, 2 H), 7.37 - 7.44 (m, 1 H), 7.49 - 7.60 (m, 1 H), 8.43 (d, *J* = 4.8 Hz, 1 H), 8.61 (s, 1 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -113.69 (s, 1 F)
2-3	596	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.91 - 1.44 (m, 12 H) 2.85 - 2.97 (m, 1 H) 3.17 (d, *J*=5.18 Hz, 1 H) 3.50 - 4.19 (m, 4 H) 4.36 - 4.85 (m, 2 H) 5.68 - 5.82 (m, 1 H) 6.11 - 6.25 (m, 1 H) 6.72 - 6.88 (m, 1 H) 7.13 - 7.59 (m, 7 H) 8.41 - 8.64 (m, 1 H). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -113.65 (m, 1 F) -113.45 (m, 1 F)

2-4	626.0	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.98 (t, *J*=6.01 Hz, 6 H) 1.18 (dd, *J*=6.63, 2.28 Hz, 6 H) 1.30 (br d, *J*=5.18 Hz, 3 H) 2.99 - 3.12 (m, 2 H) 3.17 (d, *J*=5.39 Hz, 1 H) 3.51 - 3.82 (m, 2 H) 3.97 - 4.24 (m, 2 H) 4.27 - 4.50 (m, 1 H) 4.58 - 4.78 (m, 1 H) 5.72 - 5.81 (m, 1 H) 6.15 - 6.25 (m, 1 H) 6.76 - 6.94 (m, 1 H) 7.26 - 7.41 (m, 3 H) 7.50 - 7.59 (m, 1 H) 8.66 (s, 1 H) 9.09 (s, 1 H)
3-1	638.8	^{1}H NMR (DMSO-d_6) δ: 8.45-8.58 (m, 1H), 7.48-7.58 (m, 1H), 7.14-7.38 (m, 6H), 6.74-6.92 (m, 1H), 6.20 (br d, J=17.8 Hz, 1H), 5.74-5.79 (m, 1H), 4.54-4.81 (m, 1H), 3.95-4.49 (m, 3H), 3.44-3.88 (m, 2H), 3.39 (s, 2H), 3.28 (br s, 1H), 2.97-3.08 (m, 1H), 2.14 (s, 6H), 1.21-1.37 (m, 3H), 1.15 (d, J=6.8 Hz, 3H), 1.02 (dd, J=10.1, 6.9 Hz, 3H). ^{19}F NMR (DMSO-d_6) δ: -113.30 (s, 1F)
3-2	596.0	^{1}H NMR (DMSO-d_6) δ: 8.42-8.64 (m, 1H), 7.49-7.58 (m, 1H), 7.25-7.44 (m, 7H), 6.74-6.91 (m, 1H), 6.20 (br d, J=16.4 Hz, 1H), 5.72-5.81 (m, 1H), 4.52-4.87 (m, 1H), 4.26-4.50 (m, 1H), 4.13-4.26 (m, 1H), 3.92-4.09 (m, 1H), 3.41-3.79 (m, 1H), 2.25-2.48 (m, 4H), 1.80 (dq, J=12.9, 6.5 Hz, 1H), 1.15-1.40 (m, 3H), 0.76 (d, J=6.4 Hz, 3H), 0.70 (t, J=6.6 Hz, 3H) .^{19}F NMR (DMSO-d_6) δ: -113.25 (s, 1F)
4	668.3	^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 - 7.98 (m, 1H), 7.55 - 7.40 (m, 2H), 7.39 - 7.30 (m, 1H), 7.25 (d, J=6.7 Hz, 1H), 7.21 - 7.09 (m, 1H), 6.77 - 6.28 (m, 2H), 5.93 - 5.78 (m, 1H), 4.93 - 4.21 (m, 3H), 4.04 - 3.53 (m, 5H), 3.17 - 3.03 (m, 1H), 2.97 - 2.90 (m, 6H), 2.19 (m, 3H), 1.50 (d, J=6.4 Hz, 6H),

		1.44 (d, J=6.6 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -112.27 (s, 1F)
5	582.0	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 - 1.34 (m, 9 H) 2.92 - 3.09 (m, 1 H) 3.51 - 3.80 (m, 2 H) 3.95 - 4.24 (m, 2 H) 4.26 - 4.36 (m, 1 H) 4.38 - 4.54 (m, 1 H) 4.56 - 4.74 (m, 1 H) 5.67 - 5.87 (m, 1 H) 6.10 - 6.30 (m, 1 H) 6.66 - 6.78 (m, 2 H) 6.78 - 6.94 (m, 1 H) 7.22 - 7.34 (m, 3 H) 7.37 - 7.49 (m, 2 H) 8.22 - 8.50 (m, 1 H) 10.12 - 10.38 (m, 1 H)
6	651.0	^{1}H NMR (DMSO-d_6) δ: 8.32-8.64 (m, 1H), 7.49-7.59 (m, 1H), 7.14-7.44 (m, 5H), 6.95 (d, J=1.5 Hz, 1H), 6.79 (br dd, J=16.6, 10.4 Hz, 1H), 6.18 (br d, J=16.8 Hz, 1H), 5.69-5.80 (m, 1H), 4.47-4.90 (m, 2H), 3.91-4.44 (m, 2H), 3.56-3.88 (m, 2H), 3.35 (s, 2H), 2.12 (s, 6H), 1.62-1.87 (m, 1H), 1.02-1.46 (m, 6H), 0.33-0.82 (m, 4H). ^{19}F NMR (DMSO-d_6) δ: -113.21--112.90 (m, 1F)
7	478.1	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 - 1.22 (m, 3 H), 1.23 - 1.31 (m, 3 H), 3.38 - 4.85 (m, 6 H), 5.69 - 5.80 (m, 1 H), 6.17 (dd, J = 16.7, 2.2 Hz, 1 H), 6.70 - 6.89 (m, 1 H), 7.33 - 7.46 (m, 2 H), 7.53 - 7.67 (m, 2 H), 8.34 (s, 1 H), 12.29 (br s, 1 H); ^{19}F NMR (376 MHz, DMSO-d6) δ ppm -113.69 (s, 1 F)
8	681.6	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.97 - 8.04 (m, 1 H) 7.06 - 7.21 (m, 3 H) 6.34 - 6.68 (m, 4 H) 5.75 - 5.85 (m, 1 H) 4.54 - 5.09 (m, 2 H) 4.29 - 4.45 (m, 1 H) 4.05 - 4.19 (m, 1 H) 3.63 - 3.99 (m, 4 H) 3.37 - 3.58 (m, 2 H) 2.75 - 3.11 (m, 1 H) 2.06 - 2.36 (m, 9 H) 1.22 - 1.48 (m, 12 H)

8-1	681.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.34 - 8.62 (m, 1 H) 7.15 (s, 1 H) 6.98 - 7.12 (m, 2 H) 6.77 - 6.90 (m, 1 H) 6.43 - 6.55 (m, 1 H) 6.31 - 6.40 (m, 1 H) 6.19 (br dd, *J*=16.69, 2.18 Hz, 1 H) 5.69 - 5.81 (m, 1 H) 5.16 - 5.31 (m, 2 H) 4.57 - 4.72 (m, 2 H) 3.79 - 4.25 (m, 4 H) 3.36 (s, 2 H) 2.97 - 3.09 (m, 1 H) 1.98 - 2.25 (m, 9 H) 1.00 - 1.28 (m, 12 H)
8-2	681.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.46 - 8.58 (m, 1 H) 7.04 - 7.17 (m, 3 H) 6.76 - 6.88 (m, 1 H) 6.47 (m, 1 H) 6.30 - 6.41 (m, 1 H) 6.19 (m, 1 H) 5.76 (m, 1 H) 5.14 - 5.35 (m, 2 H) 4.45 - 4.81 (m, 3 H) 3.80 - 4.08 (m, 3 H) 3.36 (s, 2 H) 2.74 - 2.88 (m, 1 H) 2.18 - 2.24 (m, 3 H) 2.16 (s, 6 H) 1.02 - 1.16 (m, 9 H) 0.78 - 0.92 (m, 3 H)
9	612.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.39 - 8.52 (m, 1 H) 8.32 (d, *J*=3.11 Hz, 1 H) 7.53 - 7.62 (m, 1 H) 7.41 - 7.50 (m, 1 H) 7.31 - 7.40 (m, 2 H) 6.50 - 6.92 (m, 2 H) 6.47 - 7.00 (m, 1 H) 6.20 (dt, *J*=16.69, 2.64 Hz, 1 H) 5.71 - 5.82 (m, 1 H) 4.45 - 4.88 (m, 2 H) 3.62 - 4.21 (m, 4 H) 2.77 - 2.93 (m, 1 H) 1.31 - 1.45 (m, 3 H) 1.19 - 1.26 (m, 3 H) 1.08 (dd, *J*=6.63, 2.90 Hz, 3 H) 0.94 (dd, *J*=12.85, 6.84 Hz, 3 H)
9-1	612.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.40 - 8.47 (m, 1 H) 8.32 (s, 1 H) 7.53 - 7.62 (m, 1 H) 7.41 - 7.48 (m, 1 H) 7.30 - 7.39 (m, 2 H) 6.45 - 7.04 (m, 3 H) 6.19 (dd, *J*=16.59, 2.49 Hz, 1 H) 5.72 - 5.80 (m, 1 H) 4.44 - 4.85 (m, 2 H) 3.68 - 4.20 (m, 4 H) 2.77 - 2.89 (m, 1 H) 1.40 (m, 3 H) 1.19 - 1.31 (m, 3 H) 1.08 (d, *J*=6.63 Hz, 3 H) 0.92 (br d, *J*=6.63 Hz, 3 H)
9-2	612.6	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.49 (s, 1 H) 8.33 (s, 1 H)

		7.58 (tdd, *J*=7.77, 7.77, 5.49, 1.76 Hz, 1 H) 7.40 - 7.48 (m, 1 H) 7.28 - 7.39 (m, 2 H) 6.52 - 6.92 (m, 3 H) 6.20 (dd, *J*=16.59, 2.28 Hz, 1 H) 5.77 (ddd, *J*=10.21, 7.52, 2.18 Hz, 1 H) 4.49 - 4.89 (m, 2 H) 3.65 - 4.19 (m, 4 H) 2.87 (dt, *J*=13.22, 6.56 Hz, 1 H) 1.33 - 1.42 (m, 3 H) 1.17 - 1.31 (m, 3 H) 1.09 (d, *J*=6.63 Hz, 3 H) 0.95 (d, *J*=6.63 Hz, 3 H)
10	626.2	^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (br d, J=5.6 Hz, 1H), 7.47 - 7.30 (m, 2H), 7.23 - 7.07 (m, 2H), 6.64 - 6.44 (m, 1H), 6.42 - 6.20 (m, 2H), 5.83 - 5.73 (m, 1H), 5.07 - 4.54 (m, 2H), 4.52 - 4.28 (m, 3H), 4.00 - 3.31 (m, 3H), 3.11 - 2.79 (m, 1H), 2.24 - 2.01 (m, 3H), 1.46 - 1.15 (m, 12H)
10-1	626.2	^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, J=5.6 Hz, 1H), 7.55 - 7.43 (m, 1H), 7.41 - 7.30 (m, 1H), 7.26 - 7.14 (m, 2H), 6.68 - 6.51 (m, 1H), 6.47 - 6.36 (m, 1H), 6.33 (br s, 1H), 5.87 - 5.80 (m, 1H), 5.14 - 4.64 (m, 2H), 4.57 - 4.33 (m, 2H), 4.07 - 3.65 (m, 4H), 2.98 - 2.85 (m, 1H), 2.36 - 2.15 (m, 3H), 1.52 - 1.18 (m, 12H); ^{19}F NMR ((37 6MHz, $CDCl_3$): δ = -112.32 (s, 1F)
10-2	626.2	^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (br s, 1H), 7.53 - 7.42 (m, 1H), 7.37 (br t, J=7.3 Hz, 1H), 7.26 - 7.20 (m, 1H), 7.14 (t, J=9.1 Hz, 1H), 6.67 - 6.49 (m, 1H), 6.47 - 6.26 (m, 2H), 5.85 - 5.75 (m, 1H), 5.16 - 4.33 (m, 3H), 4.22 - 3.63 (m, 3H), 3.39 (br d, J=11.0 Hz, 1H), 3.49 - 2.87 (m, 2H), 2.13 (m, 3H), 1.48 - 1.21 (m, 12H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -112.42 (s, 1F)

Biological Analysis

[0263] For compounds in Table 6, the following assay conditions were employed:

[0264] **Coupled Nucleotide Exchange Assay**: Purified GDP-bound KRAS protein (aa 1-169), containing both G12C and C118A amino acid substitutions and an *N*-terminal His-tag, was pre-incubated in assay buffer (25 mM HEPES pH 7.4, 10 mM $MgCl_2$, and 0.01% Triton X-100) with a compound dose-response titration for either 5 min or 2 hours (see Table 15). Following compound pre-incubation, purified SOS protein (aa 564-1049) and GTP (Roche 10106399001) were added to the assay wells and incubated for an additional 30 min (for 5 min compound pre-incubation) or 1 hour (for 2 hour compound pre-incubation). To determine the extent of inhibition of SOS-mediated nucleotide exchange, purified GST-tagged cRAF (aa 1-149), nickel chelate AlphaLISA acceptor beads (PerkinElmer AL108R), and AlphaScreen glutathione donor beads (PerkinElmer 6765302) were added to the assay wells and incubated for 10 minutes. The assay plates were then read on a PerkinElmer EnVision Multilabel Reader, using AlphaScreen® technology, and data were analyzed using a 4-parameter logistic model to calculate IC_{50} values.

[0265] **Phospho-ERK1/2 MSD Assay**: MIA PaCa-2 (ATCC® CRL-1420™) cells were cultured in RPMI 1640 Medium (ThermoFisher Scientific 11875093) containing 10% fetal bovine serum (ThermoFisher Scientific 16000044) and 1x penicillin-streptomycin-glutamine (ThermoFisher Scientific 10378016). Sixteen hours prior to compound treatment, MIA PaCa-2 cells were seeded in 96-well cell culture plates at a density of 25,000 cells/well and incubated at 37°C, 5% CO_2. A compound dose-response titration was diluted in growth media, added to appropriate wells of a cell culture plate, and then incubated at 37°C, 5% CO_2 for 2 or 4 hours. Following compound treatment, cells were stimulated with 10 ng/mL EGF (Roche 11376454001) for 10 min, washed with ice-cold Dulbecco's phosphate-buffered saline, no Ca^{2+} or Mg^{2+} (ThermoFisher Scientific 14190144), and then lysed in RIPA buffer (50 mM Tris-HCl pH 7.5, 1% Igepal, 0.5% sodium deoxycholate, 150 mM NaCl, and 0.5% sodium dodecyl sulfate) containing protease inhibitors (Roche 4693132001) and phosphatase inhibitors (Roche 4906837001). Phosphorylation of ERK1/2 in compound-treated lysates was assayed using Phospho-ERK1/2 Whole Cell Lysate kits (Meso Scale Discovery K151DWD) according to the manufacturer's protocol. Assay plates were read on a Meso Scale Discovery Sector Imager 6000, and data were analyzed using a 4-parameter logistic model to calculate IC_{50} values.

Table 6: Biochemical and Cellular Activity of Compounds

(-) denotes not tested

Ex. #	Coupled Exchange IC_{50} (μM)	p-ERK IC_{50} (MIA-PaCa-2, μM)
1-1	0.32	-
1-1-1	0.15	0.22
1-1-2	70.8	-
1-2	0.15	0.27
1-3	0.06	0.07
1-4	0.17	0.16
1-5	0.10	0.11
1-6	2.69	-
1-7	0.89	-
1-8-1	0.01	0.05
1-8-2	69.3	-
1-9	0.19	0.18
1-10	0.11	0.11
1-10-1	0.08	0.06
1-10-2	5.95	-
1-11	0.20	0.20
1-11-1	0.54	-
1-11-2	0.15	0.33
1-12	0.60	-
1-12-1	0.22	0.29
1-12-2	3.55	-
1-13	0.08	0.07
1-13-1	0.04	0.05
1-13-2	3.87	-
2-1	0.17	0.34
2-2	0.53	-
2-2-1	0.24	0.27
2-2-2	2.98	1.52
2-3	0.18	0.24
2-4	0.29	0.31
3-1	0.15	0.09
3-2	0.80	-
4	5.96	-
5	1.03	-
6	0.15	0.15
7	16.4	-
8	0.19	0.27
8-1	0.08	0.08
8-2	1.46	-

9	0.25	0.15
9-1	0.17	0.11
9-2	11.2	-
10	1.27	-
10-1	3.5	-
10-2	0.39	-

[0266] The present invention is described in connection with preferred embodiments. However, it should be appreciated that the invention is not limited to the disclosed embodiments. It is understood that, given the description of the embodiments of the invention herein, various modifications can be made by a person skilled in the art. Such modifications are encompassed by the claims below.

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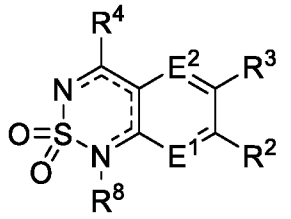
What is claimed is:

1. A compound having a structure of formula (I)



(I)

wherein

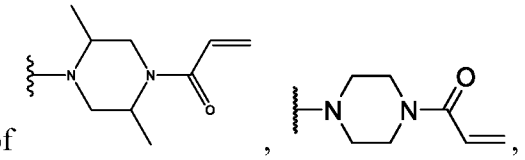
E^1 and E^2 are each independently N or CR^1;

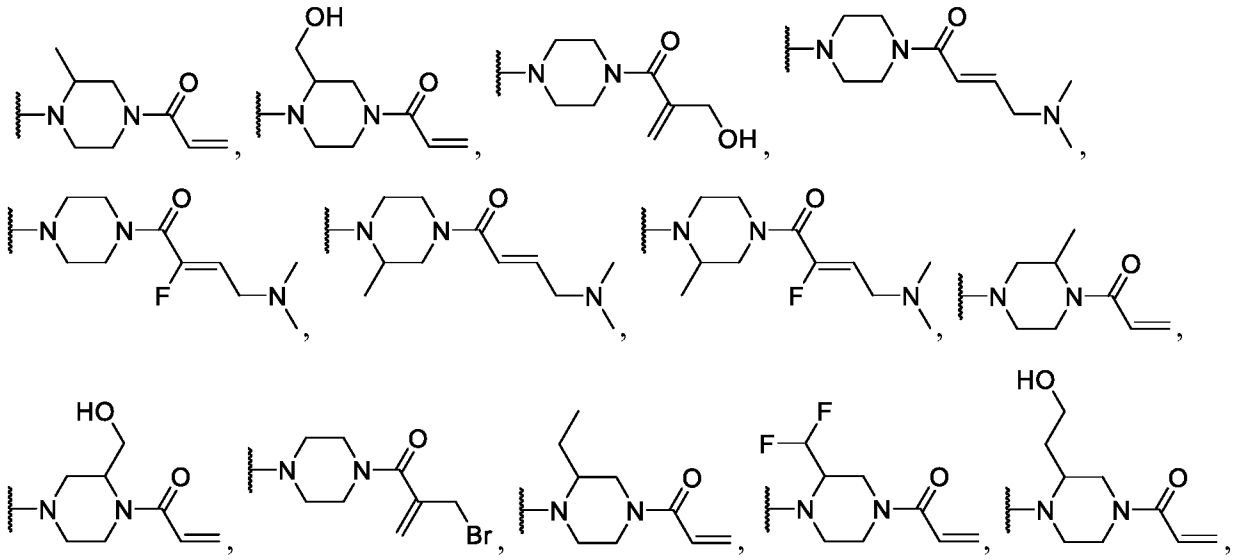
⎓ is a single or double bond as necessary to give every atom its normal valence;

R^1 is independently H, hydroxy, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N(C_{1-4}alkyl)$_2$, cyano, or halo;

R^2 is substituted aryl;

R^3 is halo, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -OC_{1-6}alkyl, C_{3-6}cycloalkyl, -C_{2-14}heterocycloalkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, aryl, or heteroaryl;

R^4 is selected from the group consisting of 



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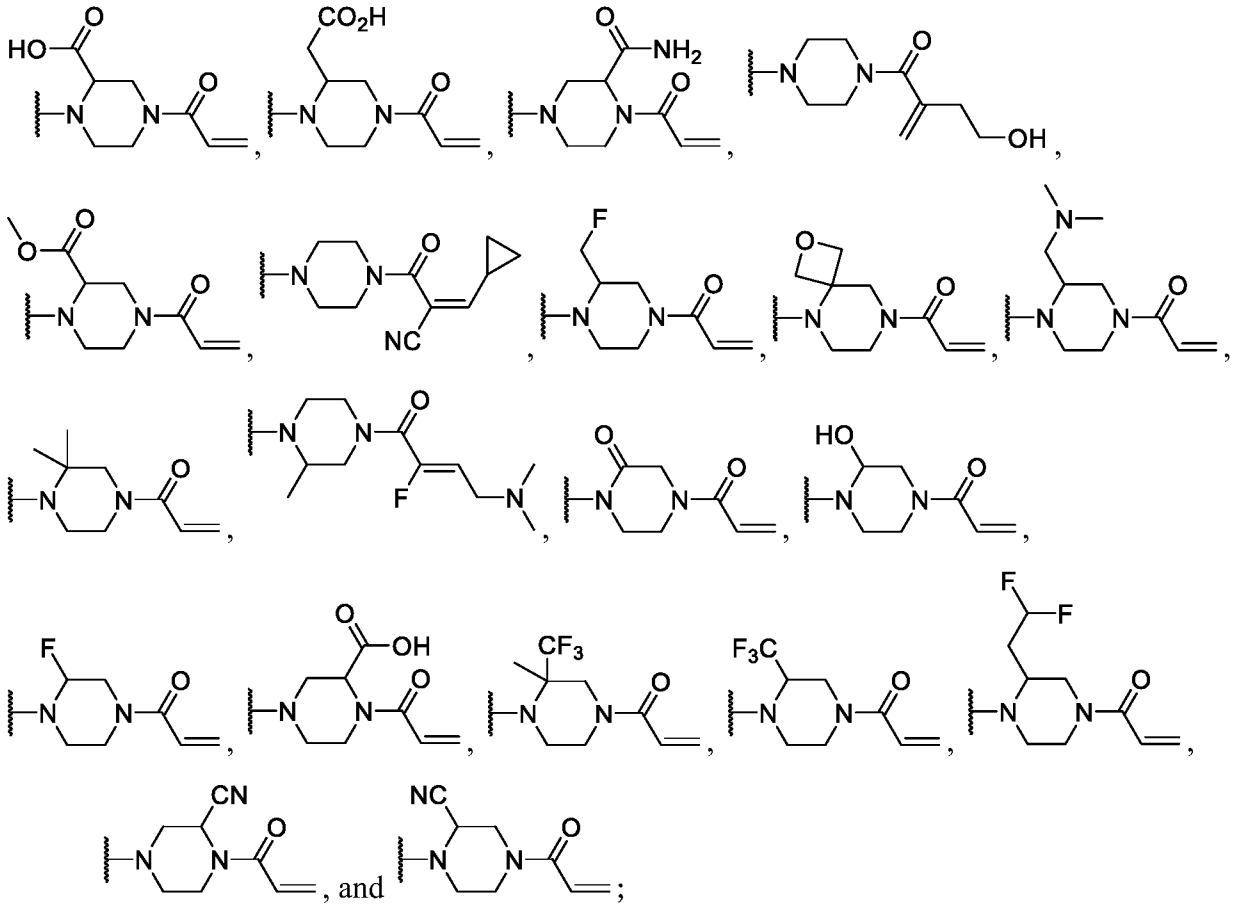

R^8 is -C_{6-14}aryl or -C_{3-14}heteroaryl;

wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups of any of the R^2, R^3 and R^8 substituents have 1, 2, 3, or 4 heteroatoms independently selected from O, N, or S, wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, and the -OC_{1-6}alkyl of any of the R^1, R^2, R^3 and R^8 substituents are unsubstituted or substituted by 1, 2, or 3 R^9 substituents independently selected from OH, -OC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, halo, -O-haloC_{1-6}alkyl, -CN, -NR^aR^b, -OSO_2R^a, -SO_2R^a, -(=O), -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, -O-$SiR^aR^bR^c$, -$SiR^aR^bR^c$, -O-(3- to 10-membered heterocycloalkyl), a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N, or S, wherein the

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cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl group of any of the R^1, R^2, R^3, R^8, and R^9 substituents can be unsubstituted or substituted with 1, 2, 3, or 4 R^{10} substituents independently selected from OH, halo, $-NR^cR^d$, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-C_{1-6}$alkyl-OH, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, $-C_{1-6}$haloalkyl, -O-haloC_{1-6}alkyl, $-SO_2R^c$, -CN, $-C(=O)NR^cR^d$, $-C(=O)R^c$, $-OC(=O)R^a$, $-C(=O)OR^c$, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups of R^{10} have 1, 2, 3, or 4 heteroatoms independently selected from O, N, or S, wherein the cycloalkyl, spirocycloalkyl, and spiroheterocycloalkyl groups of R^{10} or the heterocycloalkyl group of R^{10} may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

wherein each R^a, R^b, R^c, and R^d is independently hydrogen, OH, $-C_{1-6}$alkyl, phenyl, $-C_{1-6}$alkyl–C(=O)OH, $-C_{1-6}$alkyl–C(=O)-O-C_{1-6}alkyl, $-C_{1-6}$alkyl–3- to 12-membered cycloalkyl, $-C_{1-6}$alkyl–3- to 12-membered heterocycloalkyl, $-C_{1-6}$alkyl–6- to 12-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl group, heterocycloalkyl group of R^a, R^b, R^c, and R^d or the heterocycloalkyl group of the $-C_{1-6}$alkyl–heterocycloalkyl group of R^a, R^b, R^c, and R^d has from 1, 2, 3, or 4 heteroatoms independently selected from O, N, or S, wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the $-C_{1-6}$alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may include a double bond, and further wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the $-C_{1-6}$alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may contain a C=O group; and

the alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl groups of R^a, R^b, R^c, and R^d or the heterocycloalkyl groups of the $-C_{1-6}$alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with from 1, 2, 3, or 4 R^{12} substituents,wherein each R^{12} is

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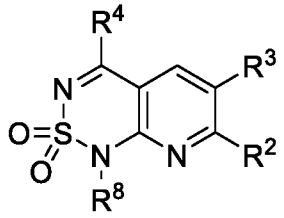
independently selected from H, OH, halo, -C_{1-6}alkyl, $N(CH_3)_2$, -C_{1-6}haloalkyl, $C(=O)CH_3$, -$C(=O)OCH_3$, or -C_{1-6}alkyl-O-C_{1-6}alkyl; or

a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

2. A compound of claim 1 having a structure of formula (Ia)



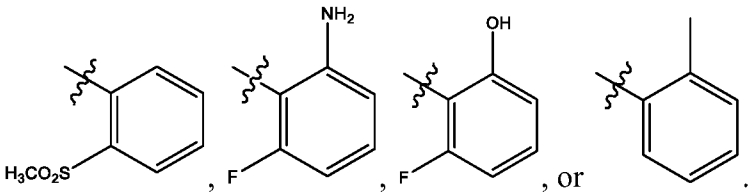
(Ia); or

a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

3. The compound of claim 1 wherein R^1 is H.

4. The compound of any one of claims 1-3 wherein R^2 is a fluorinated phenyl.

5. The compound of claim any one of claims 1 to 3 wherein R^2 is



, or .

6. The compound of any one of claims 1-5 wherein R^3 is halo.

7. The compound of claim 6 wherein R^3 is Cl.

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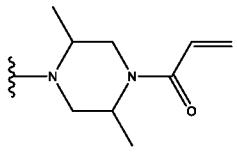
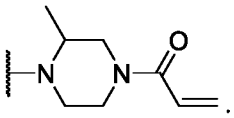
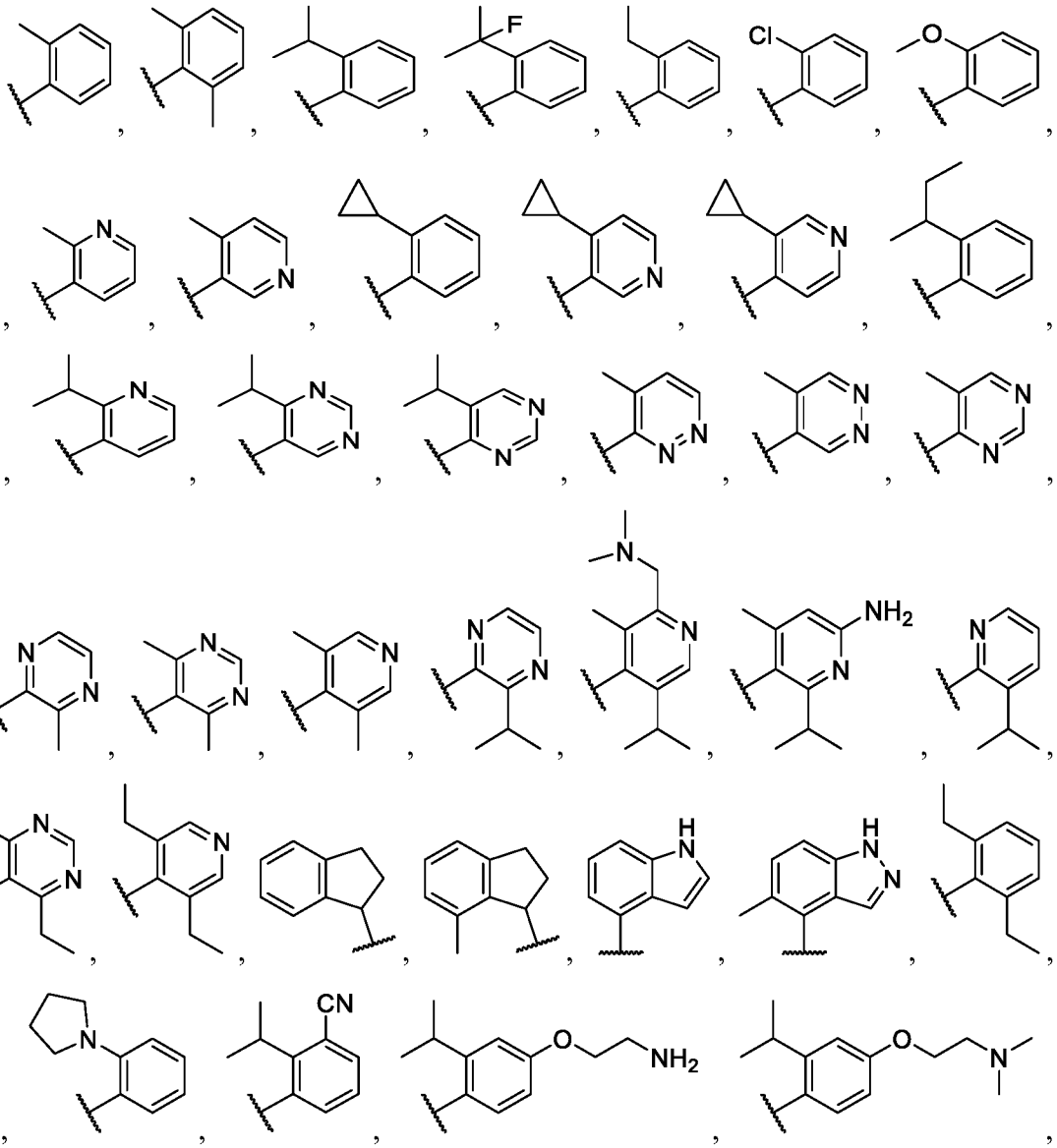
8. The compound of any one of claims 1 to 7, wherein R^4 is  or  .

9. The compound of any one of claims 1-8, wherein R^8 is selected from the group consisting of  .

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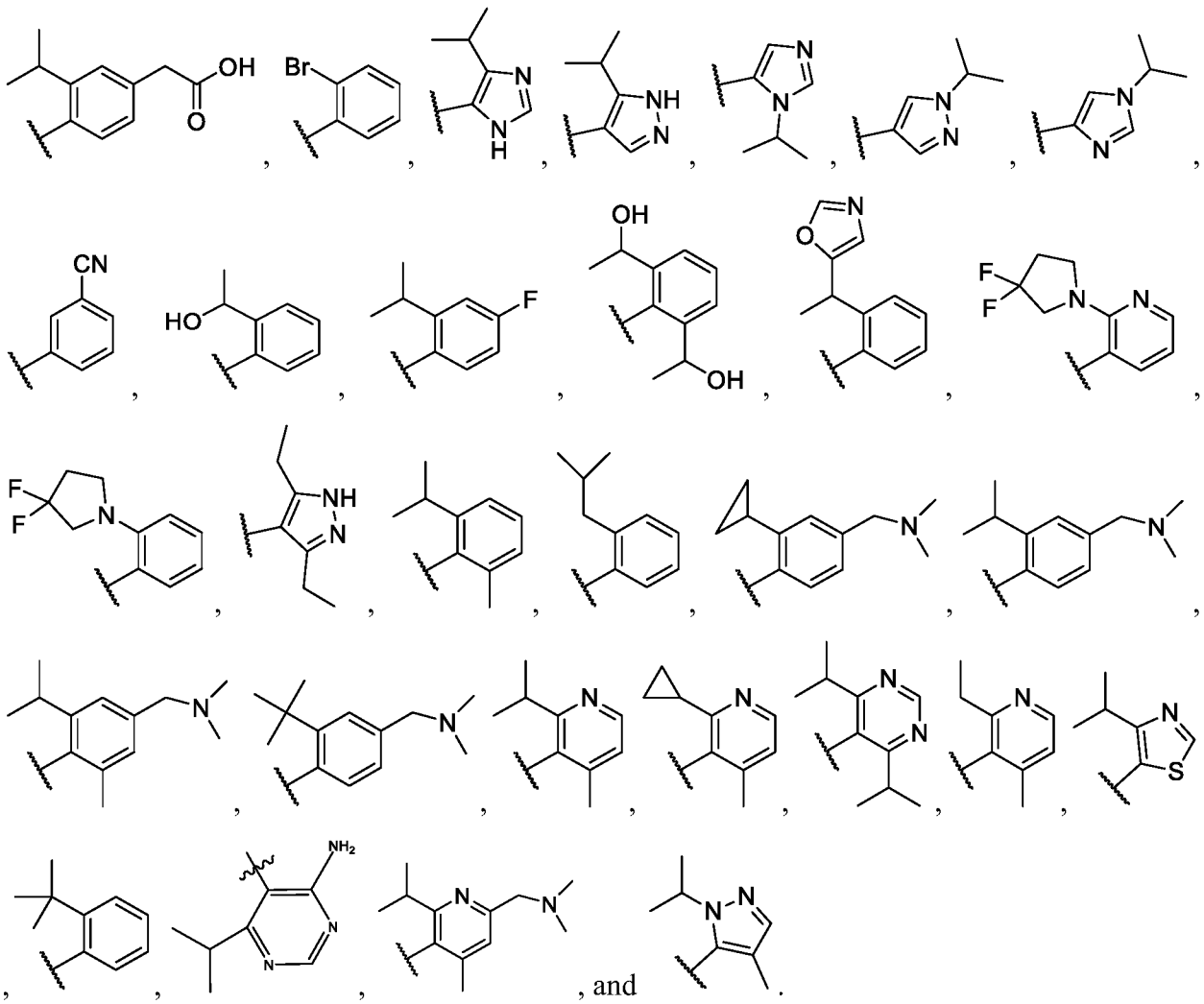

, and .

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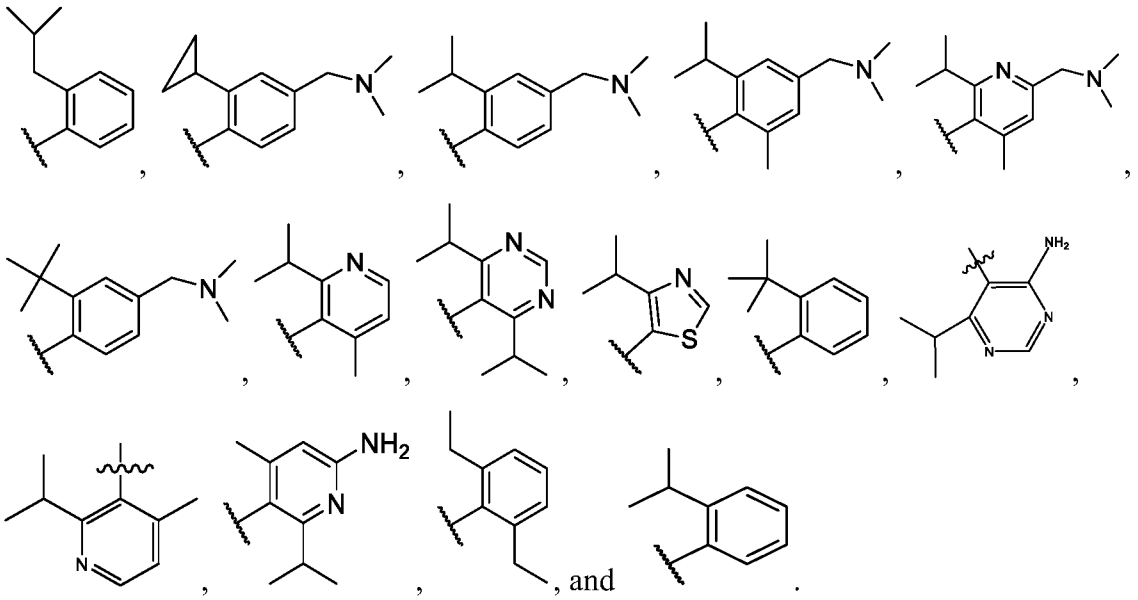
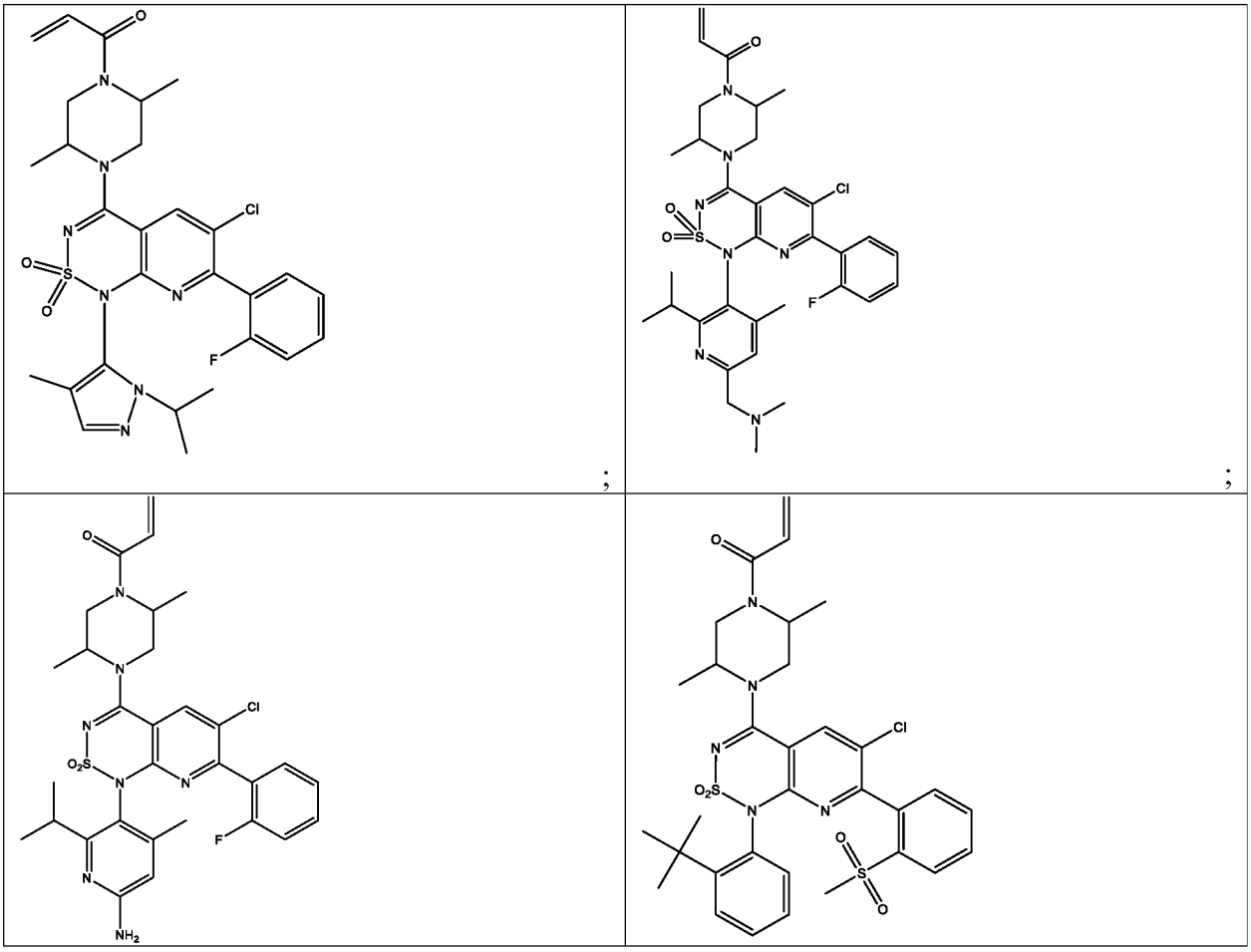
10. The compound of claim 9, wherein R^8 is selected from the group consisting of



11. A compound selected from the group consisting of:



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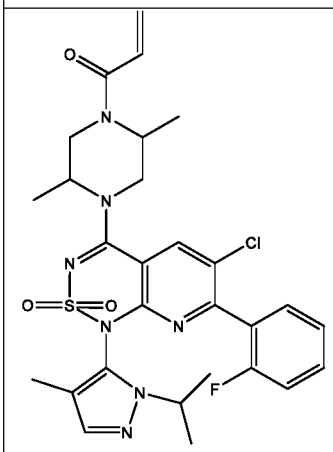
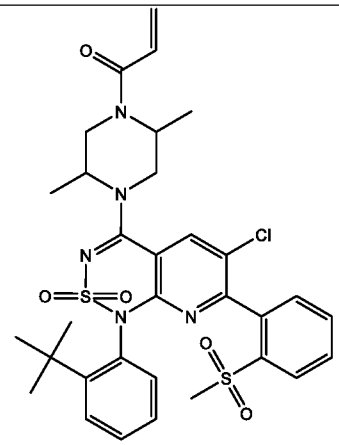
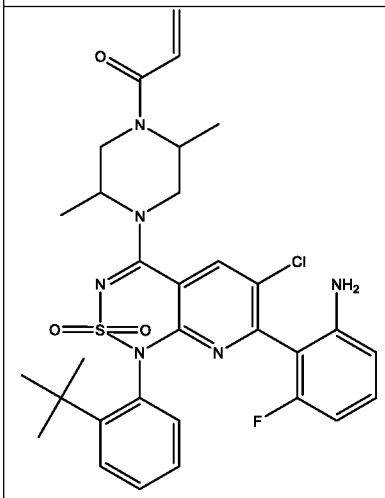
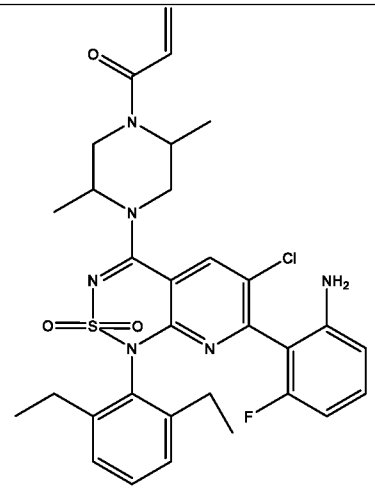
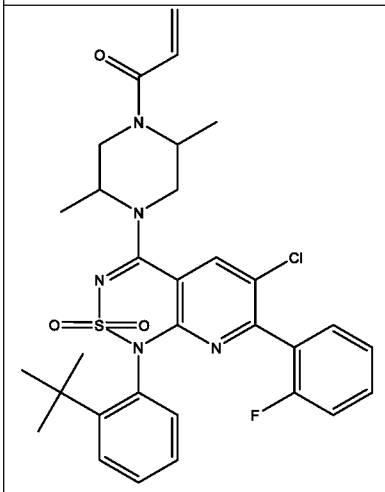
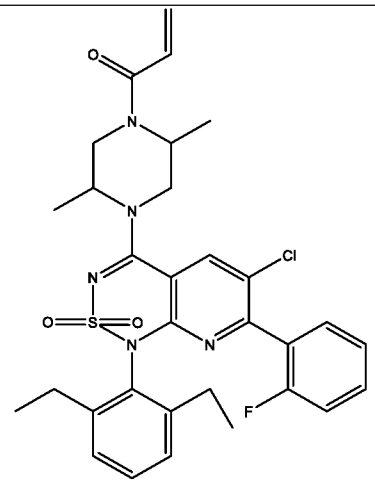
;  ;	;  ;
;  ;	;  ;
;  ;	;  ;

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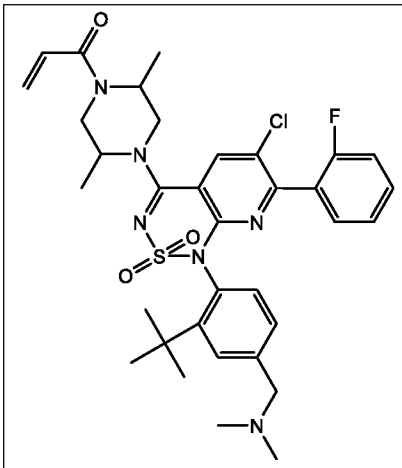
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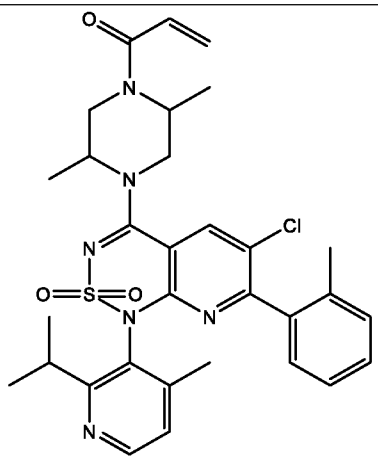
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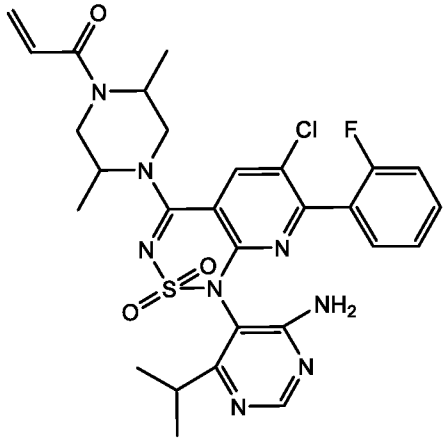
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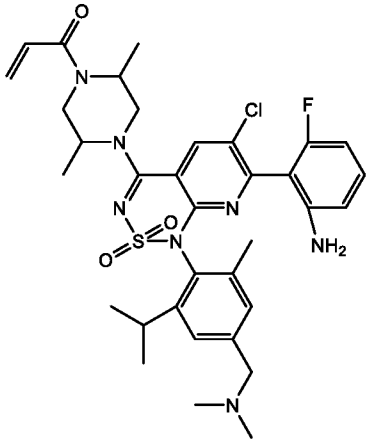
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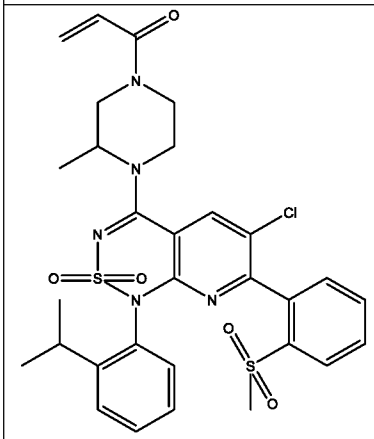
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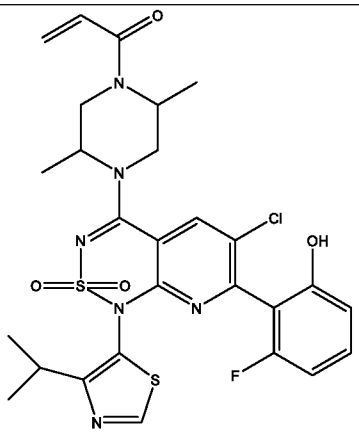
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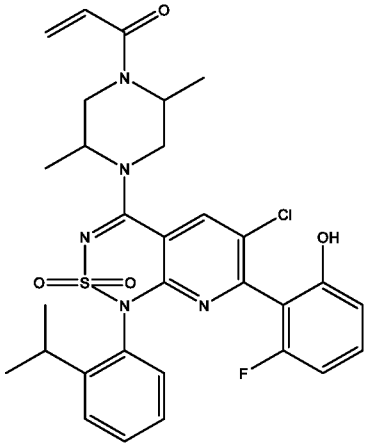

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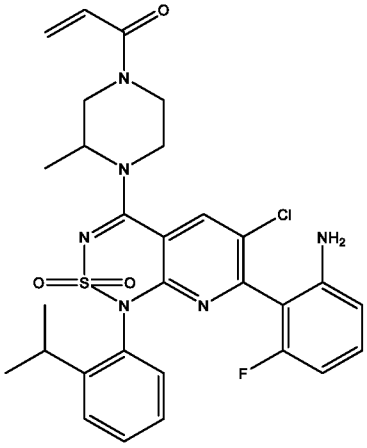

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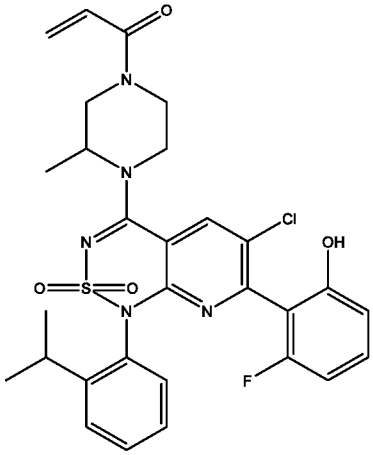

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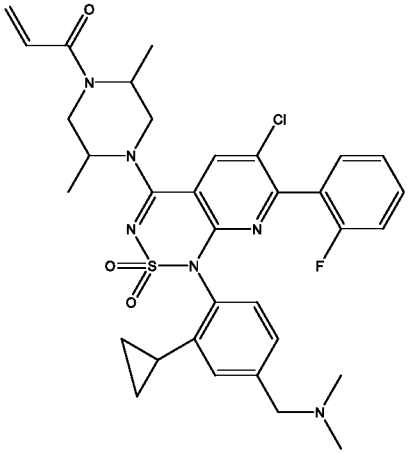

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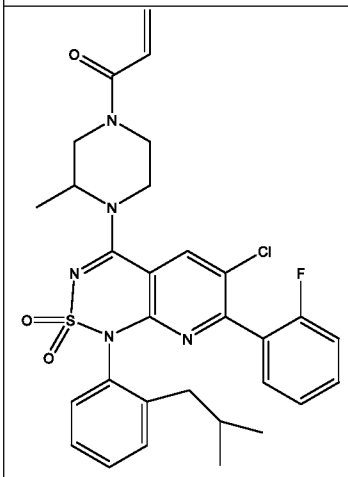

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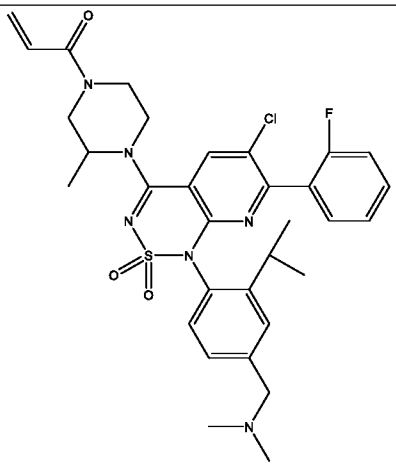

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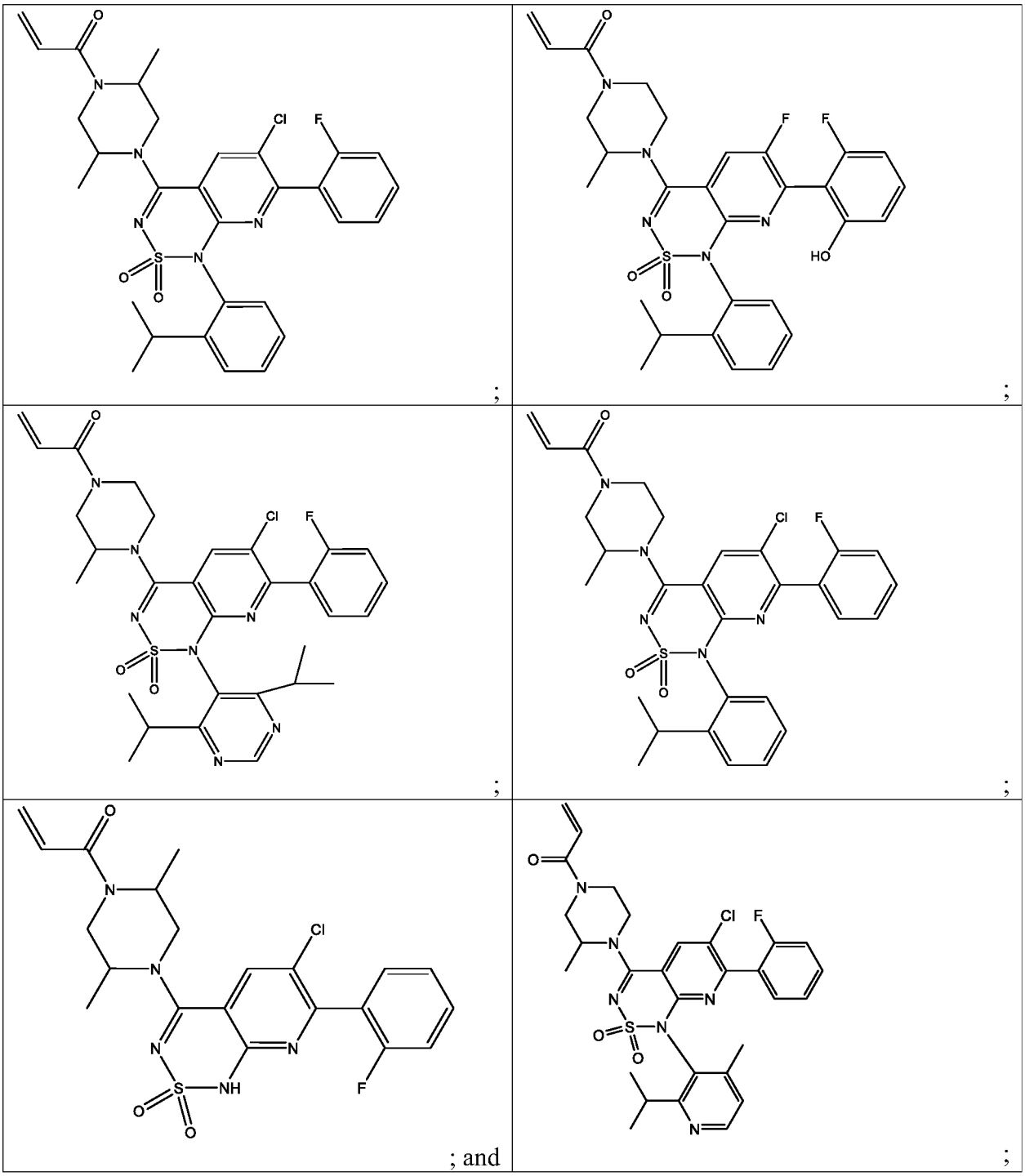

or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

12. A pharmaceutical composition comprising the compound of any one of claims 1-11 and a pharmaceutically acceptable excipient.

13. A method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of claims 1-11 or the composition of claim 12.

14. An in vitro method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of claims 1-11 or the pharmaceutical composition of claim 12.

15. A method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-11 or the composition of claim 12, wherein the cancer is mediated by a KRAS G12C mutation.

16. The method of claim 15, wherein the cancer is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.

17. The method of claim 15, wherein the cancer is non-small cell lung cancer.

18. The method of claim 15, wherein the cancer is pancreatic cancer.

19. The method of claim 15, wherein the cancer is colorectal cancer.

20. Use of the compound of any one of claims 1-11 or the composition of claim 12 in the manufacture of a medicament for treating cancer, wherein the cancer is mediated by a KRAS G12C mutation.

21. The use of claim 20, wherein the cancer is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.

22. The use of claim 20, wherein the cancer is non-small cell lung cancer.

23. The use of claim 20, wherein the cancer is pancreatic cancer.

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24. The use of claim 20, wherein the cancer is colorectal cancer.